NON-INTERVENTIONAL (NI) STUDY REPORT

PASS information

Title	Drug Utilization Study of conjugated oestrogens/ bazedoxifene (CE/BZA) in the European Union (EU)
Protocol number	B2311061
Version identifier of the final study report	Final Report Version 1.0
Date	12 March 2020
EU Post Authorisation Study (PAS) register number	EUPAS 11604
Active substance	Conjugated oestrogens/bazedoxifene (CE/BZA)
Medicinal product	DUAVIVE® modified-release tablets
Product reference	EU MA number: EU/1/14/960/001 (EU marketing authorisation granted 16 December 2014)
Procedure number	EMEA/H/C/002314/MEA 003
Marketing Authorisation Holder (MAH)	Pfizer Europe MA EEIG
Joint PASS	No
Research question and objectives	Describe baseline characteristics and utilization patterns of EU patients initiating Duavive or oestrogen + progestin (E+P) combination hormone replacement therapy (HRT).
Country(-ies) of study	All EU countries where CE/BZA was commercially available in 2016-2018 and where adequate data sources are available: Belgium, France, Italy, the Netherlands, Spain and UK.

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1. ABSTRACT (STAND-ALONE DOCUMENT)

Please refer to the stand-alone document.

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
ATC	Anatomical Therapeutic Chemical Classification System
BMI	Body Mass Index
CE/BZA	Conjugated oestrogens/bazedoxifene
CHD	Coronary heart disease
CHMP	Committee for Medicinal Products for Human Use
CSD	Cegedim Strategic Data
CVD	Cardiovascular disease
DUS	Drug Utilization Study
E+P	Oestrogen + Progestin
EMA	European Medicines Agency
EMR	Electronic medical records
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GP	General Practitioner
HEOR	Health economics and outcomes research
HRT	Hormone replacement therapy
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
IMB	Index Medical Belge (Medical Index database in Belgium)
IMS	Intercontinental Marketing Services
LPD	Longitudinal Patient Database
LRx	IMS Longitudinal Prescription Data
MAH	Marketing Authorisation Holder
MIN	Medische Index Nederland (Medical Index database in Netherlands)
PA(S)S	Post Authorisation (Safety) Study

Abbreviation	Definition
PI	Prescribing Insights (Data Source)
PRAC	Pharmacovigilance Risk Assessment Committee
PVD	Peripheral Vascular Disease
QA	Quality assurance
QC	Quality control
QMS	Quality Management System
READ	Standard clinical terminology system (incl. diagnosis codes) used in General Practice in the United Kingdom
RWE(S)	Real-world evidence (solutions)
SAP	Statistical Analysis Plan
SD	Standard deviation
SERM	Selective oestrogen receptor modulator
SmPC	Summary of Product Characteristics
SRC	Scientific review committee
THIN	The Health Improvement Network
UK	United Kingdom
VTE	Venous Thromboembolism
WHO	World Health Organization

3. INVESTIGATORS

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5. MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection Interim report 1	October 2017	22 October 2017	
End of data collection Interim report 1	January 2018	18 January 2018	
Registration in the EU PAS register	01 November 2015	08 October 2015	
Interim report 1	31 March 2018	31 March 2018	
Start of data collection Interim report 2	October 2018	15 October 2018	
End of data collection Interim report 2	December 2018	26 November 2018	
Interim report 2	31 March 2019	31 March 2019	
Start of data collection Final report	October 2019	08 October 2019	
End of data collection Final report	December 2019	25 November 2019	
Final report of study results	31 March 2020	12 March 2020	

6. RATIONALE AND BACKGROUND

In the European Union (EU), conjugated oestrogens/bazedoxifene (CE/BZA) is marketed as Duavive® and indicated for treatment of oestrogen deficiency symptoms in postmenopausal women with a uterus (with at least 12 months since the last menses) for whom treatment with progestin-containing therapy is not appropriate.[1]

At the time of marketing authorisation in 2014 it was deemed important to collect real-world data on the actual use of Duavive in the population for which it is authorised and prescribed, including characterisation of the population using the drug. As part of the description of utilization, the proportion of patients being prescribed Duavive not in accordance with the Summary of Product Characteristics (SmPC, off-label use) was estimated.

This non-interventional drug utilization study (DUS) was designated as a Post-Authorisation Safety Study (PASS) and was a commitment to the European Medicines Agency (EMA).

This final report includes study results on Duavive and oestrogen + progestin hormone replacement therapy (E+P HRT) utilization in Belgium, France, Italy, the Netherlands, Spain and United Kingdom (UK) for the time period from 31 March 2018 to 30 March 2019 (Annual Reporting Period III) and 31 March 2016 to 30 March 2019 (cumulative period beginning from Duavive launch).

7. RESEARCH QUESTION AND OBJECTIVES

7.1. Research Question

The overall aim of this study is to describe the baseline characteristics of EU patients initiating treatment with either Duavive or E+P HRT, and to describe the utilization patterns of Duavive.

7.2. Objectives

For Duavive or E+P HRT users, two sets of analyses were performed: one among those without prior use of any E+P HRT during their 12-month baseline period and another among those with prior use of E+P HRT. Each analysis addressed the following objectives:

1. Within each EU country, describe and compare baseline characteristics and medical history between Duavive and E+P HRT patients.

2. Estimate the proportion of patients that may have been prescribed Duavive outside of the specifications of the authorised product information (‘off-label use’).

   Please refer to Section 9.4.5 for the definition of Duavive off-label use.

8. AMENDMENTS AND UPDATES

Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
1	31 August 2017	substantial	Section 4	Exclusion of Finland, Germany, Sweden from the study; change of database in France, Italy, Spain	Duavive is not going to be marketed in Finland, Germany, Sweden. Change to LPD for France, Italy, Spain: compared to the LRx databases, LPD is a more comprehensive electronic medical record database (EMR), which include longitudinal patient level information.

9. RESEARCH METHODS

9.1. Study design

This is a multi-country real-world drug utilization study providing descriptive data on baseline characteristics and utilization patterns in EU patients initiating treatment with Duavive or E+P HRT.

9.2. Setting

This study utilizes longitudinal and cross-sectional secondary population-based healthcare data sources (databases) that are available in Belgium, France, Italy, the Netherlands, Spain, and the UK. Selection of countries for inclusion in this study was based on the following criteria:

- Availability of large databases that are nationally representative of prescribing practice in their respective countries, are expected to capture Duavive and E+P HRT prescriptions in their defined populations, and have established validity for drug utilization research.[2-8]

- Launch of Duavive in the country before 31 March 2016.

Data sources used for this study are listed in Sections 9.5.1 and 9.5.2.

The planned start and end dates of the study were 31 March 2016 and 30 March 2019, respectively, or the first 3 years of Duavive's EU post-authorisation period. Three consecutive periods within the entire study duration (3 years) were planned for analysis, with annual submission of reports to EMA as follows:

- Annual Reporting Period I: 31 March 2016 to 30 August 2017

- Annual Reporting Period II: 31 August 2017 to 30 March 2018

- Annual Reporting Period III: 31 March 2018 to 30 March 2019

This final report includes results for the time period from 31 March 2018 to 30 March 2019 (Annual Reporting Period III) and 31 March 2016 to 30 March 2019 (cumulative period).

9.3. Subjects

Study subjects are all patients identified in the respective databases with at least one prescription for Duavive or E+P HRT during the defined study period. The applied inclusion / exclusion criteria are minimal to ensure representativeness of 'real-world' use in the EU.

Specifically, patients had to meet both of the following inclusion criteria to be eligible for this study:

1. Patients were prescribed or dispensed at least one prescription for Duavive or E+P HRT during the defined study period.

2. In the longitudinal databases (LPD France, Italy, Spain; THIN UK; LRx Belgium and the Netherlands – see Section 9.5), patients were enrolled in the data source for at least 12 months prior to their index date. This period was necessary to determine if the patient was a new initiator and to fully describe patient's baseline characteristics.

Patients who had at least one Duavive prescription within 12 months prior to index date in the defined study period were excluded from both cohorts.

The *index date* was defined in longitudinal databases as the date of a patient's first recorded prescription of study medication (Duavive or E+P HRT) within the reported study period after the first EU launch of Duavive (both for the annual and the cumulative analysis). For E+P users, the *index date* is the date of the first prescription for any of the identified E+P products during the reported study period. In both study cohorts, only patients without prescription records for Duavive within 12 months prior to the index date are included in the analysis (see Figure 1 below).

A pre-index (i.e., baseline) period of 12 months prior to initiating Duavive or E+P HRT, was defined for the description of patient's baseline characteristics and medical history. All other data in this study are cross-sectional (i.e., no follow-up data post index date).

The E+P HRT comparator cohort consisted of patients prescribed any E+P combination product (oral, patch, or topical) that has an indication for treatment of oestrogen deficiency symptoms, or patients prescribed two E+P products concurrently (e.g., transdermal oestrogen and oral progestin). E+P HRT comparator products vary by EU country based on variations in product availability across different countries (see Appendix 2 in Annex 2). E+P HRT products that have indications for treatment of oestrogen deficiency symptoms *and* prevention of osteoporosis (as per the EU Core SmPC for HRT products)[9] were also included, as long as they are also indicated for oestrogen deficiency symptoms. Codes for specific E+P HRT combination products as well as separate oestrogen-containing products and progestin-containing products that could be prescribed concurrently are listed by country in Appendix 2 (Annex 2).

For the purposes of this study, tibolone (Livial®) was also considered as an E+P HRT and included among the comparator drugs in the countries where it is available. The rationale is that tibolone is metabolized to circulating oestrogens, progestins and androgens, and where available, is widely used.

An overview of the study population for annual and cumulative analyses is shown in Figure 1 and Figure 2 below.

Figure 1. Overview of the study population – Annual Analyses

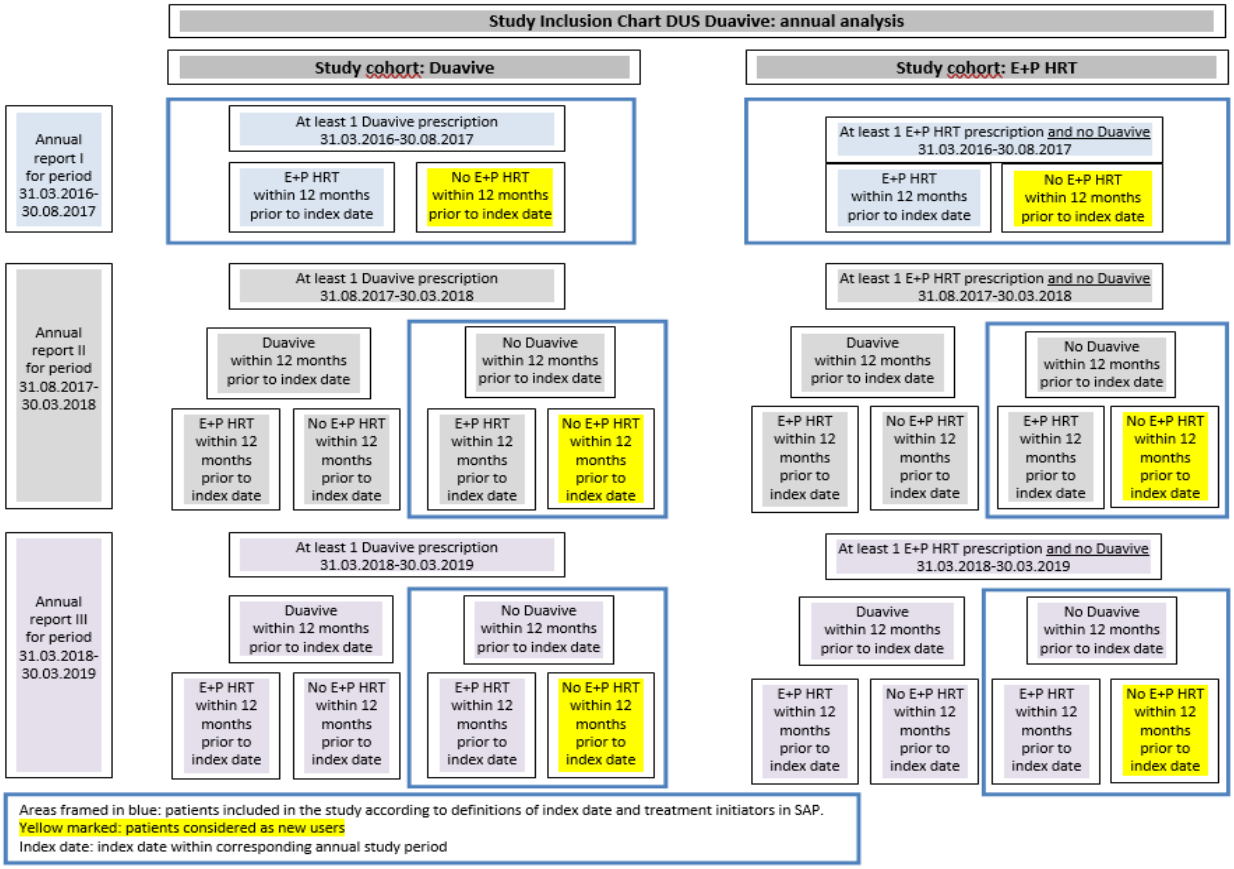
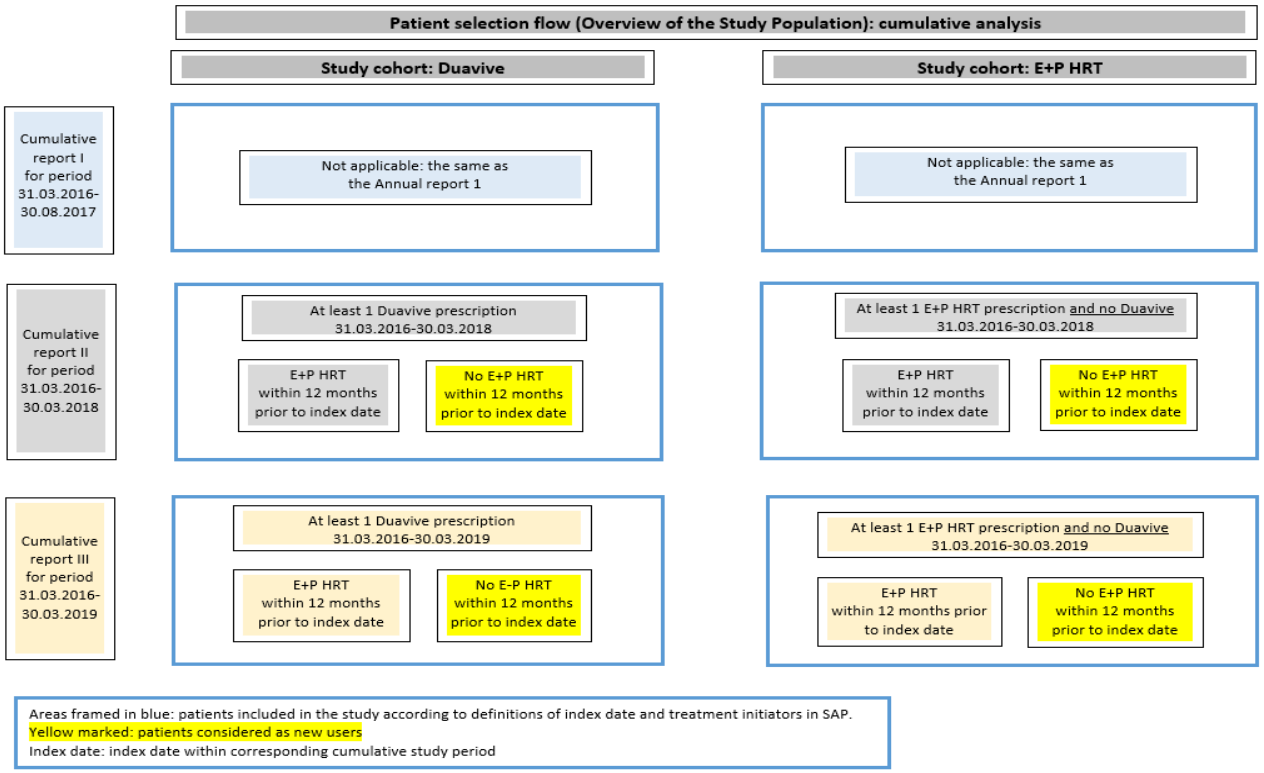


Figure 2. Overview of the study population – Cumulative Analyses



9.4. Variables

9.4.1. Variable overview

Study variables for the planned analyses and their availability in the target countries are listed in Table 2 below. Table 4 in Annex 1 to the Study Protocol contains additional details on the feasibility of study objectives/analyses in each of the target countries/data sources and a rationale for any analysis not being performed.

Table 2. Study parameters and availability by target country

Variable	Belgium***	France	Italy	The Netherlands***	Spain	UK
Baseline characteristics						
Demographic characteristics						
Age	Y	Y	Y	Y	Y	Y
Gender	Y	Y	Y	Y	Y	Y
BMI		(Y)	(Y)		(Y)	(Y)
Relevant co-morbidities	Y*	Y	Y	Y*	Y	Y
History of relevant co-medication	Y	Y	Y	Y	Y	Y
Prior safety events (risk factors)		Y	Y		Y	Y
Indication	Y*	Y	Y	Y*	Y	Y
Prior treatment with E+P HRT	Y	Y	Y	Y	Y	Y
Drug utilization Duavive						
Prescription date	Y	Y	Y	Y	Y	Y
Prescribed dose	Y*	Y	Y	Y	Y	Y
Prescribed days supply	Y*	Y	Y	Y	Y	Y
Switch from E+P HRT	Y	Y	Y	Y	Y	Y
Off-label use Duavive**	Y*	Y	Y	Y*	Y	Y

Y: available
(Y): available, but missing data expected
* restricted availability (available in cross-sectional database only – data on prescription day only)
** Detailed information on availability of single parameters characterising off-label use in target countries is provided in Annex 1 to the Study Protocol (Table 4 of Annex 1)
***Both longitudinal and cross-sectional data sources were used in Belgium and Netherlands.

In summary, taking into account the limitations in database availability or validity which precludes some analyses from being performed in a given country:

- The descriptive analyses of patient characteristics are feasible in all countries, with the exception of the BMI - a variable which can be analysed to a limited extent only in France, Italy, Spain and UK. For age in Belgium (IMS® LRx database), only pre-set age groups are available.

- Information on diagnoses is not available in the longitudinal databases for Belgium and Netherlands (IMS® LRx). The cross-sectional data sources from Belgium and Netherlands can only detect diagnoses if they occur in the same consultation as the prescribing visit. Therefore, the study can define variables for indication and co-morbidities (and related off-label use) in the above two countries to a very limited extent. Analysis of prior safety events is not possible.

The variable definitions used in the analysis are summarised in Table 3.

Table 3. Variable definitions

Parameter	Definition
Index date	Date of the patient's first record of Duavive or E+P HRT prescription in the database within the reported study period.
Index prescription	First record of Duavive or E+P HRT prescription in the database within the reported study period.
Patient's observability in longitudinal database during selected time period (e.g. 12 months pre-index)	At least one patient's record available in the database before the start of time period of interest.
Age	Age at index date was reported in 3 categories: • <40 years • 40-49 years • ⩾50 years
Gender	Gender was reported as recorded in the data source
Body Mass Index (BMI)	BMI was calculated as $\frac{\text{....}\ (\ )}{(\ )}$ at index date. If information on index date was not available, data from index date ±90 days was used. The four categories of this variable are: • <18.5: underweight • 18.5 to <25: normal range • 25 to <30: overweight • ⩾30: obese
E+P HRT in case of concurrent use of separate E and P products for HRT in longitudinal database	In case of concurrent use for HRT, separate E+P products were considered as E+P HRT, if the time between prescription dates of both substances did not exceed 30 days. The first prescription date within the analysed study period was considered as the E+P index date.
Specified co-morbidities,	ICD-10 codes of relevant co-morbidities documented within 12 months prior to index date were considered. Relevant diagnoses are listed in Table 4
Prior safety events	ICD-10 codes of safety events of interest documented within 12 months prior to index date were considered. Relevant diagnoses are listed in Table 4
Specified co-medications	ATC codes of relevant co-medications documented within 12 months prior to index date were considered. Relevant codes listed in Table 5
Prior treatment with E+P HRT (for definition of subgroups)	At least one prescription record of E+P HRT in a longitudinal database within the last 12 months before index date

Table 3. Variable definitions

Parameter	Definition
Indication for study medication	Indication was determined by presence of diagnostic codes for oestrogen deficiency or osteoporosis • From 90 days before to 90 days after index date in the main analysis and • From 365 days before to 90 days after index date in the additional analysis. Four levels for this variable are: • Oestrogen deficiency symptoms only • Osteoporosis only • Both • No oestrogen deficiency symptoms or osteoporosis or missing.
Prescription duration of Duavive (days supply)	The estimated prescription duration was based on the quantity prescribed (number of tablets) and dosage instruction recorded with the prescription. The assumed days supply was calculated as number of tablets prescribed/daily dosage prescribed. See Section 9.4.4 for details on estimating days supply in the absence of the prescribing details.
Switch from E+P HRT to Duavive	Prescription of Duavive within 30 days following the end of the last filled prescription period of E+P HRT
Presumed premenopausal women age[1] (includes women of childbearing potential)	Women age ⩽45 years (main analysis); ⩽49 years (sensitivity analysis

1. The age threshold of 45 years old (49 years in sensitivity analysis) was used as a proxy measure. These women may have been postmenopausal and in accordance with the label indication.
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

9.4.2. Demographic characteristics

9.4.2.1. Age

In both longitudinal and cross-sectional databases, age was analysed as a categorical variable (age group) in the descriptive analysis of patient demographics. The categorical variable "age group" was generated by grouping reported values of the continuous variable "age" at index date (prescription date in cross-sectional databases).

The following 3 age groups were presented:

- <40 years
- 40 to 49 years

- ≥50 years

The results are displayed as a proportion of the age categories:

1. On patient level (longitudinal databases): proportion of patients in each age group, and

2. On prescription level (cross-sectional databases): proportion of prescriptions for Duavive or E+P HRT in each age group.

9.4.2.2. Gender

Gender was analysed as a dichotomous variable.

The results were reported as:

1. Proportion of patients (longitudinal data), and

2. Proportion of prescriptions related to each gender class (cross-sectional data).

9.4.2.3. Body Mass Index (BMI)

Analysis of BMI was possible in longitudinal patient-level databases only (France, Italy, Spain and UK) and was conducted based on observations with non-missing values (see Section 9.9.3). Due to the high proportion of missing values in parameters needed for calculation of BMI, the results were available for a portion of the study population.

BMI was calculated as ($\frac{(\quad)}{(\quad)}$), and was evaluated as a categorical variable with 4 categories:

- <18.5: underweight
- ⩾18.5 to <25: normal range
- ⩾25 to <30: overweight
- ⩾30: obese

The analysis was conducted at the index date. If data on weight or height was not available at the index date, information from 90 days pre- or post-index was considered as relevant for the analysis. The proportion of patients in each BMI category is displayed.

9.4.3. Clinical characteristics

9.4.3.1. Co-morbidities

Diagnoses of specified co-morbidities of interest are listed in Table 4 below and in the Study Protocol, Annex 1, Table 4. Diagnoses were identified in data sources using International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes or READ codes[10] (Disease classification system used in UK THIN database), as

appropriate. For mapping of ICD-10 to READ codes please refer to Study Protocol, Annex 1, Table 5. Analysis was performed in accordance with the data availability in country-specific data sources (see Table 2, Section 9.4.1).

Co-morbidities were analysed as dichotomous variables. The results are presented as proportions both for “any co-morbidity” and for single diagnosis groups.

The analysis based on longitudinal data provided information on the proportion of patients who were documented with relevant co-morbidities within 12 months prior to index date (index date was included). Analysis within a standard pre-index period (12 months) enabled comparability of study results between included study cohorts and countries.

In cross-sectional databases, only information from the same consultation, but no information from the time before or after the prescription, was available. For this reason, only co-morbidities recorded on the day of prescription could be analysed, which should be considered when interpreting the results.

Table 4. ICD-10 codes relevant for scheduled analyses

Parameter	ICD-10 code
Co-morbidities	
Osteoporosis/ osteopenia	M80-M82
History of CVD event	I61-I64, I21.x, I22.0, I22.1, I22.8, I22.9
Hyperlipidemia	E78
Hypertension	I10-I15
Breast pain	N64.4
Diabetes	E10-E14
Renal disease	N17-N19
Osteoarthritis	M15-M19, M47
Major depression	F32.2; F32.3; F33.2-F33.3
Prior Safety Events (Risk factors)	
History of VTE/stroke/ CHD/ PVD event	I80-I82, O87.1, O87.3, O22.3, I26.0, I26.9, I61-I64, I20-I25 cerebral (I63.6, I67.6), I73.9
History of malignancy potentially associated with oestrogen	C50, C54, C54.1, C56, C57.8, C57.9, Z85.3
History of any malignancy	C00-C97; D00-D09; D37-D48
Indication for use	
Oestrogen deficiency symptoms	N95.1, N95.9, R23.3
Osteoporosis	M80-M82
Off-label use Duavive	
Use for treatment of osteoporosis only	M80-M82
Use in women without a uterus (hysterectomised women)	Z90.7
Known, suspected, or past history of breast cancer	C50, Z85.3
Hypersensitivity (e.g., anaphylaxis/anaphylactic reactions, urticaria, drug eruption) to the active substances or to any of the excipients	T78.2, T88.6, L50.0, L50.1, L50.9
Malignancy potentially associated with oestrogen	C50, C54, C54.1, C56, C57.8, C57.9
Venous thromboembolism (deep venous thrombosis, pulmonary embolism, and retinal vein thrombosis)	I80 (I80.0), I81, I82, I26, H34.8, H34.9
Arterial thromboembolic disease (e.g., myocardial infarction, stroke)	I21, I22, I61, I62, I63, I64
Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal	K71, K72, K75.0, K76.2, K76.3
Thrombophilic disorders (e.g., protein C, protein S, or antithrombin deficiency)	D68.5, D68.6
Porphyria	E80.0, E80.1, E80.2

ICD-10: International Classification of Diseases 10th revision, CVD: cardiovascular disease; CHD: coronary heart disease; VTE: venous thromboembolism; PVD: peripheral vascular disease

9.4.3.2. Specified co-medication

Specified medication(s) from the patient's history were evaluated as dichotomous parameter(s) analogous to analysis of co-morbidities. The results are presented both for "any medication" and for single drug classes.

A listing of relevant substance classes and respective ATC WHO codes is provided in Table 5 below.

Table 5. ATC codes relevant for co-medication analyses*

Parameter	ATC code
History of relevant co-medication	
Corticosteroids	H02
Lipid lowering agents	C10
Anti-hypertensives	C02
Anticoagulants	B01
Antiarrhythmics	C01
Antidepressants	N06A
Sedatives/ hypnotics	N05C
Antidiabetics	A10
Osteoporosis treatments (bisphosphonates, SERMs, etc)	G03XC, M05B
Local (vaginal) hormone treatments	G02B; G03C
Off-label use of Duavive	
Use with progestins, additional oestrogens or SERMs	G03C; G03AC; G03XC

SERMs: selective oestrogen receptor modulators

*Information on ATC codes for E+P HRT provided in Annex 2 (Appendix 2)

9.4.3.3. Prior treatment with E+P HRT

All scheduled analyses based on longitudinal data were stratified by prior treatment with or without E+P HRT. Prior treatment was defined as at least one prescription of E+P HRT within the 12 months prior to index date. This variable was used to define sub-groups of the analysis within the two drug cohorts (see Section 9.9.1). In addition, the proportion of Duavive and E+P HRT users with and without prior treatment was reported.

9.4.3.4. Prior safety events

Prior safety events/risk factors from patient's history were mainly analysed based on longitudinal data. As with co-morbidities and co-medications, data were extracted from the 12-month period prior to index prescription. Analyses based on cross-sectional databases were possible if respective diagnoses were recorded at the same consultation as the prescription of interest.

Three groups of safety events/risk factors from patient history were described as dichotomous (yes/no) variables:

1. *VTE/stroke/ CHD risk factor*: history of VTE/ stroke/ CHD/ PVD event,
2. *Malignancy risk factor*: history of malignancy potentially associated with oestrogen and

3. *Malignancy risk factor*: history of any malignancy.

The relevant ICD-10 and READ codes of these prior safety events are provided in Table 4 above and Table 4, Annex 1 of the Study Protocol.

Percentages were displayed both for "any event" and for each group of safety events separately.

9.4.3.5. Indication for study medication

In longitudinal patient-level databases (France, Italy, Spain, UK; see Section 9.5), indication was determined by presence of diagnostic codes for oestrogen deficiency (ICD-10 codes N95.1, N95.9, R23.3) or osteoporosis (ICD-10 codes M80-M82) recorded on the index date or within 90 days before or after the index date. Information on diagnoses is not available in the longitudinal prescription-level data sources (LRx Belgium, The Netherlands). In the cross-sectional databases (Belgium, The Netherlands), only diagnoses documented on the day of prescription were available.

Indication was analysed as a categorical variable. The following 4 categories were defined and described:

1. Prescriptions with a recorded diagnosis of oestrogen deficiency symptoms, within 90 days before or after initiation of Duavive, and without a diagnosis for prevention and/or treatment of osteoporosis in that same time period.

2. Prescriptions with a recorded diagnosis of prevention and/or treatment of osteoporosis, and without a diagnosis of oestrogen deficiency symptoms in that same time period.

3. Prescriptions with recorded diagnoses of oestrogen deficiency symptoms and with prevention and/or treatment of osteoporosis in the above time period.

4. Prescriptions without recorded diagnoses of oestrogen deficiency symptoms or prevention and/or treatment of osteoporosis in the above time period.

   For the longitudinal patient-level data, this category includes patients with at least one diagnosis other than oestrogen deficiency symptoms or osteoporosis, and patients without any diagnosis recorded within 90 days before or after index date (missing diagnosis). For the cross-sectional data sources, proportion of prescriptions without any diagnosis records on the prescription day and prescriptions with other diagnoses were reported separately.

Analyses of indication and potential off-label use of Duavive partially overlapped: categories 2 and 3 above were considered to be potential off-label use in the analysis. For details please refer to Section 9.4.5 and Table 6 in Section 9.9.4.

The full lists of ICD-10 codes and READ codes for diagnoses of oestrogen deficiency symptoms and osteoporosis are provided in Table 4 above and Table 4 in Annex 1 of the Study Protocol.

Analysis of indication in the case of concurrent use of separate oestrogen and progestin products for HRT (in longitudinal data) considered diagnoses within 90-day periods around prescription dates of both products.

An additional analysis of indication based on an extended time period for identification of relevant diagnoses was performed. The extended time period was from 365 days prior to index date to 90 days after index date. For details please refer to Section 9.9.5.

Furthermore, an additional analysis of indication for Duavive in women aged ≤45 years for identification of probable postmenopausal status was conducted. For description please refer to Section 9.9.5.

9.4.4. Duavive utilization

9.4.4.1. Dose and days supply

Duavive utilization was described using information from longitudinal and cross-sectional data sources dependent on the availability of the necessary variables in country specific databases (see Table 2, Section 9.4.1).

Analysis was performed based on the index prescription of Duavive and described as follows:

1. Prescribed daily dose, and
2. Prescription duration (days' supply).

Daily dose (number of tablets per day) was presented as a categorical variable with 3 categories:

- 1 tablet per day (recommended daily dose according to EU SmPC)
- <1 tablet per day
- >1 tablet per day

Percentages of each daily dosage category were reported.

Days supply. The prescription duration (the assumed days' supply) was analysed as a continuous variable. In case the physician's recommendation on treatment duration was provided in the Duavive prescription record, this data was evaluated. Otherwise, estimated duration was based on the quantity prescribed (number of tablets/pack size) and dosage instruction recorded with the prescription (if available). The number of refills was considered, if documented with prescription. The assumed days supply was calculated as number of tablets prescribed/daily dosage.

Analyses were performed in two ways:

1. Analysis based on observations with known values (entered in the prescription record). In this case, the proportion of prescriptions with missing information was reported.

2. Analysis using imputation to set missing values to the standard Duavive dose and supply as specified in the product label.

9.4.4.2. Switch from E+P HRT to Duavive

A switch from E+P HRT to Duavive was analysed at treatment initiation based on longitudinal data sources. A dichotomous variable "switch (yes/no)" was generated. Patients initiated on Duavive within 30 days following the end of the last filled prescription period of E+P HRT were considered switchers. The end date of the last filled prescription of E+P HRT was calculated using the last prescription start date and the duration of the last prescription. The prescription duration was based on the quantity prescribed and dosage instruction recorded with the prescription.

9.4.5. Potential off-label use of Duavive

In the EU, Duavive is indicated for *"treatment of oestrogen deficiency symptoms in postmenopausal women with a uterus (with at least 12 months since the last menses) for whom treatment with progestin-containing therapy is not appropriate"*.[1]

As part of the description of utilization, the proportion of patients being prescribed Duavive not in accordance with the product information (off-label use) was estimated as accurately as possible, given the limitations of the available data sources. Data on analysis feasibility in target countries is summarised in Table 2, Section 9.4.1.

Presence of the following criteria indicating potential off-label use in patients receiving Duavive was studied:

- Use for treatment of osteoporosis
- Use in premenopausal women (using patient age as a proxy for premenopausal status, as described below)
- Use in women over 75 years old
- Use in males
- Prescription of a non-approved dose or regimen
- Use with progestins, additional oestrogens or selective oestrogen receptor modulators (SERMs)
- Use in women without a uterus (hysterectomised women)
- Use in women with a known, suspected, or past history of breast cancer
- Use in women with hypersensitivity (e.g., anaphylaxis/anaphylactic reactions, urticaria, drug eruption) to the active substances or to any of the excipients

- Use in women with malignancy potentially associated with oestrogen
- Use in women with active or past history of venous thromboembolism (deep venous thrombosis, pulmonary embolism, and retinal vein thrombosis)
- Use in women with active or past history of arterial thromboembolic disease (e.g., myocardial infarction, stroke)
- Use in women with acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal
- Use in women with known thrombophilic disorders (e.g., protein C, protein S, or antithrombin deficiency)
- Use in women with porphyria

In the main analysis, potential off-label use was assumed when a patient had a diagnosis of osteoporosis and no diagnosis of oestrogen deficiency symptoms (indication category 2, see Section 9.4.3.5). In sensitivity analysis, off-label use was assumed when a patient had a diagnosis of osteoporosis and a diagnosis of oestrogen deficiency symptoms (indication category 3, see Section 9.4.3.5). For a detailed description of sensitivity analyses please refer to Section 9.9.4.

As premenopausal status is not explicitly recorded in the databases, age was used as a proxy measure for premenopausal status in the analysis of potential off-label use (see Section 9.4.1, Section 9.9.4):

- Premenopausal women (includes women of childbearing potential):

    1. Main analysis: women ≤45 years of age.

    2. Sensitivity analysis: women ≤49 years of age

In all countries, analysis of potential off-label use was based primarily on the longitudinal data sources. The cross-sectional databases from Belgium and Netherlands only enable restricted evaluation since only data recorded in the same consultation are recorded.

The analysis unit was the patient (longitudinal databases) and the prescription (cross-sectional databases), respectively (see Sections 9.5.1 and 9.5.2 for listing of the databases).

A summary variable indicating potential Duavive off-label use (yes/no) was created based upon evidence for any of the above criteria for potential off-label use. The results were presented as follows:

- the proportion of patients with each of the single categories included in the definition of potential off-label use (as available in respective data sources)

- the proportion of patients with potential off-label use (in total).

The proportion of patients with single categories of potential off-label use was only calculated if the relevant variable was available in the data source. In the longitudinal data sources, as with co-morbidities, data for potential off-label use components was based on the 12 months period prior to treatment initiation of Duavive (index date included). Use of Duavive with progestins, additional oestrogens or selective oestrogen receptor modulators (SERMs) was defined as both Duavive and the additional treatment being prescribed within a 10 days period.

The percentages of patients with single categories of potential off-label use were based on observations with non-missing values in the respective category. Patients with at least one category of off-label use were considered to be potential off-label users.

In Interim report 2, additional analyses of potential off-label use were performed under consideration of the modified algorithm for identification of indication for Duavive (diagnosis within 365 days prior to index date to 90 days after index date, instead of 90 days prior to index date to 90 days after index date). For details please refer to Section 9.9.5.

The components of the clinical definition by country and information on the feasibility of using single variables indicating potential off-label use are provided in Study Protocol, Annex 1, Table 4.

The ICD-10, READ and ATC codes which are relevant for analysis of potential off-label use are also summarised in Table 4, Annex 1 of the Study Protocol, and in Table 4 and Table 5 above.

Information on categories “use for prevention of breast cancer”, “undiagnosed genital bleeding”, and “untreated endometrial hyperplasia” is not available in selected data sources. These categories were not included in analysis.

9.5. Data sources and measurement

A single database for all target EU countries (Belgium, France, Italy, Netherlands, Spain, and the UK) is not available. Therefore, multiple data sources were used.

The EU data sources included were selected because they are nationally representative of prescribing practice in their respective countries, potentially able to capture Duavive and E+P HRT prescriptions in their defined populations, have relatively short data lags, and have established validity for drug utilization research.

The following electronic data sources were used:

9.5.1. Longitudinal databases

1. Longitudinal patient-level EMR databases:

    - The Health Improvement Network (THIN): UK
    - IMS Longitudinal Patient Database (LPD) databases (France, Italy and Spain)

2. Longitudinal prescription-level databases:

    - IMS Longitudinal Patient Level Prescription Database (IMS® LRx): Belgium, Netherlands

9.5.2. Cross-Sectional databases

1. IMS Medical Index

    - Belgium
    - Netherlands

For a detailed description of data sources used in this study please refer to Section 8.6 of the Study Protocol.

In an effort to obtain the most data variables for each country, this DUS is based on more than one database in Belgium and the Netherlands. The patient-level and prescription-level data sources contain complementary information and allow the DUS to address as many objectives as possible within each country. In Belgium and the Netherlands, IMS Medical Index and IMS® LRx were used as complementary data sources, as they provide information on diagnoses, which is not available in the Belgium and Netherlands prescription databases. For panel size and coverage by specialty in the IMS Medial Index Belgium and Netherlands, please refer to Annex 2. In the patient-level databases for France, Italy, Spain and UK (LPD, THIN), diagnosis information is included, therefore cross-sectional databases were not needed.

9.6. Bias

Misclassification of indication of use is possible in this study. In general, indication for use of Duavive is not explicitly recorded in the databases, but must be inferred based on diagnoses recorded within a given time frame near the prescription date. In particular, postmenopausal status is recorded incompletely. Because of these database limitations, the DUS focuses upon the presence of information suggestive of off-label use and not the absence of expected data elements.

The longitudinal data sources in this study were selected because they are nationally representative of prescribing practice in their respective countries, are expected to capture Duavive and E+P HRT prescriptions in their defined populations, have relatively short data lags, and have established validity for drug utilization research. In the cross-sectional databases reporting physicians are sampled randomly and stratified by region and speciality. While physicians participate voluntarily, this is expected to have a minimal impact on the generalisability of the study results.

In cross-sectional databases, prescriptions provided by a sample of physicians are projected to national levels which may lead to some bias in case of low numbers of reported prescriptions.

9.7. Study Size

In this DUS, drug utilization of Duavive and E+P HRT in the EU was analysed descriptively. Formal hypothesis testing was not conducted.

All individual patients identified as new initiators of Duavive or E+P HRT users in the databases during the study period were included. The numbers of patients depended on the uptake of Duavive in the EU countries in which the product was made available.

9.8. Data transformation

Variable categorisation methods are described in in Sections 9.4.2 to 9.4.5. For methods to address missing values, please refer to Section 9.9.3. Detailed methods for data transformation and data management are documented in the Statistical Analysis Plan (SAP), which is dated, filed and maintained by the Sponsor (Appendix 3).

9.9. Statistical methods

9.9.1. Main summary measures

The number of non-missing observations, means, standard deviations, medians, minimum and maximum were provided for continuous variables. Categorical variables were tabulated with absolute and relative frequencies. Percentages were presented to one decimal place.

Results obtained from different databases or countries were analysed separately and reported in parallel. Study tables reference the data source for each set of results.

Analyses based on longitudinal data were performed at patient level, dependent on availability of the relevant study variables. Results obtained from cross-sectional databases were presented at the prescription level only and projected to national levels; due to the cross-sectional nature of these sources, only medical information recorded in the same consultation (on day of prescription) was available.

Baseline characteristics were assessed during the 12-month pre-index period. All other data in this study were cross-sectional (related to time point of treatment initiation (index date)).

Within country, analyses in longitudinal databases were performed for all Duavive or E+P HRT users as a whole, as well as stratified by previous use of E+P HRT, as follows:

Duavive users:

- All Duavive users
- Duavive users without E+P HRT during the 12-month pre-index period
- Duavive users with E+P HRT during the 12-month pre-index period

E+P HRT users:

- All E+P HRT users

- E+P HRT users without E+P HRT during the 12-month pre-index period
- E+P HRT users with E+P HRT during the 12-month pre-index period

9.9.2. Main statistical methods

All analyses were performed using descriptive statistical methods only. No hypothesis testing was performed and no conclusions about statistical significance were made.

9.9.3. Missing values

Because of the descriptive design of this study, the available data were generally analysed "as reported". Missing data were only replaced for some analyses of Duavive daily dose (see Section 9.4.4.1). The corresponding value(s) was set to "missing". For the majority of parameters (e.g., patient demographic characteristics), percentages were based on the number of observations with non-missing data. An exception was applied for the analysis of the indication for prescription. The proportion of prescriptions with missing diagnosis information was reported.

Details regarding the handling of missing information on Duavive utilization are described in Section 9.4.4.

9.9.4. Sensitivity analyses

Several pre-specified sensitivity analyses were performed to further investigate potential off-label use of Duavive. Specifically, these sensitivity analyses were performed in order to:

1. Evaluate the impact of adding indication category 3 "prescriptions with recorded diagnoses of oestrogen deficiency symptoms and with prevention and/or treatment of osteoporosis" (in addition to indication category 2 "prescriptions with a recorded diagnosis of prevention and/or treatment of osteoporosis, and without a diagnosis of oestrogen deficiency symptoms") to the definition of off-label use, please refer to Section 9.4.5.

2. Assess the impact of a differing age threshold (age cut-off point of 49 years instead of 45 years) for the definition of premenopausal use of Duavive on potential off-label use estimates.

Three sensitivity analyses of potential off-label use were performed, based on two thresholds for premenopausal age (45 and 49 years) and on presence or absence of a diagnosis of oestrogen deficiency symptoms, in addition to prevention and/or treatment of osteoporosis. Other criteria for potential off-label use as listed in Section 9.4.5 remained identical for the main and the three sensitivity analyses. The resulting categories are summarized below in Table 6:

Table 6. Overview of differences between main and sensitivity analyses for potential off-label use

Analysis	Premenopausal age	Indication for treatment
Main analysis	≤45 years	diagnosis of prevention and/or treatment of osteoporosis, **and no** diagnosis of oestrogen deficiency symptoms
Sensitivity analysis I	≤49 years	diagnosis of prevention and/or treatment of osteoporosis, **and no** diagnosis of oestrogen deficiency symptoms
Sensitivity analysis II	≤45 years	diagnosis of prevention and/or treatment of osteoporosis, **and no** diagnosis of oestrogen deficiency symptoms or diagnosis of prevention and/or treatment of osteoporosis, **in addition to** diagnosis of oestrogen deficiency symptoms
Sensitivity analysis III	≤49 years	diagnosis of prevention and/or treatment of osteoporosis, **and no** diagnosis of oestrogen deficiency symptoms **or** diagnosis of prevention and/or treatment of osteoporosis **in addition to** diagnosis of oestrogen deficiency symptoms

Additional (not pre-specified) analyses of potential off-label use were performed using an extended period for identification of indication for Duavive, as specified in more detail in Section 9.9.5.

9.9.5. Amendments to the statistical analysis plan

9.9.5.1. Amendment of the original SAP

The original SAP (Version 1.0, 29 February 2016) was amended on 31 August 2017 to exclude Finland, Germany, and Sweden from the study, and to change databases in France, Italy, Spain.

9.9.5.2. Deviation from the SAP during analysis

The ATC code G03 also includes several indications other than osteoporosis. In order to better identify co-medications that are used for osteoporosis treatment, the ATC code G03 "Sex hormones and modulators of the genital system" was replaced with the ATC code G03XC "Selective oestrogen receptor modulators" (Table 6 SAP; Table 5 above).

9.9.5.3. Additional analyses based on PRAC requests

Extension of look-back period for indication of use

Based on a request by PRAC during the assessment of Interim Report 1, the Sponsor extended the period for assigning a diagnosis (i.e., indication) to Duavive prescriptions from 90 to 365 days prior to the index date. This allowed for the identification of indication for additional patients and could help to clarify whether the patient can be considered pre- or postmenopausal, as the likelihood of finding documentation of an oestrogen deficiency diagnosis (which could indicate postmenopausal status in those ≤45 or ≤49 years) is increased. These analyses were conducted in addition to the main analysis for indication with a relevant time period of 90 days. The country-specific results of these analyses are presented in Sections 10.2 to 10.7 of this report.

Additional analyses of potential off-label use of Duavive:

Relatedly, results of the additional analysis for indication were used to evaluate effects on potential off-label use, i.e. the analyses described in Section 9.9.4 were repeated using the extended time period of 365 days prior to index date to 90 days after index date for assessment of the indication.

The additional results on potential off-label use are presented in Section 10.8.1.

Additional analysis of "oestrogen deficiency symptoms" in women aged ≤45 years:

Information on pre-/postmenopausal status is not directly recorded in the databases used for the study. In the main analysis of potential off-label use age ≤45 years was considered as a proxy for premenopausal status. To investigate a potential overestimation of off-label use arising from this, an additional analysis was performed in Interim report 2, and repeated here: among women aged ≤45 who receive Duavive, the proportion of those with a documented diagnosis of oestrogen deficiency symptoms, which suggests postmenopausal status, was determined. Oestrogen deficiency symptoms were defined by ICD-10 codes N95.1 and N95.9. The results are provided in Section 10.8.2. These analyses were conducted in Italy and Spain only, given the volume of Duavive use in these countries as well as the availability of diagnosis data in the longitudinal electronic medical record databases of these countries.

Additional analysis of age in women aged ≤49 years:

Based on a request by PRAC in the final assessment report for Interim Report 2, the Sponsor analysed ages at Duavive initiation for those women aged ≤49 years in both the annual and cumulative study period (three years after launch). Data are provided for five countries: data for UK cannot be presented due to privacy protection policy reasons. The results for other countries are presented in 5-year age groups due to data protection considerations. These results are provided in Section 10.8.3.

9.10. Quality control

For the UK THIN data, following extraction of patient data from practice software, quality and consistency checks are performed at the database level to ensure that transmission of data

from health care practices to THIN is complete and accurate. These checks are performed according to IQVIA's quality management systems. Records which are incomplete or inconsistent are flagged so that they can be excluded from research if desired. The quality of THIN data has also been confirmed both externally and internally.[2,3] Participating THIN practices are given regular feedback reports on the quality of their data, as well as free training sessions that help them to improve data recording. Quality control of programming for the extraction of THIN study variables is carried out according to IQVIA's standard operating procedures.

For other IQVIA EU data sources, all of which have been widely used for pharmacoepidemiological research, quality control is conducted at several levels depending on the database. At the database level, the quality unit of the production department of IQVIA verifies continuously the quality of its sources in terms of representativeness and consistency of collected data.

At the study level, all aspects of the study from protocol development to the reporting of the results were conducted within the work-frame of IQVIA Quality Management System (QMS) and in accordance to the corresponding policies and procedures. A Quality Control plan for the study was developed and executed. The purpose of the Quality Control plan was to:

- Establish ownership for the execution of the individual Quality Control steps. The principle of the independence of Quality Control applies.
- Ensure that the Principal in Charge ensures that individuals responsible for the execution of specific Quality Control steps have knowledge, capability and experience which are adequate for the task.
- Ensure that results of the execution of the individual steps of the Quality Control plan are described and corrective actions applied and documented.

The executed Quality Control plan is subjected to a final review and approval for sufficiency and completeness from the Principal in Charge of the study.

Furthermore, the following steps were undertaken to ensure quality and accuracy of proceeding during the course of the study:

- Methodology review: The statistical analysis plan and the accompanying table shells were reviewed and approved by senior staff at the IQVIA team and at Pfizer. Any changes in the methodology considered necessary during the course of the study were recorded and also reviewed by qualified staff at IQVIA and Pfizer.
- Programming code review: All programming codes were developed by a senior programmer who has extensive programming and analysis experience.
- Statistical review: All tables of results produced during the course of the study were reviewed by senior staff at IQVIA.

IQVIA is repeatedly audited by third parties on their QMS, data, technological infrastructure and services.

9.11. Protection of human subjects

Subject information and consent

This study is based on de-identified data from existing electronic healthcare record databases without any direct enrolment of subjects. Therefore informed consent was not applicable.

Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

The final protocol, any amendments were reviewed and approved by the following local data protection agencies in the UK and Spain:

Scientific Review Committee (SRC) approval (UK)	19 January 2018
Agencia Española de medicamentos y productos sanitarios (AEMPS) classification (Spain)	14 December 2017
Medicinal Research Ethics Committee (CEIC) approval (Spain)	23 April 2018

Approval was not required in the other participating countries.

Ethical conduct of the study

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.

10. RESULTS

10.1. Participants – All Countries

10.1.1. Included patients

10.1.1.1. Annual Reporting Period III

A total of 517 patients prescribed Duavive were observed during the Annual Reporting Period III (116 in Italy, 49 in Spain, 11 in UK, 218 in Belgium and 123 in the Netherlands; no Duavive initiators were identified in France). Two hundred and forty two (242) of these Duavive users met the inclusion criteria of being enrolled in the data source for at least 12 months prior to index date and having no prior Duavive prescriptions within 12 months prior to index date. Of these 242 patients, 52 were included in Italy, 23 in Spain, 7 in the UK, 75 in Belgium and 85 in the Netherlands (Table 7). According to restrictions imposed by the UK government to protect patient privacy, patient counts <6 or any result that would make it possible to calculate patients counts <6 may not be reported. Therefore, the results on the Duavive cohort in the UK are presented in this report to very restricted extent.

A total of 124,733 patients prescribed E+P HRT were observed during the reported study period and this varied from 1,412 in Spain to 51,913 in the Netherlands in the longitudinal databases. One hundred and fifteen thousand eight hundred eighteen (115,818) E+P HRT users met the inclusion criteria (15,217 in France, 3,499 in Italy, 1,321 in Spain, 18,522 in the UK, 28,069 in Belgium and 49,190 in the Netherlands (Table 7)).

10.1.1.2. Cumulative Period

A total of 1,086 patients prescribed Duavive were observed during the cumulative study period (30 in France, 237 in Italy, 76 in Spain, 11 in UK, 544 in Belgium and 188 in the Netherlands) in the longitudinal databases. Nine hundred and eighty six (986) Duavive users met the inclusion criteria of being enrolled in the data source for at least 12 months prior to index date and having no prior Duavive prescriptions within 12 months prior to index date (22 patients in France, 223 in Italy, 73 in Spain, 11 in the UK, 480 in Belgium and 177 in the Netherlands (Table 8)).

A total of 227,602 patients prescribed E+P HRT were observed during the reported study period and this varied between 2,757 in Spain to 83,089 in the Netherlands in the longitudinal databases. Two hundred and one thousand three hundred sixteen (201,316) E+P HRT users met the inclusion criteria (29,047 patients in France, 6,288 in Italy, 2,573 in Spain, 29,799 in the UK, 57,059 in Belgium and 76,550 in the Netherlands (Table 8)).

10.1.2. E+P HRT Prescription History

10.1.2.1. Annual Reporting Period III

Table 9 presents the number of patients in each cohort with and without prior E+P HRT prescriptions during the 12 months period prior to the index date. In the Duavive cohort, the number of patients without prior use of E+P HRT was 37 (71.2%) in Italy, 16 (69.6%) in Spain, 7 (100.0%) in the UK, 56 (74.7%) in Belgium and 17 (20.0%) in the Netherlands.

In the E+P HRT study cohort the number of patients without prior use of E+P HRT was 9,698 (63.7%) in France, 1,208 (34.5%) in Italy, 591 (44.7%) in Spain, 15,890 (85.8%) in UK, 12,970 (46.2%) in Belgium and 20,165 (41.0%) in the Netherlands.

10.1.2.2. Cumulative Period

The number of patients in each cohort with and without prior E+P HRT prescriptions during the 12 months period prior to the index date for the cumulative period is shown in Table 10. In the Duavive cohort, the number of patients without prior E+P HRT treatment was 17 (77.3%) in France, 154 (69.1%) in Italy, 55 (75.3%) in Spain, 11 (100.0%) in the UK, 361 (75.2%) in Belgium and 72 (40.7%) in the Netherlands. The respective numbers of patients in the E+P HRT study cohort were 23,102 (79.5%) in France, 3,652 (58.1%) in Italy, 1,668 (64.8%) in Spain, 27,734 (93.1%) in UK, 33,991 (59.6%) in Belgium and 50,308 (65.7%) in the Netherlands.

Table 7. Patient study eligibility in the Annual Reporting Period III, longitudinal data sources

	Number of patients											
	France		Italy		Spain		UK		Belgium		Netherlands	
	n	%	n	%	n	%	n	%	n	%	n	%
Duavive cohort												
Total patients with at least 1 Duavive prescription during the study period	0	0.0	116	100.0	49	100.0	11	100.0	218	100.0	123	100.0
Excluded: Patients not enrolled in the data source for at least 12 months prior to their index date[1]			6	5.2	1	2.1	<6		17	7.8	2	1.6
Excluded: Patients with Duavive prescription within 12 months prior to index date[1]			58	50.0	25	51.0	<6		126	57.8	36	29.3
Total eligible patients[1]	**0**	**0.0**	**52**	**44.8**	**23**	**46.9**	**7**	**63.6**	**75**	**34.4**	**85**	**69.1**
E+P HRT cohort												
Total patients with at least 1 prescription E+P HRT during study period	18,158	100.0	3,695	100.0	1,412	100.0	~19,729	100.0	29,826	100.0	51,913	100.0
Excluded: Patients not enrolled in the data source for at least 12 months prior to their index date[1]	2,931	16.1	175	4.7	86	6.1	1,207	6.1	1,739	5.8	2,711	5.2
Excluded: Patients with Duavive prescription within 12 months prior to index date[1]	10	0.1	21	0.6	5	0.3	<6		18	0.1	12	0.0
Total eligible patients [1]	**15,217**	**83.8**	**3,499**	**94.7**	**1,321**	**93.6**	**18,522**	**93.9**	**28,069**	**94.1**	**49,190**	**94.8**

1. % of N patients with at least one prescription of study medication (Duavive or E+P HRT, respectively)
"~" (UK): approximate number presented to maintain anonymity in accordance with THIN privacy protection policies
<6: in accordance with THIN privacy protection policies, exact numbers masked to maintain anonymity E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

Table 8. Patient study eligibility in the Cumulative Period, longitudinal data sources

	Number of patients											
	France		Italy		Spain		UK		Belgium		Netherlands	
	n	%	n	%	n	%	n	%	n	%	n	%
Duavive cohort												
Total patients with at least 1 Duavive prescription during the study period	30	100.0	237	100.0	76	100.0	11	100.0	544	100.0	188	100.0
Excluded: Patients not enrolled in the data source for at least 12 months prior to their index date[1]	8	26.7	13	5.5	1	1.3	0	0.0	64	11.8	9	4.8
Excluded: Duavive prescription within 12 months prior to index date[1]	0	0.0	1	0.4	2	2.6	0	0.0	0	0.0	2	1.1
Total eligible patients[1]	**22**	**73.3**	**223**	**94.1**	**73**	**96.1**	**11**	100.0	**480**	**88.2**	**177**	**94.1**
E+P HRT cohort												
Total: Patients with at least 1 prescription E+P HRT during study period	38,212	100.0	6,700	100.0	2,757	100.0	32,818	100.0	64,026	100.0	83,089	100.0
Excluded: Patients were not enrolled in the data source for at least 12 months prior to their index date[1]	9,165	24.0	412	6.1	184	6.7	3,012	9.2	6,967	10.9	6,539	7.9
Excluded: Duavive prescription within 12 months prior to index date[1]	0	0.0	0	0.0	0	0.0	7	0.0	0	0.0	0	0.0
Total eligible patients[1]	**29,047**	**76.0**	**6,288**	**93.9**	**2,573**	**93.3**	**29,799**	**90.8**	**57,059**	**89.1**	**76,550**	**92.1**

1. % of N patients with at least one prescription of study medication (Duavive or E+P HRT, respectively)
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

Table 9. Patients with and without E+P HRT treatment during the 12 months prior to index date in Annual Reporting Period III

	Number of patients											
	France		Italy		Spain		UK		Belgium		Netherlands	
	n	%	n	%	n	%	n	%	n	%	n	%
Duavive cohort												
Total eligible patients in analysis for reporting period	**0**	**0.0**	**52**	**100.0**	**23**	**100.0**	**7**	**100.0**	**75**	**100.0**	**85**	**100.0**
Included: with E+P HRT during 12 months pre-index[1]	0	0.0	15	28.8	7	30.4	0	0.0	19	25.3	68	80.0
Included: without E+P HRT during 12 months pre-index[1]	0	0.0	37	71.2	16	69.6	7	100.0	56	74.7	17	20.0
E+P HRT cohort												
Total eligible patients in analysis for reporting period	**15,217**	**100.0**	**3,499**	**100.0**	**1,321**	**100.0**	**18,522**	**100.0**	**28,069**	**100.0**	**49,190**	**100.0**
Included: with E+P HRT during 12 months pre-index[1]	5,519	36.3	2,291	65.5	730	55.3	2,632	14.2	15,099	53.8	29,025	59.0
Included: without E+P HRT during 12 months pre-index[1]	9,698	63.7	1,208	34.5	591	44.7	15,890	85.8	12,970	46.2	20,165	41.0

1. % of N patients included in the respective study cohort

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

Table 10. Patients with and without E+P HRT treatment during the 12 months prior to index date in Cumulative Period

	Number of patients											
	France		Italy		Spain		UK		Belgium		Netherlands	
	n	%	n	%	n	%	n	%	n	%	n	%
Duavive cohort												
Total eligible patients in analysis for reporting period	**22**	**100.0**	**223**	**100.0**	**73**	**100.0**	**11**	**100.0**	**480**	**100.0**	**177**	**100.0**
Included: with E+P HRT during 12 months pre-index[1]	5	22.7	69	30.9	18	24.7	0	0.0	119	24.8	105	59.3
Included: without E+P HRT during 12 months pre-index[1]	17	77.3	154	69.1	55	75.3	11	100.0	361	75.2	72	40.7
E+P HRT cohort												
Total eligible patients in analysis for reporting period	**29,047**	**100.0**	**6,288**	**100.0**	**2,573**	**100.0**	**29,799**	**100.0**	**57,059**	**100.0**	**76,550**	**100.0**
Included: with E+P HRT during 12 months pre-index[1]	5,945	20.5	2,636	41.9	905	35.2	2,065	6.9	23,068	40.4	26,242	34.3
Included: without E+P HRT during 12 months pre-index[1]	23,102	79.5	3,652	58.1	1,668	64.8	27,734	93.1	33,991	59.6	50,308	65.7

1. % of N patients included in the respective study cohort

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.2. Results for Belgium

10.2.1. Participants

The number of eligible patients in Belgium is shown below in Table 11 and the number with and without E+P HRT treatment during the 12 months prior to index date is shown in Table 12. In Annual Reporting Period III, 75 (34.4%) of 218 Duavive users identified in the database were eligible for analysis; prescriptions of E+P HRT during 12 months prior to Duavive initiation were recorded in 25.3% of Duavive users. In the cumulative period, 480 (88.2%) of 544 patients prescribed Duavive were eligible for analysis; prior use of E+P HRT was reported for 24.8% of them. In the E+P HRT study cohort, 28,069 (94.1%) of 29,826 patients were included in the analysis for Annual Reporting Period III and 57,059 (89.1%) of 64,026 patients for cumulative period. The proportion of eligible patients with E+P HRT records during 12 months prior to index date was 53.8% and 40.4% in the annual and cumulative periods, respectively.

Table 11. Patient study eligibility in Belgium

	Belgium			
	Longitudinal database: LRx			
	Annual Reporting Period III		Cumulative period	
	n	%	n	%
Duavive cohort				
Total patients with at least 1 Duavive prescription during the study period	218	100.0	544	100.0
Excluded: Patients not enrolled in the data source for at least 12 months prior to their index date[1]	17	7.8	64	11.8
Excluded: Duavive prescription within 12 months prior to index date[1]	126	57.8	0	0.0
Total eligible patients[1]	**75**	**34.4**	**480**	**88.2**
E+P HRT cohort				
Total patients with at least 1 prescription E+P HRT during study period	29,826	100.0	64,026	100.0
Excluded: Patients were not enrolled in the data source for at least 12 months prior to their index date[1]	1,739	5.8	6,967	10.9
Excluded: Duavive prescription within 12 months prior to index date[1]	18	0.1	0	0.0
Total eligible patients[1]	**28,069**	**94.1**	**57,059**	**89.1**

1. % of N patients with at least one prescription of study medication (Duavive or E+P HRT, respectively)
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

Table 12. Patients with and without E+P HRT treatment during the 12 months prior to index date (Belgium)

	Belgium			
	Longitudinal database: LRx			
	Annual Reporting Period III		Cumulative period	
	n	%	n	%
Duavive cohort				
Total eligible patients in analysis for reporting period	**75**	**100.0**	**480**	**100.0**
Included: with E+P HRT during 12 months pre-index[1]	19	25.3	119	24.8
Included: without E+P HRT during 12 months pre-index[1]	56	74.7	361	75.2
E+P HRT cohort				
Total eligible patients in analysis for reporting period	**28,069**	**100.0**	**57,059**	**100.0**
Included: with E+P HRT during 12 months pre-index[1]	15,099	53.8	23,068	40.4
Included: without E+P HRT during 12 months pre-index[1]	12,970	46.2	33,991	59.6

1. % of N patients with at least one prescription of study medication (Duavive or E+P HRT, respectively)
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.2.2. Belgium – Annual Reporting Period III

10.2.2.1. Baseline Characteristics – Annual Reporting Period III – Belgium

10.2.2.1.1. *LONGITUDINAL DATA*

Demographic characteristics of patients prescribed Duavive and E+P HRT are presented in Table 13.

10.2.2.1.1.1. *Age*

In the Duavive cohort, 94.6% of patients were 50 years or older and 5.4% were 40 to 49 years; no patients were younger than 40 years. The proportion of patients aged ≥50 years was 100.0% in the subgroup with prior E+P HRT treatment and 92.7% in the subgroup without prior therapy.

In the E+P HRT cohort, 91.2% of patients were ≥50 years, 6.5% were between 40 to 49 years and 2.2% were younger than 40 years. The proportion of the age group ≥50 years was 94.6% in the subgroup with prior E+P HRT treatment and 87.3% in the subgroup without prior treatment.

10.2.2.1.1.2. Gender

In the Duavive cohort, 6.7% of patients (no patients in the subgroup with and 8.9% in the subgroup without prior E+P HRT treatment) were documented as male during the reported study period. Overall, 1.6% of patients in the E+P HRT cohort were reported as male; 0.8% in the subgroup with prior E+P HRT treatment and 2.5% were in the subgroup without prior E+P HRT treatment.

10.2.2.1.1.3. BMI

Data on this parameter are not available in the database (see Table 2 in Section 9.4.1).

Table 13. Demographic characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: Belgium; source: LRx; Annual Reporting Period III]

	Belgium											
	Longitudinal database: LRx											
	Reported study period: 31 March 2018 to 31 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients	***75***	***100.0***	***56***	***100.0***	***19***	***100.0***	***28,069***	***100.0***	***12,970***	***100.0***	***15,099***	***100.0***
Age at treatment initiation[1]												
Valid N[2]	*74*	*100.0*	*55*	*100.0*	*19*	*100.0*	*27,704*	*100.0*	*12,771*	*100.0*	*14,933*	*100.0*
<40 years	0	0.0	0	0.0	0	0.0	614	2.2	474	3.7	140	0.9
40 to 49 years	4	5.4	4	7.3	0	0.0	1,813	6.5	1,151	9.0	662	4.4
≥50 years	70	94.6	51	92.7	19	100.0	25,277	91.2	11,146	87.3	14,131	94.6
Gender[1]												
Valid N[2]	*75*	*100.0*	*56*	*100.0*	*19*	*100.0*	*27,795*	*100.0*	*12,820*	*100.0*	*14,975*	*100.0*
Female	70	93.3	51	91.1	19	100.0	27,353	98.4	12,494	97.5	14,859	99.2
Male	5	6.7	5	8.9	0	0.0	442	1.6	326	2.5	116	0.8

1. % of Valid N
2. Valid N: patients with non-missing values

Body Mass Index not available in LRx – Belgium
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.2.2.1.2. *CROSS-SECTIONAL DATA*

Demographic characteristics on the prescription level for E+P HRT for the Annual Reporting Period III (01 April 2018 to 31 March 2019) are presented in Table 14. No prescriptions for Duavive were identified in the data source for this annual period.

10.2.2.1.2.1. Age

In the E+P HRT cohort of Belgium, 64.0% of patients were ≥50 years, 14.0% between 40 to 49 years and 22.0% were younger than 40 years.

10.2.2.1.2.2. Gender

In the E+P HRT cohort, 0.3% of patients were male during the reported study period.

10.2.2.1.2.3. BMI

Data on this parameter is not available in the database (see Table 2 in Section 9.4.1).

Table 14. Demographic characteristics; Overall and Stratified by Therapy; prescription-level analysis [country: Belgium; source: IMB; Annual Reporting Period III]

	Belgium			
	Cross-Sectional database: Medical Index			
	Reported study period: 01 April 2018 to 31 March 2019[3]			
	Duavive		E+P HRT	
	n	%	n	%
Total number of prescriptions during reported period	***0***	***0.0***	***620,549***	***100.0***
Age: n (%)[1]				
Valid N[2]			*593,722*	*100.0*
<40 years			130,483	22.0
40 to 49 years			83,338	14.0
≥50 years			379,900	64.0
Gender: n (%)[1]				
Valid N[2]			*620,549*	*100.0*
Female			618,759	99.7
Male			1,789	0.3

1. % of Valid N
2. Valid N: patients with non-missing values
3. Analysis based on data from same consultation

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.2.2.2. Clinical Characteristics and Duavive Prescribing Patterns – Annual Reporting Period III - Belgium

10.2.2.2.1. *LONGITUDINAL DATA*

The results of baseline clinical characteristics are presented in Table 15 and described below. As described in the protocol, and in accordance with Table 2 in Section 9.4.1 analyses of co-morbidities, prior safety events, and indication were not possible within the Belgium database because these variables are not collected.

10.2.2.2.1.1. Co-medication

In the Duavive cohort, 48.0% of the patients had received at least one of the specified co-medications during the 12 months pre-index period (63.2% and 42.9% in the subgroups with and without prior E+P HRT treatment, respectively). In the E+P HRT cohort, at least one prescription of the specified co-medication was identified in 57.6% of the patients (70.7% and 42.3% in the subgroups with and without prior E+P HRT treatment, respectively).

Among the pre-selected drug classes, those therapies most frequently co-prescribed in the Duavive cohort were antidepressants (20.0%), local (vaginal) hormone treatments (18.7%), sedatives/hypnotics (16.0%), lipid lowering agents (12.0%), anticoagulants (9.3%), corticosteroids (8.0%) and osteoporosis treatments (bisphosphonates, SERMs, etc) (8.0%). In the E+P HRT cohort, antidepressants (20.7%), osteoporosis treatments (bisphosphonates, SERMs, etc) (19.4%), sedatives/hypnotics (18.1%), lipid lowering agents (16.4%), anticoagulants (13.3%) and corticosteroids (9.7%) were most frequently observed. For

proportions in the subgroups with and without prior E+P HRT treatment please refer to Table 15.

Table 15. Baseline clinical characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: Belgium; source: LRx; Annual Reporting Period III]

	Belgium											
	Longitudinal database: LRx											
	Reported study period: 31 March 2018 to 31 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients	***75***	***100.0***	***56***	***100.0***	***19***	***100.0***	***28,069***	***100.0***	***12,970***	***100.0***	***15,099***	***100.0***
Co-medication during 12 months pre-index period[1]												
Any co-medication	**36**	**48.0**	**24**	**42.9**	**12**	**63.2**	**16,163**	**57.6**	**5,485**	**42.3**	**10,678**	**70.7**
Corticosteroids	6	8.0	4	7.1	2	10.5	2,721	9.7	976	7.5	1,745	11.6
Lipid lowering agents	9	12.0	7	12.5	2	10.5	4,607	16.4	1,526	11.8	3,081	20.4
Anti-hypertensives	1	1.3	0	0.0	1	5.3	154	0.5	52	0.4	102	0.7
Anticoagulants	7	9.3	5	8.9	2	10.5	3,731	13.3	1,308	10.1	2,423	16.0
Antiarrhythmics	2	2.7	1	1.8	1	5.3	832	3.0	306	2.4	526	3.5
Antidepressants	15	20.0	9	16.1	6	31.6	5,821	20.7	2,241	17.3	3,580	23.7
Sedatives/ hypnotics	12	16.0	6	10.7	6	31.6	5,088	18.1	1,902	14.7	3,186	21.1
Antidiabetics	4	5.3	2	3.6	2	10.5	1,531	5.5	566	4.4	965	6.4
Osteoporosis treatments (bisphosphonates, SERMs, etc)	6	8.0	0	0.0	6	31.6	5,448	19.4	210	1.6	5,238	34.7
Local (vaginal) hormone treatments	14	18.7	9	16.1	5	26.3	854	3.0	587	4.5	267	1.8

1. % of total N

Co-morbidities, prior safety events and indication for study medication not available in LRx – Belgium
SERMs: Selective oestrogen receptor modulators
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.2.2.2.1.2. Duavive utilization in Belgium

Duavive utilization is presented in Table 16. Information on daily dose and days supply is not available in the longitudinal prescription database for Belgium. For this reason, no results on daily dose and days supply are presented.

10.2.2.2.1.2.1. Switchers from E+P HRT to Duavive

Overall, a switch from E+P HRT to Duavive at index date was identified in 9.3% of patients (36.8% in the subgroup with prior E+P HRT treatment).

Table 16. Duavive utilization: Overall and Stratified by Prior E+P HRT Treatment; prescription-level analysis [country: Belgium; source: LRx; Annual Reporting Period III]

	Belgium					
	Longitudinal database: LRx					
	Reported study period: 31 March 2018 to 31 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Total number of patients with index prescriptions	***75***	***100.0***	***56***	***100.0***	***19***	***100.0***
Number of (index) prescriptions with instruction on daily dosage available[1]	n.a.		n.a.		n.a.	
Daily dose	n.a.		n.a.		n.a.	
Days supply	n.a.		n.a.		n.a.	
Switchers from E+P HRT to Duavive[2]	**7**	**9.3**	**n. appl.**	**.**	**7**	**36.8**

1. Dose instructions on daily dose and days supply not available in LRx – Belgium;
2. Switch: prescription of Duavive within 30 days following the end of the last filled prescription period of E+P HRT

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy; n.a: not available; n.appl.: not applicable

10.2.2.2.1.3. Potential off-label use of Duavive in Belgium

The results for potential off-label use of Duavive from the main analysis (see Sections 9.4.5, 9.9.4) are presented in Table 17.

Potential off-label use was identified in 17.3% of all Duavive users (10.5% and 19.6% in subgroups with and without prior E+P HRT treatment, respectively). The reasons for potential off-label use were age over 75 years (7.1%), use in males (6.7%) and use with progestins, additional oestrogens, or selective oestrogen receptor modulators (4.0%).

After changing the presumed premenopausal age limit from 45 years to 49 years, without changing any of the other off-label criteria (sensitivity analysis I), the proportion of potential off-label users increased to 21.3% (Table 18). For proportions in subgroups with and without E+P HRT prior treatment please also refer to Table 18.

Table 17. Potential Off-label use of Duavive; Overall and Stratified by Prior E+P HRT Treatment; patient-level analysis [country: Belgium; source: LRx; Annual Reporting Period III]

	Belgium					
	Longitudinal database: LRx					
	Reported study period: 31 March 2018 to 31 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Total number of patients	***75***	***100.0***	***56***	***100.0***	***19***	***100.0***
Off-label use (total; any category)[1,2]	**13**	**17.3**	**11**	**19.6**	**2**	**10.5**
Patients with single categories of off-label use						
Use for treatment of osteoporosis only[3]	n.a.		n.a.		n.a.	
Valid N						
Use in women ≤45 years[3]	0	0.0	0	0.0	0	0.0
Valid N	*70*		*51*	*10*	*19*	
Use in women over 75 years old[3]	5	7.1	4	7.8	1	5.3
Valid N	*70*		*51*		*19*	
Use in males[3]	5	6.7	5	8.9	0	0.0
Valid N	*75*		*56*		*19*	
Prescription of non-approved dose or regimen[3]	n.a.		n.a.		n.a.	
Valid N	*75*		*56*		*19*	
Use with progestins, additional oestrogens or selective oestrogen receptor modulators (SERMs)[1]	3	4.0	2	3.6	1	5.3
Use in women without a uterus (hysterectomised women)[1]	n.a.		n.a.		n.a.	
Known, suspected, or past history of breast cancer[1]	n.a.		n.a.		n.a.	
Hypersensitivity (e.g., anaphylaxis/anaphylactic reactions, urticaria, drug eruption) to the active substances or to any of the excipients[1]	n.a.		n.a.		n.a.	
Malignancy potentially associated with oestrogen[1]	n.a.		n.a.		n.a.	
Active or past history of venous thromboembolism (deep venous thrombosis, pulmonary embolism, and retinal vein thrombosis)[1]	n.a.		n.a.		n.a.	
Active or past history of arterial thromboembolic disease (e.g., myocardial infarction, stroke)[1]	n.a.		n.a.		n.a.	
Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal[1]	n.a.		n.a.		n.a.	

Table 17. Potential Off-label use of Duavive; Overall and Stratified by Prior E+P HRT Treatment; patient-level analysis [country: Belgium; source: LRx; Annual Reporting Period III]

	Belgium					
	Longitudinal database: LRx					
	Reported study period: 31 March 2018 to 31 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Known thrombophilic disorders (e.g., protein C, protein S, or antithrombin deficiency)[1]	n.a.		n.a.		n.a.	
Porphyria[1]	n.a.		n.a.		n.a.	

Valid N: patients with non-missing values in respective category
1. % of total N patients
2. Patients with off-label use in any category mentioned below
3. % of valid N in respective category (listed below)

n.a. - not applicable as parameter is not available in country specific database
Age ⩽45 years considered as proxy for premenopausal status (Section 9.4.5)
Patients can be in more than one category of potential off-label use
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy
SERMs: selective oestrogen receptor modulators

Table 18. Sensitivity analyses for potential off-label use of Duavive; Overall and Stratified by Prior E+P HRT Treatment; patient-level analysis [country: Belgium; source: LRx; Annual Reporting Period III]

	Belgium					
	Longitudinal database: LRx					
	Reported study period: 31 March 2018 to 31 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Total number of patients during reported period	***75***	***100.0***	***56***	***100.0***	***19***	***100.0***
Main Analysis:[1,2] Definition of off-label use includes Presumed premenopausal age limit at ≤45 years	**13**	**17.3**	**11**	**19.6**	**2**	**10.5**
Sensitivity analysis I:[1,2,3,4] Definition of off-label use includes Presumed premenopausal age limit at ≤49 years	**16**	**21.3**	**14**	**24.0**	**2**	**10.5**

1. % of total N patients
2. Patients with off-label use in any category mentioned for this analysis
3. Number of patients in the categories other than presumed premenopausal age limit remained identical to Table 17

Table 18. Sensitivity analyses for potential off-label use of Duavive; Overall and Stratified by Prior E+P HRT Treatment; patient-level analysis [country: Belgium; source: LRx; Annual Reporting Period III]

	Belgium					
	Longitudinal database: LRx					
	Reported study period: 31 March 2018 to 31 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%

4. Other sensitivity analyses were not applicable as there is no information about the indication
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.2.2.2.2. *CROSS-SECTIONAL DATA*

Baseline clinical characteristics for the E+P HRT cohort are presented in Table 19 below. Data projected to national levels were analysed. No prescriptions for Duavive were identified in the data source for the Annual Reporting Period III.

10.2.2.2.2.1. Co-morbidities

The proportion of patients with any of the specified co-morbidities in the E+P HRT group was 14.6%.

10.2.2.2.2.2. Co-medication

The proportion of patients who were prescribed any of the specified co-medication in the E+P HRT group was 24.7%.

10.2.2.2.2.3. Prior safety events

No analysis was performed as data from medical history is not available in the cross-sectional database (see Table 2 in Section 9.4.1).

10.2.2.2.2.4. Indication

In the E+P HRT cohort, 78.7% of patients had documented diagnoses of oestrogen deficiency symptoms, 3.4% of patients of osteoporosis only, 2.8% of both oestrogen deficiency symptoms and osteoporosis and 15.1% of patients had documented diagnoses other than oestrogen deficiency symptoms or osteoporosis (Table 19).

Table 19. Baseline clinical characteristics; Overall and Stratified by Therapy; prescription-level analysis [country: Belgium; source: IMB; Annual Reporting Period III]

	Belgium			
	Cross-Sectional database: Medical Index			
	Reported study period: 01 April 2018 - 31 March 2019[3]			
	Duavive		E+P HRT	
	n	%	n	%
Projected number of prescriptions during reported period	***0***	***0.0***	***620,549***	***100.0***
Co-morbidities[1,2]				
Any co-morbidity	**0**	**0.0**	**90,829**	**14.6**
Osteoporosis osteopenia	0	0.0	23,698	3.8
History of CVD event	0	0.0	0	0.0
Hyperlipidemia	0	0.0	13,822	2.2
Hypertension	0	0.0	28,635	4.6
Breast pain	0	0.0	0	0.0
Diabetes	0	0.0	5,248	0.8
Renal disease	0	0.0	0	0.0
Osteoarthritis	0	0.0	10,932	1.8
Major depression	0	0.0	10,217	1.6
Co-medication[1,2]				
Any co-medication	**0**	**0.0**	**153,131**	**24.7**
Corticosteroids	0	0.0	0	0.0
Lipid lowering agents	0	0.0	2,461	0.4
Anti-hypertensives	0	0.0	0	0.0
Anticoagulants	0	0.0	4,798	0.8
Antiarrhythmics	0	0.0	1,084	0.2
Antidepressants	0	0.0	6,986	1.1
Sedatives hypnotics	0	0.0	6,794	1.1
Antidiabetics	0	0.0	2,006	0.3
Osteoporosis treatments bisphosphonates, SERMs, etc	0	0.0	71,798	11.6
Local vaginal hormone treatments	0	0.0	57,201	9.2
Indication for study medication[1,2]				
Oestrogen deficiency symptoms only	0	0.0	488,127	78.7
Osteoporosis only	0	0.0	20,900	3.4
Oestrogen deficiency symptoms and osteoporosis	0	0.0	17,580	2.8
No oestrogen deficiency symptoms or osteoporosis	0	0.0	93,940	15.1
Missing data on diagnosis	0	0.0	0	0.0

1 % of total N;
2. In the cross-sectional, prescription-level data, diagnoses and co-medications are only available if they were recorded in same consultation as the prescription.
3. In all cross-sectional data sources, data are reported per quarter, resulting in a slightly different reporting period compared to the longitudinal databases. Prior safety events not available in cross-sectional data
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

Table 19. Baseline clinical characteristics; Overall and Stratified by Therapy; prescription-level analysis [country: Belgium; source: IMB; Annual Reporting Period III]

	Belgium			
	Cross-Sectional database: Medical Index			
	Reported study period: 01 April 2018 - 31 March 2019[3]			
	Duavive		E+P HRT	
	n	%	n	%

SERMs: selective oestrogen receptor modulators; CVD: cardiovascular disease
IMB: Index Medical Belge (Medical Index database in Belgium)

10.2.2.2.2.5. Duavive utilization in Belgium

No Duavive prescriptions were recorded in the cross-sectional database during the Annual Reporting Period III, therefore no analyses of Duavive utilization (daily dose, days supply, switchers from E+P HRT to Duavive) were performed.

10.2.2.2.2.6. Potential off-label use of Duavive in Belgium

As no Duavive prescriptions were recorded in the cross-sectional database during the Annual Reporting Period III, no analyses of Duavive off-label use was performed.

10.2.3. Belgium – Cumulative Period

10.2.3.1. Baseline Characteristics – Cumulative Period - Belgium

10.2.3.1.1. *LONGITUDINAL DATA*

Demographic characteristics of patients prescribed Duavive and E+P HRT for the cumulative period (31 March 2016 to 30 March 2019) are presented in Table 20.

10.2.3.1.1.1. Age

In the Duavive cohort of Belgium, 93.4% of patients were 50 years or older, 5.3% were 40 to 49 years and 1.3% of patients were younger than 40 years. The proportion of patients aged ≥50 years was slightly higher in the subgroup with prior E+P HRT treatment (95.6%) compared to the subgroup without (92.7%).

In the E+P HRT cohort, 91.1% of patients were ≥50 years, 5.9% between 40 to 49 years and 3.0% younger than 40 years. The proportion of the age group ≥50 years was 96.7% in the subgroup with prior E+P HRT treatment and 87.3% in the subgroup without prior E+P HRT.

10.2.3.1.1.2. Gender

In the Duavive cohort 3.0% of patients (1.7% in the subgroup with and 3.4% in the subgroup without prior E+P HRT treatment) were male during the cumulative study period. Overall, 3.8% of patients in the E+P HRT cohort were male with 1.1% in the subgroup with and 5.7% in the subgroup without prior E+P HRT treatment.

10.2.3.1.1.3. BMI

Data on this parameter is not available in the database (see Table 2 in Section 9.4.1).

Table 20. Demographic characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: Belgium; source: LRx; Cumulative Period]

	Belgium											
	Longitudinal database: LRx											
	Reported study period: 31 March 2016 to 31 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients	***480***	***100.0***	***361***	***100.0***	***119***	***100.0***	***57,059***	***100.0***	***33,991***	***100.0***	***23,068***	***100.0***
Age at treatment initiation[1]												
Valid N[2]	*469*	*100.0*	*355*	*100.0*	*114*	*100.0*	*55,944*	*100.0*	*33,209*	*100.0*	*22,735*	*100.0*
<40 years	6	1.3	5	1.4	1	0.9	1,693	3.0	1,527	4.6	166	0.7
40 to 49 years	25	5.3	21	5.9	4	3.5	3,277	5.9	2,702	8.1	575	2.5
≥50 years	438	93.4	329	92.7	109	95.6	50,974	91.1	28,980	87.3	21,994	96.7
Gender[1]												
Valid N[2]	*472*	*100.0*	*357*	*100.0*	*115*	*100.0*	*56,026*	*100.0*	*33,182*	*100.0*	*22,844*	*100.0*
Female	458	97.0	345	96.6	113	98.3	53,884	96.2	31,297	94.3	22,587	98.9
Male	14	3.0	12	3.4	2	1.7	2,142	3.8	1,885	5.7	257	1.1

1. % of Valid N
2. Valid N: patients with non-missing values

Body Mass Index not available in LRx – Belgium
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.2.3.1.2. *CROSS-SECTIONAL DATA*

Demographic characteristics on the prescription level for Duavive and E+P HRT for the cumulative period (01 April 2016 to 31 March 2019) are presented in Table 21.

10.2.3.1.2.1. Age

In the Duavive cohort of Belgium, 89.9% of patients were 50 years or older, 10.1% were 40 to 49 years and no patients were younger than 40 years. In the E+P HRT cohort, 70.9% of patients were ≥50 years, 12.1% between 40 to 49 years and 17.1% were younger than 40 years.

10.2.3.1.2.2. Gender

In the Duavive cohort none of the patients were male during the reported study period. Overall, 0.3% of patients in the E+P HRT cohort were male.

10.2.3.1.2.3. BMI

Data on this parameter is not available in the database (see Table 2 in Section 9.4.1).

Table 21. Demographic characteristics; Overall and Stratified by Therapy; prescription-level analysis [country: Belgium; source: IMB; Cumulative Period]

	Belgium			
	Cross-Sectional database: Medical Index			
	Reported study period: 01 April 2016 to 31 March 2019[3]			
	Duavive		E+P HRT	
	n	%	n	%
Total number of prescriptions during reported period	***7,425***	***100.0***	***1,422,043***	***100.0***
Age: n (%)[1]				
Valid N[2]	*6,745*	*100.0*	*1,338,615*	*100.0*
<40 years	0	0.0	228,588	17.1
40 to 49 years	680	10.1	161,538	12.1
≥50 years	6,065	89.9	948,487	70.9
Gender: n (%)[1]				
Valid N[2]	*7,425*	*100.0*	*1,420,991*	*100.0*
Female	7,425	100.0	1,416,367	99.7
Male	0	0.0	4,635	0.3

1. % of Valid N
2. Valid N: patients with non-missing values
3. Analysis based on data from same consultation

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.2.3.2. Clinical Characteristics and Duavive Prescribing Patterns – Cumulative Period - Belgium

10.2.3.2.1. *LONGITUDINAL DATA*

The results on baseline clinical characteristics are presented in Table 22 below.

As described in the protocol, and in accordance with Table 2 in Section 9.4.1 analyses of co-morbidities, prior safety events, and indication were not possible because these variables are not available in the database.

10.2.3.2.1.1. Co-medication

In the Duavive cohort, 56.5% of the patients had received at least one of the specified co-medications during the 12 months pre-index period (69.7% and 52.1% in the subgroups with and without prior E+P HRT treatment, respectively). In the E+P HRT cohort, at least one prescription of the specified co-medication was identified in 55.2% of the patients (71.2% and 44.3% in the subgroups with and without prior E+P HRT treatment, respectively).

The most frequently co-prescribed drugs in the Duavive cohort were sedatives/hypnotics (20.4%), antidepressants (20.4%), local (vaginal) hormone treatment (16.3%), lipid lowering agents (12.5%), osteoporosis treatments (bisphosphonates, SERMs, etc) (10.8%) and

corticosteroids (10.2%), and in the E+P HRT cohort antidepressants (20.5%), sedatives/hypnotics (18.9%), lipid lowering agents (15.7%), osteoporosis treatments (bisphosphonates, SERMs, etc) (14.8%), and anticoagulants (12.8%). For proportions in the subgroups with and without prior E+P HRT treatment please refer to Table 22.

Table 22. Baseline clinical characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: Belgium; source: LRx; Cumulative Period]

	Belgium											
	Longitudinal database: LRx											
	Reported study period: 31 March 2016 to 31 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients	***480***	***100.0***	***361***	***100.0***	***119***	***100.0***	***57,059***	***100.0***	***33,991***	***100.0***	***23,068***	***100.0***
Co-medication during 12 months pre-index period[1]												
Any co-medication	**271**	**56.5**	**188**	**52.1**	**83**	**69.7**	**31,504**	**55.2**	**15,070**	**44.3**	**16434**	**71.2**
Corticosteroids	49	10.2	36	10.0	13	10.9	5,473	9.6	2,777	8.2	2696	11.7
Lipid lowering agents	60	12.5	47	13.0	13	10.9	8,934	15.7	4,236	12.5	4698	20.4
Anti-hypertensives	7	1.5	5	1.4	2	1.7	338	0.6	179	0.5	159	0.7
Anticoagulants	44	9.2	30	8.3	14	11.8	7,314	12.8	3,509	10.3	3805	16.5
Antiarrhythmics	15	3.1	11	3.0	4	3.4	1,685	3.0	914	2.7	771	3.3
Antidepressants	98	20.4	67	18.6	31	26.1	11,672	20.5	6,120	18.0	5552	24.1
Sedatives/ hypnotics	98	20.4	63	17.5	35	29.4	10,782	18.9	5,470	16.1	5312	23.0
Antidiabetics	27	5.6	16	4.4	11	9.2	3,128	5.5	1,641	4.8	1487	6.4
Osteoporosis treatments (bisphosphonates, SERMs, etc)	52	10.8	11	3.0	41	34.5	8,430	14.8	531	1.6	7899	34.2
Local (vaginal) hormone treatments	78	16.3	61	16.9	17	14.3	2,198	3.9	1,771	5.2	427	1.9

1. % of total N

Co-morbidities, prior safety events and indication for study medication not available in LRx – Belgium
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy
SERMs: selective oestrogen receptor modulators

10.2.3.2.1.2. Duavive utilization in Belgium

Duavive utilization is presented in Table 23. Information on daily dose and days supply is not available in the longitudinal prescription database for Belgium. For this reason, no results on daily dose and days supply are presented.

10.2.3.2.1.2.1. Switchers from E+P HRT to Duavive

Table 1 Overall, a switch from E+P HRT to Duavive at index date was identified in 12.5% of patients (50.4% in the subgroup with prior E+P HRT treatment).

Table 23. Duavive utilization; Overall and Stratified by Prior E+P HRT Treatment; prescription-level analysis [country: Belgium; source: LRx; Cumulative Period]

	Belgium					
	Longitudinal database: LRx					
	Reported study period: 31 March 2016 to 31 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Total number of patients with index prescriptions	***480***	***100.0***	***361***	***100.0***	***119***	***100.0***
Number of (index) prescriptions with instruction on daily dosage available[1]	**n.a.**		**n.a.**		**n.a.**	
Daily dose	n.a.		n.a.		n.a.	
Days supply	n.a.		n.a.	.	n.a.	
Switchers from E+P HRT to Duavive[2]	**60**	**12.5**	**n.appl.**		**60**	**50.4**

1. Dose instructions on daily dose and days supply not available in LRx – Belgium
2. Switch: prescription of Duavive within 30 days following the end of the last filled prescription period of E+P HRT

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy; n.a: not available; n.appl.: not applicable

10.2.3.2.1.3. Potential off-label use of Duavive in Belgium

The results for potential off-label use of Duavive from the main analysis (see Sections 9.4.5, 9.9.4) are presented in Table 24.

Potential off-label use was identified in 10.6% of all Duavive users (10.1% and 10.8% in subgroups with and without prior E+P HRT treatment). The reasons for potential off-label use were age ≤45 years (2.0%), age over 75 years (4.4%), use in males (3.0%) and use with progestins, additional oestrogens or selective oestrogen receptor modulators (1.7%).

After changing the presumed premenopausal age limit from 45 years to 49 years, without changing any of the other off-label parameters (sensitivity analysis I), the proportion of potential off-label users increased to 14.8% (Table 25). For proportions in subgroups with and without E+P HRT prior treatment please also refer to Table 25.

Table 24. Potential off-label use of Duavive; Overall and Stratified by Prior E+P HRT Treatment; patient-level analysis [country: Belgium; source: LRx; Cumulative Period]

	Belgium					
	Longitudinal database: LRx					
	Reported study period: 31 March 2016 to 31 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Total number of patients	***480***	***100.0***	***361***	***100.0***	***119***	***100.0***
Off-label use (total; any category)[1,2]	**51**	**10.6**	**39**	**10.8**	**12**	**10.1**
Patients with single categories of off-label use						
Use for treatment of osteoporosis only[3]	n.a.		n.a.		n.a.	
Valid N						
Use in women ≤45 years[3]	9	2.0	8	2.3	1	0.9
Valid N	*455*		*342*		*113*	
Use in women over 75 years old[3]	20	4.4	15	4.4	5	4.4
Valid N	*455*		*342*		*113*	
Use in males[3]	14	3.0	12	3.4	2	1.7
Valid N	*472*		*357*		*115*	
Prescription of non-approved dose or regimen[3]	n.a.		n.a.		n.a.	
Valid N						
Use with progestins, additional oestrogens or selective oestrogen receptor modulators (SERMs)[1]	8	1.7	4	1.1	4	3.4
Use in women without a uterus (hysterectomised women)[1]	n.a.		n.a.		n.a.	
Known, suspected, or past history of breast cancer[1]	n.a.		n.a.		n.a.	
Hypersensitivity (e.g., anaphylaxis/anaphylactic reactions, urticaria, drug eruption) to the active substances or to any of the excipients[1]	n.a.		n.a.		n.a.	
Malignancy potentially associated with oestrogen[1]	n.a.		n.a.		n.a.	
Active or past history of venous thromboembolism (deep venous thrombosis, pulmonary embolism, and retinal vein thrombosis)[1]	n.a.		n.a.		n.a.	
Active or past history of arterial thromboembolic disease (e.g., myocardial infarction, stroke)[1]	n.a.		n.a.		n.a.	
Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal[1]	n.a.		n.a.		n.a.	
Known thrombophilic disorders (e.g., protein C, protein S, or antithrombin deficiency)[1]	n.a.		n.a.		n.a.	
Porphyria[1]	n.a.		n.a.		n.a.	

Valid N: patients with non-missing values in respective category
1. % of total N patients
2. Patients with off-label use in any category mentioned below
3. % of valid N in respective category (listed below)

n.a. - not applicable as parameter is not available in country specific database
Age ≤45 years considered as proxy for premenopausal status (Section 9.4.5).
Patients can be in more than one category of potential off-label use
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

Table 24. Potential off-label use of Duavive; Overall and Stratified by Prior E+P HRT Treatment; patient-level analysis [country: Belgium; source: LRx; Cumulative Period]

	Belgium					
	Longitudinal database: LRx					
	Reported study period: 31 March 2016 to 31 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%

SERMs: selective oestrogen receptor modulators

Table 25. Sensitivity analyses for potential off-label use of Duavive; Overall and Stratified by Prior E+P HRT Treatment; patient-level analysis [country: Belgium; source: LRx; Cumulative Period]

	Belgium					
	Longitudinal database: LRx					
	Reported study period: 31 March 2016 to 31 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Total number of patients during reported period	***480***	***100.0***	***361***	***100.0***	***119***	***100.0***
Main Analysis:[1, 2] Definition of off-label use includes Presumed premenopausal age limit at ≤45 years	51	10.6	39	10.8	12	10.1
Sensitivity analysis I:[1,2,3,4] Definition of off-label use includes Presumed premenopausal age limit at ≤49 years	71	14.8	56	15.5	15	12.6

1. % of total N patients
2. Patients with off-label use in any category mentioned for this analysis
3. Number of patients in the categories other than presumed premenopausal age limit remained identical to Table 24
4. Other sensitivity analyses were not applicable as there is no information about the indication

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.2.3.2.2. *CROSS-SECTIONAL DATA*

Baseline clinical characteristics are presented in Table 26 below. Data projected to national levels were analysed.

10.2.3.2.2.1. Co-morbidities

None of the specified co-morbidities were reported in the Duavive cohort. The proportion of patients with any of the specified co-morbidities in the E+P HRT group was 14.5%.

10.2.3.2.2.2. Co-medication

None of the specified co-medications was reported in the Duavive cohort. The proportion of patients who were prescribed any of the specified co-medication in the E+P HRT group was 20.4%.

10.2.3.2.2.3. Prior safety events

No analysis was performed as data from medical history is not available in the cross-sectional database (see Table 2 in Section 9.4.1).

10.2.3.2.2.4. Indication

Duavive was prescribed for oestrogen deficiency symptoms in 90.8% of the patients. The proportion of diagnoses other than oestrogen deficiency symptoms or osteoporosis on the day of prescription was 9.2% (Table 26).

In the E+P HRT cohort, patients had documented diagnoses of oestrogen deficiency symptoms (80.6% of the patients), osteoporosis only (2.3%), both oestrogen deficiency symptoms and osteoporosis (2.2%) and diagnoses other than oestrogen deficiency symptoms or osteoporosis (14.9%).

Table 26. Baseline clinical characteristics; Overall and Stratified by Therapy; prescription-level analysis [country: Belgium; source: IMB; Cumulative Period]

	Belgium			
	Cross-Sectional database: Medical Index			
	Reported study period: 01 April 2016 - 31 March 2019[3]			
	Duavive		E+P HRT	
	n	%	n	%
Projected number of prescriptions during reported period	***7,425***	***100.0***	***1,422,043***	***100.0***
Co-morbidities[1,2]				
Any co-morbidity	**0**	**0.0**	**206,580**	**14.5**
Osteoporosis osteopenia	0	0.0	41,560	2.9
History of CVD event	0	0.0	1,103	0.1
Hyperlipidemia	0	0.0	30,022	2.1
Hypertension	0	0.0	76,036	5.3
Breast pain	0	0.0	0	0.0
Diabetes	0	0.0	19,231	1.4
Renal disease	0	0.0	0	0.0
Osteoarthritis	0	0.0	22,643	1.6
Major depression	0	0.0	23,601	1.7
Co-medication[1,2]				
Any co-medication	**0**	**0.0**	**290,381**	**20.4**
Corticosteroids	0	0.0	1,505	0.1
Lipid lowering agents	0	0.0	3,863	0.3
Anti-hypertensives	0	0.0	0	0.0
Anticoagulants	0	0.0	6,110	0.4
Antiarrhythmics	0	0.0	1,084	0.1
Antidepressants	0	0.0	17,501	1.2
Sedatives hypnotics	0	0.0	8,603	0.6
Antidiabetics	0	0.0	4,082	0.3
Osteoporosis treatments bisphosphonates, SERMs, etc	0	0.0	121,511	8.5
Local vaginal hormone treatments	0	0.0	99,992	7.0
Indication for study medication[1,2]				
Oestrogen deficiency symptoms only	6,745	90.8	1,146,022	80.6
Osteoporosis only	0	0.0	32,215	2.3
Oestrogen deficiency symptoms and osteoporosis	0	0.0	31,819	2.2
No oestrogen deficiency symptoms or osteoporosis	680	9.2	211,986	14.9
Missing data on diagnosis	0	0.0	0	0.0

1. % of total N;
2. In the cross-sectional, prescription-level data, diagnoses and co-medications are only available if they were recorded in same consultation as the prescription.
3. In all cross-sectional data sources, data are reported per quarter, resulting in a slightly different reporting period compared to the longitudinal databases. Prior safety events not available in cross-sectional data

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

Table 26. Baseline clinical characteristics; Overall and Stratified by Therapy; prescription-level analysis [country: Belgium; source: IMB; Cumulative Period]

	Belgium			
	Cross-Sectional database: Medical Index			
	Reported study period: 01 April 2016 - 31 March 2019[3]			
	Duavive		E+P HRT	
	n	%	n	%

SERMs: selective oestrogen receptor modulators; CVD: cardiovascular disease
IMB: Index Medical Belge (Medical Index database in Belgium)

10.2.3.2.2.5. Duavive utilization in Belgium

Results of Duavive utilization from the cross-sectional data source are presented in Table 27.

10.2.3.2.2.5.1. Daily dose

Daily dose recommendation was available for 19.0% of Duavive prescriptions. The standard recommended dose (1 tablet per day) was documented in 100.0% of these prescriptions.

10.2.3.2.2.5.2. Days supply

The days supply was 90.0 days in all analysed prescriptions.

Table 27. Duavive utilization; overall; prescription-level analysis [country: Belgium; source: IMB; Cumulative Period]

	Belgium	
	Cross-Sectional database: Medical Index	
	Reported study period: 01 April 2016 - 31 March 2019[2]	
	Duavive	
	n	%
Projected number of prescriptions during reported period	***7,425***	***100.0***
Number of prescriptions with instruction on daily dosage available	**1,412**	**19.0**
Daily dose[1]		
1 tablet	1,412	100.0
<1 tablet	0	0.0
>1 tablet	0	0.0
Days supply[1]		
Mean (SD)	90.0 (0.0)	
Median	90	
Minimum - maximum	(90; 90)	

1. Analysis as reported (missing data on daily dose instruction not replaced)

Table 27. Duavive utilization; overall; prescription-level analysis [country: Belgium; source: IMB; Cumulative Period]

	Belgium	
	Cross-Sectional database: Medical Index	
	Reported study period: 01 April 2016 - 31 March 2019[2]	
	Duavive	
	n	%

2. In all cross-sectional data sources, data are reported per quarter, resulting in a slightly different reporting period compared to the longitudinal databases
SD: standard deviation
IMB: Index Medical Belge (Medical Index database in Belgium)

10.2.3.2.2.6. Potential off-label use of Duavive in Belgium

The results for potential off-label use of Duavive from the cross-sectional data source (main analysis, see Sections 9.4.5, 9.9.4) are presented in Table 28. Data projected to national levels were analysed. No potential off-label use of Duavive was identified in the Belgian cross-sectional data source.

The proportion of potential off-label users increased to 9.2% (Table 29) when the premenopausal age limit was changed to 49 years (sensitivity analysis I).

Table 28. Potential off-label use of Duavive; overall; prescription-level analysis [country: Belgium; source: IMB; Cumulative Period]

	Belgium	
	Cross-Sectional database: Medical Index	
	Reported study period: 01 April 2016 - 31 March 2019	
	Duavive	
	Total	
	n	%
Total number of patients	***7,425***	***100.0***
Off-label use (total; any category)[1,2]	**0**	**0.0**
Patients with single categories of off-label use		
Use for treatment of osteoporosis only[3]	0	0.0
Valid N	*7,425*	
Use in women ≤45 years[3]	0	0.0
Valid N	*6,745*	
Use in women over 75 years old[3]	0	0.0
Valid N	*6,745*	
Use in males[3]	0	0.0
Valid N	7,425	
Prescription of non-approved dose or regimen[3]	0	0.0
Valid N	*1,412*	
Use with progestins, additional oestrogens or selective oestrogen receptor modulators (SERMs)[1]	0	0.0
Use in women without a uterus (hysterectomised women)[1]	0	0.0
Known, suspected, or past history of breast cancer[1]	0	0.0
Hypersensitivity (e.g., anaphylaxis/anaphylactic reactions, urticaria, drug eruption) to the active substances or to any of the excipients[1]	0	0.0
Malignancy potentially associated with oestrogen[1]	0	0.0
Active or past history of venous thromboembolism (deep venous thrombosis, pulmonary embolism, and retinal vein thrombosis)[1]	0	0.0
Active or past history of arterial thromboembolic disease (e.g., myocardial infarction, stroke)[1]	0	0.0
Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal[1]	0	0.0
Known thrombophilic disorders (e.g., protein C, protein S, or antithrombin deficiency)[1]	0	0.0
Porphyria[1]	0	0.0

For a given single category, proportions were only calculated if the relevant variable is available
Valid N: patients with non-missing values in respective category
1. % of total N patients
2. Patients with off-label use in any category mentioned below
3. % of valid N in respective category

n.a. - not applicable as parameter is not available in country specific database
Age ≤45 years considered as proxy for premenopausal status (Section 9.4.5)
SERMs: selective oestrogen receptor modulators
IMB: Index Medical Belge (Medical Index database in Belgium)

Table 29. Sensitivity analyses for potential off-label use of Duavive; overall; prescription-level analysis [country: Belgium; source: IMB; Cumulative Period]

	Belgium	
	Cross-Sectional database: Medical Index	
	Reported study period: 01 April 2016 - 31 March 2019	
	Duavive	
	Total	
	n	%
Total number of patients during reported period	***7,425***	***100.0***
Main Analysis:[1,2] Definition of off-label use includes Presumed premenopausal age limit at ≤45 years; Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms	0	0.0
Sensitivity analysis I:[1,2,3] Definition of off-label use includes Presumed premenopausal age limit at ≤49 years; Diagnosis of, prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms	680	9.2
Sensitivity analysis II:[1,2,3] Definition of off-label use includes Presumed premenopausal age limit at ≤45 years; Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms, OR diagnosis of prevention and/or treatment of osteoporosis, in addition to diagnosis of oestrogen deficiency symptoms	0	0.0
Sensitivity analysis III:[1,2,3] Definition of off-label use includes Presumed premenopausal age limit at ≤49 years; Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms, OR diagnosis of prevention and/or treatment of osteoporosis, in addition to diagnosis of oestrogen deficiency symptoms	680	9.2

1. % of total N patients
2. Patients with off-label use in any category mentioned for this analysis
3. Number of patients in the categories other than presumed premenopausal age limit (sensitivity analyses I and III) or diagnosis (sensitivity analyses II and III) remained identical to Table 28

IMB: Index Medical Belge (Medical Index database in Belgium)

10.3. Results for The Netherlands

10.3.1. Participants

The number of eligible patients in the Netherlands is shown below in Table 30 and the number with and without E+P HRT treatment during the 12 months prior to index date is shown in Table 31. In Annual Reporting Period III, 85 (69.1%) of overall 123 Duavive users identified in the database were eligible for analysis; prescriptions of E+P HRT during 12 months prior to Duavive initiation were recorded in 80.0% of Duavive users. In the cumulative period, 177 (94.1%) of overall 188 patients prescribed Duavive were eligible for analysis; prior use of E+P HRT was reported for 59.3% of them. In the E+P HRT study cohort, 49,190 (94.8%) of 51,913 patients were included in the analysis for Annual Reporting Period III and 76,550 (92.1%) of 83,089 patients for cumulative period. The proportion of eligible patients with E+P HRT records during 12 months prior to index date was 59.0% and 34.3% in the annual and cumulative periods, respectively.

Table 30. Patient study eligibility in the Netherlands

	Netherlands			
	Longitudinal database: LRx			
	Annual Reporting Period III		Cumulative period	
	n	%	n	%
Duavive cohort				
Total patients with at least 1 Duavive prescription during the study period	123	100.0	188	100.0
Excluded: Patients not enrolled in the data source for at least 12 months prior to their index date[1]	2	1.6	9	4.8
Excluded: Duavive prescription within 12 months prior to index date[1]	36	29.3	2	1.1
Total eligible patients[1]	**85**	**69.1**	**177**	**94.1**
E+P HRT cohort				
Total patients with at least 1 prescription E+P HRT during study period	51,913	100.0	83,089	100.0
Excluded: Patients were not enrolled in the data source for at least 12 months prior to their index date[1]	2,711	5.2	6,539	7.9
Excluded: Duavive prescription within 12 months prior to index date[1]	12	0.0	0	0.0
Total eligible patients[1]	**49,190**	**94.8**	**76,550**	**92.1**

1. % of N patients with at least one prescription of study medication (Duavive or E+P HRT, respectively)
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

Table 31. Patients with and without E+P HRT treatment during the 12 months prior to index date (Netherlands)

	Netherlands			
	Longitudinal database: LRx			
	Annual Reporting Period III		Cumulative period	
	n	%	n	%
Duavive cohort				
Total eligible patients in analysis for reporting period	**85**	**100.0**	**177**	**100.0**
Included: with E+P HRT during 12 months pre-index[1]	68	80.0	105	59.3
Included: without E+P HRT during 12 months pre-index[1]	17	20.0	72	40.7

Table 31. Patients with and without E+P HRT treatment during the 12 months prior to index date (Netherlands)

	Netherlands			
	Longitudinal database: LRx			
	Annual Reporting Period III		Cumulative period	
	n	%	n	%
E+P HRT cohort				
Total eligible patients in analysis for reporting period	**49,190**	**100.0**	**76,550**	**100.0**
Included: with E+P HRT during 12 months pre-index[1]	29,025	59.0	26,242	34.3
Included: without E+P HRT during 12 months pre-index[1]	20,165	41.0	50,308	65.7

1. % of N patients with at least one prescription of study medication (Duavive or E+P HRT, respectively)
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.3.2. Netherlands – Annual Reporting Period III

10.3.2.1. Baseline Characteristics – Annual Reporting Period III - Netherlands

10.3.2.1.1. *LONGITUDINAL DATA*

Demographic characteristics of patients prescribed Duavive and E+P HRT are presented in Table 32.

10.3.2.1.1.1. Age

In the Duavive cohort 72.9% of patients were 50 years or older, 18.8% were 40 to 49 years and 8.2% patients were younger than 40 years. The proportion of patients aged ≥50 years was higher in the subgroup with prior E+P HRT prior treatment (76.5%) compared to the subgroup without (58.8%).

In the E+P HRT cohort 67.0% of patients were ≥50 years, 19.8% between 40 to 49 years and 13.3% were younger than 40 years. The proportion of the age group ≥50 years was 71.0% in the subgroup with prior E+P HRT treatment and 61.1% in the subgroup without.

10.3.2.1.1.2. Gender

Two males (2.4%) were prescribed Duavive during the reported study period. Overall, 0.3% of patients in the E+P HRT cohort were male, with no patients in the subgroup with prior E+P HRT treatment and 0.7% in the subgroup without.

10.3.2.1.1.3. BMI

Data on this parameter is not available in the database (see Table 2 in Section 9.4.1).

Table 32. Demographic characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: Netherlands; source: LRx; Annual Reporting Period III]

	Netherlands											
	Longitudinal database: LRx											
	Reported study period: 31 March 2018 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients	***85***	***100.0***	***17***	***100.0***	***68***	***100.0***	***49,190***	***100.0***	***20,165***	***100.0***	***29,025***	***100.0***
Age at treatment initiation[1]												
Valid N[2]	85	100.0	17	100.0	68	100.0	49,188	100.0	20,163	100.0	29,025	100.0
<40 years	7	8.2	3	17.6	4	5.9	6,529	13.3	3,472	17.2	3,057	10.5
40 to 49 years	16	18.8	4	23.5	12	17.6	9,718	19.8	4,368	21.7	5,350	18.4
≥50 years	62	72.9	10	58.8	52	76.5	32,941	67.0	12,323	61.1	20,618	71.0
Gender[1]												
Valid N[2]	85	100.0	17	100.0	68	100.0	49,190	100.0	20,165	100.0	29,025	100.0
Female	83	97.6	15	88.2	68	100.0	49,054	99.7	20,031	99.3	29,023	100.0
Male	2	2.4	2	11.8	0	0.0	136	0.3	134	0.7	2	0.0

1 % of Valid N
2 Valid N: patients with non-missing values
Body Mass Index not available in LRx Netherlands
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.3.2.1.2. *CROSS-SECTIONAL DATA*

Demographic characteristics on the prescription level for E+P HRT for the Annual Reporting Period III (01 April 2018 to 31 March 2019) are presented in Table 33. No prescriptions for Duavive were identified in the data source for this annual period.

10.3.2.1.2.1. Age

In the E+P HRT cohort of the Netherlands, 80.1% of patients were ≥50 years, 15.8% between 40 to 49 years and 4.1% were younger than 40 years.

10.3.2.1.2.2. Gender

In the E+P HRT cohort none of the patients were male during the reported annual study period.

10.3.2.1.2.3. BMI

Data on this parameter is not available in the database (see Table 2 in Section 9.4.1).

Table 33. Demographic characteristics; Overall and Stratified by Therapy; prescription-level analysis [country: Netherlands; source: IMB; Annual Reporting Period III]

	Netherlands			
	Cross-Sectional database: Medical Index			
	Reported study period: 01 April 2018 to 31 March 2019[3]			
	Duavive		E+P HRT	
	n	%	n	%
Total number of prescriptions during reported period	***0***	***0.0***	***58,952***	***100.0***
Age: n (%)[1]				
Valid N[2]	*0*	*0.0*	*58,952*	*100.0*
<40 years	0	0.0	2,430	4.1
40 to 49 years	0	0.0	9,299	15.8
≥50 years			47,222	80.1
Gender: n (%)[1]				
Valid N[2]	*0*	*0.0*	*58,952*	*100.0*
Female	0	0.0	58,952	100.0
Male	0	0.0	0	0.0

1 % of Valid N
2 Valid N: patients with non-missing values
3 Analysis based on data from same consultation
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.3.2.2. Clinical Characteristics and Duavive Prescribing Patterns – Annual Reporting Period III – Netherlands

10.3.2.2.1. *LONGITUDINAL DATA*

The results of baseline clinical characteristics are presented in Table 34 below.

As described in the protocol, and in Table 2 in Section 9.4.1 analyses of co-morbidities, prior safety events, and indication were not possible because these variables are not available in the database.

10.3.2.2.1.1. Co-medication

In the Duavive cohort 56.5% of patients were recorded with at least one of the specified co-medications during the 12 months pre-index period (60.3% and 41.2% in subgroups with and without prior E+P HRT treatment, respectively). In the E+P HRT cohort at least one prescription of the specified co-medications was identified in 42.0% of patients (43.3% and 40.1% in the subgroups with and without prior E+P HRT treatment, respectively).

The most frequently co-prescribed drugs in the Duavive cohort were antidepressants (29.4%), sedatives/hypnotics (15.3%), lipid lowering agents (9.4%) and corticosteroids (9.4%). In the E+P HRT cohort they were antidepressants (17.0%), sedatives/hypnotics (14.5%), lipid lowering agents (9.4%) and corticosteroids (9.4%). For proportions in the subgroups with and without prior E+P HRT treatment please refer to Table 34.

Table 34. Baseline clinical characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: Netherlands; source: LRx; Annual Reporting Period III]

	Netherlands											
	Longitudinal database: LRx											
	Reported study period: 31 March 2018 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients	***85***	***100.0***	***17***	***100.0***	***68***	***100.0***	***49,190***	***100.0***	***20,165***	***100.0***	***29,025***	***100.0***
Co-medication during 12 months pre-index period[1]												
Any co-medication	**48**	**56.5**	**7**	**41.2**	**41**	**60.3**	**20,668**	**42.0**	**8,095**	**40.1**	**12,573**	**43.3**
Corticosteroids	8	9.4	0	0.0	8	11.8	4,600	9.4	1,732	8.6	2,868	9.9
Lipid lowering agents	8	9.4	0	0.0	8	11.8	4,630	9.4	1,364	6.8	3,266	11.3
Anti-hypertensives	0	0.0	0	0.0	0	0.0	241	0.5	110	0.5	131	0.5
Anticoagulants	2	2.4	0	0.0	2	2.9	3,659	7.4	1,171	5.8	2,488	8.6
Antiarrhythmics	4	4.7	0	0.0	4	5.9	1,105	2.2	359	1.8	746	2.6
Antidepressants	25	29.4	4	23.5	21	30.9	8,357	17.0	3,432	17.0	4,925	17.0
Sedatives/ hypnotics	13	15.3	4	23.5	9	13.2	7,157	14.5	2,888	14.3	4,269	14.7
Antidiabetics	4	4.7	0	0.0	4	5.9	1,691	3.4	602	3.0	1,089	3.8
Osteoporosis treatments (bisphosphonates, SERMs, etc)	0	0.0	0	0.0	0	0.0	889	1.8	305	1.5	584	2.0
Local (vaginal) hormone treatments	2	2.4	0	0.0	2	2.9	23	0.0	14	0.1	9	0.0

1 % of total N
Co-morbidities, prior safety events and indication for study medication not available in LRx – The Netherlands
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy
SERMs: selective oestrogen receptor modulators

10.3.2.2.1.2. Duavive utilization in the Netherlands

The results of Duavive utilization based on index prescription are presented in Table 35 below.

10.3.2.2.1.2.1. Daily dose

Daily dose recommendations were available for 83 out of 85 index Duavive prescriptions (97.6%). The standard recommended dose (1 tablet per day) was documented in all (100.0%) of these index prescriptions.

10.3.2.2.1.2.2. Days supply

In the analysis based on prescriptions with known daily dose, mean days supply was 33.7 days overall. It varied between 31.8 days and 41.0 days in the subgroups with and without prior E+P HRT treatment. The duration ranged from 28 to 84 days.

After imputation of missing values to the standard Duavive dose and supply the values were very similar to those in the analysis without replacement of missing data (Table 35).

10.3.2.2.1.2.3. Switchers from E+P HRT to Duavive

Overall, a switch from E+P HRT to Duavive at index date was identified in 16.5% of patients (20.6% in the subgroup with prior E+P HRT treatment).

Table 35. Duavive utilization; Overall and Stratified by Prior E+P HRT Treatment; prescription-level analysis [country: Netherlands; source: LRx; Annual Reporting Period III]

	Netherlands					
	Longitudinal database: LRx					
	Reported study period: 31 March 2018 to 30 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Total number of patients with index prescriptions	***85***	***100.0***	***17***	***100.0***	***68***	***100.0***
Number of (index) prescriptions with instruction on daily dosage available	**83**	**97.6**	**17**	**100.0**	**66**	**97.1**
Daily dose						
A. Analysis as reported (missing data on daily dose instruction not replaced)[1]						
1 tablet	83	100.0	17	100.0	66	100.0
<1 tablet	0	0.0	0	0.0	0	0.0
>1 tablet	0	0.0	0	0.0	0	0.0
B. Analysis based on all index prescriptions (missing data replaced)[2]						
1 tablet	85	100.0	17	100.0	68	100.0
<1 tablet	0	0.0	0	0.0	0	0.0
>1 tablet	0	0.0	0	0.0	0	0.0
Days supply						
A. Analysis as reported (missing data not replaced)[1]						
Mean (SD)	33.7 (22.5)		41.0 (33.7)		31.8 (18.8)	
Median	28		28		28	
Minimum – maximum	(28; 84)		(28; 84)		(28; 84)	
B. Analysis based on all index prescriptions (missing data replaced)[2]						
Mean (SD)	33.6 (22.2)		41.0 (33.7)		31.7 (18.5)	
Median	28		28		28	
Minimum - maximum	(28; 84)		(28; 84)		(28; 84)	
Switchers from E+P HRT to Duavive[2,3]	**14**	**16.5**	**n.appl.**		**14**	**20.6**

1 Based on N index prescriptions with instruction on daily dosage available
2 Based on total N index prescriptions
3 Switch: prescription of Duavive within 30 days following the end of the last filled prescription period of E+P HRT
SD: standard deviation; n.appl.: not applicable
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.3.2.2.1.3. Off-label use of Duavive in Netherlands

The results for potential off-label use of Duavive from the main analysis (see Sections 9.4.5, 9.9.4) are presented in Table 36.

Potential off-label use was identified in 24.7% of all Duavive users (20.6% and 41.2% in subgroups with and without prior E+P HRT treatment). The reasons for potential off-label use were use with progestins, additional oestrogens or selective oestrogen receptor modulators (16.5%), presumed premenopausal age of ≤45 years (15.7%), and use in males (2.4%).

After changing the presumed premenopausal age limit from 45 years to 49 years, without changing any of the other off-label parameters (sensitivity analysis I), the proportion of potential off-label users increased to 32.9% (Table 37). For proportions in subgroups with and without E+P HRT prior treatment please also refer to Table 37.

Table 36. Potential off-label use of Duavive; Overall and Stratified by Prior E+P HRT Treatment; patient-level analysis [country: Netherlands; source: LRx; Annual Reporting Period III]

	Netherlands					
	Longitudinal database: LRx					
	Reported study period: 31 March 2018 to 30 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Total number of patients	***85***	***100.0***	***17***	***100.0***	***68***	***100.0***
Off-label use (total; any category)[1,2]	**21**	**24.7**	**7**	**41.2**	**14**	**20.6**
Patients with single categories of off-label use						
Use for treatment of osteoporosis only[3]	n.a.		n.a.		n.a.	
Valid N						
Use in women ≤45 years[3]	13	15.7	5	33.3	8	11.8
Valid N	*83*		*15*		*68*	
Use in women over 75 years old[3]	0	0.0	0	0.0	0	0.0
Valid N	*83*		*15*		*68*	
Use in males[3]	2	2.4	2	11.8	0	0.0
Valid N	*85*		*17*		*68*	
Prescription of non-approved dose or regimen[3]	0	0.0	0	0.0	0	0.0
Valid N	*83*		*17*		*66*	
Use with progestins, additional oestrogens or selective oestrogen receptor modulators (SERMs)[1]	14	16.5	5	29.4	9	13.2
Use in women without a uterus (hysterectomised women)[1]	n.a.		n.a.		n.a.	
Known, suspected, or past history of breast cancer[1]	n.a.		n.a.		n.a.	
Hypersensitivity (e.g., anaphylaxis/anaphylactic reactions, urticaria, drug eruption) to the active substances or to any of the excipients[1]	n.a.		n.a.		n.a.	
Malignancy potentially associated with oestrogen[1]	n.a.		n.a.		n.a.	
Active or past history of venous thromboembolism (deep venous thrombosis, pulmonary embolism, and retinal vein thrombosis)[1]	n.a.		n.a.		n.a.	
Active or past history of arterial thromboembolic disease (e.g., myocardial infarction, stroke)[1]	n.a.		n.a.		n.a.	
Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal[1]	n.a.		n.a.		n.a.	

Table 36. Potential off-label use of Duavive; Overall and Stratified by Prior E+P HRT Treatment; patient-level analysis [country: Netherlands; source: LRx; Annual Reporting Period III]

	Netherlands					
	Longitudinal database: LRx					
	Reported study period: 31 March 2018 to 30 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Known thrombophilic disorders (e.g., protein C, protein S, or antithrombin deficiency)[1]	n.a.		n.a.		n.a.	
Porphyria[1]	n.a.		n.a.		n.a.	

Valid N: patients with non-missing values in respective category
1 % of total N patients
2 Patients with off-label use in any category mentioned below
3 % of valid N in respective category (listed below)
n.a. - not applicable as parameter is not available in country specific database
Age ⩽45 years considered as proxy for premenopausal status (Section 9.4.5)
Patients can be in more than one category of potential off-label use
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy
SERMs: selective oestrogen receptor modulators

Table 37. Sensitivity analyses for potential off-label use of Duavive; Overall and Stratified by Prior E+P HRT Treatment; patient-level analysis [country: Netherlands; source: LRx; Annual Reporting Period III]

	Netherlands					
	Longitudinal database: LRx					
	Reported study period: 31 March 2018 to 30 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Total number of patients during reported period	***85***	***100.0***	***17***	***100.0***	***68***	***100.0***
Main Analysis:[1,2] Definition of off-label use includes Presumed premenopausal age limit at ≤45 years	21	24.7	7	41.2	14	20.6
Sensitivity analysis I:[1,2,3,4] Definition of off-label use includes Presumed premenopausal age limit at ≤49 years	28	32.9	9	52.9	19	27.9

1 % of total N patients
2 Other sensitivity analyses were not applicable as there is no information about the indication.
3 Number of patients in the categories other than presumed premenopausal age limit remained identical to Table 36
4 Other sensitivity analyses were not applicable as there is no information about the indication
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.3.2.2.2. *CROSS-SECTIONAL DATA*

Baseline clinical characteristics for the E+P HRT cohort are presented in Table 38 below. Data projected to national levels were analysed. No prescriptions for Duavive were identified in the data source for the Annual Reporting Period III.

10.3.2.2.2.1. Co-morbidities

None of the specified co-morbidities were reported in the E+P HRT cohort.

10.3.2.2.2.2. Co-medication

None of the specified co-medications was reported in the E+P HRT cohort.

10.3.2.2.2.3. Prior safety events

No analysis was performed as data from medical history is not available in the cross-sectional database (see Table 2 in Section 9.4.1).

10.3.2.2.2.4. Indication

In the E+P HRT cohort, 83.7% of patients had documented diagnoses of oestrogen deficiency symptoms, and 16.3% of patients had documented diagnoses other than oestrogen

deficiency symptoms or osteoporosis. No patients were prescribed Duavive for osteoporosis only or for both oestrogen deficiency symptoms and osteoporosis (Table 38).

Table 38. Baseline clinical characteristics; Overall and Stratified by Therapy; prescription-level analysis [country: Belgium; source: IMB; Annual Reporting Period III]

	Netherlands			
	Cross-Sectional database: Medical Index			
	Reported study period: 01 April 2018 - 31 March 2019[3]			
	Duavive		E+P HRT	
	n	%	n	%
Projected number of prescriptions during reported period	***0***	***0.0***	***58,952***	***100.0***
Co-morbidities[1,2]				
Any co-morbidity	**0**	**0.0**	**0**	**0.0**
Osteoporosis osteopenia	0	0.0	0	0.0
History of CVD event	0	0.0	0	0.0
Hyperlipidemia	0	0.0	0	0.0
Hypertension	0	0.0	0	0.0
Breast pain	0	0.0	0	0.0
Diabetes	0	0.0	0	0.0
Renal disease	0	0.0	0	0.0
Osteoarthritis	0	0.0	0	0.0
Major depression	0	0.0	0	0.0
Co-medication[1,2]				
Any co-medication	**0**	**0.0**	**0**	**0.0**
Corticosteroids	0	0.0	0	0.0
Lipid lowering agents	0	0.0	0	0.0
Anti-hypertensives	0	0.0	0	0.0
Anticoagulants	0	0.0	0	0.0
Antiarrhythmics	0	0.0	0	0.0
Antidepressants	0	0.0	0	0.0
Sedatives hypnotics	0	0.0	0	0.0
Antidiabetics	0	0.0	0	0.0
Osteoporosis treatments bisphosphonates, SERMs, etc	0	0.0	0	0.0
Local vaginal hormone treatments	0	0.0	0	0.0
Indication for study medication[1,2]				
Oestrogen deficiency symptoms only	0	0.0	49,316	83.7
Osteoporosis only	0	0.0	0	0.0
Oestrogen deficiency symptoms and osteoporosis	0	0.0	0	0.0
No oestrogen deficiency symptoms or osteoporosis	0	0.0	9,635	16.3
Missing data on diagnosis	0	0.0	0	0.0

1. % of total N;

Table 38. Baseline clinical characteristics; Overall and Stratified by Therapy; prescription-level analysis [country: Belgium; source: IMB; Annual Reporting Period III]

	Netherlands			
	Cross-Sectional database: Medical Index			
	Reported study period: 01 April 2018 - 31 March 2019[3]			
	Duavive		E+P HRT	
	n	%	n	%

2. In the cross-sectional, prescription-level data, diagnoses and co-medications are only available if they were recorded in same consultation as the prescription.
3. In all cross-sectional data sources, data are reported per quarter, resulting in a slightly different reporting period compared to the longitudinal databases. Prior safety events not available in cross-sectional data
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy
SERMs: selective oestrogen receptor modulators; CVD: cardiovascular disease
IMB: Index Medical Belge (Medical Index database in Belgium)

10.3.2.2.2.5. Duavive utilization in the Netherlands

No Duavive prescriptions were recorded in the cross-sectional database during the Annual Reporting Period III, therefore no analyses of Duavive utilization (daily dose, days supply, switchers from E+P HRT to Duavive) were performed.

10.3.2.2.2.6. Potential off-label use of Duavive in Netherlands

As no Duavive prescriptions were recorded in the cross-sectional database during the Annual Reporting Period III, no analyses of Duavive potential off-label use were performed.

10.3.3. Netherlands – Cumulative Period

10.3.3.1. Baseline Characteristics – Cumulative Period - Netherlands

10.3.3.1.1. *LONGITUDINAL DATA*

Demographic characteristics of patients prescribed Duavive and E+P HRT for the cumulative period (31 March 2016 to 30 March 2019) are presented in Table 39.

10.3.3.1.1.1. Age

In the Duavive cohort in the Netherlands, 77.4% of patients were 50 years or older, 14.1% were 40 to 49 years and 8.5% were younger than 40 years. The proportion of patients aged ≥50 years was lower in the subgroup with prior E+P HRT treatment (69.5%) compared to the subgroup without (88.9%).

In the E+P HRT cohort, 61.4% of patients were ≥50 years, 20.9% were between 40 and 49 years and 17.6% were younger than 40 years. The proportion of patients in the age group ≥50 years was 70.6% in the subgroup with prior E+P HRT treatment and 56.6% in the subgroup without.

10.3.3.1.1.2. Gender

In the Duavive cohort there were 2 male patients (1.1%) reported in the study period. In the E+P HRT cohort 0.4% of patients were male overall, with no males in the subgroup with prior E+P HRT treatment and 0.7% in the subgroup without.

10.3.3.1.1.3. BMI

Data on this parameter is not available in the database (see Table 2 in Section 9.4.1).

Table 39. Demographic characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: Netherlands; source: LRx; Cumulative Period]

	Netherlands											
	Longitudinal database: LRx											
	Reported study period: 31 March 2016 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients	***177***	***100.0***	***72***	***100.0***	***105***	***100.0***	***76,550***	***100.0***	***50,308***	***100.0***	***26,242***	***100.0***
Age at treatment initiation[1]												
Valid N[2]	*177*	*100.0*	*72*	*100.0*	*105*	*100.0*	*76,550*	*100.0*	*50,308*	*100.0*	*26,242*	*100.0*
<40 years	15	8.5	2	2.8	13	12.4	13,497	17.6	10,594	21.1	2,903	11.1
40 to 49 years	25	14.1	6	8.3	19	18.1	16,022	20.9	11,220	22.3	4,802	18.3
≥50 years	137	77.4	64	88.9	73	69.5	47,031	61.4	28,494	56.6	18,537	70.6
Gender[1]												
Valid N[2]	*177*	*100.0*	*72*	*100.0*	*105*	*100.0*	*76,550*	*100.0*	*50,308*	*100.0*	*26,242*	*100.0*
Female	175	98.9	70	97.2	105	100.0	76,211	99.6	49,973	99.3	26,238	100.0
Male	2	1.1	2	2.8	0	0.0	339	0.4	335	0.7	4	0.0

1. % of Valid N
2. Valid N: patients with non-missing values

Body Mass Index not available in LRx Netherlands
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.3.3.1.2. *CROSS-SECTIONAL DATA*

Demographic characteristics of patients prescribed Duavive and E+P HRT for the cumulative period (01 April 2016 to 31 March 2019) are presented in Table 40.

There were no prescriptions for Duavive in the study period in the cross-sectional database.

10.3.3.1.2.1. Age

In the E+P HRT cohort, 72.4% of patients were ≥50 years, 25.1% between 40 to 49 years and 2.5% were younger than 40 years.

10.3.3.1.2.2. Gender

There were no male patients in the E+P HRT cohort.

10.3.3.1.2.3. BMI

Data on this parameter is not available in the database (see Table 2 in Section 9.4.1).

Table 40. Demographic characteristics; Overall and Stratified by Therapy; prescription-level analysis [country: Netherlands; source: Medical Index; Cumulative Period]

	Netherlands			
	Cross-Sectional database: Medical Index			
	Reported study period: 01 April 2016 to 31 March 2019[3]			
	Duavive		E+P HRT	
	n	%	n	%
Total number of prescriptions during reported period	***0***	***0.0***	***179,229***	***100.0***
Age: n (%)[1]				
Valid N[2]	*0*	*0.0*	*179,229*	*100.0*
<40 years	0	0.0	4,431	2.5
40 to 49 years	0	0.0	45,059	25.1
≥50 years	0	0.0	129,739	72.4
Gender: n (%)[1]				
Valid N[2]	*0*	*0.0*	*179,229*	*100.0*
Female	0	0.0	179,229	100.0
Male	0	0.0	0	0.0

1. % of Valid N
2. Valid N: patients with non-missing values
3. Analysis based on data from same consultation

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.3.3.2. Clinical Characteristics and Duavive Prescribing Patterns – Cumulative Period - Netherlands

10.3.3.2.1. *LONGITUDINAL DATA*

Baseline clinical characteristics are presented in Table 41 below.

As described in the protocol, and shown in Table 2 in Section 9.4.1 analyses of co-morbidities, prior safety events, and indication were not possible because these variables are not available in the database.

10.3.3.2.1.1. Co-medication

In the Duavive cohort, 62.7% of the patients had received at least one of the specified co-medications during the 12 months pre-index period (59.0% and 68.1% in the subgroups with and without prior E+P HRT treatment, respectively). In the E+P HRT cohort, at least one prescription of the specified co-medication was identified in 41.4% of the patients (45.0% and 39.6% in the subgroups with and without prior E+P HRT treatment, respectively).

The most frequently co-prescribed medications in the Duavive cohort were antidepressants (31.1%), sedatives/hypnotics (27.1%), corticosteroids (11.3%) anticoagulants (9.6%), lipid lowering agents (9.6%), and antiarrhythmics (8.5%) and in the E+P HRT cohort the most frequently co-prescribed medications were: antidepressants (17.1%), sedatives/hypnotics (14.2%), corticosteroids (9.2%), lipid lowering agents (8.9%) and anticoagulants (7.2%). For proportions in the subgroups with and without prior E+P HRT treatment please refer to Table 41.

Table 41. Baseline clinical characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: Netherlands; source: LRx; Cumulative Period]

	Netherlands											
	Longitudinal database: LRx											
	Reported study period: 31 March 2016 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients	***177***	***100.0***	***72***	***100.0***	***105***	***100.0***	***76,550***	***100.0***	***50,308***	***100.0***	***26,242***	***100.0***
Co-medication during 12 months pre-index period[1]												
Any co-medication	**111**	**62.7**	**49**	**68.1**	**62**	**59.0**	**31,726**	**41.4**	**19,926**	**39.6**	**11,800**	**45.0**
Corticosteroids	20	11.3	9	12.5	11	10.5	7,056	9.2	4,335	8.6	2,721	10.4
Lipid lowering agents	17	9.6	11	15.3	6	5.7	6,833	8.9	3,469	6.9	3,364	12.8
Anti-hypertensives	0	0.0	0	0.0	0	0.0	422	0.6	302	0.6	120	0.5
Anticoagulants	17	9.6	11	15.3	6	5.7	5,517	7.2	3,073	6.1	2,444	9.3
Antiarrhythmics	15	8.5	6	8.3	9	8.6	1,545	2.0	912	1.8	633	2.4
Antidepressants	55	31.1	19	26.4	36	34.3	13,126	17.1	8,457	16.8	4,669	17.8
Sedatives/ hypnotics	48	27.1	24	33.3	24	22.9	10,857	14.2	6,957	13.8	3,900	14.9
Antidiabetics	8	4.5	2	2.8	6	5.7	2,631	3.4	1,602	3.2	1,029	3.9
Osteoporosis treatments (bisphosphonates, SERMs, etc)	0	0.0	0	0.0	0	0.0	1,441	1.9	828	1.6	613	2.3
Local (vaginal) hormone treatments	2	1.1	0	0.0	2	1.9	63	0.1	47	0.1	16	0.1

1. % of total N

Co-morbidities, prior safety events and indication for study medication not available in LRx – Netherlands
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy
SERMs: selective oestrogen receptor modulators

10.3.3.2.1.2. Duavive utilization in the Netherlands

The results of Duavive utilization based on index prescription are presented in Table 42 below.

10.3.3.2.1.2.1. Daily dose

Daily dose recommendations were available for 173 out of 177 index Duavive prescriptions (97.7%). The standard recommended dose (1 tablet per day) was documented in 169 (97.7%) of these index prescriptions. There were 2 prescriptions where the recommended dose was <1 tablet per day and 2 where it was >1 tablet per day.

10.3.3.2.1.2.2. Days supply

In the analysis based on prescriptions with known daily dose, mean days supply was 32.5 days overall. It varied between 29.5 days and 36.9 days in the subgroups with and without prior E+P HRT treatment. The duration ranged from 14 to 112 days.

After imputation to set missing values to the standard Duavive dose and supply, the mean duration was 32.4 days overall. It varied between 29.4 and 36.7 in the subgroups with and without prior E+P HRT treatment, respectively. The duration ranged from 14 to 112 days.

10.3.3.2.1.2.3. Switchers from E+P HRT to Duavive

Overall, a switch from E+P HRT to Duavive at index date was identified in 11.9% of patients (20.0% in the subgroup with prior E+P HRT treatment).

Table 42. Duavive utilization; Overall and Stratified by Prior E+P HRT Treatment; prescription-level analysis [country: Netherlands; source: LRx; Cumulative Period]

	Netherlands					
	Longitudinal database: LRx					
	Reported study period: 31 March 2016 to 30 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Total number of patients with index prescriptions	***177***	***100.0***	***72***	***100.0***	***105***	***100.0***
Number of (index) prescriptions with instruction on daily dosage available	**173**	**97.7**	**70**	**97.2**	**103**	**98.1**
Daily dose						
A. Analysis as reported (missing data on daily dose instruction not replaced)[1]						
1 tablet	169	97.7	66	94.3	103	100.0
<1 tablet	2	1.2	2	2.9	0	0.0
>1 tablet	2	1.2	2	2.9	0	0.0
B. Analysis based on all index prescriptions (missing data replaced)[2]						
1 tablet	173	97.7	68	94.4	105	100.0
<1 tablet	2	1.1	2	2.8	0	0.0
>1 tablet	2	1.1	2	2.8	0	0.0
Days supply						
A. Analysis as reported (missing data not replaced)[1]						
Mean (SD)	32.5 (24.9)		36.9 (35.0)		29.5 (13.5)	
Median	28		28		28	
Minimum – maximum	(14; 112)		(14; 112)		(15; 84)	
B. Analysis based on all index prescriptions (missing data replaced)[2]						
Mean (SD)	32.4 (24.6)		36.7 (34.5)		29.4 (13.3)	
Median	28		28		28	
Minimum - maximum	(14; 112)		(14; 112)		(15; 84)	
Switchers from E+P HRT to Duavive[2,3]	**21**	**11.9**	**n.appl.**		**21**	**20.0**

1. Based on N index prescriptions with instruction on daily dosage available
2. Based on total N index prescriptions
3. Switch: prescription of Duavive within 30 days following the end of the last filled prescription period of E+P HRT

SD: standard deviation; n.appl.: not applicable
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.3.3.2.1.3. Potential off-label use of Duavive in Netherlands

The results for potential off-label use of Duavive from the main analysis (see Sections 9.4.5, 9.9.4) are presented in Table 43.

Potential off-label use was identified in 25.4% of all Duavive users (23.8% and 27.8% in the subgroups with and without prior E+P HRT treatment, respectively). The reasons for potential off-label use were presumed premenopausal age of ≤45 years (16.6%), age over 75 years (4.6%), use with progestins, additional oestrogens or selective oestrogen receptor modulators (6.8%), prescription of a non-approved dose (2.4%) and use in males (1.1%).

After changing the presumed premenopausal age limit from 45 years to 49 years, without changing any of the other off-label parameters (sensitivity analysis I), the proportion of potential off-label users increased to 31.6% (Table 44). For proportions in subgroups with and without E+P HRT prior treatment please refer to Table 44.

Table 43. Potential off-label use of Duavive; Overall and Stratified by Prior E+P HRT Treatment; patient-level analysis [country: Netherlands; source: LRx; Cumulative Period]

	Netherlands					
	Longitudinal database: LRx					
	Reported study period: 31 March 2016 to 30 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Total number of patients	***177***	***100.0***	***72***	***100.0***	***105***	***100.0***
Off-label use (total; any category)[1,2]	**45**	**25.4**	**20**	**27.8**	**25**	**23.8**
Patients with single categories of off-label use						
Use for treatment of osteoporosis only[3]	n.a.		n.a.		n.a.	
Valid N						
Use in women ≤45 years[3]	29	16.6	8	11.4	21	20.0
Valid N	*175*		*70*		*105*	
Use in women over 75 years old[3]	8	4.6	6	8.6	2	1.9
Valid N	*175*		*70*		*105*	
Use in males[3]	2	1.1	2	2.8	0	0.0
Valid N	*177*		*72*		*105*	
Prescription of non-approved dose or regimen[3]	4	2.4	4	6.1	0	0.0
Valid N	*169*		*66*		*103*	
Use with progestins, additional oestrogens or selective oestrogen receptor modulators (SERMs)[1]	12	6.8	6	8.3	6	5.7
Use in women without a uterus (hysterectomised women)[1]	n.a.		n.a.		n.a.	
Known, suspected, or past history of breast cancer[1]	n.a.		n.a.		n.a.	
Hypersensitivity (e.g., anaphylaxis/anaphylactic reactions, urticaria, drug eruption) to the active substances or to any of the excipients[1]	n.a.		n.a.		n.a.	
Malignancy potentially associated with oestrogen[1]	n.a.		n.a.		n.a.	
Active or past history of venous thromboembolism (deep venous thrombosis, pulmonary embolism, and retinal vein thrombosis)[1]	n.a.		n.a.		n.a.	
Active or past history of arterial thromboembolic disease (e.g., myocardial infarction, stroke)[1]	n.a.		n.a.		n.a.	
Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal[1]	n.a.		n.a.		n.a.	

Table 43. Potential off-label use of Duavive; Overall and Stratified by Prior E+P HRT Treatment; patient-level analysis [country: Netherlands; source: LRx; Cumulative Period]

	Netherlands					
	Longitudinal database: LRx					
	Reported study period: 31 March 2016 to 30 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Known thrombophilic disorders (e.g., protein C, protein S, or antithrombin deficiency)[1]	n.a.		n.a.		n.a.	
Porphyria[1]	n.a.		n.a.		n.a.	

Valid N: patients with non-missing values in respective category
1. % of total N patients
2. Patients with off-label use in any category mentioned below
3. % of valid N in respective category (listed below)

n.a. - not applicable as parameter is not available in country specific database
Age ⩽45 years considered as proxy for premenopausal status (Section 9.4.5)
Patients can be in more than one category of potential off-label use
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy
SERMs: selective oestrogen receptor modulators

Table 44. Sensitivity analyses for potential off-label use of Duavive; Overall and Stratified by Prior E+P HRT Treatment; patient-level analysis [country: Netherlands; source: LRx; Cumulative Period]

	Netherlands					
	Longitudinal database: LRx					
	Reported study period: 31 March 2016 to 30 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Total number of patients during reported period	***177***	***100.0***	***72***	***100.0***	***105***	***100.0***
Main Analysis:[1,2] Definition of off-label use includes Presumed premenopausal age limit at ≤45 years	45	25.4	20	27.8	25	23.8
Sensitivity analysis I:[1,2,3] Definition of off-label use includes Presumed premenopausal age limit at ≤49 years	56	31.6	20	27.8	36	34.3

1. % of total N patients
2. Patients with off-label use in any category mentioned for this analysis.
3. Number of patients in the categories other than presumed premenopausal age limit remained identical to Table 43

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.3.3.2.2. *CROSS-SECTIONAL DATA*

No Duavive prescriptions were identified in the database for the reported study period. Baseline clinical characteristics in E+P HRT study group are presented in Table 45 below. Data projected to national levels were analysed.

10.3.3.2.2.1. Co-morbidities

In the E+P HRT group, the proportion of patients with at least one of the specified co-morbidities was 2.8%.

10.3.3.2.2.2. Co-medication

The proportion of patients who were prescribed any of the specified co-medications in the E+P HRT group was 0.7%.

10.3.3.2.2.3. Prior safety events

Analysis was not performed, because data from medical history is not available in the cross-sectional database (see Table 2 in Section 9.4.1).

10.3.3.2.2.4. Indication

In the E+P HRT cohort 82.4% of patients received E+P HRT for oestrogen deficiency symptoms only. None of the patients received prescriptions of E+P HRT for osteoporosis only or for both osteoporosis and oestrogen deficiency symptoms. No diagnoses of oestrogen deficiency symptoms or osteoporosis were recorded for 17.1% of the patients. Data on diagnosis were missing in 0.5% of the patients.

Table 45. Baseline clinical characteristics; Overall and Stratified by Therapy; prescription-level analysis [country: Netherlands; source: Medical Index; Cumulative Period]

	Netherlands			
	Cross-Sectional database: Medical Index			
	Reported study period: 01 April 2016 - 31 March 2018[3]			
	Duavive		E+P HRT	
	n	%	n	%
Projected number of prescriptions during reported period	***0***	***0.0***	***179,229***	***100.0***
Co-morbidities[1,2]				
Any co-morbidity	**0**	**0.0**	**4,968**	**2.8**
Osteoporosis osteopenia	0	0.0	0	0.0
History of CVD event	0	0.0	0	0.0
Hyperlipidemia	0	0.0	0	0.0
Hypertension	0	0.0	4,968	2.8
Breast pain	0	0.0	0	0.0
Diabetes	0	0.0	0	0.0
Renal disease	0	0.0	0	0.0
Osteoarthritis	0	0.0	0	0.0
Major depression	0	0.0	0	0.0
Co-medication[1,2]				
Any co-medication	**0**	**0.0**	**1,234**	**0.7**
Corticosteroids	0	0.0	0	0.0
Lipid lowering agents	0	0.0	0	0.0
Anti-hypertensives	0	0.0	0	0.0
Anticoagulants	0	0.0	0	0.0
Antiarrhythmics	0	0.0	0	0.0
Antidepressants	0	0.0	0	0.0
Sedatives hypnotics	0	0.0	1,234	0.7
Antidiabetics	0	0.0	0	0.0
Osteoporosis treatments bisphosphonates, SERMs, etc	0	0.0	0	0.0
Local vaginal hormone treatments	0	0.0	0	0.0
Indication for study medication[1,2]				
Oestrogen deficiency symptoms only	0	0.0	147,638	82.4
Osteoporosis only	0	0.0	0	0.0
Oestrogen deficiency symptoms and osteoporosis	0	0.0	0	0.0

Table 45. Baseline clinical characteristics; Overall and Stratified by Therapy; prescription-level analysis [country: Netherlands; source: Medical Index; Cumulative Period]

	Netherlands			
	Cross-Sectional database: Medical Index			
	Reported study period: 01 April 2016 - 31 March 2018[3]			
	Duavive		E+P HRT	
	n	%	n	%
No oestrogen deficiency symptoms or osteoporosis	0	0.0	30,608	17.1
Missing data on diagnosis	0	0.0	983	0.5

1. % of total N
2. In the cross-sectional, prescription-level data, diagnoses and co-medications are only available if they were recorded in same consultation as the prescription
3. In all cross-sectional data sources, data are reported per quarter, resulting in a slightly different reporting period compared to the longitudinal databases. Prior safety events not available in cross-sectional data

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy
SERMs: selective oestrogen receptor modulators; CVD: cardiovascular disease

10.3.3.2.2.5. Duavive utilization in the Netherlands

No Duavive prescriptions were recorded in the cross-sectional database during the study period, therefore no analyses of Duavive utilization (daily dose, days supply, switchers from E+P HRT to Duavive) were performed.

10.3.3.2.2.6. Potential off-label use of Duavive in Netherlands

As no Duavive prescriptions were recorded in the cross-sectional database during the study period no analyses of Duavive potential off-label use were performed.

10.4. Results for UK

Note: Due to restrictions imposed by the UK government to protect patient privacy, patient counts <6 cannot be disclosed, nor any result that would make it possible to calculate patients counts <6. Such results are masked or approximated numbers presented in the tables and figures.

10.4.1. Participants

The number of eligible patients in the UK is shown in Table 46 below and the number with and without E+P HRT treatment during the 12 months prior to index date is shown in Table 47. In Annual Reporting Period III 7 (63.6%) of overall 11 Duavive users identified in the database were eligible for analysis; no patients had prescriptions of E+P HRT during 12 months prior to Duavive initiation. In the cumulative period, 11 patients prescribed Duavive were identified, all of them were eligible for analysis; no patients had prescriptions of E+P HRT during 12 months prior to Duavive initiation. In the E+P HRT study cohort, 15,890 (85.8%) of 18,522 patients were included in the analysis for Annual Reporting Period III and 27,734 (93.1%) of 29,799 patients for cumulative period. The proportion of eligible patients

with E+P HRT records during 12 months prior to index date was 14.2% and 6.9% in the annual and cumulative periods, respectively.

Table 46. Patient study eligibility in UK

	UK			
	Longitudinal database: THIN			
	Annual Reporting Period III		Cumulative period	
	n	%	n	%
Duavive cohort				
Total patients with at least 1 Duavive prescription during the study period	11	100.0	11	100.0
Excluded: Patients not enrolled in the data source for at least 12 months prior to their index date[1]	<6		0	0.0
Excluded: Duavive prescription within 12 months prior to index date[1]	<6		0	0.0
Total eligible patients[1]	**7**	**63.6**	**11**	**100.0**
E+P HRT cohort				
Total patients with at least 1 prescription E+P HRT during study period	~19,729	100.0	32,818	100.0
Excluded: Patients were not enrolled in the data source for at least 12 months prior to their index date[1]	1,207	6.1	3,012	9.2
Excluded: Duavive prescription within 12 months prior to index date[1]	<6		7	0.0
Total eligible patients[1]	**18,522**	**93.9**	**29,799**	**90.8**

1. % of N patients with at least one prescription of study medication (Duavive or E+P HRT, respectively)
"~": approximate numbers are presented to maintain anonymity in accordance with THIN privacy protection policies,
<6: exact numbers masked to maintain anonymity in accordance with THIN privacy protection policies
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

Table 47. Patients with and without E+P HRT treatment during the 12 months prior to index date (UK)

	UK			
	Longitudinal database: THIN			
	Annual Reporting Period III		Cumulative period	
	n	%	n	%
Duavive cohort				
Total eligible patients in analysis for reporting period	**7**	**100.0**	**11**	**100.0**
Included: with E+P HRT during 12 months pre-index[1]	0	0.0	0	0.0
Included: without E+P HRT during 12 months pre-index[1]	7	100.0	11	100.0
E+P HRT cohort				
Total eligible patients in analysis for reporting period	**18,522**	**100.0**	**29,799**	**100.0**
Included: with E+P HRT during 12 months pre-index[1]	2,632	14.2	2,065	6.9
Included: without E+P HRT during 12 months pre-index[1]	15,890	85.8	27,734	93.1

1. % of N patients with at least one prescription of study medication (Duavive or E+P HRT, respectively)
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.4.2. UK – Annual Reporting Period III

10.4.2.1. Baseline Characteristics – Annual Reporting Period III - UK

Demographic characteristics of patients prescribed Duavive and E+P HRT are presented in Table 48.

The number of patients included in the Duavive cohort for the Annual Reporting Period III is very low (n=7) and a considerable part of results could not be reported due to privacy protection reasons.

10.4.2.1.1. ***Age***

In the E+P HRT cohort, 77.4% of patients were 50 years or older, 20.4% were 40 to 49 years and 2.2% of patients were younger than 40 years. The proportion of the age group ≥50 years was 70.3% in the subgroup with prior E+P HRT treatment and 78.6% in the subgroup without. The results for Duavive cohort are not presented due to THIN privacy protection reasons.

10.4.2.1.2. ***Gender***

No males were prescribed Duavive during the reported study period. In the E+P HRT cohort, less than 6 patients were male. This distribution was seen equally in the subgroups with and without prior E+P HRT treatment.

10.4.2.1.3. ***BMI***

No results on BMI can be reported for the Duavive cohort. BMI values were available for a subset of 4,975 out of 18,522 patients (26.9%) in the E+P HRT cohort. Within this subset, 2.1% of patients were underweight, and about one third of patients was either normal weight (31.4%), overweight (33.2%) or obese (33.2%). Similar proportions were seen in the subgroups with and without prior E+P HRT treatment.

Table 48. Demographic characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: UK; source: THIN; Annual Reporting Period III]

	UK											
	Longitudinal database: THIN											
	Reported study period: 31 March 2018 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients	***7***	***100.0***	***7***	***100.0***	***0***	***0.0***	***18,522***	***100.0***	***15,890***	***100.0***	***2,632***	***100.0***
Age at treatment initiation[1]												
Valid N[2]	*7*	*100.0*	*7*	*100.0*	*0*	*0.0*	*18,522*	*100.0*	*15,891*	*100.0*	*2,632*	*100.0*
<40 years	*<6*		<6		0	0.0	404	2.2	343	2.2	61	2.3
40 to 49 years	<6		<6		0	0.0	3,783	20.4	3,061	19.3	722	27.4
≥50 years	<6		<6		0	0.0	14,335	77.4	12,487	78.6	1,849	70.3
Gender[1]												
Valid N[2]	*7*	*100.0*	*7*	*100.0*	*0*	0.0	*~18,520*	*100.0*	*~15,889*	*100.0*	*~2,631*	*100.0*
Female	7	100.0	7	100.0	0	0.0	18,520	100.0	15,889	100.0	2,631	100.0
Male	0	0.0	0	0.0	0	0.0	<6		<6		<6	
Body Mass Index[1]												
Valid N[2]	*<6*		*<6*		*0*	0.0	*4,975*	*26.9*	*4,340*	*27.3*	*635*	*24.1*
<18.5: underweight	<6		<6		0	0.0	105	2.1	91	2.1	14	2.2
≥18.5 to <25: normal range	<6		<6		0	0.0	1,563	31.4	1,384	31.9	179	28.2
≥25 to <30: overweight	<6		<6		0	0.0	1,653	33.2	1,445	33.3	208	32.8
≥30: obese	<6		<6		0	0.0	1,654	33.2	1,420	32.7	234	36.9

1. % of Valid N
2. Valid N: patients with non-missing values

"masked", <6: in accordance with THIN privacy protection policies, exact numbers not reported to maintain anonymity
"~" exact number of patients is obfuscated to maintain anonymity in accordance with THIN privacy protection policies,
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.4.2.2. Clinical Characteristics and Duavive Prescribing Patterns – Annual Reporting Period III - UK

Due to privacy restrictions most results for the Duavive cohort and a few results for the E+P HRT cohort are masked or approximated numbers are presented to maintain anonymity.

Furthermore, the results for Duavive cohort are based on very low number of patients (n=7) and must be interpreted with caution.

10.4.2.2.1. ***Co-morbidities***

Patient co-morbidities cannot be presented for the Duavive cohort due to the low number of observations. The proportion of patients with any of the specified co-morbidities in the E+P

HRT study group was 11.3% (11.1% and 11.3% in subgroups with and without prior E+P HRT treatment, respectively). The most frequent co-morbidities in the E+P HRT cohort were hypertension (5.6% overall, 4.5% and 5.8% in the subgroups with and without prior E+P HRT treatment, respectively) and major depression (2.7% overall, 3.5% and 2.6% in the subgroups with and without prior E+P HRT treatment, respectively) (Table 49).

10.4.2.2.2. ***Co-medication***

In the Duavive cohort, 6 of 7 patients (85.7%) received at least one prescription of specified co-medication. All of these 6 patients received local hormone treatments. Results on other co-medications of interest cannot be reported for privacy protection reasons. In the E+P HRT cohort, at least one prescription of specified co-medication was identified in 55.2% of patients (57.4% and 54.8% in the subgroups with and without prior E+P HRT treatment, respectively). The most frequently co-prescribed drugs were antidepressants (38.7%), local (vaginal) hormone treatment (11.5%), corticosteroids (8.8%), lipid lowering agents (8.5%) and sedatives/hypnotics (7.3%). For proportions in the subgroups with and without prior E+P HRT treatment please refer to Table 49.

10.4.2.2.3. ***Prior safety events***

The overall proportion of patients with any safety event in the E+P HRT cohort was 0.5% (0.4% and 0.5% in the subgroups with and without prior E+P HRT treatment). For single categories of prior safety events please refer to Table 49. For the Duavive cohort, the results are not presented for confidentiality reasons.

10.4.2.2.4. ***Indication***

Indications for use of study medication at index date are presented in Table 49 below.

In the E+P HRT cohort, 12.1% of the patients had documented diagnoses of oestrogen deficiency symptoms (10.0% and 12.4% in the subgroups with and without prior E+P HRT treatment, respectively). For 82.6% of all patients, data on the diagnosis was missing (84.3% in the subgroup with and 82.3% in the subgroup without prior E+P HRT treatment) and for 5.2% of patients a diagnosis other than oestrogen deficiency symptoms or osteoporosis was documented (5.5% in the subgroup with and 5.1% in the subgroup without prior E+P HRT treatment).

An additional analysis of the period 365 days before and 90 days after index date showed a similar prescription pattern for the E+P HRT cohort as the analysis for index date ± 90 days. In this analysis, the number of patients with missing data on diagnoses in the baseline period was reduced by 2,130 patients (from 15,295 to 13,165).

In the Duavive cohort, 6 of 7 patients (87.5%) were identified as having missing data on diagnoses in the baseline period ± 90 days around index date. The results for other indication categories cannot be presented due to privacy protection concerns.

Table 49. Baseline clinical characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: UK; source: THIN; Annual Reporting Period III]

	UK											
	Longitudinal database: THIN											
	Reported study period: 31 March 2018 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients	***7***	***100.0***	***7***	***100.0***	***0***	***0.0***	***18,522***	***100.0***	***15,890***	***100.0***	***2,632***	***100.0***
Relevant co-morbidities during 12 months pre-index period: n(%)[1]												
Any co-morbidity			**<6**	**<6**	**0**	**0.0**	**2,093**	**11.3**	**1,802**	**11.3**	**291**	**11.1**
Osteoporosis/ osteopenia	<6		<6		0	0.0	61	0.3	54	0.3	7	0.3
History of CVD event	<6		<6		0	0.0	16	0.1	16	0.1	<6	
Hyperlipidemia	<6		<6		0	0.0	64	0.3	47	0.3	17	0.6
Hypertension	<6		<6		0	0.0	1,036	5.6	918	5.8	118	4.5
Breast pain	<6		<6		0	0.0	168	0.9	150	0.9	18	0.7
Diabetes	<6		<6		0	0.0	81	0.4	67	0.4	14	0.5
Renal disease	<6		<6		0	0.0	<6		<6		<6	
Osteoarthritis	<6		<6		0	0.0	274	1.5	236	1.5	38	1.4
Major depression	<6		<6		0	0.0	504	2.7	411	2.6	93	3.5
Co-medication during 12 months pre-index period[1]												
Any relevant co-medication	**6**	**85.7**	**6**	**85.7**	**0**	**0.0**	**10,222**	**55.2**	**8,712**	**54.8**	**1,510**	**57.4**
Corticosteroids	<6		<6		0	0.0	1,634	8.8	1,416	8.9	218	8.3
Lipid lowering agents	<6		<6		0	0.0	1,566	8.5	1,391	8.8	175	6.6
Anti-hypertensives	<6		<6		0	0.0	109	0.6	96	0.6	13	0.5
Anticoagulants	<6		<6		0	0.0	602	3.3	560	3.5	42	1.6
Antiarrhythmics	<6		<6		0	0.0	281	1.5	248	1.6	33	1.3
Antidepressants	<6		<6		0	0.0	7,167	38.7	6,098	38.4	1,069	40.6
Sedatives/ hypnotics	<6		<6		0	0.0	1,351	7.3	1,160	7.3	191	7.3
Antidiabetics	<6		<6		0	0.0	509	2.7	436	2.7	73	2.8
Osteoporosis treatments (bisphosphonates, SERMs, etc.)	<6		<6		0	0.0	216	1.2	193	1.2	23	0.9
Local (vaginal) hormone treatments	**6**	**85.7**	**6**	**85.7**	0	0.0	2136	11.5	1,755	11.0	381	14.5

Table 49. Baseline clinical characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: UK; source: THIN; Annual Reporting Period III]

	UK											
	Longitudinal database: THIN											
	Reported study period: 31 March 2018 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Prior safety events during 12 months pre-index period: n(%)[1]												
Any safety event (total; any category)	**<6**		**<6**		**0**	**0.0**	**85**	**0.5**	**74**	**0.5**	**11**	**0.4**
History of VTE/stroke/ CHD/ PVD event	<6		<6		0	0.0	42	0.2	35	0.2	7	0.3
History of malignancy potentially associated with oestrogen	<6		<6		0	0.0	7	0.0	6	0.0	<6	
History of any malignancy	<6		<6		0	0.0	41	0.2	37	0.2	<6	
Indication for study medication (main analysis[1,2]												
Oestrogen deficiency symptoms only	<6		<6		0	0.0	2,232	12.1	1,969	12.4	263	10.0
Osteoporosis only	<6		<6		0	0.0	34	0.2	29	0.2	<6	
Oestrogen deficiency symptoms and osteoporosis	<6		<6		0	0.0	6	0.0	<6		<6	
No oestrogen deficiency symptoms or osteoporosis	<6		<6		0	0.0	955	5.2	811	5.1	144	5.5
Missing data on diagnosis	6	85.7	6	85.7	0	0.0	15,295	82.6	~13,081	82.3	2,219	84.3
Indication for study medication (additional analysis)[1,3]												
Oestrogen deficiency symptoms only	<6		<6		0	0.0	3,410	18.4	2,646	16.7	764	29.0
Osteoporosis only	<6		<6		0	0.0	60	0.3	52	0.3	8	0.3
Oestrogen deficiency symptoms and osteoporosis	<6		<6		0	0.0	10	0.1	8	0.1	<6	
No oestrogen deficiency symptoms or osteoporosis	<6		<6		0	0.0	1,877	10.1	1,639	10.3	238	9.0
Missing data on diagnosis	<6		<6		0	0.0	13,165	71.1	11,545	72.7	~1,622	61.6

1. % of total N
2. Time period for analysis: index date ±90 days
3. Time period for analysis: index date –365 days to index date +90 days

"masked", <6: in accordance with THIN privacy protection policies, exact numbers are not reported to maintain anonymity
"~": approximate numbers are presented to maintain anonymity
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy
SERMs: selective oestrogen receptor modulators; CVD: cardiovascular disease; VTE: venous thromboembolism; CHD: coronary heart disease; PVD: peripheral vascular disease

10.4.2.2.5. *Duavive utilization in the UK*

The number of patients in the Duavive cohort was very low (n=7). Therefore, results on daily dose, days supply, and switching cannot be reported.

10.4.2.2.6. *Potential off-label use of Duavive in the UK*

Results on potential off-label use cannot be reported.

10.4.3. UK – Cumulative Period

10.4.3.1. Baseline Characteristics – Cumulative Period - UK

Demographic characteristics of patients prescribed Duavive and E+P HRT for the cumulative period (31 March 2016 to 30 March 2019) in the UK are presented in Table 50.

The number of patients included in the Duavive cohort is very low (n=11). For this reason, most Duavive cohort results and a few results for the E+P HRT cohort are masked to maintain anonymity.

10.4.3.1.1. *Age*

In the Duavive cohort, 6 of 11 patients (54.5%) were 50 years or older. In the E+P HRT cohort 73.5% were ≥50 years, 24.0% were between 40 and 49 years and 2.5% were younger than 40 years. The proportion of the age group ≥50 years was 64.7% in the subgroup with prior E+P HRT treatment and 74.2% in the subgroup without prior E+P HRT treatment.

10.4.3.1.2. *Gender*

No males were prescribed Duavive during the reported study period. In the E+P HRT cohort 6 of the 29,799 patients were male.

10.4.3.1.3. *BMI*

No results on BMI can be reported for the Duavive cohort. BMI values were available for a subset of 8,416 out of 29,799 patients (28.2%) in the E+P HRT cohort. Within this subset, 1.9% of patients were underweight (BMI <18.5), 31.5% were in the normal weight range (BMI ≥18.5 to <25), 32.8% were overweight (BMI ≥25 to <30) and 33.8% were obese (BMI ≥30). Similar proportions occurred in the subgroups with and without prior E+P HRT treatment.

Table 50. Demographic characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: UK; source: THIN; Cumulative Period]

	UK											
	Longitudinal database: THIN											
	Reported study period: 31 March 2016 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients	***11***	***100.0***	***11***	***100.0***	***0***	***0.0***	***29,799***	***100.0***	***27,734***	***100.0***	***2,065***	***100.0***
Age at treatment initiation[1]												
Valid N[2]	*11*	*100.0*	*11*	*100.0*	*0*	*0.0*	*29,799*	*100.0*	*27,734*	*100.0*	*2,065*	*100.0*
<40 years	<6		<6		0	0.0	744	2.5	684	2.5	60	2.9
40 to 49 years	<6		<6		0	0.0	7,140	24.0	6,472	23.3	668	32.3
≥50 years	6	54.5	6	54.5	0	0.0	21,915	73.5	20,578	74.2	1,337	64.7
Gender[1]												
Valid N[2]	*11*	*100.0*	*11*	*100.0*	*0*	*0.0*	*29,799*	*100.0*	*27,734*	*100.0*	*2,065*	*100.0*
Female	11	100.0	11	100.0	0	0.0	29,793	100.0	27,728	100.0	2,065	100.0
Male	0	0.0	0	0.0	0	0.0	6	0.0	6	0.0	0	0.0
Body Mass Index[1]												
Valid N[2]	*<6*		*<6*		*0*	*0.0*	*8,415*	*28.2*	*7,905*	*28.5*	*510*	*24.7*
<18.5: underweight	<6		<6		0	0.0	158	1.9	145	1.8	13	2.5
≥18.5 to <25: normal range	<6		<6		0	0.0	2,650	31.5	2,479	31.4	171	33.5
≥25 to <30: overweight	<6		<6		0	0.0	2,760	32.8	2,588	32.7	172	33.7
≥30: obese	<6		<6		0	0.0	2,847	33.8	2,693	34.1	154	30.2

1. % of Valid N
2. Valid N: patients with non-missing values

<6: in accordance with THIN privacy protection policies, exact numbers masked to maintain anonymity
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.4.3.2. Clinical Characteristics and Duavive Prescribing Patterns – Cumulative Period - UK

Baseline clinical characteristics for the cumulative period (31 March 2016 to 30 March 2019) are presented in Table 51 below.

The number of patients included in the Duavive cohort for the cumulative is very low (n=11). For this reason, most Duavive cohort results and a few results for the E+P HRT cohort are masked to maintain anonymity.

10.4.3.2.1. ***Co-morbidities***

The results on patients' co-morbidities cannot be presented for the Duavive cohort due to the low number of observations. The overall proportion of patients with any of the specified co-morbidities in the E+P HRT study group was 12.1% (12.8% and 12.1% in the subgroups with and without prior E+P HRT treatment). The most frequent co-morbidities were hypertension (6.0% overall, 5.1% in the subgroup with and 6.0% in the subgroup without prior E+P HRT treatment), major depression (3.0% overall, 4.1% in the subgroup with and 2.9% in the subgroup without prior E+P HRT treatment) and osteoarthritis (1.6% overall, 1.4% in the subgroup with and 1.6% in the subgroup without prior E+P HRT treatment). For the other co-morbidities please refer to Table 51.

10.4.3.2.2. ***Co-medication***

In the Duavive cohort, 10 of 11 patients (90.9%) were recorded with at least one prescription of the specified co-medications; 9 of 11 patients (81.8%) received local hormone treatments. Results for other co-medications of interest cannot be reported for privacy protection reasons. In the E+P HRT cohort, at least one prescription of one of the specified co-medications was identified in 55.9% of patients (57.1% in the subgroup with and 55.8% in the subgroup without prior E+P HRT treatment). The most frequently co-prescribed drugs were antidepressants (39.0%), local (vaginal) hormone treatments (11.7%), corticosteroids (8.8%), lipid lowering agents (8.4%), sedatives/hypnotics (8.1%) and anticoagulants (3.3%). For proportions in the subgroups with and without prior E+P HRT treatment please refer to Table 51.

10.4.3.2.3. ***Prior safety events***

The overall proportion of patients with any safety event in the E+P HRT cohort was 0.5% in overall and in subgroups with and without prior E+P HRT treatment. For single categories of prior safety events please refer to Table 51. For the Duavive cohort, the results cannot be presented for confidentiality reasons.

10.4.3.2.4. ***Indication***

The results on indication for use of study medication at index date are presented in Table 51 below.
The main analysis of the period 90 days before and 90 days after index date showed that in the E+P HRT cohort, 15.5% of patients received E+P HRT treatment for oestrogen deficiency symptoms (9.9% in the subgroup with and 15.9% in the subgroup without prior E+P HRT treatment). For 78.6% of all patients in the E+P HRT cohort no diagnosis was documented

(84.5% and 78.1% in the subgroups with and without prior E+P HRT treatment, respectively) and for 5.8% a diagnosis other than oestrogen deficiency symptoms or osteoporosis was documented (5.4% and 5.8% in the subgroups with and without prior E+P HRT treatment, respectively).

An additional analysis of the period 365 days before and 90 days after index date showed a similar prescription pattern for the E+P HRT cohort. In this analysis, the number of patients with missing data on diagnoses in the baseline period was reduced by 3,019 patients (from 23,409 to 20,390).

In the Duavive cohort, 9 of 10 patients (81.8%) were identified as having missing data on diagnoses in the baseline period ± 90 days around index date. In the additional analysis based on extended period of 365 days before and 90 days after index date indication was missing for 7 of 10 patients (63.6%). The results for other indication categories cannot be presented due to privacy protection concerns.

Table 51. Baseline clinical characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: UK; source: THIN; Cumulative Period]

	UK											
	Longitudinal database: THIN											
	Reported study period: 31 March 2016 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients	***11***	***100.0***	***11***	***100.0***	***0***	***0.0***	***29,799***	***100.0***	***27,734***	***100.0***	***2,065***	***100.0***
Relevant co-morbidities during 12 months pre-index period: n(%)[1]												
Any co-morbidity	**<6**		**<6**		**0**	**0.0**	**3,608**	**12.1**	**3,344**	**12.1**	**264**	**12.8**
Osteoporosis/ osteopenia	<6		<6		0	0.0	105	0.4	92	0.3	13	0.6
History of CVD event	<6		<6		0	0.0	22	0.1	22	0.1	<6	
Hyperlipidemia	<6		<6		0	0.0	120	0.4	112	0.4	8	0.4
Hypertension	<6		<6		0	0.0	1,784	6.0	1,677	6.0	106	5.1
Breast pain	<6		<6		0	0.0	298	1.0	270	1.0	28	1.4
Diabetes	<6		<6		0	0.0	132	0.4	127	0.5	<6	
Renal disease	<6		<6		0	0.0	7	0.0	6	0.0	<6	
Osteoarthritis	<6		<6		0	0.0	465	1.6	437	1.6	28	1.4
Major depression	<6		<6		0	0.0	881	3.0	796	2.9	85	4.1
Co-medication during 12 months pre-index period[1]												
Any relevant co-medication	**10**	**90.9**	**10**	**90.9**	**0**	**0.0**	**16,644**	**55.9**	**15,464**	**55.8**	**1,180**	**57.1**
Corticosteroids	<6		<6		0	0.0	2,631	8.8	2,451	8.8	180	8.7
Lipid lowering agents	<6		<6		0	0.0	2,492	8.4	2,359	8.5	133	6.4
Anti-hypertensives	<6		<6		0	0.0	206	0.7	196	0.7	10	0.5
Anticoagulants	<6		<6		0	0.0	978	3.3	941	3.4	37	1.8
Antiarrhythmics	<6		<6		0	0.0	484	1.6	461	1.7	23	1.1
Antidepressants	<6		<6		0	0.0	11,625	39.0	10,802	38.9	823	39.9
Sedatives/ hypnotics	<6		<6		0	0.0	2,401	8.1	2,225	8.0	176	8.5
Antidiabetics	<6		<6		0	0.0	830	2.8	770	2.8	60	2.9
Osteoporosis treatments (bisphosphonates, SERMs, etc)	<6		<6		0	0.0	346	1.2	328	1.2	18	0.9
Local (vaginal) hormone treatments	9	81.8	9	81.8	0	0.0	3,475	11.7	3,211	11.6	264	12.8

Table 51. Baseline clinical characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: UK; source: THIN; Cumulative Period]

	UK											
	Longitudinal database: THIN											
	Reported study period: 31 March 2016 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Prior safety events during 12 months pre-index period: n(%)[1]												
Any safety event (total; any category)	**<6**		**<6**		**0**	**0.0**	**138**	**0.5**	**128**	**0.5**	**10**	**0.5**
History of VTE/stroke/ CHD/ PVD event	<6		<6		0	0.0	62	0.2	58	0.2	<6	
History of malignancy potentially associated with oestrogen	<6		<6		0	0.0	10	0.0	10	0.0	<6	
History of any malignancy	<6		<6		0	0.0	74	0.2	68	0.2	6	0.3
Indication for study medication (main analysis)[1,2]												
Oestrogen deficiency symptoms only	<6		<6		0	0.0	4,616	15.5	4,412	15.9	204	9.9
Osteoporosis only	<6		<6		0	0.0	50	0.2	47	0.2	<6	
Oestrogen deficiency symptoms and osteoporosis	<6		<6		0	0.0	10	0.0	9	0.0	<6	
No oestrogen deficiency symptoms or osteoporosis	<6		<6		0	0.0	1,714	5.8	1,602	5.8	112	5.4
Missing data on diagnosis	9	81.8	9	81.8	0	0.0	23,409	78.6	21,664	78.1	1745	84.5
Indication for study medication (additional analysis)[1,3]												
Oestrogen deficiency symptoms only	<6		<6		0	0.0	6,072	20.4	5,483	19.8	589	28.5
Osteoporosis only	<6		<6		0	0.0	93	0.3	85	0.3	8	0.4
Oestrogen deficiency symptoms and osteoporosis	<6		<6		0	0.0	28	0.1	20	0.1	8	0.4
No oestrogen deficiency symptoms or osteoporosis	<6		<6		0	0.0	3,216	10.8	3,010	10.9	206	10.0
Missing data on diagnosis	7	63.6	7	63.6	0	0.0	20,390	68.4	19,136	69.0	1,254	60.7

1. % of total N
2. Time period for analysis: index date ±90 days

Table 51. Baseline clinical characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: UK; source: THIN; Cumulative Period]

	UK											
	Longitudinal database: THIN											
	Reported study period: 31 March 2016 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%

3. Time period for analysis: index date – 365 days to index date +90 days
<6: masked to maintain anonymity in accordance with THIN privacy protection policies
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy
SERMs: selective oestrogen receptor modulators; CVD: cardiovascular disease; VTE: venous thromboembolism; CHD: coronary heart disease; PVD: peripheral vascular disease

10.4.3.2.5. *Duavive utilization in the UK*

The number of patients in the Duavive cohort was very low (n=11); therefore, the results of these analyses cannot be reported.

10.4.3.2.6. *Off-label use of Duavive in the UK*

Results on off-label use cannot be reported.

10.5. Results for France

10.5.1. Participants

The number of eligible patients in France is shown below in Table 52, and the number with and without E+P HRT treatment during the 12 months prior to index date is shown in Table 53. In the Annual Reporting Period III, no Duavive prescriptions were identified in the database. In the cumulative period, 22 (73.3%) of overall 30 patients prescribed Duavive were eligible for analysis; prior use of E+P HRT was reported for 22.7% of them. In the E+P HRT study cohort, 15,217 (83.8%) of 18,158 patients were included in the analysis for Annual Reporting Period III and 29,047 (76.0%) of 38,212 patients for cumulative period. The proportion of eligible patients with E+P HRT records during 12 months prior to index date was 36.3% and 20.5% in the annual and cumulative periods, respectively.

Table 52. Patient study eligibility in France

	France			
	Longitudinal database: LPD			
	Annual Reporting Period III		Cumulative period	
	n	%	n	%
Duavive cohort				
Total patients with at least 1 Duavive prescription during the study period	0	0.0	30	100.0
Excluded: Patients not enrolled in the data source for at least 12 months prior to their index date[1]			8	26.7
Excluded: Duavive prescription within 12 months prior to index date[1]			0	0.0
Total eligible patients in analysis for reporting period[1]	**0**	**0.0**	**22**	**73.3**
E+P HRT cohort				
Total patients with at least 1 prescription E+P HRT during study period	18,158	100.0	38,212	100.0
Excluded: Patients were not enrolled in the data source for at least 12 months prior to their index date[1]	2,931	16.1	9,165	24.0
Excluded: Duavive prescription within 12 months prior to index date[1]	10	0.1	0	0.0
Total eligible patients in analysis for reporting period[1]	**15,217**	**83.8**	**29,047**	**76.0**

1. % of N patients with at least one prescription of study medication (Duavive or E+P HRT, respectively)
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

Table 53. Patients with and without E+P HRT treatment during the 12 months prior to index date (France)

	France			
	Longitudinal database: LPD			
	Annual Reporting Period III		Cumulative period	
	n	%	n	%
Duavive cohort				
Total eligible patients in analysis for reporting period	**0**	**0.0**	**22**	**100.0**
Included: with E+P HRT during 12 months pre-index[1]			5	22.7
Included: without E+P HRT during 12 months pre-index[1]			17	77.3
E+P HRT cohort				
Total eligible patients in analysis for reporting period	**15,217**	**100.0**	**29,047**	**100.0**
Included: with E+P HRT during 12 months pre-index[1]	5,519	36.3	5,945	20.5
Included: without E+P HRT during 12 months pre-index[1]	9,698	64.7	23,102	79.5

1. % of N patients with at least one prescription of study medication (Duavive or E+P HRT, respectively)
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.5.2. France – Annual Reporting Period III

10.5.2.1. Baseline Characteristics – Annual Reporting Period III - France

No prescriptions for Duavive were identified in the data source for this study period. Demographic characteristics of patients prescribed E+P HRT are presented in Table 54.

10.5.2.1.1. ***Age***

In the E+P HRT cohort 83.0% were ≥ 50 years, 9.6% were between 40 and 49 years and 7.4% were younger than 40 years. The proportion of the age group ≥50 years was 90.8% in the subgroup with prior E+P HRT treatment and 78.6% in the subgroup without prior E+P HRT treatment.

10.5.2.1.2. ***Gender***

Overall, 0.4% of patients were male in the E+P HRT cohort. The proportion of male patients was 0.3% in the subgroup with prior E+P HRT treatment and 0.4% in the subgroup without prior E+P HRT treatment.

10.5.2.1.3. ***BMI***

BMI values were available for a subset of 2,770 out of 15,217 patients (18.2%) in the E+P HRT cohort. Within this subset, 4.8% of patients were underweight (BMI <18.5), 59.0% were in the normal weight range (BMI ≥18.5 to <25), 24.4% were overweight (BMI ≥ 25 to <30) and 11.8% were obese (BMI ≥30). Similar proportions were shown in subgroups with and without E+P HRT prior treatment.

Table 54. Demographic characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: France; source: LPD; Annual Reporting Period III]

	France											
	Longitudinal database: LPD											
	Reported study period: 31 March 2018 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients	***0***	***0.0***	***0***	***0.0***	***0***	***0.0***	***15,217***	***100.0***	***9,698***	***100.0***	***5,519***	***100.0***
Age at treatment initiation[1]												
Valid N[2]	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*	*15,212*	*100.0*	*9,693*	*99.9*	*5,519*	*100.0*
<40 years	0	0.0	0	0.0	0	0.0	1,125	7.4	9,67	10.0	158	2.9
40 to 49 years	0	0.0	0	0.0	0	0.0	1,458	9.6	1,109	11.4	349	6.3
≥50 years	0	0.0	0	0.0	0	0.0	12,629	83.0	7,617	78.6	5,012	90.8
Gender[1]												
Valid N[2]	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*	*15,217*	*100.0*	*9,698*	*100.0*	*5,519*	*100.0*
Female	0	0.0	0	0.0	0	0.0	15,156	99.6	9,656	99.6	5,500	99.7
Male	0	0.0	0	0.0	0	0.0	61	0.4	42	0.4	19	0.3
Body Mass Index[1]												
Valid N[2]	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*	*2,770*	*18.2*	*1,725*	*17.8*	*1,045*	*18.9*
<18.5: underweight	0	0.0	0	0.0	0	0.0	133	4.8	83	4.8	50	4.8
≥18.5 to <25: normal range	0	0.0	0	0.0	0	0.0	1,634	59.0	1,000	58.0	634	60.7
≥25 to <30: overweight	0	0.0	0	0.0	0	0.0	675	24.4	437	25.3	238	22.8
≥30: obese	0	0.0	0	0.0	0	0.0	328	11.8	205	11.9	123	11.8

1. % of Valid N
2. Valid N: patients with non-missing values

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.5.2.2. Clinical Characteristics and Duavive Prescribing Patterns – Annual Reporting Period III - France

No prescriptions for Duavive were identified in the data source for Annual Reporting Period III. Baseline clinical characteristics for the E+P HRT study group are presented in Table 55 below.

10.5.2.2.1. ***Co-morbidities***

The overall proportion of patients with any of the specified co-morbidities in the E+P HRT cohort was 14.8% (21.8% and 10.8% in subgroups with and without prior treatment with E+P HRT). The most frequent co-morbidities in the E+P HRT cohort were hypertension

(7.0% in the overall cohort, 11.6% in patients with and 4.4% in patients without prior E+P HRT), osteoarthritis (3.7% in overall, 6.3% in subgroup with and 2.2% in subgroup without prior E+P HRT) and osteoporosis/ osteopenia (overall 3.7%; 4.4% in subgroup with and 3.3% in subgroup without prior E+P HRT). For the other co-morbidities please refer to Table 55.

10.5.2.2.2. ***Co-medication***

In the E+P HRT cohort, at least one prescription of one of the specified co-medications was identified in 31.8% of patients (36.8% in the subgroup with prior E+P HRT treatment and 28.9% in the subgroup without). The most frequently co-prescribed drugs were local (vaginal) hormone treatments (15.4%), corticosteroids (7.2%), antidepressants (6.4%), lipid lowering agents (5.2%) and sedatives/hypnotics (3.8%). For proportions in the subgroups with and without prior E+P HRT treatment please refer to Table 55.

10.5.2.2.3. ***Prior safety events***

The overall proportion of patients with any safety event in the E+P HRT cohort was 1.3% (1.4% in the subgroup with prior E+P HRT and 1.2% in the subgroup without). For single categories of prior safety events please refer to Table 55.

10.5.2.2.4. ***Indication***

The results on indication for use of study medication at index date are presented in Table 55 below.

Analysis of the period 90 days before and 90 days after index date showed that in the E+P HRT cohort, 44.1% of patients received E+P HRT for oestrogen deficiency symptoms (50.6% in the subgroup with prior E+P HRT treatment and 40.4% in the subgroup without). The overall proportion of patients who were prescribed E+P HRT for osteoporosis only was 2.1% and for both oestrogen deficiency symptoms and osteoporosis 1.4%. For 52.5% of all patients in the E+P HRT cohort, no diagnosis or a diagnosis other than oestrogen deficiency symptoms or osteoporosis was documented. The corresponding values were 45.5% in the subgroup with and 56.4% in the subgroup without prior treatment with E+P HRT.

An additional analysis of the period 365 days before and 90 days after index date in the E+P HRT cohort showed the similar prescription pattern as the analysis for index date ± 90 days.

Table 55. Baseline clinical characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: France; source: LPD; Annual Reporting Period III]

	France											
	Longitudinal database: LPD											
	Reported study period: 31 March 2018 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients	***0***	***0.0***	***0***	***0.0***	***0***	***0.0***	***15,217***	***100.0***	***9,698***	***100.0***	***5,519***	***100.0***
Co-morbidities during 12 months pre-index period[1]												
Any co-morbidity	**0**	**0.0**	**0**	**0.0**	**0**		**2,252**	**14.8**	**1,051**	**10.8**	**1,201**	**21.8**
Osteoporosis/ osteopenia	0	0.0	0	0.0	0		565	3.7	323	3.3	242	4.4
History of CVD event	0	0.0	0	0.0	0		20	0.1	10	0.1	10	0.2
Hyperlipidemia	0	0.0	0	0.0	0		149	1.0	58	0.6	91	1.6
Hypertension	0	0.0	0	0.0	0		1,068	7.0	426	4.4	642	11.6
Breast pain	0	0.0	0	0.0	0		216	1.4	135	1.4	81	1.5
Diabetes	0	0.0	0	0.0	0		193	1.3	88	0.9	105	1.9
Renal disease	0	0.0	0	0.0	0		14	0.1	9	0.1	5	0.1
Osteoarthritis	0	0.0	0	0.0	0		564	3.7	215	2.2	349	6.3
Major depression	0	0.0	0	0.0	0		39	0.3	15	0.2	24	0.4
Co-medication during 12 months pre-index period[1]												
Any co-medication	**0**	**0.0**	**0**	**0.0**	**0**		**4,834**	**31.8**	**2,804**	**28.9**	**2,030**	**36.8**
Corticosteroids	0	0.0	0	0.0	0		1,098	7.2	568	5.9	530	9.6
Lipid lowering agents	0	0.0	0	0.0	0		789	5.2	309	3.2	480	8.7
Anti-hypertensives	0	0.0	0	0.0	0		43	0.3	21	0.2	22	0.4
Anticoagulants	0	0.0	0	0.0	0		411	2.7	182	1.9	229	4.1
Antiarrhythmics	0	0.0	0	0.0	0		142	0.9	56	0.6	86	1.6
Antidepressants	0	0.0	0	0.0	0		974	6.4	450	4.6	524	9.5
Sedatives/ hypnotics	0	0.0	0	0.0	0		584	3.8	277	2.9	307	5.6
Antidiabetics	0	0.0	0	0.0	0		197	1.3	86	0.9	111	2.0
Osteoporosis treatments (bisphosphonates, SERMs, etc)	0	0.0	0	0.0	0		151	1.0	71	0.7	80	1.4
Local (vaginal) hormone treatments	0	0.0	0	0.0	0		2,350	15.4	1,666	17.2	684	12.4

Table 55. Baseline clinical characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: France; source: LPD; Annual Reporting Period III]

	France											
	Longitudinal database: LPD											
	Reported study period: 31 March 2018 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Prior safety events during 12 months pre-index period[1]												
Any safety event (total; any category)	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**	**195**	**1.3**	**118**	**1.2**	**77**	**1.4**
History of VTE/stroke/ CHD/ PVD event	0	0.0	0	0.0	0	0.0	62	0.4	29	0.3	33	0.6
History of malignancy potentially associated with oestrogen	0	0.0	0	0.0	0	0.0	62	0.4	49	0.5	13	0.2
History of any malignancy	0	0.0	0	0.0	0	0.0	137	0.9	90	0.9	47	0.9
Indication for study medication (main analysis[1,2]												
Oestrogen deficiency symptoms only	0	0.0	0	0.0	0	0.0	6,708	44.1	3,918	40.4	2,790	50.6
Osteoporosis only	0	0.0	0	0.0	0	0.0	318	2.1	191	2.0	127	2.3
Oestrogen deficiency symptoms and osteoporosis	0	0.0	0	0.0	0	0.0	209	1.4	119	1.2	90	1.6
No oestrogen deficiency symptoms or osteoporosis or missing	0	0.0	0	0.0	0	0.0	7,982	52.5	5,470	56.4	2,512	45.5
Indication for study medication (additional analysis)[1,3]	0	0.0	0	0.0	0	0.0						
Oestrogen deficiency symptoms only	0	0.0	0	0.0	0	0.0	6,927	45.5	4,007	41.3	2,920	52.9
Osteoporosis only	0	0.0	0	0.0	0	0.0	338	2.2	200	2.1	138	2.5
Oestrogen deficiency symptoms and osteoporosis	0	0.0	0	0.0	0	0.0	245	1.6	136	1.4	109	2.0
No oestrogen deficiency symptoms or osteoporosis or missing	0	0.0	0	0.0	0	0.0	7,707	50.6	5,355	55.2	2,352	42.6

1. % of total N

Table 55. Baseline clinical characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: France; source: LPD; Annual Reporting Period III]

	France											
	Longitudinal database: LPD											
	Reported study period: 31 March 2018 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%

2. Time period for analysis: index date ±90 days
3. Time period for analysis: index date – 365 days to index date +90 days

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy
SERMs: selective oestrogen receptor modulators; CVD: cardiovascular disease; VTE: venous thromboembolism; CHD: coronary heart disease; PVD: peripheral vascular disease

10.5.2.2.5. *Duavive utilization in France*

Analysis of Duavive utilization was not performed because no prescriptions for Duavive were identified in the data source for this period.

10.5.2.2.6. *Potential off-label use of Duavive in France*

Potential off-label use of Duavive was not analysed because no prescriptions for Duavive were identified in the data source for this period.

10.5.3. France – Cumulative Period

10.5.3.1. Baseline Characteristics – Cumulative Period - France

Demographic characteristics of patients prescribed Duavive and E+P HRT for the cumulative period (31 March 2016 to 30 March 2019) are presented in Table 56. Overall, the number of patients in the Duavive cohort was low (n=22).

10.5.3.1.1. *Age*

In the Duavive cohort 81.8% of patients were 50 years or older, 18.2% were 40 to 49 years and no patients were younger than 40 years.

In the E+P HRT cohort 76.8% were ≥ 50 years, 12.0% were between 40 and 49 years and 11.2% were younger than 40 years. The proportion of the age group ≥50 years was 90.3% in the subgroup with prior E+P HRT treatment and 73.4% in the subgroup without prior E+P HRT treatment.

10.5.3.1.2. *Gender*

No males were prescribed Duavive during the cumulative study period. Overall, 0.4% of patients were male in the E+P HRT cohort. The proportion of male patients was 0.3% in the

subgroup with prior E+P HRT treatment and 0.4% in the subgroup without prior E+P HRT treatment.

10.5.3.1.3. ***BMI***

BMI values were available for a subset of 5 out of 22 patients (22.7%) in the Duavive cohort: 3 patients (60.0%) had a BMI indicating normal weight and 2 patients (40.0%) were categorised as overweight.

BMI values were available for a subset of 5,273 out of 29,047 patients (18.2%) in the E+P HRT cohort. Within this subset, 5.3% of patients were underweight (BMI <18.5), 57.5% were in the normal weight range (BMI ≥18.5 to < 25), 25.2% were overweight (BMI ≥ 25 to < 30) and 12.0% were obese (BMI ≥30). Similar proportions were shown in subgroups with and without E+P HRT prior treatment.

Table 56. Demographic characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: France; source: LPD; Cumulative Period]

	France											
	Longitudinal database: LPD											
	Reported study period: 31 March 2016 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients	***22***	***100.0***	***17***	***100.0***	***5***	***100.0***	***29,047***	***100.0***	***23,102***	***100.0***	***5,945***	***100.0***
Age at treatment initiation[1]												
Valid N[2]	*22*	*100.0*	*17*	*100.0*	*5*	*100.0*	*29,042*	*100.0*	*23,097*	*100.0*	*5,945*	*100.0*
<40 years	0	0.0	0	0.0	0	0.0	3,257	11.2	3,080	13.3	177	3.0
40 to 49 years	4	18.2	3	17.6	1	20.0	3,472	12.0	3,075	13.3	397	6.7
≥50 years	18	81.8	14	82.4	4	80.0	22,313	76.8	16,942	73.4	5,371	90.3
Gender[1]												
Valid N[2]	*22*	*100.0*	*17*	*100.0*	*5*	*100.0*	*29,047*	*100.0*	*23,102*	*100.0*	*5,945*	*100.0*
Female	22	100.0	17	100.0	5	100.0	28,930	99.6	23,000	99.6	5,930	99.7
Male	0	0.0	0	0.0	0	0.0	117	0.4	102	0.4	15	0.3
Body Mass Index[1]												
Valid N[2]	*5*	*22.7*	*4*	*23.5*	*1*	*20.0*	*5,273*	*18.2*	*4,192*	*18.1*	*1,081*	*18.2*
<18.5: underweight	0	0.0	0	0.0	0	0.0	279	5.3	223	5.3	56	5.2
≥18.5 to <25: normal range	3	60.0	2	50.0	1	100.0	3,032	57.5	2,368	56.5	664	61.4
≥25 to <30: overweight	2	40.0	2	50.0	0	0.0	1,327	25.2	1,075	25.6	252	23.3
≥30: obese	0	0.0	0	0.0	0	0.0	635	12.0	526	12.5	109	10.1

1. % of Valid N

Table 56. Demographic characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: France; source: LPD; Cumulative Period]

2. Valid N: patients with non-missing values
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.5.3.2. Clinical Characteristics and Duavive Prescribing Patterns – Cumulative Period - France

Baseline clinical characteristics for the cumulative period (31 March 2016 to 30 March 2019) are presented in Table 57 below.

10.5.3.2.1. *Co-morbidities*

One patient (4.5%) in the Duavive cohort was recorded with a co-morbidity in the cumulative period. The overall proportion of patients with any of the specified co-morbidities in the E+P HRT study cohort was 14.7% (22.2% and 12.8% in the subgroups with and without prior treatment with E+P HRT). The most frequent co-morbidities in the E+P HRT cohort were hypertension (6.8% overall, 11.1% in patients with and 5.7% in patients without prior E+P HRT treatment), osteoarthritis (3.9% overall, 7.0% in subgroups with and 3.1% in subgroups without prior E+P HRT treatment) and osteoporosis/ osteopenia (overall 3.5%; 4.9% in subgroup with and 3.1% in subgroups without prior E+P HRT treatment). For the other co-morbidities please refer to Table 57.

10.5.3.2.2. *Co-medication*

In the Duavive cohort at least one prescription of specified co-medications during the 12-month pre-index period was identified in 31.8% of patients. The co-prescribed drugs were local (vaginal) hormone treatments (18.2%), antidepressants (9.1%), corticosteroids (4.5%), lipid lowering agents (4.5%) and osteoporosis treatment (4.5%).

In the E+P HRT cohort, at least one prescription of one of the specified co-medications was identified in 31.5% of patients (35.4% in the subgroup with and 30.5% in the subgroup without prior E+P HRT treatment). The most frequently co-prescribed drugs were local (vaginal) hormone treatments (14.9%), corticosteroids (7.4%), antidepressants (6.5%), sedatives/hypnotics (5.1%) and lipid lowering agents (5.1%).

For proportions in the subgroups with and without prior E+P HRT treatment please refer to Table 57.

10.5.3.2.3. *Prior safety events*

No prior safety events during 12-month pre-index period were identified in the Duavive cohort. The overall proportion of patients with any safety event in the E+P HRT cohort was 1.3% (1.5% in the subgroup with prior E+P HRT treatment and 1.3% in the subgroup without). For single categories of prior safety events please refer to Table 57.

10.5.3.2.4. *Indication*

The results on indication for use of study medication at index date are presented in Table 57 below.

Analysis of the period 90 days before and 90 days after index date showed that Duavive was prescribed for oestrogen deficiency symptoms in 72.7% of patients. For the other patients (27.3%) no diagnoses of oestrogen deficiency symptoms and/ or osteoporosis were documented. These proportions were similar in the subgroup without prior E+P HRT treatment. In 76.5% of patients indication for Duavive was oestrogen deficiency symptoms and in 23.5% of patients no diagnoses of oestrogen deficiency symptoms and/ or osteoporosis were identified. In the subgroup with prior E+P HRT treatment in 60.0% of patients Duavive was prescribed for oestrogen deficiency symptoms and in 40.0% of patients there were no diagnoses of oestrogen deficiency symptoms and/ or osteoporosis documented.

In the E+P HRT cohort, 40.2% of patients received E+P HRT treatment for oestrogen deficiency symptoms (52.4% in the subgroup with prior E+P HRT treatment and 37.0% in the subgroup without). The overall proportion of patients who were prescribed E+P HRT for osteoporosis only was 2.0% and for both oestrogen deficiency symptoms and osteoporosis 1.2%. For 56.7% of all patients in the E+P HRT cohort, no diagnosis or a diagnosis other than oestrogen deficiency symptoms or osteoporosis was documented. The corresponding values were 43.6% in the subgroup with and 60.0% in the subgroup without prior E+P HRT treatment.

An additional analysis of the period 365 days before and 90 days after index date showed the same indication pattern for the Duavive cohort as the analysis for index date ±90 days. In the E+P HRT cohort the distribution among the indications was also similar when comparing the two analyses. The number of patients with "no oestrogen deficiency symptoms or osteoporosis or missing diagnoses" in the baseline period was reduced by 532 patients (from 16,459 to 15,927).

Table 57. Baseline clinical characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: France; source: LPD; Cumulative Period]

	France											
	Longitudinal database: LPD											
	Reported study period: 31 March 2016 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients	***22***	***100.0***	***17***	***100.0***	***5***	***100.0***	***29,047***	***100.0***	***23,102***	***100.0***	***5,945***	***100.0***
Co-morbidities during 12 months pre-index period[1]												
Any co-morbidity	**1**	**4.5**	**1**	**5.9**	**0**	**0.0**	**4,266**	**14.7**	**2,948**	**12.8**	**1,318**	**22.2**
Osteoporosis/ osteopenia	0	0.0	0	0.0	0	0.0	1,008	3.5	719	3.1	289	4.9

Table 57. Baseline clinical characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: France; source: LPD; Cumulative Period]

	France											
	Longitudinal database: LPD											
	Reported study period: 31 March 2016 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
History of CVD event	0	0.0	0	0.0	0	0.0	50	0.2	40	0.2	10	0.2
Hyperlipidemia	1	4.5	1	5.9	0	0.0	258	0.9	168	0.7	90	1.5
Hypertension	1	4.5	1	5.9	0	0.0	1,979	6.8	1,319	5.7	660	11.1
Breast pain	0	0.0	0	0.0	0	0.0	472	1.6	389	1.7	83	1.4
Diabetes	0	0.0	0	0.0	0	0.0	358	1.2	256	1.1	102	1.7
Renal disease	0	0.0	0	0.0	0	0.0	32	0.1	23	0.1	9	0.2
Osteoarthritis	0	0.0	0	0.0	0	0.0	1,127	3.9	710	3.1	417	7.0
Major depression	0	0.0	0	0.0	0	0.0	70	0.2	40	0.2	30	0.5
Co-medication during 12 months pre-index period[1]												
Any co-medication	**7**	**31.8**	**5**	**29.4**	**2**	**40.0**	**9,144**	**31.5**	**7,040**	**30.5**	**2,104**	**35.4**
Corticosteroids	1	4.5	0	0.0	1	20.0	2,152	7.4	1,599	6.9	553	9.3
Lipid lowering agents	1	4.5	1	5.9	0	0.0	1,473	5.1	929	4.0	544	9.2
Anti-hypertensives	0	0.0	0	0.0	0	0.0	88	0.3	63	0.3	25	0.4
Anticoagulants	0	0.0	0	0.0	0	0.0	744	2.6	499	2.2	245	4.1
Antiarrhythmics	0	0.0	0	0.0	0	0.0	287	1.0	193	0.8	94	1.6
Antidepressants	2	9.1	1	5.9	1	20.0	1,894	6.5	1,327	5.7	567	9.5
Sedatives/ hypnotics	0	0.0	0	0.0	0	0.0	1,470	5.1	1,001	4.3	469	7.9
Antidiabetics	0	0.0	0	0.0	0	0.0	378	1.3	266	1.2	112	1.9
Osteoporosis treatments (bisphosphonates, SERMs, etc)	1	4.5	1	5.9	0	0.0	312	1.1	203	0.9	109	1.8
Local (vaginal) hormone treatments	4	18.2	3	17.6	1	20.0	4,325	14.9	3,729	16.1	596	10.0

Table 57. Baseline clinical characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: France; source: LPD; Cumulative Period]

	France											
	Longitudinal database: LPD											
	Reported study period: 31 March 2016 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Prior safety events during 12 months pre-index period[1]												
Any safety event (total; any category)	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**	**385**	**1.3**	**297**	**1.3**	**88**	**1.5**
History of VTE/stroke/ CHD/ PVD event	0	0.0	0	0.0	0	0.0	147	0.5	105	0.5	42	0.7
History of malignancy potentially associated with oestrogen	0	0.0	0	0.0	0	0.0	106	0.4	96	0.4	10	0.2
History of any malignancy	0	0.0	0	0.0	0	0.0	242	0.8	196	0.8	46	0.8
Indication for study medication (main analysis[1,2]												
Oestrogen deficiency symptoms only	16	72.7	13	76.5	3	60.0	11,670	40.2	8,557	37.0	3,113	52.4
Osteoporosis only	0	0.0	0	0.0	0	0.0	569	2.0	434	1.9	135	2.3
Oestrogen deficiency symptoms and osteoporosis	0	0.0	0	0.0	0	0.0	349	1.2	242	1.0	107	1.8
No oestrogen deficiency symptoms or osteoporosis or missing	6	27.3	4	23.5	2	40.0	16,459	56.7	13,869	60.0	2,590	43.6
Indication for study medication (additional analysis)[1,3]												
Oestrogen deficiency symptoms only	16	72.7	13	76.5	3	60.0	12,073	41.6	8,803	38.1	3,270	55.0
Osteoporosis only	0	0.0	0	0.0	0	0.0	612	2.1	473	2.0	139	2.3
Oestrogen deficiency symptoms and osteoporosis	0	0.0	0	0.0	0	0.0	435	1.5	280	1.2	155	2.6
No oestrogen deficiency symptoms or osteoporosis or missing	6	27.3	4	23.5	2	40.0	15,927	54.8	13,546	58.6	2,381	40.1

1. % of total N
2. Time period for analysis: index date ±90 days
3. Time period for analysis: index date – 365 days to index date +90 days

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy
SERMs: selective oestrogen receptor modulators; CVD: cardiovascular disease; VTE: venous thromboembolism; CHD: coronary heart disease; PVD: peripheral vascular disease

10.5.3.2.5. ***Duavive utilization in France***

The results on Duavive utilization between 31 March 2016 and 30 March 2019 based on index prescription are presented in Table 58 below.

10.5.3.2.5.1. Daily dose

Daily dose recommendation was available for 3 out of 22 index Duavive prescriptions (13.6%). The standard recommended dose (1 tablet per day) was documented in all 3 cases.

10.5.3.2.5.2. Days supply

In the analysis based on prescriptions with known daily dose, mean days supply was 180.0 days overall and varied between 150.0 and 186.0 days in the subgroups with and without E+P HRT prior treatment, respectively. The duration ranged from 120 to 300 days.

After imputation to set missing values to the standard Duavive dose and supply, the mean duration was 122.9 days (114.0 days and 125.5 days in subgroups with and without prior E+P HRT treatment, respectively). The duration ranged from 28 to 300 days.

10.5.3.2.5.3. Switchers from E+P HRT to Duavive

In total, 18.2% of the patients with Duavive prescriptions had switched from prior E+P HRT treatment.

Table 58. Duavive utilization; Overall and Stratified by Prior E+P HRT Treatment; prescription-level analysis [country: France; source: LPD; Cumulative Period]

	France					
	Longitudinal database: LPD					
	Reported study period: 31 March 2016 to 30 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Total number of patients with index prescription	***22***	***100.0***	***17***	***100.0***	***5***	***100.0***
Number of (index) prescriptions with instruction on daily dosage available	**3**	**13.6**	**2**	**11.8**	**1**	**20.0**
Daily dose						
A. Analysis as reported (missing data on daily dose instruction not replaced)[1]						
1 tablet	3	100.0	2	100.0	1	100.0
<1 tablet	0	0.0	0	0.0	0	0.0
>1 tablet	0	0.0	0	0.0	0	0.0
B. Analysis based on all index prescriptions (missing data replaced)[2]						
1 tablet	22	100.0	17	100.0	5	100.0
<1 tablet	0	0.0	0	0.0	0	0.0
>1 tablet	0	0.0	0	0.0	0	0.0
Days supply						
A. Analysis as reported (missing data not replaced)[1]						
Mean (SD)	180.0 (68.4)		186.0 (74.7)		150.0 (.)	
Median	165.0		180.0		150.0	
Minimum – maximum	(120.0,300.0)		(120.0,300.0)		(150.0,150.0)	
B. Analysis based on all index prescriptions (missing data replaced)[2]						
Mean (SD)	122.9 (82.4)		125.5 (88.7)		114.0 (63.9)	
Median	112.0		112.0		112.0	
Minimum - maximum	(28.0,300.0)		(28.0,300.0)		(28.0,196.0)	
Switchers from E+P HRT to Duavive[2,3]	**4**	**18.2**	**n.appl.**		**4**	**80.0**

1. Based on N index prescriptions with instruction on daily dosage available
2. Based on total N index prescriptions
3. Switch: prescription of Duavive within 30 days following the end of the last filled prescription period of E+P HRT

SD: standard deviation; n.appl.: not applicable
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.5.3.2.6. *Potential off-label use of Duavive in France*

The results for potential off-label use of Duavive from the main analysis (see Sections 9.4.5, 9.9.4) for the reporting period from 31 March 2016 to 30 March 2019 are presented in Table 59.

Potential off-label use was identified in 2 of 22 (9.1%) Duavive users. The reason for the potential off-label use was presumed premenopausal age of ≤45 years. After changing the presumed premenopausal age limit from 45 years to 49 years (sensitivity analyses I and III), the proportion of potential off-label users increased to 18.2% (4 patients). Proportion of potential off-label use was identical in the main analysis and sensitivity analyses I and III because no patients with indication osteoporosis and oestrogen deficiency symptoms were identified in the data source (Table 60).

Table 59. Potential off-label use of Duavive; Overall and Stratified by Prior E+P HRT Treatment; patient-level analysis [country: France; source: LPD; Cumulative Period]

	France					
	Longitudinal database: LPD					
	Reported study period: 31 March 2016 to 30 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Total number of patients	***22***	***100.0***	***17***	***100.0***	***5***	***100.0***
Off-label use (total; any category)[1,2]	**2**	**9.1**	**2**	**11.8**	**0**	**0.0**
Patients with single categories of off-label use						
Use for treatment of osteoporosis only[3]	0	0.0	0	0.0	0	0.0
Valid N	*22*		*17*		*5*	
Use in women ≤45 years[3]	2	9.1	2	11.8	0	0.0
Valid N	*22*		*17*		*5*	
Use in women over 75 years old[3]	0	0.0	0	0.0	0	0.0
Valid N	*22*		*17*		*5*	
Use in males[3]	0	0.0	0	0.0	0	0.0
Valid N	*22*		*17*		*5*	
Prescription of non-approved dose or regimen[3]	0	0.0	0	0.0	0	0.0
Valid N	*3*		*2*		*1*	
Use with progestins, additional oestrogens or selective oestrogen receptor modulators (SERMs)[1]	0	0.0	0	0.0	0	0.0
Use in women without a uterus (hysterectomised women)[1]	0	0.0	0	0.0	0	0.0
Known, suspected, or past history of breast cancer[1]	0	0.0	0	0.0	0	0.0
Hypersensitivity (e.g., anaphylaxis/anaphylactic reactions, urticaria, drug eruption) to the active substances or to any of the excipients[1]	0	0.0	0	0.0	0	0.0
Malignancy potentially associated with oestrogen[1]	0	0.0	0	0.0	0	0.0
Active or past history of venous thromboembolism (deep venous thrombosis, pulmonary embolism, and retinal vein thrombosis)[1]	0	0.0	0	0.0	0	0.0
Active or past history of arterial thromboembolic disease (e.g., myocardial infarction, stroke)[1]	0	0.0	0	0.0	0	0.0
Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal[1]	0	0.0	0	0.0	0	0.0

Table 59. Potential off-label use of Duavive; Overall and Stratified by Prior E+P HRT Treatment; patient-level analysis [country: France; source: LPD; Cumulative Period]

	France					
	Longitudinal database: LPD					
	Reported study period: 31 March 2016 to 30 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Known thrombophilic disorders (e.g., protein C, protein S, or antithrombin deficiency)[1]	0	0.0	0	0.0	0	0.0
Porphyria[1]	0	0.0	0	0.0	0	0.0

Valid N: patients with non-missing values in respective category
1. % of total N patients
2. Patients with off-label use in any category mentioned below
3. % of valid N in respective category (listed below)

Age ⩽45 years considered as proxy for premenopausal status (Section 9.4.5)
Patients can be in more than one category of potential off-label use
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy;
SERMs: selective oestrogen receptor modulators

Table 60. Sensitivity analyses for potential off-label use of Duavive; Overall and Stratified by Prior E+P HRT Treatment; patient-level analysis [country: France; source: LPD; Cumulative Period]

	France					
	Longitudinal database: LPD					
	Reported study period: 31 March 2016 to 30 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Total number of patients during reported period	***22***		***17***		***5***	
Main Analysis:[1,2] Definition of off-label use includes: Presumed premenopausal age limit at ≤45 years; Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms	2	9.1	2	11.8	0	0.0
Sensitivity analysis I:[1,2,3] Definition of off-label use includes: Presumed premenopausal age limit at ≤49 years; Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms	4	18.2	3	17.6	1	20.0
Sensitivity analysis II:[1,2,3] Definition of off-label use includes: Presumed premenopausal age limit at ≤45 years; Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms, OR diagnosis of prevention and/or treatment of osteoporosis, in addition to diagnosis of oestrogen deficiency symptoms	2	9.1	2	11.8	0	0.0
Sensitivity analysis III:[1,2,3] Definition of off-label use includes: Presumed premenopausal age limit at ≤49 years; Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms, OR diagnosis of prevention and/or treatment of osteoporosis, in addition to diagnosis of oestrogen deficiency symptoms	4	18.2	3	17.6	1	20.0

1. % of total N patients
2. Patients with off-label use in any category mentioned for this analysis
3. Number of patients in the categories other than presumed premenopausal age limit (sensitivity analyses I and III) remained identical to Table 59

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.6. Results for Italy

10.6.1. Participants

The number of eligible patients in Italy is shown below in Table 61 and the number with and without E+P HRT treatment during the 12 months prior to index date is shown in Table 62. In Annual Reporting Period III, 52 (44.8%) of overall 116 Duavive users identified in the database were eligible for analysis; prescriptions of E+P HRT during 12 months prior to Duavive initiation were recorded in 28.8% of Duavive users. In the cumulative period, 223 (94.1%) of overall 237 patients prescribed Duavive were eligible for analysis; prior use of E+P HRT was reported for 30.9% of them. In the E+P HRT study cohort, 3,499 (94.7%) of 3,695 patients were included in the analysis for Annual Reporting Period III and 6,288 (93.9%) of 6,700 patients for cumulative period. The proportion of eligible patients with E+P HRT records during 12 months prior to index date was 65.5% and 41.9% in the annual and cumulative periods, respectively.

Table 61. Patient study eligibility in Italy

	Italy			
	Longitudinal database: LPD			
	Annual Reporting Period III		Cumulative period	
	n	%	n	%
Duavive cohort				
Total patients with at least 1 Duavive prescription during the study period	116	100.0	237	100.0
Excluded: Patients not enrolled in the data source for at least 12 months prior to their index date[1]	6	5.2	13	5.5
Excluded: Duavive prescription within 12 months prior to index date[1]	58	50.0	1	0.4
Total eligible patients[1]	**52**	**44.8**	**223**	**94.1**
E+P HRT cohort				
Total patients with at least 1 prescription E+P HRT during study period	3,695	100.0	6,700	100.0
Excluded: Patients were not enrolled in the data source for at least 12 months prior to their index date[1]	175	4.7	412	6.1
Excluded: Duavive prescription within 12 months prior to index date[1]	21	0.6	0	0.0
Total eligible patients[1]	**3,499**	**94.7**	**6,288**	**93.9**

1. % of N patients with at least one prescription of study medication (Duavive or E+P HRT, respectively)
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

Table 62. Patients with and without E+P HRT treatment during the 12 months prior to index date (Italy)

	Italy			
	Longitudinal database: LPD			
	Annual Reporting Period III		Cumulative period	
	n	%	n	%
Duavive cohort				
Total eligible patients in analysis for reporting period	**52**	**100.0**	**223**	**100.0**
Included: with E+P HRT during 12 months pre-index[1]	15	28.8	69	30.9
Included: without E+P HRT during 12 months pre-index[1]	37	71.2	154	69.1
E+P HRT cohort				
Total eligible patients in analysis for reporting period	**3,499**	**100.0**	**6,288**	**100.0**
Included: with E+P HRT during 12 months pre-index[1]	2,291	65.5	2,636	41.9
Included: without E+P HRT during 12 months pre-index[1]	1,208	34.5	3,652	58.1

1. % of N patients with at least one prescription of study medication (Duavive or E+P HRT, respectively)
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.6.2. Italy – Annual Reporting Period III

10.6.2.1. Baseline Characteristics – Annual Reporting Period III - Italy

Demographic characteristics of patients prescribed Duavive and E+P HRT are presented in Table 63.

10.6.2.1.1. ***Age***

In the Duavive cohort (n=52), 71.2% of patients were 50 years or older, 25.0% were 40 to 49 years old, and 3.8% were younger than 40 years. The proportion of the age group ≥50 years was 60.0% in the subgroup with prior E+P HRT treatment and 75.7% in the subgroup without.

The corresponding figures in the E+P HRT cohort (n=3,499) were 70.8%, 20.5% and 8.7%, respectively. The proportion of the age group ≥50 years was 79.2% in the subgroup with prior E+P HRT treatment and 54.8% in the subgroup without.

10.6.2.1.2. ***Gender***

No males were prescribed Duavive during the reported study period. Overall, 0.2% of patients in the E+P HRT cohort were male. Similar proportions of male patients were found in the two subgroups with and without prior E+P HRT treatment.

10.6.2.1.3. ***BMI***

BMI values were available for a subset of 7 out of 52 patients (13.5%) in the Duavive cohort: 6 patients (85.7%) had a BMI within normal range and 1 patient (14.3%) was categorised as overweight. BMI values were available for a subset of 221 out of 3,499 patients (6.3%) in the E+P HRT cohort. Within this subset, patients were categorised by their BMI values as underweight (5.4%), normal weight (55.2%), overweight (28.5%) or obese (10.9%).

Table 63. Demographic characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: Italy; source: LPD; Annual Reporting Period III]

	Italy											
	Longitudinal database: LPD											
	Reported study period: 31 March 2018 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients	***52***	***100.0***	***37***	***100.0***	***15***	***100.0***	***3,499***	***100.0***	***1,208***	***100.0***	***2,291***	***100.0***
Age at treatment initiation[1]												
Valid N[2]	*52*	*100.0*	*37*	*100.0*	*15*	*100.0*	*3,496*	*99.9*	*1,207*	*99.9*	*2,289*	*99.9*
<40 years	2	3.8	1	2.7	1	6.7	303	8.7	193	16.0	110	4.8
40 to 49 years	13	25.0	8	21.6	5	33.3	718	20.5	352	29.2	366	16.0
≥50 years	37	71.2	28	75.7	9	60.0	2,475	70.8	662	54.8	1,813	79.2
Gender[1]												
Valid N[2]	*52*	*100.0*	*37*	*100.0*	*15*	*100.0*	*3,499*	*100.0*	*1,208*	*100.0*	*2,291*	*100.0*
Female	52	100.0	37	100.0	15	100.0	3,491	99.8	1,204	99.7	2,287	99.8
Male	0	0.0	0	0.0	0	0.0	8	0.2	4	0.3	4	0.2
Body Mass Index[1]												
Valid N[2]	*7*	*13.5*	*6*	*16.2*	*1*	*6.7*	*221*	*6.3*	*89*	*7.4*	*132*	*5.8*
<18.5: underweight	0	0.0	0	0.0	0	0.0	12	5.4	7	7.9	5	3.8
≥18.5 to <25: normal range	6	85.7	5	83.3	1	100.0	122	55.2	47	52.8	75	56.8
≥25 to <30: overweight	1	14.3	1	16.7	0	0.0	63	28.5	26	29.2	37	28.0
≥30: obese	0	0.0	0	0.0	0	0.0	24	10.9	9	10.1	15	11.4

1. % of Valid N
2. Valid N: patients with non-missing values

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.6.2.2. Clinical Characteristics and Duavive Prescribing Patterns – Annual Reporting Period III - Italy

Baseline clinical characteristics are presented in Table 64 below.

10.6.2.2.1. ***Co-morbidities***

Any co-morbidity was reported in 40.4% of all patients in the Duavive cohort (26.7% and 45.9% in subgroups with and without prior E+P HRT treatment). The overall proportion of any of the specified co-morbidity in the E+P HRT study group was 34.6% (37.6% in the subgroup with and 28.7% in the subgroup without prior E+P HRT treatment). The most frequent co-morbidities in the overall Duavive cohort were osteoporosis/osteopenia (21.2%),

hypertension (19.2%), hyperlipidemia (9.6%) and osteoarthritis (5.8%). In the E+P HRT study group, hypertension was reported in 17.9%, hyperlipidemia in 10.9%, osteoporosis/osteopenia in 8.3% and osteoarthritis in 5.2% of patients. For proportions in the subgroups with and without prior E+P HRT treatment please refer to Table 64.

10.6.2.2.2. *Co-medication*

In the Duavive cohort 46.2% of patients were recorded with at least one of the specified co-medications during the 12 months pre-index period (53.3% and 43.2% in subgroups with and without prior E+P HRT treatment). In the E+P HRT cohort, at least one co-medication prescription was identified in 43.8% of the patients (43.3% in the subgroup with and 44.8% in the subgroup without prior E+P HRT treatment). The most frequently co-prescribed drugs in the Duavive cohort were corticosteroids (19.2%), antidepressants (13.5%), and osteoporosis treatments (9.6%) and lipid-lowering agents (5.8%). For the E+P HRT cohort, frequently co-prescribed drugs were corticosteroids (19.1%), antidepressants (15.4%), anticoagulants (10.0%), lipid-lowering agents (7.3%) and sedatives/hypnotics (6.1%). For proportions in the subgroups with and without prior E+P HRT treatment please refer to Table 64.

10.6.2.2.3. *Prior safety events*

In the Duavive cohort, at least one prior safety event was identified in 5.8% of all patients (0.0% and 8.1% in the subgroups with and without prior E+P HRT treatment). The overall proportion of patients with any safety event in the E+P HRT cohort was 8.1% (8.0% and 8.4% in the subgroups with and without prior E+P HRT treatment). For single categories of prior safety events please refer to Table 64.

10.6.2.2.4. *Indication*

The results on indication for use of study medication at index date are presented in Table 64 below.

Analysis of the period 90 days before and 90 days after index date showed that Duavive was prescribed for oestrogen deficiency symptoms in 44.2% of all patients, for osteoporosis only in 7.7% and for oestrogen deficiency symptoms and osteoporosis in 11.5%. For 36.5% of all patients, no diagnosis or a diagnosis other than oestrogen deficiency symptoms or osteoporosis was documented. A diagnosis of oestrogen deficiency symptoms only was documented in 40.0% of the subgroup with prior E+P HRT treatment and in 45.9% of the subgroup without prior E+P HRT treatment.

In the E+P HRT cohort, 45.3% of patients received treatment for oestrogen deficiency symptoms (48.5% and 39.4% in the subgroups with and without prior E+P HRT treatment, respectively). The overall proportion of patients prescribed E+P HRT for osteoporosis only was 2.5%, and for oestrogen deficiency symptoms and osteoporosis 3.5%. For 48.6% of all patients, no diagnosis or a diagnosis other than oestrogen deficiency symptoms or osteoporosis was documented (45.3% in the subgroup with and 55.0% in the subgroup without prior E+P HRT treatment).

An additional analysis of the period 365 days before and 90 days after index date showed a similar indication pattern for the Duavive cohort as the analysis for index date ± 90 days. The number of Duavive patients with "no oestrogen deficiency symptoms or osteoporosis or missing diagnoses" in the baseline period was reduced by 1 patient (from 19 to 18). In the E+P HRT cohort the distribution among the indications was also similar between the two analyses. The number of patients with "no oestrogen deficiency symptoms or osteoporosis or missing diagnoses" in the baseline period was reduced by 114 patients (from 1,702 to 1,588).

Table 64. Baseline clinical characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: Italy; source: LPD; Annual Reporting Period III]

	Italy											
	Longitudinal database: LPD											
	Reported study period: 31 March 2018 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients	***52***	***100.0***	***37***	***100.0***	***15***	***100.0***	***3,499***	***100.0***	***1,208***	***100.0***	***2,291***	***100.0***
Co-morbidities during 12 months pre-index period[1]												
Any co-morbidity	**21**	**40.4**	**17**	**45.9**	**4**	**26.7**	**1,209**	**34.6**	**347**	**28.7**	**862**	**37.6**
Osteoporosis/ osteopenia	11	21.2	8	21.6	3	20.0	291	8.3	84	7.0	207	9.0
History of CVD event	0	0.0	0	0.0	0	0.0	2	0.1	2	0.2	0	0.0
Hyperlipidemia	5	9.6	5	13.5	0	0.0	383	10.9	111	9.2	272	11.9
Hypertension	10	19.2	9	24.3	1	6.7	628	17.9	166	13.7	462	20.2
Breast pain	1	1.9	0	0.0	1	6.7	34	1.0	9	0.7	25	1.1
Diabetes	0	0.0	0	0.0	0	0.0	42	1.2	15	1.2	27	1.2
Renal disease	1	1.9	1	2.7	0	0.0	8	0.2	1	0.1	7	0.3
Osteoarthritis	3	5.8	3	8.1	0	0.0	181	5.2	53	4.4	128	5.6
Major depression	0	0.0	0	0.0	0	0.0	1	0.0	1	0.1	0	0.0
Co-medication during 12 months pre-index period[1]												
Any co-medication	**24**	**46.2**	**16**	**43.2**	**8**	**53.3**	**1,533**	**43.8**	**541**	**44.8**	**992**	**43.3**
Corticosteroids	10	19.2	5	13.5	5	33.3	669	19.1	277	22.9	392	17.1
Lipid lowering agents	3	5.8	3	8.1	0	0.0	255	7.3	69	5.7	186	8.1
Anti-hypertensives	0	0.0	0	0.0	0	0.0	24	0.7	4	0.3	20	0.9
Anticoagulants	4	7.7	3	8.1	1	6.7	351	10.0	160	13.2	191	8.3
Antiarrhythmics	0	0.0	0	0.0	0	0.0	38	1.1	9	0.7	29	1.3
Antidepressants	7	13.5	5	13.5	2	13.3	540	15.4	153	12.7	387	16.9
Sedatives/ hypnotics	1	1.9	0	0.0	1	6.7	214	6.1	57	4.7	157	6.9
Antidiabetics	0	0.0	0	0.0	0	0.0	70	2.0	28	2.3	42	1.8
Osteoporosis treatments (bisphosphonates, SERMs, etc)	5	9.6	4	10.8	1	6.7	90	2.6	25	2.1	65	2.8
Local (vaginal) hormone treatments	1	1.9	1	2.7	0	0.0	5	0.1	4	0.3	1	0.0
Prior safety events during 12 months pre-index period[1]												

Table 64. Baseline clinical characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: Italy; source: LPD; Annual Reporting Period III]

	Italy											
	Longitudinal database: LPD											
	Reported study period: 31 March 2018 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Any safety event (total; any category)	**3**	**5.8**	**3**	**8.1**	**0**	**0.0**	**285**	**8.1**	**102**	**8.4**	**183**	**8.0**
History of VTE/stroke/ CHD/ PVD event	0	0.0	0	0.0	0	0.0	41	1.2	21	1.7	20	0.9
History of malignancy potentially associated with oestrogen	0	0.0	0	0.0	0	0.0	21	0.6	6	0.5	15	0.7
History of any malignancy	3	5.8	3	8.1	0	0.0	252	7.2	86	7.1	166	7.2
Indication for study medication (main analysis[1,2]												
Oestrogen deficiency symptoms only	23	44.2	17	45.9	6	40.0	1,586	45.3	476	39.4	1,110	48.5
Osteoporosis only	4	7.7	3	8.1	1	6.7	87	2.5	25	2.1	62	2.7
Oestrogen deficiency symptoms and osteoporosis	6	11.5	5	13.5	1	6.7	124	3.5	42	3.5	82	3.6
No oestrogen deficiency symptoms or osteoporosis or missing	19	36.5	12	32.4	7	46.7	1,702	48.6	665	55.0	1,037	45.3
Indication for study medication (additional analysis)[1,3]												
Oestrogen deficiency symptoms only	23	44.2	17	45.9	6	40.0	1,593	45.5	477	39.5	1,116	48.7
Osteoporosis only	5	9.6	3	8.1	2	13.3	112	3.2	32	2.6	80	3.5
Oestrogen deficiency symptoms and osteoporosis	6	11.5	5	13.5	1	6.7	206	5.9	62	5.1	144	6.3
No oestrogen deficiency symptoms or osteoporosis or missing	18	34.6	12	32.4	6	40.0	1,588	45.4	637	52.7	951	41.5

1. % of total N
2. Time period for analysis: index date ±90 days
3. Time period for analysis: index date – 365 days to index date +90 days

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy
SERMs: selective oestrogen receptor modulators; CVD: cardiovascular disease; VTE: venous thromboembolism; CHD: coronary heart disease; PVD: peripheral vascular disease

10.6.2.2.5. *Duavive utilization in Italy*

The results on Duavive utilization based on index prescription are presented in Table 65 below.

10.6.2.2.5.1. Daily dose

Daily dose recommendation was available for 14 out of 52 of index Duavive prescriptions (26.9%). The standard recommended dose (1 tablet per day) was documented in all index prescriptions.

10.6.2.2.5.2. Days supply

In the analysis based on prescriptions with known daily dose (n=14), the mean days supply was 30.0 days overall and varied between 42.0 and 28.0 days in the subgroups with and without prior E+P HRT treatment. The duration ranged from 28 to 56 days.

After imputation to set missing values to the standard Duavive dose and supply, the mean duration was also 30.2 days overall (31.7 and 29.6 days in the subgroups with and without prior E+P HRT treatment). The duration ranged from 28 to 84 days.

10.6.2.2.5.3. Switchers from E+P HRT to Duavive

In total, 11.5% of the patients with Duavive prescriptions had switched from prior E+P HRT treatment.

Table 65. Duavive utilization: Overall and Stratified by Prior E+P HRT Treatment; prescription-level analysis [country: Italy; source: LPD Annual Reporting Period III]

	Italy					
	Longitudinal database: LPD					
	Reported study period: 31 March 2018 to 31 March 2018					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Total number of patients with index prescriptions	***52***	***100.0***	***37***	***100.0***	***15***	***100.0***
Number of (index) prescriptions with instruction on daily dosage available	**14**	**26.9**	**12**	**32.4**	**2**	**13.3**
Daily dose						
A. Analysis as reported (missing data on daily dose instruction not replaced)[1]						
1 tablet	14	100.0	12	100.0	2	100.0
<1 tablet	0	0.0	0	0.0	0	0.0
>1 tablet	0	0.0	0	0.0	0	0.0
B. Analysis based on all index prescriptions (missing data replaced)[2]						
1 tablet	52	100.0	37	100.0	15	100.0
<1 tablet	0	0.0	0	0.0	0	0.0
>1 tablet	0	0.0	0	0.0	0	0.0
Days supply						
A. Analysis as reported (missing data not replaced)[1]						
Mean (SD)	30.0 (7.5)		28.0 (0.0)		42.0 (19.8)	
Median	28.0		28.0		28.0	
Minimum – maximum	(28.0,56.0)		(28.0,28.0)		(28.0,56.0)	
B. Analysis based on all index prescriptions (missing data replaced)[2]						
Mean (SD)	30.2 (9.4)		29.6 (9.3)		31.7 (9.9)	
Median	28.0		28.0		28.0	
Minimum - maximum	(28.0,84.0)		(28.0,84.0)		(28.0,56.0)	
Switchers from E+P HRT to Duavive[2,3]	**6**	**11.5**	**n.appl.**		**6**	**40.0**

1. Based on N index prescriptions with instruction on daily dosage available
2. Based on total N index prescriptions
3. Switch: prescription of Duavive within 30 days following the end of the last filled prescription period of E+P

HRTSD: standard deviation; n.appl.: not applicable
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.6.2.2.6. ***Potential off-label use of Duavive in Italy***

The results for potential off-label use of Duavive in Italy from the main analysis (see Sections 9.4.5, 9.9.4) are presented in Table 66.

Potential off-label use was identified in 19.2% of all Duavive users (26.7% and 16.2% in the subgroups with and without prior E+P HRT treatment). The reasons for potential off-label use were in 9.6% of patients presumed premenopausal age of ⩽45 years, in 7.7% use for treatment of osteoporosis only and in 1.9% hypersensitivity to the active substances or excipients. For proportions in subgroups with and without prior E+P HRT treatment please refer to Table 66.

In the sensitivity analyses, the proportion of potential off-label use in Italy increased from 19.2% to 38.5% when the presumed premenopausal age limit was changed from 45 years to 49 years (sensitivity analysis I) or to 30.8% if the potential off-label indication for prescription was extended to osteoporosis with or without oestrogen deficiency symptoms (sensitivity analysis II). If both age and indication were varied (sensitivity analysis III), 48.1% of patients were potential off-label users (Table 67). Other parameters for potential off-label use remained identical for the main analysis and for the three sensitivity analyses.

Table 66. Potential off-label use of Duavive; Overall and Stratified by Prior E+P HRT Treatment; patient-level analysis [country: Italy; source: LPD; Annual Reporting Period III]

	Italy					
	Longitudinal database: LPD					
	Reported study period: 31 March 2018 - 30 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Total number of patients	***52***	***100.0***	***37***	***100.0***	***15***	***100.0***
Off-label use (total; any category)[1,2]	**10**	**19.2**	**6**	**16.2**	**4**	**26.7**
Patients with single categories of off-label use						
Use for treatment of osteoporosis only[3]	4	7.7	3	8.1	1	6.7
Valid N	*52*		*37*		*15*	
Use in women ≤45 years[3]	5	9.6	2	5.4	3	20.0
Valid N	*52*		*37*		*15*	
Use in women over 75 years old[3]	0	0.0	0	0.0	0	0.0
Valid N	*52*		*37*		*15*	
Use in males[3]	0	0.0	0	0.0	0	0.0
Valid N	*52*		*37*		*15*	
Prescription of non-approved dose or regimen[3]	0	0.0	0	0.0	0	0.0
Valid N	*14*		*12*		*2*	
Use with progestins, additional oestrogens or selective oestrogen receptor modulators (SERMs)[1]	0	0.0	0	0.0	0	0.0
Use in women without a uterus (hysterectomised women)[1]	0	0.0	0	0.0	0	0.0
Known, suspected, or past history of breast cancer[1]	0	0.0	0	0.0	0	0.0
Hypersensitivity (e.g., anaphylaxis/anaphylactic reactions, urticaria, drug eruption) to the active substances or to any of the excipients[1]	1	1.9	1	2.7	0	0.0
Malignancy potentially associated with oestrogen[1]	0	0.0	0	0.0	0	0.0
Active or past history of venous thromboembolism (deep venous thrombosis, pulmonary embolism, and retinal vein thrombosis) [1]	0	0.0	0	0.0	0	0.0
Active or past history of arterial thromboembolic disease (e.g., myocardial infarction, stroke)[1]	0	0.0	0	0.0	0	0.0
Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal[1]	0	0.0	0	0.0	0	0.0
Known thrombophilic disorders (e.g., protein C, protein S, or antithrombin deficiency)[1]	0	0.0	0	0.0	0	0.0
Porphyria[1]	0	0.0	0	0.0	0	0.0

Valid N: N patients with non-missing values in respective category
1. % of total N patients
2. Patients with off-label use in any category mentioned below
3. % of valid N in respective category (listed below)

Age ⩽45 years considered as proxy for premenopausal status (Section 9.4.5)
Patients can be in more than one category of potential off-label use
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy
SERMs: selective oestrogen receptor modulators

Table 67. Sensitivity analyses for potential off-label use of Duavive; Overall and Stratified by Prior E+P HRT Treatment; patient-level analysis [country: Italy; source: LPD; Annual Reporting Period III][§]

	Italy					
	Longitudinal database: LPD					
	Reported study period: 31 March 2018 to 30 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Total number of patients during reported period	***52***		***37***		***15***	
Main Analysis:[1,2] Definition of off-label use includes Presumed premenopausal age limit at ≤45 years; Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms	10	19.2	6	16.2	4	26.7
Sensitivity analysis I:[1,2,3] Definition of off-label use includes Presumed premenopausal age limit at ≤49 years; Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms	20	38.5	13	35.1	7	46.7
Sensitivity analysis II:[1,2,3] Definition of off-label use includes Presumed premenopausal age limit at ≤45 years; Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms, OR diagnosis of prevention and/or treatment of osteoporosis, in addition to diagnosis of oestrogen deficiency symptoms	16	30.8	11	29.7	5	33.3

Table 67. Sensitivity analyses for potential off-label use of Duavive; Overall and Stratified by Prior E+P HRT Treatment; patient-level analysis [country: Italy; source: LPD; Annual Reporting Period III]§

	Italy					
	Longitudinal database: LPD					
	Reported study period: 31 March 2018 to 30 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Sensitivity analysis III:[1,2,3] Definition of off-label use includes Presumed premenopausal age limit at ≤49 years; Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms, OR diagnosis of prevention and/or treatment of osteoporosis, in addition to diagnosis of oestrogen deficiency symptoms	25	48.1	17	45.9	8	53.3

1. % of total N patients
2. Patients with off-label use in any category mentioned for this analysis
3. Number of patients in the categories other than presumed premenopausal age limit (sensitivity analyses I and III) or indication for use (sensitivity analyses II and III) remained identical Table 66

§ Results in this table are based on an analysis of indication for Duavive (diagnoses from time period index date – 90 days to index date +90 days)

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.6.3. Italy – Cumulative Period

10.6.3.1. Baseline Characteristics – Cumulative Period - Italy

Demographic characteristics of patients prescribed Duavive and E+P HRT for the cumulative period (31 March 2016 to 30 March 2019) in Italy are presented in Table 68.

10.6.3.1.1. ***Age***

In the Duavive cohort 73.9% of patients were 50 years or older, 24.8% were 40 to 49 years and 1.4% younger than 40 years. The proportion of the age group ≥50 years was 78.3% in the subgroup with prior E+P HRT treatment and 71.9% in the subgroup without prior E+P HRT treatment.

In the E+P HRT cohort 63.1% were ≥ 50 years, 24.8% were between 40 and 49 years and 12.2% younger than 40 years. The proportion of the age group ≥50 years was 77.2% in the subgroup with prior E+P HRT treatment and 52.9% in the subgroup without prior E+P HRT treatment.

10.6.3.1.2. ***Gender***

Overall, 1 patient (0.4%) was male in the Duavive cohort and 0.3% in the E+P HRT cohort. In the Duavive cohort the patient was in the subgroup without prior E+P HRT treatment. The proportion of male patients was equally 0.3% in the subgroups with and without prior E+P HRT treatment in the E+P HRT cohort.

10.6.3.1.3. ***BMI***

BMI values were available for a subset of 23 out of 223 patients (10.3%) in the Duavive cohort. Within this subset, 8.7% of patients were underweight (BMI <18.5), 65.2% were in the normal weight range (BMI ≥18.5 to < 25), 17.4% were overweight (BMI ≥ 25 to < 30) and 8.7% obese (BMI ≥30). Similar proportions were shown in subgroups with and without E+P HRT prior treatment for patients with a BMI in the normal range (66.7% and 64.3%, respectively). In the subgroup with prior E+P HRT treatment 22.2% (2 patients) were underweight and no patients obese and in the subgroup without prior E+P HRT treatment none of the patients were underweight and 14.3% (2 patients) were obese.

BMI values were available for a subset of 435 out of 6,288 patients (6.9%) in the E+P HRT cohort. Within this subset, 6.2% of patients were underweight (BMI <18.5), 51.7% were in the normal weight range (BMI ≥18.5 to < 25), 30.3% were overweight (BMI ≥ 25 to < 30) and 11.7% were obese (BMI ≥30). Similar proportions occurred in the subgroups with and without E+P HRT prior treatment.

Table 68. Demographic characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: Italy; source: LPD; Cumulative Period]

	Italy											
	Longitudinal database: LPD											
	Reported study period: 31 March 2016 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients	***223***	***100.0***	***154***	***100.0***	***69***	***100.0***	***6,288***	***100.0***	***3,652***	***100.0***	***2,636***	***100.0***
Age at treatment initiation[1]												
Valid N[2]	*222*	*99.6*	*153*	*99.4*	*69*	*100.0*	*6,285*	*100.0*	*3,650*	*99.9*	*2,635*	*100.0*
<40 years	3	1.4	2	1.3	1	1.4	765	12.2	627	17.2	138	5.2
40 to 49 years	55	24.8	41	26.8	14	20.3	1,556	24.8	1,092	29.9	464	17.6
≥50 years	164	73.9	110	71.9	54	78.3	3,964	63.1	1,931	52.9	2,033	77.2
Gender[1]												
Valid N[2]	*223*	*100.0*	*154*	*100.0*	*69*	*100.0*	*6,288*	*100.0*	*3,652*	*100.0*	*2,636*	*100.0*
Female	222	99.6	153	99.4	69	100.0	6,270	99.7	3,641	99.7	2,629	99.7
Male	1	0.4	1	0.6	0	0.0	18	0.3	11	0.3	7	0.3
Body Mass Index[1]												
Valid N[2]	*23*	*10.3*	*14*	*9.1*	*9*	*13.0*	*435*	*6.9*	*277*	*7.6*	*158*	*6.0*
<18.5: underweight	2	8.7	0	0.0	2	22.2	27	6.2	18	6.5	9	5.7
≥18.5 to <25: normal range	15	65.2	9	64.3	6	66.7	225	51.7	146	52.7	79	50.0
≥25 to <30: overweight	4	17.4	3	21.4	1	11.1	132	30.3	82	29.6	50	31.6
≥30: obese	2	8.7	2	14.3	0	0.0	51	11.7	31	11.2	20	12.7

1. % of Valid N
2. Valid N: patients with non-missing values

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.6.3.2. Clinical Characteristics and Duavive Prescribing Patterns – Cumulative Period - Italy

Baseline clinical characteristics for the cumulative period (31 March 2016 to 30 March 2019) in Italy are presented in Table 69 below.

10.6.3.2.1. ***Co-morbidities***

In the Duavive cohort 81 patients (36.3%) were recorded with a co-morbidity in the cumulative data (43.5% and 33.1% in the subgroups with and without prior E+P HRT

treatment, respectively). The most frequent co-morbidities in the Duavive cohort were hypertension (16.1% overall, 15.9% of patients with and 16.2% of patients without prior E+P HRT treatment), osteoporosis/ osteopenia (12.1% overall; 17.4% with and 9.7% without prior E+P HRT treatment), osteoarthritis (8.5% overall, 10.1% with and 7.8% without prior E+P HRT treatment) and hyperlipidemia (8.1% overall; 10.1% with and 7.1% without prior E+P HRT treatment). For the other co-morbidities please refer to Table 69.

The overall proportion of patients with any of the specified co-morbidities in the E+P HRT study group was 31.9% (37.2% and 28.1% of patients with and without prior E+P HRT treatment, respectively). The most frequent co-morbidities in the E+P HRT cohort were hypertension (16.3% overall, 19.6% of patients with and 13.9% of patients without prior E+P HRT treatment), hyperlipidemia (9.6% overall; 11.6% with and 8.2% without prior E+P HRT treatment), osteoporosis/ osteopenia (6.4% overall; 7.3% with and 5.8% without prior E+P HRT treatment) and osteoarthritis (5.6% overall, 6.5% with and 5.0% without prior E+P HRT treatment). For the other co-morbidities please refer to Table 69.

10.6.3.2.2. ***Co-medication***

In the Duavive cohort at least one prescription of specified co-medications during the 12-month pre-index period was identified in 39.5% of patients. The most frequently co-prescribed drugs were antidepressants (16.6%), corticosteroids (14.8%), sedatives/hypnotics (7.6%), anticoagulants (4.9%), osteoporosis treatments (4.5%) and lipid lowering agents (4.0%).

In the E+P HRT cohort, at least one prescription of one of the specified co-medications was identified in 44.6% of patients (45.3% in the subgroup with and 44.1% in the subgroup without prior E+P HRT treatment). The most frequently co-prescribed drugs were corticosteroids (19.9%), antidepressants (14.2%), anticoagulants (11.5%), lipid lowering agents (7.0%), sedatives/hypnotics (5.4%), osteoporosis treatments (2.5%) and antidiabetics (2.3%).

For proportions in the subgroups with and without prior E+P HRT treatment please refer to Table 69.

10.6.3.2.3. ***Prior safety events***

In the Duavive cohort at least one prior safety event during 12-month pre-index period was identified in 5.8% of patients (in overall and in subgroups with and without prior E+P HRT treatment). The overall proportion of patients with any safety event in the E+P HRT cohort was 8.1% (8.2% in the subgroup with prior E+P HRT treatment and 8.0% in the subgroup without). For single categories of prior safety events please refer to Table 69.

10.6.3.2.4. ***Indication***

The results on indication for use of study medication at index date are presented in Table 69 below.

Analysis of the period 90 days before and 90 days after index date showed that Duavive was prescribed for oestrogen deficiency symptoms in 48.9% of patients. This proportion was

43.5% in the subgroup with and 51.3% in the subgroup without prior E+P HRT treatment. The overall proportion of patients who were prescribed Duavive for osteoporosis only was 4.9% and for both oestrogen deficiency symptoms and osteoporosis 4.5%. For 41.7% of all patients in the Duavive cohort, no diagnosis or a diagnosis other than oestrogen deficiency symptoms or osteoporosis was documented. The corresponding values were 47.8% in the subgroup with and 39.0% in the subgroup without prior E+P HRT treatment.

In the E+P HRT cohort, 42.0% of patients received E+P HRT treatment for oestrogen deficiency symptoms only (49.3% in the subgroup with prior E+P HRT treatment and 36.8% in the subgroup without). The overall proportion of patients who were prescribed E+P HRT for osteoporosis only was 2.0% and for both oestrogen deficiency symptoms and osteoporosis 3.1%. For 52.8% of all patients in the E+P HRT cohort, no diagnosis or a diagnosis other than oestrogen deficiency symptoms or osteoporosis was documented. The corresponding values were 45.1% in the subgroup with and 58.3% in the subgroup without prior E+P HRT treatment.

An additional analysis of the period 365 days before and 90 days after index date showed a similar prescription pattern for the Duavive cohort as the analysis for index date ± 90 days. The number of Duavive patients with "no oestrogen deficiency symptoms or osteoporosis or missing diagnoses" in the baseline period was reduced by 8 patients (from 93 to 85). In the E+P HRT cohort the distribution among the indications was also similar when comparing the two analyses. The number of patients with "no oestrogen deficiency symptoms or osteoporosis or missing diagnoses" in the baseline period was reduced by 171 patients (from 3,318 to 3,147).

Table 69. Baseline clinical characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: Italy; source: LPD; Cumulative Period]

	Italy											
	Longitudinal database: LPD											
	Reported study period: 31 March 2016 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients	***223***	***100.0***	***154***	***100.0***	***69***	***100.0***	***6,288***	***100.0***	***3,652***	***100.0***	***2,636***	***100.0***
Co-morbidities during 12 months pre-index period[1]												
Any co-morbidity	**81**	**36.3**	**51**	**33.1**	**30**	**43.5**	**2,009**	**31.9**	**1,028**	**28.1**	**981**	**37.2**
Osteoporosis/ osteopenia	27	12.1	15	9.7	12	17.4	404	6.4	211	5.8	193	7.3
History of CVD event	0	0.0	0	0.0	0	0.0	5	0.1	4	0.1	1	0.0
Hyperlipidemia	18	8.1	11	7.1	7	10.1	603	9.6	298	8.2	305	11.6
Hypertension	36	16.1	25	16.2	11	15.9	1,025	16.3	509	13.9	516	19.6
Breast pain	4	1.8	3	1.9	1	1.4	84	1.3	55	1.5	29	1.1
Diabetes	2	0.9	1	0.6	1	1.4	82	1.3	54	1.5	28	1.1
Renal disease	1	0.4	1	0.6	0	0.0	10	0.2	3	0.1	7	0.3
Osteoarthritis	19	8.5	12	7.8	7	10.1	353	5.6	181	5.0	172	6.5

Table 69. Baseline clinical characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: Italy; source: LPD; Cumulative Period]

	Italy											
	Longitudinal database: LPD											
	Reported study period: 31 March 2016 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Major depression	0	0.0	0	0.0	0	0.0	2	0.0	1	0.0	1	0.0
Co-medication during 12 months pre-index period[1]												
Any co-medication	**88**	**39.5**	**57**	**37.0**	**31**	**44.9**	**2,805**	**44.6**	**1,612**	**44.1**	**1,193**	**45.3**
Corticosteroids	33	14.8	18	11.7	15	21.7	1,250	19.9	773	21.2	477	18.1
Lipid lowering agents	9	4.0	9	5.8	0	0.0	441	7.0	204	5.6	237	9.0
Anti-hypertensives	0	0.0	0	0.0	0	0.0	43	0.7	24	0.7	19	0.7
Anticoagulants	11	4.9	9	5.8	2	2.9	722	11.5	478	13.1	244	9.3
Antiarrhythmics	0	0.0	0	0.0	0	0.0	79	1.3	29	0.8	50	1.9
Antidepressants	37	16.6	21	13.6	16	23.2	893	14.2	460	12.6	433	16.4
Sedatives/ hypnotics	17	7.6	11	7.1	6	8.7	340	5.4	174	4.8	166	6.3
Antidiabetics	2	0.9	2	1.3	0	0.0	145	2.3	98	2.7	47	1.8
Osteoporosis treatments (bisphosphonates, SERMs, etc)	10	4.5	6	3.9	4	5.8	157	2.5	72	2.0	85	3.2
Local (vaginal) hormone treatments	1	0.4	1	0.6	0	0.0	17	0.3	13	0.4	4	0.2
Prior safety events during 12 months pre-index period[1]												
Any safety event (total; any category)	**13**	**5.8**	**9**	**5.8**	**4**	**5.8**	**507**	**8.1**	**292**	**8.0**	**215**	**8.2**
History of VTE/stroke/ CHD/ PVD event	1	0.4	1	0.6	0	0.0	84	1.3	56	1.5	28	1.1
History of malignancy potentially associated with oestrogen	1	0.4	0	0.0	1	1.4	26	0.4	16	0.4	10	0.4
History of any malignancy	12	5.4	8	5.2	4	5.8	433	6.9	241	6.6	192	7.3
Indication for study medication (main analysis[1,2]												
Oestrogen deficiency symptoms only	109	48.9	79	51.3	30	43.5	2,644	42.0	1,345	36.8	1,299	49.3
Osteoporosis only	11	4.9	8	5.2	3	4.3	128	2.0	72	2.0	56	2.1
Oestrogen deficiency symptoms and osteoporosis	10	4.5	7	4.5	3	4.3	198	3.1	106	2.9	92	3.5
No oestrogen deficiency symptoms or osteoporosis or missing	93	41.7	60	39.0	33	47.8	3,318	52.8	2,129	58.3	1,189	45.1
Indication for study medication (additional analysis)[1,3]												
Oestrogen deficiency symptoms only	110	49.3	80	51.9	30	43.5	2,675	42.5	1,349	36.9	1,326	50.3

Table 69. Baseline clinical characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: Italy; source: LPD; Cumulative Period]

	Italy											
	Longitudinal database: LPD											
	Reported study period: 31 March 2016 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Osteoporosis only	13	5.8	7	4.5	6	8.7	178	2.8	96	2.6	82	3.1
Oestrogen deficiency symptoms and osteoporosis	15	6.7	9	5.8	6	8.7	288	4.6	156	4.3	132	5.0
No oestrogen deficiency symptoms or osteoporosis or missing	85	38.1	58	37.7	27	39.1	3,147	50.0	2,051	56.2	1,096	41.6

1. % of total N
2. Time period for analysis: index date ±90 days
3. Time period for analysis: index date – 365 days to index date +90 days

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy
SERMs: selective oestrogen receptor modulators; CVD: cardiovascular disease; VTE: venous thromboembolism; CHD: coronary heart disease; PVD: peripheral vascular disease

10.6.3.2.5. *Duavive utilization in Italy*

The results on Duavive utilization between 31 March 2016 and 30 March 2019 based on index prescription are presented in Table 70 below.

10.6.3.2.5.1. Daily dose

Daily dose recommendation was available for 59 out of 223 index Duavive prescriptions (26.5%). The standard recommended dose (1 tablet per day) was documented in 98.3% of cases, in 1 patient the recommended dose was <1 tablet per day.

10.6.3.2.5.2. Days supply

In the analysis based on prescriptions with known daily dose, mean days supply was 32.0 days overall and varied between 30.2 and 32.9 days in the subgroups with and without E+P HRT prior treatment, respectively. The duration ranged from 14 to 84 days.

After imputation to set missing values to the standard Duavive dose and supply, the mean duration was 31.5 days (32.0 days and 31.3 days in subgroups with and without prior E+P HRT treatment, respectively). The duration ranged from 14 to 168 days.

10.6.3.2.5.3. Switchers from E+P HRT to Duavive

In total, 14.8% of the patients with Duavive prescriptions had switched from prior E+P HRT treatment.

Table 70. Duavive utilization; Overall and Stratified by Prior E+P HRT Treatment; prescription-level analysis [country: Italy; source: LPD; Cumulative Period]

	Italy					
	Longitudinal database: LPD					
	Reported study period: 31 March 2016 to 31 March 2018					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Total number of patients with index prescriptions	***223***	***100.0***	***154***	***100.0***	***69***	***100.0***
Number of (index) prescriptions with instruction on daily dosage available	**59**	**26.5**	**40**	**26.0**	**19**	**27.5**
Daily dose						
A. Analysis as reported (missing data on daily dose instruction not replaced)[1]						
1 tablet	58	98.3	40	100.0	18	94.7
<1 tablet	1	1.7	0	0.0	1	5.3
>1 tablet	0	0.0	0	0.0	0	0.0
B. Analysis based on all index prescriptions (missing data replaced)[2]						
1 tablet	222	99.6	154	100.0	68	98.6
<1 tablet	1	0.4	0	0.0	1	1.4
>1 tablet	0	0.0	0	0.0	0	0.0
Days supply						
A. Analysis as reported (missing data not replaced)[1]						
Mean (SD)	32.0 (11.6)		32.9 (12.5)		30.2 (9.6)	
Median	28.0		28.0		28.0	
Minimum – maximum	(14.0,84.0)		(28.0,84.0)		(14.0,56.0)	
B. Analysis based on all index prescriptions (missing data replaced)[2]						
Mean (SD)	31.5 (14.8)		31.3 (12.8)		32.0 (18.5)	
Median	28.0		28.0		28.0	
Minimum - maximum	(14.0,168.0)		(28.0,140.0)		(14.0,168.0)	
Switchers from E+P HRT to Duavive[2,3]	**33**	**14.8**	**n.appl.**		**33**	**47.8**

1. Based on N index prescriptions with instruction on daily dosage available
2. Based on total N index prescriptions
3. Switch: prescription of Duavive within 30 days following the end of the last filled prescription period of E+P HRT

SD: standard deviation; n.appl.: not applicable
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.6.3.2.6. ***Potential off-label use of Duavive in Italy***

The results for potential off-label use of Duavive from the main analysis (see Sections 9.4.5, 9.9.4) for the reporting period from 31 March 2016 to 30 March 2019 are presented in Table 71.

Potential off-label use was identified in 15.2% of all Duavive users (17.4% and 14.3% in the subgroups with and without prior E+P HRT treatment). The reasons for potential off-label use were presumed premenopausal age of ≤45 years (9.0%), treatment for osteoporosis only (4.9%), prescription of a non-approved dose or regimen (1.7%), hypersensitivity to the active substances or excipients (1.3%), malignancy potentially associated with oestrogens (0.4%); 0.4% of patients were male.

In the sensitivity analyses, the proportion of potential off-label users increased from 15.2% to 31.8%, when the presumed premenopausal age limit was changed from 45 years to 49 years (sensitivity analysis I) or to 19.7% if the off-label indication for prescription was extended to osteoporosis with or without oestrogen deficiency symptoms (sensitivity analysis II). If both age and indication were varied (sensitivity analysis III), 35.4% of patients were potential off-label users (Table 72). Other parameters for potential off-label use remained identical for the main analysis and for the three sensitivity analyses.

Table 71. Potential off-label use of Duavive; Overall and Stratified by Prior E+P HRT Treatment; patient-level analysis [country: Italy; source: LPD; Cumulative Period]

	Italy					
	Longitudinal database: LPD					
	Reported study period: 31 March 2016 - 30 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Total number of patients	***223***	***100.0***	***154***	***100.0***	***69***	***100.0***
Off-label use (total; any category)[1,2]	**34**	**15.2**	**22**	**14.3**	**12**	**17.4**
Patients with single categories of off-label use						
Use for treatment of osteoporosis only[3]	11	4.9	8	5.2	3	4.3
Valid N	*223*		*154*		*69*	
Use in women ≤45 years[3]	20	9.0	13	8.5	7	10.1
Valid N	*222*		*153*		*69*	
Use in women over 75 years old[3]	0	0.0	0	0.0	0	0.0
Valid N	*222*		*153*		*69*	
Use in males[3]	1	0.4	1	0.6	0	0.0
Valid N	*223*		*154*		*69*	
Prescription of non-approved dose or regimen[3]	1	1.7	0	0.0	1	5.3
Valid N	*59*		*40*		*19*	
Use with progestins, additional oestrogens or selective oestrogen receptor modulators (SERMs)[1]	0	0.0	0	0.0	0	0.0
Use in women without a uterus (hysterectomised women)[1]	0	0.0	0	0.0	0	0.0
Known, suspected, or past history of breast cancer[1]	0	0.0	0	0.0	0	0.0
Hypersensitivity (e.g., anaphylaxis/anaphylactic reactions, urticaria, drug eruption) to the active substances or to any of the excipients[1]	3	1.3	2	1.3	1	1.4
Malignancy potentially associated with oestrogen[1]	1	0.4	0	0.0	1	1.4
Active or past history of venous thromboembolism (deep venous thrombosis, pulmonary embolism, and retinal vein thrombosis) [1]	0	0.0	0	0.0	0	0.0
Active or past history of arterial thromboembolic disease (e.g., myocardial infarction, stroke)[1]	0	0.0	0	0.0	0	0.0
Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal[1]	0	0.0	0	0.0	0	0.0
Known thrombophilic disorders (e.g., protein C, protein S, or antithrombin deficiency)[1]	0	0.0	0	0.0	0	0.0
Porphyria[1]	0	0.0	0	0.0	0	0.0

Valid N: N patients with non-missing values in respective category
1. % of total N patients
2. Patients with off-label use in any category mentioned below
3. % of valid N in respective category (listed below)

Age ≤45 years considered as proxy for premenopausal status (Section 9.4.5)
Patients can be in more than one category of potential off-label use
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy
SERMs: selective oestrogen receptor modulators

Table 72. Sensitivity analyses for potential off-label use of Duavive; Overall and Stratified by Prior E+P HRT Treatment; patient-level analysis [country: Italy; source: LPD; Cumulative Period][§]

	Italy					
	Longitudinal database: LPD					
	Reported study period: 31 March 2016 to 30 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Total number of patients during reported period	***223***		***154***		***69***	
Main Analysis:[1,2] Definition of off-label use includes Presumed premenopausal age limit at ≤45 years; Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms	34	15.2	22	14.3	12	17.4
Sensitivity analysis I:[1,2,3] Definition of off-label use includes Presumed premenopausal age limit at ≤49 years; Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms	71	31.8	51	33.1	20	29.0
Sensitivity analysis II:[1,2,3] Definition of off-label use includes Presumed premenopausal age limit at ≤45 years; Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms, OR diagnosis of prevention and/or treatment of osteoporosis, in addition to diagnosis of oestrogen deficiency symptoms	44	19.7	29	18.8	15	21.7
Sensitivity analysis III:[1,2,3] Definition of off-label use includes Presumed premenopausal age limit at ≤49 years; Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms, OR diagnosis of prevention and/or treatment of osteoporosis, in addition to diagnosis of oestrogen deficiency symptoms	79	35.4	56	36.4	23	33.3

1. % of total N patients
2. Patients with off-label use in any category mentioned for this analysis
3. Number of patients in the categories other than presumed premenopausal age limit (sensitivity analyses I and III) or indication for use (sensitivity analyses II and III) remained identical to Table 71

[§] Results in this table are based on an analysis of indication for Duavive (diagnoses from time period index date – 90 days to index date +90 days)

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.7. Results for Spain

10.7.1. Participants

The number of eligible patients in Spain is shown below in Table 73 and the number with and without E+P HRT treatment during the 12 months prior to index date is shown in Table 74. In Annual Reporting Period III, 23 (46.9%) of overall 49 Duavive users identified in the database were eligible for analysis; prescriptions of E+P HRT during 12 months prior to Duavive initiation were recorded in 30.4% of Duavive users. In the cumulative period, 73 (96.1%) of overall 76 patients prescribed Duavive were eligible for analysis; prior use of E+P HRT was reported for 24.7% of them. In the E+P HRT study cohort, 1,321 (93.6%) of 1,412 patients were included in the analysis for Annual Reporting Period III and 2,573 (93.3%) of 2,757 patients for cumulative period. The proportion of eligible patients with E+P HRT records during 12 months prior to index date was 55.3% and 35.2% in the annual and cumulative periods, respectively.

Table 73. Patient study eligibility in Spain

	Spain			
	Longitudinal database: LPD			
	Annual Reporting Period III		Cumulative period	
	n	%	n	%
Duavive cohort				
Total patients with at least 1 Duavive prescription during the study period	49	100.0	76	100.0
Excluded: Patients not enrolled in the data source for at least 12 months prior to their index date[1]	1	2.1	1	1.3
Excluded: Duavive prescription within 12 months prior to index date[1]	25	51.0	2	2.6
Total eligible patients[1]	**23**	**46.9**	**73**	**96.1**
E+P HRT cohort				
Total patients with at least 1 prescription E+P HRT during study period	1,412	100.0	2,757	100.0
Excluded: Patients were not enrolled in the data source for at least 12 months prior to their index date[1]	86	6.1	184	6.7
Excluded: Duavive prescription within 12 months prior to index date[1]	5	0.3	0	0.0
Total eligible patients[1]	**1,321**	**93.6**	**2,573**	**93.3**

1. % of N patients with at least one prescription of study medication (Duavive or E+P HRT, respectively)
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

Table 74. Patients with and without E+P HRT treatment during the 12 months prior to index date (Spain)

	Spain			
	Longitudinal database: LPD			
	Annual Reporting Period III		Cumulative period	
	n	%	n	%
Duavive cohort				
Total eligible patients in analysis for reporting period	**23**	**100.0**	**73**	**100.0**
Included: with E+P HRT during 12 months pre-index[1]	7	30.4	18	24.7
Included: without E+P HRT during 12 months pre-index[1]	16	69.6	55	75.3
E+P HRT cohort				
Total eligible patients in analysis for reporting period	**1,321**	**100.0**	**2,573**	**100.0**
Included: with E+P HRT during 12 months pre-index[1]	730	55.3	905	35.2
Included: without E+P HRT during 12 months pre-index[1]	591	44.7	1,668	64.8

1. % of N patients with at least one prescription of study medication (Duavive or E+P HRT, respectively)
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.7.2. Spain – Annual Reporting Period III

10.7.2.1. Baseline Characteristics – Annual Reporting Period III - Spain

Demographic characteristics of patients prescribed Duavive and E+P HRT are presented in Table 75.

Overall, the number of patients in the Duavive cohort was low (n=23).

10.7.2.1.1. ***Age***

The vast majority (69.6%) of patients in the Duavive cohort were 50 years or older, 26.1% were 40 to 49 years, and 1 patient (4.3%) was younger than 40 years.

The corresponding figures in the E+P HRT cohort in overall were 46.6%, 34.0% and 19.4%, respectively. The proportion of the age group ≥50 years was 56.8% in the subgroup with prior E+P HRT treatment and 34.2% in the subgroup without.

10.7.2.1.2. ***Gender***

No males were prescribed Duavive during the reported study period. Overall, the proportion of male patients in the E+P HRT cohort was 4.0%, 5.1% in the subgroup with and 2.7% in the subgroup without prior E+P HRT treatment.

10.7.2.1.3. ***BMI***

BMI value was available for 1 patient in the Duavive cohort (BMI in normal range). In the subset of the E+P HRT cohort with available BMI (124 out of 1,321 patients), 2.4% of patients were underweight, 33.9% of normal weight range, 34.7% overweight and 29.0% were obese; similar proportions were shown in the subgroups with and without prior E+P HRT treatment.

Table 75. Demographic characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: Spain; source: LPD; Annual Reporting Period III]

	Spain											
	Longitudinal database: LPD											
	Reported study period: 31 March 2018 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients	***23***	***100.0***	***16***	***100.0***	***7***	***100.0***	***1,321***	***100.0***	***591***	***100.0***	***730***	***100.0***
Age at treatment initiation[1]												
Valid N[2]	*23*	*100.0*	*16*	*100.0*	*7*	*100.0*	*1,250*	*94.6*	*562*	*95.1*	*688*	*94.2*
<40 years	1	4.3	1	6.3	0	0.0	242	19.4	155	27.6	87	12.6
40 to 49 years	6	26.1	3	18.8	3	42.9	425	34.0	215	38.3	210	30.5
≥50 years	16	69.6	12	75.0	4	57.1	583	46.6	192	34.2	391	56.8
Gender[1]												
Valid N[2]	*23*	*100.0*	*16*	*100.0*	*7*	*100.0*	*1,321*	*100.0*	*591*	*100.0*	*730*	*100.0*
Female	23	100.0	16	100.0	7	100.0	1268	96.0	575	97.3	693	94.9
Male	0	0.0	0	0.0	0	0.0	53	4.0	16	2.7	37	5.1
Body Mass Index[1]												
Valid N[2]	*1*	*4.3*	*1*	*6.3*	0	0.0	*124*	*9.4*	*80*	*13.5*	*44*	*6.0*
<18.5: underweight	0	0.0	0	0.0			3	2.4	3	3.8	0	0.0
≥18.5 to <25: normal range	1	100.0	1	100.0			42	33.9	28	35.0	14	31.8
≥25 to <30: overweight	0	0.0	0	0.0			43	34.7	29	36.3	14	31.8
≥30: obese	0	0.0	0	0.0			36	29.0	20	25.0	16	36.4

1. % of Valid N
2. Valid N: patients with non-missing values

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.7.2.2. Clinical Characteristics and Duavive Prescribing Patterns – Annual Reporting Period III - Spain

The results on baseline clinical characteristics are presented in Table 76 below.

10.7.2.2.1. *Co-morbidities*

In the Duavive cohort, for 30.4% of all patients, at least one co-morbidity was reported (0.0% and 43.8% in subgroups with and without prior E+P HRT treatment). The overall proportion of any of the specified co-morbidities in the E+P HRT study group was 27.3% (32.2% and 21.3% in subgroups with and without prior E+P HRT treatment, respectively). The reported co-morbidities in the Duavive study group were hyperlipidemia (17.4%), hypertension

(13.0%) and osteoporosis/ osteopenia (4.3%). In the E+P HRT study group, hyperlipidemia was reported in 16.9%, hypertension in 5.1%, osteoarthritis in 4.5%, osteoporosis/osteopenia in 2.8% and diabetes in 2.6%. Proportion of other co-morbidities was under 1%. For proportions in the subgroups with and without E+P HRT prior treatment please refer to Table 76.

10.7.2.2.2. *Co-medication*

In the Duavive cohort, 34.8% of patients were recorded with at least one of the specified co-medications during the 12 months pre-index period (14.3% and 43.8% in subgroups with and without prior E+P HRT treatment). In the E+P HRT cohort, at least one prescription of specified co-medication was identified in 40.6% of patients (46.8% and 32.8% in the subgroups with and without prior E+P HRT treatment, respectively). The co-prescribed drugs in the Duavive cohort were antidepressants (26.1%), lipid lowering agents (21.7%), anticoagulants (8.7%) and antiarrhythmics (4.3%). For the E+P HRT cohort, frequently co-prescribed were antidepressants (21.2%), lipid lowering agents (14.5%), sedatives/hypnotics (7.9%), corticosteroids (7.0%) and anticoagulants (5.9%). For proportions in the subgroups with and without E+P HRT prior treatment please refer to Table 76.

10.7.2.2.3. *Prior safety events*

In the Duavive cohort, at least one prior safety event was identified in 1 patient (4.3%) in overall (0.0% and 6.3% in the subgroups with and without prior E+P HRT treatment). The overall proportion of patients with any safety event in the E+P HRT cohort was 2.0% (1.8% and 2.2% in the subgroups with and without prior E+P HRT treatment). For single categories of prior safety events please refer to Table 76.

10.7.2.2.4. *Indication*

The results on indication for use of study medication at index date are presented in Table 76 below.

In the Duavive cohort analysis of the period 90 days before and 90 days after index date showed that Duavive was prescribed for oestrogen deficiency symptoms in 43.5% of all patients. Osteoporosis only was indication for 1 patient (4.3%). For 12 patients (52.2%), no diagnosis or a diagnosis other than oestrogen deficiency symptoms or osteoporosis was documented. A diagnosis of oestrogen deficiency symptoms was documented in 42.9% of the subgroup with prior E+P HRT treatment and in 43.8% of the subgroup without prior E+P HRT treatment.

In the E+P HRT cohort, 14.3% of patients received treatment for oestrogen deficiency symptoms (14.7% and 13.9% in the subgroups with and without prior E+P HRT treatment, respectively). The overall proportion of patients prescribed E+P HRT for osteoporosis was 2.2%, and for oestrogen deficiency symptoms and osteoporosis 2.2%. For 83.2% of all patients, no diagnosis or a diagnosis other than oestrogen deficiency symptoms or osteoporosis was documented (82.2% in the subgroup with and 84.4% in the subgroup without prior E+P HRT treatment).

An additional analysis of the period 365 days before and 90 days after index date showed the same indication pattern for the Duavive cohort as the analysis for index date ± 90 days. In the E+P HRT cohort the distribution among the indications was also similar between the two analyses. The number of patients with "no oestrogen deficiency symptoms or osteoporosis or missing diagnoses" in the baseline period was reduced by 13 patients (from 1,099 to 1,086).

Table 76. Baseline clinical characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: Spain; source: LPD; Annual Reporting Period III]

	Spain											
	Longitudinal database: LPD											
	Reported study period: 31 March 2018 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients	***23***	***100.0***	***16***	***100.0***	***7***	***100.0***	***1321***	***100.0***	***591***	***100.0***	***730***	***100.0***
Co-morbidities during 12 months pre-index period[1]												
Any co-morbidity	**7**	**30.4**	**7**	**43.8**	**0**	**0.0**	**361**	**27.3**	**126**	**21.3**	**235**	**32.2**
Osteoporosis/ osteopenia	1	4.3	1	6.3			37	2.8	10	1.7	27	3.7
History of CVD event	0	0.0	0	0.0			1	0.1	0	0.0	1	0.1
Hyperlipidemia	4	17.4	4	25.0			223	16.9	84	14.2	139	19.0
Hypertension	3	13.0	3	18.8			67	5.1	26	4.4	41	5.6
Breast pain	0	0.0	0	0.0			9	0.7	4	0.7	5	0.7
Diabetes	0	0.0	0	0.0			34	2.6	8	1.4	26	3.6
Renal disease	0	0.0	0	0.0			1	0.1	0	0.0	1	0.1
Osteoarthritis	0	0.0	0	0.0			60	4.5	21	3.6	39	5.3
Major depression	0	0.0	0	0.0			0	0.0	0	0.0	0	0.0
Co-medication during 12 months pre-index period[1]												
Any co-medication	**8**	**34.8**	**7**	**43.8**	**1**	**14.3**	**536**	**40.6**	**194**	**32.8**	**342**	**46.8**
Corticosteroids	0	0.0	0	0.0	0	0.0	92	7.0	37	6.3	55	7.5
Lipid lowering agents	5	21.7	5	31.3	0	0.0	191	14.5	69	11.7	122	16.7
Anti-hypertensives	0	0.0	0	0.0	0	0.0	4	0.3	1	0.2	3	0.4
Anticoagulants	2	8.7	2	12.5	0	0.0	78	5.9	24	4.1	54	7.4
Antiarrhythmics	1	4.3	1	6.3	0	0.0	17	1.3	8	1.4	9	1.2
Antidepressants	6	26.1	5	31.3	1	14.3	280	21.2	103	17.4	177	24.2
Sedatives/ hypnotics	0	0.0	0	0.0	0	0.0	105	7.9	37	6.3	68	9.3
Antidiabetics	0	0.0	0	0.0	0	0.0	46	3.5	13	2.2	33	4.5
Osteoporosis treatments (bisphosphonates, SERMs, etc)	0	0.0	0	0.0	0	0.0	20	1.5	7	1.2	13	1.8
Local (vaginal) hormone treatments	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Prior safety events during 12 months pre-index period[1]												
Any safety event (total; any category)	**1**	**4.3**	**1**	**6.3**	**0**	**0.0**	**26**	**2.0**	**13**	**2.2**	**13**	**1.8**

Table 76. Baseline clinical characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: Spain; source: LPD; Annual Reporting Period III]

	Spain											
	Longitudinal database: LPD											
	Reported study period: 31 March 2018 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
History of VTE/stroke/ CHD/ PVD event	0	0.0	0	0.0			8	0.6	0	0.0	8	1.1
History of malignancy potentially associated with oestrogen	1	4.3	1	6.3			3	0.2	3	0.5	0	0.0
History of any malignancy	1	4.3	1	6.3			18	1.4	13	2.2	5	0.7
Indication for study medication (main analysis[1,2]												
Oestrogen deficiency symptoms only	10	43.5	7	43.8	3	42.9	189	14.3	82	13.9	107	14.7
Osteoporosis only	1	4.3	1	6.3	0	0.0	29	2.2	9	1.5	20	2.7
Oestrogen deficiency symptoms and osteoporosis	0	0.0	0	0.0	0	0.0	4	0.3	1	0.2	3	0.4
No oestrogen deficiency symptoms or osteoporosis or missing	12	52.2	8	50.0	4	57.1	1099	83.2	499	84.4	600	82.2
Indication for study medication (additional analysis)[1,3]												
Oestrogen deficiency symptoms only	10	43.5	7	43.8	3	42.9	197	14.9	84	14.2	113	15.5
Osteoporosis only	1	4.3	1	6.3	0	0.0	33	2.5	10	1.7	23	3.2
Oestrogen deficiency symptoms and osteoporosis	0	0.0	0	0.0	0	0.0	5	0.4	1	0.2	4	0.5
No oestrogen deficiency symptoms or osteoporosis or missing	12	52.2	8	50.0	4	57.1	1086	82.2	496	83.9	590	80.8

1. % of total N
2. Time period for analysis: index date ±90 days
3. Time period for analysis: index date – 365 days to index date +90 days

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy
SERMs: selective oestrogen receptor modulators; CVD: cardiovascular disease; VTE: venous thromboembolism; CHD: coronary heart disease; PVD: peripheral vascular disease

10.7.2.2.5. *Duavive utilization in Spain*

The results on Duavive utilization based on index prescription are presented in Table 77 below.

10.7.2.2.5.1. Daily dose

Daily dose recommendation was available for 21 out of 23 index Duavive prescriptions (91.3%). The standard recommended dose (1 tablet per day) was documented in all 21 cases.

10.7.2.2.5.2. Days supply

In the analysis based on prescriptions with known daily dose, the mean number of days supply was 43.8 days overall and varied between 28.0 and 50.8 days in the subgroups with and without prior E+P HRT treatment. The duration of supply ranged from 28 to 324 days.

The same results were provided in the analysis based on all index prescriptions after imputation to set missing values, as daily dose information was available in the database for all except one index prescriptions.

10.7.2.2.5.3. Switchers from E+P HRT to Duavive

In total, 21.7% of the patients with Duavive prescriptions had switched from prior E+P HRT treatment.

Table 77. Duavive utilization; Overall and Stratified by Prior E+P HRT Treatment; prescription-level analysis [country: Spain; source: LPD; Annual Reporting Period III]

	Spain					
	Longitudinal database: LPD					
	Reported study period: 31 March 2018 to 30 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Total number of patients with index prescription	***23***	***100.0***	***16***	***100.0***	***7***	***100.0***
Number of (index) prescriptions with instruction on daily dosage available	**21**	**91.3**	**14**	**87.5**	**7**	**100.0**
Daily dose						
A. Analysis as reported (missing data on daily dose instruction not replaced)[1]						
1 tablet	21	100.0	14	100.0	7	100.0
<1 tablet	0	0.0	0	0.0	0	0.0
>1 tablet	0	0.0	0	0.0	0	0.0
B. Analysis based on all index prescriptions (missing data replaced)[2]						
1 tablet	23	100.0	16	100.0	7	100.0
<1 tablet	0	0.0	0	0.0	0	0.0
>1 tablet	0	0.0	0	0.0	0	0.0
Days supply						
A. Analysis as reported (missing data not replaced)[1]						
Mean (SD)	43.8 (62.7)		50.8 (74.8)		28.0 (0.0)	
Median	28.0		28.0		28.0	
Minimum – maximum	(28.0,324.0)		(28.0,324.0)		(28.0,28.0)	
B. Analysis based on all index prescriptions (missing data replaced)[2]						
Mean(SD)	43.8 (62.7)		50.8 (74.8)		28.0 (0.0)	
Median	28.0		28.0		28.0	
Minimum - maximum	(28.0,324.0)		(28.0,324.0)		(28.0,28.0)	
Switchers from E+P HRT to Duavive[2,3]	**5**	**21.7**	**n.appl.**		**5**	**71.4**

1. Based on N index prescriptions with instruction on daily dosage available
2. Based on total N index prescriptions
3. Switch: prescription of Duavive within 30 days following the end of the last filled prescription period of E+P HRT

SD: standard deviation; n.appl.: not applicable
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.7.2.2.6. *Potential off-label use of Duavive in Spain*

The results for potential off-label use of Duavive from the main analysis (see Sections 9.4.5, 9.9.4) are presented in Table 78.

Potential off-label use was identified in 21.7% of all Duavive users (28.6% in the subgroup with prior E+P HRT treatment and 18.8% in the subgroup without prior E+P HRT

treatment). The reasons for potential off-label use in these patients was presumed premenopausal age of ≤45 years (21.7%), treatment for osteoporosis only (4.3%), and malignancy potentially associated with oestrogens (4.3%).

In the sensitivity analyses, the proportion of potential off-label users increased from 21.7% to 30.4% when the presumed premenopausal age limit was changed from 45 years to 49 years (sensitivity analysis I). The results of the sensitivity analysis II and the main analysis were identical (21.7%) as well as those of sensitivity analyses I and III (30.4%) because no patients with indication osteoporosis and oestrogen deficiency symptoms were identified in the data source (Table 79).

Table 78. Potential off-label use of Duavive; Overall and Stratified by Prior E+P HRT Treatment; patient-level analysis [country: Spain; source: LPD; Annual Reporting Period III]

	Spain					
	Longitudinal database: LPD					
	Reported study period: 31 March 2018 to 30 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Total number of patients	***23***	***100.0***	***16***	***100.0***	***7***	***100.0***
Off-label use (total; any category)[1,2]	**5**	**21.7**	**3**	**18.8**	**2**	**28.6**
Patients with single categories of off-label use						
Use for treatment of osteoporosis only[3]	1	4.3	1	6.3	0	0.0
Valid N	*23*		*16*		*7*	
Use in women ≤45 years[3]	5	21.7	3	18.8	2	28.6
Valid N	*23*		*16*		*7*	
Use in women over 75 years old[3]	0	0.0	0	0.0	0	0.0
Valid N	*23*		*16*		*7*	
Use in males[3]	0	0.0	0	0.0	0	0.0
Valid N	*23*		*16*		*7*	
Prescription of non-approved dose or regimen[3]	0	0.0	0	0.0	0	0.0
Valid N	*21*		*14*		*7*	
Use with progestins, additional oestrogens or selective oestrogen receptor modulators (SERMs) [1]	0	0.0	0	0.0	0	0.0
Use in women without a uterus (hysterectomised women)[1]	0	0.0	0	0.0	0	0.0
Known, suspected, or past history of breast cancer[1]	0	0.0	0	0.0	0	0.0
Hypersensitivity (e.g., anaphylaxis/anaphylactic reactions, urticaria, drug eruption) to the active substances or to any of the excipients[1]	0	0.0	0	0.0	0	0.0
Malignancy potentially associated with oestrogen[1]	1	4.3	1	6.3	0	0.0
Active or past history of venous thromboembolism (deep venous thrombosis, pulmonary embolism, and retinal vein thrombosis) [1]	0	0.0	0	0.0	0	0.0
Active or past history of arterial thromboembolic disease (e.g., myocardial infarction, stroke) [1]	0	0.0	0	0.0	0	0.0
Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal[1]	0	0.0	0	0.0	0	0.0
Known thrombophilic disorders (e.g., protein C, protein S, or antithrombin deficiency)[1]	0	0.0	0	0.0	0	0.0
Porphyria[1]	0	0.0	0	0.0	0	0.0

Valid N: N patients with non-missing values in respective category
1. % of total N patients
2. Patients with off-label use in any category mentioned below
3. % of valid N in respective category (listed below)

Age ⩽45 years considered as proxy for premenopausal status (Section 9.4.5)
Patients can be in more than one category of potential off-label use
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy
SERMs: selective oestrogen receptor modulators

Table 79. Sensitivity analyses for potential off-label use of Duavive; Overall and Stratified by Prior E+P HRT Treatment; patient-level analysis [country: Spain; source: LPD; Annual Reporting Period III]

	Spain					
	Longitudinal database: LPD					
	Reported study period: 31 March 2018 to 30 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Total number of patients during reported period	***23***		***16***		***7***	
Main Analysis:[1,2] Definition of off-label use includes: Presumed premenopausal age limit at ≤45 years; Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms	5	21.7	3	18.8	2	28.6
Sensitivity analysis I:[1,2,3] Definition of off-label use includes: Presumed premenopausal age limit at ≤49 years; Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms	7	30.4	4	25.0	3	42.9
Sensitivity analysis II:[1,2,3] Definition of off-label use includes: Presumed premenopausal age limit at ≤45 years; Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms, OR diagnosis of prevention and/or treatment of osteoporosis, in addition to diagnosis of oestrogen deficiency symptoms	5	21.7	3	18.8	2	28.6
Sensitivity analysis III:[1,2,3] Definition of off-label use includes: Presumed premenopausal age limit at ≤49 years; Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms, OR diagnosis of prevention and/or treatment of osteoporosis, in addition to diagnosis of oestrogen deficiency symptoms	7	30.4	4	25.0	3	42.9

1. % of total N patients
2. Patients with off-label use in any category mentioned for this analysis
3. Number of patients in the categories other than presumed premenopausal age limit (sensitivity analyses I and III) remained identical to Table 78

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.7.3. Spain – Cumulative Period

10.7.3.1. Baseline Characteristics – Cumulative Period - Spain

Demographic characteristics of patients prescribed Duavive and E+P HRT for the cumulative period (31 March 2016 to 30 March 2019) in Spain are presented in Table 80.

10.7.3.1.1. ***Age***

In the Duavive cohort 58.9% of patients were 50 years or older, 37.0% were 40 to 49 years and 4.1% younger than 40 years. The proportion of the age group ≥50 years was 66.7% in the subgroup with prior E+P HRT treatment and 56.4% in the subgroup without prior E+P HRT treatment.

In the E+P HRT cohort 41.9% were ≥ 50 years, 36.1% were between 40 and 49 years and 22.0% younger than 40 years. The proportion of the age group ≥50 years was 59.1% in the subgroup with prior E+P HRT treatment and 32.4% in the subgroup without prior E+P HRT treatment.

10.7.3.1.2. ***Gender***

No patients were male in the Duavive cohort and 3.6% in the E+P HRT cohort (2.7% in the subgroup with and 4.1% in the subgroup without prior E+P HRT treatment).

10.7.3.1.3. ***BMI***

A BMI value was available for 2 of 73 patients (2.7%) in the Duavive cohort. Both patients were within the normal weight range (BMI ≥18.5 to < 25). BMI values were available for a subset of 287 out of 2,573 patients (11.2%) in the E+P HRT cohort. Within this subset, 3.5% of patients were underweight (BMI <18.5), 35.5% were in the normal weight range (BMI ≥18.5 to < 25), 31.7% were overweight (BMI ≥25 to <30) and 29.3% were obese (BMI ≥30). Similar proportions occurred in the subgroups with and without prior E+P HRT treatment.

Table 80. Demographic characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: Spain; source: LPD; Cumulative Period]

	Spain											
	Longitudinal database: LPD											
	Reported study period: 31 March 2016 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients	***73***	***100.0***	***55***	***100.0***	***18***	***100.0***	***2,573***	***100.0***	***1,668***	***100.0***	***905***	***100.0***
Age at treatment initiation[1]												
Valid N[2]	*73*	*100.0*	*55*	*100.0*	*18*	*100.0*	*2,433*	*94.6*	*1,569*	*94.1*	*864*	*95.5*
<40 years	3	4.1	3	5.5	0	0.0	535	22.0	452	28.8	83	9.6
40 to 49 years	27	37.0	21	38.2	6	33.3	879	36.1	609	38.8	270	31.3
≥50 years	43	58.9	31	56.4	12	66.7	1,019	41.9	508	32.4	511	59.1
Gender[1]												
Valid N[2]	*73*	*100.0*	*55*	*100.0*	*18*	*100.0*	*2,573*	*100.0*	*1,668*	*100.0*	*905*	*100.0*
Female	73	100.0	55	100.0	18	100.0	2,480	96.4	1,599	95.9	881	97.3
Male	0	0.0	0	0.0	0	0.0	93	3.6	69	4.1	24	2.7
Body Mass Index[1]												
Valid N[2]	*2*	*2.7*	*2*	*3.6*	0	0.0	*287*	*11.2*	*204*	*12.2*	*83*	*9.2*
<18.5: underweight	0	0.0	0	0.0			10	3.5	7	3.4	3	3.6
≥18.5 to <25: normal range	2	100.0	2	100.0			102	35.5	72	35.3	30	36.1
≥25 to <30: overweight	0	0.0	0	0.0			91	31.7	70	34.3	21	25.3
≥30: obese	0	0.0	0	0.0			84	29.3	55	27.0	29	34.9

1. % of Valid N
2. Valid N: patients with non-missing values

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.7.3.2. Clinical Characteristics and Duavive Prescribing Patterns – Cumulative Period - Spain

Baseline clinical characteristics for the cumulative period (31 March 2016 to 30 March 2019) in Spain are presented in Table 81 below.

10.7.3.2.1. ***Co-morbidities***

In the Duavive cohort 26.0% of all patients were recorded with a co-morbidity in the database of the cumulative data (27.8% and 25.5% in the subgroups with and without prior E+P HRT treatment, respectively). The most frequent co-morbidities in the Duavive cohort were hypertension (11.0% overall; 16.7% in the subgroup with and 9.1% in the subgroup

without prior E+P HRT treatment) and hyperlipidemia (11.0% overall; 11.1% and 10.9% in the subgroups with and without prior E+P HRT treatment, respectively).

The overall proportion of patients with any of the specified co-morbidities in the E+P HRT cohort was 25.9% (33.1% and 21.9% in the subgroups with and without prior E+P HRT treatment, respectively). The most frequent co-morbidities in the E+P HRT cohort were hyperlipidemia (16.5% overall; 19.7% in the subgroup with and 14.8% in the subgroup without prior E+P HRT treatment), hypertension (5.2% overall, 6.6% in the subgroup with and 4.5% in the subgroup without prior E+P HRT treatment), osteoarthritis (4.5% overall, 7.4% in the subgroup with and 2.9% in the subgroup without prior E+P HRT treatment), osteoporosis/ osteopenia (2.4% overall; 4.2% in the subgroup with and 1.4% in the subgroup without prior E+P HRT treatment) and diabetes (2.3% overall; 4.0% in the subgroup with and 1.4% in the subgroup without prior E+P HRT treatment). For the other co-morbidities please refer to Table 81.

10.7.3.2.2. ***Co-medication***

In the Duavive cohort at least one prescription of specified co-medications during the 12-month pre-index period was identified in 38.4% of patients. The most frequently co-prescribed drugs were antidepressants (23.3%), lipid lowering agents (13.7%), sedatives/hypnotics (8.2%), anticoagulants (4.1%), antiarrhythmics (2.7%) and antidiabetics (2.7%).

In the E+P HRT cohort, at least one prescription of one of the specified co-medications was identified in 40.2% of patients (46.3% in the subgroup with and 36.9% in the subgroup without prior E+P HRT treatment). The most frequently co-prescribed drugs were antidepressants (20.7%), lipid lowering agents (13.9%), sedatives/hypnotics (7.1%), anticoagulants (6.2%), corticosteroids (6.1%) and antidiabetics (3.0%). For proportions in the subgroups with and without prior E+P HRT treatment please refer to Table 81.

10.7.3.2.3. ***Prior safety events***

Two prior safety events (2.7%) during 12-month pre-index period were identified in the Duavive cohort (1 in the subgroup with and 1 in the subgroup without prior E+P HRT treatment). The overall proportion of patients with any safety event in the E+P HRT cohort was 2.0% (1.9% in the subgroup with prior E+P HRT treatment and 2.0% in the subgroup without). For single categories of prior safety events please refer to Table 81.

10.7.3.2.4. ***Indication***

The results on indication for use of study medication at index date are presented in Table 81 below.

Analysis of the period 90 days before and 90 days after index date showed that Duavive was prescribed for oestrogen deficiency symptoms in 46.6% of patients. Duavive was prescribed for oestrogen deficiency symptoms only in 50.0% of patients with prior E+P HRT treatment and 45.5% of patients without prior E+P HRT treatment. Osteoporosis only was the indication for 5.5% of the patients, all of them had not received prior E+P HRT prescriptions. No patient received Duavive with oestrogen deficiency and osteoporosis as an indication. For

47.9% of patients (50.0% with prior E+P HRT treatment and 47.3% of patients without prior E+P HRT) no record of oestrogen deficiency symptoms or osteoporosis as indication was identified.

In the E+P HRT cohort, 14.0% of patients received E+P HRT treatment for oestrogen deficiency symptoms (16.9% in the subgroup with prior E+P HRT treatment and 12.5% in the subgroup without). The overall proportion of patients who were prescribed E+P HRT for osteoporosis only was 1.9% and for both oestrogen deficiency symptoms and osteoporosis 0.2%. For 83.9% of all patients in the E+P HRT cohort, no diagnosis or a diagnosis other than oestrogen deficiency symptoms or osteoporosis was documented. The corresponding values were 79.6% in the subgroup with and 86.2% in the subgroup without prior E+P HRT treatment.

An additional analysis of the period 365 days before and 90 days after index date showed the same indication pattern for the Duavive cohort as the analysis for index date ± 90 days. In the E+P HRT cohort the distribution among the indications was also similar between the two analyses.

Table 81. Baseline clinical characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: Spain; source: LPD; Cumulative Period]

	Spain											
	Longitudinal database: LPD											
	Reported study period: 31 March 2016 – 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients	***73***	***100.0***	***55***	***100.0***	***18***	***100.0***	***2,573***	***100.0***	***1,668***	***100.0***	***905***	***100.0***
Co-morbidities during 12 months pre-index period[1]												
Any co-morbidity	**19**	**26.0**	**14**	**25.5**	**5**	**27.8**	**666**	**25.9**	**366**	**21.9**	**300**	**33.1**
Osteoporosis/ osteopenia	4	5.5	4	7.3	0	0.0	61	2.4	23	1.4	38	4.2
History of CVD event	0	0.0	0	0.0	0	0.0	1	0.0	0	0.0	1	0.1
Hyperlipidemia	8	11.0	6	10.9	2	11.1	425	16.5	247	14.8	178	19.7
Hypertension	8	11.0	5	9.1	3	16.7	135	5.2	75	4.5	60	6.6
Breast pain	0	0.0	0	0.0	0	0.0	12	0.5	8	0.5	4	0.4
Diabetes	2	2.7	1	1.8	1	5.6	59	2.3	23	1.4	36	4.0
Renal disease	0	0.0	0	0.0	0	0.0	1	0.0	0	0.0	1	0.1
Osteoarthritis	0	0.0	0	0.0	0	0.0	116	4.5	49	2.9	67	7.4
Major depression	0	0.0	0	0.0	0	0.0	1	0.0	0	0.0	1	0.1
Co-medication during 12 months pre-index period[1]												
Any co-medication	**28**	**38.4**	**21**	**38.2**	**7**	**38.9**	**1,034**	**40.2**	**615**	**36.9**	**419**	**46.3**
Corticosteroids	1	1.4	1	1.8	0	0.0	156	6.1	95	5.7	61	6.7
Lipid lowering agents	10	13.7	8	14.5	2	11.1	358	13.9	195	11.7	163	18.0
Anti-hypertensives	0	0.0	0	0.0	0	0.0	8	0.3	5	0.3	3	0.3
Anticoagulants	3	4.1	3	5.5	0	0.0	159	6.2	94	5.6	65	7.2
Antiarrhythmics	2	2.7	2	3.6	0	0.0	25	1.0	17	1.0	8	0.9
Antidepressants	17	23.3	12	21.8	5	27.8	533	20.7	319	19.1	214	23.6
Sedatives/ hypnotics	6	8.2	4	7.3	2	11.1	182	7.1	118	7.1	64	7.1
Antidiabetics	2	2.7	1	1.8	1	5.6	76	3.0	35	2.1	41	4.5
Osteoporosis treatments (bisphosphonates, SERMs, etc)	1	1.4	1	1.8	0	0.0	35	1.4	15	0.9	20	2.2
Local (vaginal) hormone treatments	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Prior safety events during 12 months pre-index period[1]												
Any safety event (total; any category)	**2**	**2.7**	**1**	**1.8**	**1**	**5.6**	**51**	**2.0**	**34**	**2.0**	**17**	**1.9**
History of VTE/stroke/ CHD/ PVD event	0	0.0	0	0.0	0	0.0	16	0.6	8	0.5	8	0.9
History of malignancy potentially associated with oestrogen	1	1.4	1	1.8	0	0.0	3	0.1	2	0.1	1	0.1
History of any malignancy	2	2.7	1	1.8	1	5.6	35	1.4	26	1.6	9	1.0

Table 81. Baseline clinical characteristics; Overall and Stratified by Therapy and Prior E+P HRT Treatment; patient-level analysis [country: Spain; source: LPD; Cumulative Period]

	Spain											
	Longitudinal database: LPD											
	Reported study period: 31 March 2016 – 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Indication for study medication (main analysis[1,2]												
Oestrogen deficiency symptoms only	34	46.6	25	45.5	9	50.0	361	14.0	208	12.5	153	16.9
Osteoporosis only	4	5.5	4	7.3	0	0.0	48	1.9	20	1.2	28	3.1
Oestrogen deficiency symptoms and osteoporosis	0	0.0	0	0.0	0	0.0	6	0.2	2	0.1	4	0.4
No oestrogen deficiency symptoms or osteoporosis or missing	35	47.9	26	47.3	9	50.0	2,158	83.9	1,438	86.2	720	79.6
Indication for study medication (additional analysis)[1,3]												
Oestrogen deficiency symptoms only	34	46.6	25	45.5	9	50.0	375	14.6	213	12.8	162	17.9
Osteoporosis only	4	5.5	4	7.3	0	0.0	55	2.1	21	1.3	34	3.8
Oestrogen deficiency symptoms and osteoporosis	0	0.0	0	0.0	0	0.0	8	0.3	3	0.2	5	0.6
No oestrogen deficiency symptoms or osteoporosis or missing	35	47.9	26	47.3	9	50.0	2,135	83.0	1,431	85.8	704	77.8

1. % of total N
2. Time period for analysis: index date ±90 days
3. Time period for analysis: index date – 365 days to index date +90 days

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy
SERMs: selective oestrogen receptor modulators; CVD: cardiovascular disease; VTE: venous thromboembolism; CHD: coronary heart disease; PVD: peripheral vascular disease

10.7.3.2.5. *Duavive utilization in Spain*

The results on Duavive utilization between 31 March 2016 and 30 March 2019 based on index prescription are presented in Table 82 below.

10.7.3.2.5.1. Daily dose

Daily dose recommendation was available for 67 out of 73 index Duavive prescriptions (91.8%). The standard recommended dose (1 tablet per day) was documented in all the cases.

10.7.3.2.5.2. Days supply

In the analysis based on prescriptions with known daily dose, mean days supply was 38.4 days overall and varied between 28.0 and 41.8 days in the subgroups with and without prior E+P HRT treatment, respectively. The duration ranged from 28 to 324 days.

The days supply did not change after imputation to set missing values to the standard Duavive dose and supply.

10.7.3.2.5.3. Switchers from E+P HRT to Duavive

In total, 15.1% of the patients with Duavive prescriptions had switched from prior E+P HRT treatment.

Table 82. Duavive utilization; Overall and Stratified by Prior E+P HRT Treatment; prescription-level analysis [country: Spain; source: LPD; Cumulative Period]

	Spain					
	Longitudinal database: LPD					
	Reported study period: 31 March 2016 to 30 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Total number of patients with index prescription	***73***	***100.0***	***55***	***100.0***	***18***	***100.0***
Number of (index) prescriptions with instruction on daily dosage available	**67**	**91.8**	**49**	**89.1**	**18**	**100.0**
Daily dose						
A. Analysis as reported (missing data on daily dose instruction not replaced)[1]						
1 tablet	67	100.0	49	100.0	18	100.0
<1 tablet	0	0.0	0	0.0	0	0.0
>1 tablet	0	0.0	0	0.0	0	0.0
B. Analysis based on all index prescriptions (missing data replaced)[2]						
1 tablet	73	100.0	55	100.0	18	100.0
<1 tablet	0	0.0	0	0.0	0	0.0
>1 tablet	0	0.0	0	0.0	0	0.0
Days supply						
A. Analysis as reported (missing data not replaced)[1]						
Mean (SD)	38.4 (43.8)		41.8 (50.1)		28.0 (0.0)	
Median	28.0		28.0		28.0	
Minimum – maximum	(28.0,324.0)		(28.0,324.0)		(28.0,28.0)	

Table 82. Duavive utilization; Overall and Stratified by Prior E+P HRT Treatment; prescription-level analysis [country: Spain; source: LPD; Cumulative Period]

	Spain					
	Longitudinal database: LPD					
	Reported study period: 31 March 2016 to 30 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
B. Analysis based on all index prescriptions (missing data replaced)[2]						
Mean (SD)	38.4 (43.8)		41.8 (50.1)		28.0 (0.0)	
Median	28.0		28.0		28.0	
Minimum - maximum	(28.0,324.0)		(28.0,324.0)		(28.0,28.0)	
Switchers from E+P HRT to Duavive[2,3]	**11**	**15.1**	**n.appl.**		**11**	**61.1**

1. Based on N index prescriptions with instruction on daily dosage available
2. Based on total N index prescriptions

SD: standard deviation; n.appl.: not applicable

3. Switch: prescription of Duavive within 30 days following the end of the last filled prescription period of E+P HRT

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.7.3.2.6. *Potential off-label use of Duavive in Spain*

The results for potential off-label use of Duavive from the main analysis (see Sections 9.4.5, 9.9.4) for the reporting period from 31 March 2016 to 30 March 2019 are presented in Table 83.

Potential off-label use was identified in 28.8% of all Duavive users (16.7% and 32.7% in the subgroups with and without prior E+P HRT treatment). The reasons for potential off-label use were presumed premenopausal age of ≤45 years (24.7%), treatment for osteoporosis only (5.5%), hypersensitivity to the active substances or excipients (1.4%) and malignancy potentially associated with oestrogens (1.4%).

In the sensitivity analyses, the proportion of potential off-label users increased from 28.8% to 45.2% when the presumed premenopausal age limit was changed from 45 years to 49 years (sensitivity analysis I). The results of the sensitivity analysis II and the main analysis were identical (28.8%) as well as those of sensitivity analyses I and III (45.2%) because no patients with indication osteoporosis and oestrogen deficiency symptoms were identified in the data source (Table 84).

Table 83. Potential off-label use of Duavive; Overall and Stratified by Prior E+P HRT Treatment; patient-level analysis [country: Spain; source: LPD; Cumulative Period]

	Spain					
	Longitudinal database: LPD					
	Reported study period: 31 March 2016 to 30 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Total number of patients	***73***	***100.0***	***55***	***100.0***	***18***	***100.0***
Off-label use (total; any category)[1,2]	**21**	**28.8**	**18**	**32.7**	**3**	**16.7**
Patients with single categories of off-label use						
Use for treatment of osteoporosis only[3]	4	5.5	4	7.3	0	0.0
Valid N	*73*		*55*		*18*	
Use in women ≤45 years[3]	18	24.7	15	27.3	3	16.7
Valid N	*73*		*55*		*18*	
Use in women over 75 years old[3]	0	0.0	0	0.0	0	0.0
Valid N	*73*		*55*		*18*	
Use in males[3]	0	0.0	0	0.0	0	0.0
Valid N	*73*		*55*		*18*	
Prescription of non-approved dose or regimen[3]	0	0.0	0	0.0	0	0.0
Valid N	*67*		*49*		*18*	
Use with progestins, additional oestrogens or selective oestrogen receptor modulators (SERMs) [1]	0	0.0	0	0.0	0	0.0
Use in women without a uterus (hysterectomised women)[1]	0	0.0	0	0.0	0	0.0
Known, suspected, or past history of breast cancer[1]	0	0.0	0	0.0	0	0.0
Hypersensitivity (e.g., anaphylaxis/anaphylactic reactions, urticaria, drug eruption) to the active substances or to any of the excipients[1]	1	1.4	1	1.8	0	0.0
Malignancy potentially associated with oestrogen[1]	1	1.4	1	1.8	0	0.0
Active or past history of venous thromboembolism (deep venous thrombosis, pulmonary embolism, and retinal vein thrombosis) [1]	0	0.0	0	0.0	0	0.0
Active or past history of arterial thromboembolic disease (e.g., myocardial infarction, stroke) [1]	0	0.0	0	0.0	0	0.0
Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal[1]	0	0.0	0	0.0	0	0.0
Known thrombophilic disorders (e.g., protein C, protein S, or antithrombin deficiency)[1]	0	0.0	0	0.0	0	0.0
Porphyria[1]	0	0.0	0	0.0	0	0.0

Valid N: N patients with non-missing values in respective category
1. % of total N patients
2. Patients with off-label use in any category mentioned below
3. % of valid N in respective category (listed below)

Age ⩽45 years considered as proxy for premenopausal status (Section 9.4.5)
Patients can be in more than one category of potential off-label use
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy
SERMs: selective oestrogen receptor modulators

Table 84. Sensitivity analyses for potential off-label use; Overall and Stratified by Prior E+P HRT Treatment; patient-level analysis [country: Spain; source: LPD; Cumulative Period]

	Spain					
	Longitudinal database: LPD					
	Reported study period: 31 March 2016 to 30 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Total number of patients during reported period	***73***		***55***		***18***	
Main Analysis:[1,2] Definition of off-label use includes Presumed premenopausal age limit at ≤45 years; Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms	21	28.8	18	32.7	3	16.7
Sensitivity analysis I:[1,2,3] Definition of off-label use includes Presumed premenopausal age limit at ≤49 years; Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms	33	45.2	27	49.1	6	33.3
Sensitivity analysis II:[1,2,3] Definition of off-label use includes Presumed premenopausal age limit at ≤45 years; Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms, OR diagnosis of prevention and/or treatment of osteoporosis, in addition to diagnosis of oestrogen deficiency symptoms	21	28.8	18	32.7	3	16.7

Table 84. Sensitivity analyses for potential off-label use; Overall and Stratified by Prior E+P HRT Treatment; patient-level analysis [country: Spain; source: LPD; Cumulative Period]

	Spain					
	Longitudinal database: LPD					
	Reported study period: 31 March 2016 to 30 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Sensitivity analysis III:[1,2,3]	33	45.2	27	49.1	6	33.3
Definition of off-label use includes						
Presumed premenopausal age limit at ≤49 years;						
Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms, OR diagnosis of prevention and/or treatment of osteoporosis, in addition to diagnosis of oestrogen deficiency symptoms						

1. % of total N patients
2. Patients with off-label use in any category mentioned for this analysis
3. Number of patients in the categories other than presumed premenopausal age limit (sensitivity analyses I and III) remained identical to Table 83

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.8. Other Analyses

10.8.1. Additional Analysis of Indication and Potential Off-label Use

As described in Section 9.9.5.3, additional analyses were performed with an extended baseline period for identifying and assigning an indication for Duavive treatment. The time period was extended to 365 days prior to index date to 90 days after index date (instead of 90 days prior to index date to 90 days after index date).

For indication of use, this extension of the historical period from 90 to 365 days prior to index date did not lead to any further identification and assignment of indication for France and Spain (see Sections 10.5 and 10.7), (i.e., no change in results with regards to potential off-label use were observed). In Belgium and the Netherlands, these analyses were not possible as a diagnosis is not recorded in the LRx longitudinal databases. In the UK, the available sample size was too limited (see Section 10.4). Therefore, only results of the additional analyses for Italy are presented here.

10.8.1.1. Additional Analysis – Annual Reporting Period III (Italy)

10.8.1.1.1. ***Additional analysis of indication:***

As shown in Table 85, by increasing the historical period to 365 days prior to index date, no changes in the number of patients with oestrogen deficiency symptoms only or oestrogen deficiency symptoms and osteoporosis were identified. The number of patients with a documented diagnosis of osteoporosis only increased from 4 (7.7%) to 5 (9.6%). Consequently, the percentage of patients with neither oestrogen deficiency symptoms nor osteoporosis or missing diagnoses was reduced from 19 (36.5%) to 18 (34.6%).

Table 85. Additional analysis for indication according to time period around index date; overall and stratified by therapy and prior E+P HRT treatment [country: Italy; source: LPD; Annual Reporting Period III]

	Italy											
	Longitudinal database: LPD											
	Reported study period: 31 March 2018 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	N	%	N	%
Total number of patients	***52***	***100.0***	***37***	***100.0***	***15***	***100.0***	***3,073***	***100.0***	***736***	***100.0***	***2,337***	***100.0***
Indication for study medication (main analysis)[1,2]												
Oestrogen deficiency symptoms only	23	44.2	17	45.9	6	40.0	1,586	45.3	476	39.4	1,110	48.5
Osteoporosis only	4	7.7	3	8.1	1	6.7	87	2.5	25	2.1	62	2.7
Oestrogen deficiency symptoms and osteoporosis	6	11.5	5	13.5	1	6.7	124	3.5	42	3.5	82	3.6
No oestrogen deficiency symptoms or osteoporosis or missing	19	36.5	12	32.4	7	46.7	1,702	48.6	665	55.0	1,037	45.3
Indication for study medication (additional analysis)[1,3]												
Oestrogen deficiency symptoms only	23	44.2	17	45.9	6	40.0	1,593	45.5	477	39.5	1,116	48.7
Osteoporosis only	5	9.6	3	8.1	2	13.3	112	3.2	32	2.6	80	3.5
Oestrogen deficiency symptoms and osteoporosis	6	11.5	5	13.5	1	6.7	206	5.9	62	5.1	144	6.3
No oestrogen deficiency symptoms or osteoporosis or missing	18	34.6	12	32.4	6	40.0	1,588	45.4	637	52.7	951	41.5

1. % of total N
2. Time period for analysis: index date ±90 days
3. Time period for analysis: index date – 365 days to index date +90 days

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.8.1.1.2. *Additional Analyses of Potential Off-label use of Duavive (Italy)*

Effects of the extension of the historical period on the percentage of patients with potential off-label use were also evaluated. Results are presented in Table 86. In comparison to the analyses presented in Table 67 (where indications from 90 days before to 90 days after index date were considered), a slight increase in the total proportion of potential off-label users was observed in the main analysis (from 19.2% to 21.2%) and sensitivity analysis II (from 30.8% to 32.7%). This was due to the addition of one patient with a diagnosis of osteoporosis.

Table 86. Additional analysis: Sensitivity analyses for potential off-label use; overall and stratified by prior E+P HRT treatment; patient-level analysis based on an extended time period around index date [country: Italy; source: LPD; Annual Reporting Period III]§

	Italy					
	Longitudinal database: LPD					
	Reported study period: 31 March 2018 to 30 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Total number of patients during reported period	***52***		***37***		***15***	
Main Analysis:[1,2] Definition of off-label use includes Presumed premenopausal age limit at ≤45 years; Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms	11	21.2	6	16.2	5	33.3
Sensitivity analysis I:[1,2,3] Definition of off-label use includes Presumed premenopausal age limit at ≤49 years; Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms	20	38.5	13	35.1	7	46.7
Sensitivity analysis II:[1,2,3] Definition of off-label use includes Presumed premenopausal age limit at ≤45 years; Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms, OR diagnosis of prevention and/or treatment of osteoporosis, in addition to diagnosis of oestrogen deficiency symptoms	17	32.7	11	29.7	6	40.0

Table 86. Additional analysis: Sensitivity analyses for potential off-label use; overall and stratified by prior E+P HRT treatment; patient-level analysis based on an extended time period around index date [country: Italy; source: LPD; Annual Reporting Period III]§

	Italy					
	Longitudinal database: LPD					
	Reported study period: 31 March 2018 to 30 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Sensitivity analysis III:[1,2,3]	25	48.1	17	45.9	8	53.3
Definition of off-label use includes						
Presumed premenopausal age limit at ≤49 years;						
Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms, OR diagnosis of prevention and/or treatment of osteoporosis, in addition to diagnosis of oestrogen deficiency symptoms						

§ Results in this table are based on additional analysis of indication for Duavive (diagnoses from time period index date – 365 days to index date+90 days)
1. % of total N patients
2. Patients with off-label use in any category mentioned for this analysis
3. Number of patients in the categories other than presumed premenopausal age limit (sensitivity analyses I and III) or indication for use (sensitivity analyses II and III) remained identical to Table 66

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.8.1.2. Additional Analysis – Cumulative Period (Italy)

10.8.1.2.1. ***Additional analysis of indication:***

As shown in Table 87 the number of patients with a documented diagnosis of oestrogen deficiency symptoms only increased by 1 patient (from 48.9% to 49.3%) after increasing the baseline period from 90 to 365 days. Thirteen (13) patients (5.8%) instead of 11 patients (4.9%) were identified with osteoporosis only. The percentage of patients with both oestrogen deficiency symptoms and osteoporosis increased from 4.5% (10 patients) to 6.7% (15 patients). Consequently, the percentage of patients with neither oestrogen deficiency symptoms nor osteoporosis or with missing diagnoses was reduced from 41.7% to 38.1%.

Table 87. Additional analysis for indication, according to time period around index date; overall and stratified by therapy and prior E+P HRT treatment [country: Italy; source: LPD; Cumulative Period]

	Italy											
	Longitudinal database: LPD											
	Reported study period: 31 March 2016 to 30 March 2019											
	Duavive						E+P HRT					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients	***223***	***100.0***	***154***	***100.0***	***69***	***100.0***	***6,288***	***100.0***	***3,652***	***100.0***	***2,636***	***100.0***
Indication for study medication (main analysis)[1,2]												
Oestrogen deficiency symptoms only	109	48.9	79	51.3	30	43.5	2,644	42.0	1,345	36.8	1,299	49.3
Osteoporosis only	11	4.9	8	5.2	3	4.3	128	2.0	72	2.0	56	2.1
Oestrogen deficiency symptoms and osteoporosis	10	4.5	7	4.5	3	4.3	198	3.1	106	2.9	92	3.5
No oestrogen deficiency symptoms or osteoporosis or missing	93	41.7	60	39.0	33	47.8	3,318	52.8	2,129	58.3	1,189	45.1
Indication for study medication (additional analysis)[1,3]												
Oestrogen deficiency symptoms only	110	49.3	80	51.9	30	43.5	2,675	42.5	1,349	36.9	1,326	50.3
Osteoporosis only	13	5.8	7	4.5	6	8.7	178	2.8	96	2.6	82	3.1
Oestrogen deficiency symptoms and osteoporosis	15	6.7	9	5.8	6	8.7	288	4.6	156	4.3	132	5.0
No oestrogen deficiency symptoms or osteoporosis or missing	85	38.1	58	37.7	27	39.1	3,147	50.0	2,051	56.2	1,096	41.6

1. % of total N
2. Time period for analysis: index date ±90 days
3. Time period for analysis: index date – 365 days to index date +90 days

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.8.1.2.2. *Additional Analyses of Potential Off-label use of Duavive in Italy*

Effects of the extension of the historical period on the percentage of patients with potential off-label use were also evaluated. Results for Italy are presented in Table 88. In comparison to the analyses presented in Table 72 (where indications from 90 days before to 90 days after index date were considered), an increase in the total proportion of potential off-label users was observed in the main analysis (from 15.2% to 16.6%) and sensitivity analysis I (from 31.8% to 32.7%) due to the addition of patients with a diagnosis of osteoporosis, and in sensitivity analyses II and III (from 19.7% to 22.4% and from 35.4% to 37.7%, respectively)

due to the addition of patients with a diagnosis of osteoporosis in conjunction with or without a diagnosis of oestrogen deficiency symptoms.

Table 88. Additional analysis: Sensitivity analyses for potential off-label use; overall and stratified by prior E+P HRT treatment; patient-level analysis based on an extended time period around index date [country: Italy; source: LPD; Cumulative Period]

	Italy					
	Longitudinal database: LPD					
	Reported study period: 31 March 2016 to 30 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Total number of patients during reported period	***223***		***154***		***69***	
Main Analysis:[1,2] Definition of off-label use includes Presumed premenopausal age limit at ≤45 years; Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms	37	16.6	22	14.3	15	21.7
Sensitivity analysis I:[1,2,3] Definition of off-label use includes Presumed premenopausal age limit at ≤49 years; Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms	73	32.7	51	33.1	22	31.9
Sensitivity analysis II:[1,2,3] Definition of off-label use includes Presumed premenopausal age limit at ≤45 years; Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms, OR diagnosis of prevention and/or treatment of osteoporosis, in addition to diagnosis of oestrogen deficiency symptoms	50	22.4	30	19.5	20	29.0

Table 88. Additional analysis: Sensitivity analyses for potential off-label use; overall and stratified by prior E+P HRT treatment; patient-level analysis based on an extended time period around index date [country: Italy; source: LPD; Cumulative Period]

	Italy					
	Longitudinal database: LPD					
	Reported study period: 31 March 2016 to 30 March 2019					
	Duavive					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%
Sensitivity analysis III:[1,2,3]	84	37.7	57	37.0	27	39.1
Definition of off-label use includes						
Presumed premenopausal age limit at ≤49 years;						
Diagnosis of prevention and/or treatment of osteoporosis, and no diagnosis of oestrogen deficiency symptoms, OR diagnosis of prevention and/or treatment of osteoporosis, in addition to diagnosis of oestrogen deficiency symptoms						

§ Results in this table are based on additional analysis of indication for Duavive (diagnoses from time period index date – 365 days to index date+90 days)
1. % of total N patients
2. Patients with off-label use in any category mentioned for this analysis
3. Number of patients in the categories other than presumed premenopausal age limit (sensitivity analyses I and III) or indication for use (sensitivity analyses II and III) remained identical to Table 71

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.8.2. Additional Analysis of Indication "Oestrogen Deficiency Symptoms" in Age Group ≤45 years

In the main analysis of potential off-label use of Duavive, age ≤45 years was considered as a proxy for premenopausal status. As described in Section 9.9.5.3, an additional analysis for the indication "oestrogen deficiency symptoms" in women aged ≤45 years was performed for Italy and Spain, as a diagnosis of oestrogen deficiency symptoms may indicate postmenopausal status.

10.8.2.1. Additional Analysis of Indication in Age group ≤45 years – Italy

As shown in Table 89, 1 of 5 women aged ≤45 years (20.0%) were identified in Annual Reporting Period III with "oestrogen deficiency symptoms only" as the indication for Duavive, suggesting postmenopausal status. The proportion remained the same when the historical period for identification of diagnoses was extended to 365 days prior to index date.

In the cumulative period, 6 of 20 women (30.0%) aged ≤45 years were identified with an indication for Duavive of "oestrogen deficiency symptoms only"; this proportion was 35.0%

(7 of 20 women), if the historical period for identification of diagnoses was extended to 365 days prior to index date.

Table 89. Additional analysis: Indication for Duavive in age group ≤45 years; overall and stratified by prior E+P HRT treatment; patient-level analysis [country: Italy; source: LPD; Annual III and Cumulative Periods]

	Italy											
	Longitudinal database: LPD											
	Annual Reporting Period III 31 March 2018 to 30 March 2019						Cumulative period 31 March 2016 to 30 March 2019					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Total number of females	***52***	***100.0***	***37***	***100.0***	***15***	***100.0***	***222***	***100.0***	***153***	***100.0***	***69***	***100.0***
Total number of females aged ≤45 years[1]	**5**	**9.6**	**2**	**5.4**	**3**	**20.0**	**20**	**9.0**	**13**	**8.5**	**7**	**10.1**
Indication for study medication (main analysis[2,3]												
Oestrogen deficiency symptoms only	1	20.0	1	50.0	0	0.0	6	30.0	4	30.8	2	28.6
Osteoporosis only	0	0.0	0	0.0	0	0.0	2	10.0	2	15.4	0	0.0
Oestrogen deficiency symptoms and osteoporosis	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
No oestrogen deficiency symptoms or osteoporosis or missing	4	80.0	1	50.0	3	100.0	12	60.0	7	53.8	5	71.4
Indication for study medication (additional analysis)[2,4]												
Oestrogen deficiency symptoms only	1	20.0	1	50.0	0	0.0	7	35.0	4	30.8	3	42.9
Osteoporosis only	0	0.0	0	0.0	0	0.0	1	5.0	1	7.7	0	0.0
Oestrogen deficiency symptoms and osteoporosis	0	0.0	0	0.0	0	0.0	1	5.0	1	7.7	0	0.0
No oestrogen deficiency symptoms or osteoporosis or missing	4	80.0	1	50.0	3	100.0	11	55.0	7	53.8	4	57.1

1. % of total N females
2. % of total N female patients in age group ⩽45 years
3. Time period for analysis: index date ±90 days
4. Time period for analysis: index date – 365 days to index date +90 days

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.8.2.2. Additional Analysis of Indication in Age group ≤45 years – Spain

As shown in Table 90, no female patients were identified in the Annual Reporting Period III with indication for Duavive "oestrogen deficiency symptoms only" suggesting postmenopausal status. This proportion remained the same if the historical period for identification of diagnoses was extended to 365 days prior to index date.

In the cumulative period, 4 of 18 women (22.2%) aged ≤45 years were identified with indication for Duavive "oestrogen deficiency symptoms only"; this proportion remained the same if the historical period for identification of diagnoses was extended to 365 days prior to index date.

Table 90. Additional analysis: Indication for Duavive in age group ≤45 years; overall and stratified by prior E+P HRT treatment; patient-level analysis [country: Spain; source: LPD; Annual and Cumulative Periods]

	Spain											
	Longitudinal database: LPD											
	Annual Reporting Period III 31 March 2018 to 30 March 2019						Cumulative period 31 March 2016 to 30 March 2019					
	Total		Without prior treatment E+P HRT		With prior treatment E+P HRT		Total		Without prior treatment E+P HRT		With prior treatment E+P HRT	
	n	%	n	%	n	%	n	%	n	%	n	%
Total number of females	***23***	***100.0***	***16***	***100.0***	***7***	***100.0***	***73***	***100.0***	***55***	***100.0***	***18***	***100.0***
Total number of females aged ≤45 years[1]	**5**	**21.7**	**3**	**18.8**	**2**	**28.6**	**18**	**24.7**	**15**	**27.3**	**3**	**16.7**
Indication for study medication (main analysis[2,3]												
Oestrogen deficiency symptoms only	0	0.0	0	0.0	0	0.0	4	22.2	4	26.7	0	0.0
Osteoporosis only	1	20.0	1	33.3	0	0.0	2	11.1	2	13.3	0	0.0
Oestrogen deficiency symptoms and osteoporosis	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
No oestrogen deficiency symptoms or osteoporosis or missing	4	80.0	2	66.7	2	100.0	12	66.7	9	60.0	3	100.0
Indication for study medication (additional analysis)[2,4]												
Oestrogen deficiency symptoms only	0	0.0	0	0.0	0	0.0	4	22.2	4	26.7	0	0.0
Osteoporosis only	1	20.0	1	33.3	0	0.0	2	11.1	2	13.3	0	0.0
Oestrogen deficiency symptoms and osteoporosis	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
No oestrogen deficiency symptoms or osteoporosis or missing	4	80.0	2	66.7	2	100.0	12	66.7	9	60.0	3	100.0

1. % of total N females
2. % of total N female patients in age group ≤45 years
3. Time period for analysis: index date ±90 days
4. Time period for analysis: index date – 365 days to index date +90 days

E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

10.8.3. Additional Analysis of Age at Duavive Initiation Among Women Aged ≤49 years

Data on women's age at Duavive initiation date in the annual and cumulative period three years after launch in Belgium, France, Italy, the Netherlands and Spain are presented in

Table 91 and Table 92 below. Data for the UK cannot be presented due to privacy concerns. The vast majority of women aged 49 years or younger who initiated Duavive are between 40 to 49 years of age.

Table 91. Age of female Duavive initiators in age group ≤49 years during Annual Reporting Period III

	Reported study period: 31 March 2018 to 30 March 2019				
	Belgium (LRx)	**France (LPD)**	**Italy (LPD)**	**The Netherlands (LRx)**	**Spain (LPD)**
	n (%)[1]	**n (%)[1]**	**n (%)[1]**	**n (%)[1]**	**n (%)[1]**
Total females[2]	**75 (100.0)**	**0**	**52 (100.0)**	**83 (100.0)**	**23 (100.0)**
Total females ≤49 years	**3 (4.0)**	**0**	**15 (28.8)**	**21 (25.3)**	**7 (30.4)**
0-4 years	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
5-9 years	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
10-14 years	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
15-19 years	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
20-24 years	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.6)	0 (0.0)
25-29 years	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)
30-34 years	0 (0.0)	0 (0.0)	1 (1.9)	2 (2.4)	0 (0.0)
35-39 years	0 (0.0)	0 (0.0)	1 (1.9)	2 (2.4)	0 (0.0)
40-44 years	0 (0.0)	0 (0.0)	2 (3.8)	5 (6.0)	3 (13.0)
45-49 years	3 (4.0)	0 (0.0)	11 (21.2)	9 (10.8)	3 (13.0)

1. % of total number females
2. observations with non-missing values

Table 92. Age of female Duavive initiators in age group ≤49 years during Cumulative Period

	Reported study period: 31 March 2016 to 30 March 2019				
	Belgium (LRx)	**France (LPD)**	**Italy (LPD)**	**The Netherlands (LRx)**	**Spain (LPD)**
	n (%)[1]	**n (%)[1]**	**n (%)[1]**	**n (%)[1]**	**n (%)[1]**
Total females[2]	**458 (100.0)**	**22 (100.0)**	**222 (100.0)**	**175(100.0)**	**73 (100.0)**
Total females ≤49 years	**29 (6.3)**	**4 (18.2)**	**57 (25.7)**	**38 (21.7)**	**30 (40.0)**
0-4 years	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
5-9 years	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
10-14 years	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
15-19 years	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
20-24 years	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
25-29 years	1 (0.2)	0 (0.0)	0 (0.0)	2 (1.1)	1 (1.3)
30-34 years	0 (0.0)	0 (0.0)	1 (0.5)	2 (1.1)	1 (1.3)
35-39 years	1 (0.2)	0 (0.0)	1 (0.5)	11 (6.3)	1 (1.3)
40-44 years	4 (0.9)	2 (9.1)	13 (5.9)	6 (3.4)	11 (14.7)
45-49 years	20 (4.4)	2 (9.1)	42 (18.9)	17 (9.7)	16 (21.3)

1. % of total number females
2. observations with non-missing values

10.9. Adverse events / adverse reactions

This study utilized unstructured data (e.g., narrative fields in the database) that were converted to structured (i.e., coded) data solely by a computer using automated/algorithmic methods and/or data that already existed as structured data in an electronic database. In these data sources, it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual patient. Thus, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available and adverse events are not reportable as individual AE reports.

11. DISCUSSION

11.1. Key results

11.1.1. Study participants

11.1.1.1. Annual Reporting Period III (31 March 2018 to 30 March 2019)

The overall number of patients identified with Duavive prescriptions in longitudinal data sources in Annual Reporting Period III varied between 11 in UK, 49 in Spain, 116 in Italy, 123 in the Netherlands and 218 in Belgium. No patients prescribed Duavive in Annual Reporting Period III were identified in France. Approximately 31% to 66% of Duavive users were excluded due to use of Duavive within 12 months prior to index date or no enrolment in the database for at least 12 months prior to index date. The number of patients included in the Duavive cohort ranged between 7 in the UK, 23 in Spain, 52 in Italy, 75 in Belgium and 85 in the Netherlands (Table 93). A minority of Duavive initiators were recorded with prior use of E+P HRT in all countries except in Netherlands where 80% had prior use.

The number of patients included in the E+P HRT cohort ranged from 1,321 in Spain to 49,190 in the Netherlands. In contrast to the Duavive cohort, in Italy, Spain and Belgium the proportion of patients who previously used E+P HRT was higher than the proportion of patients without prior E+P HRT treatment. In the Netherlands, the majority of patients in both study cohorts received previous E+P HRT. In the UK and to a lesser extent in France, the opposite was observed among E+P HRT users.

Table 93. Number of patients included in the analysis for the Annual Reporting Period III (longitudinal data sources)

	Number of patients included					
	Duavive cohort			E+P HRT cohort		
	Total	Without prior treatment E+P HRT	With prior treatment E+P HRT	Total	Without prior treatment E+P HRT	With prior treatment E+P HRT
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
France	0 (0.0)	0 (0.0)	0 (0.0)	15,217 (100.0)	9,698 (63.7)	5,519 (36.3)
Italy	52 (100.0)	37 (71.2)	15 (28.8)	3,499 (100.0)	1,208 (34.5)	2,291 (65.5)
Spain	23 (100.0)	16 (69.6)	7 (30.4)	1,321 (100.0)	591 (44.7)	730 (55.3)
UK*	7 (100.0)	7 (100.0)	0 (0.0)	18,522 (100.0)	15,890 (85.8)	2,632 (14.2)
Belgium	75 (100.0)	56 (74.7)	19 (25.3)	28,069 (100.0)	12,970 (46.2)	15,099 (53.8)
Netherlands	85 (100.0)	17 (20.0)	68 (80.0)	49,190 (100.0)	20,165 (41.0)	29,025 (59.0)

* Results cannot be reported in case of <6 observations in accordance with THIN privacy protection policies
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

The number of patients in the Duavive cohorts in the UK and in Spain was low. In the UK, based on sales data (not shown; Pfizer data on file), nationally very few patients have initiated treatment with Duavive since its launch, which is consistent with the low overall sample size (n=7) of Duavive users in the UK found for this report. A considerable portion of results on Duavive use in the UK could not be presented in the report due to data privacy concerns. In Spain, the small sample size (n=23) and likely imprecision around estimates should be considered when interpreting the results.

No Duavive prescriptions were identified in the cross-sectional databases in Belgium and the Netherlands (Table 94 below).

Table 94. Number of prescriptions included in the analysis for the Annual Reporting Period III from cross-sectional data sources (data projected to national level)

	Number of prescriptions (projected to national level)	
	Duavive cohort	E+P HRT cohort
Belgium	0	620,549
Netherlands	0	58,952

11.1.1.2. Cumulative Period (31 March 2016 to 30 March 2019) in all countries

The total number of patients included in the cumulative period presented in this report is summarised in Table 95 for longitudinal and Table 96 for cross-sectional data sources.

In the longitudinal databases, the number of patients included in the Duavive cohort varied between 11 in the UK, 22 in France, 73 in Spain, 177 in the Netherlands, 223 in Italy and 480 in Belgium. In the cumulative period, a minority of Duavive initiators were recorded with prior use of E+P HRT in all countries with exception of the Netherlands where 59% had prior

use. These results were consistent with those for the Annual Reporting Period III. The proportion of Duavive initiators with prior E+P HRT in Belgium, Italy, Spain and UK was similar in the annual and cumulative periods.

The number of patients included in the E+P HRT cohort ranged from 2,573 in Spain to 76,550 in the Netherlands. The proportion of patients who did not have a mention of prior E+P HRT treatment ("new initiators") ranged from 58.1% in Italy to 93.1% in the UK. The number of patients included in the E+P HRT cohort in the cumulative period ranged from 2,573 in Spain to 76,550 in the Netherlands. A minority of patients was recorded with prior use of E+P HRT in all countries; the proportion ranged from 7% in the UK to 41% in Italy. These findings were consistent with the Duavive cohort in all countries with exception of the Netherlands, where the majority of Duavive users were reported with previous use of E+P HRT.

Table 95. Number of patients included in the analysis for the cumulative period (longitudinal data sources)

	Number of patients					
	Duavive cohort			E+P HRT cohort		
	Total	Without prior treatment E+P HRT	With prior treatment E+P HRT	Total	Without prior treatment E+P HRT	With prior treatment E+P HRT
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
France	22 (100.0)	17 (77.3)	5 (22.7)	29,047 (100.0)	23,102 (79.5)	5,945 (20.5)
Italy	223 (100.0)	154 (69.1)	69 (30.9)	6,288 (100.0)	3,652 (58.1)	2,636 (41.9)
Spain	73 (100.0)	55 (75.3)	18 (24.7)	2,573 (100.0)	1,668 (64.8)	905 (35.2)
UK*	11 (100.0)	11 (100.0)	0 (0.0)	29,799 (100.0)	27,734 (93.1)	2,065 (6.9)
Belgium	480 (100.0)	361 (75.2)	119 (24.8)	57,059 (100.0)	33,991 (59.6)	23,068 (40.4)
Netherlands	177 (100.0)	72 (40.7)	105 (59.3)	76,550 (100.0)	50,308 (65.7)	26,242 (34.3)

* Results cannot be reported in case of <6 observations in accordance with THIN privacy protection policies
E+P HRT: Oestrogen +Progestin Hormone Replacement Therapy

The number of patients in the Duavive cohort in UK was very low; thus, a considerable portion of results on Duavive use in the UK could not be presented due the privacy protection policies. The number of patients in the Duavive cohort in France was also low (n=22). While analyses were conducted for this country, the small sample size should be considered when interpreting the results.

Table 96. Number of prescriptions included in the analysis for the cumulative period from cross-sectional data sources (data projected to national level)

	Number of prescriptions (projected to national level)	
	Duavive cohort	E+P HRT cohort
Belgium	7,425	1,422,043
The Netherlands	0	179,229

11.1.2. Indication

11.1.2.1. Annual Reporting Period III (31 March 2018 to 30 March 2019)

In the Duavive cohort, analysis of indication was possible in Italy and Spain only. An indication for oestrogen deficiency symptoms was present in 44% of Duavive users in both countries. This analysis was not possible in other countries: no Duavive prescriptions were identified in France, information on diagnoses is not available in Belgium and the Netherlands; no results could be reported for the UK due to government privacy protection restrictions. In the E+P HRT cohort, diagnosis of oestrogen deficiency symptoms was reported in 12% (UK) to 84% (the Netherlands) of the patients.

In Italy, the overall proportion of patients with oestrogen deficiency symptoms only was similar in patients with Duavive prescriptions and in patients on E+P HRT treatment (44% and 45%, respectively); a considerable difference was observed between the Duavive and E+P HRT cohorts within the Spanish database (44% vs. 14%, respectively).

Overall, osteoporosis was rarely observed among patients with Duavive prescriptions (4% in Spain and 8% in Italy). These findings are similar in range to those patients with E+P HRT prescriptions (from 0.2% in UK to 2% in France, Italy and Spain and 3% in Belgium).

Presence of codes for both oestrogen deficiency symptoms and osteoporosis among patients with Duavive prescriptions was recorded in Italy (12% of patients), but not in the other countries. For patients with E+P HRT prescriptions the percentage ranged from <0.1% in UK to 4% in Italy.

Neither oestrogen deficiency symptoms nor osteoporosis were recorded for 37% (Italy) to 52% (Spain) of the patients with Duavive prescriptions. This also includes patients with no information recorded on any diagnosis/indication. In the E+P HRT cohort the proportion of patients without these diagnostic codes varied between 15% (Belgium) and 88% (UK).

The extension of the historical period to 365 days in the Duavive cohort made no difference in the results for Spain. In Italy, 1 additional patient (5 instead of 4) with a documented diagnosis of osteoporosis only was identified. The percentage of patients with a diagnosis of oestrogen deficiency symptoms only or both oestrogen deficiency symptoms and osteoporosis remained unchanged. As a result of the additional analyses, the percentage of patients with neither oestrogen deficiency symptoms nor osteoporosis or missing diagnoses was slightly reduced from 37% to 35%.

11.1.2.2. Cumulative Period (31 March 2016 to 30 March 2019)

An indication for oestrogen deficiency symptoms only was present in 47% (Spain) to 91% (Belgium) of the patients with Duavive prescriptions and 14% (Spain) to 82% (the Netherlands) of the patients with E+P HRT prescriptions. In Italy and Belgium, the proportion of patients with oestrogen deficiency symptoms was slightly higher in patients with Duavive prescriptions than in patients with E+P HRT treatment; this proportion was considerably higher in France (73% vs 40%) and Spain (47% vs 14%).

Overall, osteoporosis only was not an indication for Duavive prescriptions in Belgium and France and rarely observed in Italy (5%) and Spain (5%). Similar proportions were found among patients with E+P HRT prescriptions (from 0.2% in UK to 2% in Belgium, France, Italy and Spain).

An indication of both oestrogen deficiency symptoms and osteoporosis for prescriptions of Duavive was recorded in Italy (4%), but not in the other countries. This proportion among patients with E+P HRT prescriptions was similar and ranged from 0% in the Netherlands to 3% in Italy.

No oestrogen deficiency symptoms or osteoporosis were recorded for 9% (Belgium) to 48% (Spain) of the patients with Duavive prescriptions. This also includes patients with no information on any diagnosis/indication. For patients with E+P HRT prescriptions this proportion was about double (15% (Belgium) to 84% (Spain)).

The extension of the historical period to 365 days in the Duavive cohort made no difference in the results for Spain and France, and a minor difference for Italy, mostly due to additional patients with osteoporosis only or with both oestrogen deficiency symptoms and osteoporosis. As a result of the additional analyses, the percentage of patients with neither oestrogen deficiency symptoms nor osteoporosis or with missing diagnoses was reduced from 42% (93 patients) to 38% (85 patients). Therefore, the lack of information on indication was not due to the original baseline period being too short (i.e., 90 days).

11.1.3. Potential Off-label use

11.1.3.1. Annual Reporting Period III (31 March 2018 to 30 March 2019)

The range of potential off-label use among Duavive users in the main analysis was from 17% (Belgium) to 25% (the Netherlands) of patients; of those characterised with potential off-label use, the reason was most often due to use by women under age 45 years.

Other criteria which indicated potential off-label use were use for osteoporosis only (4% to 8% across countries), hypersensitivity to Duavive (1 patient/ 2% in Italy), concomitant prescriptions of SERMs (4%-16% in Belgium and the Netherlands), use in patients >75 years (7% in Belgium), malignancy related to oestrogens (4.3% in Spain). In France, no patients prescribed Duavive were recorded during this reporting period.

In Italy, the proportion of potential Duavive off-label use in the main analysis was 19% (10 of 52 patients). This proportion varied in sensitivity analyses between 31% (16 patients) and 48% (25 patients). The reason for potential off-label use in the main analysis was premenopausal age in 5 patients (10%), use for osteoporosis only in 4 patients (8%) and for 1 patient (2%) it was hypersensitivity to Duavive.

In Spain, the sample size was 23 patients, of which 5 patients (22%) in the main analysis and 5 to 7 patients (22% to 30%) in the sensitivity analyses were categorised as potential off-label users. The reasons for potential off-label use in the main analysis for 5 patients (22%) was potentially premenopausal age, and for 1 patient (4%) it was either use for osteoporosis or malignancy potentially associated with oestrogens.

No results for the UK were reported to comply with restrictions imposed by the UK government to protect patient privacy.

In the longitudinal prescription-level databases in Belgium and the Netherlands, potential off-label use can only be partially identified, because variables related to diagnoses (indication for use, co-morbidities, events from medical history) are not available. What is available in these sources to assess off-label use is age, gender, and dose. In the longitudinal databases, the proportion of potential off-label use in Belgium varied between 17% (13 of 75 patients) in the main and 21% (16 of 75 patients) in the sensitivity analysis. In the Netherlands, the proportion of potential off-label use was 25% (21 of 85 patients) in the main analysis and 33% (28 of 85 patients) in the sensitivity analysis. Potential off-label use was related to presumed premenopausal age in 13 patients (16%), concomitant prescriptions of SERMs (14 patients / 16%) and use in males (2 patients / 2%).

11.1.3.2. Cumulative Period (31 March 2016 to 30 March 2019)

In summary, potential off-label use in the main analysis was observed in 9% (2 of 22 patients) in France to 29% (21 of 73 patients) in Spain, mostly due to use by women under age 45 years. An additional analysis of indication for Duavive in age group ≤45 years performed in Italy and Spain showed that the proportion of women aged ≤45 with a diagnosis of oestrogen deficiency symptoms only (suggesting postmenopausal status) was 30% (6 of 20 patients) in Italy and 22% (4 of 18 patients) in Spain. It should be noted, that absence of the diagnosis codes in the database does not necessarily mean absence of the indication.

Other criteria of potential off-label use were diagnostic codes for osteoporosis observed in relation to Duavive prescription (0% to 5%), hypersensitivity to Duavive (1% in Italy and Spain), concomitant prescriptions of SERMs (2% and 7% in Belgium and the Netherlands), prescription of a non-approved dose (2% in Italy and the Netherlands), and malignancy related to oestrogens (<1% in Italy and 1% in Spain). In Belgium 4% and in the Netherlands 5% of patients were >75 years of age; 3% of patients in Belgium, 1% in the Netherlands and <1% in Italy were documented as male.

In France, the proportion of potential Duavive off-label use in the main analysis was 9% (2 of 22 patients), entirely due to age ≤45 years. A change in the presumed premenopausal age limit from 45 to 49 years showed an increase in the proportion of potential off-label users to 18%, caused by an increase in the number of patients who were potentially premenopausal from 2 to 4.

In Italy, the proportion of potential Duavive off-label use in the main analysis was 15% (34 of 223 patients). This proportion varied in sensitivity analyses between 20% (44 patients) and 35% (79 patients). The reason for potential off-label use in the main analysis was age ≤45 years in 9% (20 patients), use for osteoporosis only in 5% (11 patients), hypersensitivity to Duavive in 1% (3 patients) and for 1 patient (<1%) it was either prescription of non-approved dose or malignancy potentially associated with oestrogens; 1 patient was documented as male.

In Spain, potential off-label use was identified in the main analysis in 29% (21 of 73 Duavive users, ranging from 29% (21 patients) to 45% (33 patients) in the sensitivity analyses. The

reasons for potential off-label use in the main analysis were age ≤45 years in 25% (18 patients), use for osteoporosis only in 5% (4 patients), either hypersensitivity to Duavive or malignancy potentially associated with oestrogens in 1% (1 patient).

No results for the UK were reported to comply with restrictions imposed by the UK government to protect patient privacy.

In the longitudinal prescription-level databases in Belgium and the Netherlands, potential off-label use can only be partially identified, because variables related to diagnoses (indication, co-morbidities, events from medical history) are not available. The proportion of potential off-label use in Belgium varied between 11% (51 of 480 patients) and 15% (71 of 480 patients) in the main analysis and the sensitivity analysis where off-label use included

a presumed premenopausal age limit at ⩽49 years. In the longitudinal prescription-level database for the Netherlands, the proportion of potential off-label use was 25% (45 of 177 patients) in the main analysis and 32% (56 of 177 patients) in the sensitivity analysis including a presumed premenopausal age limit at ⩽49 years. Potential off-label use was related to presumed premenopausal age (⩽45 years) in 16% (29 patients), age above 75 years (8 patients / 5%), prescription of non-approved dose or regimen (4 patients / 2%) or concomitant prescriptions of SERMs (12 patients / 7%); 2 patients (1%) were males.

11.2. Limitations

Possible off-label use of Duavive can only be defined by objective factors that are also accurately contained in the data sources. The operational definitions of off-label use are subject to limitations of the data sources and may result in over- or underestimation of off-label use due to misclassification. Data source limitations that impact identifying off-label use include: no recording of postmenopausal status and the necessity to use age as a proxy, limited patient history on prior treatments, and a lack of explicit recording of indication for use (i.e., for most sources, this needs to be inferred from proximate diagnoses). In most cases, the indication for product usage is not explicitly recorded as such in the electronic data. Therefore, the indication for use was inferred from diagnoses of either oestrogen deficiency or osteoporosis that are recorded within 90 days before or after product initiation. Furthermore, an additional analysis was performed including the time period from 365 days before to 90 days after the index date. This identified the indication for a limited number of additional patients. Specifically, more complete recording of oestrogen deficiency as the treatment indication could show that many of the Duavive patients under age 45 years were truly postmenopausal and thus not using the product off-label. Overestimation of hypersensitivity to Duavive was possible: ICD-10 codes for hypersensitive conditions recorded in the data sources within 12 months prior to Duavive initiation were considered to possibly be related to the excipients included in the Duavive tablets. However, ICD-10 codes indicating hypersensitivity do not provide information on which substance may have caused the hypersensitivity reaction, resulting in an overestimation in case the hypersensitivity reaction had been caused by a substance unrelated to Duavive.

The uptake of Duavive was slower than anticipated following EU launch, explaining the relatively small numbers of patients available for analysis of the study, particularly in the

UK, France and Spain. Therefore, imprecision of estimates should be considered where the total uptake of Duavive was low.

Patients in the longitudinal patient-level data sources (LPD, THIN) may receive care from a practice or health system not captured in the data source, and these data would not be recorded in the database. However, the external validity of several of these sources has been established (e.g., THIN, LPD).[2-8]

In the IQVIA patient-level databases (LPD), patients can be followed-up only within participating physician offices. The patients cannot be tracked across different physician offices in France, and Italy; in Spain, patient visits across specialties can be linked only if the specialists are based in the same office. For this reason, an underreporting of diagnoses and medications might be present in the IQVIA LPD databases.

Duavive patients who are switchers from E+P HRT can be defined in most data sources. However, the reason for a switch is not recorded in any of the data sources.

Not all analyses are feasible in every database due to lack of the necessary study variables in a given data source, e.g. data on diagnoses is not available in the longitudinal prescription-level data sources used for Belgium and the Netherlands (which is why the cross-sectional sources for those countries were added). In addition, gender is not directly available from prescription data. In the longitudinal prescription databases from Belgium and the Netherlands, patients' gender is inferred from the most frequent gender associated with the first name. This may sometimes lead to misclassification.

In the cross-sectional data sources, only data recorded on the prescription day is available, which causes substantial underreporting of diagnoses and co-medication. Furthermore, the results obtained from cross-sectional databases are projected to national levels. In case of low numbers of prescriptions, the precision of projected results can be low and interpretability of these results would be limited.

11.3. Interpretation

Patient counts for Duavive found in the data sources were relatively low. However, this finding represents the real-world use of Duavive, rather than an artefact of sampling. The EU data sources in this study were selected because they are nationally representative of prescribing practice in their respective countries. Further, it is clear that the chosen databases captured the target population. Depending on the country, between 2,757 and 83,089 E+P HRT patients were identified in the databases, suggesting that the data sources used were able to capture the patient population relevant for this study. It can thus be concluded that Duavive uptake in these countries is low.

Corresponding to the low patient counts in this study, Duavive sales numbers in the UK, France and Spain are persistently low. Thus, the MAH does not expect that an extension of the study in these countries would result in a meaningful increase in patient counts or improvement in the accuracy of study results.

Uptake of Duavive is higher in Italy, Belgium, and the Netherlands, and while usage is low compared to that of E+P HRT, precision of estimates is less of a concern. As the aim of this study is to describe patient characteristics and drug utilization, sample size and power calculations are not applicable, and an extension of the study in these countries is not expected to change study conclusions.

In the countries with a sufficient number of Duavive users in the longitudinal data sources (cumulative data for Italy, Belgium, the Netherlands), baseline characteristics of Duavive and E+P HRT users were similar with regard to gender and co-morbidities (available in Italy only). In Italy and the Netherlands, the proportion of Duavive users under 40 years of age was lower than in the E+P HRT cohort (1% vs. 12% and 8% vs. 18%, respectively). A possible explanation for this age difference could be related to possible use of oestrogen + progestin combinations for indications other than hormone replacement therapy in younger females.

The proportion of relevant co-medications in the medical history was similar among Duavive and E+P HRT users with the exception of anticoagulants in Italy (5% and 11%, respectively), local hormone treatments in Belgium (16% and 4%, respectively) and antiarrhythmics (8% and 2%, respectively), antidepressants (31% and 17%, respectively) and sedatives/hypnotics (27% and 14%, respectively) in the Netherlands. The reasons for these differences between cohorts are not clear. A higher proportion of co-medications in Duavive than in E+P HRT users in the Netherlands may be associated with the higher proportion of older patients in the Duavive cohort. Reasons for differences in anti-coagulant and local hormone treatment use in Italy and Belgium (respectively) are unknown, but the possibility of chance cannot be excluded.

Most potential off-label use was due to use of Duavive in women under age 45 years old. In the European Union Duavive is indicated for treatment of "oestrogen deficiency symptoms in postmenopausal women with a uterus (with at least 12 months since the last menses) for whom treatment with progestin-containing therapy is not appropriate." There is no standard definition of postmenopausal status based on age or other criteria in secondary electronic healthcare data. For analyses of potential off-label use, the MAH used age 45 years or younger as a proxy for premenopausal status; the age threshold was extended to 49 years or younger for sensitivity analyses. However, menopause can occur at a range of ages. For instance, a meta-analysis of 36 studies spanning 35 countries found overall mean age of menopause to be 48.8 years (95% CI 48.3–49.2); the mean age across six studies in 6 European countries was 50.54 (95% CI 50.04 -51.05), with means across individual studies ranging from 49.8 in Poland to 51.3 in Germany.[11] Indeed, it is estimated that 5% of women naturally experience "early menopause", or menopause between 40-45 years of age.[12] Thus, use of Duavive prior to 49 years of age does not necessarily correlate to off-label use by premenopausal women.

Oestrogen deficiency due to menopause is likely to be underrecorded in electronic healthcare data sources. Nonetheless, a separate evaluation in Italy and Spain revealed that up to 30% of the women ≤45 years of age receiving Duavive also had a documented diagnosis of oestrogen deficiency symptoms, suggesting postmenopausal status and therefore, overestimation of off-label use is likely.

Presence of codes for an off-label indication is a better indicator of off-label use than absence of expected data elements (e.g., oestrogen deficiency). In some study countries (Italy and Spain) use of Duavive in patients with osteoporosis was noted, though frequency was low. However, it is possible that oestrogen deficiency symptoms had also been diagnosed in these patients but were not recorded in the data source. Diagnoses/data elements suggesting off-label use other than potential premenopausal age were rarely observed, suggesting that overall, physicians consider the requirements of the product information when prescribing Duavive.

11.4. Generalisability

Selected data sources for this study were designed to be representative of the underlying general population in the countries.[2-8] For example, the prescription-level data sources (LRx) cover over 35% of prescriptions in the retail channel of Belgium and 75% in the Netherlands.

In all target countries, inclusion criteria applied were minimal and did not restrict patients by specific baseline characteristics such as demographics, insurance status, co-morbidities, region, or other, to maximise external validity. Taking the known limitations of the databases into consideration, the study results are generalisable to the target countries.

12. OTHER INFORMATION

None

13. CONCLUSIONS

This final report was based on data from the time period 31 March 2016 to 30 March 2019. While the number of patients who initiated treatment with Duavive in all included countries is low, overall prescribing patterns were comparable between Duavive and E+P HRT. When Duavive was prescribed, it was most often prescribed to an appropriate population (i.e., female patients, mostly 50 years or older, correct indication) and in the dosage recommended in the Summary of Product Characteristics (SmPC). The results of this study suggest the proportion of potential off-label use of Duavive is low in clinical practice.

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15. LIST OF SOURCE TABLES AND FIGURES

Not applicable

APPENDICES

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Appendix 1. Signatures

Appendix 2. Protocol

Appendix 2.1 Amended Protocol, Final version amended; 31 August 2017

Appendix 2.2 Amended Annex 1 to Protocol, Final version; 31 August 2017

Appendix 3. Amended Statistical Analysis Plan, Version 2.0 amended; 31 August 2017

ANNEX 2. ADDITIONAL INFORMATION

Appendix 1. CROSS-SECTIONAL DATA SOURCES: PANEL SIZE AND COVERAGE BY SPECIALTY

IMS Medical Index: Panel size (number of physicians) by specialty (2015)

COUNTRY	Specialties Covered	Panel Size	Universe	Coverage (Panel/Universe)
Belgium	General medicine	170	13,258	1.3%
	Internal medicine	30	1,430	2.1%
	Gastro-Enterolog.	30	1,102	2.7%
	Paediatricians	30	1,265	2.4%
	Gynaecologist	30	1,531	2.0%
	Neuro./Psych	30	2,759	1.1%
	Cardiologists	30	1,543	1.9%
	Dermatologist	30	765	3.9%
	Rheumatologist	20	226	8.8%
	Physiologist	20	520	3.8%
	Orthopedists	20	1,072	1.9%
	Ophthalmologist	20	1,053	1.9%
	O.R.L.	20	663	3.0%
	Pneumo./Pulmolog	20	612	3.3%
	Urologists	20	435	4.6%
	Total	**520**	**28,234**	**1.8%**
The Netherlands	GPs	140	8,683	1.6%
	GPs Assistants	90	6,773	1.3%
	Cardiology	20	857	2.3%
	Dermatology	20	458	4.4%
	Gynecology/Obstetrics	20	914	2.2%
	Internal medicine	30	2,162	1.4%
	Neurology	20	766	2.6%
	Otorhinolaryngology	20	471	4.2%
	Pediatrics	20	1,236	1.6%
	Psychiatry	30	1,910	1.6%
	Respiratory diseases	20	503	4.0%
	Total	**430**	**24,733**	**1.7%**

Appendix 2. Drug names and codes for E+P HRT by country

E+P HRT Combination Products

DRUG NAME	ATC CODE
BELGIUM (includes Luxembourg)	
ACTIVELLE	G03FA01
ANGELIQ	G03FA17
CLIMEN	G03HB01
CLIMODIEN	G03FA15
CYCLO PROGYNOVA	G03FB01 / G03FB09
DIVIVA	G03FA12
DUOGESTAN	G03FA12
ENADIOL	G03FA12
ESTALIS	G03FA01 /G03CA53
ESTRAPAK	G03CA03
FEMOSTON	G03FB08
HERIA	G03CX01 / G03DC05
KLIOGEST	G03FA01
MERICOMB	G03FB05
MERIGEST	G03FA01
LIVIVAL*	G03CX01
NAEMIS	G03FB12
PREMPAK	G03FA10
PREMPRO	G03CA57
TIBOLINIA*	G03CX01
TOTELLE SEKVENS	G03FB05
TRISEQUENS	G03FB05
TRIVINA	G03FA12
FRANCE	
ACTIVELLE	G03FA01
ANGELIQ	G03FA17
AVADENE	G03AA10 / G03AB06 / G03CA03
CLIMASTON*	G03FB08 /G03FA14
CLIMEN	G03HB01
CLIMODIEN	G03FA15
CUMORIT	G03CA53 / G03FA04
DIVINA	G03FB06 /G03FA12
DIVISEQ	G03FB06
DUOVA	G03FB06 /G03FA12
ESTRADIOL + NORÉTHISTÉRONE*	G03FA01
FEM7 COMBI	G03FA11 /G03A03 / G03FB09
FEMOSTON	G03FB08
FEMSEPTEVO*	G03FB09
KLIOGEST	G03FA01
LIVIAL	G03CX01 / G03DC05

E+P HRT Combination Products

DRUG NAME	ATC CODE
NAEMIS	G03FB12
NOVOFEMME*	G03FB05
SUCCESSIA	G03AA10 / G03AB06 / G03CA03
SYNERGON	G03CA07 / G03CC04 / G03DA04
TRISEQUENS	G03FB05
TROPHIGIL*	G03FA04
ITALY	
ACTIVELLE	G03FA01
ANGELIQ	G03FA17
CLIMEN*	G03HB01
CLIOVELLE	G03FA01
COMBISEVEN*	G03FB09
CYCLABIL	G03FB01
DIVINA	G03FB06 /G03FA12
DIVITREN	G03FB06
ESTALIS	G03FA01 /G03CA53
ESTRACOMB*	G03FB05
ESTRAPAK	G03CA03
EVOREL PAK	G03CA03
FEMITY*	G03FA11
FEMOSTON	G03FB08
FEMSEVEN COMBI	G03FA11 /G03A03 / G03FB09
FILENA*	G03FA12
INDIVINA	G03FA12
KLIOGEST	G03FA01
LIVIAL	G03CX01 / G03DC05
MENOVIS*	G03FA04
MERICOMB	G03FB05
MERIGEST	G03FA01
NAEMIS*	G03FB12
NUVELLE*	G03FB09
PREMELLE*	G03FB06 / G03FA12
PREMIA*	G03FA12
PREMPAK*	G03FB07
SEQUIDOT	G03FB05
TOTELLE SEKVENS	G03FB05
TRISEQUENS	G03FB05
NETHERLANDS	
ACTIVELLE	G03FA01
ANGELIQ	G03FA17
CLIMEN	G03HB01
CLIMODIEN	G03FA15
CYCLOCUR*	G03CA03
CYCLO PROGYNOVA	G03FB01 / G03FB09
DIVINA*	G03FB01
ESTRACOMB TTS*	G03FB05
ESTRAPAK	G03CA03
FEM 7 SEQUI	G03FB05

E+P HRT Combination Products

DRUG NAME	ATC CODE
FEMOSTON	G03FB08
KLIOGEST	G03FA01
LIVIAL	G03CX01 / G03DC05
PREMARIN PLUS*	G03FB07
PREMELLE 5*	G03FB06
PREMELLE CYCLE 10*	G03FB06
PREMPAK	G03FA10
PREMPAK C	G03FA10
PREMPHASE	G03CA57
PREMPRO	G03CA57
PRIMOSISTON*	G03FB05
TIBOLINIA*	G03CX01
TRISEQUENS	G03FB05
ZUMESTON*	G03FB08
SPAIN	
ABSORLENT PLUS	G03CA03 / G03FB05
ACTIVELLE	G03FA01
ANGELIQ	G03FA17
AUROCLIM	G03AA07 / G03AB03 / G03CA53 / G03FA11 / G03FB09
BOLTIN	G03CX01 / G03DC05
CLIMEN	G03HB01
CLIMODIEN	G03FA15
CLISIN	G03HB01
CYCLO PROGYNOVA	G03FB01 / G03FB09
DIENOGEST / ESTROGENO*	G03FA15
DILENA	G03FB06
DUOFEMME	G03FB05
ENDOMINA*	G03FB05
ESTALIS	G03FA01 /G03CA53
ESTRACOMB*	G03FB05
ESTRAPAK	G03CA03
EVIANA	G03FA01
MEDROXIPROGESTERONA Y ESTROGENO*	G03FB06
MERIGEST	G03FA01
MERIGEST COMBI	G03FB05
MEVAREN	G03FA15 / G03AB08
NORETISTERONA / ESTROGENO*	G03FA01 / G03FB05
NORGESTREL / ESTROGENO*	G03FB01
NUVELLE	G03CA03
PERIFEM*	G03FB06
PREMPHASE	G03CA57
PREMPRO	G03CA57
PRIMOSISTON	G03FA01
PROGYLUTON*	G03FB01 / G03FA10
TRISEQUENS	G03FB05

E+P HRT Combination Products

DRUG NAME	ATC CODE
UK	
SUBSTANCE	**Gemscript THIN[#]**
ADGYN*	91328998
ESTRADIOL / DROSPIRENONE*	86831998, 86832998
CLIMAGEST*	87898979, 87901979, 97765998
ESTRADIOL VALERATE / NORETHISTERONE*	88912998, 90523998, 91086998, 91412998, 91546998, 93164979, 93165979, 97625997, 90523998, 93164979, 93165979, 97625997, 91086998, 91412998, 91546998, 88912998, 97625998
CLINORETTE*	71840979, 86050998
ESTRADIOL / LEVONORGESTREL*	60462979, 89212998, 90645998, 90646998, 91469998, 95657997, 95657998
CONJUGATED ESTROGENS & MEDROXYPROGESTERONE*	89171979, 89173979, 89176979, 91114998, 87549998, 87550998, 91113998, 87953998
CONJUGATED OESTROGENS AND NORGESTREL*	94252992, 89684979, 89685979, 94472998, 98892998, 99219998, 95698997, 95698998, 94472997, 98839998, 98840998, 93764992, 94309992
CYCLO-PROGYNOVA*	87890979, 94162998, 97458997, 97458998
ESTRADIOL & NORETHISTERONE ACETATE*	97765997, 89399998, 91412996, 88320998, 91423998, 91862998, 92440998, 93174979, 88889998, 89722979, 89723979, 89725979, 97759996, 92586998, 94517998, 92251998, 97759998, 92585998, 91412997, 91680998
ESTRADIOL AND (ESTRADIOL WITH NORETHISTERONE) AND (ESTRADIOL) TRIPHASIC*	94161997
EVOREL SEQUI*	87082979, 87085979, 88887997, 88887998, 90083998
ESTRADIOL / DYDROGESTERONE*	88207998, 88635979, 88638979, 89803998, 92171998, 90620998, 91307997, 54611979, 54612979, 91052998, 91307998, 91388998, 91388997, 91388996, 89359998
FEMOSTON*	87080979, 91389998, 87079979, 91389997, 91389996
FEMSEVEN*	85664979, 89321998
ESTRADIOL VALERATE / MEDROXYPROGESTERONE*	90617998, 90618996, 90618997, 90618998, 91350996, 91350997, 91350998
TRISEQUENS*	87461979, 94161998, 97482997, 97482998

* This code/drug name has been added since the protocol had been written
[#] For analysis in UK THIN, drug names/ATC codes were translated to Gemscript THIN

Oestrogen-containing Products

DRUG NAME	ATC CODE
BELGIUM (includes Luxembourg)	
AACIFEMINE	G03CA04
AERODIOL	G03CA03
CLIMARA	G03CA03
DERMESTRIL	G03CA03
DIMENFORMON	G03CA03
DISTILBENE	G03CB02 / L02AA01
ENADIOL	G03FA01 / G03FA12
ESTRADERM	G03CA03
ESTRADIOL NOVT	G03CA03
ESTRADOT	G03CA03
ESTRAMON	G03CA03
ESTREVA	G03CA03
ESTROFEM	G03CA03
FEMSEVEN	G03FB01
MENO-IMPLANT	G03CA03
MENOREST	G03CA03
OESTROGEL	G03CA03
OVESTIN	G03CA04
PREMARIN	G03CA57
PROGYNOVA	G03CA03
SYSTEN	G03CA03
ZUMENON	G03CA03
FRANCE	
AERODIOL	G03CA03
BLISSEL*	G03CA04
CLIMARA	G03CA03
COLPOTROPHINE*	G03CA09
DELIDOSE	G03CA03
DEPOFEMIN	G03CA03
DERMESTRIL	G03CA03
DISTILBENE*	G03CB02
ESTRADERM	G03CA03
ESTRADIOL NOVT	G03CA03
ESTRADIOL TEVA	G03CA03
ESTRADOT	G03CA03
ESTRAPATCH THS	G03CA03
ESTREVA	G03CA03
ESTROFEM	G03CA03
ETHINYLESTRAD ITAF	G03CA07
ETHINYLESTRAD SNFI	G03CA07
EVAFILM	G03CA07
FEMSEPT*	G03CA03
GELISTROL*	G03CA04
GYDRELLE*	G03CA04

Oestrogen-containing Products

DRUG NAME	ATC CODE
MENOREST	G03CA03
OESCLIM	G03CA03
OESTRODOSE*	G03CA03
OESTROGEL	G03CA03
OROMONE*	G03CA03
OVESTIN	G03CA04
PHYSIOGINE*	G03CA04
PREMARIN	G03CA57
PROGYNOVA	G03CA03
PROMESTRIÈNE*	G03CA09
PROVAMES*	G03CA03
SYSTEN	G03CA03
THAIS	G03CA03
THAISSEPT*	G03CA03
TROPHICREME*	G03CA04
VIVELLEDOT*	G03CA03
ZUMENON	G03CA03
ITALY	
AERODIOL	G03CA03
ARMONIL RCDT	G03CA03
BLISSEL*	G03CA04
CLIMADERM	G03CA03
CLIMARA	G03CA03
COLPOGYN*	G03CA04
COLPOTROPHINE*	G03CA09
DERMESTRIL	G03CA03
DIVIGEL	G03CA03
EPHELIA	G03CA03
EPIESTROL	G03CA03
ESCLIMA*	G03CA03
ESTRADERM	G03CA03
ESTRADIOLO AMSA	G03CA03
ESTRADIOLO ANGELIN	G03CA03
ESTREVA	G03CA03
ESTRING*	G03CA03
ESTROCLIM	G03CA03
ESTRODOSE*	G03CA03
ESTROFEM	G03CA03
ETINILESTRADIOLO	G03CA01
FEMSEVEN*	G03CA03
GELESTRA	G03CA03
GELISTROL*	G03CA04
GINAIKOS*	G03CA03
MENOREST	G03CA03
ORTHO GYNEST*	G03CA04
OVESTIN	G03CA04
PREMARIN	G03CA57

Oestrogen-containing Products

DRUG NAME	ATC CODE
PROGYNON	G03CA03
PROGYNOVA	G03CA03
RU-EST	G03CA03
SANDRENA*	G03CA03
SYSTEN	G03CA03
TROFOGIN*	G03CA04
VAGIFEM*	G03CA03
ZERELLA 50*	G03CA03
NETHERLANDS	
AACIFEMINE	G03CA04
AERODIOL	G03CA03
CETURA	G03CA03
CLIMARA	G03CA03
DAGYNIL	G03CA57
DERMESTRIL	G03CA03
DIMENFORMON*	G03CA03
ESTRADERM	G03CA03
ESTRADERM MX*	G03CA03
ESTRADERM TTS*	G03CA03
ESTRADIOL WEEK-HEX*	G03CA03
ESTRADIOL WEEK-SDZ*	G03CA03
ESTRADIOL-AEN	G03CA03
ESTRADIOL-ATX	G03CA03
ESTRADIOL-HEX*	G03CA03
ESTRADIOL-MYLA	G03CA03
ESTRADIOL-NOVT	G03CA03
ESTRADIOL-PCH*	G03CA03
ESTRADIOL-RAT*	G03CA03
ESTRADIOL-SDZ*	G03CA03
ESTRADIOL-TEVA	G03CA03
ESTRADOT	G03CA03
ESTROFEM	G03CA03
FEMSEVEN	G03FB01
LYNORAL	G03CA01
MENO-IMPLANT	G03CA03
MENOREST	G03CA03
OVESTIN	G03CA04
PREMARIN	G03CA57
PROGYNON DEPOT*	G03CA03
PROGYNOVA	G03CA03
SANDRENA	G03CA03
SYNAPAUSE E3*	G03CC06
SYSTEN	G03CA03
ZUMENON	G03CA03
SPAIN	
ABSORLENT MATRIX	G03CA03
ALCIS	G03CA03

Oestrogen-containing Products

DRUG NAME	ATC CODE
CLIOGAN	G03CA03
COLPOTROFIN*	G03CA09
DERMESTRIL	G03CA03
ENDOMINA	G03FA01
EQUIN	G03CA57
ESPRASONE*	G03CA03
ESTRADERM*	G03CA03
ESTRADIOL NOVT	G03CA03
ESTRADOT	G03CA03
ESTRAPATCH*	G03CA03
ESTRIOL*	G03CA04
ESTROFFIK*	G03CA03
ESTROGENOS CONJUGADOS*	G03CA57
EVOPAD*	G03CA03
GELISTROL*	G03CA04
LENZETTO*	G03CA03
LONGAPLEX*	G03CA57
MENOREST	G03CA03
MERIESTRA*	G03CA03
MERIMONO	G03CA03
OESTRACLIN	G03CA03
OVESTIN	G03CA04
POSTMENOP	undefined
PREMARIN	G03CA57
PROGYNON	G03CA03
PROGYNOVA	G03CA03
PROMESTRIENO*	G03CA09
SYSTEN	G03CA03
UK	
SUBSTANCE	**Gemscript THIN[#]**
ESTRADIOL*	97330998, 98734998, 83430998, 85964998, 85974998, 87043998, 87048998, 88329998, 88331998, 89209996, 89627998, 89629998, 90834998, 91090996, 91620996, 93073996, 93308979, 93311979, 94519996, 88826998, 91457998, 92962997, 93354979, 96371992
ESTRADIOL ACETATE*	90813998
ESTRADIOL HEMIHYDRATE*	88935998
ESTRADIOL VALERATE*	91859998, 93341979, 93696998, 94737998, 97457998, 91865998, 93321979, 93325979, 93696997, 94737997, 96747998, 97457997
ETHINYLESTRADIOL*	93578998, 97993997, 97993996, 99602989, 94990992
CONJUGATED ESTROGENS*	99220996, 96609997, 99220997, 96609996, 84780998, 84781998, 93211979, 96609998, 99220998
DIETHYLSTILBESTROL*	92792998, 95608992, 95730990, 97120996, 97120997, 97120998, 98363990
ESTRADIOL WITH ESTRONE AND ESTRIOL*	96745998, 96746998
ESTRIOL*	96744997, 99295997, 95363992, 99295998, 96744998

* This code/drug name has been added since the protocol had been written

[#] For analysis in UK THIN, drug names/ATC codes were translated to Gemscript THIN

Progestin-containing Products

DRUG NAME	ATC CODE
BELGIUM (includes Luxembourg)	
UTROGESTAN	G03DA04
LUTENYL	G03AA14
ORGAMETRIL	G03DC03
DUPHASTON	G03DB01
PRIMOLUT NOR	G03AC01
DEPO PROVERA	G03AC06
VISANNE	G03DB08
CRINONE	G03DA04
COLPRONE	G03DA03
NOGEST	G03DB04
NOMEGESTROL STAD	G03DB04
PROLUTON	G03DA04
FRANCE	
ACÉTATE DE NOMÉGESTROL*	G03DB04
CHLORMADINONE DCI	G03DB06
CHLORMADINONE MYLA	G03DB06
CHLORMADINONE QUALIMED*	G03DB06
CHLORMADINONE SDZ	G03DB06
CHLORMADINONE TEVA	G03DB06
COLPRONE	G03DA03
CRINONE*	G03DA04
DEPO PROVERA*	G03DA02
DUPHASTON	G03DB01
DYDROGESTÉRONE*	G03DB01
ESTIMA Gé*	G03DA04
EVAPAUSE	G03DA04
GEPROMI	G03DA04
GESTORAL	G03AC06
HYDROXYPROGES BAYR	G03DA03
LUTENYL	G03AA14
LUTERAN	G03DB06
MÉDROGESTONE*	G03DB03
MENAELLE*	G03DA04
NOMEGESTROL ARROW	G03DB04
NOMEGESTROL BIOG	G03DB04
NOMEGESTROL MYLAN	G03DB04
NOMEGESTROL SANDOZ	G03DB04
NOMEGESTROL STAD	G03DB04
NOMEGESTROL TEVA	G03DB04
NOMEGESTROL ZENTIV	G03DB04
NORISTERAT*	G03DC02
NORLUTEN*	G03DC02

Progestin-containing Products

DRUG NAME	ATC CODE
ORGAMETRIL	G03DC03
PRECYCLAN	G03DA02/ G03AC06/C03AA01/N05BC51
PRIMOLUT NOR	G03AC01
PROGEFFIK	G03DA04
PROGESTAN GE*	G03DA04
PROGESTERONE BIOGARAN*	G03DA04
PROGESTERONE DCI	G03DA04
PROGESTERONE MYLA	G03DA04
PROGESTERONE NOVT	G03DA04
PROGESTERONE SERV	G03DA04
PROGESTERONE TEVA	G03DA04
PROGESTOGEL*	G03DA04
PROGIRON*	G03DA04
PROMÉGESTONE*	G03DB07
SURGESTONE	G03DB07
TOCOGESTAN	G03DA04
UTROGESTAN	G03DA04
VISANNE	G03DB08
ITALY	
COLPRONE	G03DA03
CRINONE	G03DA04
DEPO PROVERA	G03AC06
DUPHASTON	G03DB01
ESOLUT*	G03DA04
FARLUTAL*	G03DA02
GESTANON	G03DC01
LENTOGEST	G03DA03
LUTENYL	G03AA14
LUTEONORM*	G03DC06
LUTOGIN	G03DA04
NOMEGESTROL FARMIT*	G03DB04
NOMEGESTROL FIN	G03DB04
PLEYRIS*	G03DA04
PRIMOLUT NOR	G03AC01
PROGEFFIK	G03DA04
PROGESTERONE L.U.	G03DA04
PROGESTOGEL	G03DA04
PROLUTON	G03DA03
PROMETRIUM	G03DA04
PRONTOGEST	G03DA04
VISANNE	G03DB08
NETHERLANDS	
COLPRO*	G03DB03
CRINONE*	G03DA04
DEPO PROVERA	G03AC06
DUPHASTON	G03DB01

Progestin-containing Products

DRUG NAME	ATC CODE
GESTANON*	G03DA04
LUTINUS*	G03DA04
ORGAMETRIL	G03DC03
PRIMOLUT NOR	G03AC01
PROGESTAN	G03DA04
PROGESTINE*	G03DA04
ULTROGESTAN	G03DA04
UTROGESTAN	G03DA04
SPAIN	
COLPRO*	G03DB03
COLPRONE	G03DA03
CRINONE	G03DA04
DARSTIN	G03DA04
DUPHASTON	G03DB01
ESOLUT	G03DA04
LINESTRENOL*	G03DC03
MEDROXIPROGESTERONA*	G03DA02
NORETISTERONA*	G03DC02
ORGAMETRIL	G03DC03
PRIMOLUT NOR	G03AC01
PROGEFFIK	G03DA04
PROGESTERONA*	G03DA04
PROGESTOGEL*	G03DA04
PROGEVERA	G03AC06
PROLUTON	G03DA04
UTROGESTAN	G03DA04
VISANNE	G03DB08
UK	
SUBSTANCE	**Gemscript THIN[#]**
NORETHISTERONE*	95700998, 97454998
HYDROXYPROGESTERONE*	96191998
HYDROXYPROGESTERONE CAPROATE*	99207998, 96191997, 99207997
MEDROXYPROGESTERONE*	94484996
MEDROXYPROGESTERONE ACETATE*	99581998, 98869998, 97921998

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