

Part VI: Summary of the risk management plan

Summary of risk management plan for tramadol hydrochlorid, paracetamol by Krka

This is a summary of the risk management plan (RMP) for tramadol hydrochlorid, paracetamol by Krka. The RMP details important risks of tramadol hydrochlorid, paracetamol by Krka, how these risks can be minimised, and how more information will be obtained about tramadol hydrochlorid, paracetamol by Krka's risks and uncertainties (missing information).

Tramadol hydrochlorid, paracetamol by Krka's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how tramadol hydrochlorid, paracetamol by Krka should be used.

Important new concerns or changes to the current ones will be included in updates of tramadol hydrochlorid, paracetamol by Krka's RMP.

I. The medicine and what it is used for

Tramadol hydrochlorid, paracetamol by Krka is authorised for moderate to severe pain (see SmPC for the full indication). It contains tramadol hydrochloride/paracetamol as the active substance and it is given orally.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of tramadol hydrochlorid, paracetamol by Krka, together with measures to minimise such risks and the proposed studies for learning more about tramadol hydrochlorid, paracetamol by Krka's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of tramadol hydrochlorid, paracetamol by Krka, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of tramadol hydrochlorid, paracetamol by Krka is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of tramadol hydrochlorid, paracetamol by Krka are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of tramadol hydrochlorid, paracetamol by Krka. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

For immediate-release formulation of tramadol/paracetamol no safety concerns have been identified.

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Important missing information	None

For prolonged-release formulation of tramadol/paracetamol the following safety concerns have been identified.

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none"> • Hepatotoxicity in patients with pre-existing hepatic conditions or using high doses • Overdose • Dependence, tolerance, abuse
Important potential risks	<ul style="list-style-type: none"> • Off label use
Missing information	<ul style="list-style-type: none"> • Use in paediatric population under 12 years of age

II.B Summary of important risks

For immediate-release formulation of tramadol/paracetamol no safety concerns have been identified.

Applies only to prolonged-release formulation:

Hepatotoxicity in patients with pre-existing hepatic conditions or using high doses	
Risk minimisation measures	<p>Routine risk minimization measures:</p> <p>SmPC sections:</p> <ul style="list-style-type: none">• 4.2 with warning not to use <Invented name> in case of severe hepatic impairment. In case of moderate hepatic impairment prolongation of the dosage interval should be considered.• 4.3, whereby severe hepatic impairment is a contraindication.• 4.4 with warning not to use <Invented name> in case of severe hepatic impairment. In case of moderate hepatic impairment prolongation of the dosage interval should be considered. Furthermore, warnings regarding possibility of hepatic toxicity in case overdose occurs, taking into account prolonged release nature of the product is included.• 4.8 includes hepatic transaminases increase as adverse drug reaction.• 4.9, whereby liver damage as an outcome of overdose is included. Furthermore, information on patient groups at higher risk for paracetamol toxicity and the possibility of a delay in occurrence and culmination of clinical signs of liver damage following overdose with prolonged-release formulation is included. <p>PL section:</p> <ul style="list-style-type: none">• 2 with advice not to take <Invented name> or take special care in case of liver problems or liver problems. Furthermore, a warning on possibility of liver damage in case of paracetamol overdose is included.• 3, whereby information on how to take <Invented name> in case of liver diseases is included. Furthermore, possibility of irreversible liver damage following overdose is included.• 4, whereby side effect of raised liver enzymes is included <p>Routine risk minimisation activities recommending specific clinical measures to address the risk:</p>

	<ul style="list-style-type: none"> • Recommendations for treatment in case of overdose to minimise the risk of serious hepatic damage are included in SmPC sections 4.9. <p>Routine risk minimisation activities recommending specific clinical measures to address the risk:</p> <ul style="list-style-type: none"> • SmPC section 4.4 recommends using antidote as soon as possible following overdose. • SmPC section 4.9 includes recommendations for treatment of overdose that applies only to prolonged release formulation of paracetamol. <p>Packaging:</p> <p>a warning not to use any other non-prescription paracetamol containing medicine while taking <Invented name>. Immediate medical advice should be sought in the event of an overdose, even if you feel well.</p> <p>Pack size:</p> <p>Various pack sizes exists and the treating physician can prescribe an appropriate pack size of <Invented name>, taking into account the individual needs of the patients, the nature of the treated diseases and potential for misuse. In Poland only, the pack size is limited to a maximum of 30 tablets.</p> <p>Legal status:</p> <p>Prescription only medicine.</p> <p>Additional risk minimisation measures:</p> <p><i>DHPC for HCPs who are likely to prescribe <Invented name> prolonged-release formulation</i></p> <p><i>DHPC for HCPs who are likely to treat patients or receive inquiries on paracetamol overdose</i></p>
Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities:</p> <p>KKLR412020 - Active surveillance study of overdose with prolonged-release formulation of tramadol/paracetamol to evaluate the effectiveness of measures aimed to reduce the risk of hepatotoxicity after overdose with Doreta SR.</p>

	See section II.C of this summary for an overview of the post-authorisation development plan.
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Overdose

Risk minimisation measures

Routine risk communication:

SmPC sections

- 4.2, which includes recommendation for physicians on prescribing an appropriate pack size of <Invented name>, taking into account the individual needs of the patients, the nature of the treated diseases and potential for misuse.
- 4.4 with a warning not to exceed the maximum daily dose and not to use any other paracetamol or tramadol containing products concurrently without medical supervision. Furthermore, information on prolonged absorption of paracetamol, resulting in delayed hepatotoxicity is included.
- 4.5 with information on concomitant use of other opioid derivatives, which increase the risk of respiratory depression in cases of overdose.
- 4.8 lists abuse and drug dependence as undesirable effect.
- 4.9, whereby manifestations of overdose and treatment guidelines groups at higher risk for paracetamol toxicity are presented.

PL section

- 2, whereby warning on taking other drugs, including other drugs containing tramadol or paracetamol, to relieve pain without medical supervision is included. This can result in overdose. Furthermore, precautions regarding different dosing schedule of prolonged-release tablets and recommendation on not to take higher doses than were prescribed by a doctor are included. The potential outcomes of overdose and how to recognize liver damage are also included.
- 3, whereby the potential manifestations and outcomes of overdose and how to recognize liver damage are included. Additionally, instruction on what to do in case higher doses have been taken, is included.
- 4, which lists drug dependence as a side effect.

Overdose	
	<p>Routine risk minimisation activities recommending specific clinical measures to address the risk:</p> <ul style="list-style-type: none"> • Recommendations on how to recognize and manage an overdose to minimise the risk of serious consequences are included in SmPC sections 4.9 <p>Routine risk minimisation activities recommending specific clinical measures to address the risk:</p> <ul style="list-style-type: none"> • SmPC section 4.4 recommends using antidote as soon as possible following overdose. • SmPC section 4.9 includes recommendations for treatment of overdose that applies only to prolonged release formulation of paracetamol <p>Packaging:</p> <p>A warning not to use any other non-prescription paracetamol containing medicine while taking <Invented name>. Immediate medical advice should be sought in the event of an overdose, even if you feel well.</p> <p>Pack size:</p> <p>Various pack sizes exists and the treating physician can prescribe an appropriate pack size of <Invented name>, taking into account the individual needs of the patients, the nature of the treated diseases and potential for misuse. In Poland only, the pack size is limited to a maximum of 30 tablets.</p> <p>Legal status:</p> <p>Prescription only medicine.</p> <p>Additional risk minimisation measures (applies only to prolonged-release formulation):</p> <p><i>DHPC for HCPs who are likely to prescribe <Invented name> prolonged-release formulation</i></p>
Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities:</p> <p>KKLR412020 - Active surveillance study of overdose with prolonged-release formulation of tramadol/paracetamol to</p>

Overdose	
	<p>evaluate the effectiveness of measures aimed to reduce the risk of hepatotoxicity after overdose with Doreta SR.</p> <p>See section II.C of this summary for an overview of the post-authorisation development plan.</p>

Dependence, tolerance, abuse	
Risk minimisation measures	<p>Routine risk minimization measures</p> <p>SmPC sections:</p> <ul style="list-style-type: none"> • 4.2, whereby the lowest effective dose for analgesia is recommended. Furthermore, recommendations not to exceed the maximum daily dose or administer <Invented name> for longer than is strictly necessary are included. There is additional warning on regular monitoring in case repeated use or long term treatment with <Invented name> is required. Recommendation for physicians on prescribing an appropriate pack size of <Invented name>, taking into account the individual needs of the patients, the nature of the treated diseases and potential for misuse is also included. • 4.3, whereby <Invented name> is contraindicated in acute intoxication with alcohol, hypnotic drugs, centrally-acting analgesics, opioids or psychotropic drugs. • 4.4 with warning not to exceed the maximum daily dose and not to use any other paracetamol (including over the counter) or tramadol hydrochloride containing products concurrently without medical supervision. There is further warning that tolerance and physical and/or psychological dependence may develop, even at therapeutic doses, and that the clinical need for analgesic treatment should be reviewed regularly. Furthermore, recommendation to prescribe treatment only for short period and under medical supervision in opioid-dependent patients and patients with a history of drug abuse or dependence is included. Additionally, information is included on symptoms of withdrawal reactions. • 4.8 lists abuse and drug dependence as undesirable effects. <p>PL sections:</p> <ul style="list-style-type: none"> • 2 informs on not taking <Invented name> in acute poisoning with alcohol, sleeping pills, pain relievers or other psychotropic medicines (medicines that affect mood

	<p>and emotions). Furthermore, special care is recommended in patients dependent on any other medicines used to relieve pain. Recommendation not to take <Invented name> with other medicines containing paracetamol or tramadol is included. A warning not to take <Invented name> with other medicines containing paracetamol or tramadol and not to take higher doses than recommended is also included.</p> <ul style="list-style-type: none"> • 3, with recommendation not to exceed the maximum daily dose and taking the tablets for as short a time as possible. • 4, where abuse and drug dependence as side effects are listed. <p>Pack size:</p> <p>Various pack sizes exists and the treating physician can prescribe an appropriate pack size of <Invented name>, taking into account the individual needs of the patients, the nature of the treated diseases and potential for misuse. In Poland only, the pack size is limited to a maximum of 30 tablets.</p> <p>Legal status:</p> <p>Prescription only medicine.</p> <p>Additional risk minimisation measures:</p> <p><i>DHPC for HCPs who are likely to prescribe <Invented name> prolonged-release formulation</i></p>
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Off label use	
Risk minimisation measures	<p>Routine risk communication:</p> <p>SmPC section:</p> <ul style="list-style-type: none"> • 4.1 with information on indication • 4.2 with the same information as in section 4.1 and additional information on posology, including the need for individualization of dosage and maximum daily dosage and the recommendation not to use the product in children below the age of 12 years. Furthermore, method of administration and adaptation of treatment in patients with specific comorbidities are presented. • 4.3, whereby contraindications are presented.

	<ul style="list-style-type: none"> • 4.4 with warning not to exceed the maximum dose or use <Invented name> in children below 12 years of age and not to use any other paracetamol or tramadol containing products or sedatives concurrently. Furthermore, warning against the use in patients with specific comorbidities is included. • 4.5, whereby concomitant use with specific drugs is contraindicated, not recommended or should be taken into consideration. • 4.6 with information against the use in pregnancy and being cautious during breast-feeding <p>PL sections:</p> <ul style="list-style-type: none"> • 1 with information on indication and target age group. • 2, whereby contraindications and the use during pregnancy and breast-feeding are presented. Furthermore, warning regarding the use of <Invented name> in patients with certain comorbidities or taking certain other drugs concurrently is included. • 3 with information on how to take <Invented name>. Furthermore, information against the use in children under 12 years is included. <p>Packaging:</p> <p>Information on method and route of administration and a warning not to use any other non-prescription paracetamol containing medicine while taking <Invented name> are included.</p> <p>Legal status:</p> <p>Prescription only medicine.</p> <p>Additional risk minimisation measures:</p> <p><i>DHPC for HCPs who are likely to prescribe <Invented name> prolonged-release formulation</i></p>
<p>Additional pharmacovigilance activities</p>	<p>Additional pharmacovigilance activities:</p> <p>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.</p> <p>See section II.C of this summary for an overview of the post-authorisation development plan.</p>

Use in paediatric population under 12 years of age	
Risk minimisation measures	<p>Routine risk minimisation measures:</p> <p>SmPC section:</p> <ul style="list-style-type: none"> • 4.2 with information that the product should be used in patients 12-year old and older. • 4.4, whereby posology in patients 12 years and older is provided. <p>PL sections:</p> <ul style="list-style-type: none"> • 1 and 3 with information that the product should only be taken by adults and adolescents over 12 years of age. <p>Legal status:</p> <p>Prescription only medicine.</p> <p>Additional risk minimisation measures:</p> <p><i>None</i></p>
Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities:</p> <p>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.</p> <p>See section II.C of this summary for an overview of the post-authorisation development plan.</p>

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

Not applicable.

II.C.2 Other studies in post-authorisation development plan

Applies only to prolonged-release formulation:

- **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.**

Purpose of the study:

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 altered pharmacokinetic properties of paracetamol due to the nature of the formulation makes overdoses with modified-release paracetamol difficult to treat in emergency situations using the standard antidote for immediate-release paracetamol overdoses.

Following an Article 31 referral procedure (EMA/H/A-31/1445) the CMDh and the PRAC decided that the advantages of a longer-acting product do not outweigh the complications of managing an overdose of the medicine. In February 2018, the marketing authorisations of the medicinal products containing modified-release paracetamol were suspended by the European Commission (C(2018) 1151 final). Consequently, Doreta SR was withdrawn from all EU markets.

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

Research question:

The aim of this study is 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 of immediate-release fixed dose combinations of tramadol/paracetamol pre- and post-RMM dissemination in 3 European countries.

Secondary objectives:

- To describe the demographic characteristics of patients prescribed with Doreta SR and immediate-release FDCs of tramadol/paracetamol pre- and post-RMM.
 - To describe the characteristics of prescribers of Doreta SR and immediate-release FDCs of tramadol/paracetamol pre- and post-RMM.
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- **KKLR412020. Active surveillance of overdose with a prolonged-release formulation of tramadol/paracetamol.**

Purpose of the study:

Acute overdoses of paracetamol may lead to serious adverse events, of which hepatotoxicity is the main concern as it can lead to liver failure and death. Massive overdose with modified-release paracetamol can result in a prolonged and unpredictable pattern of paracetamol absorption. Standard treatment guidelines for overdose of immediate-release paracetamol are not designed for these extended periods of absorption. Several Risk Minimization Measures (RMMs) aimed at reducing the risk of overdose and the risk of hepatotoxicity following overdose are proposed to address this issue.

The general objective of this study is to obtain data on effectiveness of proposed RMMs to support a positive safety profile of Tramadol hydrochloride/paracetamol 75/650 mg prolonged-release tablets.

Research question:

Research question addresses the characteristics of overdose with OMP including the frequency, concomitant factors of impact, population demographic characteristics, drug exposure in the acute overdose cases, therapeutic strategy and outcomes. It states: What are the characteristics of OMP acute overdose poisoning?

Primary endpoints:

To determine total number of overdose cases with Tramadol hydrochloride/paracetamol 75/650 mg prolonged-release tablets and rate of serious sequelae of the overdose cases with respect to total number of overdose cases.

Secondary endpoints:

To describe:

- Demographic parameters
- Vital signs
- Comorbidities
- Concomitant therapy
- Drug exposure and clinical/laboratory characteristics
- Therapy characteristics
- Outcomes

in patients overdosing with Tramadol hydrochloride/paracetamol 75/650 mg prolonged-release tablets.