



Krka, d. d., Novo mesto
DUS of the prescribing practices of Doreta SR and tramadol/paracetamol combinations
V2.0 dated 25 January 2024
Study No.: KKLR402019

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POST-AUTHORISATION SAFETY STUDY (PASS)

Final Study Report

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
Version	V2.0
Date of last version of the final study report	25 January 2024
EU PAS/ENCePP register number	EUPAS 47961
Active substance	Tramadol and paracetamol, ATC code: N02AJ13 Pharmacotherapeutic group: analgesics, other opioids in combination with non-opioid analgesics
Medicinal product	Doreta SR 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

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Marketing authorisation holder(s)	Krka, d. d., Novo mesto
Joint PASS	No
Research question 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 (IR) fixed-dose combinations (FDCs) of tramadol/paracetamol pre-RMM and post-RMM implantation Secondary objectives: To describe the demographic characteristics of patients prescribed with Doreta SR and IR FDCs of tramadol/paracetamol pre- and post-RMM implementation To describe the characteristics of prescribers of Doreta SR and IR FDCs of tramadol/paracetamol pre- and post-RMM implementation
Country(-ies) of study	The Czech Republic, Hungary, and Poland

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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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Final report Approval and Sign-off

I confirm that I have read the contents of this final report. I approve the final report in its current form.

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1. MARKETING AUTHORISATION HOLDER(S)

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2. ABSTRACT

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
Keywords	Drug Utilisation Study (DUS), Doreta SR, IR Fixed-dose combination (FDC) of tramadol hydrochloride and paracetamol, prescription pattern, and risk minimisation measures (RMM)
Rationale and background	Doreta SR (SR, sustained-release) (Krka, d. d., Novo mesto) is a 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, the 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 IR paracetamol are not designed for these extended periods of absorption. In February 2018, the MA 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.

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	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 Public Health and Pharmaceutical Centre (NNGYK) 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 NNGYK, commented that reporting of overdose or any adverse drug reaction (ADR) in general is poor and the information collected does not provide a real world overview. Therefore, the NNGYK condition for lifting the MA suspension for Doreta SR is if a Drug Utilisation Study (DUS) was conducted in at least 3 EU member states post lifting of the suspension. This study allowed obtaining an insight into the prescribing practices of Doreta SR and partially the effectiveness of implemented RMMs.
Research question and objectives	Research question and objectives: This study aimed to describe the prescribing practices before and after the implementation of Risk Minimisation Measures (RMMs) for Doreta SR proposed by the MAH (i.e., changes in the product information, changes in the product packaging and dissemination of DHPC).

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	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 indication • Duration of dispensed prescriptions per treatment • Concomitant diagnoses • 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 implementation. • To describe the characteristics of prescribers of Doreta SR and IR FDCs of tramadol/paracetamol pre- and post-RMM implementation.
Study design	Study design: This was a cross-sectional pre-post, DUS conducted using secondary data in outpatient settings. It consisted of two distinct study periods: pre-RMM period and post-RMM period.



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	The pre-RMM period was defined from the date of the first launch to the date of suspension of Doreta SR in each country as follows: • Czech Republic: 01 December 2016 to 30 April 2018 • Poland: 01 February 2016 to 31 March 2018 • Hungary: 01 March 2017 to 31 March 2018 The post-RMM period started from the start date of re-launch of Doreta SR in each country as follows: • Czech Republic: 12 March 2021 to 11 September 2022 • Poland: 05 March 2021 to 04 September 2022 • Hungary: 09 March 2021 to 30 September 2022
Setting	Source population included electronic dispensed pharmacy data from three European countries, Czech Republic, Poland, and Hungary. Study population consisted of any dispensed prescriptions of oral FDCs of tramadol/paracetamol during the study periods.
Subjects and study size	Any dispensed prescriptions of oral FDCs of tramadol/paracetamol during the study periods. Sub-population: • Dispensed prescriptions of Doreta SR • Dispensed prescriptions of IR FDCs of tramadol/paracetamol Study size: The final study sample size calculation was driven by all prescriptions of Doreta SR or IR FDCs of tramadol/paracetamol dispensed in the pre-defined periods of the selected databases.

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Variables and data sources	The exposure was defined as any dispensed prescriptions of Doreta SR and IR FDC of tramadol and paracetamol-containing products during the study period. The brand names were only used for the definition of Doreta SR. IR FDCs of tramadol and paracetamol was considered at the substance level as one sub-population only. Exposure was 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 were also 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). The following established pharmacy data in Poland and the claims data in Hungary and the Czech Republic were used for data extraction: • Czech Republic: IQVIA Longitudinal Prescription Data (LRx); claims database • Poland: IQVIA LifeLink database (IQVIA LRx) • Hungary: National Health Insurance Fund (NHIF) Administration
Results	The number of dispensed prescriptions of Doreta SR in the pre-RMM period and in the post-RMM period were 40,143 and 59,687 in the Czech Republic, 1,103,380 and 1,311,049 in Poland, and 43,601 and 56,710 in Hungary, respectively. The number of dispensed prescriptions of IR FDCs of tramadol/paracetamol in the pre-RMM period and in the post-RMM period were 168,842 and 239,112 in the Czech Republic, 1,556,992 and 1,452,126 in Poland, and 97,620 and 977,564 in Hungary, respectively.

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	The mean (Standard deviation [SD]) of the total doses (mg) per dispensed prescription for Doreta SR in the pre-RMM period and in the post-RMM period were 38,400 (33,396) and 49,837 (44,513) in the Czech Republic, 37,529 (23,915) and 47,183 (32,878) in Poland, and 21,797 (9,177) and 24,581 (8,283) in Hungary, respectively. The mean (SD) of the total doses (mg) per dispensed prescription for IR FDCs of tramadol/paracetamol in the pre-RMM period and in the post-RMM period were 22,202 (17,335) and 24,793 (20,664) in the Czech Republic, 21,024 (13,072) and 26,263 (20,243) in Poland, and 13,182 (5,345) and 16,338 (8,650) in Hungary, respectively. In the Czech Republic and Hungary, dorsalgia was the predominant indication for both Doreta SR and IR FDCs of tramadol/paracetamol in both periods. However, in the Czech Republic less than 10% of prescriptions included information about the treatment indication. The mean (SD) duration (days) of dispensed prescriptions of Doreta SR in the pre-RMM period and in the post-RMM period was 26 (23) and 34 (31) in the Czech Republic, 26 (16) and 33 (23) in Poland, and 30 (13) and 34 (11) in Hungary, respectively. The mean (SD) duration (days) of dispensed prescriptions IR FDCs of tramadol/paracetamol was 15 (12) and 17 (14) in the Czech Republic and 15 (9) and 18 (14) in Poland, and 36 (14) and 41 (18) in Hungary, respectively in the pre-RMM period and in the post-RMM period. In Hungary, during both periods, primary hypertension was the most prevalent concomitant diagnosis for dispensed prescriptions of both drugs. The majority of concomitantly dispensed prescriptions with Doreta SR were in the opioid category (N02A) in the pre-RMM and post-RMM periods, 38,577 (73.45%) and
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	68,055 (79.97%) in the Czech Republic, 602,551 (91.05%) and 689,911 (91.99%) in Poland, and 32,829 (61.52%) and 39,654 (70.33%) in Hungary, respectively. Concerning other paracetamol-containing products (N02BE), not many prescriptions were concomitantly dispensed with Doreta SR in the pre-RMM and post-RMM periods, 6 (0.01%) and 6 (0.01%) in the Czech Republic, 4,479 (0.68%) and 2,886 (0.38%) in Poland and 1,125 (2.11%) and 1,214 (2.15%) in Hungary, respectively. Observing the similar trends as with Doreta SR, the majority of concomitantly dispensed prescriptions with IR FDCs of tramadol/paracetamol were in the opioid category (N02A) in the pre-RMM and post-RMM periods, 90,327 (67.15%) and 119,421 (67.71%) in the Czech Republic, 763,009 (90.28%) and 737,451 (91.08%) in Poland and 51,053 (53.55%) and 269,607 (60.96%) in Hungary, respectively. Furthermore, concerning other paracetamol-containing products (N02BE), not many prescriptions were concomitantly dispensed with IR FDCs of tramadol/paracetamol in the pre-RMM and post-RMM periods, 8 (0.01%) and 12 (0.01%) in the Czech Republic, 6,275 (0.74%) and 3,719 (0.46%) in Poland and 2,731 (2.86%) and 15,753 (3.56%) in Hungary, respectively. Among drugs with known interactions with tramadol/paracetamol, we only observed dispensed prescriptions for carbamazepine in both periods. Concomitant use of carbamazepine was reduced during the post-RMM period compared to the pre-RMM period in the Czech Republic and Poland. In both periods, both drugs were mainly dispensed to patients aged 50 years or older across countries. In all three countries, most prescriptions for both medications were dispensed to females. In the Czech Republic and Poland, the dispensed prescriptions of Doreta SR and IR FDCs of tramadol/paracetamol were predominantly written by general practitioners in both periods.
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Discussion	This study aims to describe the prescribing practices before and after disseminating the RMMs in the three selected European countries: the Czech Republic, Poland, and Hungary. This report provides results based on cumulative data recorded over the 17-month pre-RMM period in the Czech Republic, the 26-month pre-RMM period in Poland and the 13-month pre-RMM period in Hungary. The post-RMM period was 18 months in the Czech Republic and Poland and slightly longer (~19 months) in Hungary. The number of prescriptions dispensed of both drugs increased across countries in the post-RMM period, except for Poland, where the number of IR FDCs of tramadol/paracetamol was slightly less than in the pre-RMM period. In the Czech Republic and Hungary, the more extended post-RMM period contributed to this increase. The total doses of both drugs in all three countries were higher during the post-RMM period than during the pre-RMM period. Furthermore, during both periods, the median duration (days) of dispensed prescriptions for Doreta SR per treatment was longer than for IR FDCs of tramadol/paracetamol in the Czech Republic and Poland. The longer duration of prescriptions of Doreta SR dispensed per treatment may indicate that Doreta SR was used to treat chronic pain conditions. It should also be noted that in Hungary, the median duration (days) of prescriptions dispensed for Doreta SR per treatment was the same as for IR FDCs of tramadol/paracetamol during both periods. In all three countries, during both periods, opioids (N02A) were the most common prescriptions dispensed. Moreover, in all three countries during both periods, no prescriptions were dispensed for monoamine oxidase inhibitors, which must not be taken with tramadol/paracetamol. Across countries, most prescriptions for Doreta SR and IR FDC of tramadol/paracetamol were dispensed to elderly people and females during both periods.
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	The study has certain limitations. There were no data available on the following variables: age of patients as a continuous variable in all three countries, prescriber characteristics in Hungary, treatment indications in Poland, and concomitant diagnosis in the Czech Republic and Poland. Furthermore, only ~6% of dispensed prescriptions included information about gender and treatment indications in the Czech Republic. Information regarding over-the-counter (OTC) dispensing for both drugs were unavailable in all three countries. Doreta SR and IR FDC tramadol/paracetamol have the same Anatomical Therapeutic Chemical (ATC) codes, so it is possible that Doreta SR has been misclassified. Furthermore, Hungary does not export results less than 10. Data from the Czech Republic, Poland, and Hungary are presented in this report. They broadly represent the general population in these three countries in terms of age, gender, and ethnicity. A pre-defined sample size was achieved for both periods in three countries. Therefore, the study results can be generalised to all three countries in both periods. In conclusion, the report provides insights into prescribing patterns of Doreta SR and IR FDCs of tramadol/paracetamol during the pre-RMM and post-RMM periods. The drugs were generally dispensed at higher doses and for a more extended duration in the post-RMM period. It is possible that prescribers intended to provide more medication refills to patients due to the coronavirus disease 2019 (COVID-19) pandemic. In Hungary, dorsalgia was the most prevalent indication for dispensed prescriptions. In both periods, opioids were mainly dispensed with Doreta SR and IR FDCs. No prescriptions in the Czech Republic and Poland as well as zero to nine prescriptions in Hungary for monoamine oxidase inhibitors, which must not be taken together with FDC of tramadol/paracetamol, were dispensed in both periods. Across both periods, elderly
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	individuals and women were most likely to be prescribed Doreta SR and IR FDC of tramadol/paracetamol. General practitioners primarily prescribed both drugs.
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Name(s) and affiliation(s) of principal investigator(s)	Dorothea von Bredow, PhD, Engagement Manager EMEA Real World Methods and Evidence Generation, IQVIA



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3. 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
COVID-19	Coronavirus Disease 2019
DHPC	Direct Healthcare Professional Communication
DUS	Drug Utilisation Study
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology & Pharmacovigilance
FDC	Fixed-Dose Combination
GVP	Good Pharmacovigilance Practice
GP	General Practitioners
GPPs	Good Pharmacoepidemiology Practices
ICD	International Classification of Diseases
IEC	Independent Ethics Committee
IQR	Interquartile Range
IRB	Institutional Review Board
IR	Immediate-Release
LRx	Longitudinal Prescription Data
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder

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Abbreviation	Definition
NFC	New Form Classification
NHIF	National Health Insurance Fund (Administration Hungary)
NNGYK	National Public Health and Pharmaceutical Centre
OTC	Over-The-Counter
PASS	Post-Authorisation Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
RMMs	Risk Minimisation Measures
RX	Recipe (the Latin word)
SD	Standard Deviation
SOPs	Standard Operating Procedures
SR	Sustained-Release

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4. INVESTIGATORS

Responsible Party	Name and Affiliation
Sponsor	Krka, d. d., Novo mesto
MAH responsible for submissions to Health Authority	KRKA, d. d., Novo mesto Šmarješka cesta 6 SI-8501 Novo mesto Slovenia Phone: +386 7 331 21 11 E-mail: info@krka.biz www.krka.si
Contracting vendor	IQVIA
Principal Investigator	Dorothea von Bredow, PhD, Engagement Manager EMEA Real World Methods and Evidence Generation IQVIA
Main Author	Leila Karimi, MD, MSc, DSc; Associate Director Pharmacoepidemiology, Real World Evidence Solutions, IQVIA

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IQVIA project team	• Leila Karimi, Lead Epidemiologist MD, MSc, DSc; Associate Director Pharmacoepidemiology, Real World Evidence Solutions, IQVIA • Dorothea von Bredow, PhD, Engagement Manager EMEA Real World Methods and Evidence Generation, IQVIA • Intissar Bourahla, MSc, Associate Principal, Real World Evidence, IQVIA • Joanna Cichór, Assoc Data Scientist Mgr, Real World Evidence, IQVIA
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5. OTHER RESPONSIBLE PARTIES

This study was performed by IQVIA, a contract research organisation (CRO), including development of study materials (the protocol), data management, analysis, and reporting, with input, review, and approval of Krka, d. d., Novo mesto.



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6. MILESTONES

Milestone	Planned date	Actual date	Comments
Date of first Institutional Review Board (IRB) / Independent Ethics Committee (IEC) approval	NA	-	-
Date of last IEC/IRB approval	NA	-	-
Start of data collection	Q1-2023	Q2-2023	Delay is due to the change of the database in the Czech Republic and Hungary
End of data collection	Q1-2023	Q4-2023	Delay is due to the change of the database in Hungary
Registration in the EU PAS register	-	06 July 2022	-
Final report of study results	29 June 2023	15 December 2023	Delay is due to the change of the database in Hungary

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

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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, the Czech Republic, Lithuania, Latvia, Estonia, Bulgaria, Romania, Poland, and Portugal). It has been the only registered prolonged-release formulation of the two ingredients in these countries up to this date, except for Portugal, where other formulations have also been 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 IR 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 IR paracetamol are not designed for these extended periods of absorption.

An Article 31 referral procedure (EMA/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 Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) 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 MA 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.

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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 Public Health and Pharmaceutical Centre (NNGYK), 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 NNGYK:

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 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 DHPC to prescribers including information on RMMs 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, Czech Republic, Portugal, Romania, Slovakia, and Slovenia

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- 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 and paracetamol combinations focusing on overdose cases every 6 months and submission of findings to concerned authorities

With respect to intensive monitoring, the NNGYK commented that reporting of overdose or any ADR in general is poor and the information collected does not provide a real world overview. Therefore, the NNGYK condition for lifting the MA suspension for Doreta SR was to conduct a Drug Utilisation Study (DUS) in at least three EU member states post lifting of the suspension. The study presented in this report, while not providing any information regarding overdoses or ADRs, does provide insight into Doreta SR prescribing practices and partially the effectiveness of implemented RMMs.

This DUS was 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

Research question and objectives:

This study aimed to describe the prescribing practices before and after the implementation of Risk Minimisation Measures (RMMs) for Doreta SR proposed by the MAH (i.e., changes in the product information, changes in the product packaging and dissemination of DHPC).

Primary objectives:

To describe the use of Doreta SR and IR FDCs of tramadol and 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

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- Concomitant diagnoses
- 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 and paracetamol in the pre- and post-RMM implementation.
- To describe the characteristics of prescribers of Doreta SR and IR FDCs of tramadol and paracetamol pre- and post-RMM implementation.

9. AMENDMENTS AND UPDATES

The fifth amendment of the study protocol, protocol version 5.0, was finalised on 27 September 2023. It concerned an updated wording on the study size (protocol sections 4 and 9.5) and milestones. The protocol v5.0 has been submitted to and approved by NNGYK (10 October 2023).

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10. RESEARCH METHODS

10.1 Study Design

This was a cross-sectional pre-post DUS, conducted using secondary data in outpatient settings. It consisted of two distinct study periods: pre-RMM period and post-RMM period.

10.2 Setting

10.2.1 Source Population

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

10.2.2 Study Population

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

10.2.3 Study Time Period

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

- Czech Republic: 01 December 2016 to 30 April 2018
- Poland: 01 February 2016 to 31 March 2018
- Hungary: 01 March 2017 to 31 March 2018

The post-RMM period started from the start date of re-launch of Doreta SR, on 5, 9, and 12 March 2021 in Poland, Hungary, and the Czech Republic, respectively, and continued for 18 months. The distribution of the DHPC has been initiated at the end of December 2020, 11 March 2021, and at the end of February 2021 in Poland, Hungary, and the Czech Republic, respectively.



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The post-RMM period was in each country as follows:

- Czech Republic: 12 March 2021 to 11 September 2022
- Poland: 05 March 2021 to 4 September 2022
- Hungary: 09 March 2021 to 30 September 2022

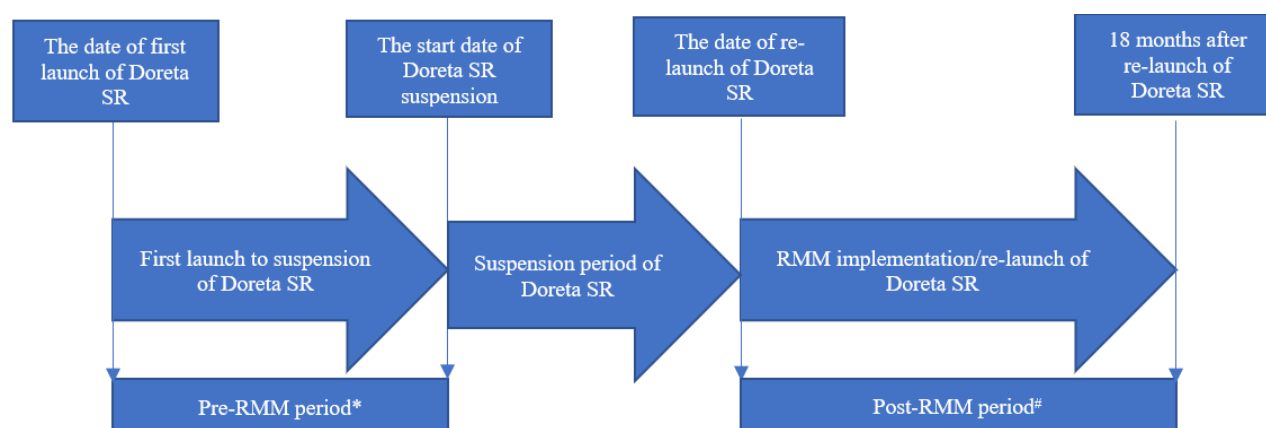


Figure 1: Study periods

*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 was 18 months and it started from 5, 9, and 12 March 2021 in Poland, Hungary, and the Czech Republic, respectively. SR: Sustained-Release.

10.3 Subjects

In this study, all statistical units were dispensed prescriptions.

10.3.1 Inclusion Criteria

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

10.3.2 Exclusion Criteria

None



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10.3.3 Sub-Populations

- Doreta SR
- IR FDCs of tramadol/paracetamol

10.4 Variables

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

10.4.1 Exposures

Exposure was any dispensed prescription of oral FDCs of tramadol and 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 were considered. IR FDCs of tramadol and paracetamol was considered at the substance level as one sub-population only (ATC code N02AJ13).

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

The following variables regarding the exposure were 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)

10.4.2 Paracetamol-containing Drugs

- Paracetamol-containing drugs (ATC code: N02BE)

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10.4.3 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 2.

10.4.4 Drugs With Known Interactions With FDC of Tramadol/Paracetamol

Doreta SR 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.

10.4.5 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

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10.4.6 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

10.5 Data Sources

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

In Poland, IQVIA LifeLink (IQVIA LRx) was used. It is a database of longitudinal records of prescribed and dispensed prescriptions at the patient level collected from retail pharmacies (**Table 1**).

In Hungary, National Health Insurance Fund (Administration Hungary) (NHIF) Claims database, highly trusted solution with detailed patient level insights on patient journey covering 100% of population was 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.



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Table 1: Summary of databases considered for the DUS

Country	Czech Republic	Poland	Hungary
Name /type of the data source	IQVIA LRx claims	IQVIA LRx	NHIF Claims
Size of the panel	~20% of population	78% of population	100% of population
Data available since	2015	2012	2008
Data refresh time	3-4 months lag	Monthly	2-3 months lag
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	Prescription issue date not available Rx purchase date	Available
Indication of the prescriptions of Doreta SR or IR FDCs of tramadol/paracetamol	ICD-10, partially available, coverage:~6% of transactions	Not available	ICD-10

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Country	Czech Republic	Poland	Hungary
Co-diagnosis of the prescriptions of Doreta SR or IR FDCs of tramadol/paracetamol	Not available	Not available	ICD-10
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:~ 6% of transactions	Available	Available
Prescriber specialty	Available	Available	Available
Prescribers' work setting (hospital, office)	Not available	Available	Not available

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10.5.1 Database Details

Czech Republic: IQVIA LRx claims database

IQVIA LRx claims database represents a selection of the Czech Republic payers' data on reimbursed prescription medications. There is currently coverage of approximately 20% of the 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 data for 12% of patients is not available at all.

The payer coverage has slightly varied throughout the time, 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: International Classification of Diseases (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 prescribers is filled in the majority of cases.
- Patient info: Age (grouped by 10 years), 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 by 3-4 months.

The quality control steps were specified as followings:

- Panel fulfilment, verify correct recording of all collaborating payers who participated in the quarter is loaded correctly
- Incomplete or out-of-reference data: the records were bridged to existing records within the ICD-10 or product references
- Data consistency:

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- 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 were no discrepancies in the dosage, for example, intrauterine contraceptive on daily dosage

Poland: IQVIA LifeLink (IQVIA LRx)

IQVIA LRx in Poland (6) is a database of computerised longitudinal records of dispensed prescriptions at the anonymised patient level collected from retail pharmacies. IQVIA LRx was created in 2012 and data is updated monthly. The data is captured from approximately 6500 retail pharmacies representing coverage of 45% retail of the country (Dec 2019). The following information is available in the IQVIA LRx database:

- Drug therapy: prescribed and dispensed drugs (ATC- European Pharmaceutical Marketing Research Association [EPHRA]), substance, brand, manufacturer, form (New Form Classification (NFC) 123 classification), strength, quantity, pack size
- Other: realised 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.

IQVIA LRx database in Poland is regularly monitored and there are some automated quality checks that are run with each update process. Among others, the following quality checks are being applied:

- Overall Rx market trends: data is monitored with each update to ensure that the overall trends are reasonable and justified based on what is happening on the market, in case of discrepancies, the issue is discussed and data is re-updated
- Rare diseases: to ensure full anonymity of patients, rare transactions for specific products are removed from the database
- A number of additional administrative checks are also being applied

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Hungary: NHIF Claims database

For Hungary, the NHIF Claims database's content, rules, and possibilities for retrospective RWE research were used:

- 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, and International Classification of Procedures in Medicine)
- 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., OTC medication) are not represented.
- The NHIF data service lags behind by 2-3 months.

The detailed information on quality management at NHIF is available at the below website:

[HTTPS://WWW.ENG.RFZO.RS/INDEX.PHP/QUALITY-MANAGEMENT-AT-NHIF](https://www.eng.rfzo.rs/index.php/quality-management-at-nhif)

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10.5.2 Enrolment/Baseline

Not Applicable

10.5.3 Follow-up

Not Applicable

10.5.4 Discontinuation

Not Applicable

10.6 Bias

10.6.1 Information Bias

The ATC codes are the same for Doreta SR and other IR FDC tramadol and paracetamol-containing products. This might result in misclassification of the Doreta SR if prescribers did not use the correct brand name; or if the pharmacy did not dispense the right brand name. Due to the coronavirus disease 2019 (COVID-19) pandemic, there had been delays in treatments, examinations, operations, and checks for patients that did not pose a risk of death or impairment of mobility and were professionally justifiable. It is likely that in the first months of the pandemic in 2020, the number of hospitalisations and ambulatory care visits due to causes other than COVID-19 were decreased which could have resulted in a decrease in the number of prescriptions. Dispensing data are not necessarily indicative of consumption, as medicines may be dispensed but not used.

10.6.2 Selection Bias

Since this is a non-interventional observational study, minimal inclusion and exclusion criteria are desirable for data extraction to minimise potential selection bias and represent real clinical practice.

10.7 Study Size

The final study sample size was driven by the number of dispensed prescriptions of Doreta SR or IR FDCs of tramadol/paracetamol available in the data sources in the target countries.

In general, as the proportions were not known in advance, we considered them to be 50% (maximum uncertainty). Such a hypothesis yielded the most conservative i.e., the largest sample size. It showed that to

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achieve sufficient accuracy, i.e., within a margin of accuracy $\pm 5\%$, of the estimation by a two-sided 95% Confidence Interval(CI) for a proportion (p) 50%, a sample size of 384 Doreta SR and 384 IR FDCs of tramadol/paracetamol dispensed prescriptions was required in each country (the Czech Republic, Hungary, and Poland) and each period (pre- RMM and post-RMM periods) (**Table 2**).

Calculation used the following formula (normal approximation):

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

With n sample size, p observed percentage, ε_{α} 1.96 for 95% CI, e Precision.

Table 2: Required number of patients by acceptable precision

	Observed percentage (accuracy): p(1-p)				
Precision	10% (90%)	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

All prescriptions of Doreta SR or IR FDCs of tramadol/paracetamol, dispensed in the pre-defined periods of the selected databases, will be included in the analysis. Preliminary feasibility counts (**Table 3**) indicated that the numbers of dispensed prescriptions for Doreta SR ranged from 110,000 - 120,000 in Hungary, 116,000 - 120,000 in the Czech Republic to 260,000 – 270,000 in Poland in the pre-RMM period. If we considered



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maximum uncertainty (50%), the estimated sample size (the numbers of dispensed prescriptions for Doreta SR during the pre-RMM period) in the target countries provided a precision of <1%.

10.7.1 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 was deemed feasible for the pre-RMM period (**Table 3**).

Table 3: Number of Doreta SR prescription records in the pre-RMM period

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

*The feasibility counts were from the sell data in each country which is different from the databases included in this study.

10.8 Data Transformation

Not Applicable

10.9 Statistical Analyses

10.9.1 General Considerations

The statistical analyses were mainly descriptive and 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 was the dispensed prescription. Continuous variables are presented as means with standard deviation (SD) and as medians with interquartile range (IQR), where appropriate. Categorical variables are presented as counts (n), proportions (%) with 95% CI, where relevant.

All analyses were performed using appropriate statistical software (Python).

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10.9.2 Primary Analysis

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

10.9.2.1 Prescribing patterns

This analysis compared the prescribing practices of Doreta SR and the IR FDC of tramadol/paracetamol before and after the dissemination of RMMs. The statistical unit for this analysis was the prescription of oral FDCs of tramadol/paracetamol during the study period. The tables were stratified by pre-implementation and post-implementation period. The tables were produced for each sub-population and each country separately.

- **Total Dose dispensed**

The total dose dispensed was analysed as a continuous variable, separately for Doreta SR and IR FDC tramadol/paracetamol, based on the below calculation:

Total dose dispensed = Strength x Number of pills in the pack x Number of packs dispensed per prescription

The total dose dispensed for Doreta SR and IR FDC tramadol/Paracetamol was also calculated per indications for dispensed prescriptions for the Czech Republic and Hungary.

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

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

10.9.2.2 Treatment indication

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



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As the indication of the prescription was not available in Poland, the proportions of dispensed prescriptions of Doreta SR (or IR FDCs of tramadol/paracetamol) by indication was evaluated in the Czech Republic (only available for ~6% of transactions) and Hungary.

10.9.2.3 Concomitant diagnoses

The co-diagnoses for treatment were analysed as counts (n) and proportion (%), separately for Doreta SR and IR FDC tramadol/paracetamol, based ICD10 codes. This information was available only for Hungary.

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

10.9.2.4 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). During both periods, concomitant prescriptions were analysed as count (n) and proportion (%), separately for Doreta SR and IR FDC tramadol/Paracetamol, based on directly using ATC codes, if available.

In addition, for a post-hoc analysis in the Czech Republic and Poland, a window for concomitant prescriptions calculation was defined as another prescription dispensed within 30 days before Doreta SR or IR FDC tramadol/paracetamol prescription, or within 30 days after Doreta SR or IR FDC tramadol/paracetamol prescription.

10.9.3 Secondary Analysis

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

10.9.3.1 Patient characteristics as mentioned on dispensed prescriptions

To describe the prescribing practices of Doreta SR and IR FDC tramadol/paracetamol before and after the dissemination of RMMs, the following variables were considered for Czech Republic, Poland, and Hungary:

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- **Age**

Age was analysed as a categorical variable with the following categories for Czech Republic, Hungary, and Poland:

- <20 years
- 20-49 years
- ≥ 50 years

- **Gender**

Gender was analysed as counts (n), proportions (%) separately for Doreta SR and IR FDC tramadol/paracetamol.

10.9.3.2 Prescriber characteristics as mentioned on dispensed prescriptions

The following prescriber characteristics were analysed to describe the prescribing practices of Doreta SR and IR FDC tramadol and paracetamol before and after the dissemination of RMMs:

- Type of speciality

Type of speciality was analysed as counts (n), proportions (%) separately for Doreta SR and IR FDC tramadol/paracetamol.

- Work setting

Work setting was presented with the following categories:

- hospital
- office

Work setting was analysed as counts (n), proportions (%) separately for Doreta SR and IR FDC tramadol/paracetamol. The data used to describe the work settings of prescribers was not available in Hungary and Czech Republic.



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10.9.4 Missing Values

No imputation on missing data was done. Missing data were presented in the tables.

10.9.5 Sensitivity Analyses

Not applicable.

10.9.6 Amendments to the Statistical Analysis Plan

Concomitant diagnoses information is not available in Czech Republic. Therefore, only information about the main indication was analysed. For clarification we updated the following sentence: “Total dose dispensed = Strength * Number of pills in the pack * Number of packs dispensed per prescription”.

10.10 Quality Control

10.10.1 IQVIA Quality Control

The study used existing databases, which are being used widely for research. The study was executed in line with all applicable regulations and guidelines – such as best-practice guidelines applicable to non-interventional PASS, including but not limited to the European Network of Centres for Pharmacoepidemiology & Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, the ENCePP Checklist for Study Protocols, and the Guidelines for Good Pharmacoepidemiology Practices (GPPs) of the International Society for Pharmacoepidemiology (ISPE), as well as the specific IQVIA Standard Operating Procedures (SOPs) on retrospective analysis.

For the IQVIA EU data sources, quality control is conducted at several levels depending on the database. At the database level, the quality unit of the production department of IQVIA verifies continuously the quality of its sources in terms of representativeness and consistency of collected data. All study programs, log files, and output files are stored on the secure server. If the study is being conducted by a third party, the datasets and analytic programs will be stored according to the vendor’s procedures.

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10.11 Data Management

The study used existing data with anonymised information on the individual patients. The study was conducted according to IQVIA health SOPs. The data management and statistical analysis were performed using appropriate statistical software (Python). Oversight for data analyses was coordinated by the country-specific IQVIA Real World Evidence Central team. A Lead Statistician worked with the relevant multi-country databases to ensure homogeneity in data extraction. The data was accessed and extracted by trained employees of IQVIA, and queries, extraction, and analyses were conducted on IQVIA (password-protected) computers only. Datasets extracted from each database were stored at the database level to allow future analysis, if needed. This study followed the relevant data management guidelines in the ENCePP and the International Conference on Harmonisation (ICH).



11. RESULTS

This section presents the results of analyses of the prescribing practices of the Doreta SR and IR FDCs of tramadol/paracetamol in the pre-RMM and post-RMM periods. Although no statistical tests have been performed in the analyses for the report, prescribing patterns within each study period are described to ease the reading of the report.

11.1 Results in the Czech Republic

11.1.1 Primary Analyses In The Czech Republic

11.1.1.1 Total dose per dispensed prescription

A total of 40,143 prescriptions for Doreta SR were dispensed during the pre-RMM period and 59,687 during the post-RMM period. The mean (SD) of the total doses (mg) per dispensed prescription for Doreta SR was 38,400 (33,396) and 49,837 (44,513) in the pre-RMM and post-RMM periods, respectively. The median (IQR) of the total dose (mg) per dispensed prescription for Doreta SR was 21,750 (50,750) in the pre-RMM period and 43,500 (43,500) in the post-RMM period (Table 4). The total doses of tramadol and paracetamol for Doreta SR are also provided separately, as shown in Table 4.1 and Table 4.2 in Annex 4. Also, Table 5.1 in Annex 5 shows Doreta SR packs dispensed in the Czech Republic, a post-hoc analysis.

Table 4: Total dose per dispensed prescription for Doreta SR sub-population in pre-RMM and post-RMM periods – the Czech Republic

Czech Republic		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	40,143	59,687
Total dose dispensed (mg)	Mean (SD)	38,400 (33,396)	49,837 (44,513)
	Median [IQR]	21,750 (50,750)	43,500 (43,500)
	Missing (N)	0	0

Total dose dispensed = Strength * Number of pills in the pack * Number of packs dispensed per prescription; strength= dose of tramadol in mg plus dose of paracetamol in mg per pill



The number of dispensed prescriptions for IR FDCs of tramadol/paracetamol were 168,842 during the pre-RMM period and 239,112 during the post-RMM period. As for the total dose (mg) per dispensed prescription for IR FDCs of tramadol/paracetamol, the mean (SD) was 22,202 (17,335) during the pre-RMM period and 24,793 (20,664) during the post-RMM period. During the pre-RMM and post-RMM periods, the median (IQR) of the total dose (mg) per dispensed prescription of IR FDCs of tramadol/paracetamol was 21,750 (10,875) and 21,750 (21,750), respectively (**Table 5**). The total doses of tramadol and paracetamol for IR FDCs of tramadol/paracetamol are separately provided as shown in **Table 4.3** and **Table 4.4** in Annex 4.

Table 5: Total dose per dispensed prescription for IR FDCs of tramadol/paracetamol in pre-RMM and post-RMM periods - the Czech Republic

Czech Republic		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	168,842	239,112
Total dose dispensed (mg)	Mean (SD)	22,202 (17,335)	24,793 (20,664)
	Median [IQR]	21,750 (10,875)	21,750 (21,750)
	Missing (N)	0	0

Total dose dispensed = Strength * Number of pills in the pack * Number of packs dispensed per prescription; strength= dose of tramadol in mg plus dose of paracetamol in mg per pill

11.1.1.2 Treatment indication

In the Czech Republic, more than 90% of prescriptions which were dispensed in the pre-RMM and post-RMM periods did not include information about the treatment indication for Doreta SR and IR FDCs of tramadol/paracetamol. According to the available information, dorsalgia was the most prevalent indication for both drugs in both periods (**Table 6** and **Table 7**).



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Table 6: Indications for dispensed prescriptions for Doreta SR sub-population in pre-RMM and post-RMM periods - the Czech Republic

Czech Republic		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	40,143	59,687
The top 5 indications for dispensed prescriptions	Dorsalgia	183 (0.46%)	701 (1.17%)
	Primary Hypertension	62 (0.15%)	97 (0.16%)
	Other intervertebral disc diseases	45 (0.11%)	157 (0.26%)
	Other dorsopathies (neck)	42 (0.10%)	76 (0.13%)
	Gonarthrosis (Knee Osteoarthritis)	26 (0.06%)	97 (0.16%)
	Missing (N)	39,205 (97.66%)	56,667 (94.94%)

Table 7: Indications for dispensed prescriptions for IR FDCs of tramadol/paracetamol sub-population in pre-RM and post-RMM periods - the Czech Republic

Czech Republic		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	168,842	239,112
The top 5 indications for dispensed prescriptions *	Dorsalgia	1,628 (0.96%)	4,897 (2.05%)
	Other intervertebral disc diseases	246 (0.15%)	821 (0.34%)
	Primary Hypertension	239 (0.14%)	377 (0.16%)

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Czech Republic		Pre-RMM period	Post-RMM period
	Gonarthrosis (Knee Osteoarthritis)	227 (0.13%)	759 (0.32%)
	Other dorsopathies (neck)	227 (0.13%)	571 (0.24%)
	Coxarthrosis (hip)	161 (0.10%)	559 (0.23%)
	Missing (N)	161,429 (95.61%)	217,192 (90.83%)

* Top 5 can be different in Pre-RMM period and Post-RMM period. Above table includes combined Top 5 from Pre-RMM period and Post-RMM period.

Regarding Doreta SR prescriptions dispensed for dorsalgia, the mean (SD) of total dose (mg) per dispensed prescription was 43,817 (41,131) and 56,873 (50,513) in the pre-RMM and post-RMM periods, respectively, with a median (IQR) 21,750 (50,750) in the pre-RMM period and 43,500 (43,500) in the post-period (**Table 8**). The total doses of tramadol and paracetamol for Doreta SR by treatment indications are provided separately, as shown in **Table 4.5** and **Table 4.6** in Annex 4.

Table 8: Total dose dispensed in mg per indications per dispensed prescription for Doreta SR sub-population in pre-RMM and post-RMM periods - the Czech Republic

Czech Republic		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	40,143	59,687
Total dose dispensed in mg per dorsalgia for dispensed prescriptions	Mean (SD)	43,817 (41,131)	56,873 (50,513)
	Median [IQR]	21,750 (50,750)	43,500 (43,500)
	Missing (N)	0	0
	Mean (SD)	36,250 (27,894)	48,470 (31,312)

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Czech Republic		Pre-RMM period	Post-RMM period
Total dose dispensed in mg per primary hypertension for dispensed prescriptions	Median [IQR]	21,750 (48,938)	43,500 (32,625)
	Missing (N)	0	0
Total dose dispensed in mg per other intervertebral disc diseases for dispensed prescriptions	Mean (SD)	43,419 (41,673)	57,192 (46,227)
	Median [IQR]	32,625 (43,500)	65,250 (43,500)
	Missing (N)	0	0
Total dose dispensed in mg per other dorsopathies (neck) for dispensed prescriptions	Mean (SD)	36,682 (35,266)	62,531 (54,740)
	Median [IQR]	32,625 (32,625)	65,250 (43,500)
	Missing (N)	0	0
Total dose dispensed in mg per Gonarthrosis (knee osteoarthritis) for dispensed prescriptions	Mean (SD)	44,197 (43,258)	49,890 (44,288)
	Median [IQR]	38,062 (54,375)	21,750 (43,500)
	Missing (N)	0	0

As for IR FDCs of tramadol/paracetamol prescriptions dispensed for dorsalgia, the mean (SD) of total dose (mg) per dispensed prescription was 18,982 (16,619) and 22,193 (23,203) in the pre-RMM and post-RMM periods, respectively, with a median (IQR) of 10,875 (10,875) in both periods (**Table 9**). The total doses of tramadol and paracetamol for IR FDCs of tramadol/paracetamol per treatment indications are provided separately, as shown in **Table 4.7** and **Table 4.8** in Annex 4.

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Table 9: Total dose dispensed in mg per indications per dispensed prescriptions for IR FDCs of tramadol/paracetamol sub-population in pre-RMM and post-RMM periods - the Czech Republic

Czech Republic		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	168,842	239,112
Total dose dispensed in mg per dorsalgia for dispensed prescriptions	Mean (SD)	18,982 (16,619)	22,193 (23,203)
	Median [IQR]	10,875 (10,875)	10,875 (10,875)
	Missing (N)	0	0
Total dose dispensed in mg per other intervertebral disc diseases for dispensed prescriptions	Mean (SD)	19,908 (13,755)	27,252 (22,541)
	Median [IQR]	10,875 (10,875)	21,750 (21,750)
	Missing (N)	0	0
Total dose dispensed in mg per primary hypertension for dispensed prescriptions	Mean (SD)	25,193 (18,039)	25,510 (19,185)
	Median [IQR]	21,750 (21,750)	21,750 (21,750)
	Missing (N)	0	0
Total dose dispensed in mg per gonarthrosis (knee osteoarthritis) for dispensed prescriptions	Mean (SD)	20,009 (15,187)	22,829 (21,927)
	Median [IQR]	10,875 (10,875)	21,750 (10,875)
	Missing (N)	0	0
Total dose dispensed in mg per other dorsopathies	Mean (SD)	17,822 (15,096)	19,249 (14,724)
	Median [IQR]	10,875 (10,875)	10,875 (10,875)

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Czech Republic		Pre-RMM period	Post-RMM period
(neck) for dispensed prescriptions	Missing (N)	0	0
Total dose dispensed in mg per Coxarthrosis (hip) for dispensed prescriptions	Mean (SD)	22,583 (13,876)	22,360 (18,756)
	Median [IQR]	21,750 (10,875)	10,875 (10,875)
	Missing (N)	0	0

11.1.1.3 Duration of dispensed prescriptions per treatment

The mean (SD) of duration (days) of dispensed prescriptions of Doreta SR per treatment in the pre-RMM and the post-RMM periods, respectively, was 26 (23) and 34 (31) with a median (IQR) of 15 (35) and 30 (30) (**Table 10**). The mean (SD) of duration (days) of prescriptions of IR FDCs of tramadol/paracetamol dispensed per treatment was 15 (12) in the pre-RMM period and 17 (14) in the post-RMM periods. Accordingly, the median (IQR) was 15 (8) and 15 (15) in the pre-RMM and post-RMM periods, respectively (**Table 11**).

Table 10: Duration of dispensed prescriptions per treatment for Doreta SR sub-population in pre-RMM and post-RMM periods - the Czech Republic

Czech Republic		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	40,143	59,687
Duration of dispensed prescriptions per treatment (days)	Mean (SD)	26 (23)	34 (31)
	Median [IQR]	15 (35)	30 (30)
	Missing (N)	0	0

Duration = Total dose dispensed / Daily dose information

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Table 11: Duration of dispensed prescriptions per treatment for IR FDCs of tramadol/paracetamol sub-population in pre-RMM and post-RMM periods - the Czech Republic

Czech Republic		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	168,842	239,112
Duration of dispensed prescriptions per treatment (in days)	Mean (SD)	15 (12)	17 (14)
	Median [IQR]	15 (8)	15 (15)
	Missing (N)	0	0

Duration = Total dose dispensed / Daily dose information

11.1.1.4 Concomitant prescriptions

During the pre-RMM and post-RMM periods, 52,524 and 85,100 prescriptions were dispensed concomitantly with Doreta SR, respectively (**Table 12**). The majority of concomitantly dispensed prescriptions in the pre-RMM and post-RMM periods were opioids (N02A), 38,577 (73.45%) in the post-RMM period and 68,055 (79.97%), in the post-RMM period. Among the drugs of interest with known interaction with tramadol/paracetamol, only carbamazepine was concomitantly dispensed, with 887 (1.69%) prescriptions during the pre-RMM period and with 706 (0.83%) prescriptions during the post-RMM period. Regarding other paracetamol-containing products (N02BE), not many prescriptions were concomitantly dispensed with Doreta SR, 6 (0.01%) in the pre-RMM period and 6 (0.01%) in the post-RMM period. **Table 12** presents detailed information about concomitant prescriptions. In addition, in a post-hoc analysis, concomitant prescriptions were analysed within a window of 30 days before or after the date of dispensing Doreta SR (**Table 4. 9** in Annex 4). The results followed the similar trend as the main analysis.



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Table 12: Concomitant prescriptions for Doreta SR sub-population in pre-RMM and post-RMM periods - the Czech Republic

Czech Republic		Pre-RMM period	Post-RMM period
Number of co-prescriptions	Count (N)	52,524	85,100
	Other paracetamol- containing products (ATC code: N02BE)	6 (0.01%)	6 (0.01%)
	Other analgesics		
	• Opioids (ATC code: N02A):	38,577 (73.45%)	68,055 (79.97%)
	○ Natural opium alkaloids	3,100 (5.90%)	3,910 (4.59%)
	○ Phenylpiperidine derivatives	1,736 (3.31%)	3,224 (3.79%)
	○ Diphenylpropylamine derivatives	16 (0.03%)	39 (0.05%)
	○ Benzomorphan derivatives	0 (0.00%)	0 (0.00%)
	○ Oripavine derivatives	627 (1.19%)	855 (1.00%)
	○ Morphinan derivatives	1 (0.00%)	2 (0.00%)
	○ Opioids in combination with antispasmodics	0 (0.00%)	0 (0.00%)
	○ Opioids in combination with non-opioid	21,260 (40.48%)	47,908 (56.30%)
	○ Other opioids	11,837 (22.54%)	12,117 (14.24%)

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Czech Republic		Pre-RMM period	Post-RMM period
	Other analgesics and antipyretics (ATC code: N02B)	11,731 (22.33%)	14,280 (16.78%)
	○ Salicylic acid and derivatives	1,925 (3.66%)	2,083 (2.45%)
	○ Pyrazolones	9,806 (18.67%)	12,197 (14.33%)
	○ Other analgesics and antipyretics	0 (0.00%)	0 (0.00%)
	Antimigraine preparations (ATC code: N02C)	1,323 (2.52%)	2,053 (2.41%)
	○ Ergot alkaloids (ATC code: N02CA)	0 (0.00%)	0 (0.00%)
	○ Ergot alkaloids (ATC code: N02CB)	0 (0.00%)	0 (0.00%)
	○ Selective serotonin (5-HT ₁) agonists	1,323 (2.52%)	1,931 (2.27%)
	○ Calcitonin gene-related peptide (CGRP)	0 (0.00%)	122 (0.14%)
	○ Other antimigraine preparations	0 (0.00%)	0 (0.00%)
	Drug with known interaction with tramadol/paracetamol		
	Monoamine oxidase inhibitors (MAOIs)	0 (0.00%)	0 (0.00%)
	Carbamazepine	887 (1.69%)	706 (0.83%)
	Opioid-type pain relievers:	0 (0.00%)	0 (0.00%)
	○ Buprenorphine	0 (0.00%)	0 (0.00%)

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Czech Republic		Pre-RMM period	Post-RMM period
	○ Buprenorphine, combinations	0 (0.00%)	0 (0.00%)
	○ Nalbuphine	0 (0.00%)	0 (0.00%)
	○ Pentazocine	0 (0.00%)	0 (0.00%)

For IR FDCs of tramadol/paracetamol, there were 134,518 and 176,361 concomitant prescriptions, in the pre-RMM and post-RMM periods, respectively (**Table 13**). During both periods, the majority of concomitantly dispensed prescriptions were in the opioid category (N02A), 90,327 (67.15%) during the pre-RMM period and 119,421 (67.71%) during the post-RMM period. Regarding drugs with known interactions with tramadol/paracetamol, 948 (1.31%) and 1,093 (1.06%) prescription of carbamazepine, 2,546 (1.89%) and 2,640 (1.50%) prescriptions of buprenorphine combinations were dispensed, respectively, in the pre-RMM and the post-RMM periods. Regarding other paracetamol-containing products (N02BE), not many prescriptions were concomitantly dispensed with IR FDCs of tramadol/paracetamol, 8 (0.01%) in the pre-RMM period and 12 (0.01%) in the post-RMM period. **Table 13** provides detailed information about concomitant prescriptions for IR FDCs of tramadol/paracetamol in both periods. In addition, in a post-hoc analysis, concomitant prescriptions were analysed within in a window of 30 days before or after the date of dispensing of IR FDCs of tramadol/paracetamol (**Table 4. 10** in Annex 4). The results followed the similar trend as the main analysis.

Table 13: Concomitant prescriptions for IR FDCs of tramadol/paracetamol sub-population in pre-RMM and post-RMM periods - the Czech Republic

Czech Republic		Pre-RMM period	Post-RMM period
Number of co-prescriptions	Count (N)	134,518	176,361

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Czech Republic		Pre-RMM period	Post-RMM period
	Other paracetamol-containing products (ATC code: N02BE)	8 (0.01%)	12 (0.01%)
	Other analgesics		
	• Opioids (ATC code: N02A):	90,327 (67.15%)	119,421 (67.71%)
	○ Natural opium alkaloids	8,553 (6.36%)	9,575 (5.43%)
	○ Phenylpiperidine derivatives	5,721 (4.25%)	9,693 (5.50%)
	○ Diphenylpropylamine derivatives	92 (0.07%)	176 (0.10%)
	○ Benzomorphan derivatives	0 (0.00%)	0 (0.00%)
	○ Oripavine derivatives	1,929 (1.43%)	2,327 (1.32%)
	○ Morphinan derivatives	8 (0.01%)	29 (0.02%)
	○ Opioids in combination with antispasmodics	0 (0.00%)	0 (0.00%)
	○ Opioids in combination with non-opioid analgesics	37,943 (28.21%)	63,933 (36.25%)
	○ Other opioids	36,081 (26.82%)	33,688 (19.10%)
	Other analgesics and antipyretics (ATC code: N02B)	36,940 (27.46%)	47,289 (26.81%)
	○ Salicylic acid and derivatives	6,200 (4.61%)	6,390 (3.62%)
	○ Pyrazolones	30,740 (22.85%)	40,899 (23.19%)
	○ Other analgesics and antipyretics	0 (0.00%)	0 (0.00%)

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Czech Republic		Pre-RMM period	Post-RMM period
	Antimigraine preparations (ATC code: N02C)	4,667 (3.47%)	6,936 (3.93%)
	○ Ergot alkaloids (ATC code: N02CA)	0 (0.00%)	0 (0.00%)
	○ Ergot alkaloids (ATC code: 02CB)	0 (0.00%)	0 (0.00%)
	○ Selective serotonin (5-HT ₁) agonists	4,667 (3.47%)	6,576 (3.73%)
	○ Calcitonin gene-related peptide (CGRP)	0 (0.00%)	360 (0.20%)
	○ Other antimigraine preparations	0 (0.00%)	0 (0.00%)
	Drug with known interaction with tramadol/paracetamol		
	Monoamine oxidase inhibitors (MAOIs)	0 (0.00%)	0 (0.00%)
	Carbamazepine	2,546 (1.89%)	2,640 (1.50%)
	Opioid-type pain relievers:	0 (0.00%)	0 (0.00%)
	○ Buprenorphine	0 (0.00%)	0 (0.00%)
	○ Buprenorphine, combinations	30 (0.02%)	63 (0.04%)
	○ Nalbuphine	0 (0.00%)	0 (0.00%)
	○ Pentazocine	0 (0.00%)	0 (0.00%)

11.1.2 Secondary Analyses In The Czech Republic

11.1.2.1 Patient characteristics

In the pre-RMM period, 76,68% of Doreta SR prescriptions were dispensed to patients aged 50 years or older; similarly, 79.60% during the post-RMM period. Information about gender were available only for ~6% of

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dispensed prescription for Doreta SR, 3.93% and 3.48% of the prescriptions for Doreta SR were dispensed to females, respectively, in the pre-RMM and the post-RMM periods (**Table 14**).

As for IR FDCs of tramadol/paracetamol, the results were similar to those of Doreta SR in terms of age and gender. In the pre-RMM and post-RMM periods, 76.50% and 77.60% of tramadol/paracetamol IR FDCs were dispensed to patients aged 50 years or older, respectively. Information about gender were missing for ~92% of dispensed prescription for IR FDCs of tramadol/paracetamol, 6.06% and 5.14% of the prescriptions for IR FDCs of tramadol/paracetamol were dispensed to females, respectively, in the pre-RMM and the post-RMM periods (**Table 15**).

Table 14: Patient's demographic characteristics for Doreta SR sub-population in pre-RMM and post-RMM periods in the pre-RMM period - the Czech Republic

Czech Republic		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	40,143	59,687
Age (years)	<20 years	50 (0.12%)	49 (0.08%)
	20-49 years	8,301 (20.68%)	10,490 (17.58%)
	≥50 years	30,783 (76.68%)	47,508 (79.60%)
	Missing (N)	1,009 (2.51%)	1,640 (2.75%)
Gender	Male	837 (2.09%)	1,305 (2.19%)
	Female	1,576 (3.93%)	2,079 (3.48%)
	Missing (N)	37,730 (93.99%)	56,303 (94.33%)



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Table 15: Patient's demographic characteristics for IR FDCs of tramadol/paracetamol sub-population in pre-RMM and post-RMM periods in the pre-RMM period - the Czech Republic

Czech Republic		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	168,842	239,112
Age (years)	<20 years	415 (0.25%)	417 (0.17%)
	20-49 years	35,747 (21.17%)	46,231 (19.33%)
	≥50 years	129,162 (76.50%)	185,557 (77.60%)
	Missing (N)	3,518 (2.08%)	6,907 (2.89%)
Gender	Male	5,016 (2.97%)	6,707 (2.80%)
	Female	10,225 (6.06%)	12,302 (5.14%)
	Missing (N)	153,601 (90.97%)	220,103 (92.05%)

11.1.2.2 Prescriber characteristics

As shown in **Table 16**, prescriptions of Doreta SR were mainly prescribed by general practitioners (GP; 63.97% during the pre-RMM period and 62.60% during the post-RMM period), followed by neurologist (15.95 % during the pre-RMM period and 14.77% during the post-RMM period) and orthopaedics (4.04% during the pre-RMM period and 4.51% during the post-RMM period) .

Table 16: Prescriber characteristics for Doreta SR sub-population in pre-RMM and post-RMM periods - the Czech Republic

Czech Republic		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	40,143	59,687

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Czech Republic		Pre-RMM period	Post-RMM period
Top 5 specialities*	General practitioners	25,680 (63.97%)	37,367 (62.60%)
	Neurology	6,404 (15.95%)	8,816 (14.77%)
	Orthopaedics	1,623 (4.04%)	2,693 (4.51%)
	Surgery	1,128 (2.81%)	1,377 (2.31%)
	Internal medicine	1,001 (2.49%)	1,475 (2.47%)
	Rheumatology	946 (2.36%)	1,483 (2.48%)
	Missing (N)	265 (0.37%)	540 (0.52%)

* Top 5 can be different in Pre-RMM period and Post-RMM period. Above table includes combined Top 5 from Pre-RMM period and Post-RMM period.

The prescriber characteristics of IR FDCs of tramadol/paracetamol are similar to those observed for Doreta SR (**Table 17**). The majority of IR FDCs of tramadol/paracetamol prescriptions were prescribed by GP (56.08% in the pre-RMM period and 56.28% in the post-RMM period), followed by neurologists (13.47% in the pre-RMM period and 12.57% in the post-RMM period) and orthopaedics (7.54% in the pre-RMM period and 7.33% in the post-RMM period).

Table 17: Prescriber characteristics for IR FDCs of tramadol/paracetamol sub-population in pre-RMM and post-RMM periods - the Czech Republic

Czech Republic		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	168,842	239,112
	GP	94,684 (56.08%)	134,573 (56.28%)

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Czech Republic		Pre-RMM period	Post-RMM period
Top 5 specialities*	Neurology	22,749 (13.47%)	30,052 (12.57%)
	Orthopaedics	12,739 (7.54%)	17,515 (7.33%)
	Surgery	10,141 (6.01%)	14,137 (5.91%)
	Internal medicine	5,950 (3.52%)	7,740 (3.24%)
	Missing (N)	1,653 (0.98%)	2,373 (0.99%)

* Top 5 can be different in Pre-RMM period and Post-RMM period. Above table includes combined Top 5 from Pre-RMM period and Post-RMM period.

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11.2 Results in Poland

11.2.1 Primary Analyses In Poland

11.2.1.1 Total dose per dispensed prescription

A total of 1,103,380 prescriptions for Doreta SR were dispensed during the pre-RMM period and 1,311,049 during the post-RMM period. The mean (SD) of the total doses (mg) per dispensed prescription for Doreta SR was 37,529 (23,915) and 47,183 (32,878) in the pre-RMM and post-RMM periods, respectively. The median (IQR) of the total dose (mg) per dispensed prescription for Doreta SR was 32,625 (21,750) in the pre-RMM period and 43,500 (43,500) in the post-RMM period (Table 18). The total doses of tramadol and paracetamol for Doreta SR are also provided separately, as shown in Table 4.11 and Table 4.12 in Annex 4. Also, Table 5.2 in Annex 5 shows Doreta SR packs dispensed in Poland, a post-hoc analysis.

Table 18: Total dose per dispensed prescription for Doreta SR sub-population in pre-RMM and post-RMM periods - Poland

Poland		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	1,103,380	1,311,049
Total dose dispensed (mg)	Mean (SD)	37,529 (23,915)	47,183 (32,878)
	Median [IQR]	32,625 (21,750)	43,500 (43,500)

Total dose dispensed = Strength * Number of pills in the pack * Number of packs dispensed per prescription; strength= dose of tramadol in mg plus dose of paracetamol in mg per pill

For IR FDCs of tramadol/paracetamol, the number of dispensed prescriptions were 1,556,992 during the pre-RMM period and 1,452,126 during the post-RMM period. As for the total dose (mg) per dispensed prescription for IR FDCs of tramadol/paracetamol, the mean (SD) was 21,024 (13,072) during the pre-RMM period and 26,263 (20,243) during the post-RMM period. During the pre-RMM and post-RMM periods, the median (IQR) of the total dose (mg) per dispensed prescription of IR FDCs of tramadol and paracetamol was



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21,750 (10,875) and 21,750 (21,750), respectively (**Table 19**). The total doses of tramadol and paracetamol for IR FDCs of tramadol/paracetamol are also provided separately, as shown in **Table 4.13** and **Table 4.14** in Annex 4.

Table 19: Total dose per dispensed prescription for IR FDCs of tramadol/paracetamol in pre-RMM and post-RMM periods – Poland

Poland		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	1,556,992	1,452,126
Total dose dispensed (mg)	Mean (SD)	21,024 (13,072)	26,263 (20,243)
	Median [IQR]	21,750 (10,875)	21,750 (21,750)
	Missing (N)	0	0

Total dose dispensed = Strength * Number of pills in the pack * Number of packs dispensed per prescription; strength= dose of tramadol in mg plus dose of paracetamol in mg per pill

11.2.1.2 Duration of dispensed prescriptions per treatment

The mean (SD) of duration (days) of dispensed prescriptions of Doreta SR per treatment in the pre-RMM and the post-RMM periods, respectively, was 26 (16) and 33 (23), with a median (IQR) of 23 (15) and 30 (30) (**Table 20**). The mean (SD) of duration (days) of prescriptions of IR FDCs of tramadol/paracetamol dispensed per treatment was 15 (9) in the pre-RMM period and 18 (14) in the post-RMM periods, with a median (IQR) of 15 (8) and 15 (15) in the pre-RMM and post-RMM periods, respectively (**Table 21**).

Table 20: Duration of dispensed prescriptions per treatment for Doreta SR sub-population in pre-RMM and post-RMM periods - Poland

Poland		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	1,103,380	1,311,049

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Poland		Pre-RMM period	Post-RMM period
Duration of dispensed prescriptions per treatment (days)	Mean (SD)	26 (16)	33 (23)
	Median [IQR]	23 (15)	30 (30)
	Missing (N)	0	0

Duration = Total dose dispensed / Daily dose information

Table 21: Duration of dispensed prescriptions per treatment for IR FDCs of tramadol/paracetamol sub-population in pre-RMM and post-RMM periods - Poland

Poland		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	1,556,992	1,452,126
Duration of dispensed prescriptions per treatment (days)	Mean (SD)	15 (9)	18 (14)
	Median [IQR]	15 (8)	15 (15)
	Missing (N)	0	0

Duration = Total dose dispensed / Daily dose information

11.2.1.3 Concomitant prescriptions

During the pre-RMM and post-RMM periods, 661,799 and 749,960 concomitant prescriptions were dispensed for Doreta SR, respectively (**Table 22**). The majority of concomitantly dispensed prescriptions were opioids (N02A), 602,551 (91.05%) in the pre-RMM period and 689,911 (91.99%) in the post-RMM period. Among the drugs of interest with known interaction with tramadol/paracetamol, only carbamazepine was concomitantly dispensed, with 40,680 (6.15%) prescriptions during the pre-RMM period and with 29,404 (3.92%) prescriptions during the post-RMM period. Regarding other paracetamol-containing products (N02BE), not many prescriptions were concomitantly dispensed with Doreta SR, 4,479 (0.68%) in the pre-RMM period and 2,886 (0.38%) in the post-RMM period. **Table 22** presents detailed information about

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concomitant prescriptions for Doreta SR in both periods. In a post-hoc analysis, concomitant prescriptions were analysed when another prescription dispensed within in a window of 30 days before or after date of dispensing Doreta SR (**Table 4. 15** in Annex 4). The results followed the similar trend as the main analysis.

Table 22: Concomitant prescriptions for Doreta SR sub-population in pre-RMM and post-RMM periods - Poland

Poland		Pre-RMM period	Post-RMM period
Number of co-prescriptions	Count (N)	661,799	749,960
	Other paracetamol- containing products ATC code: N02BE	4,479 (0.68%)	2,886 (0.38%)
	Other analgesics		
	• Opioids (ATC code: N02A):	602,551 (91.05%)	689,911 (91.99%)
	○ Natural opium alkaloids	31,291 (4.73%)	34,985 (4.66%)
	○ Phenylpiperidine derivatives	16,555 (2.50%)	16,159 (2.15%)
	○ Diphenylpropylamine derivatives	466 (0.07%)	534 (0.07%)
	○ Benzomorphan derivatives	0 (0.00%)	0 (0.00%)
	○ Oripavine derivatives	56,028 (8.47%)	71,225 (9.50%)
	○ Morphinan derivatives	0 (0.00%)	0 (0.00%)
	○ Opioids in combination with antispasmodics	0 (0.00%)	0 (0.00%)
	○ Opioids in combination with non-opioid analgesics	367,664	481,085 (64.15%)

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Poland		Pre-RMM period	Post-RMM period
	○ Other opioids	130,547 (19.73%)	85,923 (11.462.%)
	- Other analgesics and antipyretics (ATC code: N02B)	6,036 (0.91%)	6,875 (0.92%)
	○ Salicylic acid and derivatives	489 (0.07%)	207 (0.03%)
	○ Pyrazolones	4,107 (0.62%)	5,626 (0.75%)
	○ Other analgesics and antipyretics	1,440 (0.22%)	1,042 (0.14%)
	- Antimigraine preparations (ATC code: N02C)	8,053 (1.22%)	20,884 (2.78%)
	○ Ergot alkaloids (ATC code: N02CA)	395 (0.06%)	195 (0.03%)
	○ Ergot alkaloids (ATC code: N02CB)	0 (0.00%)	0 (0.00%)
	○ Selective serotonin (5-HT ₁) agonists	5,054 (0.76%)	17,331 (2.31%)
	○ Calcitonin gene-related peptide (CGRP) antagonists	0 (0.00%)	9 (0.00%)
	○ Other antimigraine preparations	2,604 (0.39%)	3,354 (0.45%)
	Drug with known interaction with tramadol/paracetamol		
	Monoamine oxidase inhibitors (MAOIs)	0 (0.00%)	0 (0.00%)
	Carbamazepine	40,680 (6.15%)	29,404 (3.92%)
	Opioid-type pain relievers:	0 (0.00%)	0 (0.00%)
	○ Buprenorphine	0 (0.00%)	0 (0.00%)
	○ Buprenorphine, combinations	0 (0.00%)	0 (0.00%)

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Poland		Pre-RMM period	Post-RMM period
	○ Nalbuphine	0 (0.00%)	0 (0.00%)
	○ Pentazocine	0 (0.00%)	0 (0.00%)

For IR FDCs of tramadol/paracetamol, there were 845,205 and 809,633 concomitant prescriptions for IR FDCs of tramadol/paracetamol, in the pre-RMM and post-RMM periods, respectively (**Table 23**). During both periods, the majority of concomitantly dispensed prescriptions were in the opioid category (N02A), 763,009 (90.28%) during the pre-RMM period and 737,451 (91.08%).during the post-RMM period. Regarding drugs with known interactions with tramadol/paracetamol, prescriptions of carbamazepine were the only ones dispensed, with 55,600 (6.58%) and 34,601 (4.27%).of concomitant prescriptions, respectively, in the pre-RMM and post-RMM periods. Regarding other paracetamol-containing products (N02BE), not many prescriptions were concomitantly dispensed with IR FDCs of tramadol/paracetamol, 6,275 (0.74%) in the pre-RMM period and 3,719 (0.46%) in the post-RMM period. **Table 23** provides detailed information about concomitant prescriptions for IR FDCs of tramadol/paracetamol in both periods. In a post-hoc analysis, concomitant prescriptions were analysed in a window of 30 days before or after the dispensing date of FDCs of tramadol/paracetamol, (**Table 4. 16** in Annex 4). The results followed the similar trend as the main analysis.

Table 23: Concomitant prescriptions for IR FDCs of tramadol/paracetamol sub-population in pre-RMM and post-RMM periods - Poland

Poland		Pre-RMM period	Post-RMM period
Number of co-prescriptions	Count (N)	845,205	809,633
	Other paracetamol- containing products (ATC code: N02BE)	6,275 (0.74%)	3,719 (0.46%)

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Poland	Pre-RMM period	Post-RMM period
Other analgesics • Opioids (ATC code: N02A): ○ Natural opium alkaloids ○ Phenylpiperidine derivatives ○ Diphenylpropylamine derivatives ○ Benzomorphan derivatives ○ Oripavine derivatives ○ Morphinan derivatives ○ Opioids in combination with antispasmodics ○ Opioids in combination with non-opioid analgesics ○ Other opioids Other analgesics and antipyretics (ATC code: N02B) ○ Salicylic acid and derivatives ○ Pyrazolones ○ Other analgesics and antipyretics Antimigraine preparations (ATC code: N02C) ○ Ergot alkaloids (ATC code: N02CA)		
	763,009 (90.28%)	737,451 (91.08%)
	32,393 (3.83%)	30,370 (3.75%)
	16,909 (2.00%)	14,814 (1.83%)
	561 (0.07%)	442 (0.05%)
	0 (0.00%)	0 (0.00%)
	58,020 (6.86%)	64,334 (7.95%)
	0 (0.00%)	0 (0.00%)
	0 (0.00%)	0 (0.00%)
	498,993 (59.04%)	542,100 (66.96%)
	156,133 (18.47%)	85,391 (10.55%)
	8,672 (1.03%)	8,441 (1.04%)
	658 (0.08%)	185 (0.02%)
	6,264 (0.74%)	7,131 (0.88%)
	1,750 (0.21%)	1,125 (0.14%)
	11,649 (1.38%)	25,421 (3.14%)
	543 (0.06%)	231 (0.03%)

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Poland		Pre-RMM period	Post-RMM period
	○ Ergot alkaloids (ATC code: 02CB)	0 (0.00%)	0 (0.00%)
	○ Selective serotonin (5-HT ₁) agonists	7,248 (0.86%)	21,151 (2.61%)
	○ Calcitonin gene-related peptide (CGRP) antagonists	0 (0.00%)	6 (0.00%)
	○ Other antimigraine preparations	3,858 (0.46%)	4,037 (0.50%)
Drug with known interaction with tramadol/paracetamol			
	Monoamine oxidase inhibitors (MAOIs)	0 (0.00%)	0 (0.00%)
	Carbamazepine	55,600 (6.58%)	34,601 (4.27%)
	Opioid-type pain relievers:	0 (0.00%)	0 (0.00%)
	○ Buprenorphine	0 (0.00%)	0 (0.00%)
	○ Buprenorphine, combinations	0 (0.00%)	0 (0.00%)
	○ Nalbuphine	0 (0.00%)	0 (0.00%)
	○ Pentazocine	0 (0.00%)	0 (0.00%)

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11.2.2 Secondary Analyses In Poland

11.2.2.1 Patient characteristics

In the pre-RMM period, 87.60% of Doreta SR prescriptions were dispensed to patients aged 50 years or older; similarly, 84.91% during the post-RMM period. Over 60% of Doreta SR prescriptions were dispensed to women in both periods (**Table 24**).

As for IR FDCs of tramadol/paracetamol, the results were similar to those of Doreta SR in terms of age and gender. In the pre-RMM and post-RMM periods, 84.74% and 82.83% of tramadol/paracetamol IR FDCs were dispensed to patients aged 50 years or older, respectively. During both periods, about 60% of the prescriptions for IR FDCs of tramadol/paracetamol were dispensed to females (**Table 25**).

Table 24: Patient's demographic characteristics for Doreta SR sub-population in pre-RMM and post-RMM periods in the pre-RMM period - Poland

Poland		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	1,103,380	1,311,049
Age (years)	<20 years	1,320 (0.12%)	1,516 (0.12%)
	20-49 years	135,553 (12.29%)	196,275 (14.97%)
	>50 years	966,507 (87.60%)	1,113,258 (84.91%)
	Missing (N)	0 (0.00%)	0 (0.00%)
Gender	Male	386,307 (35.01%)	487,300 (37.17%)
	Female	717,073 (64.99%)	823,749 (62.83%)
	Missing (N)	0 (0.00%)	0 (0.00%)



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Table 25: Patient's demographic characteristics for IR FDCs of tramadol/paracetamol sub-population in pre-RMM and post-RMM periods in the pre-RMM period - Poland

Poland		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	1,556,992	1,452,126
Age (years)	<20 years	4,089 (0.26%)	3,736 (0.26%)
	20-49 years	233,437 (14.99%)	245,549 (16.91%)
	>50 years	1,319,466 (84.74%)	1,202,841 (82.83%)
	Missing (N)	0 (0.00%)	0 (0.00%)
Gender	Male	555,889 (35.70%)	560,916 (38.63%)
	Female	1,001,103 (64.30%)	891,210 (61.37%)
	Missing (N)	0 (0.00%)	0 (0.00%)

11.2.2.2 Prescriber characteristics

Prescriptions of Doreta SR were mainly prescribed by GPs (75.57% during the pre-RMM period and 71.96% during the post-RMM period), followed by orthopaedics (5.83% during the pre-RMM period and 7.55% during the post-RMM period) and neurologist (4.71% during the pre-RMM period and 4.88 during the post-RMM period). Most prescribers, 77.66%, and 77.38%, worked in outpatient settings during the pre-RMM and post-RMM periods, respectively (**Table 26**).



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Table 26: Prescriber characteristics for Doreta SR sub-population in pre-RMM and post-RMM periods - Poland

Poland		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	1,103,380	1,311,049
Top 5 specialities	General practitioners	833,813 (75.57%)	943,463 (71.96%)
	Orthopaedics & Traumatology	64,353 (5.83%)	99,029 (7.55%)
	Neurology	51,960 (4.71%)	64,040 (4.88%)
	Rheumatology	28,684 (2.60%)	27,535 (2.10%)
	General Surgery	27,881 (2.53%)	34,539 (2.63%)
	Missing (N)	0 (0.00%)	0 (0.00%)
Work settings	Hospital	56,196 (5.09%)	82,217 (6.27%)
	Outpatient	856,836 (77.66%)	1,014,465 (77.38%)
	Outpatient/Hospital	190,348 (17.25%)	208,634 (15.91%)
	Other	0 (0.00%)	5,733 (0.44%)
	Missing (N)	0 (0.00%)	0 (0.00%)

The prescriber characteristics of IR FDCs of tramadol/paracetamol were similar to those observed for Doreta SR. The majority of IR FDCs of tramadol/paracetamol prescriptions were prescribed by GPs (68.58% in the pre-RMM period and 64.40% in the post-RMM period), followed by orthopaedics (11.75% in the pre-RMM period and 14.28% in the post-RMM period) and neurologists (5.69% in the pre-RMM period and 5.62% in the post-RMM period).

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the post-RMM period). Furthermore, 71.47% and 70.05% of prescribers in the pre-RMM and post-RMM periods, respectively, worked in outpatient settings (**Table 27**).

Table 27: Prescriber characteristics for IR FDCs of tramadol/paracetamol sub-population in pre-RMM and post-RMM periods - Poland

Poland		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	1,556,992	1,452,126
Top 5 specialities	General practitioners	1,067,849 (68.58%)	935,106 (64.40%)
	Orthopaedics & Traumatology	182,976 (11.75%)	207,387 (14.28%)
	Neurology	88,557 (5.69%)	81,618 (5.62%)
	General Surgery	74,640 (4.79%)	80,837 (5.57%)
	Rheumatology	39,794 (2.56%)	26,631 (1.83%)
	Missing (N)	0 (0.00%)	0 (0.00%)
Work settings	Hospital	126,530 (8.13%)	135,539 (9.33%)
	Outpatient	1,112,794 (71.47%)	1,017,197 (70.05%)
	Outpatient/Hospital	317,668 (20.40%)	293,492 (20.21%)
	Other	0 (0.00%)	5,898 (0.41%)
	Missing (N)	0 (0.00%)	0 (0.00%)

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11.3 Results in Hungary

11.3.1 Primary Analyses In Hungary

11.3.1.1 Total dose per dispensed prescription

A total of 43,601 prescriptions for Doreta SR were dispensed during the pre-RMM period and 56,710 during the post-RMM period. The mean (SD) of the total doses (mg) per dispensed prescription for Doreta SR was 21,797 (9,177) and 24,581 (8,283) in the pre-RMM and post-RMM periods, respectively. The median (IQR) of the total dose (mg) per dispensed prescription for Doreta SR was 21,750 (0) in both periods (**Table 28**). The total doses of tramadol and paracetamol for Doreta SR are also provided separately, as s shown in **Table 4.17** and **Table 4.18** in Annex 4.

Table 28: Total dose per dispensed prescription for Doreta SR sub-population in pre-RMM and post-RMM periods - Hungary

Hungary		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	43,601	56,710
Total dose dispensed (mg)	Mean (SD)	21,797 (9,177)	24,581 (8,283)
	Median [IQR]	21,750 (0)	21,750 (0)
	Missing (N)	0	0

Total dose dispensed = Strength * Number of pills in the pack * Number of packs dispensed per prescription; strength= dose of tramadol in mg plus dose of paracetamol in mg per pill

The number of dispensed prescriptions for IR FDCs of tramadol/paracetamol were 97,620 during the pre-RMM period and 977,564 during the post-RMM period. As for the total dose (mg) per dispensed prescription for IR FDCs of tramadol/paracetamol, the mean (SD) was 13,182 (5,345) during the pre-RMM period and 16,338 (8,650) during the post-RMM period. During the pre-RMM and post-RMM periods, the median (IQR) of the total dose (mg) per dispensed prescription of IR FDCs of tramadol/paracetamol was 10,875 (0) and 10,875



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(10,875), respectively (**Table 29**). The total tramadol and paracetamol doses for IR FDCs of tramadol/paracetamol are also provided separately as shown in **Table 4.19** and **Table 4.20** in Annex 4.

Table 29: Total dose per dispensed prescription for IR FDCs of tramadol/paracetamol in pre-RMM and post-RMM periods - Hungary

Hungary		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	97,620	977,564
Total dose dispensed	Mean (SD)	13,182 (5,345)	16,338 (8,650)
	Median [IQR]	10,875 (0)	10,875 (10,875)
	Missing (N)	0	0

Total dose dispensed = Strength * Number of pills in the pack * Number of packs dispensed per prescription; strength= dose of tramadol in mg plus dose of paracetamol in mg per pill

11.3.1.2 Duration of dispensed prescriptions per treatment

The mean (SD) of duration (days) of dispensed prescriptions of Doreta SR per treatment in the pre-RMM and the post-RMM periods, respectively, was 30 (13) and 34 (11) with a median (IQR) of 30 (0) in both periods (**Table 30**). The mean (SD) of duration days of prescriptions of IR FDCs of tramadol/paracetamol dispensed per treatment was 36 (14) in the pre-RMM period and 41 (18) in the post-RMM periods, with a median (IQR) was 30 (0) and 30 (30) in the pre-RMM and post-RMM periods, respectively (**Table 31**).



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Table 30: Duration of dispensed prescriptions per treatment for Doreta SR sub-population in pre-RMM and post-RMM periods - Hungary

Hungary		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	43,601	56,710
Duration of dispensed prescriptions per treatment (in days)	Mean (SD)	30 (13)	34 (11)
	Median [IQR]	30 (0)	30 (0)
	Missing (N)	0	0

Duration = Total dose dispensed / Daily dose information

Table 31: Duration of dispensed prescriptions per treatment for IR FDCs of tramadol/paracetamol sub-population in pre-RMM and post-RMM periods - Hungary

Hungary		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	97,620	977,564
Duration of dispensed prescriptions per treatment (in days)	Mean (SD)	36 (14)	41 (18)
	Median [IQR]	30 (0)	30 (30)
	Missing (N)	0	0

Duration = Total dose dispensed / Daily dose information

11.3.1.3 Treatment indication

Detailed description of top five indications for dispensed prescriptions of Doreta SR is shown in **Table 32**.

In Hungary, dorsalgia (~20%) was the most prevalent indication for dispensed prescriptions of Doreta SR and followed by intervertebral disc disorders (~ 12%) in both periods.

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Table 32: Indications for dispensed prescriptions for Doreta SR sub-population in pre-RMM and post-RMM periods - Hungary

Hungary		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	43,601	56,710
The top 5 indications for dispensed prescriptions	Dorsalgia	8,457 (19.40%)	11,341 (20.00%)
	Thoracic, thoracolumbar, and lumbosacral intervertebral disc disorders	5,380 (12.34%)	6,685 (11.79%)
	Spondylosis	3,925 (9.00%)	4,003 (7.06%)
	Osteoarthritis of knee	3,898 (8.94%)	4,579 (8.07%)
	Pain, unspecified	3,207 (7.36%)	4,771 (8.41%)
	Missing (N)	0 (0.00%)	0 (0.00%)

Detailed description of top five indications for dispensed prescriptions of IR FDCs of tramadol/paracetamol is shown in **Table 33**. The same trend as for Doreta SR is seen for dispensed prescriptions of IR FDCs of tramadol/paracetamol, dorsalgia as the prevalent indication (~20%) and followed by intervertebral disc disorders (~11%) in both periods.

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Table 33: Indications for dispensed prescriptions for IR FDCs of tramadol/paracetamol sub-population in pre-RMM and post-RMM periods - Hungary

Hungary		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	97,620	977,564
The top 5 Indications for dispensed prescriptions	Dorsalgia	18,709 (19.17%)	210,672 (21.55%)
	Thoracic, thoracolumbar, and lumbosacral intervertebral disc disorders	11,674 (11.96%)	100,982 (10.33%)
	Spondylosis	9,732 (9.97%)	75,757 (7.75%)
	Osteoarthritis of knee	8,713 (8.93%)	72,237 (7.39%)
	Pain, unspecified	7,464 (7.65%)	105,807 (10.82%)
	Missing (N)	0 (0.00%)	0 (0.00%)

Regarding Doreta SR prescriptions dispensed for dorsalgia, the mean (SD) of total dose (mg) per dispensed prescription was 21,055 (8,775) and 24,040 (7,310) in the pre-RMM and post-RMM periods, respectively, with a median (IQR) 21,750 (0) in both periods (**Table 34**). The total doses of tramadol and paracetamol for Doreta SR, by treatment indications, are provided separately, as shown in **Table 4. 21** and **Table 4. 22** in Annex 4.



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Table 34: Total dose dispensed in mg per indications for dispensed prescriptions for Doreta SR sub-population in pre-RMM and post-RMM periods – Hungary

Hungary		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	43,601	56,710
Total dose dispensed in mg per dorsalgia for dispensed prescriptions	Mean (SD)	21,055 (8,775)	24,040 (7,310)
	Median [IQR]	21,750 (0)	21,750 (0)
	Missing (N)	0	0
Total dose dispensed in mg per thoracic, thoracolumbar, and lumbosacral intervertebral disc disorders for dispensed prescriptions	Mean (SD)	21,489 (8,987)	24,655 (8,442)
	Median [IQR]	21,750 (0)	21,750 (0)
	Missing (N)	0	0
Total dose dispensed in mg per spondylosis for dispensed prescriptions	Mean (SD)	22,367 (9,349)	23,766 (7,490)
	Median [IQR]	21,750 (0)	21,750 (0)
	Missing (N)	0	0
Total dose dispensed in mg per osteoarthritis of knee for dispensed prescriptions	Mean (SD)	22,457 (9,562)	24,287(7,454)
	Median [IQR]	21,750 (0)	21,750 (0)
	Missing (N)	0	0
Total dose dispensed in mg per pain, unspecified for dispensed prescriptions	Mean (SD)	22,030 (9,719)	24,918 (8,362)
	Median [IQR]	21,750 (0)	21,750 (0)

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Hungary		Pre-RMM period	Post-RMM period
	Missing (N)	0	0

As for IR FDCs of tramadol/paracetamol prescriptions dispensed for dorsalgia, the mean (SD) of total dose (mg) per dispensed prescription was 12,810 (4,894) and 15,707 (8,242), with a median (IQR) of 10,875 (0) and 10,875 (10,875) in the pre-RMM and post-RMM periods, respectively (**Table 35**). The total doses of tramadol and paracetamol for IR FDCs of tramadol/paracetamol per treatment indications are provided separately, as shown in **Table 4. 23** and **Table 4. 24** in Annex 4.

Table 35: Total dose dispensed in mg per indications for dispensed prescriptions for IR FDCs of tramadol/paracetamol sub-population in pre-RMM and post-RMM periods – Hungary

Hungary		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	97,620	977,564
Total dose dispensed in mg per dorsalgia for dispensed prescriptions	Mean (SD)	12,810 (4,894)	15,707 (8,242)
	Median [IQR]	10,875 (0)	10,875 (10,875)
	Missing (N)	0	0
Total dose dispensed in mg per thoracic, thoracolumbar, and lumbosacral intervertebral disc disorders for dispensed prescriptions	Mean (SD)	13,062 (5,116)	16,545 (8,802)
	Median [IQR]	10,875 (0)	10,875 (10,875)
	Missing (N)	0	0
	Mean (SD)	12,928 (5,033)	16,391 (8,585)
	Median [IQR]	10,875 (0)	10,875 (10,875)

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Hungary		Pre-RMM period	Post-RMM period
Total dose dispensed in mg	Missing (N)	0	0
Total dose dispensed in mg per osteoarthritis of knee for dispensed prescriptions	Mean (SD)	13,276 (5,176)	16,501 (8,466)
	Median [IQR]	10,875 (0)	10,875 (10,875)
	Missing (N)	0	0
Total dose dispensed in mg per pain, unspecified for dispensed prescriptions	Mean (SD)	13,530 (5,847)	16,479 (8,755)
	Median [IQR]	10,875 (0)	10,875 (10,875)
	Missing (N)	0	0

11.3.1.4 Concomitant diagnoses

Detailed description of top 20 co-diagnosis for in dispensed prescriptions for Doreta SR is presented in

Table 36. In both periods, primary hypertension was the most prevalent concomitant diagnosis for dispensed prescriptions of Doreta SR and followed by disorders of lipoprotein metabolism and other lipidaemia (~4%) and type 2 diabetes mellitus (~4%).

Table 36: Concomitant diagnoses in dispensed prescriptions for Doreta SR sub-population in pre-RMM and post-RMM periods - Hungary

Hungary		Pre-RMM period	Post-RMM period
Number of co-prescriptions	Count (N)	1,327,230	2,264,466

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Hungary		Pre-RMM period	Post-RMM period
Concomitant diagnoses in dispensed prescriptions	Essential (primary) hypertension	294,584 (22.20%)	544,719 (24,06%)
	Disorders of lipoprotein metabolism and other lipidaemia	49,383 (3.72%)	96,114 (4,24%)
	Type 2 diabetes mellitus	45,889 (3.46%)	95,551 (4,22%)
	Chronic Ischaemic heart disease	44,428 (3.35%)	63,003 (2,78%)
	Gastro-oesophageal reflux disease	44,241 (3.33%)	99,703 (4,40%)
	Dorsalgia	37,136 (2.80%)	56,984 (2.52%)
	Angina pectoris	32,622 (2.46%)	52,796 (2.33%)
	Other anxiety disorders	27,879 (2.10%)	42,810 (1.89%)
	Osteoporosis without current pathological fracture	26,901 (2.03%)	43,109 (1.90%)
	Other chronic obstructive pulmonary disease	22,066 (1.66%)	34,518 (1.52%)
	Other and unspecified dermatitis	21,928 (1.65%)	31,473 (1.39%)

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Hungary		Pre-RMM period	Post-RMM period
	Spondylosis	21,423 (1.61%)	25,177 (1.11%)
	Osteoarthritis of knee	20,262 (1.53%)	24,801 (1.10%)
	Thoracic, thoracolumbar, and lumbosacral intervertebral disc disorders	18,773 (1.41%)	0 (0.00%)
	Asthma	17,927 (1.35%)	31,885 (1.41%)
	Type 1 diabetes mellitus	17,081 (1.29%)	24,958 (1.10%)
	Heart failure	17,021 (1.28%)	29,320 (1.29%)
	Gout	15,862 (1.20%)	28,763 (1.27%)
	Other joint disorder, not elsewhere classified	15,522 (1.17%)	25,505 (1.13%)
	Atrial fibrillation and flutter	14,179 (1.07%)	32,011 (1.41%)
	Functional dyspepsia	0 (0.00%)	24,968 (1.1%)
	Missing (N)	0	0

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Detailed description of top 20 co-diagnosis for dispensed prescriptions for IR FDCs of tramadol/paracetamol is shown in **Table 37**. In both periods, primary hypertension was the most prevalent (~23%) concomitant diagnosis for dispensed prescriptions of Doreta SR and followed by disorders of lipoprotein metabolism.

Table 37: Concomitant diagnoses in dispensed prescriptions for IR FDCs of tramadol/paracetamol sub-population in pre-RMM and post-RMM periods - Hungary

Hungary		Pre-RMM period	Post-RMM period
Number of co-prescriptions	Count (N)	2,923,106	20,906,426
Concomitant diagnoses in dispensed prescriptions	Essential (primary) hypertension	651,939(22.30%)	5,082,599 (24.31%)
	Disorders of lipoprotein metabolism and other lipidaemia	112,341(3.84%)	891,471 (4.26%)
	Chronic Ischaemic heart disease	101,579(3.48%)	615,581 (2.94%)
	Gastro-oesophageal reflux disease	98,434(3.37%)	899,678 (4.30%)
	Type 2 diabetes mellitus	97,533(3.34%)	842,418 (4.03%)
	Dorsalgia	80,592 (2.76%)	491,585 (2.35%)
	Angina pectoris	76,181 (2.61%)	508,983 (2.43%)
	Osteoporosis without current pathological fracture	64,139 (2.19%)	380,856 (1.82%)

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Hungary		Pre-RMM period	Post-RMM period
	Other anxiety disorders	58,751 (2.01%)	398,843 (1.91%)
	Other chronic obstructive pulmonary disease	51,305 (1.76%)	327,570 (1.57%)
	Other and unspecified dermatitis	48,578 (1.66%)	298,905 (1.43%)
	Spondylosis	45,998 (1.57%)	219,979 (1.05%)
	Asthma	42,820 (1.46%)	294,530 (1.41%)
	Osteoarthritis of knee	41,699 (1.43%)	208,750 (1.00%)
	Thoracic, thoracolumbar, and lumbosacral intervertebral disc disorders	40,300 (1.38%)	0 (0.00%)
	Type 1 diabetes mellitus	37,691 (1.29%)	222,770 (1.07%)
	Heart failure	36,563 (1.25%)	284,298 (1.36%)
	Gout	32,663 (1.12%)	254,273 (1.22%)
	Other joint disorder, not elsewhere classified	31,995 (1.09%)	232,371 (1.11%)
	Atrial fibrillation and flutter	31,691 (1.08%)	314,570 (1.50%)

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Hungary		Pre-RMM period	Post-RMM period
	Functional dyspepsia	0 (0.00%)	239,451 (1.15%)
	Missing (N)	10	0

11.3.1.5 Concomitant prescriptions

During the pre-RMM and post-RMM periods, 53,364 and 56,384 concomitant prescriptions were dispensed for Doreta SR, respectively (**Table 38**). The majority of concomitantly dispensed prescriptions were opioids (N02A), 32,829 (61.52%) in the pre-RMM period and 39,654 (70.33%) in the post-RMM period. Among the drugs of interest with known interaction with tramadol/paracetamol, only carbamazepine was concomitantly dispensed, with 2,920 (5.47%) prescriptions during the pre-RMM period and with 4,036 (7.16%) prescriptions during the post-RMM period. Regarding other paracetamol-containing products (N02BE), not many prescriptions were concomitantly dispensed with Doreta SR, 1,125 (2.11%) in the pre-RMM period and 1,214 (2.15%) in the post-RMM period. **Table 38** presents detailed information about concomitant prescriptions for Doreta SR in both periods.

Table 38: Concomitant prescriptions for Doreta SR sub-population in pre-RMM and post-RMM periods - Hungary

Hungary		Pre-RMM period	Post-RMM period
Number of co-prescriptions	Count (N)	53,364	56,384
	Other paracetamol- containing products ATC code: N02BE	1,125 (2.11%)	1,214 (2.15%)
	Other analgesics		

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Hungary		Pre-RMM period	Post-RMM period
	• Opioids (ATC code: N02A) :	32,829 (61.52%)	39,654 (70.33%)
	○ Natural opium alkaloids	2,051 (3.84%)	3,396 (6.02%)
	○ Phenylpiperidine derivatives	4,041 (7.57%)	8,027 (14.24%)
	○ Diphenylpropylamine derivatives	<10 (0.00%)	<10 (0.00%)
	○ Benzomorphan derivatives	<10 (0.00%)	<10 (0.00%)
	○ Oripavine derivatives	<10 (0.00%)	<10 (0.00%)
	○ Morphinan derivatives	<10 (0.00%)	<10 (0.00%)
	○ Opioids in combination with antispasmodics	<10 (0.00%)	<10 (0.00%)
	○ Opioids in combination with non-opioid	<10 (0.00%)	<10 (0.00%)
	○ Other opioids	26,737 (50.10%)	28,231 (50.07%)
	Other analgesics and antipyretics (ATC code: N02B)	15,019 (28.14%)	9,532 (16.91%)
	○ Salicylic acid and derivatives	585 (1.10%)	806 (1.43%)
	○ Pyrazolones	14,434 (27.05%)	8,726 (15.48%)
	○ Other analgesics and antipyretics	<10 (0.00%)	<10 (0.00%)
	Antimigraine preparations (ATC code: N02C)	1,470 (2.75%)	1,868 (3.31%)
	○ Ergot alkaloids (ATC code: N02CA)	629 (1.18%)	244 (0.43%)
	○ Corticosteroid derivatives (ATC code:	<10 (0.00%)	<10 (0.00%)

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Hungary		Pre-RMM period	Post-RMM period
	○ Selective serotonin (5-HT ₁) agonists	270 (0.51%)	904 (1.60%)
	○ Calcitonin gene-related peptide (CGRP)	<10 (0.00%)	<10 (0.00%)
	○ Other antimigraine preparations	571 (1.07%)	720 (1.28%)
Drug with known interaction with tramadol/paracetamol			
	Monoamine oxidase inhibitors (MAOIs)	<10 (0.00%)	<10 (0.00%)
	Carbamazepine	2,920 (5.47%)	4,036 (7.16%)
	Opioid-type pain relievers:	<10 (0.00%)	<10 (0.00%)
	○ Buprenorphine	<10 (0.00%)	<10 (0.00%)
	○ Buprenorphine, combinations	<10 (0.00%)	<10 (0.00%)
	○ Nalbuphine	<10 (0.00%)	<10 (0.00%)
	○ Pentazocine	<10 (0.00%)	<10 (0.00%)

For IR FDCs of tramadol/paracetamol, there were 95,337 and 442,256 concomitant prescriptions for IR FDCs of tramadol/paracetamol in the pre-RMM and post-RMM periods, respectively (**Table 39**). The majority of concomitantly dispensed prescriptions were in the opioid category (N02A), 51,053 (53.55%) in the pre-RMM period and 269,607 (60.96%) in the post-RMM period. Only carbamazepine, a drug with known interactions with tramadol/paracetamol, was concomitantly dispensed, 5,671 (5.95%) and 39,542 (8.94%), respectively, in the pre-RMM and post-RMM periods. Regarding other paracetamol-containing products (N02BE), not many prescriptions were concomitantly dispensed with IR FDCs of tramadol/paracetamol, 2,731 (2.86%) in the pre-RMM period and 15,753 (3.56%) in the post-RMM period. **Table 39** provides detailed information about concomitant prescriptions for IR FDCs of tramadol/paracetamol.

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Table 39: Concomitant prescriptions for IR FDCs of tramadol/paracetamol sub-population in pre-RMM and post-RMM periods - Hungary

Hungary		Pre-RMM period	Post-RMM period
Number of co-prescriptions	Count (N)	95,337	442,256
	Other paracetamol- containing products (ATC code: N02BE)	2,731 (2.86%)	15,753 (3.56%)
	Other analgesics		
	• Opioids (ATC code: N02A) :	51,053 (53.55%)	269,607 (60.96%)
	○ Natural opium alkaloids	3,078 (3.23%)	21,723 (4.91%)
	○ Phenylpiperidine derivatives	5,817 (6.10%)	56,656 (12.81%)
	○ Diphenylpropylamine derivatives	<10 (0.00%)	<10 (0.00%)
	○ Benzomorphan derivatives	<10 (0.00%)	<10 (0.00%)
	○ Oripavine derivatives	<10 (0.00%)	<10 (0.00%)
	○ Morphinan derivatives	<10 (0.00%)	<10 (0.00%)
	○ Opioids in combination with antispasmodics	<10 (0.00%)	<10 (0.00%)
	○ Opioids in combination with non-opioid analgesics	<10 (0.00%)	<10 (0.00%)
	○ Other opioids	42,158 (44.22%)	191,228 (43.24%)
	Other analgesics and antipyretics (ATC code: N02B)	32,870 (34.48%)	100,232 (22.66%)

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Hungary		Pre-RMM period	Post-RMM period
	○ Salicylic acid and derivatives	1,235 (1.30%)	6,489 (1.47%)
	○ Pyrazolones	31,635 (33.18%)	93,743 (21.20%)
	○ Other analgesics and antipyretics	<10 (0.00%)	<10 (0.00%)
	Antimigraine preparations (ATC code: N02C)	3,010 (3.16%)	16,487(3.73%)
	○ Ergot alkaloids (ATC code: N02CA)	1,124 (1.18%)	2,792 (0.63%)
	○ Corticosteroid derivatives (ATC code: N02CB)	<10 (0.00%)	<10 (0.00%)
	○ Selective serotonin (5-HT ₁) agonists	535 (0.56%)	6,531 (1.48%)
	○ Calcitonin gene-related peptide (CGRP) antagonists	<10 (0.00%)	<10 (0.00%)
	○ Other antimigraine preparations	1,351 (1.42%)	7,164 (1.62%)
	Drug with known interaction with tramadol/paracetamol		
	Monoamine oxidase inhibitors (MAOIs)	<10 (0.00%)	<10 (0.00%)
	Carbamazepine	5,671 (5.95%)	39,542 (8.94%)
	Opioid-type pain relievers:	<10 (0.00%)	<10 (0.00%)
	○ Buprenorphine	<10 (0.00%)	<10 (0.00%)
	○ Buprenorphine, combinations	<10 (0.00%)	<10 (0.00%)
	○ Nalbuphine	<10 (0.00%)	<10 (0.00%)
	○ Pentazocine	<10 (0.00%)	<10 (0.00%)

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11.3.2 Secondary Analyses In Hungary

11.3.2.1 Patient characteristics

In the pre-RMM period, 89.51% of Doreta SR prescriptions were dispensed to patients aged 50 years or older; similarly, 87.18% during the post-RMM period. In total 71.04% and 65.68% of the prescriptions for Doreta SR were dispensed to females, respectively, in the pre-RMM and the post-RMM periods (**Table 40**).

As for IR FDCs of tramadol/paracetamol, the results were similar to those of Doreta SR in terms of age and gender. In the pre-RMM and post-RMM periods, 90.33% and 87.90% of tramadol and paracetamol IR FDCs were dispensed to patients aged 50 years or older, respectively. Overall, 73.46% and 69.60% of the prescriptions for IR FDCs of tramadol/paracetamol were dispensed to females (**Table 41**).

Table 40: Patient's demographic characteristics for Doreta SR sub-population in pre-RMM and post-RMM periods in the pre-RMM period - Hungary

Hungary		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	43,601	56,710
Age (years)	<20 years	14 (0.03%)	43 (0.08%)
	20-49 years	4,559 (10.46%)	7,227 (12.74%)
	≥50 years	39,028 (89.51%)	49,440 (87.18%)
	Missing (N)	0	0
Gender	Male	12,625 (28.96%)	19,464 (34.32%)
	Female	30,976 (71.04%)	37,246 (65.68%)
	Missing (N)	0	0

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Table 41: Patient's demographic characteristics for IR FDCs of tramadol/paracetamol sub-population in pre-RMM and post-RMM periods in the pre-RMM period - Hungary

Hungary		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	97,620	977,564
Age (years)	<20 years	52 (0.05%)	940 (0.10%)
	20-49 years	9,389 (9.62%)	117,391 (12.01%)
	≥50 years	88,179 (90.33%)	859,233 (87.90%)
	Missing (N)	0	0
Gender	Male	25,910 (26.54%)	297,197 (30.40%)
	Female	71,710 (73.46%)	680,367 (69.60%)
	Missing (N)	0	0

11.4 Other Analyses

Not applicable

11.5 Adverse Events/Adverse Reactions

Not applicable



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12. DISCUSSION

12.1 Key Results

The number of dispensed prescriptions of Doreta SR in the pre-RMM period and in the post-RMM period were 40,143 and 59,687 in the Czech Republic, 1,103,380 and 1,311,049 in Poland, and 43,601 and 56,710 in Hungary, respectively. The number of dispensed prescriptions of IR FDCs of tramadol/paracetamol in the pre-RMM period and in the post-RMM period were 168,842 and 239,112 in the Czech Republic, 1,556,992 and 1,452,126 in Poland, and 97,620 and 977,564 in Hungary, respectively. Across the included countries, the number of dispensed prescriptions of both drugs increased in the post-RMM period compared to the pre-RMM period, with the exception of Poland where the number of dispensed IR FDCs of tramadol/paracetamol was slightly lower in comparison to the number in the pre-RMM period. Of note, in Hungary, the dispensed prescriptions for IR FDC tramadol/paracetamol were ten times higher in the post-RMM period compared to the pre-RMM period.

Over the post-RMM period, the total doses per dispensed prescription of both drugs were higher than those during the pre-RMM period in all three countries. The mean (SD) of the total doses (mg) per dispensed prescription of Doreta SR in the pre-RMM period and in the post-RMM period were 38,400 (33,396) and 49,837 (44,513) in the Czech Republic, 37,529 (23,915) and 47,183 (32,878) in Poland, and 21,797 (9,177) and 24,581 (8,283) in Hungary, respectively. For the total doses per dispensed prescription of IR FDCs of tramadol/paracetamol, a similar trend as for Doreta SR was observed. The mean (SD) of the total doses (mg) for dispensed prescriptions of IR FDCs of tramadol/paracetamol in the pre-RMM period and in the post-RMM period were 22,202 (17,335) and 24,793 (20,664) in the Czech Republic, 21,024 (13,072) and 26,263 (20,243) in Poland, and 13,182 (5,345) and 16,338 (8,650) in Hungary, respectively.

In the Czech Republic and Hungary, dorsalgia was the most prevalent indication for dispensed prescriptions of both drugs in both periods. However, less than 10% of prescriptions included information about the treatment indication for Doreta SR and IR FDCs of tramadol/paracetamol in the Czech Republic.

In the Czech Republic, we observed a larger total dose (mg) of dispensed prescriptions of Doreta SR for dorsalgia, with a mean (SD) of 43,817 (41,131) and 56,873 (50,513) in the Czech Republic and 21,055 (8,775) and 24,040 (7,310) in Hungary, in the pre-RMM and post-RMM periods, respectively. Regarding of IR FDCs

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of tramadol/paracetamol, we also observed a larger total dose (mg) of dispensed prescriptions in the Czech Republic during both periods.

In Hungary, during both periods, primary hypertension was the most prevalent concomitant diagnosis for dispensed prescriptions of both drugs.

We observed a longer duration (days) of dispensed prescriptions of Doreta SR per treatment in the post-RMM period compared to the pre-RMM period, with a mean (SD) of 26 (23) days and 34 (31) days in the Czech Republic, 26 (16) days and 33 (23) days in Poland, and 30 (13) days and 34 (11) days in Hungary, respectively in the pre-RMM and the post-RMM periods. Likewise, the same pattern of an increase of duration of dispensed prescriptions of Doreta SR per treatment was observed for IR FDCs of tramadol/paracetamol in both periods, with a mean number of days (SD) of 15 (12) and 17 (14) in the Czech Republic and 15 (9) in Poland and 18 (14), and 36 (14) and 41 (18) in Hungary, respectively, in the pre-RMM and post-RMM periods.

During both periods, the majority of concomitantly dispensed prescriptions with Doreta SR were in the opioid category (N02A) in the pre-RMM and in the post-RMM periods, 38,577 (73.45%) and 68,055 (79.97%) in the Czech Republic, 602,551 (91.05%) and 689,911 (91.99%) in Poland, and 32,829 (61.52%) and 39,654 (70.33%) in Hungary, respectively. Concerning other paracetamol-containing products (N02BE), not many prescriptions were concomitantly dispensed with Doreta SR in the pre-RMM and post-RMM periods, 6 (0.01%) and 6 (0.01%) in the Czech Republic, 4,479 (0.68%) and 2,886 (0.38%) in Poland and 1,125 (2.11%) and 1,214 (2.15%) in Hungary, respectively. Regarding concomitantly dispensed prescriptions with IR FDCs of tramadol/paracetamol, the same trend as Doreta SR was observed in both periods across countries.

Among drugs with known interactions with tramadol/paracetamol, we observed only dispensed prescriptions for carbamazepine in the pre-RMM and in the post-RMM periods. To note, fewer prescriptions for carbamazepine were dispensed in the post-RMM periods in the Czech Republic and Poland, with 887 (1.69%) prescriptions during the pre-RMM compared to 706 (0.83%) during the post-RMM period in the Czech Republic, and 40,680 (6.15%) during the pre-RMM compared to 29,404 (3.92%) during the post-RMM period in Poland. However, slightly more prescriptions for carbamazepine were dispensed in the post-RMM periods in Hungary, 2,920 (5.47%) during the pre-RMM period compared to 4,036 (7.16%) during the post-RMM



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period. Similarly, only concomitant dispensed prescriptions of carbamazepine, from the category of drugs with known interactions with tramadol/paracetamol, were observed for IR FDCs of tramadol/paracetamol. In both periods, the majority of both drugs were dispensed to patients aged 50 years or older across countries. In all three countries, the majority of prescriptions for both medications were dispensed to females. It has been observed both in the Czech Republic and Poland that the dispensed prescriptions of Doreta SR and IR FDCs of tramadol/paracetamol were predominantly written by GPs in both periods. A note should be made regarding the lack of information available on prescriber characteristic in Hungary.

12.2 Limitations

In addition to the limitations related to risk of bias previously described in Section 10.6, further limitations specific to this report with respect to Hungary, Poland, and the Czech Republic are described below.

General limitation

As discussed in the background, the current study could not provide any information about overdoses or ADRs; however, it would be a valid method to provide some insight into the prescription practice in the pre-RMM and post-RMM periods.

Limitations related to the databases

- Age of patients as continuous variable was not available. In addition, information on gender for patients were available only for ~6% of dispensed prescriptions in the Czech Republic.
- Prescriber characteristics were not available in Hungary.
- Indications and co-diagnosis of the dispensed prescriptions were not available in Poland. In the Czech Republic, co-diagnosis of the dispensed prescriptions was also not available. The information on indications of the dispensed prescriptions was only available for ~6% of dispensed prescriptions.
- In all three countries, information on OTC prescriptions were not available.



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- All information is at the prescription level and there was 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 was lag time of 3-4 months for the IQVIA LRx claims database in the Czech Republic and 2-3 months for the NHIF Claims databases in Hungary. The lag time resulted in a longer timeline for this report.

Limitations related to the analytical approaches

- The ATC codes are the same for Doreta SR and IR FDC tramadol and paracetamol-containing products. This might result in misclassification of the Doreta SR if prescribers did not use the correct brand name; or if the pharmacy did not dispense the right brand name.
- In Hungary, results were not exported from the database if the count of individual data in the patient group was less than ten. This anonymisation rule has been used in compliance with the local policies in regard to anonymisation and the risk of identification in observational research.
- In Hungary, the post-RMM period was slightly longer than 18 months. It led to overestimating the number of prescriptions for both drugs in the post-RMM period.
- In the Czech Republic, for both Doreta SR and IR FDC of tramadol/paracetamol prescriptions, the daily data is available for 61% in the pre-RMM and post-RMM periods. For the remaining prescriptions, the data is available only with year-month information. It resulted in:
 - having a longer period, therefore, overestimating of the number of prescriptions of both drugs in both periods.
 - overestimating of the number of prescriptions which concomitantly dispensed with either Doreta SR or IR FDC tramadol and paracetamol when we run a post-hoc analysis (**Table 4. 9, Table 4. 10, Table 4. 15, and Table 4. 16** in Annex 4). We considered 30 days window for concomitant calculation but for prescriptions with only year-month information, the window can be 2 months.

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- In IQVIA datasets, the Czech Republic and Poland, we were able to run post-hoc analyses (**Table 5.1** and **Table 5.2** in Annex 5) to check the robustness of our results. However, we did not run any post-hoc analysis in Hungary as it was an external data source that we could not access directly.

12.3 Interpretation

This study aims to describe the prescribing practices before and after disseminating the RMMs in the three selected European countries: the Czech Republic, Poland, and Hungary. With the obtained numbers of dispensed prescriptions in each period, the number for each country exceeds the minimum number of dispensed prescriptions necessary to achieve sufficient precision of estimated proportions. This report provides results based on cumulative data recorded over the 17-month pre-RMM period in the Czech Republic, the 26-month pre-RMM period in Poland and the 13-month pre-RMM period in Hungary. The post-RMM period was 18 months in the Czech Republic and Poland and slightly longer (~19 months) in Hungary.

The number of prescriptions dispensed for Doreta SR in the post-RMM period was higher than in the pre-RMM period in all countries. In the Czech Republic and Hungary, the more extended post-RMM period contributed to this increase. Likewise, the total prescriptions for IR FDC tramadol/paracetamol dispensed in the post-RMM were more significant than in the pre-RMM period in the Czech Republic and Hungary. In Poland, however, this number was slightly lower during the post-RMM period. Compared to the pre-RMM period in Hungary, the number of prescriptions for IR FDC tramadol/paracetamol was ten times higher in the post-RMM period. Hungary's huge increase could not be attributed to any specific cause.

Both drugs were dispensed at higher total doses per dispensed prescription during the post-RMM period than during the pre-RMM period in all three countries. The total dose was calculated by multiplying the strength by the number of pills in the pack and the number of packs dispensed to the patient. Furthermore, the analysis showed that both drugs were dispensed for longer periods/ more days during the post-RMM period than during the pre-RMM period. These factors may have contributed to the increased total doses for both drugs in the post-RMM period. The results on the total doses dispensed prescriptions of both drugs across all three countries shall be interpreted considering the COVID-19 pandemic. Compared to the pre-RMM period, due to the COVID-19 pandemic, prescribers may have intended to provide patients with considerable medication refills. Therefore, it is plausible that they may have prescribed for a longer duration and larger packs of Doreta SR

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during the post-RMM period. According to a post-hoc analyses in both the Czech Republic and Poland, slightly larger packs (including more pills) of Doreta SR were dispensed during the post-RMM period; the analysis was not available for Hungary.

Furthermore, during both periods, the median duration (days) of dispensed prescriptions for Doreta SR per treatment was longer than for IR FDCs of tramadol/paracetamol in the Czech Republic and Poland. The longer duration of prescriptions of Doreta SR dispensed per treatment may indicate that Doreta SR was used to treat chronic pain conditions. It should also be noted that in Hungary, the median duration (days) of prescriptions dispensed for Doreta SR per treatment was the same as for IR FDCs of tramadol/paracetamol during both periods. In Hungary, primary hypertension was the most prevalent concomitant diagnosis for both drugs in both periods. Only ~6% of prescriptions dispensed in the Czech Republic included information on treatment indications. However, primary hypertension was the second indication for treatment that could have been mistakenly recorded as a treatment indication when it was actually a concomitant diagnosis. Hungary's results support this conclusion.

In all three countries, during both periods, prescriptions for opioids (N02A) were the most prevalent type of concomitant prescriptions (with a proportion ranging from 54 to 93%), dispensed within 30 days before/after Doreta SR or IR FDC tramadol/paracetamol prescription. The use of opioids is often the only option for patients suffering from severe pain, and they may also be a viable option for certain patient groups, such as the elderly. Additionally, FDCs containing tramadol and paracetamol may provide effective analgesia at lower opioid doses than monotherapy opioids (7). Regarding drugs which interact with FDC of tramadol/paracetamol, in the Czech Republic and Poland, there were no prescriptions for monoamine oxidase inhibitors dispensed concurrently with either study drug, in Hungary, zero to nine prescriptions of monoamine oxidase inhibitors might be dispensed concurrently with the study drugs. Only a number of prescriptions for carbamazepine, which is not recommended to be taken with Doreta SR, were dispensed concomitantly in both periods in all three selected countries.

Sex- and age-related patterns in the use of Doreta SR and IR FDC of tramadol/paracetamol were similar to those observed for the use of analgesics (8,9), most of the prescriptions were dispensed to elderly people and female in both periods across countries.

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Over half (ranging from 56% to 76%) of Doreta SR and IR FDC prescriptions were written by GPs. Based on the healthcare systems in the Czech Republic and Poland, this is to be expected.

12.4 Generalizability

This report is based on databases available in the Czech Republic, Poland, and Hungary. They broadly represent the general population regarding age, sex, and ethnicity in these three countries. In the current study, a pre-defined sample size was achieved for both periods in all three countries. This makes the study results generalisable for the three countries in both periods.

13. OTHER INFORMATION

Independent Ethics Committee (IEC) / Institutional Review Board (IRB) is not applicable for data base studies: National Competent Authorities were notified before the start of data extraction.

14. CONCLUSION

This report provides insights into the prescribing patterns of Doreta SR and IR FDCs of tramadol/paracetamol in the pre-RMM and post-RMM periods in the Czech Republic, Poland, and Hungary. Generally, both drugs were dispensed in increased doses and for a more extensive duration in the post-RMM period. It is possible that prescribers intended to provide significant medication refills to patients due to the COVID-19 pandemic. In Hungary, dorsalgia was the most prevalent indication for dispensed prescriptions. For both periods, opioids were predominantly dispensed with Doreta SR and IR FDCs of tramadol and paracetamol. No prescriptions in the Czech Republic and Poland as well as zero to nine prescriptions in Hungary for monoamine oxidase inhibitors, which must not be taken together with FDC of tramadol/paracetamol, were dispensed in both periods. As evidenced by sex- and age-related patterns in the use of analgesics, Doreta SR and IR FDC of tramadol/paracetamol were most commonly prescribed to elderly individuals and women in both periods. Both drugs were primarily prescribed by general practitioners.



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16. APPENDICES

Annex 1. List of stand-alone documents

No	Document reference number	Date
1	Protocol version 5/ amendment 5	27 September 2023
2	Statistical Analysis Plan version 1.4	01 March 2023



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Annex 2. Analgesics and paracetamol-containing drugs ATC codes

Analgesics	ATC
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	N02CB
Selective serotonin (5-HT ₁) agonists	N02CC
Calcitonin gene-related peptide (CGRP) antagonists	N02CD
Other antimigraine preparations	N02CX

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Annex 3. 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 the following:	
Carbamazepine	N03AF01 carbamazepine
Opioid-type pain relievers	
Buprenorphine	N02AE01 buprenorphine N07BC51 buprenorphine, combinations
Nalbuphine	N02AF02 nalbuphine
Pentazocine	N02AD01 pentazocine

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Annex 4. Supplementary tables

Table 4.1: Total dose of tramadol per dispensed prescription for Doreta SR sub-population in pre-RMM and post-RMM periods - the Czech Republic

Czech Republic		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	40,143	59,687
Total dose dispensed (mg)	Mean (SD)	3,972 (3,455)	5,156 (4,605)
	Median [IQR]	2,250 (5,250)	4,500 (4,500)
	Missing (N)	0	0

Total dose dispensed = Strength * Number of pills in the pack * Number of packs dispensed per prescription; strength= dose of tramadol in mg per pill

Table 4.2: Total dose of paracetamol per dispensed prescription for Doreta SR sub-population in pre-RMM and post-RMM periods - the Czech Republic

Czech Republic		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	40,143	59,687
Total dose dispensed (mg)	Mean (SD)	34,427 (29,941)	44,682 (39,908)

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Czech Republic		Pre-RMM period	Post-RMM period
	Median [IQR]	19,500 (45,500)	39,000 (39,000)
	Missing (N)	0	0

Total dose dispensed = Strength * Number of pills in the pack * Number of packs dispensed per prescription; strength= dose of paracetamol in mg per pill

Table 4.3: Total dose of tramadol per dispensed prescription for IR FDCs of tramadol and paracetamol in pre-RMM and post-RMM periods - the Czech Republic

Czech Republic		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	168,842	239,112
Total dose dispensed (mg)	Mean (SD)	2,297 (1,793)	2,565 (2,138)
	Median [IQR]	2,250 (1 125)	2,250 (2 250)
	Missing (N)	0	0

Total dose dispensed = Strength * Number of pills in the pack * Number of packs dispensed per prescription; strength= dose of tramadol in mg per pill

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Table 4.4: Total dose of paracetamol per dispensed prescription for IR FDCs of tramadol and paracetamol in pre-RMM and post-RMM periods - the Czech Republic

Czech Republic		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	168,842	239,112
Total dose dispensed (mg)	Mean (SD)	19,905 (15,542)	22,229 (18,526)
	Median [IQR]	19,500 (9,750)	19,500 (19,500)
	Missing (N)	0	0

Total dose dispensed = Strength * Number of pills in the pack * Number of packs dispensed per prescription; strength= dose of paracetamol in mg per pill

Table 4.5: Total dose of tramadol dispensed in mg per indications for dispensed prescriptions for Doreta SR sub-population in pre-RMM and post-RMM periods - the Czech Republic

Czech Republic		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	40,143	59,687
Total dose of tramadol dispensed in mg per dorsalgia for dispensed prescriptions	Mean (SD)	4,533 (4,255)	5,883 (5,225)
	Median [IQR]	2,250 (5,250)	4,500 (4,500)
	Missing (N)	0	0

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Czech Republic		Pre-RMM period	Post-RMM period
Total dose of tramadol dispensed in mg per primary hypertension for dispensed prescriptions	Mean (SD)	3,750 (2,886)	5,014 (3,239)
	Median [IQR]	2,250 (5,062)	4,500 (3,375)
	Missing (N)	0	0
Total dose of tramadol dispensed in mg per other intervertebral disc disease for dispensed prescriptions	Mean (SD)	4,492 (4,311)	5,916 (4,782)
	Median [IQR]	3,375 (4,500)	6,750 (4,500)
	Missing (N)	0	0
Total dose of tramadol dispensed in mg per other dorsopathies neck for dispensed prescriptions	Mean (SD)	3,795 (3,648)	6,469 (5,663)
	Median [IQR]	3,375 (3,375)	6,750 (4,500)
	Missing (N)	0	0
Total dose of tramadol dispensed in mg per Gonarthrosis (knee osteoarthritis) for dispensed prescriptions	Mean (SD)	4,572 (4,475)	5,161 (4,582)
	Median [IQR]	3,938 (5,625)	2,250 (4,500)
	Missing (N)	0	0

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Table 4.6: Total dose of paracetamol dispensed in mg per indications for dispensed prescriptions for Doreta SR sub-population in pre-RMM and post-RMM periods - the Czech Republic

Czech Republic		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	40,143	59,687
Total dose of paracetamol dispensed in mg per dorsalgia for dispensed prescriptions	Mean (SD)	39,284 (36,876)	50,989 (45,287)
	Median [IQR]	19,500 (45,500)	39,000 (39,000)
	Missing (N)	0	0
Total dose of paracetamol dispensed in mg per primary hypertension for dispensed prescriptions	Mean (SD)	32,500 (25,009)	43,456 (28,073)
	Median [IQR]	19,500 (43,875)	39,000 (29,250)
	Missing (N)	0	0
Total dose of paracetamol dispensed in mg per other intervertebral disc disease for dispensed prescriptions	Mean (SD)	38,928 (37,362)	51,275 (41,445)
	Median [IQR]	29,250 (39,000)	58,500 (39,000)
	Missing (N)	0	0
Total dose of paracetamol dispensed in mg per other dorsopathies neck for dispensed prescriptions	Mean (SD)	32,887 (31,618)	56,062 (49,077)
	Median [IQR]	29,250 (29,250)	58,500 (39,000)

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Czech Republic		Pre-RMM period	Post-RMM period
	Missing (N)	0	0
Total dose of paracetamol dispensed in mg per Gonarthrosis (knee osteoarthritis) for dispensed prescriptions	Mean (SD)	39,625 (38,783)	44,729 (39,707)
	Median [IQR]	34,125 (48,750)	19,500 (39,000)
	Missing (N)	0	0

Table 4.7: Total dose of tramadol dispensed in mg per indications for dispensed prescriptions for IR FDCs of tramadol/paracetamol sub-population in pre-RMM and post-RMM periods - Czech Republic

Czech Republic		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	168,842	239,112
Total dose of tramadol dispensed in mg per dorsalgia for dispensed prescriptions	Mean (SD)	1,964 (1,719)	2,296 (2,400)
	Median [IQR]	1,125 (1,125)	1,125 (1,125)
	Missing (N)	0	0
Total dose of tramadol dispensed in mg per other intervertebral disc disease for dispensed prescriptions	Mean (SD)	2,059 (1,423)	2,819 (2,332)
	Median [IQR]	1,125 (1,125)	2,250 (2,250)

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Czech Republic		Pre-RMM period	Post-RMM period
	Missing (N)	0	0
Total dose of tramadol dispensed in mg per primary hypertension for dispensed prescriptions	Mean (SD)	2,606 (1,866)	2,639 (1,985)
	Median [IQR]	2,250 (2,250)	2,250 (2,250)
	Missing (N)	0	0
Total dose of tramadol dispensed in mg per gonarthrosis (knee osteoarthritis) for dispensed prescriptions	Mean (SD)	2,070 (1,571)	2,362 (2,268)
	Median [IQR]	1,125 (1,125)	2,250 (1,125)
	Missing (N)	0	0
Total dose of tramadol dispensed in mg per other dorsopathies neck for dispensed prescriptions	Mean (SD)	1,844 (1,562)	1,991 (1,523)
	Median [IQR]	1,125 (1,125)	1,125 (1,125)
	Missing (N)	0	0
Total dose of tramadol dispensed in mg per Coxarthrosis (hip) for dispensed prescriptions	Mean (SD)	2,336 (1,435)	2,313 (1,940)
	Median [IQR]	2,250 (1,125)	1,125 (1,125)
	Missing (N)	0	0

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Table 4.8: Total dose of paracetamol dispensed in mg per indications for dispensed prescriptions for IR FDCs of tramadol/paracetamol sub-population in pre-RMM and post-RMM periods - Czech Republic

Czech Republic		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	168,842	239,112
Total dose of paracetamol dispensed in mg per dorsalgia for dispensed prescriptions	Mean (SD)	17,019 (14,900)	19,897 (20,803)
	Median [IQR]	9,750 (9,750)	9,750 (9,750)
	Missing (N)	0	0
Total dose of paracetamol dispensed in mg per other intervertebral disc disease for dispensed prescriptions	Mean (SD)	17,849 (12,332)	24,432 (20,209)
	Median [IQR]	9,750 (9,750)	19,500 (19,500)
	Missing (N)	0	0
Total dose of paracetamol dispensed in mg per primary hypertension for dispensed prescriptions	Mean (SD)	22,587 (16,173)	22,871 (17,200)
	Median [IQR]	19,500 (19,500)	19,500 (19,500)
	Missing (N)	0	0
Total dose of paracetamol dispensed in mg per	Mean (SD)	17,939 (13,616)	20,468 (19,659)

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Czech Republic		Pre-RMM period	Post-RMM period
gonarthrosis (knee osteoarthritis) for dispensed prescriptions	Median [IQR]	9,750 (9,750)	19,500 (9,750)
	Missing (N)	0	0
Total dose of paracetamol dispensed in mg per other dorsopathies neck for dispensed prescriptions	Mean (SD)	15,978 (13,534)	17,257 (13,201)
	Median [IQR]	9,750 (9,750)	9,750 (9,750)
	Missing (N)	0	0
Total dose of paracetamol dispensed in mg per Coxarthrosis (hip) for dispensed prescriptions	Mean (SD)	20,247 (12,441)	20,047 (16,816)
	Median [IQR]	19,500 (9,750)	9,750 (9,750)
	Missing (N)	0	0

Table 4. 9: Concomitant prescriptions for Doreta SR sub-population in pre-RMM and post-RMM periods (30-day window) - the Czech Republic

Czech Republic		Pre-RMM period	Post-RMM period
Number of co-prescriptions	Count (N)	19,801	29,042
	Other paracetamol- containing products (ATC code: N02BE)	0 (0.00%)	1 (0.00%)

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Czech Republic		Pre-RMM period	Post-RMM period
	Other analgesics		
	• Opioids (ATC code: N02A) :	12,529 (63.27%)	20,354 (70.08%)
	○ Natural opium alkaloids	1,048 (5.29%)	1,714 (5.90%)
	○ Phenylpiperidine derivatives	639 (3.23%)	1,394 (4.80%)
	○ Diphenylpropylamine derivatives	13 (0.07%)	40 (0.14%)
	○ Benzomorphan derivatives	0 (0.00%)	0 (0.00%)
	○ Oripavine derivatives	216 (1.09%)	393 (1.35%)
	○ Morphinan derivatives	0 (0.00%)	0 (0.00%)
	○ Opioids in combination with antispasmodics	0 (0.00%)	0 (0.00%)
	○ Opioids in combination with non-opioid	5,500 (27.78%)	11,214 (38.61%)
	○ Other opioids	5,113 (25.82%)	5,599 (19.28%)
	Other analgesics and antipyretics (ATC code: N02B)	6,517 (32.91%)	7,910 (27.24%)
	○ Salicylic acid and derivatives	1,327 (6.70%)	1,136 (3.91%)
	○ Pyrazolones	5,190 (26.21%)	6,774 (23.32%)
	○ Other analgesics and antipyretics	0 (0.00%)	0 (0.00%)
	Antimigraine preparations (ATC code : N02C)	441 (2.23%)	544 (1.87%)

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Czech Republic		Pre-RMM period	Post-RMM period
	○ Ergot alkaloids (ATC code: N02CA)	0 (0.00%)	0 (0.00%)
	○ Ergot alkaloids (ATC code: N02CB)	0 (0.00%)	0 (0.00%)
	○ Selective serotonin (5-HT ₁) agonists	441 (2.23%)	520 (1.79%)
	○ Calcitonin gene-related peptide (CGRP)	0 (0.00%)	24 (0.08%)
	○ Other antimigraine preparations	0 (0.00%)	0 (0.00%)
	Drug with known interaction with tramadol/paracetamol		
	Monoamine oxidase inhibitors (MAOIs)	0 (0.00%)	0 (0.00%)
	Carbamazepine	314 (1.59%)	233 (0.80%)
	Opioid-type pain relievers:	0 (0.00%)	0 (0.00%)
	○ Buprenorphine	0 (0.00%)	0 (0.00%)
	○ Buprenorphine, combinations	0 (0.00%)	0 (0.00%)
	○ Nalbuphine	0 (0.00%)	0 (0.00%)
	○ Pentazocine	0 (0.00%)	0 (0.00%)

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Table 4. 10: Concomitant prescriptions for IR FDCs of tramadol/paracetamol sub-population in pre-RMM and post-RMM periods (30-day window)- the Czech Republic

Czech Republic		Pre-RMM period	Post-RMM period
Number of co-prescriptions	Count (N)	72,592	102,749
	Other paracetamol-containing products (ATC code: N02BE)	2 (0.00%)	1 (0.00%)
	Other analgesics		
	• Opioids (ATC code: N02A) :	45,950 (63.30%)	64,320 (62.60%)
	○ Natural opium alkaloids	4,541 (6.26%)	5,261 (5.12%)
	○ Phenylpiperidine derivatives	3,254 (4.48%)	5,799 (5.64%)
	○ Diphenylpropylamine derivatives	75 (0.10%)	187 (0.18%)
	○ Benzomorphan derivatives	0 (0.00%)	0 (0.00%)
	○ Oripavine derivatives	1,077 (1.48%)	1,469 (1.43%)
	○ Morphinan derivatives	4 (0.01%)	12 (0.01%)
	○ Opioids in combination with antispasmodics	0 (0.00%)	0 (0.00%)
	○ Opioids in combination with non-opioid analgesics	18,567 (25.58%)	32,421 (31.55%)
	○ Other opioids	18,432 (25.39%)	19,171 (18.66%)
	Other analgesics and antipyretics (ATC code: N02B)	24,088 (33.18%)	34,766 (33.84%)

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Czech Republic		Pre-RMM period	Post-RMM period
	○ Salicylic acid and derivatives	3,933 (5.42%)	4,876 (4.75%)
	○ Pyrazolones	20,155 (27.76%)	29,890 (29.09%)
	○ Other analgesics and antipyretics	0 (0.00%)	0 (0.00%)
	Antimigraine preparations (ATC code: N02C)	1,601 (2.21%)	2,535 (2.47%)
	○ Ergot alkaloids (ATC code: N02CA)	0 (0.00%)	0 (0.00%)
	○ Ergot alkaloids (ATC code: 02CB)	0 (0.00%)	0 (0.00%)
	○ Selective serotonin (5-HT ₁) agonists	1,601 (2.21%)	2,440 (2.37%)
	○ Calcitonin gene-related peptide (CGRP)	0 (0.00%)	95 (0.09%)
	○ Other antimigraine preparations	0 (0.00%)	0 (0.00%)
Drug with known interaction with tramadol/paracetamol			
	Monoamine oxidase inhibitors (MAOIs)	0 (0.00%)	0 (0.00%)
	Carbamazepine	948 (1.31%)	1,093 (1.06%)
	Opioid-type pain relievers:	0 (0.00%)	0 (0.00%)
	○ Buprenorphine	0 (0.00%)	0 (0.00%)
	○ Buprenorphine, combinations	3 (0.00%)	34 (0.03%)
	○ Nalbuphine	0 (0.00%)	0 (0.00%)
	○ Pentazocine	0 (0.00%)	0 (0.00%)

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Table 4.11: Total dose of tramadol per dispensed prescription for Doreta SR sub-population in pre-RMM and post-RMM periods - Poland

Poland		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	1,103,380	1,311,049
Total dose dispensed (mg)	Mean (SD)	3,882 (2,474)	4,881 (3,401)
	Median [IQR]	3,375 (2,250)	4,500 (4,500)
	Missing (N)	0	0

Total dose dispensed = Strength * Number of pills in the pack * Number of packs dispensed per prescription; strength= dose of tramadol in mg per pill

Table 4.12: Total dose of paracetamol per dispensed prescription for Doreta SR sub-population in pre-RMM and post-RMM periods - Poland

Poland		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	1,103,380	1,311,049
Total dose dispensed (mg)	Mean (SD)	33,646 (21,441)	42,302 (29,477)
	Median [IQR]	29,250 (19,500)	39,000 (39,000)
	Missing (N)	0	0

Total dose dispensed = Strength * Number of pills in the pack * Number of packs dispensed per prescription; strength= dose of paracetamol in mg per pill

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Table 4.13: Total dose of tramadol per dispensed prescription for IR FDCs of tramadol/paracetamol in pre-RMM and post-RMM periods - Poland

Poland		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	1,556,992	1,452,126
Total dose dispensed (mg)	Mean (SD)	2,175 (1,352)	2,717 (2,094)
	Median [IQR]	2,250 (1,125)	2,250 (2,250)
	Missing (N)	0	0

Total dose dispensed = Strength * Number of pills in the pack * Number of packs dispensed per prescription; strength= dose of tramadol in mg per pill

Table 4.14: Total dose of paracetamol per dispensed prescription for IR FDCs of tramadol/paracetamol in pre-RMM and post-RMM periods - Poland

Poland		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	1,556,992	1,452,126
Total dose dispensed (mg)	Mean (SD)	18,849 (11,720)	23,546 (18,149)
	Median [IQR]	19,500 (9,750)	19,500 (19,500)
	Missing (N)	0	0

Total dose dispensed = Strength * Number of pills in the pack * Number of packs dispensed per prescription; strength= dose of paracetamol in mg per pill

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Table 4. 15: Concomitant prescriptions for Doreta SR sub-population in pre-RMM and post-RMM periods – Poland (with 30 days window)

Poland		Pre-RMM period	Post-RMM period
Number of co-prescriptions	Count (N)	277,966	425,781
	Other paracetamol- containing products ATC code: N02BE	1,476 (0.53%)	1,162 (0.27%)
	Other analgesics		
	• Opioids (ATC code: N02A) :	256,072 (92.12%)	397,221 (93.29%)
	○ Natural opium alkaloids	11,420 (4.11%)	16,270 (3.82%)
	○ Phenylpiperidine derivatives	7,534 (2.71%)	7,778 (1.83%)
	○ Diphenylpropylamine derivatives	103 (0.04%)	232 (0.05%)
	○ Benzomorphan derivatives	0 (0.00%)	0 (0.00%)
	○ Oripavine derivatives	28,554 (10.27%)	42,296 (9.93%)
	○ Morphinan derivatives	0 (0.00%)	0 (0.00%)
	○ Opioids in combination with antispasmodics	0 (0.00%)	0 (0.00%)
	○ Opioids in combination with non-opioid analgesics	154,895 (55.72%)	278,312 (65.37%)
	○ Other opioids	53,566 (19.27%)	52,333 (12.29%)
	- Other analgesics and antipyretics (ATC code: N02B)	2,553 (0.92%)	3,648 (0.86%)
	○ Salicylic acid and derivatives	114 (0.04%)	78 (0.02%)

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Poland		Pre-RMM period	Post-RMM period
	○ Pyrazolones	1,811 (0.65%)	3,040 (0.71%)
	○ Other analgesics and antipyretics	628 (0.23%)	530 (0.12%)
	- Antimigraine preparations (ATC code: N02C)	3,131 (1.13%)	10,044 (2.36%)
	○ Ergot alkaloids (ATC code: N02CA)	150 (0.05%)	73 (0.02%)
	○ Ergot alkaloids (ATC code: N02CB)	0 (0.00%)	0 (0.00%)
	○ Selective serotonin (5-HT ₁) agonists	1,898 (0.68%)	8,565 (2.01%)
	○ Calcitonin gene-related peptide (CGRP) antagonists	0 (0.00%)	4 (0.00%)
	○ Other antimigraine preparations	1,083 (0.39%)	1,402 (0.33%)
	Drug with known interaction with tramadol/paracetamol		
	Monoamine oxidase inhibitors (MAOIs)	0 (0.00%)	0 (0.00%)
	Carbamazepine	14,734 (5.30%)	13,706 (3.22%)
	Opioid-type pain relievers:	0 (0.00%)	0 (0.00%)
	○ Buprenorphine	0 (0.00%)	0 (0.00%)
	○ Buprenorphine, combinations	0 (0.00%)	0 (0.00%)
	○ Nalbuphine	0 (0.00%)	0 (0.00%)
	○ Pentazocine	0 (0.00%)	0 (0.00%)

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Table 4. 16: Concomitant prescriptions for IR FDCs of tramadol/paracetamol sub-population in pre-RMM and post-RMM periods – Poland (with 30 days window)

Poland		Pre-RMM period	Post-RMM period
Number of co-prescriptions	Count (N)	318,252	422,024
	Other paracetamol- containing products (ATC code: N02BE)	1,982 (0.62%)	1,674 (0.40%)
	Other analgesics		
	• Opioids (ATC code: N02A) :	289,562 (90.99%)	392,671 (93.04%)
	○ Natural opium alkaloids	9,825 (3.09%)	12,564 (2.98%)
	○ Phenylpiperidine derivatives	5,751 (1.81%)	6,799 (1.61%)
	○ Diphenylpropylamine derivatives	120 (0.04%)	122 (0.03%)
	○ Benzomorphan derivatives	0 (0.00%)	0 (0.00%)
	○ Oripavine derivatives	25,907 (8.14%)	35,959 (8.52%)
	○ Morphinan derivatives	0 (0.00%)	0 (0.00%)
	○ Opioids in combination with antispasmodics	0 (0.00%)	0 (0.00%)
	○ Opioids in combination with non-opioid analgesics	190,808 (59.96%)	296,376 (70.23%)
	○ Other opioids	57,151 (17.96%)	40,851 (9.68%)
	Other analgesics and antipyretics (ATC code: N02B)	4,037 (1.27%)	5,143 (1.22%)

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Poland		Pre-RMM period	Post-RMM period
	○ Salicylic acid and derivatives	183 (0.06%)	56 (0.01%)
	○ Pyrazolones	3,064 (0.96%)	4,432 (1.05%)
	○ Other analgesics and antipyretics	790 (0.25%)	655 (0.16%)
	Antimigraine preparations (ATC code: N02C)	3,857 (1.21%)	8,893 (2.11%)
	○ Ergot alkaloids (ATC code: N02CA)	183 (0.06%)	108 (0.03%)
	○ Ergot alkaloids (ATC code: 02CB)	0 (0.00%)	0 (0.00%)
	○ Selective serotonin (5-HT ₁) agonists	2,339 (0.73%)	7,347 (1.74%)
	○ Calcitonin gene-related peptide (CGRP) antagonists	0 (0.00%)	2 (0.00%)
	○ Other antimigraine preparations	1,335 (0.42%)	1,436 (0.34%)
	Drug with known interaction with tramadol/paracetamol		
	Monoamine oxidase inhibitors (MAOIs)	0 (0.00%)	0 (0.00%)
	Carbamazepine	18,814 (5.91%)	13,643 (3.23%)
	Opioid-type pain relievers:	0 (0.00%)	0 (0.00%)
	○ Buprenorphine	0 (0.00%)	0 (0.00%)
	○ Buprenorphine, combinations	0 (0.00%)	0 (0.00%)
	○ Nalbuphine	0 (0.00%)	0 (0.00%)
	○ Pentazocine	0 (0.00%)	0 (0.00%)

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Table 4.17: Total dose of tramadol per dispensed prescription for Doreta SR sub-population in pre-RMM and post-RMM periods - Hungary

Hungary		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	43,601	56,710
Total dose dispensed	Mean (SD)	2,255 (949)	2,543 (857)
	Median [IQR]	2,250 (0)	2,250 (0)
	Missing (N)	0	0

Total dose dispensed = Strength * Number of pills in the pack * Number of packs dispensed per prescription; strength= dose of tramadol in mg per pill

Table 4.18: Total dose of paracetamol per dispensed prescription for Doreta SR sub-population in pre-RMM and post-RMM periods - Hungary

Hungary		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	43,601	56,710
Total dose dispensed	Mean (SD)	19,542 (8,228)	22,038 (7,426)
	Median [IQR]	19,500 (0)	19,500 (0)
	Missing (N)	0	0

Total dose dispensed = Strength * Number of pills in the pack * Number of packs dispensed per prescription; strength= dose of paracetamol in mg per pill

Table 4.19: Total dose of tramadol per dispensed prescription IR FDCs of tramadol/paracetamol in pre-RMM and post-RMM periods - Hungary

Hungary	Pre-RMM period	Post-RMM period
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Number of prescriptions	Count (N)	97,620	977,564
Total dose dispensed	Mean (SD)	1,364 (553)	1,690 (895)
	Median [IQR]	1,125 (0)	1,125 (1,125)
	Missing (N)	0	0

Total dose dispensed = Strength * Number of pills in the pack * Number of packs dispensed per prescription; strength= dose of tramadol in mg per pill

Table 4.20: Total dose of paracetamol per dispensed prescription for IR FDCs of tramadol/paracetamol in pre-RMM and post-RMM periods - Hungary

Hungary		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	97,620	977,564
Total dose dispensed	Mean (SD)	11,818 (4,792)	14,648 (7,755)
	Median [IQR]	9,750 (0)	9,750 (9,750)
	Missing (N)	0	0

Total dose dispensed = Strength * Number of pills in the pack * Number of packs dispensed per prescription; strength= dose of paracetamol in mg per pill

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Table 4. 21: Total dose of tramadol dispensed in mg per indications for dispensed prescriptions for Doreta SR sub-population in pre-RMM and post-RMM periods – Hungary

Hungary		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	43,601	56,710
Total dose of tramadol dispensed in mg per dorsalgia for dispensed prescriptions	Mean (SD)	2,178 (908)	2,487 (756)
	Median [IQR]	2,250 (0)	2,250 (0)
	Missing (N)	0	
Total dose of tramadol dispensed in mg per thoracic, thoracolumbar, and lumbosacral intervertebral disc disorders for dispensed prescriptions	Mean (SD)	2,223 (930)	2,551 (873)
	Median [IQR]	2,250 (0)	2,250 (0)
	Missing (N)	0	0
Total dose of tramadol dispensed in mg per spondylosis for dispensed prescriptions	Mean (SD)	2,314 (967)	2,459 (775)
	Median [IQR]	2,250 (0)	2,250 (0)
	Missing (N)	0	0
Total dose of tramadol dispensed in mg per osteoarthritis of knee for dispensed prescriptions	Mean (SD)	2,323 (989)	2,512 (771)
	Median [IQR]	2,250 (0)	2,250 (0)

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	Missing (N)	0	0
Total dose of tramadol dispensed in mg per pain, unspecified for dispensed prescriptions	Mean (SD)	2,279 (1,005)	2,578 (865)
	Median [IQR]	2,250 (0)	2,250 (0)
	Missing (N)	0	0

Table 4. 22: Total dose of paracetamol dispensed in mg per indications for dispensed prescriptions for Doreta SR sub-population in pre-RMM and post-RMM periods – Hungary

Hungary		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	43,601	56,710
Total dose of paracetamol dispensed in mg per dorsalgia for dispensed prescriptions	Mean (SD)	18,877 (7,867)	21,553 (6,554)
	Median [IQR]	19,500 (0)	19,500 (0)
	Missing (N)	0	0
Total dose of paracetamol dispensed in mg per thoracic, thoracolumbar, and lumbosacral intervertebral disc disorders for dispensed prescriptions	Mean (SD)	19,266 (8,057)	22,105 (7,569)
	Median [IQR]	19,500 (0)	19,500 (0)
	Missing (N)	0	0

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Total dose of paracetamol dispensed in mg per spondylosis for dispensed prescriptions	Mean (SD)	20,053 (8,382)	21,307 (6,715)
	Median [IQR]	19,500 (0)	19,500 (0)
	Missing (N)	0	0
Total dose of paracetamol dispensed in mg per osteoarthritis of knee for dispensed prescriptions	Mean (SD)	20,134 (8,573)	21,774 (6,683)
	Median [IQR]	19,500 (0)	19,500 (0)
	Missing (N)	0	0
Total dose of paracetamol dispensed in mg per pain, unspecified for dispensed prescriptions	Mean (SD)	19,751 (8,713)	22,341 (7,497)
	Median [IQR]	19,500 (0)	19,500 (0)
	Missing (N)	0	0

Table 4. 23: Total dose of tramadol dispensed in mg per indications for dispensed prescriptions for IR FDCs of tramadol/paracetamol sub-population in pre-RMM and post-RMM periods – Hungary

Country = Hungary		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	97,620	977,564
Total dose of tramadol dispensed in mg per	Mean (SD)	1,325 (506)	1,625 (853)

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Country = Hungary		Pre-RMM period	Post-RMM period
dorsalgia for dispensed prescriptions	Median [IQR]	1,125 (0)	1,125 (1,125)
	Missing (N)	0	0
Total dose of tramadol dispensed in mg per thoracic, thoracolumbar, and lumbosacral intervertebral disc disorders for dispensed prescriptions	Mean (SD)	1,351 (529)	1,712 (911)
	Median [IQR]	1,125 (0)	1,125 (1,125)
	Missing (N)	0	0
Total dose of tramadol dispensed in mg per spondylosis for dispensed prescriptions	Mean (SD)	1,337 (521)	1,696 (888)
	Median [IQR]	1,125 (0)	1,125 (1,125)
	Missing (N)	0	0
Total dose of tramadol dispensed in mg per osteoarthritis of knee for dispensed prescriptions	Mean (SD)	1,373 (535)	1,707 (876)
	Median [IQR]	1,125 (0)	1,125 (1,125)
	Missing (N)	0	0
Total dose of tramadol dispensed in mg per pain, unspecified for dispensed prescriptions	Mean (SD)	1,400 (605)	1,705 (906)
	Median [IQR]	1,125 (0)	1,125 (1,125)

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Country = Hungary		Pre-RMM period	Post-RMM period
	Missing (N)	0	0

Table 4. 24: Total dose of paracetamol dispensed in mg per indications for dispensed prescriptions for IR FDCs of tramadol/paracetamol sub-population in pre-RMM and post-RMM periods – Hungary

Hungary		Pre-RMM period	Post-RMM period
Number of prescriptions	Count (N)	97,620	977,564
Total dose of paracetamol dispensed in mg per dorsalgia for dispensed prescriptions	Mean (SD)	11,484 (4,387)	14,082 (7,390)
	Median [IQR]	9,750 (0)	9,750 (9,750)
	Missing (N)	0	0
Total dose of paracetamol dispensed in mg per thoracic, thoracolumbar, and lumbosacral intervertebral disc disorders for dispensed prescriptions	Mean (SD)	11,711 (4,587)	14,833 (7,891)
	Median [IQR]	9,750 (0)	9,750 (9,750)
	Missing (N)	0	0
Total dose of paracetamol dispensed in mg per spondylosis for dispensed prescriptions	Mean (SD)	11,590 (4,512)	14,695 (7,697)
	Median [IQR]	9,750 (0)	9,750 (9,750)

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Hungary		Pre-RMM period	Post-RMM period
	Missing (N)	0	0
Total dose of paracetamol dispensed in mg per osteoarthritis of knee for dispensed prescriptions	Mean (SD)	11,903 (4,640)	14,794 (7,591)
	Median [IQR]	9,750 (0)	9,750 (9,750)
	Missing (N)	0	0
Total dose of paracetamol dispensed in mg per pain, unspecified for dispensed prescriptions	Mean (SD)	12,130 (5,242)	14,774 (7,849)
	Median [IQR]	9,750 (0)	9,750 (9,750)
	Missing (N)	0	0

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Annex 5. Doreta SR packs

Table 5.1: Doreta SR packs dispensed in the Czech Republic

Pack information	Total in Pre-RMM period	Shares in Pre-RMM period	Total in Post-RMM period	Shares in Post-RMM period
37,5mg+325mg, n=10	1,181	3%	886	1%
37,5mg+325mg, n=20	1,890	5%	1,819	3%
37,5mg+325mg, n=30	8,862	22%	9,765	16%
37,5mg+325mg, n=90	1,729	4%	4,182	7%
75mg+650mg, n=10	785	2%	492	1%
75mg+650mg, n=20	1,497	4%	1,013	2%
75mg+650mg, n=30	15,720	39%	19,813	33%
75mg+650mg, n=90	8,479	21%	21,717	36%
Total	40,143	100%	59,687	100%

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Table 5.2: Doreta SR packs dispensed in Poland

Pack information	Total in Pre-RMM period	Shares in Pre-RMM period	Total in Post-RMM period	Shares in Post-RMM period
37,5mg+325mg, n=10	9,597	1%	10,581	1%
37,5mg+325mg, n=20	9,945	1%	11,067	1%
37,5mg+325mg, n=30	42,289	4%	45,450	3%
37,5mg+325mg, n=60	425,966	39%	389,988	30%
37,5mg+325mg, n=90	99,549	9%	167,420	13%
75mg+650mg, n=10	8,387	1%	8,066	1%
75mg+650mg, n=20	8,570	1%	4,715	0%
75mg+650mg, n=30	47,184	4%	44,630	3%
75mg+650mg, n=60	341,793	31%	343,055	26%
75mg+650mg, n=90	110,100	10%	286,077	22%
Total	1,103,380	100%	1,311,049	100%

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