Title: A drug utilisation study to assess the effectiveness of risk minimisation measures and describe the prescribing practices of Doreta SR and tramadol/paracetamol combinations in Europe

Study number: KKLR402019

February 23, 2023, Version 4

Krka, d. d., Novo mesto

Protocol Approval and Sign-off

I confirm that I have read the contents of this protocol and its attachments. I approve the protocol in its current form.

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For PASS Studies only

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PASS Information

Title	A drug utilisation study to assess the effectiveness of risk minimisation measures and describe the prescribing practices of Doreta SR and tramadol/paracetamol combinations in European countries
Protocol version identifier	Version 4
Date of last version of protocol	23 February, 2023
EU PAS register number	The study will be registered as a category 3 study at the time of the final protocol submission
Active substance	Tramadol and paracetamol, ATC code: N02AJ13 Pharmacotherapeutic group: analgesics, other opioids in combination with non-opioid analgesics
Medicinal product (s)	DORETA SR, DORETA and all oral fixed-dose combinations of tramadol hydrochloride and paracetamol
Product reference	Not applicable, the product is not centrally authorised.
Procedure number	HU/H/0190/003/DC
Marketing authorisation holder(s)	Krka, d. d., Novo mesto
Joint PASS	No
Research questions and objectives	**Research question:** This study aims to describe the prescribing practices before and after the implementation of the RMMs for Doreta SR (i.e., changes in the Product Information, changes in the product packaging and dissemination of Direct Healthcare Professional Communication [DHPC]). **Primary objective:** To describe the use of Doreta SR and immediate-release fixed dose combinations of tramadol/paracetamol pre-RMM and post-RMM implantation in 3 European countries
Country(-ies) of study	Czech Republic, Hungary, and Poland
Author	Leila Karimi MD, MSc, DSc, IQVIA Real World Evidence Solutions Supervised by: Massoud Toussi, MD, MSc, PhD, IQVIA Real World Evidence Solutions

Marketing Authorisation Holder(s)

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This protocol contains confidential information that should only be disclosed to those persons responsible for execution and organization of the study and on condition that all such persons agree not to further disseminate it.

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2. List of Abbreviations

Abbreviation	Definition
ADR	Adverse Drug Reaction
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
CI	Confidence interval
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures – Human
DHPC	Direct Healthcare Professional Communication
DUS	Drug Utilisation Study
DRG	Diagnoses-related Group
EDC	Electronic Data Capture
EMA	European Medicines Agency
EphMRA	European Pharmaceutical Marketing Research Association
FDC	Fixed-Dose Combination
GDPR	General Data Protection Regulation
GVP	Good Pharmacovigilance Practice
ICD	International Classification of Diseases
ICPM	International Classification of Procedures in Medicine
IQR	Interquartile Range
IR	Immediate Release
LRx	Longitudinal Prescription Data
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
NFC	New Form Classification
NHIF	National Health Insurance Fund (Administration Hungary)
OTC	Over the Counter
PRAC	Pharmacovigilance Risk Assessment Committee
RMMs	Risk Minimisation Measures
RX	Recipe (the Latin word)
SAP	Statistical Analysis Plan
SD	Standard Deviation
SR	Sustained Release
TBD	To Be Determined

3. Responsible Parties

Responsible Party	Name and Affiliation
MAH	Krka, d. d., Novo mesto
Principal Investigator	Dorothea von Bredow, PhD, Engagement Manager EMEA Real World Methods and Evidence Generation IQVIA
IQVIA project team	• Scientific oversight: Massoud Toussi, MD, MSc, PhD; Real World Evidence Solutions • Lead Epidemiologist Leila Karimi MD, MSc, DSc; Associate Director IQVIA Real World Evidence Solutions

4. Abstract

Full study title: A drug utilisation study to assess the effectiveness of risk minimisation measures and describe the prescribing practices of Doreta SR and tramadol/paracetamol combinations in European countries

Rationale and background:

Doreta SR (SR, sustained-release) (Krka, d. d., Novo mesto) is a fixed-dose combination (FDC) drug containing 75 mg of tramadol hydrochloride and 650 mg of paracetamol in the form of prolonged-release tablets. Due to the prolonged-release properties, Doreta SR enables convenient twice-daily dosing and offers more consistent pain relief without the need of dosing during night-time compared to the immediate-release (IR) FDC of tramadol hydrochloride and paracetamol. In 2015/2016, Doreta SR was granted a marketing authorisation (MA) in 11 EU Member States (Hungary (Reference Member State), Slovenia, Slovakia, Czech Republic, Lithuania, Latvia, Estonia, Bulgaria, Romania, Poland and Portugal). However, the nature of the formulation and the resulting altered pharmacokinetic properties of paracetamol make overdoses with prolonged -release paracetamol difficult to treat with the standard antidote typically used for IR paracetamol overdoses. Massive overdose with prolonged-release paracetamol can result in a prolonged and unpredictable pattern of paracetamol absorption. Standard treatment guidelines for overdose of immediate-release paracetamol are not designed for these extended periods of absorption. In February 2018, the marketing authorisations of the medicinal products containing prolonged-release paracetamol were suspended by the European Commission (C (2018) 1151 final). Consequently, Doreta SR was withdrawn from all EU markets.

The European Commission has declared that lifting of the suspension of MA is possible if the marketing-authorisation holders (MAHs) can provide evidence in support of proportionate, feasible and effective measures to prevent the risk of overdose and minimise the risk of hepatic injury following intentional or accidental overdoses with prolonged-release paracetamol-containing products.

In June 2019, Krka obtained scientific advice from the competent authority in the Reference Member State, the Hungarian National Institute of Pharmacy and Nutrition (OGYÉI) with the intention to lift the suspension of MA in all affected EU markets. Krka proposed several risk minimisation measures (RMMs) (i.e., changes in the product information, changes in the product packaging and dissemination of Direct Healthcare Professional Communication [DHPC]). With respect to intensive monitoring, the OGYÉI commented that reporting of overdose or any ADR in general is very poor and the information collected does not provide a real-world overview. Therefore, the OGYÉI condition for lifting the MA suspension for Doreta SR is if a Drug Utilisation Study (DUS) will be conducted in at least 3 EU member states post lifting of the suspension. This study will allow obtaining an insight into the prescribing practices of Doreta SR and partially the effectiveness of implemented risk minimisation measures.

Research question and objectives:

This study aims to describe the prescribing practices before and after the implementation of RMMs for Doreta SR proposed by the MAH (i.e., changes in the product information, changes in the product packaging and dissemination of Direct Healthcare Professional Communication [DHPC]).

Primary objectives:

To describe the use of Doreta SR and IR FDCs of tramadol/paracetamol pre- and post-RMM implementation in terms of:

• Total dose dispensed

• Indication of the dispensed prescriptions

• Total dose dispensed per indications

• Duration of dispensed prescriptions per treatment

• Comorbidities

• Concomitant dispensed prescriptions (other paracetamol-containing products and other analgesics, drugs with known interactions with oral fixed-dose combinations of tramadol hydrochloride and paracetamol).

Secondary objectives:

• To describe the demographic characteristics of patients prescribed with Doreta SR and IR FDCs of tramadol/paracetamol pre- and post-RMM.

• To describe the characteristics of prescribers of Doreta SR and IR FDCs of tramadol/paracetamol pre- and post-RMM.

Study design:

This is a cross-sectional pre-post, drug utilisation study conducted using secondary data in outpatient settings. It consists of 2 distinct study periods: pre-RMM period and post-RMM period.

The pre-RMM period is defined from the date of the first launch to the date of suspension of Doreta SR in each country as follows:

• Czech Republic: December 2016 to April 2018.

• Hungary: March 2017 to March 2018

• Poland: February 2016 to March 2018

The post-RMM period will start from the start date of re-launch of Doreta SR, 5, 9, and 12 March 2021 in Poland, Hungary, and the Czech Republic, respectively, and continue for18 months.

Population:

Any dispensed prescriptions of oral FDCs of tramadol/paracetamol during the study periods.

Sub-population:

- Doreta SR
- IR FDCs of tramadol/paracetamol

Variables*:*

The exposure is defined as any dispensed prescriptions of Doreta SR and IR FDC of tramadol /paracetamol containing products during the study period. The brand names will only be used for the definition of Doreta SR. IR FDCs of tramadol/paracetamol will be considered at the substance level as one sub-population only.

Exposure will be described by active substance, dispensing date, dispensed drug quantity (mg), pack size or days of supply, form, strength, recommended dose (if available).

The following variables will also be considered: indications for dispensed prescriptions, concomitant diagnoses in dispensed prescriptions, concomitant prescriptions, age and gender of patients as mentioned on the dispensed prescriptions (if available), and the specialty and work setting of prescribers as mentioned on the dispensed prescriptions (if available).

Data Sources:

The following established pharmacy data in Poland and the claims data in Hungary and Czech Republic will be utilised for data extraction:

- Czech Republic: IQVIA Longitudinal Prescription Data (LRx); claims database
- Hungary: National Health Insurance Fund Administration (NHIF)
- Poland: IQVIA LifeLink database

Study size:

All FDC tramadol/paracetamol in pre-defined periods of the selected databases will be included in the analysis.

The Doreta SR dispensing data was checked in the selected databases and ranged from 110,000 - 120,000 in Hungary, 116,000 - 120,000 in the Czech Republic to 26,000 – 270,000 in Poland in the pre-RMM periods. If we consider maximum uncertainty (50%), the estimated sample size (the Doreta SR dispensing data) in the target countries will provide a precision of 1%. As the proportions are not known in advance, we consider them to be 50%. Such a hypothesis yields the most conservative i.e., the largest sample size. Consequently, the required sample size for a proportion of 50% with a precision of 5% would be 384 Doreta SR and 384 immediate release FDCs of

tramadol/paracetamol dispensed prescriptions in each country (Czech Republic, Hungary and Poland) and each period (pre-RMM and post-RMM periods).

Data analysis:

The statistical unit for all the statistical analyses will be the dispensed prescription. Continuous variables will be presented as means with standard deviation (SD) and as medians with interquartile range (IQR), where appropriate. Categorical variables will be presented as counts (n), proportions (%) with 95% confidence interval (CI), where relevant. Results for the pre-RMM and post-RMM periods will be presented separately. All analyses will be descriptive and stratified by sub-populations and country. A statistical analysis plan (SAP) will be developed and will describe all planned analyses in detail, along with any specifications for tables, listings, and figures to be produced. Missing data will not be replaced. All analyses will be performed using appropriate statistical software (i.e., SAS® Version 9.4 or later, or similar relevant software). A report summarising the results of the study will be developed.

Milestones:

Registration in the EU PASS register: The study will be registered as a category 3 study, as per GVP Module V, at the time of the final protocol submission/approval.

Start of data collection (pre-RMM period): Q1 2023

End of data collection (pre-RMM period): Q1 2023

Start of data collection (post-RMM period): Q1 2023

End of data collection (post-RMM period): Q1 2023

Final report of study results: 30 June 2023

5. Amendments and Updates

Section	Updates
Protocol V2 (22 June 2021) Krka informed IQVIA about the start date of re-launch of Doreta SR, (the post-RMM periods), consequently the protocol was updated.	
4. Abstract	The post-RMM periods was defined as: "The post-RMM period will start from the start date of re-launch of Doreta SR, 5, 9, and 12 March 2021 in Poland, Hungary, and the Czech Republic, respectively, and continue for18 months." The duration of the study was emendated as 18 months The milestones were updated.
6. Milestones	Start of data collection (pre-RMM period): Q4 2022 End of data collection (pre-RMM period): Q4 2022 Start of data collection (post-RMM period): Q4 2022 End of data collection (post-RMM period): Q4 2022 Final report of study results: Q2 2023
9.2.3 Study Time Period	The post-RMM periods and the duration of the study were updated.
Figure 1	Following the update of the post-RMM periods, the F**igure 1** and the footnote were updated.
Protocol V3 (19 January 2022): Data for the post-RMM period will not be available from the IQVIA LifeLink in Hungary, therefore, data from National Health Insurance Fund (NHIF) Administration in Hungary will be used for both pre- and post-RMM periods.	
2. List of Abbreviations	Following the update of the protocol, three new abbreviations were added.

4. Abstract	National Health Insurance Fund (NHIF) Administration will be used in Hungary. Estimated size of the Doreta SR dispensed prescriptions in the pre-RMM period for Hungary was updated. Following the update of the data source in Hungary, the milestones were updated.
6. Milestones	Start of data collection (post-RMM period): Q1 2023 End of data collection (post-RMM period): Q1 2023 Final report of study results: 30 June 2023
9.3.1 Exposures	Some minor editorial corrections were applied
9.4 Data Sources	Following the update of the data source in Hungary, this section was updated.
9.4.1 Database Details	Following the update of the data source in Hungary, the detail information about the NHIF database was added to the protocol. In **Table 1**, summary of the information about the NHIF database was updated. Some minor editorial corrections were applied.
9.5.1 Feasibility	In **Table 3**, the related information, the name of database and estimation of the Doreta SR dispensed prescriptions in the pre-RMM period for Hungary, was updated.
9.7.3.1 Patient characteristics as mentioned on dispensed prescriptions	Following the update of the data source in Hungary, this section was updated, age range and gender are available in the NHIF.
9.9.2 Limitation of data sources	Following the update of the data source in Hungary, the limitations of the data source in Hungary was updated.

13.References	Following the update of the data source in Hungary, the references list was updated.
Protocol V4 (9 February 2023): Data from the IQVIA Diagnostic Insights database in the Czech Republic will not be available, therefore, data from IQVIA LRx claims database in the Czech Republic will be used for both pre- and post-RMM periods.	
2. List of Abbreviations	Following the update of the protocol, one new abbreviation was added.
4. Abstract	IQVIA LRx claims database will be used in the Czech Republic. Estimated size of the Doreta SR dispensed prescriptions in the pre-RMM period for the Czech Republic was updated.
Milestone.	Start and end dates of data extraction for pre-RMM period were updated :
9.4 Data Sources	Following the use of the IQVIA LRx claims database in the Czech Republic, this section was updated.
9.4.1 Database Details	The detail information about IQVIA LRx claims database was added to the protocol. In **Table 1**, summary of the information about the IQVIA LRx claims database was updated.
9.5.1 Feasibility	In **Table 3**, the related information, the name of database and estimation of the Doreta SR dispensed prescriptions in the pre-RMM period for the Czech Republic, was updated.
9.7.3.1 Patient characteristics as mentioned on dispensed prescriptions	Following the use of the IQVIA LRx claims database in the Czech Republic, this section was updated.

9.9.2 Limitation of data sources	Following the use of the IQVIA LRx claims database in the Czech Republic, the limitations of the data source have been updated.

6. Milestones

Milestone	Planned date
Registration in the EU PASS register	The study will be registered as a category 3 study, as per GVP Module V, at the time of the final protocol submission/approval.
Start of data collection (pre-RMM period)	Q1 2023
End of data collection (pre-RMM period)	Q1 2023
Start of data collection (post-RMM period)	Q1 2023
End of data collection (post-RMM period)	Q1 2023
Final report of study results	30 June 2023

The final study timelines will depend on the actual outcomes of the regulatory procedures, agreed periods of the RMM implementation and the re-launch of Doreta SR in the target markets.

7. Rationale and Background

Doreta SR (SR, sustained-release) (Krka, d. d., Novo mesto) is a fixed-dose combination (FDC) drug containing 75 mg of tramadol hydrochloride and 650 mg of paracetamol in the form of prolonged-release tablets. It is indicated for symptomatic treatment of moderate to severe pain in adults and adolescents over the age of 12 years. Its use should be restricted to patients whose moderate to severe pain can be treated with a combination of tramadol and paracetamol and who would benefit from the use of a prolonged-release formulation. Tramadol is an opioid pain medication that is used to treat moderate to severe pain. Paracetamol is a mild analgesic used in combination with opioid pain medications such as tramadol, to treat moderate to severe pain. Due to the prolonged-release properties, Doreta SR enables convenient twice-daily dosing and offers more consistent pain relief without the need of dosing during night-time compared to the immediate-release (IR) FDC of tramadol hydrochloride and paracetamol. In 2015/2016, Doreta SR was granted a marketing authorisation (MA) in 11 EU Member States (Hungary (Reference Member State), Slovenia, Slovakia, Czech Republic, Lithuania, Latvia, Estonia, Bulgaria, Romania, Poland, and Portugal). It is the only registered prolonged-release formulation of the two ingredients in these countries up to this date, except for Portugal, where other formulations were also registered. The maximum allowed daily dose of Doreta SR is four tablets per day (equivalent to 300 mg tramadol hydrochloride and 2600 mg paracetamol).

Safety concerns for prolonged-release paracetamol-containing products

Acute overdoses of paracetamol may lead to serious adverse events (AEs) including, most importantly, hepatotoxicity, which can lead to liver failure and death within days. The nature of the formulation and the resulting altered pharmacokinetic properties of paracetamol makes overdoses with prolonged-release paracetamol difficult to treat in emergencies with the standard antidote typically used for immediate-release paracetamol overdoses.

Massive overdose with prolonged-release paracetamol can result in a prolonged and unpredictable pattern of paracetamol absorption. Standard treatment guidelines for the overdose of immediate-release paracetamol are not designed for these extended periods of absorption.

An Article 31 referral procedure (EMEA/H/A-31/1445) was triggered by Sweden in July 2016, reporting on overdose cases with prolonged-release paracetamol as a single ingredient. (1) In December 2017, the CMDh (Coordination Group for Mutual Recognition and Decentralised Procedures - Human) endorsed a European Medicines Agency (EMA) recommendation to suspend marketing of prolonged- or prolonged-release products containing paracetamol. The recommendation was made by the Pharmacovigilance Risk Assessment Committee (PRAC) at the EMA. The CMDh and the PRAC decided that the advantages of a longer-acting product do not outweigh the complications of managing an overdose of the medicine. In February 2018, the marketing authorisations of the medicinal products containing prolonged-release paracetamol were suspended by the European Commission (C (2018) 1151 final) (2). Consequently, Doreta SR was withdrawn from all EU markets.

Re-launch and requirements for lifting the marketing authorisation suspension

The European Commission has declared that lifting of the suspension of MA is possible if the marketing-authorisation holders (MAHs) can provide evidence in support of proportionate, feasible and effective measures to prevent the risk of overdose and minimise the risk of hepatic injury following intentional or accidental overdoses with prolonged-release paracetamol-containing products. In June 2019, Krka obtained scientific advice from the competent authority in the Reference Member State, the Hungarian National Institute of Pharmacy and Nutrition (OGYÉI), with the intention to lift the suspension of MA in all affected EU markets. Krka proposed several risk minimisation measures (RMMs) (3), of which the following seemed acceptable to the OGYÉI:

1. Changes in Doreta SR product information, sections 4.1, 4.2, 4.4, and 4.9:

- Narrowing the indication for use
- Strengthen the warnings regarding the safe use of Doreta SR
- Additional information/instructions for treatment in case of overdose

2. Changing the outer packaging design to distinguish clearly between the IR (Immediate Release) and the prolonged-release formulations

3. Additional warning on the outer package regarding the concomitant use of any other paracetamol-containing product

4. Distribution of Direct Healthcare Professional Communication (DHPC) to Poison Information Centres and hospitals with the recommendation for managing overdose

5. Distribution of Direct Healthcare Professional Communication (DHPC) to prescribers including information on risk minimisation measures to help safer use of Doreta SR

6. Intensive monitoring of Doreta SR use, including:

- Collection of overdose cases through spontaneous reports supplemented with targeted follow-up
- Active collection of data from the Poison Information Centres in Hungary, Poland, and Slovenia
- Regular search of literature and EudraVigilance for any new significant safety information/ADRs (adverse drug reactions)
- Monthly evaluation of all collected overdose cases and reporting to concerned authorities in case of essential safety findings
- Reporting of all cases of overdose to the EMA and/or other regulatory agencies
- Evaluation of the safety profile of all Krka's tramadol/paracetamol combinations focusing on overdose cases every six months and submission of findings to concerned authorities

With respect to intensive monitoring, the OGYÉI commented that reporting of overdose or any ADR in general is very poor and the information collected does not provide a real-world overview. Therefore, the OGYÉI condition for lifting the MA suspension for Doreta SR is if

a Drug Utilisation Study (DUS) will be conducted in at least 3 EU member states post lifting of the suspension. While it is admitted that the present study does not provide any information about overdoses or ADRs, it will allow obtaining an insight into the prescribing practices of Doreta SR and partially the effectiveness of implemented risk minimisation measures.

This DUS will be conducted according to the Guideline on good pharmacovigilance practices (GVP) (4)- Module VIII (Rev 3) dated 9 October 2017 (EMA/813938/2011 Rev 3).

8. Research Questions and Objectives

This study aims to describe the prescribing practices before and after the implementation of RMMs for Doreta SR proposed by the MAH (i.e., changes in the Product Information, changes in the product packaging and dissemination of Direct Healthcare Professional Communication [DHPC]).

8.1 Primary Objectives

To describe the use of Doreta SR and IR FDCs of tramadol/paracetamol during pre- and post-RMM implementation in terms of:

- Total dose dispensed
- Indication of the dispensed prescriptions
- Total dose dispensed per indication
- Duration of dispensed prescriptions per treatment
- Comorbidities
- Concomitant prescriptions
    - Other paracetamol-containing products
    - Other analgesics
    - Drugs with known interactions with oral fixed-dose combinations of tramadol hydrochloride and paracetamol

8.2 Secondary Objectives

- To describe patients' demographic characteristics treated with Doreta SR and IR FDCs of tramadol/paracetamol during pre- and post-RMM.

- To describe the prescriber characteristics of Doreta SR and IR FDCs of tramadol/paracetamol pre- and post-RMM.

8.3 Exploratory Objective

None

9. Research Methods

9.1 Study Design

The drug utilisation study is a cross-sectional pre-post, conducted using secondary data in outpatient settings. It consists of two distinct study periods: pre-RMM period and post-RMM period.

9.2 Setting

9.2.1 Source Population

Electronic dispensed pharmacy data from three European countries, Czech Republic, Hungary, and Poland.

9.2.2 Study Population

Any dispensed prescriptions of oral FDCs of tramadol/paracetamol during the study periods (see below).

9.2.3 Study Time Period

The pre-RMM period is defined from the date of the first launch to the date of suspension of Doreta SR in each country as follows:

- Czech Republic: December 2016 to April 2018
- Hungary: March 2017 to March 2018
- Poland: February 2016 to March 2018

The post-RMM period will start from the start date of re-launch of Doreta SR, 5, 9, and 12 March 2021 in Poland, Hungary, and the Czech Republic, respectively, and continue for18 months. The distribution of the DHPC has been initiated the end December 2020, 11 March 2021, and the end of February 2021 in Poland, Hungary, and the Czech Republic, respectively.

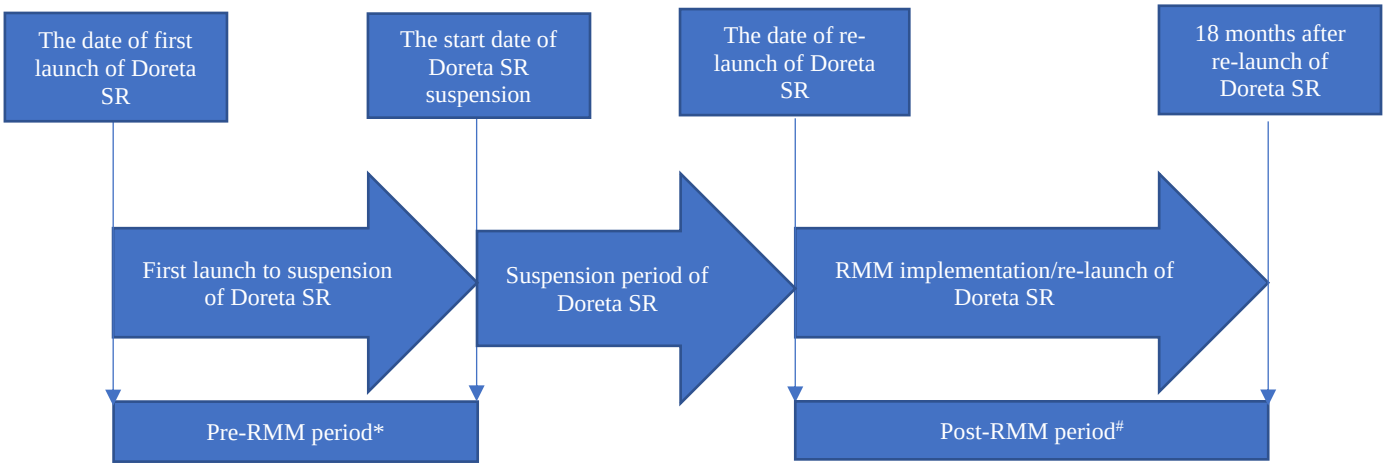

Figure 1: **Study periods**

*December 2016 to April 2018, March 2017 to March 2018, and February 2016 to March 2018 in the Czech Republic, Hungary, and Poland, respectively. #The post-RMM period will be 18 months and it will start from 5, 9, and 12 March 2021 in Poland, Hungary, and the Czech Republic, respectively.

9.2.4 Index Date

Not Applicable

9.2.5 Follow-up Period and Censoring

Not Applicable

9.2.6 Case Definition

Not Applicable

9.2.7 Patient Selection

All statistical units in this study will be dispensed prescriptions.

9.2.7.1 Inclusion Criteria

Any dispensed prescriptions of oral FDCs of tramadol/paracetamol during the study periods.

9.2.7.2 Exclusion Criteria

None

9.2.8 Sub-Populations

- Doreta SR
- IR FDCs of tramadol/paracetamol

9.3 Variables

In order to meet the objectives of the DUS, the selection of variables was done as far as they are captured in established data sources.

9.3.1 Exposures

Exposures will be any dispensed prescription of oral FDCs of tramadol/paracetamol (Doreta SR or IR FDCs of tramadol/paracetamol) with Anatomical Therapeutic Chemical (ATC) code: N02AJ13, during one of the pre-defined study periods. Brand names (only for Doreta SR), and generics are considered. IR FDCs of tramadol/paracetamol will be considered at the substance level as one sub-population only (ATC code N02AJ13).

Exposure will be described by dispensing date, duration, and (average) daily dose, and will be reported for each substance.

The following variables regarding the exposure will be extracted from the data sources:

- Active substance
- Date of dispensed prescriptions (if available)
- Pack size or days of supply
- Strength
- Form
- Recommended dose (if available)
- Drug quantity in dispensed prescriptions (mg)

9.3.2 Paracetamol containing drugs

- Paracetamol containing drugs (ATC code: N02BE)

9.3.3 Analgesics

- Opioids (ATC code: N02A)
- Other analgesics and antipyretics (ATC code: N02B)
- Antimigraine preparations (ATC code: N02C)

The details of ATC codes are presented in Annex 3.1.

9.3.4 Drugs with known interactions with FDC of tramadol/paracetamol

Doreta SR is must not be taken together with the following (5)**:**

- Monoamine oxidase inhibitors (MAOIs)

Doreta SR is not recommended to be taken with the following (5)**:**

- Carbamazepine, commonly used to treat epilepsy or facial neuralgia (severe pain attacks in the face)
- Opioid-type pain relievers, used to treat moderate to severe pain, e.g., buprenorphine, nalbuphine and pentazocine.

The details ATC codes are presented in Annex 3.2.

9.3.5 Outcomes

9.3.5.1 Primary Outcomes

- Total dose dispensed
- Indications for dispensed prescriptions
- Total dose dispensed in mg per indications for dispensed prescriptions
- Duration of dispensed prescriptions per treatment (in days)
- Concomitant diagnoses in dispensed prescriptions
- Concomitant prescriptions:
  - Other paracetamol-containing products
  - Other analgesics
  - Drugs with known interactions with tramadol, paracetamol, or both

9.3.5.2 Secondary Outcomes

- Patient characteristics as mentioned on the dispensed prescriptions
  - Age

- Gender
- Prescriber characteristics as mentioned on the dispensed prescriptions (when available)
  - Speciality
  - Work setting

9.3.5.3 Tertiary Outcomes

None

9.3.6 Other Variables

None

9.4 Data Sources

In the Czech Republic, IQVIA LRx claims database will be used. It consists of electronic data capture (EDC) of prescription details from primary care practices and specialists in real-life setting.

In Hungary, NHIF Claims database, highly trusted solution with detailed patient level insights on patient journey covering 100% of population will be used. The NHIF Claims database contains detailed provision data (medicine, out- and inpatient services) from the whole Hungarian population of 9,797,561 subjects (Hungarian Central Statistical Office data, 2017). Retrospective analyses include data from 1 January 2008.

In Poland, IQVIA LifeLink will be used. It is a database of longitudinal records of prescribed and dispensed prescriptions at the patient level collected from retail pharmacies.

Table 1: Summary of databases considered for the DUS

Country	**Czech Republic**	**Hungary**	**Poland**
Name /type of the data source	**IQVIA LRx claims**	**NHIF Claims**	**IQVIA LifeLink**
Size of the panel	~20% of population	100% of the general population	28 million patients out of ~38 million citizens
Data available since	2015	2008	2012
Data refresh time	3-4 months lag	2-3 months lag	Monthly
Brand name	Available	Available	Available
Dispensed drug quantity	Available	Available	Available
Dispensed drug form	Available	Available	Available
Dispensed drug strength	Available	Available	Available
Dispensed drug pack size	Available	Available	Available
Method of drug administration	Not available	Available	Available
Rx dispensed date	Available	Available	Prescription issue date not available Rx purchase date available
Indication of the prescriptions of Doreta SR or IR FDCs of tramadol/paracetamol	ICD-10, 5%	ICD-10	Not available
Co-diagnosis of the prescriptions of Doreta SR or IR FDCs of tramadol/paracetamol	ICD-10 level but with partial coverage: 23% of transactions	ICD-10	Not available
Concomitant prescription of any other paracetamol product	ATC, dispensing date	ATC, dispensing date	ATC, dispensing date

Concomitant prescription of any other analgesics	ATC, dispensing date	ATC, dispensing date	ATC, dispensing date
Concomitant prescription of drugs with known interactions with FDCs of tramadol/paracetamol	ATC, dispensing date	ATC, dispensing date	ATC, dispensing date
Age	Age range	Age range	Age range
Gender	Partially available, coverage: 8% of transactions	Available	Available
Prescriber specialty	Available	Available	Available
Prescribers' work setting (hospital, office)	Not available	Not available	Available

9.4.1 Database Details

Czech Republic: IQVIA LRx claims database

IQVIA LRx claims database represents a selection of Czech Republic payers' data on reimbursed prescription medications. There is currently coverage of approximately 20% of Czech Republic patients in LRx format, while another 68% is available only in the form of the number of patients/units sold monthly/quarterly/yearly for a given brand, WHO-ATC1-WHO-ATC5 code. Approximately 12% of patients have no data available at all.

The payer coverage has varied throughout the time slightly, but the core 20% has reliable and complete data back to the start of 2017 (Stable panel of 20% available from 2017, smaller coverage available from 2015).

- Products: A product's national medicine authority code (SUKL) is matched against the IQVIA product database, enabling full information, such as product brand, pack type, corporation, ATC group, strengths, Generics vs Originals and Biological vs non-Biological splits, and other information to be obtained about the product.
- Diagnoses: ICD-10 code can be attributed to each transaction; however, the rate of completeness is not consistent across the whole dataset: some ATC groups are closely to 100% filled, others (e.g., Doreta & IR FDCs) only in the range of 5%.
- Specialties: The specialty of prescribing HCP is filled in in the majority of cases

- Patient info: Age (grouped by 10), Gender (not fully filled in), their payer, region where the prescription was dispensed, potentially all patient prescribing history can be found.
- Patient ID and the information about which payers our panel covers cannot be shared with the client.

The IQVIA LRx claims database lags behind with 3-4 months.

The quality control steps will be specified as followings:

1. Panel fulfilment, verify correct recording of all collaborating payers who participated in the quarter is loaded correctly
2. Incomplete or out-of-reference data: the records are bridged to existing records within the International Classification of Diseases (ICD 10) or product references
3. Data consistency:
    - Check the correlation of product and diagnoses data about the patient's age and sex, for example, pregnancy in a man or a child
    - Check dosage to ensure that there are no discrepancies in the dosage, for example, intrauterine contraceptive on daily dosage

Hungary: NHIF Claims database

IQVIA proposes to use NHIF claim database's content, rules and possibilities for retrospective RWE research:

- Deep-dive offers 100% data coverage on reimbursed healthcare solutions and demographics in addition to straight dispensing
- Highly trusted results by key decision makers including NHIF, government
- NHIF data available since 2008 on patient level

NHIF's database structure:

- Demography database (gender, age range, date of death)
- Drug database (type of service (brand), date of service, ATC, volume, ICD, and territory)
- Inpatient and outpatient services database (date of service, place of service, ICD, Diagnoses-related Group [DRG], and International Classification of Procedures in Medicine [ICPM])
- Medical imaging procedures database (date of service, place of service, and ICD)

In order to protect patient privacy rights, NHIF has made his own provision:

Results could not be exported from the database if the count of individual data in the patient group is less than 10.

Data queries could not be focused for the sample of one: individual, physician, hospital and etc.

Although the NHIF database includes all the financed health-services, disease specific parameters are not registered, except age range and gender

Non-reimbursed services (e.g., over the counter medication) are not represented

The NHIF data service lags behind with 2-3 months.

Poland: IQVIA LifeLink

IQVIA LifeLink in Poland (6) is a database of computerized longitudinal records of dispensed prescriptions at the anonymized patient-level collected from retail pharmacies. IQVIA LifeLink was created in 2013, and data are updated monthly. The data are captured from approximately 6500 retail pharmacies representing coverage of 45% retail of the country (Dec 2019). The following information is available in the IQVIA LifeLink database:

• Drug therapy: prescribed and dispensed drugs (ATC-EPhMRA), substance, brand, manufacturer, form (NFC 123 classification), strength, quantity, pack size

• Other: realized reimbursement level, patient age, (only as categorical variable), and gender as mentioned on the prescriptions.

In brief, IQVIA pharmacy panel data provides input to many data services offered by IQVIA. Consequently, maintaining high quality and timely data delivery is vital for our operations and to ensure meeting the highest IQVIA standards. Also, the quality check algorithms are built-in processes of data collection.

Limitations: indication and co-diagnosis of the dispensed prescriptions are not available in Poland.

9.4.2 Linkage Methods

None

9.5 Sample Size

The study sample size estimates are based on the precision of the proportions of dispensed prescriptions of Doreta SR or immediate release FDCs of tramadol/paracetamol as mentioned below for each country and each period.

As the proportions are not known in advance, we consider them to be 50% (maximum uncertainty). Such a hypothesis yields the most conservative i.e., the largest sample size. Consequently, the required sample size for a proportion of 50% with a precision of 5% would

be 384 Doreta SR and 384 immediate release FDCs of tramadol/paracetamol dispensed prescriptions in each country (Czech Republic, Hungary and Poland) and each period (pre-RMM and post-RMM periods).

Calculation use the following formula (normal approximation):

$$e = \sqrt{\frac{p(1-p)}{n}} \times \varepsilon_{\alpha}$$

With n sample size, p observed percentage, εα 1.96 for 95% CI, *e* Precision.

Table 2: Required number of patients by acceptable precision

	Observed percentage (accuracy): p(1-p)				
Precision	**10%**	**20%**	**30% (70%)**	**40%**	**50% (50%)**
± 1.0%	3,458	6,147	8,068	9,220	9,604
± 2.0%	864	1,537	2,017	2,305	2,401
± 3.0%	384	683	896	1,024	1,067
± 4.0%	216	384	504	576	600
± 5.0%	139	246	323	369	384
± 6.0%	96	171	224	256	267
± 7.0%	71	125	165	188	196
± 10.0%	35	62	81	92	96

9.5.1 Feasibility

The sample sizes of the Doreta SR dispensed prescriptions in the pre-RMM period from each country have been estimated and described in table below. Accordingly, the study is deemed feasible for the pre-RMM period. Its feasibility for the post-RMM period depends on the market uptake of Doreta SR after its re-launch.

Table 3: Estimation of the Doreta SR dispensed prescriptions in the pre-RMM period

Country	**Czech Republic**	**Hungary**	**Poland**
Name /type of the data source	**IQVIA LRx claims database**	**NHIF Claims database**	**IQVIA LifeLink**
The pre RMM period	December 2016 - April 2018	March 2017 - March 2018	February 2016 - March 2018
Number of Doreta SR prescription (sell out) records in the pre-RMM period	116,000 - 120,000 prescriptions (transactions)	110,000 – 120,000	260,000 – 270,000

9.6 Data Management

The DUS will be conducted according to the Standard Operating Procedures (SOPs) of IQVIA's Primary Intelligence and IQVIA's Real-World & Analytics Solutions.

The processes for database management differ by country. Generally, the data are stored at the database level and analysed locally. High data quality standards will be maintained, and processes and procedures utilised to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis.

This study will follow relevant chapters of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (7) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (8) guidelines for data management.

9.7 Data Analysis

9.7.1 General Considerations

Given the study objectives, the analyses will be mainly descriptive and will be conducted by country, by study period (the pre-RMM and post-RMM periods) and by sub-population.

The statistical unit for all the statistical analyses will be the dispensed prescription. Continuous variables will be presented as means with standard deviation (SD) and as medians with interquartile range (IQR), where appropriate. Categorical variables will be presented as counts (n), proportions (%) with 95% confidence interval (CI), where relevant.

A statistical analysis plan (SAP) will be developed prior to data extraction, and will describe all planned analyses in detail, along with any specifications for tables, listings, and figures to be produced.

All analyses will be performed using appropriate statistical software (i.e., SAS® Version 9.4 or later, or similar relevant software). A report summarising the results of the study will be developed.

9.7.2 Main analyses

The main analysis will describe the practices prescribing Doreta SR and the IR FDC of tramadol/paracetamol during the pre-RMM and post-RMM periods. Descriptive statistics will be provided for the prescription, indication of treatment, co-diagnosis of treatment, use of other medication characteristics.

Categorical variables will be presented as counts (n), proportions (%), and 95 % CI when relevant. Continuous variables will be presented as means with SD and as medians with IQR, when appropriate.

In each study period, by country and by indication, the following analyses will be conducted in sub-population of drugs (i.e., Doreta SR or IR FDC tramadol/paracetamol)

9.7.2.1 Prescribing patterns

- **Total Dose prescribed**

The total dose prescribed will be analysed as a continuous variable separately for Doreta SR and IR FDC tramadol/Paracetamol based on the below calculation:

Dosage = Strength*Number of units (pills) dispensed

The total dose prescribed for Doreta SR and IR FDC tramadol/Paracetamol will also be calculated per indications for dispensed prescriptions.

- **Duration of dispensed prescriptions per treatment (in days)**

The average dispensed duration of treatment will be analysed as a continuous variable separately for Doreta SR and IR FDC tramadol/paracetamol based on directly captured daily dose information, whenever available.

9.7.2.2 Treatment indication

The main diagnosis for treatment will be analysed as counts (n) and proportion (%) separately for Doreta SR and IR FDC tramadol/Paracetamol based on directly using ICD10, if available.

As the indication of the prescription is not available in Poland, the proportions of dispensed prescriptions of Doreta SR (or IR FDCs of tramadol/paracetamol) by indication will be evaluated in the Czech Republic (only available for 5% of transactions) and Hungary.

9.7.2.3 Concomitant diagnoses

The co-diagnoses for treatment will be analysed as counts (n) and proportion (%) separately for Doreta SR and IR FDC tramadol/Paracetamol based ICD10 codes, if available.

The 20 most frequent co-diagnoses will be described in the results section.

9.7.2.4 Concomitant prescriptions

Concomitant prescriptions comprise of three separate categories as follows 1) other paracetamol- containing products, 2) other analgesics, and 3) drug with known interaction with tramadol/paracetamol (Annex 3.1 and 3.2). Concomitant prescriptions will be analysed as count (n) and proportion (%) separately for Doreta SR and IR FDC tramadol/Paracetamol based on directly using ATC codes, if available.

9.7.3 Secondary analyses

In order to provide more insights into the prescribing practice, we will report patient and prescriber characteristics, as mentioned on the prescriptions, separately for Doreta SR and IR FDC tramadol/Paracetamol, if available.

9.7.3.1 Patient characteristics as mentioned on dispensed prescriptions

- Age will be analysed as categorical variable (age range) separately for Doreta SR and IR FDC tramadol/Paracetamol based on directly captured daily dose information, if available.

- Gender will be analysed as counts (n), proportions (%) separately for Doreta SR and IR FDC tramadol/Paracetamol. In the Czech Republic, gender is only available for 8% of transactions.

The data used to describe the demographic characteristics of patients (age as continuous variable) and work settings of prescribers are not available in Hungary and the Czech Republic.

9.7.3.2 Prescriber characteristics as mentioned on dispensed prescriptions

- Type of speciality

- Work setting (hospital, office)

The data used to describe the work settings of prescribers are not available in Hungary and Czech Republic.

9.7.4 Handling of Missing Data

Due to the nature of real-world data, some data points might be missing from the databases for several reasons. The number and type of missing values will be recorded and reported in

the final study report. We report the missing data and do not use any imputation methods to replace them. Statistical calculations (i.e., the denominator) will be adjusted accordingly for the analysis.

9.7.5 Interim Analysis

None

9.8 Quality Control

The study will include existing databases, which are currently used widely for research purposes. The study will be executed in line with all applicable regulations and guidelines such as best-practice guidelines applicable to non-interventional DUS, including but not limited to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, the ENCePP Checklist for Study Protocols, and the Guidelines for Good Pharmacoepidemiology Practices of the International Society of Pharmacoepidemiology (ISPE GPP) as well as the specific IQVIA SOPs. All study programs, log files, and output files will be stored on the secure server.

9.8.1 IQVIA Quality Management System (QMS)

At the study level, all aspects of the study from protocol development to the reporting of the results are conducted within the work-frame of IQVIA Quality Management System (QMS) and in accordance with the appropriate global procedure.

A Quality Control checklist will be developed and executed for the study, which will include quality control on study methodology, statistical analysis plan, programming, data management and analysis, study results, conclusions and study report. Furthermore:

- The study Quality Control plan will establish ownership for the execution of the individual Quality Control steps. The principle of the independence of Quality Control applies
- Individuals responsible for the execution of specific Quality Control steps must have knowledge, capability and experience which are adequate for the task.
- The result of the execution of the individual steps of the Quality Control plan will be documented, and include the required corrective actions, if any.
- The execution of any required corrective action will be documented.

9.8.2 Approaches for Validating the Results

The quality control for validating the results will be conducted at three levels:

1. At the statistical analysis level: all data management and statistical analysis programs developed and used in the analysis will be documented. All versions generated will be dated, kept with accompanying documentation and archived. The original database will be stored. A derived database will be created for the new versions of the data in order to include recoding and computing of new variables, especially stratification of continuous variables, combination of modalities for categorical variables, calculation of composite indicators, etc.

2. At the results level, a data review will be done to ensure data integrity. A statistical analysis report including all the results will be provided for review and discussion. The final statistical report will consider the reviewers' comments.

3. At the study level, all aspects of the study will be conducted according to the SOPs of IQVIA Real World & Analytics Solutions. The study documents have been approved by people competent in medical and safety areas of IQVIA. According to the SOPs, an independent review of the DUS results and report will be conducted by a person who was not in charge of their preparation.

9.8.3 Record Retention

The MAHs must maintain an adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, documentation of IRB/EC and governmental approval/notification (if required) and study reports.

IQVIA will retain records and documents pertaining to the conduct of this study for at least five years after completion of the study, in accordance with IQVIA Standards. The length of storage can be extended based on MAH-specific SOPs or for the length of time required by relevant national or local health authorities, whichever is longer. After that period, the documents may be destroyed, subject to local regulations.

9.9 Strengths and Limitations of the Research Methods

9.9.1 Strengths

- The data sources have readily available data for the pre-RMM period, and future data for the post-RMM period will be collected routinely.
- The selected countries are the main market of Doreta SR.
- Coverage of these databases is substantially high in each target country.
- The study results are generalizable due to:
    - The comprehensive coverage data collection
    - The setting in which the data are being collected

- Compared with a study conducted through the electronic medical records containing prescriptions, in this DUS, all prescriptions are dispensed at the pharmacies; therefore, it is closer to real-life practice.

9.9.2 Limitation of data sources

- **Information on patient and prescriber characteristics**
  - Age of patients as continuous variable is not available. In addition, information on gender for patients are not fully available in the Czech Republic
  - Prescriber characteristics are not available in Hungary and the Czech Republic.
  - Indications and co-diagnosis of the dispensed prescriptions are not available in Poland and are not fully available in the Czech Republic
  - All information is at the prescription level and there is no linkage with patients' level, thus clinical information could be missed. But by design, we decided this study to be a prescription-based study rather than a patient-based study.
  - There is no linkage at patient level between prescriptions; therefore, the patients cannot be followed.
- **Misclassification of FDC tramadol/Paracetamol containing products**

The ATC codes are the same for Doreta SR and other IR FDC tramadol/Paracetamol containing products. This might result in misclassification of the Doreta SR if prescribers do not use the correct brand name; or if the pharmacy does not dispense the right brand name.

- **Data lag time**

The IQVIA LRx claims database in the Czech Republic lags behind with 3-4 months. The NHIF Claims databases used for Hungary lags behind with 2-3 months.

- **General limitation**

Finally, as discussed in the background, the present study does not provide any information about overdoses or ADRs; however, it is a valid method and can provide some insight into the prescription practice in the pre-RMM and post-RMM periods.

9.9.3 Other Aspects

9.9.4 Changes to the Protocol

None

9.9.5 Study Management

This study will be performed by IQVIA, with guidance, input, review and approval of the MAH, including development of materials, data management, analysis and reporting.

10. Protection of Human Subjects

This DUS is non-interventional, and analysis is based on secondary data use. No identifying data are collected in any of the planned approaches.

The study will be conducted in agreement with the regulation (EU) 2016/679 of the European Parliament on the protection of natural persons regarding the processing of personal data and on the free movement of such data (General Data Protection Regulation, GDPR).

Regulatory and ethical requirements will be followed in each country. The study will comply with the module VIII of the good pharmacovigilance practices (GVP).

Although EU Pharmacovigilance Directive (DIR 2010/84/EU) is a legal act, it does not carry the same binding force of a regulation; each Member State can determine how best to transpose the Directive into local legislation. As a result, the submission requirements for PASS vary throughout the EU, with some countries being more onerous than others. IQVIA includes experts dedicated to the review and advisement on the regulations and guidelines applicable to this study in the participating countries.

The study will be submitted to ethical review boards (ERBs) for approval wherever required by local law. Regulatory authorities will be notified, and approval sought as required by local laws and regulations. Progress reports will be submitted to ERBs and regulatory authorities as required by local laws and regulations.

10.1.1 Required submissions and approvals in the study target countries

All three databases are IQVIA intellectual property, therefore, no submissions and approvals are required in each target country.

11. Management and Reporting of Adverse Events/ Adverse Reactions

Pursuant to the EMA requirements for reporting of adverse events for secondary data (GVP module VI, VI.C.1.2.1.2), adverse event reporting will not be conducted as part of this study given the study objectives will be met using secondary data.

12. Plans for Disseminating and Communicating Study Results

The final report will be communicated to the OGYÉI according to the timelines. In accordance with the 2010 EU pharmacovigilance legislation, the protocol of this study will be entered the publicly available EU PAS register. Updates to the study protocol in case of substantial amendments and the final study report will also be entered in the register.

13. References

1. Salmonson H, Sjöberg G, Brogren J. The standard treatment protocol for paracetamol poisoning may be inadequate following overdose with modified release formulation: a pharmacokinetic and clinical analysis of 53 cases. Clin Toxicol (Phila). 2018 Jan;56(1):63–8.

2. COMMISSION IMPLEMENTING DECISION of 19.2.2018; https://ec.europa.eu/health/documents/community-register/2018/20180219139834/dec_139834_en.pdf.

3. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module XVI; https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-xvi-risk-minimisation-measures-selection-tools_en-3.pdf.

4. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies (Rev 3) [resource on the Internet]. 2017 [revision 13 October 2017; cited 05 September 2018]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf.

5. Public Assessment Report; Doreta SR; https://www.ogyei.gov.hu/kiseroirat/ph/ph_0000119267.pdf.

6. Kostev K, Kurylo P, Kosik J, Jacob L. One-Year Persistence with Donepezil, Memantine, and Rivastigmine in More than 66,000 Elderly Patients Followed in Poland. J Alzheimers Dis. 2019;70(3):899–905.

7. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology; EMA/95098/2010 Rev.7 http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml.

8. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH); https://www.ich.org/.

Annexes

Annex 1. List of stand-alone documents

Annex 2. ENCePP Checklist

Annex 3. Additional documents

Annex 1. List of stand-alone documents

None

Annex 2. ENCePP Checklist

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

EU PAS Register® number: **Study reference number (if applicable):**

Section 1: Milestones		**Yes**	**No**	**N/A**	**Section Number**
1.1	Does the protocol specify timelines for				6
	1.1.1 Start of data collection[1]	☒	☐	☐	6
	1.1.2 End of data collection[2]	☒	☐	☐	6
	1.1.3 Progress report(s)	☐	☐	☒	
	1.1.4 Interim report(s)	☐	☐	☒	
	1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
	1.1.6 Final report of study results.	☒	☐	☐	6

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Comments:

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
	2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
	2.1.2 The objective(s) of the study?	☒	☐	☐	8
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8, 9.2
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☐	☒	
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2, 9.4
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2
	4.2.2 Age and sex	☒	☐	☐	9.3
	4.2.3 Country of origin	☒	☐	☐	9.2
	4.2.4 Disease/indication	☒	☐	☐	9.3
	4.2.5 Duration of follow-up	☐	☐	☒	

Section 4: Source and study populations		Yes	No	N/A	Section Number
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

Section 5: Exposure definition and measurement		Yes	No	N/A	Section Number
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement		Yes	No	N/A	Section Number
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.7
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias		Yes	No	N/A	Section Number
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	

Section 7: Bias		Yes	No	N/A	Section Number
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

Section 8: Effect measure modification		Yes	No	N/A	Section Number
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources		Yes	No	N/A	Section Number
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
	9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	Annex3.1
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4, 9.7
	9.3.3 Covariates and other characteristics?	☒	☐	☐	9.4, 9.7
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan		Yes	No	N/A	Section Number
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3	Are descriptive analyses included?	☒	☐	☐	9.7
10.4	Are stratified analyses included?	☒	☐	☐	9.7
10.5	Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7	Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.8	Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

Section 11: Data management and quality control		Yes	No	N/A	Section Number
11.1	Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8
11.2	Are methods of quality assurance described?	☒	☐	☐	9.8
11.3	Is there a system in place for independent review of study results?	☒	☐	☐	9.8

Comments:

Section 12: Limitations		Yes	No	N/A	Section Number
12.1	Does the protocol discuss the impact on the study results of:				9.9
	12.1.1 Selection bias?	☒	☐	☐	9.9
	12.1.2 Information bias?	☒	☐	☐	9.9
	12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2	Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

Comments:

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Leila Karimi

Date:

Signature: _____

Annex 3. Additional documents

Annex 3.1. Analgesics and paracetamol containing drugs ATC codes

Analgesics	Anatomical Therapeutic
Opioids	**N02A**
Natural opium alkaloids	N02AA
Phenylpiperidine derivatives	N02AB
Diphenylpropylamine derivatives	N02AC
Benzomorphan derivatives	N02AD
Oripavine derivatives	N02AE
Morphinan derivatives	N02AF
Opioids in combination with antispasmodics	N02AG
Opioids in combination with non-opioid analgesics	N02AJ
Other opioids	N02AX
Anilides (Paracetamol containing product)	N02BE
Other analgesics and antipyretics	**N02B**
Salicylic acid and derivatives	N02BA
Pyrazolones	N02BB
Other analgesics and antipyretics	N02BG
Antimigraine preparations	**N02C**
Ergot alkaloids	N02CA
Corticosteroid derivatives	02CB
Selective serotonin (5-HT1) agonists	N02CC
Calcitonin gene-related peptide (CGRP) antagonists	N02CD
Other antimigraine preparations	N02CX

Annex 3.2. Drugs which interact with FDC of tramadol/paracetamol ATC codes

Drugs	ATC Codes
Doreta SR must not be taken together with the following:	
Monoamine oxidase inhibitors (MAOIs)	N06AF
Doreta SR is not recommended to be taken with the following:	
Carbamazepine	N03AF01 carbamazepine
Opioid-type pain relievers	
Buprenorphine	N02AE01 buprenorphine N07BC51 buprenorphine, combinations
Nalbuphine	N02AF02 nalbuphine
Pentazocine	N02AD01 pentazocine