Public Assessment Report

Update

Name of the Product:

Doreta SR

75 mg/650 mg prolonged release tablets

(tramadol hydrochloride/paracetamol)

Procedure number: HU/H/0190/003/DC

Marketing authorisation holder: Krka d.d.

Date: 17-05-2021

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
HU/H/0190/003/II/035	To update the risk management plan (RMP) for tramadol/paracetamol 75 mg/650 mg prolonged-release tablet to version 3.0 to 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 the product, thus lifting the suspension of the marketing authorization of the product imposed by the (2018)1151 of 19 Feb 2018 Commission implementing decision issued following the EMEA/H/A-31/1445 referral procedure pursuant to Article 31 of Directive 2001/83/EC.	NA	28-10-2020	Approved	NA

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

SCIENTIFIC DISCUSSION

Summary of decisions preceding the variation procedure

In 2017, the PRAC recommended the suspension of prolonged-release paracetamol containing products including combinations. The reason of it was that overdose has frequently occurred due to intentional or unintentional misuse. Treatment of overdose of the prolonged release formulation is not included in treatment protocol in several member states, and this raise a serious risk of hepatotoxicity. PRAC concluded that the benefit-risk balance of modified release paracetamol and paracetamol/tramadol containing products is no longer favourable and recommended that the marketing authorisations of these products should be suspended.

The European Commission 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 modified-release paracetamol-containing medicinal products.

The Marketing authorisation holder (MAH) sought the advice of Hungarian NCA acting as an RMS in regard of risk minimisation measures in 2019. The principles of the measures to be taken in order to ensure the positive benefit/risk ratio of the medicinal product were agreed by the RMS. The view of RMS has been shared with CMS countries (CZ, PL, PT, RO, SK and SLO) and no objections have emerged at the time. However, the majority of concerned member states proposed to seek PRAC advice or at least to inform CMD(h) before the termination of type II variation procedure .
PRAC highlighted that the condition for lifting of the suspension are to be assessed at national level or in case of MRP/DCP by each MS involved in the procedure.

Based on RMS advice the MAH submitted a type II variation for amending the Risk Management Plan (RMP) in order to include further risk minimisation measures that would ensure a positive benefit/risk ratio of the product, hereby lifting its suspension of the MA and allowing its return on the market.

According to the European Commission, the lifting of the suspension of marketing authorisation is possible if the MAH can provide evidences

1. to prevent the risk of overdose
2. to minimise the risk of hepatic injury following intentional or accidental overdoses

<u>Prevention of the risk of overdose:</u>

The MAH proposals for prevention of overdose made during the variation application are presented below.
- The indication of the product has been further restricted to patients who are not adequately controlled by an immediate release formulation
- The change in the outer packaging leads to a better distinction from the immediate-release Doreta namely the risk of medication error can be reduced
- Inclusion of an additional warning on the outer packaging regarding concomitant use of other paracetamol-containing products
- Restriction of use only to adults
- The MAH proposed to add a warning against concomitant use with any other paracetamol-containing product on the outer package.
- The risk of overdose was suggested to be decreased also by strengthening the warning to hepatotoxicity and to highlight the difference of IR and PR formulation.

<u>Minimisation the risk of hepatic injury</u>

To minimise the risk of hepatic injury following intentional or accidental overdoses, the marketing authorisation holder proposed a treatment algorithm.

The MAH proposed also the communication of the above risk minimisation measures in a DHPC. Two DHPC letters were proposed, one to warn for the risk of overdose and consequent hepatic injury and another about the proposed treatment protocol of a potential overdose.

Assessment of effectiveness of risk minimisation measures

The MAH proposed intensive monitoring using targeted follow-up of all cases of spontaneous reporting and performing evaluation of all individual safety reports on a monthly basis. The company would like to have contact points in poisoning centres to collect information actively on overdose cases.

The benefit-risk evaluation of Doreta SR will be performed six-monthly.

To assess the effectiveness of risk minimisation measures the company plans a drug utilization study (DUS) to analyse prescription practices, prevention of overdose cases and effectiveness of treatment of overdoses before and after the implementation of these new RMMs. The DUS is planned in at least 3 member states although all of concerned member states wish to have the analysis of the data on each own country. The results of DUS should be presented in the next PSUR with a data lock point of 1 August 2023.

Conclusion

The RMS was of the opinion that the proposed risk minimisation measures which should be proportionate and feasible according to European Commission, have additional benefit in prevention of either accidental or intentional overdose therefore, the proposal of the marketing authorisation holder meets the first criterion of European Commission’s decision in respect of lifting the suspension.

Risk Management Plan

The MAH has submitted an updated Risk Management Plan for tramadol/paracetamol 75 mg/650 mg prolonged-release tablets in order to provide evidences 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 the product. Thus the lifting the suspension of the marketing authorization of the product imposed by the (2018)1151 of 19 Feb 2018 Commission implementing decision issued following the EMEA/H/A-31/1445 referral procedure pursuant to Article 31 of Directive 2001/83/EC becomes achievable.

Summary table of Safety concerns
The applicant has revised the safety concerns in order to comply with assessor's comments and the revised RMP guidance (EMA/838713/2011. Rev.2) in which the definitions of the important identified risk, important potential risk and missing information have been changed:

Summary of safety concerns	
Important identified risks	Hepatotoxicity in patients with pre-existing hepatic conditions or using high doses Overdose Dependence, tolerance, abuse
Important potential risks	Off label use
Missing information	Use in paediatric population under 12 years of age

Pharmacovigilance Plan

Routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to KRKA's products containing paracetamol-tramadol in immediate formulation.
The 'Targeted questionnaires for follow up of Doreta SR overdose cases' as routine pharmacovigilance activity were deleted to reduce administrative burden of physicians (proposed case report form of active surveillance study contained the same information as targeted questionnaire).

In the case of prolonged-release formulation of the product additional pharmacovigilance activities have been introduced.

KKLR402019 - 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. Beside the „off-label use" as an important potential risk, 'Use in paediatric population under 12 years of age' as missing information is also addressed in this study.

KKLR412020. Active surveillance of overdose with a prolonged-release formulation of tramadol/paracetamol to evaluate the effectiveness of measures aimed to reduce the risk of hepatotoxicity after overdose with Doreta SR.

Risk Minimisation Measures

Routine risk minimisation measures (i.e. wording in SmPC, PL and classification as a prescription only medicine) are considered sufficient to manage all of the safety concerns connected to KRKA's products containing paracetamol-tramadol in immediate formulation.

In the case of prolonged-release formulation of the product, dissemination of DHPC letter (DHPC= Direct Healthcare Professional Communication) has been introduced as additional risk minimisation measure to inform HCPs about update of SmPC with new safety information in order to minimise the risk for overdose and hepatic injury.