## VI.2 Elements for a Public Summary

### *VI.2.1 Overview of disease epidemiology*

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Pain, depending its intensity, is subdivided into mild, moderate, or severe, wheres, depending on its duration, can be acute or chronic, where chronic pain may persist from months to years.

A large-scale, internet-based 2008 National Health and Wellness Survey performed in the United Kingdom, France, Spain, Germany and Italy estimated that 49.7 million persons reported pain. Of these, 29.4 million (59.20%) reported moderate pain and 9.0 million reported mild pain. The prevalence of pain across all pain severity categories increases with age. The highest prevalence for moderate pain results within the age interval comprised from 40 to 59 years.

Oral formulations of Dexketoprofen trometamol (dexketoprofen) are indicated in the short-term, symptomatic treatment of pain of mild to moderate intensity, such as musculo-skeletal pain, dysmenorrhoea, dental pain.

### *VI.2.2 Summary of treatment benefits*

The efficacy of dexketoprofen in the symptomatic treatment of pain has been extensively demonstrated. Dexketoprofen is at least as effective as ketoprofen, given at equivalent doses, and as other comparative Non-Steroideal Anti-Inflammatory Drugs, in different pain models. In some cases, dexketoprofen was shown to be more effective than ketoprofen.

Oral dexketoprofen, at doses up to a maximum of 75 mg/day (12.5 mg every 4-6 hours or 25 mg every 8 hours) is indicated for the symptomatic treatment of pain of mild to moderate intensity in the adult population. A total of 2,969 patients had been exposed to oral dexketoprofen in clinical trials, whereas 2,031 and 438 patients were exposed to comparator drugs or placebo, respectively.

In general, the studies were conducted in young to middle-aged males or females for the short-term treatement of:

- Dental pain where dexketoprofen provided an analgesic effect superior to placebo, faster than that obtained with dipyrone, and comparable to ketoprofen and ibuprofen;
- Painful menstruations (primary dysmenorrhoea) where dexketoprofen was superior to placebo and comparable to that of ketoprofen.
- Musculo-skeletal pain (back pain, osteoarthritis and ankle sprains) where dexketoprofen was effective as the control drugs (i.e. tramadol, dextropropoxiphene/paracetamol, paracetamol/codeine, ketoprofen and diclofenac);
- Post-operative pain, given alone or in addition to opioids according to the intensity of pain, have shown that dexketoprofen reduces the requirements for opioids by about 25 to 35% in the first post-operative day, thus reducing the risks associated with their use.

Furthermore, a wide post-marketing experience (more than 1,000 millions daily doses administered so far) has confirmed the effectiveness of dexketoprofen in the real clinical practice.

In conclusion, the analyses of efficacy and safety data collected do not indicate any change in the consolidated benefit risk balance of the formulations. Consequently, such data indicate that benefits are largely positive.

### *VI.2.3 Unknowns relating to treatment benefits*

Dexketoprofen has a consolidated post-marketing experience. There is no evidence that its efficacy is either enhanced or reduced in specific populations or circumstances. Dexketoprofen has been studied in both adult men and women, and in individuals older than 60 years but not in either the paediatric population or pregnant women, therefore it cannot be used in these populations.

### *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 bleeding associated or not with perforation in patients at risk for developing these events. | The most frequent adverse effects of dexketoprofen involves the gastrointestinal tract and includes nausea and / vomiting, abdominal pain, diarrhoea, dyspepsia, gastritis, constipation, dry mouth and flatulence.<br>Peptic ulcers, peptic ulcer haemorrhage or perforation and pancreatitis may occur rarely. Elderly patients, patients which already had gastric or intestinal bleeding/perforations, or patients exposed to long treatments are at higher risk of complications. | Yes, you may prevent or minimise the problem by:<br>- taking the lowest effective dose of the drug;<br>- restricting the duration of the treatment;<br>- taking the drug soon after you have eaten;<br>- Paying attention to avoid taking other medicines which may cause gastrointestinal problems;<br>- alerting your doctor if you feel stomach pain, heartburn, or you note bleeding or black stools. |
| Hepatic reactions to drug. | Medications such as dexketoprofen can on rare occasions induce several different forms of hepatic injury.<br>The severity of the liver injury from dexketoprofen ranges from alterations of biochemical parameters in blood to liver failure. | Yes, you may prevent or minimise the problem by:<br>- taking the lowest effective dose of the drug;<br>- restricting the duration of the treatment;<br>- Paying attention to avoid taking other medicines which may cause liver problems;<br>- alerting your doctor if fever starts after you have taken the drug or if your skin become yellow. |

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|---|---|---|
| Acute renal dysfunction. | Medications such as dexketoprofen can on rare occasions induce several different forms of kidney injury. | Yes, you may prevent or minimise the problem 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>- Paying attention to avoid taking other medicines which may cause renal problems;<br>- alerting your doctor if you stop urinating. |
| Reactions due to long-term administration of the drug. | The long-term use of drugs like dexketoprofen increases the risk of gastrointestinal, renal, liver and haematological (blood-related) adverse reactions. | Yes, you may prevent or minimise the problem by:<br>- taking the lowest effective dose of the drug;<br>- restricting the duration of the treatment; |
| Serious skin reactions | Medications such as dexketoprofen may be associated, on very rare occasions, with development of a very serious skin (or bullous) reactions such as Stevens Johnson Syndrome and Toxic Epidermal Necrolysis.<br>The vast majority of skin reactions are usually non serious and only a few clinical situations could it really be dangerous for the patient's life. | Yes, you may prevent or minimise the problem by:<br>- stopping immediately the drug at the appearance of a skin rash, or any lesion inside the mouth or on the genitals, or any sign of an allergy |
| Rapid swelling of skin, mouth, larynx and tongue (Angioedema) | Medications such as dexketoprofen may be associated, on very rare occasions, with development of swelling of skin, mouth, larynx and tongue (angioedema) which, depending on the affected part of the skin, could be a serious problem. | Yes, you may prevent or minimise the problem by:<br>- stopping immediately the drug at the appearance of a skin rash, or if you note rapid swelling of skin, mouth, larynx and tongue. |
| Foetal malformation | Dexketoprofen may have serious affects on foetal health and should not be taken during the third trimester of pregnancy. If required during the first and second trimester, the dose and schedule should be adjusted. Use during pregnancy should always be controlled by a physician. | Yes, you may prevent or minimise the problem by:<br>- alerting your doctor before taking the drug if you are pregnant;<br>- stopping immediately the drug during the third trimester of pregnancy. |

**Important potential risks**

Table VI.2.4.2 Summary of important potential risks

| Risk | What is known |
|---|---|
| Cardiac and cerebrovascular ADRs. | If you have heart problems, previous stroke or think that you might be at risk of these conditions (for example if you have high blood pressure, diabetes or high cholesterol or are a smoker) you should discuss your treatment with your doctor or pharmacist; medicines such as |

| Risk | What is known |
|---|---|
| | dexketoprofen may be associated with a small increased risk of heart attack ("myocardial infarction") or stroke. Any risk is more likely with high doses and prolonged treatment. Do not exceed the recommended dose or duration of treatment. |
| Reduction in the number of red, white blood cells and platelets not due to gastrointestinal bleeding, and disorder in the bone marrow that produces blood elements. | Medications such dexketoprofen can very rarely induce bone marrow toxicity, thus decreasing the number of red, white blood cells and platelets in the absence of gastrointestinal bleeding. |
| | |

**Missing information**

Table VI.2.4.3. Summary of Missing information

| Risk | What is known |
|---|---|
| Use in children. | The use of dexketoprofen has not been studied in paediatric population; therefore, there is no data on the safety and efficacy of the product in the cited population.<br>Paediatric problems related to dexketoprofen include allergies, asthma exacerbations and serious gastrointestinal events. The analysis of reported cases in children and adolescents showed these events are similar to those occurring in adults. |

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

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for dexketoprofen can be found in the Annex 2 of this RMP.

This medicine has no additional risk minimisation measures.

### *VI.2.6 Planned post authorisation development plan*

Neither planned studies nor studies imposed by the Committee for Medicinal Products for Human Use (CHMP) / Pharmacovigilance Risk Assessment Committee (PRAC) / National Competent Authorities (NCA) are foreseen for the aforementioned product. Therefore, there is no need to perform with post-authorisation efficacy studies (PAES) or post-authorisation safety studies (PASS).

**List of studies in post authorisation development plan**

Not applicable, there are no planned studies for investigating safety or efficacy concerns.

**Studies which are a condition of the marketing authorisation**

Not applicable, there are no studies conditioning the marketing authorisation.

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

| Version | Date | Safety concerns | Comment |
|---|---|---|---|
| v. 1.0 | 21-Jun-2013 | Important identified risks:<br>-GI haemorrhage and perforation in high risk patients.<br>-Hepatic ADRs.<br>-Acute renal failure.<br>-ADRs following long-term use.<br>-Toxic epidermal necrolysis, Stevens-Johnson Syndrome and Angioedema<br><br>Important potential risks:<br>-Cardiac ADRs<br>-Pancytopenia, anaemia not related to GI bleeding and aplastic anaemia.<br>-Ocular ADRs.<br>-Respiratory and cardio-respiratory arrest (injective formulation only).<br><br>Missing information:<br>-ADRs in the paediatric population | |
| v. 1.1 | 13-Jun-2014 | Important identified risks:<br>-GI haemorrhage and perforation in high risk patients.<br>-Hepatic ADRs.<br>-Acute renal failure.<br>-ADRs following long-term use.<br>-Toxic epidermal necrolysis, Stevens-Johnson Syndrome<br>-Angioedema<br>-Foetal toxicity<br><br>Important potential risks:<br>-Cardiac ADRs<br>-Pancytopenia, anaemia not related to GI bleeding and aplastic anaemia.<br>-Ocular ADRs.<br>-Respiratory and cardio-respiratory arrest (injective formulation only).<br><br>Missing information:<br>-ADRs in the paediatric population | "Safety concerns identified in non-clinical studies" have been updated. Effects on renal and reproductive system was added as important identified risks identified in non-clinical data and confirmed by clinical data.<br><br>The important identified risk "Toxic epidermal necrolysis, Stevens-Johnson Syndrome and Angioedema" has been devided in two different risk: "Toxic epidermal necrolysis, Stevens-Johnson Syndrome" and "Angioedema".<br><br>The important identified Risk "Foetal Toxicity" has been added. |

| Version | Date | Safety concerns | Comment |
|---|---|---|---|
| v. 1.2 | 12 Sept 2014 | Important identified risk:<br>-GI haemorrhage and perforation in high risk patients.<br>-Hepatic ADRs.<br>-Acute renal failure.<br>-ADRs following long-term use.<br>-Toxic epidermal necrolysis, Stevens-Johnson Syndrome<br>-Angioedema<br>-Foetal toxicity<br><br>Important potential risks:<br>-Cardiac ADRs<br>-Pancytopenia, anaemia not related to GI bleeding and aplastic anaemia.<br>-Ocular ADRs.<br>-Respiratory and cardio-respiratory arrest (injective formulation only).<br><br>Missing information:<br>-ADRs in the paediatric population | In this new RMP has been added a new formulation: Hard capsules containing 25 mg.<br><br>No changes concern the identified/potential risk or missing informations. |
| V1.3 | 27Oct-2014 | Important identified risk:<br>-GI haemorrhage and perforation in high risk patients.<br>-Hepatic ADRs.<br>-Acute renal failure.<br>-ADRs following long-term use.<br>-Toxic epidermal necrolysis, Stevens-Johnson Syndrome<br>-Angioedema<br>-Foetal toxicity<br><br>Important potential risks:<br>-Cardiac ADRs<br>-Pancytopenia, anaemia not related to GI bleeding and aplastic anaemia.<br>-Ocular ADRs.<br><br>Missing information:<br>-ADRs in the paediatric population | The important potential risk "Respiratory and cardio-respiratory arrest" has been removed as not acting the oral formulation. |
| V1.4 | 16-Nov-2016 | Important identified risk:<br>-GI haemorrhage and perforation in high risk patients.<br>-Hepatic ADRs.<br>-Acute renal failure.<br>-ADRs following long-term use.<br>-Severe skin reaction (toxic epidermal necrolysis and Stevens-Johnson Syndrome)<br>-Severe allergic reactions and other hypersensitivity disorders<br>-Foetal toxicity<br><br>Important potential risks:<br>-Cardiovascular and cerebrovascular | The important identified risk "Toxic epidermal necrolysis and Stevens-Johnson syndrome" has been renamed as “Skin reactions (Toxic epidermal necrolysis and Stevens-Jonhson syndrome".<br><br>The important identified risk "Angioedema" has been renamed as "Severe allergic reactions and other hypersensitivity |

| Version | Date | Safety concerns | Comment |
|---|---|---|---|
| | | ADRs<br>-Pancytopenia, anaemia not related to GI bleeding and aplastic anaemia.<br><br>Missing information:<br>-Use in the paediatric population | disorders".<br><br>The important potential risk “Cardiac ADRs” has been renamed as “Cardiovascular and cerebrovascular ADRs”.<br><br>The important potential risk "Ocular ADRs" has been removed.<br><br>The important potential risk “ADRs in the paediatric population” has been renamed as “Use in the paediatric population”. |

Summary EU-Risk Management Plan