SEASONIQUE PASS DUS
Final Study Report

Title	A Drug Utilization Study of SEASONIQUE in Europe
Version	Version 1.0
Date of last version of the final study report	NA
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Active substance	levonorgestrel (LNG)/ ethinyl estradiol (EE) G03AD01 / G03CA01
Medicinal product	SEASONIQUE
Product reference	N/A
Procedure number	FR/H/0516/001
Marketing authorisation holder(s)	Theramex Ireland Limited, 3rd Floor, Kilmore House, Park Lane, Spencer Dock, Dublin 1 D01YE64, Ireland
Joint PASS	No
Research question and objectives	To characterize drug utilization patterns of SEASONIQUE in European countries
Country(-ies) of study	France, Italy and Belgium
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This study was conducted in accordance with all relevant regulatory requirements, including, where applicable, the Declaration of Helsinki (and its amendments), the guideline on good pharmacovigilance practices (GVP) Module VIII – post-authorisation safety studies, and the guidelines for good pharmacoepidemiology practice (GPP) (ISPE).

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1. ABSTRACT

Title	A Drug Utilization Study of SEASONIQUE in Europe
Keywords	levonorgestrel, ethinyl estradiol, drug utilization pattern, extended oral contraceptive
Rationale and background	SEASONIQUE is a novel extended combined oral contraceptive (COC) containing fixed-dose combination of 0.15 mg levonorgestrel (LNG)/0.03 mg ethinyl estradiol (EE) for 84 days, followed by 0.01 mg EE for seven days. The product may improve the compliance along with reduction in the risk of unwanted pregnancies by providing continuity and decreasing the scheduled withdrawal bleedings. Market authorisation for SEASONIQUE was granted in various European countries in 2015. The European Medicines Agency (EMA) has requested a drug utilization study (DUS) to describe the utilization patterns of SEASONIQUE in Europe during routine clinical practice.
Research question and objectives	The primary objective was to characterize drug utilization patterns of SEASONIQUE in France, Italy and Belgium. The drug utilization pattern of SEASONIQUE described patients' characteristics/demographics, and indication by physician panel in the outpatient settings (i.e., primary care and specialists [gynaecologists] {only for France}) for each of the targeted countries.
Study design	A retrospective cohort study using secondary databases (electronic medical records database [EMR])
Setting	The study captured data from female patients in outpatient settings. A national representative sample of general practitioners (GPs) were included for each country. In addition, for France only, a panel of specialists (gynaecologists) were included. Study period – France: October 2015- September 2018, Italy: June 2015-

	May 2018, Belgium: December 2015- November 2018
Subjects and study size, including dropouts	The sample size for the study was dependent on the data availability in the longitudinal EMR. The study included patients who received at least one prescription for SEASONIQUE during three-year study period from the three different databases as follows: 269 patients in the French GP panel, 232 patients in the Italian GP panel, 224 patients in the Belgian GP panel and 659 patients in the French gynaecologist panel.
Variables and data sources	Data on demographics, patient and treatment characteristics of SEASONIQUE use, and medical history were extracted for each patient. Comorbidities and concomitant medications information were also included. The following characteristics were examined: 1. Duration of use (uninterrupted use) 2. Indication of use (diagnosis related to the SEASONIQUE prescription) 3. Use of prior combined hormonal contraception (CHC) before SEASONIQUE initiation 4. Switch patterns of patients using SEASONIQUE and changes to a different COC and concomitant use of other COC or other forms of contraception Exposure was defined as one or more recorded written prescription for SEASONIQUE during the study period for each country. Data was obtained from European Union (EU) automated healthcare databases, Longitudinal EMR (IQVIA [formerly IMS] Longitudinal Patient Database [LPD]®), from three selected countries in which the product was marketed (France, Italy and Belgium).
Results	Across all countries and panels, majority of patients were ≤ 35 years old and, based on the SEASONIQUE exposure status, patients were either naïve or new users. Patients included in the study had no prior history of deep venous thrombosis (DVT)/pulmonary embolism (PE), breast

	cancers and other gynaecological cancers at baseline. The primary indication associated with a prescription of SEASONIQUE was contraception (70.6% of patients in the French GP panel, 41.8% of patients in the Italian GP panel, 81.2% of patients in the Belgian GP panel and 61.3% in the French gynaecologist panel). Additionally, menstrual migraine was reported as an indication in almost 15% of patients in the French GP panels. The study reported that up to 22.7% of total patients were using hormonal/non-hormonal contraceptives prior to the index date. Majority of patients that switched presented a switch in contraception from CHC to SEASONIQUE at index date.
Discussion	The study incorporated real-world data sources from various European countries to explore the demographics of SEASONIQUE users informing on the drug utilization patterns of this extended contraceptive regimen. The study reveals that SEASONIQUE was prescribed predominantly for contraceptive purposes, followed by an indication on prevention of menstrual migraine. The results of the study showed that prescribing indications for SEASONIQUE were comparable across all the participating countries.
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
ATC	Anatomical therapeutic chemical
ATE	Arterial thromboembolic event
BMI	Body mass index
BP	Blood pressure
CHC	Combined hormonal contraceptive
CI	Confidence interval
COC	Combined oral contraceptive
CSD	Cegedim Strategic Data
CV	Cardiovascular
CVA	Cerebrovascular accidents
DUS	Drug utilization study
DVT	Deep venous thrombosis
EE	Ethinyl estradiol
EMA	European Medicines Agency
EMR	Electronic medical records
EU	European Union

Abbreviation	Definition
GP	General practitioner
ICD-9-CM	International Classification of Diseases, ninth revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, tenth revision, Clinical Modification
IS	Ischaemic stroke
LNG	Levonorgestrel
N/A	Not applicable
OC	Oral contraceptive
PASS	Post-authorisation safety study
PE	Pulmonary embolism
RWD	Real-world data
SD	Standard deviation
SOP	Standard operating procedures
VTE	Venous thromboembolic event

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5. MILESTONES

Study Milestones

Milestone	Planned date	Actual date	Comments
Registration in the EU PAS register	Prior to data collection	12 September 2018	
Start of data collection	15 January 2019	15 January 2019	
End of data collection	15 July 2019	30 March 2019	study data was available
Interim report 1	25 September 2019	25 September 2019	
Final report of study results	30 March 2020	13 February 2020	

6. RATIONALE AND BACKGROUND

SEASONIQUE is a 91-day extended combined oral contraceptive (COC), containing a fixed-dose combination of 0.15 mg of levonorgestrel (LNG) and 0.03 mg ethinyl estradiol (EE) to be taken without interruption for 84 days, followed by 0.01 mg EE tablets for seven days (1). The extended regimen of SEASONIQUE is a modification of the standard 28-day cyclic regimen and is designed to increase the number of days of combined active tablets administration. Consequently, this regimen results in fewer scheduled withdrawal bleeding episodes per year than would regularly occur with conventional COCs. The extended regimen COC may improve compliance and reduce the risk of unwanted pregnancies by providing continuity and decreasing scheduled withdrawal bleeding to four episodes per year.

The standard 28-day cyclic regimen, consisting of 21 days of active combination pills followed by seven pill-free days or seven days of placebo pills, was designed to induce withdrawal bleeding once every 28 days (13 times per year). The monthly bleeding concept was designed to imitate the normal menstrual cycle as it was presumed that regular withdrawal bleeding was essential to the acceptance of oral contraceptives (OCs) by women and society. However, this bleeding is not a physiologic menstrual period. Moreover, the presence of cyclic bleeding is not essential for the contraceptive action of OCs. Therefore, research was conducted to reduce the length of the hormone-free interval (HFI) in an attempt to decrease estrogen-related withdrawal symptoms associated with traditional OCs (2, 3).

The marketing authorisation for SEASONIQUE was granted in Europe in various countries starting from 2015. The doses of this fixed-combination COC, i.e., 0.15 mg LNG and 0.03 mg EE, are already approved and used in other COCs authorised in Europe (4). In Europe, the first extended regimen OC was authorised in 2012 (Yvidually, which contains drospirenone and ethinylestradiol, and intended to be taken up to 120 days continuously). SEASONIQUE is the first LNG-containing extended regimen approved in Europe. SEASONIQUE was approved in the United States in May 2006 and in Canada in March 2010.

Given that the clinical program does not necessarily reflect the actual utilization patterns of women treated with SEASONIQUE, utilization patterns of this new extended regimen in routine clinical practice are not entirely known. Hence, in the context of the regulatory submission for market authorisation of SEASONIQUE in Europe, the European Medicines Agency (EMA) requested a post-authorisation safety study (PASS) to describe the drug utilization patterns with SEASONIQUE during routine clinical practice.

7. RESEARCH QUESTIONS AND OBJECTIVES

7.1 Primary Objective

The primary objective of the study was to characterize drug utilization patterns of SEASONIQUE in European countries.

7.2 Secondary Objective

None.

8. AMENDMENTS AND UPDATES

None.

9. RESEARCH METHODS

9.1 Study Design

This was a retrospective cohort study using secondary databases electronic medical records (EMR) from France, Italy and Belgium. These countries were selected based on the product launch and availability of longitudinal secondary databases. The study period began from the time SEASONIQUE data was first captured in the database of the selected countries (France, Italy and Belgium) until three years after the product was first captured. The three-year study period for three countries were: October 2015-September 2018 for France, June 2015-May 2018 for Italy and

December 2015-November 2018 for Belgium. The date of receiving the first prescription of SEASONIQUE in the study period was defined as the index date. The study period included the index date and the follow-up period. A baseline time period of six months prior to the first captured drug (index date) was also considered in order to evaluate the baseline characteristics of patients.

9.2 Setting

The study population included female patients in the outpatient settings of the three European countries: France, Italy and Belgium. A national representative sample of GPs were considered for each country. In addition, for France only, a panel of specialists (gynaecologists) were also considered.

9.3 Subjects

The analysis population included female patients receiving at least one prescription for SEASONIQUE during a three-year period after product launch.

Study participants were followed from index date until the earliest of the following censoring dates: end of the study period or end of enrolment in the database.

Among the analysis population who had at least one prescription record for SEASONIQUE during the study period, a subset of patients with at least six months of continuous membership enrolment prior to the first SEASONIQUE prescription was defined, if feasible. A minimum of six months continuous enrolment/membership within the database before the index date was used to obtain information about the relevant medical history and use of COC drugs before start of SEASONIQUE and also to allow for an adequate number of patients in the subgroup without significantly reducing precision.

If preliminary counts indicated a large population with at least six months of history, this group was considered to be the main analysis group and patients without six months baseline in the database were excluded. The group was defined as a large population if it represented 80% of the whole

population. If the proportion of patients with at least six months history was less than 80% all patients (with or without six months baseline period) were included in the main study population.

9.3.1 Inclusion Criteria

Patients were included in the study if they met the following criteria:

- Female gender
- Had a record of at least one written prescription for SEASONIQUE during the study period

9.3.2 Exclusion Criteria

No exclusion criteria were applied to examine SEASONIQUE use in real-life setting.

9.4 Variables

To describe the drug utilization patterns of SEASONIQUE in the outpatient setting in France, Italy and Belgium the following parameters were considered:

I. Duration of SEASONIQUE (uninterrupted use): The duration (days) of uninterrupted use of SEASONIQUE was defined as the following:

- For patients with at least a gap of more than 30 days between two prescriptions, the duration of uninterrupted use of SEASONIQUE was considered as the time between the index date and the date of the preceding prescription (+91 days) of the first gap of more than 30 days.
- For patients without a gap of more than 30 days between two prescription time and not followed until the end of the study period, the duration of uninterrupted use of SEASONIQUE was considered as the time between the index date and the date of the last prescription of SEASONIQUE + 91 days.
- For patients without a gap of more than 30 days between two prescription time and followed until the end of the study period: The duration of uninterrupted use of

SEASONIQUE was considered as the time between the index date and the date of the end of the study period.

NB: When calculating the duration of uninterrupted use, patients with overlapping prescriptions were identified and each overlap time was considered twice.

II. SEASONIQUE indication (diagnosis related to the SEASONIQUE prescription):

- Since prescriptions were not linked to a specific indication in the database, a proxy was used to define the indication for prescribing the COC at index date. Diagnoses related to prescribing COC were a priori defined using ICD-10-CM codes to represent the approved indications for COC and indications known to be potentially associated with COCs. The list of diagnoses was based on the American College of Obstetricians and Gynaecologists (ACOG) Practice Bulletin on Non-contraceptive Uses of Hormonal Contraceptives and included contraceptive management, acne, premenstrual syndrome and genital bleeding disorders (5). The ICD-10-CM diagnosis codes for defining the diagnoses related to prescribing COC are described in ANNEX 2.1.

- A time window of one month before or after the index date was used. Therefore, any ICD-10-CM code for the pre-defined diagnosis potentially related to prescribing COC recorded in the within one-month time window was considered in the analysis as a potential reason for prescription.

III. Use of prior CHC before SEASONIQUE initiation

IV. Switch patterns of patients using SEASONIQUE and changes to a different COC and concomitant use of other COC or other forms of contraception also.

Enrolment/Baseline

Baseline characteristics, medical history and demographic information were collected for each patient during the baseline period (= period of six months prior to the index date) and in the period of three

months prior to the index date for the hypertension information based on medical codes and terms and/or from detailed clinical data in the patient medical record, if available, including:

- Demographic characteristics of SEASONIQUE users:
  - Age at index date
    - <15 years
    - ≥15 to ≤35 years
    - >35 to <50 years
    - ≥50 years
  - Smoking status
  - Height/weight (body mass index [BMI])
    - Underweight (BMI<18.5)
    - Normal (18.5≤BMI<25) (Kg/m^2)
    - Overweight (25≤BMI≤30) (Kg/m^2)
    - Obese (BMI>30) (Kg/m^2)
- Information on type of prescriber (physician panel)
- Medical history of the following diagnoses:
  - Thromboembolic event
    - Venous thromboembolic event (VTE), defined as deep venous thrombosis (DVT) and/or pulmonary embolism (PE). The ICD-10-CM diagnosis codes for defining VTE outcomes are described in ANNEX 2.3.
    - Arterial thromboembolic event (ATEs), including acute myocardial infarction (AMI), ischemic stroke (IS) and cerebrovascular accidents (CVA) The ICD-

10-CM diagnosis codes for defining ATE outcomes are described in ANNEX 2.4.

- Breast cancers and other gynaecological cancers - Breast, cervical, endometrial and ovary cancers were identified. ICD-10-CM diagnosis codes for defining gynaecological cancers are described in ANNEX 2.5.
- Previous major surgery (including lower limb orthopaedic surgery), major lower extremity or pelvic trauma within three months before treatment initiation. Surgery events were searched and identified as free text in the diagnosis and medical acts information.

- Chemotherapy: Chemotherapies were searched and identified as free text in the diagnosis and medical acts information.
- Diastolic blood pressure (BP) (mmHg): The nearest measurement to the index date in the period of three months prior to the index date was considered as the diastolic BP at baseline.
- Systolic BP (mmHg): The nearest measurement to the index date in the period of three months prior to the index date was considered as the systolic BP at baseline.
- Hypertension at index date: women were considered to have hypertension if:
    - In the period of three months prior to the index date, one or more diagnosis of hypertension ICD-10-CM I10, I11, I12, I13, I15 were recorded.

      AND/OR
    - In the period of three months prior to the index date, at least two measurements of BP were above the hypertensive threshold (systolic BP ≥ 140 mmHg or diastolic BP ≥90 mmHg).

      AND/OR
    - In the period of three months prior to the index date, one or more antihypertensive drugs had been taken by the patient (ATC code C02 Antihypertensives).

- Polycystic ovary syndrome (PCOS) ICD-10-CM E28.2
- Migraine: ICD-10-CM G43
- Hyperlipidaemia ICD-10-CM E78.1; E78.2; E78.3. E78.4. E78.5
- Diagnosis of systemic lupus erythematosus (SLE): ICD-10-CM M32; L93.0
- Diabetes mellitus:
    - Diagnosis ICD-10-CM E10 (Type 1 diabetes mellitus), E11 (Type 2 diabetes mellitus)
    - diabetes drugs: the list of anti-diabetic therapies developed and maintained by the European Pharmaceutical Market Research Association (EphMRA) are described in ANNEX 2.6. Data on concomitant medication use (including medications prescribed for the treatment of cardiovascular (CV) disease [including anticoagulant use]), diabetes, and other chronic medical conditions
- Pregnancy
    - Pregnancy and pregnancy outcomes were identified for women if they had at least one of the diagnosis codes, or procedures described in ANNEX 2.7
    - Pregnancy was defined as follows, if feasible:
        - Previous pregnancy: three months or longer before index date
        - Recent pregnancy: within three months before index date
        - Prospective pregnancy: after index date

Exposure

Exposure was defined as one or more recorded written prescription for SEASONIQUE during the study period. By definition, starters of this newly launched product would only include patients who have not taken SEASONIQUE before. SEASONIQUE prescriptions were identified using the Anatomical Therapeutic Chemical (ATC) classification system code for SEASONIQUE. The date of

first record of SEASONIQUE prescription (i.e., exposure start date or cohort entry date) in the database during the study period was defined as the index date. The duration of each prescription was determined from the date of prescription and the total prescription quantity.

Drug utilization patterns of SEASONIQUE were described using all the available data from the date of first prescription until the end of study period or end of enrolment in the database. Examination of the entire medical history available prior to index date (i.e., six months of continuous enrolment or beyond) for COC use, allowed for differentiation between various groups of users. The following definitions were used to identify naïve users, new users, re-starters and switchers in the sub-population (6),where:

- **Naïve users (starting use)** were defined as women with first ever exposure to SEASONIQUE during the study period and no use of any dispensed CHC prior to the index date.
- **New users** were defined as women starting use of SEASONIQUE after a break of at least 12 weeks from any prescription of CHC prior to the index date.
- **Re-starters** were defined as women who started SEASONIQUE after a break of 4-11 weeks of using other CHC prior to the index date (new definition)[1].
- **Switchers** were defined as women starting SEASONIQUE after a different CHC preparation with a break of less than four weeks prior to the index date.

9.5 Data Sources and Measurement

All patient information on exposure and outcomes were obtained from existing European real-world data sources: IQVIA Longitudinal Patient Database® (LPD) databases were used in the outpatient

[1] The definition of restarters was amended to clarify that women had 'started' SEASONIQUE after a break of 4-11 weeks as opposed to 'restarted' SEASONIQUE. By definition the latter is not possible as all women included in the study and categorized into one of the four user groups at baseline could not have had previous exposure to SEASONIQUE.

setting of primary care providers (GPs) in France, Italy and Belgium and the specialist setting (gynaecologists) in France only.

- France – IQVIA RWD EMR France[2,3] provides a nationally representative sample of two panels of interest, about 1200 primary care physicians and 120 gynaecologists
- Italy – IQVIA RWD EMR Italy[3] provides a nationally representative sample of about 900 primary care physicians (560 practices)
- Belgium – IQVIA[3] RWD EMR Belgium[4] provides a nationally representative sample of about 300 primary care physicians

The databases consist of data collected from primary care practices and specialists on encounters of healthcare providers with patients in real-life setting. The characteristics of patients and practices within each database are representative of the primary care practices in the respective country (7).

Information on events deemed important by the physician was recorded in the patient's EMR. However, complete records of diagnoses or events requiring hospitalization were not available in the databases. Information on the variables collected in the IMS databases are provided in ANNEX 2.2.

Information on patient demographics, medical diagnoses, laboratory test results, and drug therapy were directly obtained from the practice computer system of the healthcare providers during daily recording. The therapeutic classifications in the database were mapped to the ATC classification system. Signs, symptoms, diagnoses, and diagnostic tests were mapped to ICD codes. To ensure confidentiality of patient information, the data were anonymized at the collection stage using encrypted identifiers for the physician and individual. Contributor physicians received advisory feedback on the quality of data collection in their practice, with individual feedback reports on data

[2] Formerly CSD Longitudinal patient database
[3] Formerly IMS
[4] Formerly Cegedim Strategic Data [CSD] Longitudinal patient database®

reported by the practice compared to data from other practices. Information on the general characteristics of the databases in France, Italy and Belgium are provided in Table 9.5-1.

Existing automated healthcare databases were selected for this drug utilization study (DUS) as at least partial data are readily available, allowing for collection of the study results in a reasonable time frame. In addition, the breadth of information on drug use made these data most suitable for examining drug utilization patterns in routine clinical practice settings.

Table 9.5-1: General Characteristics of the Databases

Characteristics	France		Italy	Belgium
Physician panel	IQVIA EMR GPs	IQVIA EMR Gynaecologists	IQVIA EMR GPs	IQVIA EMR GPs
Data collection methodology	Physicians' software	Physicians' software	Physicians' software	Physicians' software
Panel size (number of physicians)	1,200 GPs	120 Gynaecologists	900 GPs	300 GPs
National coverage	~2.0% of all GPs	~2.5% of Gynaecologists	~2.0% of all GPs	~2.4% of all GPs
Number of active patients	1,800,000	240,000	750,000	370,000
Average length of enrolment in database	7-8 years	4 years	10 years	8 years
Patient ID unique cross physicians' panel (GPs and Gynaecologists)	No	No	N/A	N/A
Diagnostic coding system	ICD-10-CM	ICD-10-CM	ICD-9-CM	ICD-10-CM

EMR=electronic medical records; GP=general practitioner; GYN=Gynaecologists; ICD=International Classification of Diseases, N/A: not applicable

9.6 Bias

The potential for selection bias of women being prescribed SEASONIQUE was a possible inherent bias/limitation of an observational for this study. Potential bias was addressed by stratification on key baseline characteristics such as country, age, specialty, type and size of setting, etc.

For evaluating a potential bias due to size of practice (risk of over-representativity of practices including a high volume of patients), the number of physicians according to the number of prescriptions of SEASONIQUE and the number of physicians according the number of patients taking SEASONIQUE were described.

Misclassification of exposure or outcome is identified as a potential limitation of observational studies. Assessment of SEASONIQUE exposure was based on the EMRs of written prescriptions rather than information on dispensed prescriptions or actual intake. Thus, patients might have been classified as exposed when they have been prescribed with the drug, but there is no evidence that the drug is actually dispensed or taken by the patient. While EMRs data may not represent the actual medication used these data have been extensively studied and provide sound and fairly unbiased information on medication use from real-world data.

Misclassification may also occur due to underreporting of diagnoses or events in the databases, because these databases were not designed for research purpose. For SEASONIQUE, which is usually intended for long-term use, the indication for use may not be directly available in the medical records. The physician may not document the indication for which the drug is prescribed every time a prescription is issued. Lack of recording of drug indication or diagnosis was more likely to occur for conditions that are chronic or drugs that are prescribed for chronic use, such as the case for SEASONIQUE. This underreporting may limit the accuracy for assigning indication of use. In addition, it should be noted that the actual indication changes over time. As the indication of use may not be recorded for most of the prescriptions, the indication was inferred from medical diagnoses recorded around the time of the written prescription to allow for a wide window to capture the indication.

Nonetheless, since the study was conducted in EMR databases from the time SEASONIQUE was launched in Europe, it was expected that the indication for which the drug was prescribed was more readily available. Patients seeking care outside the EMR practice setting would not have that utilization recorded in the database. In addition, in the IQVIA RWD EMR, anonymized patients

cannot be tracked across panels, practices or specialties. Therefore, double counting of patients cannot be completely ruled out when more than one panel was analysed.

The duration of SEASONIQUE treatment (in days) was evaluated using the number of packs prescribed. In cases where this information was not available, the treatment duration could not be exactly determined. Therefore, it might be possible that if patients were misusing the drug, the actual treatment duration could be shorter compared to the length of the prescribing recommendations (by physician or labelling).

Information on pregnancy was expected to be limited since the drug was prescribed for three months and there was no way to know whether the woman stopped taking the drug during those three months (information on drug consumption is not available) or continued. Additionally, the date of conception may not be recorded in the database. Consequently, it was not possible to accurately estimate whether the women were still on the drug while pregnant.

9.7 Study Size

The study size for this study was dependent on the data availability in the three IQVIA healthcare databases.

For each country-specific database and setting, a preliminary number of female patients treated with SEASONIQUE by panel and country was conducted. Based on these numbers and on the projected sales of the product, it was estimated that by 2018, the number of female patients treated with SEASONIQUE by country and setting would be 167 and 724 in France (primary care and gynaecologist, respectively), 134 in Italy (primary care) and 88 in Belgium (primary care). Overall, the estimated total number of users in the study databases was approximately 1110.

Based on the study primary objective, sample size was calculated for the proportion of female patients' prior use of CHC medication before SEASONIQUE initiation in each country. Since no relevant background/historical data was available from which to derive this proportion in advance, it was assumed that among all patients using this drug in each country, the expected proportion (p) of

female patients with prior use of CHC medication before SEASONIQUE initiation was 50%. Given this assumption (i.e., p= 0.5, which would yield the largest sample size per country), a confidence interval of 95% and margin of error of 5%, the required sample size, using the following formula, was 385 users per country, i.e., a total sample size of approximately 1155 female patients was estimated.

$$n = t2.p\,(1-p)/e\,2$$

The precision achieved with various assumptions was calculated; results are provided in Table 9.7-1.

Table 9.7-1: Sample Sizes for Different Estimates of Proportions and Varying Precisions of the Estimates

	Proportion of users					
	0.01	**0.02**	**0.05**	**0.1**	**0.2**	**0.5**
Precision=0.01	381	753	1825	3458	6147	9604
Precision=0.02	96	189	457	865	1537	2401
Precision=0.05	16	31	73	139	246	385
Precision=0.1	4	8	19	35	62	97
Precision=0.2	1	2	5	9	16	25

9.8 Data Transformation

Not applicable.

9.9 Statistical Methods

9.9.1 Main Summary Measures

Given the objectives, analyses were mainly descriptive. Categorical variables were presented as counts (n), percentages (%) and confidence interval (95% CI) where relevant. Continuous variables were presented as counts, means with standard deviation (SD), or medians, minimum and maximum and inter quartile range (IQR), where appropriate. The distribution of the number of prescriptions,

frequency and duration of use, by physician panel (primary care, gynaecologists) and country (i.e., database) was described. All data analyses were performed using appropriate statistical analysis software (SAS version 9.4, SAS Institute Inc., Cary, NC, USA).

9.9.2 Main Statistical Measures

The main study analysis described the prescribing patterns among female patients treated with SEASONIQUE in outpatient settings in selected European countries. For each country descriptive statistics were provided for demographics and other patient characteristics of patients prescribed SEASONIQUE, treatments and diagnosis characteristics, including duration of use, indication and type of prescriber.

A subset of patients with at least six months of continuous membership/enrolment within the database prior to first SEASONIQUE prescription (i.e., index date) were examined. Where preliminary counts indicated a large population (i.e. more than 80% of the whole population) this group served as the main analysis group

The analysis was performed separately per database in the target country and by physician panel in the outpatient settings (i.e., primary care, gynaecologists). Data from the different databases was not pooled. The statistical unit was either the prescription or the patient, as appropriate; the statistical unit was the patient for information such as demographical and clinical characteristics and medical history, and the SEASONIQUE prescription for information such as indication, number of prescriptions and treatment duration.

9.9.3 Missing Values

The number and percentage of missing data was calculated and reported. Missing values for the variables were reported as missing and no imputation was conducted.

9.9.4 Sensitivity Analyses

Not applicable.

9.9.5 Amendments to the Statistical Analysis Plan

None.

9.10 Quality Control

9.10.1 Output Quality Checks

At the database level, the quality unit of IQVIA production department continuously verified the quality of its numerous physician panels in terms of panel representativeness, consistency of collected data, and validation of coding of physicians' verbatim. Data collected by physicians in routine practice and transcribed into the patient EMR were anonymized and transferred to the database daily in accordance with national legislation. The data are hosted on servers located in datacentres belonging to IQVIA, which ensures a high level of data security and confidentiality. All programming code developed for this study by the executing researcher was reviewed independently by a senior researcher. The study was executed in line with the data vendor's quality management system.

10. RESULTS

This final report presents results for the overall three-year study period.

Analysis Population:

All the included patients along with analysis population has been described in Figure 1, Figure 2, Figure 3 and Figure 4.

Figure 1: Analysis population - France – GPs

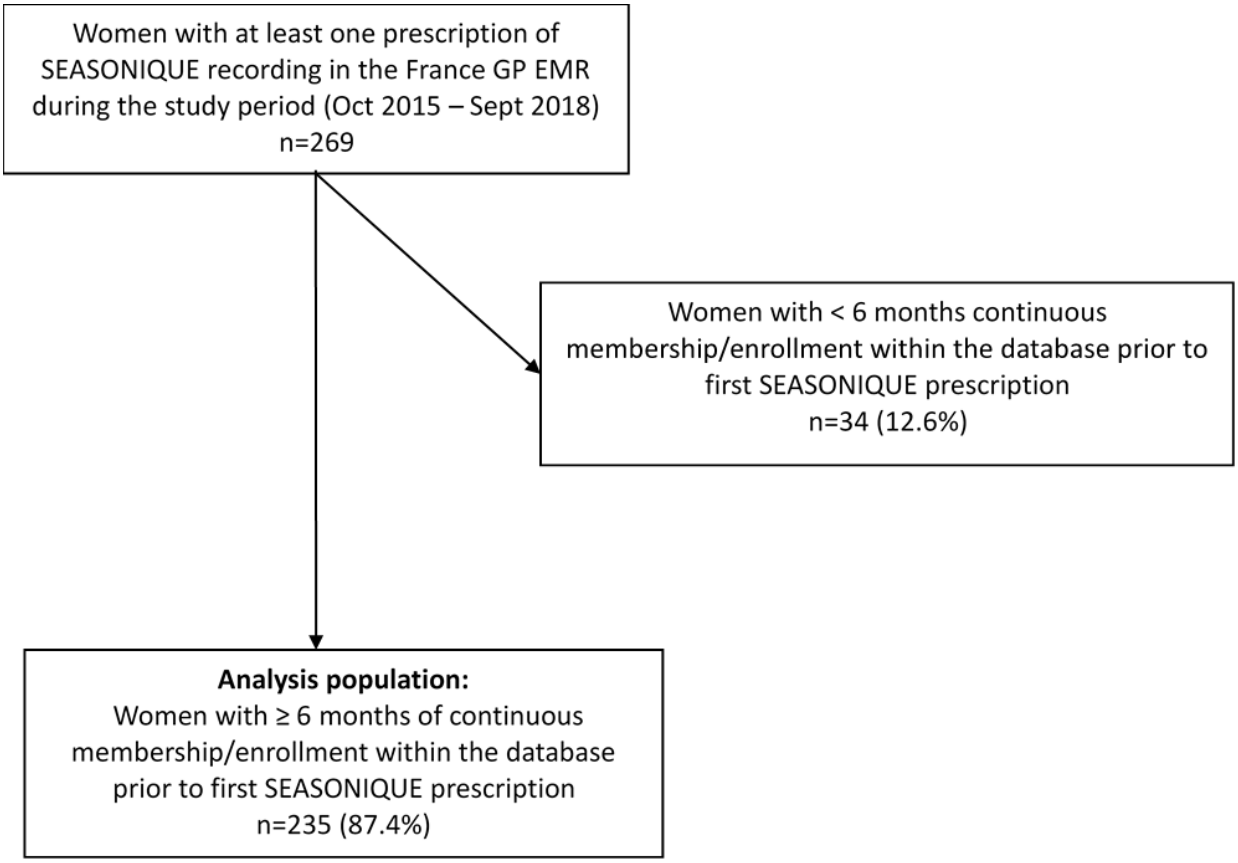


Figure 2: Analysis population - Italy – GPs

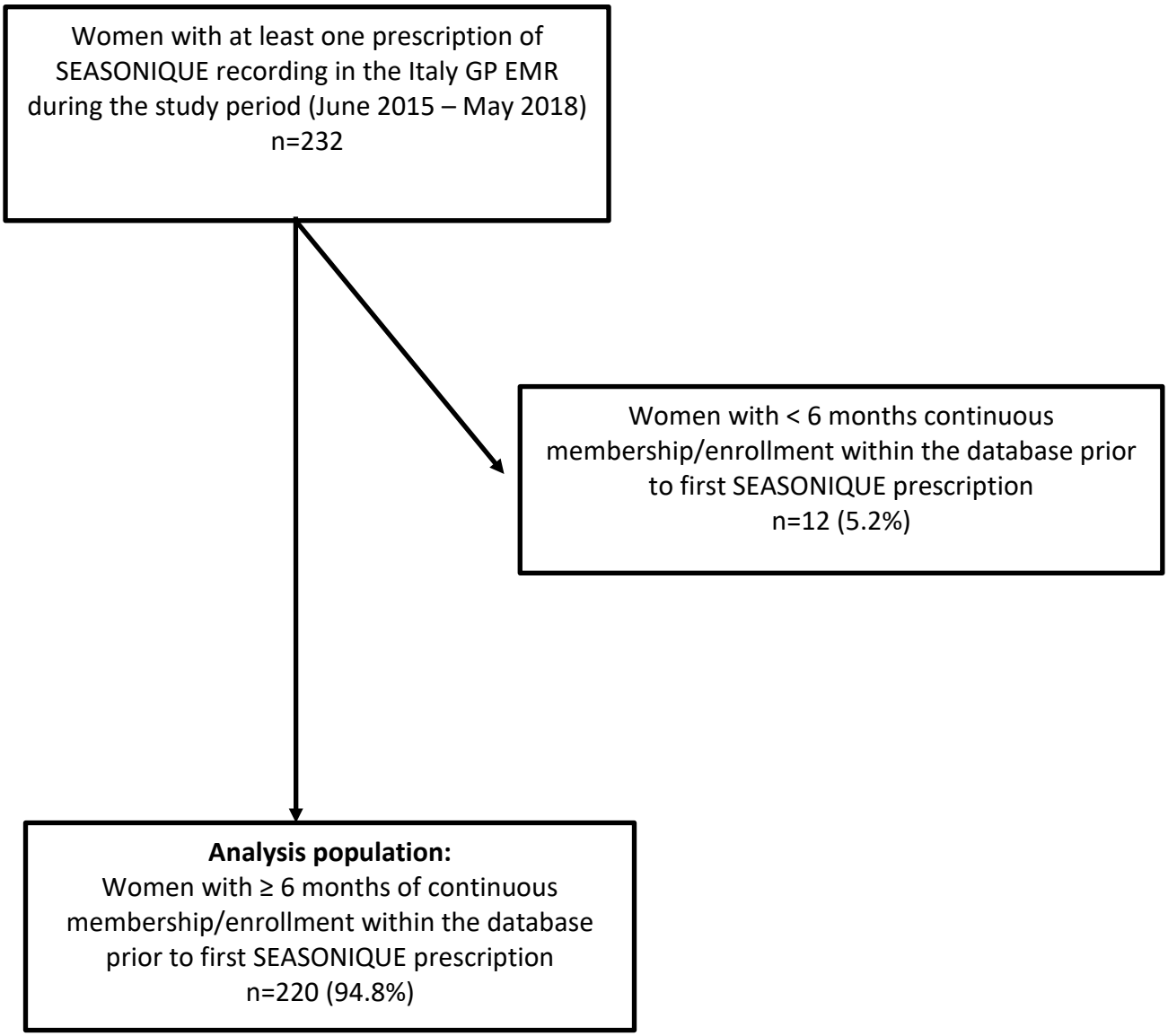


Figure 3: Analysis population - Belgium – GPs

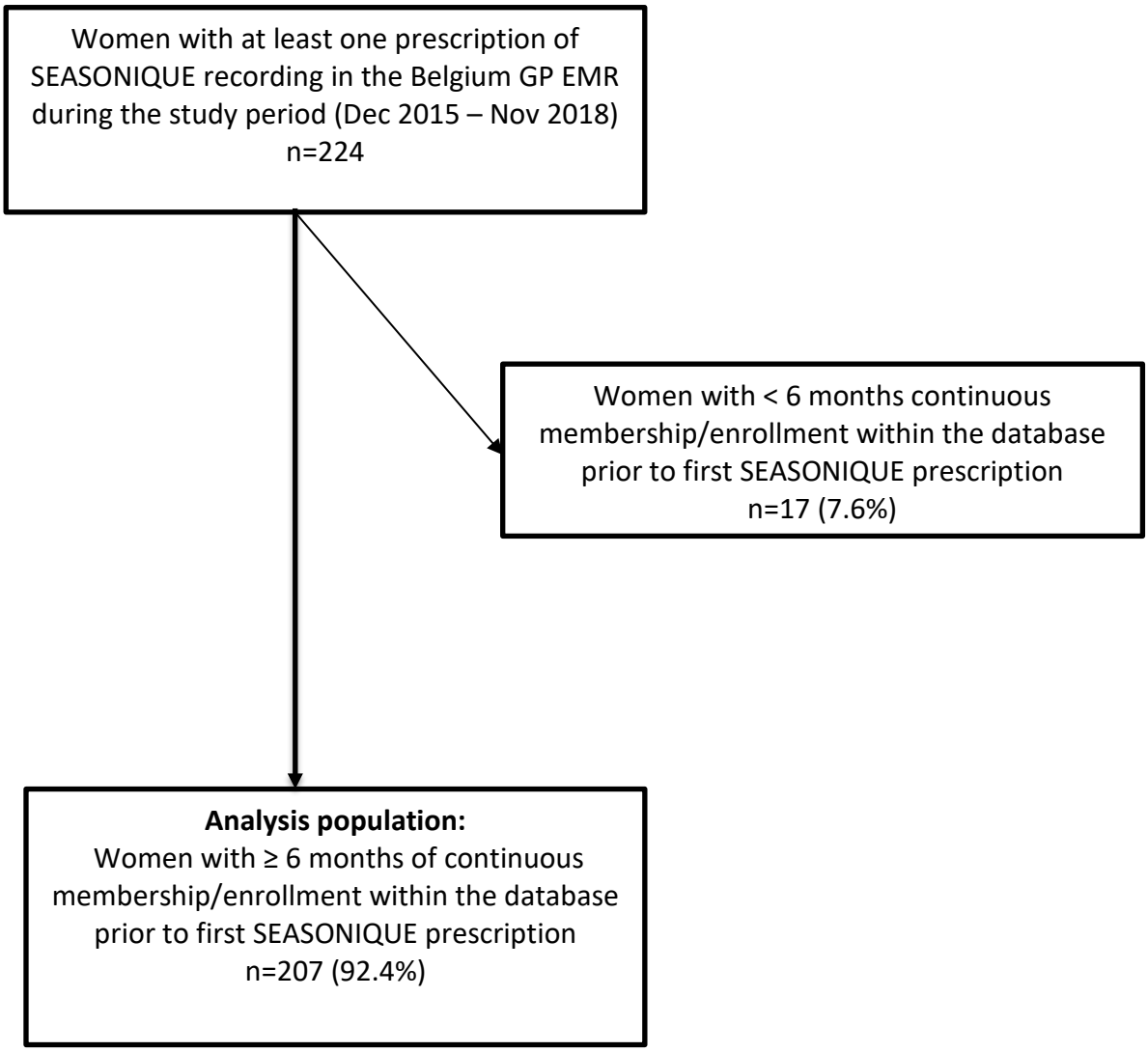
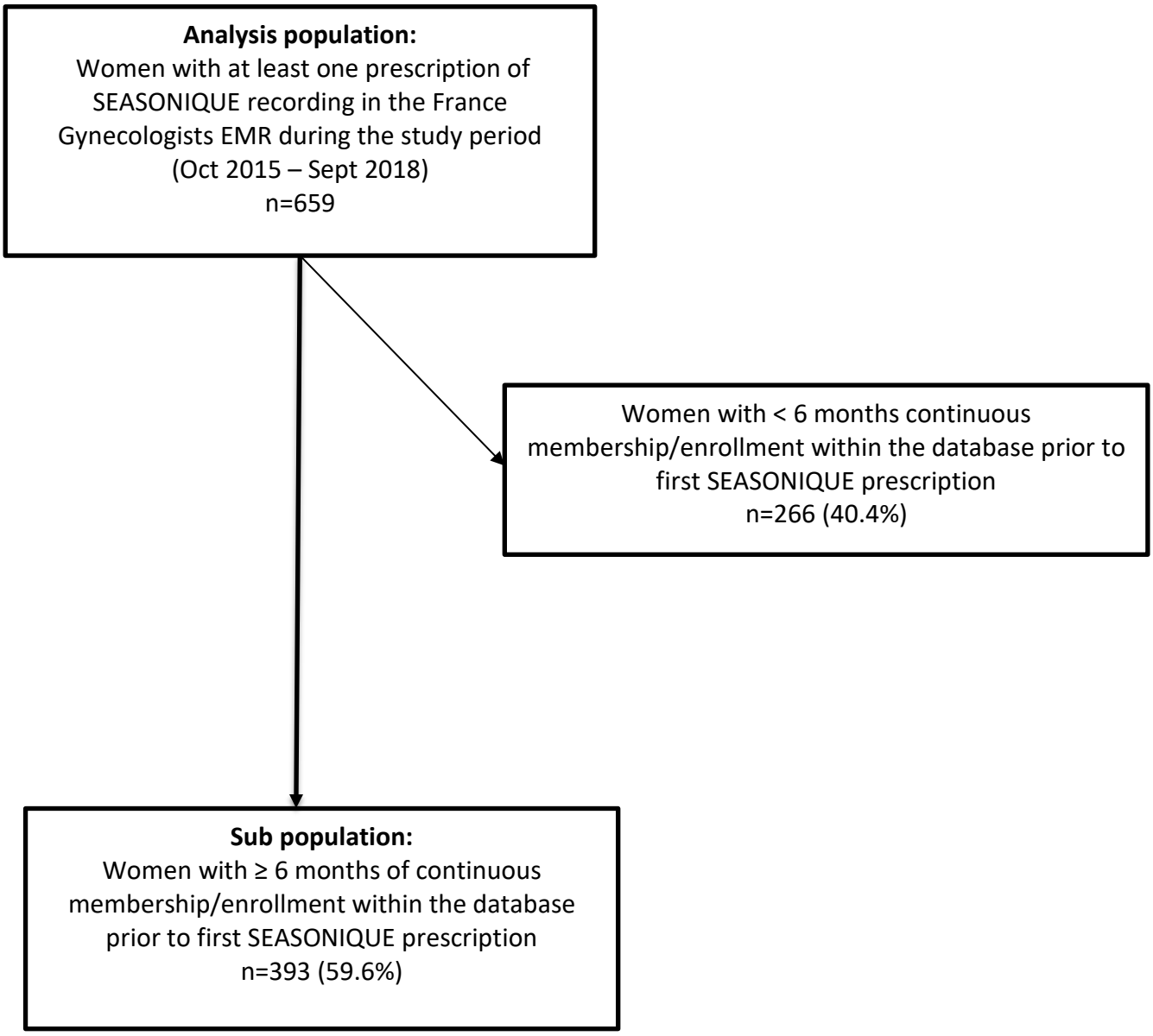


Figure 4: Analysis population - France – Gynaecologists



10.1 Participants

All patients included in the study, along with the analysis population, are described in Figure 1, Figure 2, Figure 3 and Figure 4 below. The total analysis population across French GP, Italian GP, Belgian GP and French gynaecologist panels are presented in Table 10.1-1, Table 10.1-2, Table 10.1-3 and Table 10.1-4, respectively.

A total of 269 patients were identified in the French GP panel as having received at least one prescription of SEASONIQUE (Figure 1). Among these patients, 34 (12.6%) patients had less than six months of continuous membership/enrolment within the database prior to first prescription of SEASONIQUE and were excluded from the analysis. Consequently, a total of 235 (87.4%) patients were eligible and included in the analyses. Of the analysis population (N=235), 45.1% were new users, 34.9% were naïve users, 12.8% were switchers and 7.2% were re-starters (Table 10.1-1).

Table 10.1-1: Total analysis population– France – GPs

	Analysis population (Total number of patients = 235)
Naïve users[1]	82 (34.9%)
New users[2]	106 (45.1%)
Re-starters[3]	17 (7.2%)
Switchers[4]	30 (12.8%)

[1] Naïve users (starting use) are defined as women with first ever exposure to SEASONIQUE during the study period and no use of any dispensed combined hormonal contraceptive (CHC) prior to the index date

[2] New users are defined as women starting use of SEASONIQUE after a break of at least 12 weeks for any prescription of CHC prior to the index date

[3] Re-starters are defined as women who start SEASONIQUE after a break of 4-11 weeks of using other CHC prior to the index date

[4] Switchers are defined as women starting SEASONIQUE after a different CHC preparation with a break of less than four weeks prior to the index date.

Figure 2 shows the Italian GP panel. Over the three-year study period a total of 232 patients were identified in the Italian GP panel as having received at least one prescription of SEASONIQUE. Among these patients, 220 (94.8%) had more than six months of continuous membership/enrolment within the database prior to first prescription of SEASONIQUE and were included as the analysis population. Twelve patients had less than six months of continuous membership/enrolment and were excluded from the analysis. Of the analysis population (N=220), 55.0 % were new users, 33.2% were naïve users, 7.7% were re-starters and 4.1% were switchers (Table 10.1-2).

Table 10.1-2: Total analysis population– Italy – GPs

	Analysis population (Total number of patients = 220)
Naïve users[1]	73 (33.2%)
New users[2]	121 (55.0%)
Re-starters[3]	17 (7.7%)
Switchers[4]	9 (4.1%)

[1] Naïve users (starting use) are defined as women with first ever exposure to SEASONIQUE during the study period and no use of any dispensed combined hormonal contraceptive (CHC) prior to the index date

[2] New users are defined as women starting use of SEASONIQUE after a break of at least 12 weeks for any prescription of CHC prior to the index date

[3] Re-starters are defined as women who start SEASONIQUE after a break of 4-11 weeks of using other CHC prior to the index date

[4] Switchers are defined as women starting SEASONIQUE after a different CHC preparation with a break of less than four weeks prior to the index date.

Figure 3 shows the Belgian GP panel. Over the three-year study period a total of 224 patients were identified in the Belgian GP panel as having received at least one prescription of SEASONIQUE. Among these patients, 207 (92.4%) had more than six months of continuous membership/enrolment within the database prior to first prescription of SEASONIQUE and were included as the analysis population. Seventeen patients had less than six months of continuous membership/enrolment and were excluded from the analysis. Of the analysis population (N=207), 34.8% were naïve users, 32.4% were new users 26.6% were switchers and 6.3% were re-starters (Table 10.1-3).

Table 10.1-3: Total analysis population– Belgium – GPs

	Analysis population (Total number of patients = 207)
Naïve users[1]	72 (34.8%)
New users[2]	67 (32.4%)
Re-starters[3]	13 (6.3%)
Switchers[4]	55 (26.6%)

[1] Naïve users (starting use) are defined as women with first ever exposure to SEASONIQUE during the study period and no use of any dispensed combined hormonal contraceptive (CHC) prior to the index date

[2] New users are defined as women starting use of SEASONIQUE after a break of at least 12 weeks for any prescription of CHC prior to the index date

[3] Re-starters are defined as women who start SEASONIQUE after a break of 4-11 weeks of using other CHC prior to the index date

[4] Switchers are defined as women starting SEASONIQUE after a different CHC preparation with a break of less than four weeks prior to the index date

Figure 4 shows the French gynaecologist panel. Over the three-year study period a total of 659 patients were identified in French gynaecologist panel as having received at least one prescription of SEASONIQUE. Among these patients, 393 (59.6%) had more than six months of continuous membership/enrolment within the database prior to first prescription of SEASONIQUE. Therefore, the main analysis was performed for the total of 659 patients as <80% patients had more than six months of baseline enrolment. The subset of women with at least six months of continuous membership/enrolment were analysed separately as a sub-population (see section 10.3.9). Of the 659 patients included in the French gynaecologist panel, 50.8% were naïve users, 30.3% were new users, 14.9% were switchers and 3.9% were re-starters (Table 10.1-4).

Table 10.1-4: Total analysis population- France Gynaecologists

	Analysis population (Total number of patients = 659)
Naïve users[1]	335 (50.8%)
New users[2]	200 (30.3%)
Re-starters[3]	26 (3.9%)
Switchers[4]	98 (14.9%)

	Analysis population (Total number of patients = 659)

[1] Naïve users (starting use) are defined as women with first ever exposure to SEASONIQUE during the study period and no use of any dispensed combined hormonal contraceptive (CHC) prior to the index date
[2] New users are defined as women starting use of SEASONIQUE after a break of at least 12 weeks for any prescription of CHC prior to the index date
[3] Re-starters are defined as women who start SEASONIQUE after a break of 4-11 weeks of using other CHC prior to the index date
[4] Switchers are defined as women starting SEASONIQUE after a different CHC preparation with a break of less than four weeks prior to the index date.

10.2 Descriptive Data

10.2.1 Patient Demographics

Patient demographics in the French GP, Italian GP, Belgian GP and French gynaecologist panels are described in Table 10.2-1, Table 10.2-2, Table 10.2-3 and Table 10.2-4, respectively.

The mean (SD) age of patients in the French GP panel was 27.2 (9.37) years with 78% of patients ≤35 years of age. The mean (SD) weight was 62.7 (11.41) kg with 65.6% patients within the normal BMI category. For all patients smoking and alcohol status were missing (Table 10.2-1).

Table 10.2-1: Patient's demographics characteristics at index date in France – GPs

		Analysis population (Total number of patients = 235)[1]
Age at index date (years)	N	231
	Mean (SD)	27.2 (9.37)
	Median [Q1 - Q3]	24.0 [19.0-34.0]
	Range [min - max]	[14.0,51.0]
	Missing	4
Age at index date (years) – categories	<15 years	2 (0.9%)[2]
	≥ 15 to ≤ 35 years	178 (77.1%)[2]
	>35 to <50 years	50 (21.6%)[2]
	≥ 50 years	1 (0.4%)[2]
	Missing	4
Weight (kg)	N	81
	Mean (SD)	62.7 (11.41)
	Median [Q1 - Q3]	60.0 [56.0-67.0]
	Range [min - max]	[41.0-96.0]

		Analysis population (Total number of patients = 235)[1]
	Missing	154
Height (cm)	N	135
	Mean (SD)	164.9 (6.44)
	Median [Q1 - Q3]	165.0 [160.0-169.0]
	Range [min - max]	[149.0-178.0]
	Missing	100
BMI value (kg/m^2)	N	64
	Mean (SD)	23.2 (4.12)
	Median [Q1 - Q3]	21.9 [20.1-25.7]
	Range [min - max]	[16.8-35.3]
	Missing	171
BMI value (kg/m^2) – categories	Underweight (BMI<18.5)	3 (4.7%)[2]
	Normal (18.5≤BMI<25)	42 (65.6%)[2]
	Overweight (25≤BMI≤30)	14 (21.9%)[2]
	Obese (BMI>30)	5 (7.8%)[2]
Smoking status	Yes	0
	No	0
	Missing	235
Number of cigarettes per day[3]	Mean (SD)	N/A
	Median [Q1 - Q3]	N/A
	Range [min - max]	N/A
	Missing	N/A
Alcohol drinker	Yes	0
	No	0
	Missing	235

Abbreviations: BMI: Body Mass Index, Q1-Q3: Median (1st quartile-3rd quartile), Min: Minimum, Max: Maximum, N/A: not applicable, SD: Standard Deviation
[1] Demographic information was collected during the baseline period
[2] The percentage per category relative to non-missing data
[3] For patients with a smoking status of yes

The mean (SD) age of patients in the Italian GP panel was 34.2 (9.34) years with 52.8% of patients ≤35 years. The mean (SD) weight was 61.3 (10.03) kg with 76.5% of patients having a normal BMI.

Less than one fifth of patients (18.2%) were smokers with a mean (SD) number of cigarettes per day of 12.5 (5.00). Alcohol status was missing for the majority of patients (Table 10.2-2).

Table 10.2-2: Patient's demographic characteristics at index date in Italy – GPs

		Analysis population (Total number of patients = 220)[1]
Age at index date (years)	N	216
	Mean (SD)	34.2 (9.34)
	Median [Q1 - Q3]	35.0 [26.0-42.0]
	Range [min - max]	[15.0-53.0]
	Missing	4
Age at index date (years) – categories	<15 years	0
	≥ 15 to ≤ 35 years	114 (52.8%)[2]
	>35 to <50 years	98 (45.4%)[2]
	≥ 50 years	4 (1.9%)[2]
	Missing	4
Weight (kg)	N	17
	Mean (SD)	61.3 (10.03)
	Median [Q1 - Q3]	58.0 [55.0-65.0]
	Range [min - max]	[46.7-90.0]
	Missing	203
Height (cm)	N	106
	Mean (SD)	164.5 (5.91)
	Median [Q1 - Q3]	163.5 [161.0-168.0]
	Range [min - max]	[148.0-181.0]
	Missing	114
BMI value (kg/m^2)	N	17
	Mean (SD)	22.2 (3.97)
	Median [Q1 - Q3]	21.8 [20.1-23.0]
	Range [min - max]	[17.8-33.9]
	Missing	203
BMI value (kg/m^2) – categories	Underweight (BMI<18.5)	2 (11.8%)[2]
	Normal (18.5≤BMI<25)	13 (76.5%)[2]
	Overweight (25≤BMI≤30)	1 (5.9%)[2]
	Obese (BMI>30)	1 (5.9%)[2]
Smoking status	Yes	4 (18.2%)[2]

		Analysis population (Total number of patients = 220)[1]
	No	18 (81.8%)[2]
	Missing	198
Number of cigarettes per day[3]	Mean (SD)	12.5 (5.00)
	Median [Q1 - Q3]	10.0 [10.0-15.0]
	Range [min - max]	[10.0-20.0]
	Missing	0
Alcohol drinker	Yes	5 (100%)[2]
	No	0
	Missing	215

Abbreviations: BMI: Body Mass Index, Q1-Q3: Median (1st quartile-3rd quartile), Min: Minimum, Max: Maximum, SD: Standard Deviation
[1] Demographic information was collected during the baseline period
[2] The percentage per category relative to non-missing data
[3] For patients with a smoking status of yes

The mean (SD) age of patients in the Belgian GP panel was 30.2 (10.39) years with 67.1% of patients ≤35 years. The mean (SD) weight was 66.8 (17.17) kg with 38.9% of patients having a normal BMI. More than 50% of patients were classified as overweight or obese. Smoking and alcohol status were missing for the majority of patients (Table 10.2-3).

Table 10.2-3: Patient's demographics characteristics at index date in Belgium – GPs

		Analysis population (Total number of patients = 207)[1]
Age at index date (years)	N	207
	Mean (SD)	30.2 (10.39)
	Median [Q1 - Q3]	28.0 [22.0-39.0]
	Range [min - max]	[12.0-55.0]
Age at index date (years) – categories	<15 years	3 (1.4%)[2]
	≥ 15 to ≤ 35 years	136 (65.7%)[2]
	>35 to <50 years	63 (30.4%)[2]
	≥ 50 years	5 (2.4%)[2]
Weight (kg)	N	28
	Mean (SD)	66.8 (17.17)
	Median [Q1 - Q3]	64.0 [57.0-74.0]

		Analysis population (Total number of patients = 207)[1]
	Range [min - max]	[36.0-108.0]
	Missing	179
Height (cm)	N	51
	Mean (SD)	166.8 (6.92)
	Median [Q1 - Q3]	166.0 [161.0-171.0]
	Range [min - max]	[153.0-182.0]
	Missing	156
BMI value (kg/m^2)	N	18
	Mean (SD)	26.2 (6.64)
	Median [Q1 - Q3]	25.0 [22.4-27.5]
	Range [min - max]	[17.6-42.6]
	Missing	189
BMI value (kg/m^2) - categories	Underweight (BMI<18.5)	1 (5.6%)[2]
	Normal (18.5≤BMI<25)	7 (38.9%)[2]
	Overweight (25≤BMI≤30)	7 (38.9%)[2]
	Obese (BMI>30)	3 (16.7%)[2]
Smoking status	Yes	7 (77.8%)[2]
	No	2 (22.2%)[2]
	Missing	198
Number of cigarettes per day[3]	Mean (SD)	8.0 (N/A)
	Median [Q1 - Q3]	8.0 [N/A-N/A]
	Range [min - max]	[N/A-N/A]
	Missing	6
Alcohol drinker	Yes	5 (6.3%)[2]
	No	74 (93.7%)[2]
	Missing	128

Abbreviations: BMI: Body Mass Index, Q1-Q3: Median (1st quartile-3rd quartile), Min: Minimum, Max: Maximum, N/A: not applicable, SD: Standard Deviation

[1] Demographic information was collected for each patient from the database during the period prior to the index date

[2] The percentage per category relative to non-missing data

[3] For patients with a smoking status of yes

For the French gynaecologist panel, a total of 484 patients (73.6%) were in the age group ≥ 15 to ≤35 years and 68.1% had a normal BMI. The smoking and alcohol intake status was unknown for almost the entire population (Table 10.2-4).

Table 10.2-4: Patient's demographic characteristics at index date in France – Gynaecologists

		Analysis population (Total number of patients =659)[1]
Age at index date (years)	N	658
	Mean (SD)	29.3 (8.80)
	Median [Q1 - Q3]	29.0 [22.0-36.0]
	Range [min - max]	[15.0-52.0]
	Missing	1
Age at index date (years) – classes	<15 years	0
	≥ 15 to ≤ 35 years	484 (73.6%)[2]
	>35 to <50 years	167 (25.4%)[2]
	≥ 50 years	7 (1.1%)[2]
	Missing	1
Weight (kg)	N	184
	Mean (SD)	61.7 (12.40)
	Median [Q1 - Q3]	60.0 [53.0-68.0]
	Range [min - max]	[40.0-107.0]
	Missing	475
Height (cm)	N	190
	Mean (SD)	165.1 (6.19)
	Median [Q1 - Q3]	165.0 [160.0-170.0]
	Range [min - max]	[148.0-180.0]
	Missing	469
BMI value (Kg/m^2)	N	135
	Mean (SD)	22.6 (4.01)
	Median [Q1 - Q3]	21.6 [20.1-24.4]
	Range [min - max]	[16.2-39.3]
	Missing	524
BMI value (Kg/m^2) - classes	Underweight (BMI<18.5)	13 (9.6%)[2]
	Normal (18.5≤BMI<25)	92 (68.1%)[2]
	Overweight (25≤BMI≤30)	22 (16.3%)[2]
	Obese (BMI>30)	8 (5.9%)[2]
Smoking status	Yes	1 (100.0%)[2]
	No	0
	Missing	658

		Analysis population (Total number of patients =659)[1]
Number of cigarettes per day[3]	Mean (SD)	3.00 (N/A)
	Median [Q1 - Q3]	3.00 [N/A-N/A]
	Range [min - max]	[N/A-N/A]
	Missing	0
Alcohol drinker[2]	Yes	0
	No	0
	Missing	659

Abbreviations: BMI: Body Mass Index, Q1-Q3: Median (1st quartile-3rd quartile), Min: Minimum, Max: Maximum, N/A: not applicable, SD: Standard Deviation
[1] Demographic information was collected during the baseline period
[2] The percentage per category relative to non-missing data
[3] For patients with a smoking status of yes

10.2.2 Medical History

Prespecified medical history of patients in the French GP, Italian GP, Belgian GP and French gynaecologist panels is described in Table 10.2-5, Table 10.2-6, Table 10.2-7 and Table 10.2-8, respectively. Among patients in the French GP panel, the most prevalent comorbidities (recorded anytime in the patient's medical history) were hypertension (1.3%) and subarachnoid haemorrhage (0.4%). However, the mean systolic/diastolic BP (where specified) was in the normal range. Trauma and major surgery within the last three months before treatment initiation was reported in one patient (0.4%). None of the patients had a history of DVT/PE, breast cancers or other gynaecological cancers (Table 10.2-5).

Table 10.2-5: Medical history of patients at index date in France – GP

		Analysis population (Total number of patients = 235)[1]
Deep venous thrombosis (DVT)		
	Phlebitis and thrombophlebitis of unspecified site	0
	Phlebitis and thrombophlebitis of femoral vein	0
	Phlebitis and thrombophlebitis of other deep vessels of lower extremities	0
	Phlebitis and thrombophlebitis of lower extremities, unspecified	0
	Phlebitis and thrombophlebitis of unspecified site	0

		Analysis population (Total number of patients = 235)[1]
	Total	0
Pulmonary Embolism (PE)		
	Pulmonary embolism	0
Arterial thromboembolic event (ATEs)*	Acute myocardial infarction (AMI)	0
	Subarachnoid haemorrhage	1 (0.4%)[6]
	Intracerebral haemorrhage	0
	Cerebral infarction due to thrombosis of cerebral arteries	0
	Stroke not specified as haemorrhage or infarction	0
	Total	1 (0.4%)[6]
Breast cancers and other gynaecological cancers	Colon	0
	Rectum	0
	Breast	0
	Cervix uteri	0
	Overlapping sites of cervix uteri	0
	Cervix uteri, unspecified	0
	Corpus uteri, endometrium	0
	Total	0
Trauma and major surgery within 3 months before treatment initiation*	Lower limb orthopaedic surgery	0
	Major lower extremity surgery	0
	Pelvic trauma surgery	0
	Other	1 (0.4%)
	Total	1 (0.4%)
Chemotherapy	Total	0
Systolic blood pressure (mmHg)[3] / Diastolic blood pressure (mmHg)[2]	N	21
	Mean (SD)	118.5 (11.64) / 71.9 (8.15)
	Median [Q1 - Q3]	120.0 [110.0-127.0] / 70.0 [70.0-80.0]
	Range [min - max]	[90.0-140.0] / [60.0-90.0]
	Missing	214
Hypertension[4]	Total	3 (1.3%)[6]
Diabetes diagnosis[5]	Total	0

		Analysis population (Total number of patients = 235)[1]
Anti-diabetic drugs use	1	0
	2	0
	3+	0
Hyperlipidaemia	Total	0
Systemic lupus erythematosus (SLE)	Total	0

Abbreviations: Q1-Q3: Median (1st quartile-3rd quartile), SD: Standard Deviation
[1] All medical history will be collected for each patient during the baseline period (= period of 6 months prior the index date) except for blood pressure measurement (diastolic and systolic blood pressure), hypertension, trauma and major surgery
[2] Diastolic blood pressure (mmHg): The nearest measurement in the period of 3 months prior to the index date
[3] Systolic blood pressure (mmHg): The nearest measurement in the period of 3 months prior to the index date
[4] Women will be considered to have hypertension if:
-->In the period of 3 months prior the index date, one or more diagnosis of hypertension ICD-10-CM I10, I11, I12, I13, I15 have been recorded.
AND/OR
->In the period of 3 months prior to the index date, at least two measurements of blood pressure (BP) are above the hypertensive threshold (systolic BP ≥ 140 mmHg or diastolic BP ≥90 mmHg)).
AND/OR
-->In the period of 3 months prior to the index date, one or more antihypertensive drugs have been taken by the patient (ATC code C02 Antihypertensives).
*Multiple answers are possible
[5] Type 1 and 2 diabetes
[6] This is the percentage of total cohort

Among patients in the Italian GP panel, the most prevalent comorbidities (recorded anytime in the patient's medical history) were hypertension (4.1%) and diabetes (1.4%). However, the mean systolic/ diastolic BP (where specified) was in the normal range. Trauma and major surgery within the last three months before treatment initiation was reported in one patient (0.5%). None of the patients had a history of DVT/PE, breast cancers or other gynaecological cancers (Table 10.2-6).

Table 10.2-6: Medical history of patients at index date in Italy – GPs

		Analysis population (Total number of patients = 220)[1]
Deep venous thrombosis (DVT)		
	Phlebitis and thrombophlebitis of unspecified site	0
	Phlebitis and thrombophlebitis of femoral vein	0

		Analysis population (Total number of patients = 220)[1]
	Phlebitis and thrombophlebitis of other deep vessels of lower extremities	0
	Phlebitis and thrombophlebitis of lower extremities, unspecified	0
	Phlebitis and thrombophlebitis of unspecified site	0
	Total	0
Pulmonary Embolism (PE)		
	Pulmonary embolism	0
Arterial thromboembolic event (ATEs)	Acute myocardial infarction (AMI)	0
	Subarachnoid haemorrhage	0
	Intracerebral haemorrhage	0
	Cerebral infarction due to thrombosis of cerebral arteries	0
	Stroke, not specified as haemorrhage or infarction	0
	Total	0
Endometrial cancer, ovarian cancer, and colorectal cancer	Colon	0
	Rectum	0
	Breast	0
	Cervix uteri	0
	Overlapping sites of cervix uteri	0
	Cervix uteri, unspecified	0
	Corpus uteri, endometrium	0
	Total	0
Trauma and major surgery within 3 months before treatment initiation	Lower limb orthopaedic surgery	0
	Major lower extremity surgery	0
	Pelvic trauma surgery	0
	Other	1 (0.5%)
	Total	1 (0.5%)
Chemotherapy	Total	0
Systolic blood pressure (mmHg)[3] / Diastolic blood pressure (mmHg)[2]	N	13
	Mean (SD)	121.4 (17.45) / 77.8 (13.01)
	Median [Q1 - Q3]	120.0 [110.0-131.0] / 80.0 [70.0-80.0]

		Analysis population (Total number of patients = 220)[1]
	Range [min - max]	[93.0-154.0] / [61.0-100.0]
	Missing	207
Hypertension[4]	Total	9 (4.1%)
Diabetes diagnosis[5]	Total	3 (1.4%)[6]
Anti-diabetic drugs use	1	0
	2	0
	3+	0
Hyperlipidaemia	Total	1 (0.5%)[6]
Systemic lupus erythematosus (SLE)	Total	0

Abbreviations: Q1-Q3: Median (1st quartile-3rd quartile), SD: Standard Deviation
[1] All medical history will be collected for each patient during the baseline period (= period of 6 months prior the index date) except for blood pressure measurement (diastolic and systolic blood pressure), hypertension, trauma and major surgery
[2] Diastolic blood pressure (mmHg): The nearest measurement in the period of 3 months prior to the index date
[3] Systolic blood pressure (mmHg): The nearest measurement in the period of 3 months prior to the index date
[4] Women will be considered to have hypertension if:
-->In the period of 3 months prior the index date, one or more diagnosis of hypertension ICD-10-CM I10, I11, I12, I13, I15 have been recorded.
AND/OR
->In the period of 3 months prior to the index date, at least two measurements of blood pressure (BP) are above the hypertensive threshold (systolic BP ≥ 140 mmHg or diastolic BP ≥90 mmHg)).
AND/OR
-->In the period of 3 months prior to the index date, one or more antihypertensive drugs have been taken by the patient (ATC code C02 Antihypertensives).
*Multiple answers are possible
[5] Type 1 and 2 diabetes
[6] This is the percentage of total cohort

Among patients in the Belgian GP panel, the most prevalent comorbidities (recorded anytime in the patient's medical history) were hypertension and hyperlipidaemia reported in four (1.9%) patients each. However, the mean systolic/ diastolic BP (where specified) was in the normal range. None of the patients reported trauma and major surgery within the last three months before treatment initiation. Additionally, none of the patients had a history of DVT/PE, breast cancers or other gynaecological cancers (Table 10.2-7).

Table 10.2-7: Medical history of patients at index date in Belgium – GPs

		Analysis population (Total number of patients = 207)[1]
Deep venous thrombosis (DVT)		
	Phlebitis and thrombophlebitis of unspecified site	0
	Phlebitis and thrombophlebitis of femoral vein	0
	Phlebitis and thrombophlebitis of other deep vessels of lower extremities	0
	Phlebitis and thrombophlebitis of lower extremities, unspecified	0
	Phlebitis and thrombophlebitis of unspecified site	0
	Total	0
Pulmonary Embolism (PE)		
	Pulmonary embolism	0
Arterial thromboembolic event (ATEs)	Acute myocardial infarction (AMI)	0
	Subarachnoid haemorrhage	0
	Intracerebral haemorrhage	0
	Cerebral infarction due to thrombosis of cerebral arteries	0
	Stroke not specified as haemorrhage or infarction	0
	Total	0
Endometrial cancer, ovarian cancer, and colorectal cancer	Colon	0
	Rectum	0
	Breast	0
	Cervix uteri	0
	Overlapping sites of cervix uteri	0
	Cervix uteri, unspecified	0
	Corpus uteri, endometrium	0
	Total	0
Trauma and major surgery within 3 months before treatment initiation	Lower limb orthopaedic surgery	0
	Major lower extremity surgery	0
	Pelvic trauma surgery	0
	Other	0
	Total	0
Chemotherapy	Total	0

		Analysis population (Total number of patients = 207)[1]
Systolic blood pressure (mmHg)[3] / Diastolic blood pressure (mmHg)[2]	N	14
	Mean (SD)	120.6 (12.88) / 73.0 (9.44)
	Median [Q1 - Q3]	117.0 [110.0-130.0] / 70.0 [70.0-80.0]
	Range [min - max]	[105.0-144.0] / [60.0-92.0]
	Missing	193
Hypertension	Total	4 (1.9%)
Diabetes diagnosis[5]	Total	1 (0.5%)[6]
Anti-diabetic drugs use	1	0
	2	0
	3+	0
Hyperlipidaemia	Total	4 (1.9%)[6]
Systemic lupus erythematosus (SLE)	Total	0

Abbreviations: Q1-Q3: Median (1st quartile-3rd quartile), SD: Standard Deviation
[1] All medical history will be collected for each patient during the baseline period (= period of 6 months prior the index date) except for blood pressure measurement (diastolic and systolic blood pressure), hypertension, trauma and major surgery
[2] Diastolic blood pressure (mmHg): The nearest measurement in the period of 3 months prior to the index date
[3] Systolic blood pressure (mmHg): The nearest measurement in the period of 3 months prior to the index date
[4] women will be considered to have hypertension if:
-->In the period of 3 months prior the index date, one or more diagnosis of hypertension ICD-10-CM I10, I11, I12, I13, I15 have been recorded.
AND/OR
->In the period of 3 months prior to the index date, at least two measurements of blood pressure (BP) are above the hypertensive threshold (systolic BP ≥ 140 mmHg or diastolic BP ≥90 mmHg)).
AND/OR
-->In the period of 3 months prior to the index date, one or more antihypertensive drugs have been taken by the patient (ATC code C02 Antihypertensives).
*Multiple answers are possible
[5]Type 1 and 2 diabetes
[6] This is the percentage of total cohort

Among patients in the French gynaecologist panel, two patients (0.3%) reported trauma and major surgeries within last three months before treatment initiation. The mean systolic/ diastolic BP (where specified) was in the normal range. None of the patients had a history of DVT/PE, breast cancers or other gynaecological cancers (Table 10.2-8).

Table 10.2-8: Medical history of patients at index date in France – Gynaecologists

		Analysis population (Total number of patients = 659)[1]
Deep venous thrombosis (DVT)		
	Phlebitis and thrombophlebitis of unspecified site	0
	Phlebitis and thrombophlebitis of femoral vein	0
	Phlebitis and thrombophlebitis of other deep vessels of lower extremities	0
	Phlebitis and thrombophlebitis of lower extremities, unspecified	0
	Phlebitis and thrombophlebitis of unspecified site	0
	Total	0
Pulmonary Embolism (PE)		
	Pulmonary embolism	0
Arterial thromboembolic event (ATEs)		0
	Acute myocardial infarction (AMI)	
	Subarachnoid haemorrhage	0
	Intracerebral haemorrhage	0
	Cerebral infarction due to thrombosis of cerebral arteries	0
	Stroke not specified as haemorrhage or infarction	0
	Total	0
Breast cancers and other gynaecological cancers		0
	Colon	
	Rectum	0
	Breast	0
	Cervix uteri	0
	Overlapping sites of cervix uteri	0
	Cervix uteri, unspecified	0
	Corpus uteri, endometrium	0
	Total	0
Trauma and major surgery within 3 months before treatment initiation*		
	Lower limb orthopaedic surgery	0
	Major lower extremity surgery	0
	Pelvic trauma surgery	2 (0.3%)
	Other	0
	Total	2 (0.3%)

		Analysis population (Total number of patients = 659)[1]
Chemotherapy	Total	0
Systolic blood pressure (mmHg)[3] / Diastolic blood pressure (mmHg)[2]	N	4
	Mean (SD)	124.3 (11.79) / 76.5 (7.90)
	Median [Q1 - Q3]	125.0 [115.0-133.5] / 75.0 [70.0-83.0]
	Range [min - max]	[110.0-137.0] / [70.0-86.0]
	Missing	655
Hypertension[4]	Total	0
Diabetes diagnosis[5]	Total	0
Anti-diabetic drugs use	1	0
	2	0
	3+	0
hyperlipidaemia	Total	0
Diagnosis of systemic lupus erythematosus (SLE)	Total	0

Abbreviations: Q1-Q3: Median (1st quartile-3rd quartile), SD: Standard Deviation

[1] All medical history will be collected for each patient during the baseline period (= period of 6 months prior the index date) except for blood pressure measurement (diastolic and systolic blood pressure), hypertension, trauma and major surgery

[2] Diastolic blood pressure (mmHg): The nearest measurement in the period of 3 months prior to the index date

[3] Systolic blood pressure (mmHg): The nearest measurement in the period of 3 months prior to the index date

[4] Women will be considered to have hypertension if:

-->In the period of 3 months prior the index date, one or more diagnosis of hypertension ICD-10-CM I10, I11, I12, I13, I15 have been recorded.

AND/OR

->In the period of 3 months prior to the index date, at least two measurements of blood pressure (BP) are above the hypertensive threshold (systolic BP ≥ 140 mmHg or diastolic BP ≥90 mmHg)).

AND/OR

-->In the period of 3 months prior to the index date, one or more antihypertensive drugs have been taken by the patient (ATC code C02 Antihypertensives).

*Multiple answers are possible

[5]Type 1 and 2 diabetes

[6] This is the percentage of total cohort

10.3 Outcome Data

10.3.1 Potential Indications for Prescribing Combined Oral Contraceptive

Prespecified potential indications for prescribing COC in the six months baseline period and after index were explored across the French GP, Italian GP, Belgian GP and French gynaecologist panels and have been described in Table 10.3-1, Table 10.3-2, Table 10.3-3 and Table 10.3-4, respectively. A patient in each panel could have had more than one potential indication so counts are not mutually exclusive.

In the French GP panel, 20% of patients were prescribed COCs for contraception. A total of 10 patients (4.3%) in the panel were prescribed COCs for prevention of menstrual migraines, 2.1% of the patients were prescribed COCs for the treatment of dysmenorrhea and 0.4% as treatment for acne. Around 14% patients were using COCs before initiation with SEASONIQUE (Table 10.3-1).

Table 10.3-1: Potential indications for prescribing COC in France – GPs

		Analysis population (Total number of patients = 235)[1,3]
Contraceptive management		
	Encounter for general counselling and advice on contraception (Z30.xx)	47 (20.0%)
Menstrual cycle (ir)regularity (cycle control) and Treatment of menorrhagia		
	Excessive and frequent menstruation with regular cycle (N92.x)	0
Treatment of dysmenorrhea*		
	Primary dysmenorrhea (N94.4)	1 (0.4%)
	Secondary dysmenorrhea (N94.5)	1 (0.4%)
	Dysmenorrhea, unspecified (N94.6)	3 (1.3%)
	Total	5 (2.1%)
Inducing amenorrhea for lifestyle considerations*		
	Primary amenorrhea (N91.0)	0

		Analysis population (Total number of patients = 235)[1,3]
	Secondary amenorrhea (N91.1)	0
	Amenorrhea, unspecified (N91.2)	0
	Total	0
Treatment of premenstrual syndrome		
	Premenstrual tension syndrome (N94.3)	0
Prevention of menstrual migraines*		
	Migraine (G43)	0
	Migraine without aura (G43.0)	0
	Migraine with aura (G43.1)	0
	Other migraine (G43.8)	0
	Migraine, unspecified (G43.9)	10 (4.3%)
	Total	10 (4.3%)
Treatment of acne or hirsutism*		
	Hirsutism (L68.0)	0
	Acne (L70)	0
	Acne vulgaris (L70.0)	0
	Acne conglobata (L70.1)	0
	Other acne (L70.8)	0
	Acne, unspecified (L70.9)	1 (0.4%)
	Total	1 (0.4%)
Improved bone mineral density		
	Osteoporosis (M81.0)	0
Treatment of bleeding due to leiomyomas		
	Leiomyoma (D25.x)	0
Treatment of pelvic pain due to endometriosis*		
	Polycystic ovarian syndrome (E28.2)	0
	Endometriosis (N80)	0
	Endometriosis of uterus (N80.0)	0
	Endometriosis of ovary (N80.1)	0
	Endometriosis of pelvic peritoneum (N80.3)	0
	Other endometriosis (N80.8)	0
	Endometriosis, unspecified (N80.9)	0
	Total	0

		Analysis population (Total number of patients = 235)[1,3]
Use of prior combined oral contraceptives (COC) before SEASONIQUE initiation[2]	Yes	32 (13.6%)
	No	203 (86.4%)

[1] Including the baseline period (6 months prior the index date) and the follow-up period
[2] In the baseline period
[3] Not including SEASONIQUE
*Multiple responses are possible between categories or within a category

In the Italian GP panel, 18.2% of patients were prescribed COCs for contraception. A total of eight patients (3.6%) were prescribed COCs for the treatment of dysmenorrhea (unspecified), eight patients (3.6%) for excessive and frequent menstruation with regular cycle, and six patients (2.7%) were prescribed COCs for the treatment of pelvic pain due to endometriosis Around 14% of the patients were using COCs before initiation with SEASONIQUE (Table 10.3-2).

Table 10.3-2: Potential indications for prescribing COC in Italy – GPs

		Analysis population (Total number of patients = 220)[1,3]
Contraceptive management		
	Encounter for general counselling and advice on contraception (Z30.xx)	40 (18.2%)
Menstrual cycle (ir)regularity (cycle control) and Treatment of menorrhagia		
	Excessive and frequent menstruation with regular cycle (N92.x)	8 (3.6%)
Treatment of dysmenorrhea*		
	Primary dysmenorrhea (N94.4)	0
	Secondary dysmenorrhea (N94.5)	0
	Dysmenorrhea, unspecified (N94.6)	8 (3.6%)
	Total	8 (3.6%)
Inducing amenorrhea for lifestyle considerations*		
	Primary amenorrhea (N91.0)	0
	Secondary amenorrhea (N91.1)	0
	Amenorrhea, unspecified (N91.2)	0
	Total	0

		Analysis population (Total number of patients = 220)[1,3]
Treatment of premenstrual syndrome		
	Premenstrual tension syndrome (N94.3)	0
Prevention of menstrual migraines*		
	Migraine (G43)	0
	Migraine without aura (G43.0)	
	Migraine with aura (G43.1)	0
	Migraine, unspecified (G43.9)	0
	Total	0
Treatment of acne or hirsutism*		
	Hirsutism (L68.0)	0
	Acne (L70)	0
	Acne vulgaris (L70.0)	0
	Acne conglobata (L70.1)	0
	Other acne (L70.8)	0
	Acne, unspecified (L70.9)	0
	Total	0
Improved bone mineral density		
	Osteoporosis (M81.0)	0
Treatment of bleeding due to leiomyomas		
	Leiomyoma (D25.x)	3 (1.4%)
Treatment of pelvic pain due to endometriosis*		
	Polycystic ovarian syndrome (E28.2)	0
	Endometriosis (N80)	0
	Endometriosis of uterus (N80.0)	0
	Endometriosis of ovary (N80.1)	1 (0.5%)
	Endometriosis of pelvic peritoneum (N80.3)	0
	Other endometriosis (N80.8)	1 (0.5%)
	Endometriosis, unspecified (N80.9)	5 (2.3%)
	Total	6 (2.7%)
Use of prior combined oral contraceptives (COC) before SEASONIQUE initiation[2]	Yes	30 (13.6%)
	No	190 (86.4%)

	Analysis population (Total number of patients = 220)[1,3]

[1] Including the baseline period (6 months prior the index date) and the follow-up period
[2] In the baseline period
[3] Not including SEASONIQUE
*Multiple responses are possible between categories or within a category

In the Belgian GP panel, 26.1% patients were prescribed COCs for contraception purposes. A total of 12 patients (5.8%) were prescribed COCs for the prevention of menstrual migraines, two patients (1.0%) were prescribed COCs for excessive and frequent menstruation with regular cycle and two patients (1.0%) for the treatment of acne. Nearly 15% of the patients were using COCs before initiation with SEASONIQUE (Table 10.3-3).

Table 10.3-3: Potential indications for prescribing COC in Belgium – GPs

		Analysis population (Total number of patients = 207)[1,3]
Contraceptive management		
	Encounter for general counselling and advice on contraception (Z30.xx)	54 (26.1%)
Menstrual cycle (ir)regularity (cycle control) and Treatment of menorrhagia		
	Excessive and frequent menstruation with regular cycle (N92.x)	2 (1.0%)
Treatment of dysmenorrhea*		
	Primary dysmenorrhea (N94.4)	0
	Secondary dysmenorrhea (N94.5)	0
	Dysmenorrhea, unspecified (N94.6)	1 (0.5%)
	Total	1 (0.5%)
Inducing amenorrhea for lifestyle considerations*		
	Primary amenorrhea (N91.0)	0
	Secondary amenorrhea (N91.1)	0
	Amenorrhea, unspecified (N91.2)	0
	Total	0
Treatment of premenstrual syndrome		

		Analysis population (Total number of patients = 207)[1,3]
	Premenstrual tension syndrome (N94.3)	0
Prevention of menstrual migraines*		
	Migraine (G43)	12 (5.8%)
	Migraine without aura (G43.0)	0
	Migraine with aura (G43.1)	0
	Other migraine (G43.8)	0
	Migraine, unspecified (G43.9)	0
	Total	12 (5.8%)
Treatment of acne or hirsutism*		
	Hirsutism (L68.0)	0
	Acne (L70)	2 (1.0%)
	Acne vulgaris (L70.0)	0
	Acne conglobata (L70.1)	0
	Other acne (L70.8)	0
	Acne, unspecified (L70.9)	0
	Total	2 (1.0%)
Improved bone mineral density		
	Osteoporosis (M81.0)	0
Treatment of bleeding due to leiomyomas		
	Leiomyoma (D25.x)	0
Treatment of pelvic pain due to endometriosis*		
	Polycystic ovarian syndrome (E28.2)	0
	Endometriosis (N80)	0
	Endometriosis of uterus (N80.0)	0
	Endometriosis of ovary (N80.1)	0
	Endometriosis of pelvic peritoneum (N80.3)	0
	Other endometriosis (N80.8)	0
	Endometriosis, unspecified (N80.9)	0
	Total	0
Use of prior combined oral contraceptives (COC) before SEASONIQUE initiation[2]	Yes	30 (14.5%)
	No	177 (85.5%)

	Analysis population (Total number of patients = 207)[1,3]

[1] Including the baseline period (6 months prior the index date) and the follow-up period
[2] In the baseline period
[3] Not including SEASONIQUE
*Multiple responses are possible between categories or within a category

In the French gynaecologist panel, 17.6% of patients were prescribed COCs for contraception purposes. A total of 28 patients (4.2%) were prescribed COCs for the treatment of dysmenorrhea, 10 (1.5%) patients were prescribed COCs for treatment of excessive and frequent menstruation with regular cycle and 10 (1.5%) patients for the prevention of menstrual migraines. Nearly eight percent of patients were using COCs before initiation with SEASONIQUE (Table 10.3-4).

Table 10.3-4: Potential indications for prescribing COC in France – Gynaecologists

		Analysis population (Total number of patients = 659)[1,3]
Contraceptive management		
	Encounter for general counselling and advice on contraception (Z30.xx)	116 (17.6%)
Menstrual cycle (ir)regularity (cycle control) and Treatment of menorrhagia		
	Excessive and frequent menstruation with regular cycle (N92.x)	10 (1.5%)
Treatment of dysmenorrhea*		
	Primary dysmenorrhea (N94.4)	6 (0.9%)
	Secondary dysmenorrhea (N94.5)	5 (0.8%)
	Dysmenorrhea, unspecified (N94.6)	19 (2.9%)
	Total	28 (4.2%)
Inducing amenorrhea for lifestyle considerations*		
	Primary amenorrhea (N91.0)	1 (0.2%)

		Analysis population (Total number of patients = 659)[1,3]
	Secondary amenorrhea (N91.1)	0
	Amenorrhea, unspecified (N91.2)	0
	Total	1 (0.2%)
Treatment of premenstrual syndrome		
	Premenstrual tension syndrome (N94.3)	0
Prevention of menstrual migraines*		
	Migraine (G43)	0
	Migraine without aura (G43.0)	0
	Migraine with aura (G43.1)	1 (0.2%)
	Other migraine (G43.8)	0
	Migraine, unspecified (G43.9)	9 (1.4%)
	Total	10 (1.5%)
Treatment of acne or hirsutism*		
	Hirsutism (L68.0)	0
	Acne (L70)	0
	Acne vulgaris (L70.0)	0
	Acne conglobata (L70.1)	0
	Other acne (L70.8)	0
	Acne, unspecified (L70.9)	7 (1.1%)
	Total	7 (1.1%)
Improved bone mineral density		
	Osteoporosis (M81.0)	0
Treatment of bleeding due to leiomyomas		
	Leiomyoma (D25.x)	0
Treatment of pelvic pain due to endometriosis*		
	Polycystic ovarian syndrome (E28.2)	4 (0.6%)
	Endometriosis (N80)	0
	Endometriosis of uterus (N80.0)	1 (0.2%)
	Endometriosis of ovary (N80.1)	0
	Endometriosis of pelvic peritoneum (N80.3)	0
	Other endometriosis (N80.8)	0
	Endometriosis, unspecified (N80.9)	4 (0.6%)
	Total	7 (1.1%)

		Analysis population (Total number of patients = 659)[1,3]
Use of prior combined oral contraceptives (COC) before SEASONIQUE initiation[2]	Yes	50 (7.6%)
	No	609 (92.4%)

[1] Including the baseline period (6 months prior the index date) and the follow-up period
[2] In the baseline period
[3] Not including SEASONIQUE
*Multiple responses are possible between categories or within a category

10.3.2 Potential Indications for Prescribing SEASONIQUE

Prespecified potential indications for prescribing SEASONIQUE in the French GP, Italian GP, Belgian GP and French gynaecologist panels is described in Table 10.3-5, Table 10.3-6, Table 10.3-7 and Table 10.3-8, respectively. A patient in each panel could have had more than one potential indication so counts are not mutually exclusive.

Majority of the patients (70.6%) in the French GP panel were prescribed SEASONIQUE at index date for contraception purposes. A total of 34 patients (14.5%) were prescribed SEASONIQUE for prevention of menstrual migraines (Table 10.3-5).

Table 10.3-5: Potential indications for prescribing SEASONIQUE at index date in France – GPs

		Analysis population (Total number of patients = 235)[1]
Contraceptive management		
	Encounter for general counselling and advice on contraception (Z30.xx)	166 (70.6%)
Menstrual cycle (ir)regularity (cycle control) and Treatment of menorrhagia*		
	Excessive and frequent menstruation with regular cycle (N92.x)	0
Treatment of dysmenorrhea		
	Primary dysmenorrhea (N94.4)	0
	Secondary dysmenorrhea (N94.5)	0
	Dysmenorrhea, unspecified (N94.6)	0
	Total	0

		Analysis population (Total number of patients = 235)[1]
Inducing amenorrhea for lifestyle considerations*		
	Primary amenorrhea (N91.0)	0
	Secondary amenorrhea (N91.1)	0
	Amenorrhea, unspecified (N91.2)	0
	Total	0
Treatment of premenstrual syndrome		
	Premenstrual tension syndrome (N94.3)	0
Prevention of menstrual migraines*		
	Migraine (G43)	0
	Migraine without aura (G43.0)	0
	Migraine with aura (G43.1)	0
	Other migraine (G43.8)	0
	Migraine, unspecified (G43.9)	34 (14.5%)
	Total	34 (14.5%)
Treatment of acne or hirsutism*		
	Hirsutism (L68.0)	0
	Acne (L70)	0
	Acne vulgaris (L70.0)	0
	Acne conglobata (L70.1)	0
	Other acne (L70.8)	0
	Acne, unspecified (L70.9)	0
	Total	0
Improved bone mineral density		
	Osteoporosis (M81.0)	0
Treatment of bleeding due to leiomyomas		
	Leiomyoma (D25.x)	0
Treatment of pelvic pain due to endometriosis*		0
	Polycystic ovarian syndrome (E28.2)	0
	Endometriosis (N80)	0
	Endometriosis of uterus (N80.0)	0
	Endometriosis of ovary (N80.1)	0
	Endometriosis of pelvic peritoneum (N80.3)	0
	Other endometriosis (N80.8)	0
	Endometriosis, unspecified (N80.9)	0
	Total	0

	Analysis population (Total number of patients = 235)[1]

[1] A time window of one month before or after the index date was used. Therefore, any ICD-10-CM code for the pre-defined diagnosis potentially related to prescribing SEASONIQUE recorded in the ±1-month time window was considered in the analysis as a potential reason for prescription.
* Multiple responses are possible between categories or within a category

A total of 41.8% patients in the Italian GP panel were prescribed SEASONIQUE at index date for contraception purposes. A total of 4 patients (1.8%) were prescribed with SEASONIQUE for prevention of menstrual migraines (Table 10.3-6).

Table 10.3-6: Potential indications for prescribing SEASONIQUE at index date in Italy – GPs

		Analysis population (Total number of patients = 220)[1]
Contraceptive management		
	Encounter for general counselling and advice on contraception (Z30.xx)	92 (41.8%)
Menstrual cycle (ir)regularity (cycle control) and Treatment of menorrhagia*		
	Excessive and frequent menstruation with regular cycle (N92.x)	0
Treatment of dysmenorrhea		
	Primary dysmenorrhea (N94.4)	0
	Secondary dysmenorrhea (N94.5)	0
	Dysmenorrhea, unspecified (N94.6)	0
	Total	0
Inducing amenorrhea for lifestyle considerations*		
	Primary amenorrhea (N91.0)	0
	Secondary amenorrhea (N91.1)	0
	Amenorrhea, unspecified (N91.2)	0
	Total	0
Treatment of premenstrual syndrome		
	Premenstrual tension syndrome (N94.3)	0
Prevention of menstrual migraines*		

		Analysis population (Total number of patients = 220)[1]
	Migraine (G43)	0
	Migraine without aura (G43.0)	0
	Migraine with aura (G43.1)	0
	Other migraine (G43.8)	0
	Migraine, unspecified (G43.9)	4 (1.8%)
	Total	4 (1.8%)
Treatment of acne or hirsutism*		
	Hirsutism (L68.0)	0
	Acne (L70)	0
	Acne vulgaris (L70.0)	0
	Acne conglobata (L70.1)	0
	Other acne (L70.8)	0
	Acne, unspecified (L70.9)	0
	Total	0
Improved bone mineral density		
	Osteoporosis (M81.0)	0
Treatment of bleeding due to leiomyomas		
	Leiomyoma (D25.x)	0
Treatment of pelvic pain due to endometriosis*		
	Polycystic ovarian syndrome (E28.2)	0
	Endometriosis (N80)	0
	Endometriosis of uterus (N80.0)	0
	Endometriosis of ovary (N80.1)	0
	Endometriosis of pelvic peritoneum (N80.3)	0
	Other endometriosis (N80.8)	0
	Endometriosis, unspecified (N80.9)	0
	Total	0

[1] A time window of one month before or after the index date was used. Therefore, any ICD-10-CM code for the pre-defined diagnosis potentially related to prescribing SEASONIQUE recorded in the ±1-month time window was considered in the analysis as a potential reason for prescription.
* Multiple responses are possible between categories or within a category

Majority of the patients (81.2%) in the Belgian GP panel were prescribed SEASONIQUE at index date for contraception purposes. A total of 24 patients (11.6%) were prescribed SEASONIQUE for prevention of menstrual migraines (Table 10.3-7).

Table 10.3-7: Potential indications for prescribing SEASONIQUE at index date in Belgium – GPs

		Analysis population (Total number of patients = 207)[1]
Contraceptive management		
	Encounter for general counselling and advice on contraception (Z30.xx)	168 (81.2%)
Menstrual cycle (ir)regularity (cycle control) and Treatment of menorrhagia*		
	Excessive and frequent menstruation with regular cycle (N92.x)	0
Treatment of dysmenorrhea		
	Primary dysmenorrhea (N94.4)	0
	Secondary dysmenorrhea (N94.5)	0
	Dysmenorrhea, unspecified (N94.6)	0
	Total	0
Inducing amenorrhea for lifestyle considerations*		
	Primary amenorrhea (N91.0)	0
	Secondary amenorrhea (N91.1)	0
	Amenorrhea, unspecified (N91.2)	0
	Total	0
Treatment of premenstrual syndrome		
	Premenstrual tension syndrome (N94.3)	0
Prevention of menstrual migraines*		
	Migraine (G43)	0
	Migraine without aura (G43.0)	0
	Migraine with aura (G43.1)	0
	Other migraine (G43.8)	0
	Migraine, unspecified (G43.9)	24 (11.6%)
	Total	24 (11.6%)
Treatment of acne or hirsutism*		
	Hirsutism (L68.0)	0
	Acne (L70)	0
	Acne vulgaris (L70.0)	0
	Acne conglobata (L70.1)	0
	Other acne (L70.8)	0
	Acne, unspecified (L70.9)	0
	Total	0

		Analysis population (Total number of patients = 207)[1]
Improved bone mineral density		
	Osteoporosis (M81.0)	0
Treatment of bleeding due to leiomyomas		
	Leiomyoma (D25.x)	0
Treatment of pelvic pain due to endometriosis*		
	Polycystic ovarian syndrome (E28.2)	0
	Endometriosis (N80)	0
	Endometriosis of uterus (N80.0)	0
	Endometriosis of ovary (N80.1)	0
	Endometriosis of pelvic peritoneum (N80.3)	0
	Other endometriosis (N80.8)	0
	Endometriosis, unspecified (N80.9)	0
	Total	0

[1] A time window of one month before or after the index date was used. Therefore, any ICD-10-CM code for the pre-defined diagnosis potentially related to prescribing SEASONIQUE recorded in the ±1-month time window was considered in the analysis as a potential reason for prescription.
* Multiple responses are possible between categories or within a category

Majority of the patients (61.3%) in French gynaecologist panel were prescribed SEASONIQUE at index date for contraception purposes. A total of 61 patients (9.3%) were prescribed with SEASONIQUE for prevention of menstrual migraines (Table 10.3-8).

Table 10.3-8: Potential indications for prescribing SEASONIQUE at index date in France – Gynaecologists

		Analysis population (Total number of patients = 659)[1]
Contraceptive management		
	Encounter for general counselling and advice on contraception (Z30.xx)	404 (61.3%)
Menstrual cycle (ir)regularity (cycle control) and Treatment of menorrhagia		

		Analysis population (Total number of patients = 659)[1]
	Excessive and frequent menstruation with regular cycle (N92.x)	0
Treatment of dysmenorrhea*		
	Primary dysmenorrhea (N94.4)	0
	Secondary dysmenorrhea (N94.5)	0
	Dysmenorrhea, unspecified (N94.6)	0
	Total	0
Inducing amenorrhea for lifestyle considerations*		
	Primary amenorrhea (N91.0)	0
	Secondary amenorrhea (N91.1)	0
	Amenorrhea, unspecified (N91.2)	0
	Total	0
Treatment of premenstrual syndrome		
	Premenstrual tension syndrome (N94.3)	0
Prevention of menstrual migraines*		
	Migraine (G43)	0
	Migraine without aura (G43.0)	0
	Migraine with aura (G43.1)	0
	Other migraine (G43.8)	0
	Migraine, unspecified (G43.9)	61 (9.3%)
	Total	61 (9.3%)
Treatment of acne or hirsutism*		
	Hirsutism (L68.0)	0
	Acne (L70)	0
	Acne vulgaris (L70.0)	0
	Acne conglobata (L70.1)	0
	Other acne (L70.8)	0
	Acne, unspecified (L70.9)	0
	Total	0
Improved bone mineral density		
	Osteoporosis (M81.0)	0
Treatment of bleeding due to leiomyomas		
	Leiomyoma (D25.x)	0

		Analysis population (Total number of patients = 659)[1]
Treatment of pelvic pain due to endometriosis*		
	Polycystic ovarian syndrome (E28.2)	0
	Endometriosis (N80)	0
	Endometriosis of uterus (N80.0)	0
	Endometriosis of ovary (N80.1)	0
	Endometriosis of pelvic peritoneum (N80.3)	0
	Other endometriosis (N80.8)	0
	Endometriosis, unspecified (N80.9)	0
	Total	0

[1] A time window of one month before or after the index date was used. Therefore, any ICD-10-CM code for the pre-defined diagnosis potentially related to prescribing SEASONIQUE recorded in the ±1-month time window will be considered in the analysis as a potential reason for prescription.
* Multiple responses are possible between categories or within a category

10.3.3 Concomitant Medication Use

Prespecified concomitant medication, only referring to medications for CV disease (including anticoagulant use), diabetes, and other COCs, at index date in the French GP, Italian GP, Belgian GP and French gynaecologist panels are described in Table 10.3-9, Table 10.3-10, Table 10.3-11 and Table 10.3-12, respectively.

Concomitant CV and/or diabetes medication use was reported in 7.2% of patients in the French GP panel. The vasoprotectives were the most common concomitant treatment prescribed by French GP panel (52.9%) followed by beta blocking agents (29.4%). Concomitant use of SEASONIQUE and other COCs were reported in approximately 2.0% of patients in the French GP panel (Table 10.3-9).

Table 10.3-9: Concomitant medication use at index date in France – GPs

		Analysis population (Total number of patients = 235)[1]
Concomitant medications use[2]	Yes	17 (7.2%)
	No	218 (92.8%)
If yes, detail of the concomitant medications uses:		
Medications for CV disease[3,4]		
	C01 Cardiac therapy	1 (5.9%)
	C02 Antihypertensives	0

		Analysis population (Total number of patients = 235)[1]
	C03 Diuretics	0
	C04 Peripheral vasodilators	0
	C05 Vasoprotectives	9 (52.9%)
	C07 Beta blocking agents	5 (29.4%)
	C08 Calcium channel blockers	1 (5.9%)
	C09 Agents acting on the renin angiotensin system	2 (11.8%)
	C10 lipid modifying agents	0
Medications for Diabetes[3,4]		
	A10H Sulphonylurea	0
	A10J Biguanide	0
	A10K Glitazone	0
	A10L Alpha-glucosidase inhibitor	0
	A10M Glinide	0
	A10N DPP-4 inhibitor	0
	A10P SGLT2 inhibitor	0
	A10X Other	0
Concomitant use of SEASONIQUE and other COCs	Yes	5 (2.1%)
	No	230 (97.9%)
Details[4]	Desogestrel and estrogen	0
	Levonorgestrel and estrogen[5]	4 (80.0%)
	Gestodene and estrogen	0
	Progestogens and estrogens, sequential preparation	1 (20.0%)
	Nomegestrol and estrogen	1 (20.0%)
	Drospirenone and estrogen	0
	Dienogest and estrogen	0

[1] Including a time window of 3 months before and after index date
[2] Data on concomitant medication use including medications prescribed for the treatment of CV disease (including anticoagulant use) and diabetes
[3] WHO ATC 2nd level
[4] Multiple answers are possible
[5] Not including SEASONIQUE

Concomitant CV and/or diabetes medication use was reported in 8.6% of patients in the Italian GP panel (Table 10.3-10). The beta blocking agents were the most common concomitant treatment prescribed by the Italian GP panel (42.1%), followed by vasoprotectives (21.1%) and agents acting

on the renin angiotensin system (15.8%). Concomitant use of SEASONIQUE and other COCs was reported in <1.0 % of patients in the Italian GP panel (Table 10.3-10).

Table 10.3-10: Concomitant medication use at index date in Italy – GPs

		Analysis population (Total number of patients = 220)[1]
Concomitant medications use[2]	Yes	19 (8.6%)
	No	201 (91.4%)
If yes, detail of the concomitant medications uses:		
Medications for CV disease[3,4]		
	C01 Cardiac therapy	1 (5.3%)
	C02 Antihypertensives	0
	C03 Diuretics	2 (10.5%)
	C04 Peripheral vasodilators	0
	C05 Vasoprotectives	4 (21.1%)
	C07 Beta blocking agents	8 (42.1%)
	C08 Calcium channel blockers	1 (5.3%)
	C09 Agents acting on the renin angiotensin system	3 (15.8%)
	C10 lipid modifying agents	0
Medications for Diabetes[3,4]		
	A10H Sulphonylurea	0
	A10J Biguanide	0
	A10K Glitazone	0
	A10L Alpha-glucosidase inhibitor	0
	A10M Glinide	0
	A10N DPP-4 inhibitor	0
	A10P SGLT2 inhibitor	0
	A10X Other	0
Concomitant use of SEASONIQUE and other COCs	Yes	1 (0.5%)
	No	219 (99.5%)
Details[4]	Desogestrel and estrogen	0
	Levonorgestrel and estrogen[5]	0
	Gestodene and estrogen	1 (100.0%)
	Progestogens and estrogens, sequential preparation	0
	Nomegestrol and estrogen	0

		Analysis population (Total number of patients = 220)[1]
	Drospirenone and estrogen	0
	Dienogest and estrogen	0

[1] Including a time window of 3 months before and after index date
[2] Data on concomitant medication use including medications prescribed for the treatment of CV disease (including anticoagulant use) and diabetes
[3] WHO ATC 2nd level
[4] Multiple answers are possible
[5] Not including SEASONIQUE

Concomitant CV and/or diabetes medication use was reported in 8.7% patients in the Belgian GP panel. The beta blocking agents were the most common concomitant treatment prescribed by the Belgian GP panel (44.4%) followed by vasoprotectives (22.2%) and lipid modifying agents (22.2%). Concomitant use of SEASONIQUE and other COCs was reported in <3.0% of patients in the Belgian GP panel (Table 10.3-11).

Table 10.3-11: Concomitant medication use at index date in Belgium – GPs

		Analysis population (Total number of patients = 207)[1]
Concomitant medications use[2]	Yes	18 (8.7%)
	No	189 (91.3%)
If yes, detail of the concomitant medications uses:		
Medications for CV disease[3,4]		
	C01 Cardiac therapy	1 (5.6%)
	C02 Antihypertensives	0
	C03 Diuretics	0
	C04 Peripheral vasodilators	0
	C05 Vasoprotectives	4 (22.2%)
	C07 Beta blocking agents	8 (44.4%)
	C08 Calcium channel blockers	1 (5.6%)
	C09 Agents acting on the renin angiotensin system	2 (11.1%)
	C10 Lipid modifying agents	4 (22.2%)
Medications for Diabetes[3,4]		
	A10H Sulphonylurea	0
	A10J Biguanide	0
	A10K Glitazone	0

		Analysis population (Total number of patients = 207)[1]
	A10L Alpha-glucosidase inhibitor	0
	A10M Glinide	0
	A10N DPP-4 inhibitor	0
	A10P SGLT2 inhibitor	0
	A10X Other	0
Concomitant use of SEASONIQUE and other COCs	Yes	6 (2.9%)
	No	201 (97.1%)
Details[4]	Desogestrel and estrogen	1 (16.7%)
	Levonorgestrel and estrogen[5]	1 (16.7%)
	Gestodene and estrogen	1 (16.7%)
	Progestogens and estrogens, sequential preparation	0
	Nomegestrol and estrogen	2 (33.3%)
	Drospirenone and estrogen	0
	Dienogest and estrogen	0

[1] Including a time window of 3 months before and after index date
[2] Data on concomitant medication use including medications prescribed for the treatment of CV disease (including anticoagulant use) and diabetes
[3] WHO ATC 2nd level
[4] Multiple answers are possible
[5] Not including SEASONIQUE

Concomitant CV and/or diabetes medication use was found to be very low in the French gynaecologist panel (0.5%). The vasoprotectives were the most common concomitant treatment prescribed by the French gynaecologist panel (66.7%) followed by cardiac therapy (33.3%). Concomitant use of SEASONIQUE and other COCs were reported in 6.7% of patients in the French gynaecologist panel, with the combination of levonorgestrel and estrogen being the predominant COC (77.3%) (Table 10.3-12).

Table 10.3-12: Concomitant medication use at index date in France – Gynaecologists

		Analysis population (Total number of patients = 659)[1]
Concomitant medications use	Yes	3 (0.5%)
	No	656 (99.5%)

		Analysis population (Total number of patients = 659)[1]
If yes, detail of the concomitant medications use[2]:		
Medications for CV disease[3,4]		
	C01 Cardiac therapy	1 (33.3%)
	C02 Antihypertensives	0
	C03 Diuretics	0
	C04 Peripheral vasodilators	0
	C05 Vasoprotectives	2 (66.7%)
	C07 Beta blocking agents	0
	C08 Calcium channel blockers	0
	C09 Agents acting on the renin angiotensin system	0
	C10 lipid modifying agents	0
Medications for Diabetes[3,4]		
	A10H Sulphonylurea	0
	A10J Biguanide	0
	A10K Glitazone	0
	A10L Alpha-glucosidase inhibitor	0
	A10M Glinide	0
	A10N DPP-4 inhibitor	0
	A10P SGLT2 inhibitor	0
	A10X Other	0
Concomitant use of SEASONIQUE and other COCs	Yes	44 (6.7%)
	No	615 (93.3%)
Details[4]	Desogestrel and estrogen	4 (9.1%)
	Levonorgestrel and estrogen[5]	34 (77.3%)
	Gestodene and estrogen	2 (4.5%)
	Progestogens and estrogens, sequential preparation	0
	Nomegestrol and estrogen	0
	Drospirenone and estrogen	3 (6.8%)
	Dienogest and estrogen	1 (2.3%)

	Analysis population (Total number of patients = 659)[1]

[1] Including a time window of 3 months before and after index date
[2] Data on concomitant medication use including medications prescribed for the treatment of CV disease (including anticoagulant use) and diabetes
[3] WHO ATC 2nd level
[4] Multiple answers are possible
[5] Not including SEASONIQUE

10.3.4 Patient Switch Patterns

Patterns of switching contraceptives in patients using SEASONIQUE, changes to a different COC and concomitant use of other COC or other forms of contraception in the French GP, Italian GP, Belgian GP and French gynaecologist panels is described in Table 10.3-13, Table 10.3-14, Table 10.3-15 and Table 10.3-16, respectively.

In the French GP panel, 1.7% of patients switched their contraceptive before the index date (Table 10.3-13). Half of these patients switched from a CHC (not including SEASONIQUE) to "other contraceptives" (i.e. contraceptive implant, intrauterine device) and half from "other contraceptives" to CHC. At index date, 15.7% of patients switched to SEASONIQUE from another contraceptive, the majority of which switched from a CHC (81.1%). After index date, only 7.7% of the patients switched from SEASONIQUE to another contraceptive, the majority of which switched to a CHC (66.7%) (Table 10.3-13).

Table 10.3-13: Switch patterns in France – GPs

		Analysis population (Total number of patients = 235)[1]
Switch patterns		
	Before index date[2]	4 (1.7%)
	CHC[3] to Other contraceptives[4]	2 (50.0%)
	Other contraceptives[4] to CHC[3]	2 (50.0%)
Number of switches before SEASONIQUE initiation	0 (no switch)	231 (98.3%)
	1	4 (1.7%)
	> 1	0
	At index date	37 (15.7%)

		Analysis population (Total number of patients = 235)[1]
	CHC[3] to SEASONIQUE[5]	30 (81.1%)
	Other contraceptives[4] to SEASONIQUE[5]	7 (18.9%)
	After index date[6]	18 (7.7%)
	SEASONIQUE[5] to CHC[3]	12 (66.7%)
	SEASONIQUE[5] to other contraceptives[4]	6 (33.3%)

[1] Switch must have occurred with a break of less than 4 weeks
[2] All history prior to index date
[3] Not including SEASONIQUE
[4] Other forms of contraception (contraceptive implant, intrauterine device, etc.)
[5] Switchers are defined as women starting SEASONIQUE after a different CHC preparation with a break of less than four weeks prior to the index date
[6] In the study period after inclusion

In the Italian GP panel, only one patient (0.5%) switched contraceptive before the index date and this was from "other contraceptives" to CHC. At index date, 4.5% patients switched to SEASONIQUE from another contraceptive, the majority of which switched from a CHC (90.0%). However, after the index date only 5.0% of the patients switched from SEASONIQUE to another contraceptive, the majority of which switched to a CHC (90.9%) (Table 10.3-14).

Table 10.3-14: Switch patterns in Italy – GPs

		Analysis population (Total number of patients = 220)[1]
Switch patterns		
	Before index date[2]	1 (0.5%)
	CHC[3] to Other contraceptives[4]	0
	Other contraceptives[4] to CHC[3]	1 (100.0%)
Number of switches before SEASONIQUE initiation	0 (no switch)	219 (99.5%)
	1	1 (0.5%)
	> 1	0
	At index date	10 (4.5%)
	CHC[3] to SEASONIQUE[5]	9 (90.0%)
	Other contraceptives[4] to SEASONIQUE[5]	1 (10.0%)
	After index date[6]	11 (5.0%)

		Analysis population (Total number of patients = 220)[1]
	SEASONIQUE[5] to CHC[3]	10 (90.9%)
	SEASONIQUE[5] to other contraceptives[4]	1 (9.1%)

[1] Switch must have occurred with a break of less than 4 weeks
[2] All history prior to index date
[3] Not including SEASONIQUE
[4] Other forms of contraception (contraceptive implant, intrauterine device, etc.)
[5] Switchers are defined as women starting SEASONIQUE after a different CHC preparation with a break of less than four weeks prior to the index date
[6] In the study period after inclusion

In the Belgian GP panel, 5.3% of patients switched contraceptive before the index date. Of these, 63.6% switched from CHC to "other contraceptives" and 54.5% switched from "other contraceptives" to CHC. Two patients switched more than once before SEASONIQUE initiation. At the index date, 30.9% of patients switched to SEASONIQUE from another contraceptive, the majority of which switched from a CHC (82.8%). However, after index date only 9.2% of the patients switched from SEASONIQUE to another contraceptive, the majority of which switched to a CHC (78.9%) (Table 10.3-15).

Table 10.3-15: Switch patterns in Belgium – GPs

		Analysis population (Total number of patients = 207)[1]
Switch patterns		
	Before index date[2]	11 (5.3%)
	CHC[3] to Other contraceptives[4]	7 (63.6%)
	Other contraceptives[4] to CHC[3]	6 (54.5%)
Number of switches before SEASONIQUE initiation	0 (no switch)	196 (94.7%)
	1	9 (4.3%)
	> 1	2 (1.0%)
	At index date	64 (30.9%)
	CHC[3] to SEASONIQUE[5]	53 (82.8%)
	Other contraceptives[4] to SEASONIQUE[5]	11 (17.2%)
	After index date[6]	19 (9.2%)
	SEASONIQUE[5] to CHC[3]	15 (78.9%)
	SEASONIQUE[5] to other contraceptives[4]	4 (21.1%)

	Analysis population (Total number of patients = 207)[1]

[1] Switch must have occurred with a break of less than 4 weeks
[2] All history prior to index date
[3] Not including SEASONIQUE
[4] Other forms of contraception (contraceptive implant, intrauterine device, etc.)
[5] Switchers are defined as women starting SEASONIQUE after a different CHC preparation with a break of less than four weeks prior to the index date
[6] In the study period after inclusion

In the French gynaecologist panel, 1.4% of patients switched contraceptive before the index date. Of these, 77.8% switched from CHC to other contraceptive and 55.6% switched from "other contraceptives" to CHC. At index date, 19.7% of patients switched to SEASONIQUE from another contraceptive, of which the majority switched from CHC (73.8%). After index date, 12.4% of the patients switched from SEASONIQUE to another contraceptive, half of which switched to a CHC and half to "other contraceptives" (Table 10.3-16).

Table 10.3-16: Switch patterns in France – Gynaecologists

		Analysis population (Total number of patients = 659)[1]
Switch patterns[1]		
	Before index date[2]	9 (1.4%)
	CHC[3] to Other contraceptives[4]	7 (77.8%)
	Other contraceptives[4] to CHC[3]	5 (55.6%)
Number of switches before SEASONIQUE initiation	0 (no switch)	650 (98.6%)
	1	6 (0.9%)
	> 1	3 (0.5%)
	At index date	130 (19.7%)
	CHC[3] to SEASONIQUE[5]	96 (73.8%)
	Other contraceptives[4] to SEASONIQUE[5]	34 (26.2%)
	After index date[6]	82 (12.4%)
	SEASONIQUE[5] to CHC[3]	41 (50.0%)
	SEASONIQUE[5] to other contraceptives[4]	41 (50.0%)

	Analysis population (Total number of patients = 659)[1]

[1] Switch must have occurred with a break of less than 4 weeks
[2] All history prior to index date
[3] Not including SEASONIQUE
[4] Other forms of contraception (contraceptive implant, intrauterine device, etc.)
[5] Switchers are defined as women starting SEASONIQUE after a different CHC preparation with a break of less than four weeks prior to the index date
[6] In the study period after inclusion

10.3.5 Pregnancy, Contraceptive Use and Lactation

Pregnancy, contraceptive use and lactation in the French GP, Italian GP, Belgian GP and French gynaecologist panels is described in Table 10.3-17, Table 10.3-18, Table 10.3-19 and Table 10.3-20, respectively.

Pregnancy events are not limited to the period of SEASONIQUE exposure and could have occurred in the period outside of SEASONIQUE exposure (i.e. in the baseline period [6 months prior the index date]; in the follow-up period during the gap between two periods of SEASONIQUE exposure; in the follow-up period between the last SEASONIQUE prescription and until the end of the 3 year follow-up period).

In the French GP panel, 12.8% of patients reported at least one pregnancy during the study period (plus the six months baseline period). Of all the reported pregnancies in French GP panel, 43.3% pregnancies resulted in an abortive outcome. A total of 4.3% of pregnancies were recent (within three months of index date) and 11.5% were prospective pregnancies (after the index date). Majority of patients (79.6%) were not using contraceptives prior to the index date. None of the patients were lactating at index date (Table 10.3-17).

Table 10.3-17: Pregnancy, contraceptive use and lactation in France – GPs

		Analysis population (Total number of patients = 235)
Pregnancy[1] during the study period[2]	Yes	30 (12.8%)
	No	205 (87.2%)
Pregnancy with abortive outcome during the study period[2]	Yes	13 (43.3%)[6]

		Analysis population (Total number of patients = 235)
	No	17 (56.7%)[6]
Pregnancy according to the time period[3]	Previous pregnancy within 2 years' time frame before the index date	19 (8.1%)
	Previous pregnancy within 2- 5 years' time frame before the index date	25 (10.6%)
	Previous pregnancy within 5 -10 years' time frame before the index date	18 (7.7%)
	Recent pregnancy: (within 3 months before index date)	10 (4.3%)
	Prospective pregnancy (after index date)	27 (11.5%)
Contraceptive[4] use prior to the index date[5]	Yes	48 (20.4%)
	No	187 (79.6%)
Lactation at the index date[6]	Yes	0
	No	235 (100.0%)

[1] At least one pregnancy
[2] Including the baseline period (6 months prior the index date) and the follow up period (from the index date until the earliest of the following censoring dates: end of the study period or end of enrolment in the database)
[3] Maximum of 10 years (The results on pregnancies are approximate, because the status of the pregnancy is not available in the databases.
it is also possible that the same pregnancy is in two different periods)
[4] Hormonal or non-hormonal
[5] At index date = information recorded in the baseline period (6 months prior to the index date)
[6] This percentage is of those with pregnancy during study period (N=30)

In the Italian GP panel, 9.5% of patients reported pregnancy during the study period (plus the six months baseline period). None of the reported pregnancies resulted in an abortive outcome. A total of 2.3% of pregnancies were recent and 4.1% were prospective pregnancies. The majority of patients (79.1%) were not using contraceptives prior to the index date. None of the patients were lactating at the index date (Table 10.3-18).

Table 10.3-18: Pregnancy, contraceptive use and lactation in Italy – GPs

		Analysis population (Total number of patients = 220)
Pregnancy[1] during the study period[2]	Yes	21 (9.5%)
	No	199 (90.5%)

		Analysis population (Total number of patients = 220)
Pregnancy with abortive outcome during the study period[2]	Yes	0
	No	21 (100.0%)[6]
Pregnancy according to the time period[3]	Previous pregnancy within 2 years' time frame before the index date	31 (14.1%)
	Previous pregnancy within 2- 5 years' time frame before the index date	38 (17.3%)
	Previous pregnancy within 5 -10 years' time frame before the index date	40 (18.2%)
	Recent pregnancy: (within 3 months before index date)	5 (2.3%)
	Prospective pregnancy (after index date)	9 (4.1%)
Contraceptive[4] use prior to the index date[5]	Yes	46 (20.9%)
	No	174 (79.1%)
Lactation at the index date[6]	Yes	0
	No	220 (100.0%)

[1] At least one pregnancy
[2] Including the baseline period (6 months prior the index date) and the follow up period (from the index date until the earliest of the following censoring dates: end of the study period or end of enrolment in the database)
[3] Maximum of 10 years (The results on pregnancies are approximate, because the status of the pregnancy is not available in the databases. It is also possible that the same pregnancy is in two different periods)
[4] Hormonal or non-hormonal
[5] At index date = information recorded in the baseline period (6 months prior to the index date)
[6] This percentage is of those with pregnancy during study period (N=21)

In the Belgian GP panel, 2.9% of patients reported pregnancy during the study period (plus the six months baseline period). Of all the reported pregnancies in Belgian GP panel, 16.7% pregnancies resulted in an abortive outcome. A total of 1.4% of pregnancies were recent and 2.9% were prospective pregnancies. The majority of the patients (77.3%) were not using contraceptives prior to the index date. None of the patients in Belgian GP panel were lactating at the index date (Table 10.3-19).

Table 10.3-19: Pregnancy, contraceptive use and lactation in Belgium – GPs

		Analysis population (Total number of patients = 207)
Pregnancy[1] during the study period[2]	Yes	6 (2.9%)
	No	201 (97.1%)
Pregnancy with abortive outcome during the study period[2]	Yes	1 (16.7%)[6]
	No	5 (83.3%)[6]
Pregnancy according to the time period[3]	Previous pregnancy within 2 years' time frame before the index date	7 (3.4%)
	Previous pregnancy within 2- 5 years' time frame before the index date	12 (5.8%)
	Previous pregnancy within 5 -10 years' time frame before the index date	13 (6.3%)
	Recent pregnancy: (within 3 months before index date)	3 (1.4%)
	Prospective pregnancy (after index date)	6 (2.9%)
Contraceptive[4] use prior to the index date[5]	Yes	47 (22.7%)
	No	160 (77.3%)
Lactation at the index date[6]	Yes	0
	No	207 (100.0%)

[1] At least one pregnancy
[2]Including the baseline period (6 months prior the index date) and the follow up period (from the index date until the earliest of the following censoring dates: end of the study period or end of enrolment in the database)
[3] Maximum of 10 years (The results on pregnancies are approximate, because the status of the pregnancy is not available in the databases. It is also possible that the same pregnancy is in two different periods)
[4] Hormonal or non-hormonal
[5] At index date = information recorded in the baseline period (6 months prior to the index date)
[6] This percentage is of those with pregnancy during study period (N=6)

In the French gynaecologist panel, 15.8% of patients reported pregnancy during the study period (plus the six months baseline period). Of the reported pregnancies, 47.1% resulted in an abortive outcome. A total of 3.2% pregnancies were recent and 11.2% were prospective pregnancies. The majority of patients (86.2%) were not using contraceptives prior to the index date. None of the patients in French gynaecologist panel were lactating at the index date (Table 10.3-20).

Table 10.3-20: Pregnancy, contraceptive use and lactation in France – Gynaecologists

		Analysis population (Total number of patients = 659)
Pregnancy[1] during the study period[2]	Yes	104 (15.8%)
	No	555 (84.2%)
Pregnancy with abortive outcome during the study period[2]	Yes	49 (47.1%)[6]
	No	55 (52.9%)[6]
Pregnancy according to the time period[3]	Previous pregnancy within 2 years' time frame before the index date	67 (10.2%)
	Previous pregnancy within 2- 5 years' time frame before the index date	50 (7.6%)
	Previous pregnancy within 5 -10 years' time frame before the index date	19 (2.9%)
	Recent pregnancy: (within 3 months before index date)	21 (3.2%)
	Prospective pregnancy (after index date)	74 (11.2%)
Contraceptive[4] use prior to the index date[5]	Yes	91 (13.8%)
	No	568 (86.2%)
Lactation at the index date[6]	Yes	0
	No	659 (100.0%)

[1] At least one pregnancy
[2]Including the baseline period (6 months prior the index date) and the follow up period (from the index date until the earliest of the following censoring dates: end of the study period or end of enrolment in the database)
[3] Maximum of 10 years (The results on pregnancies are approximate, because the status of the pregnancy is not available in the databases. It is also possible that the same pregnancy is in two different periods)
[4] Hormonal or non-hormonal
[5] At index date = information recorded in the baseline period (6 months prior to the index date)
[6] This percentage is of those with pregnancy during study period (N=104)

10.3.6 SEASONIQUE Exposure

SEASONIQUE exposure in the French GP, Italian GP, Belgian GP and French gynaecologist panels is described in Table 10.3-21, Table 10.3-22,Table 10.3-23 and Table 10.3-24, respectively.

The mean (SD), number of SEASONIQUE prescriptions per patient in the French GP panel was 1.5 (1.08). The majority of patients (71.1%) had a single SEASONIQUE prescription. Of those patients for whom at least one prespecified indication for prescribing SEASONIQUE was provided during the

follow up period (n=177), all had a single indication. The majority of patients had a single episode of SEASONIQUE treatment (86.0%). Furthermore, the majority of patients had no overlapping prescriptions of SEASONIQUE (83.8%). The median (1st quartile-3rd quartile [Q1-Q3]), duration of uninterrupted use of SEASONIQUE was 6.0 [3.0-6.4] months and the median ([Q1-Q3]) follow-up of patients in the French GP panel was 15.6 [7.5-22.7] months (Table 10.3-21).

Table 10.3-21: Analysis of SEASONIQUE exposure - France – GPs

		Analysis population (Total number of patients =235)[1]
Number of SEASONIQUE prescriptions per patient	Mean (SD)	1.5 (1.08)
	Median [Q1 - Q3]	1.0 [1.0-2.0]
	Range [min - max]	[1.0-9.0]
Number of SEASONIQUE prescriptions per patient (category)	1 SEASONIQUE prescription	167 (71.1%)
	2 SEASONIQUE prescriptions	35 (14.9%)
	> 2 SEASONIQUE prescriptions	33 (14.0%)
Number of indications associated with the SEASONIQUE prescription[2]	1 indication	177 (100.0%)
	2 indications	0
	3 indications	0
	> 3 indications	0
	Missing	58
Number of treatments episodes[3] of SEASONIQUE (category)	1 episode of SEASONIQUE	202 (86.0%)
	2 episodes of SEASONIQUE	29 (12.3%)
	> 2 episodes of SEASONIQUE	4 (1.7%)
Number of patients with overlapping prescriptions[4] of SEASONIQUE (category)	0 overlapping	197 (83.8%)
	1 overlapping	22 (9.4%)
	2 overlapping	10 (4.3%)
	> 2 overlapping	6 (2.6%)
Duration of SEASONIQUE (uninterrupted use) (months)	Mean (SD)	6.0 (3.36)
	Median [Q1 – Q3]	6.0 [3.0-6.4]
	Range [min - max]	[3.0-12.9]

		Analysis population (Total number of patients =235)[1]
Follow-up duration (months)	Mean (SD)	16.2 (10.36)
	Median [Q1 – Q3]	15.6 [7.5-22.7]
	Range [min - max]	[0.0-36.1]

Abbreviations: Q1-Q3: Median (1st quartile-3rd quartile), SD: Standard Deviation
[1] In the follow up period
[2] Only diagnoses related to prescribing SEASONIQUE in the follow up period have been taken into account here
[3] An episode of therapy will be defined as a period of continuous usage of one or a series of prescriptions for SEASONIQUE for the same patient
[4] A successive prescription for the same COC filled during the time period of the previous prescription (resulting in an overlap)

The mean (SD), number of SEASONIQUE prescriptions per patient in the Italian GP panel was 2.8 (2.43). Approximately 46% of patients had a single SEASONIQUE prescription, 12.7% had two prescriptions and 40.9% had more than two prescriptions. Of those patients for whom at least one prespecified indication for prescribing SEASONIQUE was provided during the follow up period (n=135), all had a single indication. Majority of patients had a single episode of SEASONIQUE treatment (80.9%). Furthermore, the majority of patients (56.4%) had no overlapping prescriptions of SEASONIQUE. The median [Q1 - Q3] duration of uninterrupted use was 3.1 [3.0-3.4] and the median [Q1 - Q3] follow-up duration of patients in the Italian GP panel was 24.4 [16.1-32.4] months (Table 10.3-22).

Table 10.3-22: Analysis of SEASONIQUE exposure - Italy – GPs

		Analysis population (Total number of patients =220)[1]
Number of SEASONIQUE prescriptions per patient	Mean (SD)	2.8 (2.43)
	Median [Q1 - Q3]	2.0 [1.0-4.0]
	Range [min - max]	[1.0-12.0]
Number of SEASONIQUE prescriptions per patient (category)	1 SEASONIQUE prescription	102 (46.4%)
	2 SEASONIQUE prescriptions	28 (12.7%)
	> 2 SEASONIQUE prescriptions	90 (40.9%)
Number of indications associated with the SEASONIQUE prescription[2]	1 indication	135 (100.0%)
	2 indications	0

		Analysis population (Total number of patients =220)[1]
	3 indications	0
	> 3 indications	0
	Missing	85
Number of treatments episodes[3] of SEASONIQUE (category)	1 episode of SEASONIQUE	178 (80.9%)
	2 episodes of SEASONIQUE	34 (15.5%)
	> 2 episodes of SEASONIQUE	8 (3.6%)
Number of patients with overlapping prescriptions[4] of SEASONIQUE (category)	0 overlapping	124 (56.4%)
	1 overlapping	38 (17.3%)
	2 overlapping	38 (17.3%)
	> 2 overlapping	20 (9.1%)
Duration of SEASONIQUE (uninterrupted use) (months)	Mean (SD)	3.4 (1.15)
	Median [Q1 - Q3]	3.1 [3.0-3.4]
	Range [min - max]	[3.0-12.4]
Follow-up duration (months)	Mean (SD)	23.2 (10.51)
	Median [Q1 - Q3]	24.4 [16.1-32.4]
	Range [min - max]	[0.0-36.1]

Abbreviations: Q1-Q3: Median (1st quartile-3rd quartile), SD: Standard Deviation
[1] In the follow up period
[2] Only diagnoses related to prescribing SEASONIQUE in the follow up period have been taken into account here
[3] An episode of therapy will be defined as a period of continuous usage of one or a series of prescriptions for SEASONIQUE for the same patient
[4] A successive prescription for the same COC filled during the time period of the previous prescription (resulting in an overlap)

The mean (SD), number of SEASONIQUE prescriptions per patient in the Belgian GP panel was 1.9 (1.56). Over half of the patients (57.5%) had a single SEASONIQUE prescription. Of those patients for whom at least one prespecified indication for prescribing SEASONIQUE was provided during the follow up period (n=174), all had a single indication. The majority of patients had a single episode of treatment (76.3%). Furthermore, the majority of patients (73.4%) had no overlapping prescription of SEASONIQUE. The median [Q1 - Q3] duration of uninterrupted SEASONIQUE use was 3.0 [3.0-6.0] and the median [Q1 - Q3] follow-up duration of patients was 16.0 [10.9-23.9] months (Table 10.3-23).

Table 10.3-23: Analysis of SEASONIQUE exposure - Belgium – GPs

		Analysis population (Total number of patients = 207)[1]
Number of SEASONIQUE prescriptions per patient	Mean (SD)	1.9 (1.56)
	Median [Q1 - Q3]	1.0 [1.0-2.0]
	Range [min - max]	[1.0-10.0]
Number of SEASONIQUE prescriptions per patient (category)	1 SEASONIQUE prescription	119 (57.5%)
	2 SEASONIQUE prescriptions	41 (19.8%)
	> 2 SEASONIQUE prescriptions	47 (22.7%)
Number of indications associated with the SEASONIQUE prescription[2]	1.	174 (100.0%)
	2.	0
	3.	0
	> 3	0
	Missing	33
Number of treatments episodes[3] of SEASONIQUE (category)	1 episode of SEASONIQUE	158 (76.3%)
	2 episodes of SEASONIQUE	40 (19.3%)
	> 2 episodes of SEASONIQUE	9 (4.3%)
Number of patients with overlapping prescriptions[4] of SEASONIQUE (category)	0 overlapping	152 (73.4%)
	1 overlapping	34 (16.4%)
	2 overlapping	15 (7.2%)
	> 2 overlapping	6 (2.9%)
Duration of SEASONIQUE (uninterrupted use) (months)	Mean (SD)	4.8 (2.76)
	Median [Q1 - Q3]	3.0 [3.0-6.0]
	Range [min - max]	[3.0-12.8]
Follow-up duration (months)	Mean (SD)	17.0 (9.05)
	Median [Q1 - Q3]	16.0 [10.9-23.9]
	Range [min - max]	[0.0-36.1]

	Analysis population (Total number of patients = 207)[1]

Abbreviations: Q1-Q3: Median (1st quartile-3rd quartile), SD: Standard Deviation
[1] In the follow up period
[2] Only diagnoses related to prescribing SEASONIQUE in the follow up period have been taken into account here
[3] An episode of therapy will be defined as a period of continuous usage of one or a series of prescriptions for SEASONIQUE for the same patient
[4] A successive prescription for the same COC filled during the time period of the previous prescription (resulting in an overlap)

The mean (SD), number of SEASONIQUE prescriptions per patient in the French gynaecologist panel was 1.3 (0.73). The majority of patients (76.0%), had a single SEASONIQUE prescription. Of those patients for whom at least one prespecified indication for prescribing SEASONIQUE was provided during the follow up period (n=469), all had a single indication. The majority of patients had single episode of SEASONIQUE treatment (88.2%). Furthermore, the majority of patients (86.9%) had no overlapping prescriptions of SEASONIQUE. The median [Q1 - Q3] duration of uninterrupted use was 6.0 [3.0-12.0] and the median [Q1 - Q3] follow-up of patients in the French gynaecologist panel was 10.3[0.0-20.6] months (Table 10.3-24).

Table 10.3-24: Analysis of SEASONIQUE exposure - France – Gynaecologists

		Analysis population (Total number of patients = 659)[1]
Number of SEASONIQUE prescriptions per patient	Mean (SD)	1.3 (0.73)
	Median [Q1 - Q3]	1.0 [1.0-1.0]
	Range [min - max]	[1.0-6.0]
Number of SEASONIQUE prescriptions per patient (category)	1 SEASONIQUE prescription	501 (76.0%)
	2 SEASONIQUE prescriptions	108 (16.4%)
	> 2 SEASONIQUE prescriptions	50 (7.6%)
Number of indications associated with the SEASONIQUE prescription[2]	1 indication	469 (100.0%)
	2 indications	0
	3 indications	0
	> 3 indications	0
	Missing	190

		Analysis population (Total number of patients = 659)[1]
Number of treatments episodes[3] of SEASONIQUE (category)	1 episode of SEASONIQUE	581 (88.2%)
	2 episodes of SEASONIQUE	65 (9.9%)
	> 2 episodes of SEASONIQUE	13 (2.0%)
Number of patients with overlapping prescriptions[4] of SEASONIQUE (category)	0 overlapping	573 (86.9%)
	1 overlapping	70 (10.6%)
	2 overlapping	13 (2.0%)
	> 2 overlapping	3 (0.5%)
Duration of SEASONIQUE (uninterrupted use) (months)	Mean (SD)	7.2 (4.15)
	Median [Q1 - Q3]	6.0 [3.0-12.0]
	Range [min - max]	[3.0-13.3]
Follow-up duration (months)	Mean (SD)	11.8 (11.54)
	Median [Q1 - Q3]	10.3 [0.0-20.6]
	Range [min - max]	[0.0-36.1]

Abbreviations: Q1-Q3: Median (1st quartile-3rd quartile), SD: Standard Deviation
[1] In the follow up period
[2] Only diagnoses related to prescribing SEASONIQUE in the follow up period have been taken into account here
[3] An episode of therapy will be defined as a period of continuous usage of one or a series of prescriptions for SEASONIQUE for the same patient
[4] A successive prescription for the same COC filled during the time period of the previous prescription (resulting in an overlap)

10.3.7 SEASONIQUE Prescription by Physicians

The description of number of physicians according to the number of prescriptions of SEASONIQUE in the French GP, Italian GP, Belgian GP and French gynaecologist panels is described in Table 10.3-25, Table 10.3-26, Table 10.3-27 and Table 10.3-28, respectively.

Among the 148 physicians prescribing SEASONIQUE in the French GP panel, the majority (56.8%) prescribed a single prescription for SEASONIQUE during the study period. A total of 22.3% physicians prescribed either two or three SEASONIQUE prescriptions (Table 10.3-25). A limited number of physicians prescribed >10 prescriptions over the study period, with the maximum number in the range of 26-30 (1.4%).

Table 10.3-25: Number of Physicians according to the number of prescriptions of SEASONIQUE - France – GPs

		SEASONIQUE physicians (Total number of Physicians = 148)
Number of Physicians according to the number of prescriptions of SEASONIQUE	Physicians with 1 prescription of SEASONIQUE	84 (56.8%)[1]
	Physicians with 2 prescriptions of SEASONIQUE	21 (14.2%)
	Physicians with 3 prescriptions of SEASONIQUE	12 (8.1%)
	Physicians with 4 prescriptions of SEASONIQUE	8 (5.4%)
	Physicians with 5 prescriptions of SEASONIQUE	8 (5.4%)
	Physicians with 6 prescriptions of SEASONIQUE	4 (2.7%)
	Physicians with 7 prescriptions of SEASONIQUE	3 (2.0%)
	Physicians with 8 prescriptions of SEASONIQUE	1 (0.7%)
	Physicians with 9 prescriptions of SEASONIQUE	2 (1.4%)
	Physicians with 10 prescriptions of SEASONIQUE	1 (0.7%)
	Physicians with 11 prescriptions of SEASONIQUE	0
	Physicians with 12 prescriptions of SEASONIQUE	0
	Physicians with 13 prescriptions of SEASONIQUE	0
	Physicians with 14 prescriptions of SEASONIQUE	0
	Physicians with 15 prescriptions of SEASONIQUE	1 (0.7%)
	Physicians with 16 prescriptions of SEASONIQUE	1 (0.7%)
	Physicians with 17 prescriptions of SEASONIQUE	0
	Physicians with 18 prescriptions of SEASONIQUE	0
	Physicians with 19 prescriptions of SEASONIQUE	0
	Physicians with a Range [min - max] of 20 -25 prescriptions of SEASONIQUE	0
	Physicians with a Range [min - max] of 26 -30 prescriptions of SEASONIQUE	2 (1.4%)
	Physicians with prescriptions of SEASONIQUE > 30	0

Among the 181 physicians, prescribing SEASONIQUE in the Italian GP panel, 34.3% prescribed a single prescription for SEASONIQUE during the study period. The max number of prescriptions per physician was 19, which was reported for 1.1% of physicians. A total of 29.3% physicians prescribed either two or three SEASONIQUE prescriptions (Table 10.3-26).

Table 10.3-26: Number of Physicians according to the number of prescriptions of SEASONIQUE - Italy – GPs

		SEASONIQUE physicians (Total number of Physicians = 181)
Number of Physicians according to the number of prescriptions of SEASONIQUE	Physicians with 1 prescription of SEASONIQUE	62 (34.3%)
	Physicians with 2 prescriptions of SEASONIQUE	31 (17.1%)
	Physicians with 3 prescriptions of SEASONIQUE	22 (12.2%)
	Physicians with 4 prescriptions of SEASONIQUE	15 (8.3%)
	Physicians with 5 prescriptions of SEASONIQUE	13 (7.2%)
	Physicians with 6 prescriptions of SEASONIQUE	7 (3.9%)
	Physicians with 7 prescriptions of SEASONIQUE	9 (5.0%)
	Physicians with 8 prescriptions of SEASONIQUE	8 (4.4%)
	Physicians with 9 prescriptions of SEASONIQUE	1 (0.6%)
	Physicians with 10 prescriptions of SEASONIQUE	4 (2.2%)
	Physicians with 11 prescriptions of SEASONIQUE	3 (1.7%)
	Physicians with 12 prescriptions of SEASONIQUE	1 (0.6%)
	Physicians with 13 prescriptions of SEASONIQUE	3 (1.7%)
	Physicians with 14 prescriptions of SEASONIQUE	0
	Physicians with 15 prescriptions of SEASONIQUE	0
	Physicians with 16 prescriptions of SEASONIQUE	0
	Physicians with 17 prescriptions of SEASONIQUE	0
	Physicians with 18 prescriptions of SEASONIQUE	0
	Physicians with 19 prescriptions of SEASONIQUE	2 (1.1%)
	Physicians with a Range [min - max] of 20 -25 prescriptions of SEASONIQUE	0
	Physicians with a Range [min - max] of 26 -30 prescriptions of SEASONIQUE	0
	Physicians with prescriptions of SEASONIQUE > 30	0

Among the 100 physicians prescribing SEASONIQUE in the Belgian GP panel, 31% prescribed a single prescription for SEASONIQUE during the study period. A total of 37.0% physicians prescribed either two or three SEASONIQUE prescriptions (Table 10.3-27). The maximum number of prescriptions prescribed by a physician ranged between 26-30; this was reported for three physicians (3.0%).

Table 10.3-27: Number of Physicians according to the number of prescriptions of SEASONIQUE - Belgium – GPs

		SEASONIQUE physicians (Total number of Physicians = 100)
Number of Physicians according to the number of prescriptions of SEASONIQUE	Physicians with 1 prescription of SEASONIQUE	31 (31.0%)
	Physicians with 2 prescriptions of SEASONIQUE	18 (18.0%)
	Physicians with 3 prescriptions of SEASONIQUE	19 (19.0%)
	Physicians with 4 prescriptions of SEASONIQUE	8 (8.0%)
	Physicians with 5 prescriptions of SEASONIQUE	6 (6.0%)
	Physicians with 6 prescriptions of SEASONIQUE	2 (2.0%)
	Physicians with 7 prescriptions of SEASONIQUE	2 (2.0%)
	Physicians with 8 prescriptions of SEASONIQUE	3 (3.0%)
	Physicians with 9 prescriptions of SEASONIQUE	1 (1.0%)
	Physicians with 10 prescriptions of SEASONIQUE	1 (1.0%)
	Physicians with 11 prescriptions of SEASONIQUE	3 (3.0%)
	Physicians with 12 prescriptions of SEASONIQUE	0
	Physicians with 13 prescriptions of SEASONIQUE	0
	Physicians with 14 prescriptions of SEASONIQUE	0
	Physicians with 15 prescriptions of SEASONIQUE	1 (1.0%)
	Physicians with 16 prescriptions of SEASONIQUE	-
	Physicians with 17 prescriptions of SEASONIQUE	1 (1.0%)
	Physicians with 18 prescriptions of SEASONIQUE	0
	Physicians with 19 prescriptions of SEASONIQUE	0
	Physicians with a Range [min - max] of 20 -25 prescriptions of SEASONIQUE	1 (1.0%)
	Physicians with a Range [min - max] of 26 -30 prescriptions of SEASONIQUE	3 (3.0%)
	Physicians with prescriptions of SEASONIQUE > 30	0

Among the 75 gynaecologist prescribers, 17.3% prescribed a single prescription for SEASONIQUE during the study period. Approximately 15% of gynaecologists prescribed more than 20 prescriptions during the study period with 4.0% prescribing >30 prescriptions (Table 10.3-28).

Table 10.3-28: Number of Gynaecologists according to the number of prescriptions of SEASONIQUE - France

		SEASONIQUE physicians (Total number of Gynaecologists= 75)
Number of Gynaecologists according to the number of prescriptions of SEASONIQUE	Physicians with 1 prescription of SEASONIQUE	13 (17.3%)
	Physicians with 2 prescriptions of SEASONIQUE	7 (9.3%)
	Physicians with 3 prescriptions of SEASONIQUE	5 (6.7%)
	Physicians with 4 prescriptions of SEASONIQUE	6 (8.0%)
	Physicians with 5 prescriptions of SEASONIQUE	3 (4.0%)
	Physicians with 6 prescriptions of SEASONIQUE	4 (5.3%)
	Physicians with 7 prescriptions of SEASONIQUE	4 (5.3%)
	Physicians with 8 prescriptions of SEASONIQUE	4 (5.3%)
	Physicians with 9 prescriptions of SEASONIQUE	1 (1.3%)
	Physicians with 10 prescriptions of SEASONIQUE	3 (4.0%)
	Physicians with 11 prescriptions of SEASONIQUE	3 (4.0%)
	Physicians with 12 prescriptions of SEASONIQUE	1 (1.3%)
	Physicians with 13 prescriptions of SEASONIQUE	-
	Physicians with 14 prescriptions of SEASONIQUE	1 (1.3%)
	Physicians with 15 prescriptions of SEASONIQUE	3 (4.0%)
	Physicians with 16 prescriptions of SEASONIQUE	1 (1.3%)
	Physicians with 17 prescriptions of SEASONIQUE	1 (1.3%)
	Physicians with 18 prescriptions of SEASONIQUE	2 (2.7%)
	Physicians with 19 prescriptions of SEASONIQUE	2 (2.7%)
	Physicians with a Range [min - max] of 20 -25 prescriptions of SEASONIQUE	4 (5.3%)
	Physicians with a Range [min - max] of 26 -30 prescriptions of SEASONIQUE	4 (5.3%)
	Physicians with prescriptions of SEASONIQUE > 30	3 (4.0%)

10.3.8 Physicians by Patients Taking SEASONIQUE

The number of physicians with number of patients taking SEASONIQUE in the French GP, Italian GP, Belgian GP and French gynaecologist panels is described in Table 10.3-29, Table 10.3-30, Table 10.3-31 and Table 10.3-32, respectively.

Among the 148 SEASONIQUE prescribers from the French GP panel, the majority (66.2%) had a single patient taking SEASONIQUE during the study period (Table 10.3-29).

Table 10.3-29: Number of Physicians according to the number of patients taking SEASONIQUE – France – GPs

		SEASONIQUE physicians (Total number of physicians = 148)
Number of Physicians according to the number of patients taking SEASONIQUE	Physicians with 1 patient taking SEASONIQUE	98 (66.2%)
	Physicians with 2 patients taking SEASONIQUE	27 (18.2%)
	Physicians with 3 patients taking SEASONIQUE	9 (6.1%)
	Physicians with 4 patients taking SEASONIQUE	3 (2.0%)
	Physicians with 5 patients taking SEASONIQUE	4 (2.7%)
	Physicians with 6 patients taking SEASONIQUE	4 (2.7%)
	Physicians with 7 patients taking SEASONIQUE	1 (0.7%)
	Physicians with 8 patients taking SEASONIQUE	0
	Physicians with 9 patients taking SEASONIQUE	0
	Physicians with 10 patients taking SEASONIQUE	1 (0.7%)
	Physicians with 11 patients taking SEASONIQUE	0
	Physicians with 12 patients taking SEASONIQUE	0
	Physicians with 13 patients taking SEASONIQUE	0
	Physicians with 14 patients taking SEASONIQUE	0
	Physicians with 15 patients taking SEASONIQUE	0
	Physicians with 16 patients taking SEASONIQUE	0
	Physicians with 17 patients taking SEASONIQUE	1 (0.7%)
	Physicians with 18 patients taking SEASONIQUE	0
	Physicians with 19 patients taking SEASONIQUE	0
	Physicians with a Range [min - max] of 20 -25 patients taking SEASONIQUE	0
	Physicians with a Range [min - max] of 26 -30 patients taking SEASONIQUE	0
	Physicians with patients taking SEASONIQUE > 30	0

Among the 181 SEASONIQUE physician prescribers from the Italian GP panel, the majority (76.8%) had a single patient taking SEASONIQUE during the study period (Table 10.3-30).

Table 10.3-30: Number of Physicians according to the number of patients taking SEASONIQUE - Italy – GPs

		SEASONIQUE physicians (Total number of Physicians = 181)
Number of Physicians according to the number of patients taking SEASONIQUE	Physicians with 1 patient taking SEASONIQUE	139 (76.8%)
	Physicians with 2 patients taking SEASONIQUE	34 (18.8%)
	Physicians with 3 patients taking SEASONIQUE	7 (3.9%)
	Physicians with 4 patients taking SEASONIQUE	1 (0.6%)
	Physicians with 5 patients taking SEASONIQUE	0
	Physicians with 6 patients taking SEASONIQUE	0
	Physicians with 7 patients taking SEASONIQUE	0
	Physicians with 8 patients taking SEASONIQUE	0
	Physicians with 9 patients taking SEASONIQUE	0
	Physicians with 10 patients taking SEASONIQUE	0
	Physicians with 11 patients taking SEASONIQUE	0
	Physicians with 12 patients taking SEASONIQUE	0
	Physicians with 13 patients taking SEASONIQUE	0
	Physicians with 14 patients taking SEASONIQUE	0
	Physicians with 15 patients taking SEASONIQUE	0
	Physicians with 16 patients taking SEASONIQUE	0
	Physicians with 17 patients taking SEASONIQUE	0
	Physicians with 18 patients taking SEASONIQUE	0
	Physicians with 19 patients taking SEASONIQUE	0
	Physicians with a Range [min - max] of 20 -25 patients taking SEASONIQUE	0
	Physicians with a Range [min - max] of 26 -30 patients taking SEASONIQUE	0
	Physicians with patients taking SEASONIQUE > 30	0

Among the 100 SEASONIQUE physician prescribers from the Belgian GP panel, the majority (54.0%) had a single patient taking SEASONIQUE during the study period (Table 10.3-31).

Table 10.3-31: Number of Physicians according to the number of patients taking SEASONIQUE – Belgium – GPs

		SEASONIQUE physicians (Total number of Physicians = 100)
Number of Physicians according to the number of patients taking SEASONIQUE	Physicians with 1 patient taking SEASONIQUE	54 (54.0%)

		SEASONIQUE physicians (Total number of Physicians = 100)
	Physicians with 2 patients taking SEASONIQUE	23 (23.0%)
	Physicians with 3 patients taking SEASONIQUE	7 (7.0%)
	Physicians with 4 patients taking SEASONIQUE	8 (8.0%)
	Physicians with 5 patients taking SEASONIQUE	0
	Physicians with 6 patients taking SEASONIQUE	1 (1.0%)
	Physicians with 7 patients taking SEASONIQUE	2 (2.0%)
	Physicians with 8 patients taking SEASONIQUE	1 (1.0%)
	Physicians with 9 patients taking SEASONIQUE	2 (2.0%)
	Physicians with 10 patients taking SEASONIQUE	0
	Physicians with 11 patients taking SEASONIQUE	1 (1.0%)
	Physicians with 12 patients taking SEASONIQUE	0
	Physicians with 13 patients taking SEASONIQUE	0
	Physicians with 14 patients taking SEASONIQUE	1 (1.0%)
	Physicians with 15 patients taking SEASONIQUE	0
	Physicians with 16 patients taking SEASONIQUE	0
	Physicians with 17 patients taking SEASONIQUE	0
	Physicians with 18 patients taking SEASONIQUE	0
	Physicians with 19 patients taking SEASONIQUE	0
	Physicians with a Range [min - max] of 20 -25 patients taking SEASONIQUE	0
	Physicians with a Range [min - max] of 26 -30 patients taking SEASONIQUE	0
	Physicians with patients taking SEASONIQUE > 30	0

Among the 75 French gynaecologist prescribers, 21.3% had a single patient taking SEASONIQUE during the study period, followed by 13.3% having prescribed SEASONIQUE for two patients. Six (8.0%) gynaecologists had prescribed SEASONIQUE for ≥ 20 patients, with 4.0% prescribing for >30 patients (Table 10.3-32).

Table 10.3-32: Number of Gynaecologists according to the number of patients taking SEASONIQUE – France

		SEASONIQUE physicians (Total number of Gynaecologists = 75)
Number of Gynaecologists according to the number of patients taking SEASONIQUE	Physicians with 1 patient taking SEASONIQUE	16 (21.3%)
	Physicians with 2 patients taking SEASONIQUE	10 (13.3%)

		SEASONIQUE physicians (Total number of Gynaecologists = 75)
	Physicians with 3 patients taking SEASONIQUE	4 (5.3%)
	Physicians with 4 patients taking SEASONIQUE	4 (5.3%)
	Physicians with 5 patients taking SEASONIQUE	4 (5.3%)
	Physicians with 6 patients taking SEASONIQUE	7 (9.3%)
	Physicians with 7 patients taking SEASONIQUE	5 (6.7%)
	Physicians with 8 patients taking SEASONIQUE	0
	Physicians with 9 patients taking SEASONIQUE	3 (4.0%)
	Physicians with 10 patients taking SEASONIQUE	2 (2.7%)
	Physicians with 11 patients taking SEASONIQUE	2 (2.7%)
	Physicians with 12 patients taking SEASONIQUE	4 (5.3%)
	Physicians with 13 patients taking SEASONIQUE	1 (1.3%)
	Physicians with 14 patients taking SEASONIQUE	2 (2.7%)
	Physicians with 15 patients taking SEASONIQUE	1 (1.3%)
	Physicians with 16 patients taking SEASONIQUE	1 (1.3%)
	Physicians with 17 patients taking SEASONIQUE	1 (1.3%)
	Physicians with 18 patients taking SEASONIQUE	1 (1.3%)
	Physicians with 19 patients taking SEASONIQUE	1 (1.3%)
	Physicians with a Range [min - max] of 20 -25 patients taking SEASONIQUE	3 (4.0%)
	Physicians with a Range [min - max] of 26 -30 patients taking SEASONIQUE	0
	Physicians with patients taking SEASONIQUE > 30	3 (4.0%)

10.3.9 Additional Analysis

Since for the French gynaecologist panel <80% of patients had at least six months of history, the main analysis was performed on the total population The sub-population of patients with at least six months of history in the French gynaecologist panel is described in Table 10.3-33 and Table 10.3-34.

Of the analysis population (N=393) in the French gynaecologist panel, 50.6% were new users, 24.4% were naïve users, 19.3% were switchers and 5.6% were re-starters (Table 10.3-33). A total of 273 patients (69.6%) were in the age group ≥ 15 to ≤ 35 years and 75.0% had a normal BMI. The smoking and alcohol intake status was unknown for almost the entire sub-population (Table 10.3-34).

Table 10.3-33: Total analysis population- France – Gynaecologists Sub-population of women with at least six months of history

	Sub-population of women with at least 6 months of history (N=393)
Naïve users[1]	96 (24.4%)
New users[2]	199 (50.6%)
Re-starters[3]	22 (5.6%)
Switchers[4]	76 (19.3%)

[1] Naïve users (starting use) are defined as women with first ever exposure to SEASONIQUE during the study period and no use of any dispensed combined hormonal contraceptive (CHC) prior to the index date
[2] New users are defined as women starting use of SEASONIQUE after a break of at least 12 weeks for any prescription of CHC prior to the index date
[3] Re-starters are defined as women who start SEASONIQUE after a break of 4-11 weeks of using other CHC prior to the index date
[4] Switchers are defined as women starting SEASONIQUE after a different CHC preparation with a break of less than four weeks prior to the index date

Table 10.3-34: Patient's demographics characteristics at index date in France – Gynaecologists Sub-population of women with at least six months of history

		Analysis population (Total number of patients = 393)[1]
Age at index date (years)	N	392
	Mean (SD)	30.2 (8.45)
	Median [Q1 - Q3]	30.0 [23.0-37.0]
	Range [min - max]	[15.0-51.0]
	Missing	1
Age at index date (years) – categories	<15 years	0
	≥ 15 to ≤ 35 years	273 (69.6%)[2]
	>35 to <50 years	118 (30.1%)[2]
	≥ 50 years	1 (0.3%)2
	Missing	1
Weight (kg)	N	96
	Mean (SD)	61.1 (12.01)
	Median [Q1 - Q3]	58.9 [53.2-66.3]
	Range [min - max]	[40.0-107.0]
	Missing	297

		Analysis population (Total number of patients = 393)[1]
Height (cm)	N	131
	Mean (SD)	165.5 (6.00)
	Median [Q1 - Q3]	165.0 [160.0-170.0]
	Range [min - max]	[153.0-180.0]
	Missing	262
BMI value (Kg/m^2)	N	76
	Mean (SD)	22.4 (3.91)
	Median [Q1 - Q3]	21.4 [20.3-23.5]
	Range [min - max]	[16.2-39.3]
	Missing	317
BMI value (Kg/m^2) - categories[2]	Underweight (BMI<18.5)	6 (7.9%)[2]
	Normal (18.5≤BMI<25)	57 (75.0%)[2]
	Overweight (25≤BMI≤30)	8 (10.5%)[2]
	Obese (BMI>30)	5 (6.6%)[2]
Smoking status[2]	Yes	1 (100.0%)[2]
	No	0
	Missing	392
Number of cigarettes per day[3]	Mean (SD)	3.00 (N/A)
	Median [Q1 - Q3]	3.00 [N/A-N/A]
	Range [min - max]	[N/A-N/A]
	Missing	0
Alcohol drinker[2]	Yes	0
	No	0
	Missing	393

Abbreviations: BMI: Body Mass Index, Q1: Median (1st quartile), Q3: Median (3rd quartile), Min: Minimum, Max: Maximum, N/A: not applicable,
SD: Standard Deviation
[1] Demographic information was collected for each patient from the database during the period prior to the index date
[2] The percentage per category relative to non-missing data
[3] For patients with a smoking status of yes

10.4 Main Results

The main analysis included the drug utilization of SEASONIQUE use, including duration of use and indication.

10.5 Other Analyses

Not applicable

10.6 Adverse Events/Adverse Reactions

This study is based on the secondary use of data. Adverse events (AEs) and adverse drug reactions (ADRs) were not measured.

11. DISCUSSION

The study incorporated real-world data sources from various European countries to explore the demographics of SEASONIQUE users informing on the drug utilization patterns of this extended contraceptive regimen. The study reveals that SEASONIQUE was prescribed predominantly for contraceptive purposes, followed by an indication on prevention of menstrual migraine. The results of the study showed that prescribing indications for SEASONIQUE were comparable across all the participating countries.

11.1 Key Results

A total of 235 patients in the French GP database, 220 in the Italian GP database, 207 in the Belgian GP database and 659 in the French gynaecologist panel were included in the main analysis over a three-year study period. Across all four data sources, the majority of patients were ≤ 35 years and none of the patients were above 55 years of age. For French GP and Belgian GP panels, there were a few cases (≤3) of SEASONIQUE use in patients aged <15 years. In terms of prior medical history, none of the patients in the study had a history of DVT/PE, breast cancer or other gynaecological cancers. SEASONIQUE was prescribed in a small number of patients who had experienced trauma or major surgeries within the last three months of treatment initiation (0.3% [French gynaecologist] to 0.5% [Italian GP panel]) and patients with risk factors for ATE (e.g. diabetes, hypertension) as evident by comorbidities reported at index and/or concomitant medication used at index.

Overall, based on prior CHC exposure status, the majority of included patients in the study across all panels were either naïve or new users of SEASONIQUE. The most common indication associated with prescription of SEASONIQUE across all four panels was found in line with the approved indication of SEASONIQUE (i.e. for contraceptive management). SEASONIQUE prescription for contraceptive management was reported in the range of 41.8% (Italian GP panel) to 81.2% patients (Belgian GP panel). Additionally, SEASONIQUE was prescribed for menstrual migraines in approximately 1.8% (Italian GP panel) to up to nearly 14.5% of patients (French GP panel). No further prespecified indications were reported across all panels and countries.

The study also reported that up to 22.7% of patients were using hormonal/non-hormonal contraceptives in the six-month baseline period. Use of prior COC before SEASONIQUE initiation ranged from approximately 8% (French gynaecologist panel) to 15% (Belgian GP panel). Indications for prescribing COC prior to SEASONIQUE and after index date, were similar to those for SEASONIQUE. For those patients who switched contraceptive to SEASONIQUE with a break of less than four weeks at index date (4.5% [Italian GP panel] to 30.9% [Belgian GP panel]), the majority across all four panels (>70%) presented a switch from CHC to SEASONIQUE.

Average SEASONIQUE exposure ranged from 1.3 prescriptions (French gynaecologist panel) to 2.8 prescriptions (Italian GP panel) while most patients across all four panels had a single treatment episode. For French GP, Italian GP and Belgian GP panels, more than half of the physicians had only one patient for whom they had prescribed SEASONIQUE. For French gynaecologists only 21.3% of physicians had prescribed SEASONIQUE for one patient; the distribution of number of patients per physician was more widespread with 8.0% of gynaecologists prescribing SEASONIQUE for ≥20 patients. These results are as expected as specialists may be more familiar with the use of extended regimens of oral contraception and thus more likely to prescribe this for a higher proportion of their patients. After starting SEASONIQUE, patients were also reported to have switched to another contraceptive. The proportion of patients switching was highest for the French gynaecologist panel (12.4%), of which half switched to another CHC and half switched to other contraceptives. For

patients switching after index date for French GP (7.7%), Italian GP (5.0%) and Belgian GP (9.2%) panels, more than two thirds of patients switched to another CHC.

A total of 30/235 patients (12.8%) in the French GP panel, 21/ 220 patients (9.5%) in the Italian GP, 6/207 patients (2.9%) in the Belgian GP and 104/659 patients (15.8%) in French gynaecologists' panel, had a reported pregnancy during the study period and including the six-month baseline period. Of the reported pregnancies, abortive outcomes were reported in 43.3% in the French GP panel, 16.7% in the Belgian GP panel, no patients in the Italian GP panel and in 47.1% of patients in the French gynaecologist panel.

The pregnancy related events should be interpreted with caution. The events were reported during the study period plus the baseline period (i.e. including the six months prior to starting SEASONIQUE) and do not take in to account whether the patient was continuously exposed to SEASONIQUE during the follow-up period. Therefore, the pregnancy could have occurred in a period outside of SEASONIQUE exposure i.e. women were not taking SEASONIQUE at the time they fell pregnant. For this reason, no conclusions can be drawn, and the pregnancy related events cannot be attributed to the lack of effectiveness of SEASONIQUE, which has been well established in the development program. This DUS was not designed to evaluate the effectiveness of SEASONIQUE as a contraceptive.

11.2 Limitations

- IQVIA EMR databases used in the study had limitations consistent with a provider-sourced EMR database. Although the quality of data collection was monitored by database owners, the information provided by the physicians in health records could still be underreported. This is likely as there is a substantial amount of missing information.
- Misclassification of exposure or outcome was a potential limitation of this study. Assessment of SEASONIQUE exposure was based on the EMR of written prescriptions rather than information on dispensed prescriptions (days of supply) or actual intake.

- Due to the nature of selected secondary databases that capture only reimbursed drugs, the number of European countries where SEASONIQUE, which is a non-reimbursed product, is available in a database was very limited. The selection of the countries was based on product launch and availability of longitudinal secondary databases and may not be representative of COC prescription habits in Europe.
- Only the French database provided data on SEASONIQUE prescriptions by gynaecologists as well as primary care providers. Absence of data from SEASONIQUE-prescribing gynaecologists in Belgium and Italy will limit to some extent the generalizability of the study results.
- In France, no link between the panel of GPs and Gynaecologists was possible. Panels of specialists were independent of GP panels; therefore, an overlap between patients included in primary health practices and in those from specialists could occur. However, the probability is minimal, given the 2-2.5% coverage of each panel.
- Given the nature of selected databases where anonymized patients cannot be tracked across panels, practices or specialties, detailed information on duration of SEASONIQUE use was limited.
- The duration of SEASONIQUE treatment (in days) was evaluated using the number of packages prescribed. In cases where this information was not available, the treatment duration could not be exactly determined. Additionally, where treatment patterns suggest that the actual treatment duration could have been shorter compared with the length of the prescribing recommendations (by physician or labelling), the reason (e.g., stockpile or potential misuse) cannot be discerned. Thus, patients might be classified as exposed when they have actually stopped taking the drug or not ever started the drug. In this manner, prescription duration might not be necessarily identical to actual use and consumption behaviour and may result in apparent shorter or longer treatment durations.
- Pregnancies were estimated by diagnoses codes in the patient's EMR but cannot always be reliably dated. Since the drug is prescribed for three months, there is no way to know whether

the woman stopped taking the drug during those three months (information on drug consumption is not available). In addition, the date of conception may not be recorded in the database. Consequently, it was not possible to estimate accurately whether a patient was still taking the drug while pregnant.

- The most common concomitant medications reported in the study at index were for CV disease. No conclusion can be made regarding CV disease or any other events that may be associated with SEASONIQUE exposure, as this data was not collected.

11.3 Interpretation

The study incorporated real-world data sources from various European countries to explore the demographics of female patients prescribed SEASONIQUE and corresponding SEASONIQUE utilization patterns, offering an insight into the utilization of this extended contraceptive regimen. However, as the clinical practice patterns differ from one country to the other, certain variations may occur, and the care practice and treatment practice patterns across specialty and countries was unavailable. As a consequence, no between country comparisons or pooled data analysis was performed. Due to inclusion of multiple data sources across three European countries, thorough information related to patient characteristics and SEASONIQUE utilization patterns was readily available.

11.4 Generalizability

The IQVIA EMR data sources from France, Italy and Belgium included in this study were selected to be representative of European countries. The national coverage of the EMR data sources with respect to physician ranged from 2-2.4% in France, Italy and Belgium and approximately 2.5% for French gynaecologists.

In all of the target countries, all SEASONIQUE prescriptions issued to patients and available in the databases during the study period were included. Furthermore, no further restrictions regarding demographic characteristics, insurance status, comorbidities, region, or other, which could affect the

external validity of results, were applied. Taking the known limitations of the databases into consideration, the findings presented in the report, are generalizable for the targeted countries France, Italy and Belgium. The results are also extendable to other European countries as France, Italy and Belgium represent Central, Southern and Northern European countries with different cultures and healthcare systems.

12. OTHER INFORMATION

Not applicable

13. CONCLUSION

This real-world study was conducted to characterize the drug utilization pattern of the extended contraceptive regimen, SEASONIQUE in selected European countries. The study revealed that SEASONIQUE was prescribed predominantly for contraceptive purposes and prevention of menstrual migraine. The study results showed that, the prescribing indications for SEASONIQUE were comparable across all the countries.

14. REFERENCES

1. Seasonique prescribing information. 2010 [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021840s008lbl.pdf.
2. Archer DF. Menstrual-cycle-related symptoms: a review of the rationale for continuous use of oral contraceptives. Contraception. 2006;74(5):359-66.
3. Sulak PJ, Scow RD, Preece C, Riggs MW, Kuehl TJ. Hormone withdrawal symptoms in oral contraceptive users. Obstetrics & Gynecology. 2000;95(2):261-6.
4. EMA. EMA Seasonique assessment report 2014 [Available from: https://www.ema.europa.eu/en/documents/referral/seasonique-article-294-referral-assessment-report_en.pdf.
5. Obstetricians A. ACOG Practice Bulletin No. 110: noncontraceptive uses of hormonal contraceptives. Obstet Gynecol. 2010;115(1):206-18.
6. Lidegaard Ø, Nielsen LH, Skovlund CW, Skjeldestad FE, Løkkegaard E. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. Bmj. 2011;343:d6423.
7. Becher H, Kostev K, Schroder-Bernhardi D. Validity and representativeness of the" Disease Analyzer" patient database for use in pharmaco-epidemiological and pharmacoeconomic studies. International journal of clinical pharmacology and therapeutics. 2009;47(10):617.

15. APPENDICES

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

ANNEX 1.1 Protocol

Seasonique DUS study_Protocol.pdf

ANNEX 1.2 SAP

Statistical Analysis Plan.pdf

ANNEX 1.3 Results

THERAMEX SEASONIQUE DUS- S

ANNEX 2. ADDITIONAL INFORMATION

ANNEX 2.1 Diagnoses related to prescribing combined oral contraceptives

Below is list of diagnoses related to prescribing COC based on the American College of Obstetricians and Gynaecologists (ACOG) Practice Bulletin on Non-contraceptive Uses of Hormonal Contraceptives.

Diagnoses related to prescribing combined oral contraceptives

ICD-10-CM codes:

Contraceptive management

Z30.xx Encounter for general counselling and advice on contraception (excluding Z30.2 Encounter for sterilization)

Menstrual cycle (ir)regularity (cycle control)

N92.x Excessive, frequent and irregular menstruation

Treatment of menorrhagia

N92.x Excessive and frequent menstruation with regular cycle

Treatment of dysmenorrhea

N94.4 Primary dysmenorrhea

N94.5 Secondary dysmenorrhea

N94.6 Dysmenorrhea, unspecified

Inducing amenorrhea for lifestyle considerations

N91.0 Primary amenorrhea

N91.1 Secondary amenorrhea

N91.2 Amenorrhea, unspecified

Treatment of premenstrual syndrome

N94.3 Premenstrual tension syndrome

Prevention of menstrual migrainesG43.X

G43.x Migraine

Decrease in risk of endometrial cancer, ovarian cancer, and colorectal cancer

C54.1 Malignant neoplasm of endometrium C56 Malignant neoplasm of ovary

C18.7 Malignant neoplasm of colon

C20 Malignant neoplasm of rectum

Treatment of acne or hirsutism

L70 Acne

L68.0 Hirsutism

Improved bone mineral density

M81.0 Osteoporosis

Treatment of bleeding due to leiomyomas

D25.x Leiomyoma of uterus

Treatment of pelvic pain due to endometriosis

N80.x Endometriosis

E28.2 PCOS (polycystic ovarian syndrome)

ANNEX 2.2 Variables collected in IMS databases

Characteristics	**Variable**	**Collected in database (Y/N/partial)**
Demography	Year of birth	Y
	Age (year) at index date	Y
	Sex	Y
	Ethnicity	N
	Socioeconomic status	Partial
	Marital status	Partial
Clinical data	Height	Partial
	Weight	Partial
	BMI	Partial
	Blood pressure (diastolic. systolic)	Partial
	Heart rate	Partial
	Waist circumference	Partial
Risk factor assessments	Smoking status	Partial
	Number of cigarettes / days	Partial
	Alcohol drinker	Partial
	Level of alcoholism	Partial
Treatment prescriptions	National codification for drug code	Y
	Brand name	Y
	Strength	Y

	Molecule	Y
	ATC Code	Y
	NB dose/pack	Y
	Date of prescription	Y
	Treatment duration in days OR Treatment duration in packs	Y
Characteristics	**Variable**	**Collected in database (Y/N/partial)**
	renewals prescriptions	Y
	Daily dose	Y
Diagnosis and medical history	Diagnosis linked to the prescription	Y
	Date of diagnosis	Y
	Comorbidities	Y
	Patient medical and family medical history	Y
Healthcare utilization	Referrals to specialist care	Ya
	Hospitalization (for any cause)	Ya
	Cause of hospitalization	Ya
Laboratory tests	Prescriptions	Y
	Test results	Ya
Imaging	Prescriptions	Ya
	Test results	N
Death	Death date	N

	Cause of death	N
Physician	Physician age	N
	Physician gender	Y
	Physician practice region	Y

a-not mandatory.

ANNEX 2.3 Venous thromboembolism outcome definitions

1. VENOUS THROMBOEMBOLISM OUTCOME DEFINITIONS

Patients will be identified as having a VTE outcome if they had at least one of the diagnosis codes that also met the corresponding place of service and diagnosis location criteria.

Venous Thromboembolic Event (VTE)

VTE, defined as deep venous thrombosis (DVT) and/or pulmonary embolism (PE) *ICD-10-CM codes*:

Deep Venous Thrombosis (DVT)

I80.1 Phlebitis and thrombophlebitis of femoral vein

I80.2 Phlebitis and thrombophlebitis of other deep vessels of lower extremities

I80.3 Phlebitis and thrombophlebitis of lower extremities, unspecified

Pulmonary Embolism (PE)

I26 Pulmonary Embolism

ANNEX 2.4 Arterial Thromboembolic event

Patients will be identified as having a CV outcome if they had at least one of the diagnosis codes that also met the corresponding place of service and diagnosis location criteria.

Arterial Thromboembolic events (ATEs)

Arterial thromboembolic events (ATEs), including acute myocardial infarction (AMI), ischemic stroke (IS) and cerebrovascular accidents (CVA) *ICD-10-CM codes:*

Acute myocardial infarction (AMI)

I21	Acute myocardial infarction

Stroke

I60	Subarachnoid haemorrhage
I61	Intracerebral haemorrhage
I63	Cerebral infarction
I64	Stroke, not specified as haemorrhage or infarction

ANNEX 2.5 Gynaecological Cancers

Gynaecological cancers will be identified for women if they had the following diagnosis codes, or procedures.

Gynaecological Cancers

ICD-10-CM codes:

Breast cancer

C50	Malignant neoplasm of breast

Cervical cancer

C53	Malignant neoplasm of cervix uteri

Endometrial cancer

C54.1	Malignant neoplasm of corpus uteri, Endometrium

Ovary cancer

C56 Malignant neoplasm of ovary

ANNEX 2.6 EphMRA ATC: Anti-Diabetic

THERAPIES

EphMRA ATC: ANTI-DIABETIC THERAPIES	
A10H	Sulphonylurea
A10J	Biguanide
A10J1	Biguanide, plain
A10J2	Biguanide/sulphonylurea
A10J9	Biguanide combinations, other
A10K	Glitazone (i.e. Thiazolidinedione)
A10K1	Glitazone, plain
A10K2	Glitazone/sulphonylurea
A10K3	Glitazone/biguanide
A10K9	Glitazone combinations, other
A10L	Alpha-glucosidase inhibitor
A10M	Glinide
A10M1	Glinide, plain
A10M3	Glinide/biguanide
A10M9	Glinide combinations, other
A10N	DPP-4 inhibitor
A10N1	DPP-4 inhibitor, plain
A10N3	DPP-4 inhibitor/biguanide

A10N9	DPP-4 inhibitor combinations, other
A10P	SGLT2 inhibitor
A10P1	SGLT2 inhibitor, plain
A10P3	SGLT2 inhibitor/biguanide
A10P5	SGLT2 inhibitor/DPP4 inhibitor
A10P9	SGLT2 inhibitor combination, other
A10X	Other (includes the injectable amylin analog/pramlintide)
A10X1	Anti-diabetic multitherapy combinations

ANNEX 2.7 Pregnancy identification and outcome definitions

Pregnancy and pregnancy outcomes will be identified for women if they had at least one of the diagnosis codes, or procedures.

Pregnancy Identification &Outcomes

ICD-10-CM codes:

Pregnancy diagnosis codes

Z32.1	Pregnancy confirmed
Z34.X	Supervision of normal pregnancy
Z35.X	Supervision of high-risk pregnancy
Z36.X	Antenatal screening
Z37.X	Outcome of delivery
Z38.X	Liveborn infants according to place of birth

Delivery diagnosis codes

080-084	Outcome of delivery

Pregnancy with abortive outcome

000	Ectopic pregnancy
001	Hydatidiform mole
002	Other abnormal products of conception

003	Spontaneous abortion
004	Medical abortion
005	Other abortion
006	Unspecified abortion
007	Failed attempted abortion
008	Complications following abortion and ectopic and molar pregnancy