**Risk Management Plan of a fixed combination of Dexketoprofen trometamol and Tramadol hydrochloride (oral formulation)**

# Part VI: Summary of the risk management plan by product

## VI.1 Elements for summary tables in the EPAR

### VI.1.1 Summary table of Safety concerns

Table VI.1.1.1 Summary of safety concerns

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | ▪ GI bleeding, ulceration and perforation in high risk patients<br>▪ Respiratory depression<br>▪ Acute renal failure<br>▪ Seizures<br>▪ Hepatic ADRs<br>▪ Severe skin reactions (Toxic epidermal necrolysis and Stevens-Johnson Syndrome)<br>▪ Severe allergic reactions and other hypersensitivity disorders<br>▪ Foetal toxicity<br>▪ Cardiovascular and cerevascular ADRs |
| Important potential risks | ▪ Pancytopenia, anaemia not related to GI bleeding and aplastic anaemia<br>▪ Off-label use, misuse, abuse<br>▪ Serotonin syndrome due to concomitant treatment with serotoninergic drugs |
| Missing information | ▪ Use in paediatric population |

### VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

There are no on-going or planned additional pharmacovigilance activities in place for DKP-TRAM.

### VI.1.3 Summary of Post authorisation efficacy development plan

Not applicable. No post-authorisation studies are planned.

### VI.1.4 Summary table of Risk Minimisation Measures

Table VI.1.4.1 Summary of risk minimisation measures

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| **Identified Risks** | | |
| GI bleeding, ulceration and and perforation in high risk patients | **Wording in the following sections of the SmPC:**<br>Section 4.2 Posology and method of administration;<br>Section 4.3 Contraindications;<br>Section 4.4 Special warnings and precautions for use ;<br>Section 4.5 Interaction with other medicinal products and other form of interaction;<br>Section 4.8 Undesirable effects. | None proposed |
| | **Wording in the following sections of the PL:**<br>Section 2 What you need to know before you take DKP-TRAM<br>– Do not take DKP-TRAM;<br>– Warnings and precautions;<br>Section 3 How to take DKP-TRAM;<br>Section 4 Possible side effects. | |
| | Routine pharmacovigilance monitoring and literature review. | |
| Respiratory depression | **Wording in the following sections of the SmPC:**<br>Section 4.3 Contraindication;<br>Section 4.4 Special warnings and precautions for use;<br>Section 4.5 Interaction with other medicinal products and other form of interaction;<br>Section 4.8 Undesirable effects;<br>Section 4.9 Overdose. | None proposed |
| | **Wording in the following sections of the PL:**<br>Section 2 What you need to know before you take DKP-TRAM<br>– Do not take DKP-TRAM;<br>– Warnings and precautions;<br>Section 3 How to take DKP-TRAM. | |
| | Routine pharmacovigilance monitoring and literature review. | |
| Acute renal failure | **Wording in the following sections of the SmPC:**<br>Section 4.2 Posology and method of administration;<br>Section 4.3 Contraindications;<br>Section 4.4 Special warnings and precautions for use;<br>Section 4.5 Interactions with other medicinal products and other form of interaction;<br>Section 4.8 Undesirable effects. | None proposed |
| | **Wording in the following sections of the PL:** | |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | Section 2 What you need to know before you take DKP-TRAM<br>– Do not take DKP-TRAM;<br>– Warnings and precautions;<br>Section 4 Possible side effects. | |
| | Routine pharmacovigilance monitoring and literature review. | |
| Seizures | **Wording in the following sections of the SmPC:**<br>Section 4.3 Contraindications;<br>Section 4.4 Special warnings and precautions for use;<br>Section 4.5 Interaction with other medicinal products and other form of interaction;<br>Section 4.8 Undesirable effects. | None proposed |
| | **Wording in the following sections of the PL:**<br>Section 2 What you need to know before you take DKP-TRAM<br>– Do not take DKP-TRAM;<br>– Warnings and precautions;<br>Section 3 How to take DKP-TRAM;<br>Section 4 Possible side effects. | |
| | Routine pharmacovigilance monitoring and literature review. | |
| Hepatic ADRs | **Wording in the following sections of the SmPC:**<br>Section 4.2 Posology and method of administration;<br>Section 4.3 Contraindications;<br>Section 4.4 Special warnings and precautions for use;<br>Section 4.8 Undesirable effects. | None proposed |
| | **Wording in the following sections of the PL:**<br>Section 2 What you need to know before you take DKP-TRAM<br>– Do not take DKP-TRAM;<br>– Warnings and precautions;<br>Section 4 Possible side effects. | |
| | Routine pharmacovigilance monitoring and literature review. | |
| Severe skin reactions (Toxic epidermal necrolysis and Stevens-Johnson Syndrome) | **Wording in the following sections of the SmPC:**<br>Section 4.4 Special warnings and precautions for use;<br>Section 4.8 Undesirable effects. | None proposed |
| | **Wording in the following sections of the PL:**<br>Section 4 Possible side effects. | |
| | Routine pharmacovigilance monitoring and | |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | literature review. | |
| Severe allergic reactions and other hypersensitivity disorders | **Wording in the following sections of the SmPC:**<br>Section 4.3 Contraindications;<br>Section 4.4 Special warnings and precautions for use;<br>Section 4.8 Undesirable effects. | None proposed |
| | **Wording in the following sections of the PL:**<br>Section 2 What you need to know before you take DKP-TRAM<br>– Do not take DKP-TRAM;<br>Section 4 Possible side effects. | |
| | Routine pharmacovigilance monitoring and literature review. | |
| Foetal toxicity | **Wording in the following sections of the SmPC:**<br>Section 4.3 Contraindications;<br>Section 4.4 Special warnings and precautions for use;<br>Section 4.6 Pregnancy and lactation. | None proposed |
| | **Wording in the following sections of the PL:**<br>Section 2 What you need to know before you take DKP-TRAM<br>- Do not take DKP-TRAM;<br>- Warnings and precautions;<br>- Pregnancy and breast-feeding. | |
| | Routine pharmacovigilance monitoring and literature review. | |
| Cardiovascular and cerebrovascular ADRs | **Wording in the following sections of the SmPC:**<br>Section 4.3 Contraindications;<br>Section 4.4 Special warnings and precautions for use;<br>Section 4.5 Interaction with other medicinal products and other forms of interaction;<br>Section 4.8 Undesirable effects. | None proposed |
| | **Wording in the following sections of the PL:**<br>Section 2 What you need to know before you take DKP-TRAM<br>– Do not take DKP-TRAM;<br>– Warnings and precautions;<br>Section 4 Possible side effects. | |
| | Routine pharmacovigilance monitoring and literature review. | |
| **Potential Risks** | | |
| Pancytopenia, anaemia not related to GI bleeding and aplastic anaemia | **Wording in the following sections of the SmPC:**<br>Section 4.3 Contraindications; | None proposed |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | Section 4.4 Special warnings and precautions for use;<br>Section 4.5 Interaction with other medicinal products and other form of interaction;<br>Section 4.8 Undesirable effects. | |
| | **Wording in the following sections of the PL:**<br>Section 2 What you need to know before you take DKP-TRAM<br>– Do not take DKP-TRAM;<br>– Warnings and precautions. | |
| | Routine pharmacovigilance monitoring and literature review. | |
| Off label use, misuse, abuse | **Wording in the following section of the SmPC:**<br>Section 4.4 Special warnings and precautions for use;<br>Section 4.8 Undesirable effects. | None proposed |
| | **Wording in the following section of the PL:**<br>Section 2 What you need to know before you take DKP-TRAM<br>– Warnings and precautions;<br>Section 4 Possible side effects. | |
| | Medicinal product subject to medical prescription;<br>Routine pharmacovigilance monitoring and literature review. | |
| Serotonin syndrome due to concomitant use with serotoninergic drugs | **Wording in the following section of the SmPC:**<br>Section 4.3 Contraindications;<br>Section 4.5 Interaction with other medicinal products and other form of interaction | None proposed |
| | **Wording in the following section of the PL:**<br>Section 2 What you need to know before you take DKP-TRAM<br>– Do not take DKP-TRAM;<br>– Warnings and precautions. | |
| | Medicinal product subject to medical prescription;<br>Routine pharmacovigilance monitoring and literature review. | |
| **Missing information** | | |
| Use in paediatric population | **Wording in the following sections of the SmPC:**<br>Section 4.2 Posology and method of administration | None proposed |
| | **Wording in the following sections of the PL:** | |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | Section 2 What you need to know before you take<br>– Do not take. | |
| | Medicinal product subject to medical prescription;<br>Routine pharmacovigilance monitoring and literature review. | |

## VI.2 Elements for a Public Summary

### VI.2.1 Overview of disease epidemiology

Pain can have a profound negative impact on day-to-day quality of life. Pain has a substantial association with (lack of) productivity and absenteeism. In a 2008 survey conducted across 5 European countries (UK, France, Spain, Germany, Italy), increasing severity of pain was associated with incremental reductions in the probability of being employed full-time.

In this survey a significant proportion of patients experienced moderate (59.16%) or severe (22.54%) pain in the month prior to the survey. Population prevalence of daily pain is 8.85% (moderate, 4.79%; severe, 3.47%). Prevalence increases with age, with highest rates for moderate and severe pain between 40 to 59 years of age. Prevalence is typically higher in women and individuals of lower socio-economic strata.

### VI.2.2 Summary of treatment benefits

DKP-TRAM is indicated for the treatment of moderate to severe pain in adults. The efficacy of DKP-TRAM has been demonstrated in clinical trials across different pain models. A total of 696 patients were exposed to DKP-TRAM in clinical trials, whereas 1192 (dexketoprofen, 567; tramadol, 564; ibuprofen, 61) and 376 patients were exposed to active comparators or placebo, respectively.
In general, the studies were conducted in young to middle-aged males or females.

- Healthy volunteer study (n=35): to assess the pharmacokinetics of DKP-TRAM in healthy subjects.
- Dental pain (extraction of third molar tooth, n=611). Analgesic effect after 6 hours post dose was compared for DKP-TRAM vs DKP, TRAM, placebo or ibuprofen. The DKP-TRAM combination was more effective than comparators.
- Post-operative visceral pain (abdominal hysterectomy, n=606). Analgesic effect after 6 hours post dose was compared between DKP-TRAM combinations versus DKP and TRAM administered individually. The DKP-TRAM combination was more effective than the single agents.
- Post-operative somatic pain (hip athroplasty, n=641). Analgesic effect was compared between DKP-TRAM combinations versus DKP and TRAM administered individually. The DKP-TRAM combination was more effective than the single agents.

Analyses of clinical trial data suggests a favourable and clinically relevant benefit risk profile.

### VI.2.3 Unknowns relating to treatment benefits

There are no element to suspect that the patients not included in clinical trials, but belonging to the target population, should not benefit of dexketoprofen-tramadol combination.

Outside the condition for wich the product is contraindicated, no experience has been collected in clinical trials on children and adolescents (but the product is indicated for adults).In elderlies and in patients with impaired liver and renal function for whom the elimination may be prolonged ,start therapy at reduced dose and close monitoring should be considered.

### VI.2.4 Summary of safety concerns

**Important identified risks**

Table VI.2.4.1 Summary of important identified risks

| Risk | What is known | Preventability |
|---|---|---|
| Gastric or intestinal ulceration with or without bleeding or perforation in high risk patients | Peptic ulcers with or without bleeding and perforation may occur rarely. The risk is higher in elderly patients, in patients with a history of gastrointestinal toxicity, in patients with pre-existing gastric or intestinal bleeding / perforations, and patients with prolonged exposure to drug. | The risk of these events may be minimised by<br>- taking the lowest effective dose of the drug;<br>- restricting the duration of treatment;<br>- taking the drug soon after food;<br>- avoiding other medicines which may cause gastrointestinal problems<br>- combining with protective agents (e.g. misoprostol or proton pump inhibitors) |
| Respiratory depression | Respiratory depression may occur very rarely. The risk is higher in patients with other lung or brain diseases or those receiving other medications for pain or for psychiatric treatment. | The risk of these events may be minimised by<br>- taking the lowest effective dose of the drug;<br>- restricting the duration of treatment<br>- avoiding other medicines or situations which may cause respiratory depression<br>-contraindicating in “Severe respiratory depression“ |
| Kidney related adverse events | Kidney injury and dysfunction have been reported rarely | The risk of these events may be minimised by:<br>- taking the lowest effective dose of the drug;<br>- restricting the duration of the treatment;<br>- drinking an adequate amount of water during the treatment;<br>- avoiding other medicines which may cause nephrotoxicity |
| Seizures | Convulsions may occur very rarely. The risk is higher in | The risk of these events may be minimised by |

| Risk | What is known | Preventability |
|---|---|---|
| | patients with pre-existing seizure disorder, and those receiving medications for psychiatric treatment | - not administering the products in patients with epilepsy not adequately controlled by treatment (contraindication)<br>- taking the lowest effective dose of the drug;<br>- restricting the duration of treatment |
| Liver related adverse events | Liver related adverse reactions may occur rarely.<br>Severity is typically mild (altered liver function tests), but rare cases of liver failure have been reported | The risk of these events may be minimised by:<br>- the product must not be administered in patients with severely impaired hepatic function (contraindication)<br>- taking the lowest effective dose of the drug;<br>- restricting the duration of the treatment;<br>- avoiding other medicines which may cause liver problems |
| Serious skin reactions | Most skin reactions associated with DKP-TRAM are mild. Very rare serious skin reactions (that may have serious complications) have been reported. | Discontinue the medication in case of skin rash, lesions in the mouth, genitalia, or any sign of allergy. |
| Rapid swelling of skin, mouth, larynx and tongue | Very rare events have been reported. Though typically mild, these reactions may have serious consequences depending on the affected sites. | Discontinue the medication in case of skin, mouth, tongue swelling or in case of increasing difficulty in breathing |
| Congenital anomalies or toxicity on nursling ) | DKP-TRAM should not be taken in pregnancy due to the (minimal) risk of congenital anomalies and in lactation period | The product must not be administered during pregnancy and lactation (contraindications). |
| Cardiac or cerebrovascular related adverse events | DKP-TRAM may be associated with a small increase in the risk of arterial thrombotic events (for example myocardial infarction or stroke). | The risk of these events may be minimised by<br>- taking the lowest effective dose of the drug;<br>- restricting the duration of treatment |

**Important potential risks**

Table VI.2.4.2 Summary of important potential risks

| Risk | What is known |
|---|---|
| Decreased number of red blood cells (RBCs), white blood cells (WBCs) and decreased function of blood clotting mechanism | DKP-TRAM may very rarely induce bone marrow toxicity, leading to decrease in the number of RBCs, WBCs and decreased function of the blood clotting mechanism. |

| Risk | What is known |
|---|---|
| Off label use, misuse, abuse | On long-term use, tolerance, psychic and physical dependence may develop. |
| | |
| Severe effects on nervous system (serotoninergic syndrome) during the concomitant use of other drugs | Serotonin syndrome (Confusion, Rapid heart rate and high blood pressure, Dilated pupil, Loss of muscle coordination or twitching muscles, Muscle rigidit, Heavy sweating, Diarrhea, Headache, Shivering, Goose bumps) can occur with concomitant use of some drugs wich act on the nervous system and increase the serotonin levels such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors, tricyclic antidepressants and mirtazapine). Severe serotonin syndrome can be life-threatening. |

**Missing information**

Table VI.2.4.3 Summary of Missing information

| Risk | What is known |
|---|---|
| Adverse events in paediatric population | DKP-TRAM has not been studied in children and adolescents and must not be taken in the paediatric population. However, data on use of dexketoprofen and tramadol (single agents) in children suggests that DKP-TRAM may have a similar safety profile in children as in adults. |

### VI.2.5 Summary of risk minimisation measures by safety concern

Information about the above mentioned safety concerns are reported in the section 4.3, 4.4, 4.5, 4.6, 4.8 of the DKP-TRAM's proposed SmpC and in the respective section of the package leaflet. This drug has no additional risk minimisation measures

### VI.2.6 Planned post authorisation development plan

Not applicable.

No studies are currently planned.

### VI.2.7 Summary of changes to the Risk Management Plan over time

A summary of most important changes to the Risk Management plans over time are described in Table VI.2.7.1

Table VI.2.7.1

| Version | Date | Safety concerns | Comment |
|---|---|---|---|
| V1.1 | 08-Sep-2015 | The Important identified risk “GI haemorrhage and perforation in high risk patients” has been renamed in “ GI bleeding, ulceration and perforation”<br><br>The Important identified risk “Epilepsy” has been renamed in “Seizure”<br><br>The Important identified risk “Hepatic events” has been renamed in “Hepatic ADRs”.<br><br>The Important identified risk “Toxic epidermal necrolysis and Stevens-Lohnson Syndrome” has been renamed in “Severe skin reaction (Toxic epidermal necrolysis and Stevens-johnson Syndrome)”<br><br>The followings Important identified risks have been delated: “Angioedema”, “ADRs following long term use”, “Foetal toxicity”, “Other bleedings events”, “Other gastrointestinal events”.<br><br>The followings Important identified risks have been inserted: “Severe allergic reactions and other hypersensitivity disorders”, “Use during pregnancy and lactation”, “Cardiovascular and cerebrovascular ADRs”.<br><br>The Important potential risk “Cardiac events” has been deleted”.<br><br>The Important potential risk “Pancytopenia, anaemia not related to GI bleeding and aplastic anaemia” has been renamed in “Pancytopenia, anaemia not related to GI bleeding”.<br><br>The Important potential risk “Ocular events” has been renamed in “retinic phototoxicity”.<br><br>The Important potential risk “Serotonin syndrome” has been inserted.<br><br>The Missing information “ADRs in paediatric population” has been renamed in “Use in children”. | |
| | | | |

| | | | |
|---|---|---|---|
| V1.2 | 16-Nov-2015 | The Important identified risk " GI bleeding, ulceration and perforation" has been renamed in "Gastrointestinal haemorrage and perforation in high risk patients!<br><br>The Important identified risk "Use during pregnancy and lactation" has been renamed in "Foetal toxicity".<br><br>The Important potential risk "Pancytopenia, anaemia not related to GI bleeding" has been renamed in "Pancytopenia, anaemia not related to GI bleeding and aplastic anaemia".<br><br>The Important potential risk "Retinic phototoxicity" has been delated.<br><br>The important potential risk "Serotonine syndrome" has been renamed in "Serotonine syndrome due to concomitant treatment with serotoninergic drugs".<br><br>The Missing information "Use in children" has been renamed in "ADRs in paediatric population". | |
| V1.3 | 28-dec-2015 | The missing information "ADRs in paediatric population" has been renamed in "Use in paedriatic population". | |