EU Risk Management Plan for tramadol

RMP version to be assessed as part of this application:

RMP Version number: 3.0

Data lock point for this RMP: 17.02.2022

Date of final sign off: 17.02.2022

Rationale for submitting an updated RMP: Renewal procedure

Summary of significant changes in this RMP:

- Update of RMP to be in line with the revised guidance document (28 March 2017 EMA/838713/2011 Rev 2*) and the new template (31 October 2018 EMA/164014/2018 Rev.2.0.1)
- Removal of all safety concerns to be in line with the criteria established in the revised RMP guidance document EMA/838713/2011 Rev 2* Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems.
- Update of all sections of RMP due to removal of all safety concerns
- Update of Part I: Product(s) Overview to include information regarding tramadol, capsules, hard
- Update of part II Module SV to include post-authorisation exposure

Details of the currently approved RMP:

Version number: 2.1

Approved with procedure: EE/H/0262,0269/001-003/DC

Date of approval (opinion date): 05.10.2018

Approved with procedure: ME national procedure

Date of approval (opinion date): 04.02.2020

Approved with procedure: UZ national procedures (TRA11-UZ-NAT-1-KRKA, TRA11-UZ-NAT-2-KRKA)

Date of approval (opinion date): 29.12.2020

Version number: 2.0

Approved with procedure: HR/H/0126/001/DC

Date of approval (opinion date): 20.07.2018

Approved with procedure: KO national procedure

Date of approval (opinion date): 26.11.2018

Version number: 1.1

Approved with procedure: MT/H/0272/001/DC

Date of approval (opinion date): 11.9.2018

Version number: 1.0

Approved with procedure: MT/H/0259/001/DC

Date of approval (opinion date): 21.05.2018

Approved with procedure: MT/H/0260/001-002/DC

Date of approval (opinion date): 25.05.2018

Version number: 1.2

Approved with procedure: HR/H/0104/003/DC

Date of approval (opinion date): 14.12.2017

Approved with procedure: UZ national procedure (TRA11-UZ-NAT-4-KRKA)

Date of approval (opinion date): 21.07.2017

Version number: 1.1

Approved with procedure: HR/H/0104/001-002/DC

Date of approval (opinion date): 28.11.2017

QPPV name: Irena Orel MD, MSc

QPPV signature:

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Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	tramadol hydrochloride
Pharmacotherapeutic group(s) (ATC Code)	Analgesics, other opioids (N02AX02)
Marketing Authorisation Holder or Applicant	KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia and Krka's subsidiaries
Medicinal products to which this RMP refers	3
Invented name(s) in the European Economic Area (EEA)	tramadol
Marketing authorisation procedure	decentralised
Brief description of the product	Chemical class Tramadol is a centrally acting opioid analgesic.
	Summary of mode of action Tramadol is a non-selective pure agonist at mu-, delta- and kappa opioid receptors with a higher affinity for the mu-receptor. Other mechanisms which may contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release.
	Important information about its composition Not applicable.
Hyperlink to the Product Information	Please refer to module 1.3.1 of dossier.
Indication(s) in the EEA	Current (if applicable): Treatment of moderate to severe pain.
	Proposed (if applicable): /
Dosage in the EEA	Current (if applicable): Posology <u>Solution for injection / infusion:</u> The dose should be adjusted to the intensity of the pain and the sensitivity of the individual patient. The lowest effective dose for

analgesia should generally be selected. Daily doses of 400 mg active substance should not be exceeded, unless there are special medical circumstances (e.g. in cancer pain and severe postoperative pain).

Unless otherwise prescribed, <Invented name> solution for injection/infusion should be administered as follows:

Adults and children over 12 years of age

Dosage form	Single dose	Maximum daily dose
<Invented name> 50 mg solution for injection/infusion	50 to 100 mg every 4 to 6 hours (1 to 2 ampoules)	400 mg (up to 8 ampoules)
<Invented name> 100 mg solution for injection/infusion	100 mg every 4 to 6 hours (1 ampoule)	400 mg (up to 4 ampoules)

If there is no sufficient pain relief after administration of a single dose of 50 mg tramadol hydrochloride within 30 to 60 minutes, a second single dose of 50 mg can be administered.
If in severe pain the demand is likely to be higher, the higher single dose of <Invented name> solution for injection/infusion (100 mg tramadol hydrochloride) may be given as the initial dose.

Depending on the pain, the effect lasts for 4-6 hours. For the treatment of severe postoperative pain even higher doses may be necessary for on-demand analgesia in the early postoperative period. Requirements over period of 24 hours are generally not higher than during conventional administration.

<u>Capsules, hard:</u>

The dose should be adjusted to the intensity of the pain and the sensitivity of the individual patient. The lowest effective dose for analgesia should generally be selected. The total daily dose of 400 mg active substance should not be exceeded, except in special circumstances.

Unless otherwise prescribed, <Invented name> should be administered as follows:

Adults and adolescents aged 12 years and over

Dosage form	Single dose	Total daily dose
<Invented name>	50-100 mg Every 4 to 6 hours (1 to 2 hard capsules)	400 mg (Up to 8 hard capsules)

	If there is no sufficient pain relief after administration of a single dose of 50 mg tramadol hydrochloride within 30 to 60 minutes, a second single dose of 50 mg can be administered. If in severe pain the demand is likely to be higher, the higher single dose of <Invented name> (100 mg tramadol hydrochloride) may be given as the initial dose. **Acute Pain:** An initial dose of 100 mg is usually necessary. This can be followed by doses of 50 or 100 mg at 4 - 6 hourly intervals, and duration of treatment should be matched to clinical need. **Pain Associated with Chronic Conditions:** An initial dose of 50 mg is advised and then titration according to pain severity. The need for continued treatment should be assessed at regular intervals as withdrawal symptoms and dependence have been reported. <u>Prolonged-release tablets</u> The dose should be adjusted to the intensity of the pain and the sensitivity of the individual patient. The lowest effective dose for analgesia should generally be selected. The total daily dose of 400 mg active substance should not be exceeded, except in special circumstances. *Adults and adolescents above the age of 12 years:* The usual initial dose is 50-100 mg tramadol hydrochloride twice daily, morning and evening. If an initial dose lower than 100 mg is required, alternative tramadol hydrochloride containing product should be used. If pain relief is insufficient, the dose may be titrated upwards to 150 mg or 200 mg tramadol hydrochloride twice daily.
	Proposed (if applicable): /
Pharmaceutical form(s) and strengths	Current (if applicable): Solution for injection, 50 mg/1ml Solution for injection, 100 mg/2ml Hard capsules, 50 mg Prologned-release tablets 100 mg Prolonged-release tablets 150 mg Prolonged-release tablets 200 mg
	Proposed (if applicable): Not applicable.
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Not applicable.

Part II: Module SII - Non-clinical part of the safety specification

Not applicable.

Part II: Module SIII - Clinical trial exposure

Not applicable.

Part II: Module SIV - Populations not studied in clinical trials

Not applicable.

Part II: Module SV - Post-authorisation experience

SV.1.1 Method used to calculate exposure

The patient exposure was estimated by the calculation of "Patient years" taking into consideration sales of all corresponding medicinal products for tramadol authorized in the reference interval (from 1.1.2005 to 31.1.2022) and the Daily Defined Dose (DDD) of 300 mg for the product according to the WHO.

The calculation procedure was as follows:
First we calculated the number of Patient years for each formulation and strength (N_{pat}) by multiplying the number of sold formulation of strength by the strength and then dividing the product by its DDD and 365,25.

The equation: $N_{pat} = N_{form}$ x strength (mg) / DDD (mg) x 365,25

Finally, we summed the figures for individual strengths and formulations to obtain the total number of Patient years.
We had obtained the value of DDD in the ATC/DDD index 2021, available on the website of the WHO collaborating centre for drug statistics and methodology.

SV.1.2 Exposure

The post-approval exposure in the period from January 1, 2005 to January 31, 2022 for tramadol was a total of 491.818 patient years.

Part II: Module SVI - Additional EU requirements for the safety specification

Not applicable.

Part II: Module SVII - Identified and potential risks

Justification of removal of all safety concerns in comparison with the list of safety concerns published on CMDh website: the proposed safety concerns published on CMDh website do not correspond with criteria established in the GVP Module V, revision 2. Only those safety concerns should be included in the RMP that are likely to have an impact on the risk-benefit balance and are actively managed via specific clinical actions (as described in the SmPC) such as measurements of laboratory parameters and monitoring for specific signs and symptoms.
In line with the GVP Module V - Risk management systems (EMA/838713/2011 Rev2*, March 2017) and Guidance on the format of the RMP (EMA/164014/2018 Rev.2.0.1, October 2018) currently in force, the important identified and potential risks are those for which additional measures or clinical actions in the pharmacovigilance plan and/or in the risk minimization section or SmPC should be adopted. There are no important safety concerns - risks which require additional pharmacovigilance actions, additional risk minimization actions or specific clinical actions to be taken, and which would likely to have an impact on the risk-benefit balance of the product, that would be required to be included in the safety specification, therefore all of the important identified risks, important potential risks and missing information were removed from the safety specification of tramadol.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

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

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection is considered necessary.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are proposed.

III.3 Summary Table of additional Pharmacovigilance activities

No additional pharmacovigilance activities are proposed.

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine Risk Minimisation Measures

Not applicable.

V.2. Additional Risk Minimisation Measures

Not applicable.

V.3 Summary of risk minimisation measures

Not applicable.

Part VI: Summary of the risk management plan

Summary of risk management plan for tramadol by Krka (tramadol hydrochloride)

This is a summary of the risk management plan (RMP) for tramadol by Krka. The RMP details important risks of tramadol by Krka and how more information will be obtained about tramadol by Krka's risks and uncertainties (missing information).
Tramadol by Krka's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how tramadol by Krka should be used.
Important new concerns or changes to the current ones will be included in updates of tramadol by Krka's RMP.

I. The medicine and what it is used for

Tramadol by Krka is authorised for treatment of moderate to severe pain. It contains tramadol as the active substance and it is given orally or by injection or infusion.

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

Important risks of tramadol by Krka, together with measures to minimise such risks and the proposed studies for learning more about tramadol 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 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*.

II.A List of important risks and missing information

Important risks of tramadol 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 administered / 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 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);

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of tramadol by Krka.

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

There are no studies required for tramadol by Krka.

Part VII: Annexes

Annex 1 – EudraVigilance Interface

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Not applicable.

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not applicable.

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable.

Annex 7 - Other supporting data (including referenced material)

Not applicable.

Annex 8 – Summary of changes to the risk management plan over time

Version	**Approval date** **Procedure**	**Change**
1.1	At the time of authorisation HR/H/0104/001-002/DC (for solution for injections)	Not applicable

	28.11.2017	
1.2	At the time of authorisation HR/H/0104/003/DC (capsules, hard) 14.12.2017 UZ national procedure (TRA11-UZ-NAT-4-KRKA) 21.7.2017	**Safety concerns** Missing information: - Added "Use in paediatric population under 12 years of age" (applicable only for Tramadol capsules hard 50 mg) Added "Use in paediatric population under 14 years of age" (applicable only for Tramadol hydrochloride prolonged-release tablets 100 mg, 150 mg, 200 mg)
1.0	At the time of authorisation MT/H/0259/001/DC (capsules, hard) 21.5.2018 MT/H/0260/001-002/DC (solution for injection) 25.5.2018	Not applicable. Initial RMP.
1.1	At the time of authorisation MT/H/0272/001/DC (oral drops, solution) 11.9.2018	Additional pharmaceutical form (oral drops, solution) added
2.0	At the time of authorisation HR/H/0126/001/DC 20.7.2018 KO national procedure 26.11.2018	- Update of RMP to be in line with the new EU template for RMP (EMA/164014/2018 Rev.2.0.1) - New pharmaceutical form (prolonged-release tablets; new formulation) added
2.1	At the time of authorisation EE/H/0262/001-003/DC 5.10.2018 EE/H/0269/001-003/DC 5.10.2018 ME national procedure 4.2.2020 UZ national procedures 29.12.2022	- Administrative change in Part I: Product(s) Overview - Update of Part II :Module SV (post-authorisation exposure added)