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## **Betreff: Ketoprofen – hältige Arzneispezialitäten –Änderungen der Fach- und Gebrauchsinformationen**

Sehr geehrte Damen und Herren,

basierend auf Daten aus Spontanberichten und auf der Evaluierung des PSURs im EU-HBD-workshoring Projekt, kam die CHMP Pharmacovigilance Working Party in der Sitzung vom Jänner 2012 zu der Empfehlung, europaweit Ergänzungen mit folgendem Wortlaut in die **Fach- und Gebrauchsinformation** aller Ketoprofen– hältigen Arzneispezialitäten (ausgenommen jene zur topischen Anwendung) aufzunehmen.

### **1. Fachinformation**

#### **4.3 Contraindications**

*applies to solid forms, syrup, IV and IM*

Ketoprofen is contraindicated in patients who have a history of hypersensitivity reactions such as bronchospasm, asthmatic attacks, rhinitis, urticaria or other allergic-type reactions to ketoprofen, Acetylsalicylic acid (ASA) or other Non Steroidal Anti Inflammatory Drugs (NSAIDs).

Severe, rarely fatal, anaphylactic reactions have been reported in such patients (see section 4.8) (*last statement applies to solid forms and syrup only*).

Ketoprofen is contraindicated in patients with hypersensitivity to any of the excipients of the drug.

Ketoprofen is also contraindicated in the third trimester of pregnancy.

Ketoprofen is contraindicated in the following cases:

- severe heart failure
- active peptic ulcer, or any history of gastrointestinal bleeding, ulceration or perforation
- haemorrhagic diathesis
- severe hepatic insufficiency
- severe renal insufficiency.

applies to IV and IM only

Ketoprofen is contraindicated in cases of cerebrovascular bleeding or any other active bleeding.

applies to solid forms (suppositories) only

Ketoprofen is contraindicated in cases of rectitis or history of proctorrhagia (*rectal administration only*).

applies to IM only

Ketoprofen is contraindicated in patients with hemostatic disorders or ongoing anticoagulant therapy.

#### **4.4 Special warnings and precautions for use**

applies to solid forms, syrup, IV and IM

The use of <Invented name> with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms.

Elderly:

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2).

Gastrointestinal (GI) bleeding, ulceration and perforation:

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events.

Some epidemiological evidence suggests that ketoprofen may be associated with a high risk of serious gastrointestinal toxicity, relative to some other NSAIDs, especially at high doses (see also section 4.2 and 4.3).

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see

section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and 4.5).

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving <Invented name>, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8).

Serious skin reactions some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Ketoprofen should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for ketoprofen.

At the start of treatment, renal function must be carefully monitored in patients with heart failure, cirrhosis and nephrosis, in patients receiving diuretic therapy, in patients with chronic renal impairment, particularly if the patient is elderly. In these patients, administration of ketoprofen may induce a reduction in renal blood flow caused by prostaglandin inhibition and lead to renal decompensation.

Caution is required in patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

As with other NSAIDs, in the presence of an infectious disease, it should be noted that the anti-inflammatory, analgesic and the antipyretic properties of ketoprofen may mask the usual signs of infection progression such as fever.

In patients with abnormal liver function tests or with a history of liver disease, transaminase levels should be evaluated periodically, particularly during long-term therapy.

Rare cases of jaundice and hepatitis have been described with ketoprofen (*last statement applies to solid forms and syrup only*).

The use of NSAIDs may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of the NSAID should be considered.

Patients with asthma combined with chronic rhinitis, chronic sinusitis, and/or nasal polyposis have a higher risk of allergy to aspirin and/or NSAIDs than the rest of the population. Administration of this medicinal product can cause asthma attacks or bronchospasm, particularly in subjects allergic to aspirin or NSAIDs (see section 4.3).

*applies to solid forms and syrup only*

As with all NSAIDs, careful consideration should be given when treating patients with existing uncontrolled hypertension, congestive heart failure, established ischemic heart disease, peripheral arterial disease, and/or cerebrovascular disease, as well as, before initiating long term treatment in patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

If visual disturbances, such a blurred vision, occur treatment should be discontinued.

*applies to IV and IM only*

- Risk of gastro-intestinal bleeding: the relative risk increases in subjects who have a low body weight. If gastrointestinal bleeding or ulcer occur, treatment must be discontinued immediately.
- Blood counts and liver and kidney function tests should be carried out during long-term treatment.
- Hyperkalemia:  
Hyperkalemia promoted by diabetes or concomitant treatment with potassium-sparing agents (see Interactions).  
Potassium levels must be monitored regularly under these circumstances.

*applies to IV only*

Ketoprofen can be used in combination with morphine derivatives if pain is severe.

*applies to syrup only*

Ketoprofen syrup contains 600 mg/ml of sucrose.

*applies to formulations containing lactose*

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.



## 4.5 Interaction with other medicinal products and other forms of interaction

**applies to solid forms, syrup, IV and IM**

### **Not recommended medicinal product associations**

#### **Other NSAIDs (including cyclooxygenase-2 selective inhibitors) and high dose salicylates:**

Increased risk of gastrointestinal ulceration and bleeding.

#### **Anticoagulants (heparin and warfarin) and platelet aggregation inhibitors (i.e. ticlopidine, clopidogrel):**

Increased risk of bleeding (see section 4.4).

If coadministration is unavoidable, patient should be closely monitored.

#### **Lithium:**

Risk of elevation of lithium plasma levels, sometimes reaching toxic levels due to decreased lithium renal excretion. Where necessary, plasma lithium levels should be closely monitored and the lithium dosage levels adjusted during and after NSAID therapy.

#### **Methotrexate at doses greater than 15 mg/week:**

Increased risk of haematologic toxicity of methotrexate, particularly if administered at high doses (>15 mg/week), possibly related to displacement of protein-bound methotrexate and to its decreased renal clearance.

Allow at least 12 hours between the discontinuation or initiation of ketoprofen treatment and the administration of methotrexate (*last statement applies to IV/IM only*).

### **Medicinal product associations requiring precautions for use**

#### **Diuretics:**

Patients and particularly dehydrated patients taking diuretics are at a greater risk of developing renal failure secondary to a decrease in renal blood flow caused by prostaglandin inhibition. Such patients should be rehydrated before initiating coadministration therapy and renal function monitored when the treatment is started (see section 4.4).



**ACE inhibitors and Angiotensin II Antagonists:**

In patients with compromised renal function (e.g. dehydrated patients or elderly patients) the co-administration of an ACE inhibitor or Angiotensin II antagonist and agents that inhibit cyclooxygenase may result in further deterioration of renal function, including possible acute renal failure.

**Methotrexate at doses lower than 15 mg/week:**

During the first weeks of combination treatment, full blood count should be monitored weekly. If there is any alteration of the renal function or if the patient is elderly, monitoring should be done more frequently.

**Medicinal product associations to be taken into account**

**Antihypertensive agents (beta-blockers, angiotensin converting enzyme inhibitors, diuretics):**

Risk of decreased antihypertensive potency (inhibition of vasodilator prostaglandins by NSAIDs).

**Thrombolytics:**

Increased risk of bleeding.

**Selective serotonin reuptake inhibitors (SSRIs):**

Increased risk of gastrointestinal bleeding (see section 4.4).

***Applies to solid forms and syrup only***

Medicinal product associations requiring precautions for use

**Corticosteroids:** increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

**Pentoxifylline:**

There is an increased risk of bleeding. More frequent clinical monitoring and monitoring of bleeding time is required.

**Medicinal product associations to be taken into account**

**Probenecid:**

Concomitant administration of probenecid may markedly reduce the plasma clearance of ketoprofen.

***applies to IV and IM only***

**Risks related to hyperkalemia:** Certain medicinal products or therapeutic categories can promote hyperkalemia, i.e. potassium salts, potassium-sparing diuretics, converting enzyme inhibitors, angiotensin II receptor blockers, NSAIDs, heparins (low molecular-weight or unfractionated), cyclosporin, tacrolimus and trimethoprim. The occurrence of hyperkalemia can depend on the presence of co-factors. This risk is enhanced when the drugs mentioned above are administered concomitantly.

**Risks related to antiplatelet effect:** Several substances are involved in interactions due to their antiplatelet effects: tirofiban, eptifibarid, abcixiab and iloprost. The use of several antiplatelet drugs enhances the risk of bleeding.

**Combinations to be taken into consideration:**

- **Cyclosporin, tacrolimus:**

Risk of additive nephrotoxic effects, particularly in elderly subjects.

## **4.6 Pregnancy and lactation**

### Pregnancy

***applies to solid forms, syrup, IV and IM***

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, ketoprofen should not be given unless clearly necessary. If ketoprofen is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis; the mother and the neonate, at the end of pregnancy, to:
- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, ketoprofen is contraindicated during the third trimester of pregnancy.

#### Lactation

*applies to solid forms, syrup, IV and IM*

No data are available on excretion of ketoprofen in human milk. Ketoprofen is not recommended in nursing mothers.

#### **4.7 Effects on ability to drive and use machines**

*applies to solid forms, IV and IM*

Patients should be warned about the potential for somnolence, dizziness or convulsions and be advised not to drive or operate machinery if these symptoms occur.

*applies to IV and IM only*

Patients should be warned of possible visual disturbances. If patients experience this, they should not drive or use machines.

#### **4.8 Undesirable effects**

Gastrointestinal\*: The most commonly-observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration. Less frequently, gastritis has been observed.



Classification of expected frequencies (*frequencies are only applicable to the oral formulations*):

Very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data).

*applies to the syrup formulation only*

Vomiting, diarrhoea and hypersensitivity reactions have been reported in clinical trials in infants and children.

*applies to solid forms, syrup, IV and IM*

The following adverse reactions have been reported with ketoprofen in adults:

#### Blood and lymphatic system disorders

- rare: haemorrhagic anaemia
- not known: agranulocytosis, thrombocytopenia, bone marrow failure (*last term applies only to solids and syrup*)

#### Immune system disorders

- not known: anaphylactic reactions (including shock)

#### Psychiatric disorders

- not known: mood altered

#### Nervous system disorders

- uncommon: headache, dizziness, somnolence
- rare: paraesthesia (*applies only to solids and syrup*)
- not known: convulsions, dysgeusia (*last term applies only to solids and syrup*)

#### Eye disorders

- rare: vision blurred (see section 4.4)

#### Ear and labyrinth disorders

- rare: tinnitus

#### Cardiac disorders

- not known: heart failure

#### Vascular disorders

- not known: hypertension, vasodilatation (*last term applies only to solids and syrup*)

#### Respiratory, thoracic and mediastinal disorders

- rare: asthma
- not known: bronchospasm (particularly in patients with known hypersensitivity to ASA and other NSAIDs), rhinitis

#### Gastrointestinal disorders

- common: dyspepsia (*applies only to solids and syrup*), nausea, abdominal pain (*abdominal pain applies only to solids and syrup*), vomiting
- uncommon: constipation, diarrhoea, flatulence (*flatulence applies only to solids and syrup*), gastritis
- rare ulcerative stomatitis\*, peptic ulcer
- not known: exacerbation of colitis and Crohn's disease (*applies only to solids and syrup*), gastrointestinal haemorrhage and perforation, melaena\*, haematemesis\*

#### Hepatobiliary disorders

- rare: hepatitis, transaminases increased, elevated serum bilirubin due to hepatitis disorders

#### Skin and subcutaneous disorders

- uncommon: rash, pruritis
- not known: photosensitivity reaction, alopecia, urticaria, aggravation of chronic urticaria (*aggravation of chronic urticaria applies to IV and IM only*), angioedema, bullous eruption including Stevens-Johnson syndrome and toxic epidermal necrolysis

#### Renal and urinary disorders

- not known: renal failure acute, tubulointerstitial nephritis, nephritic syndrome, renal function tests abnormal (*last term applies only to solids and syrup*)

General disorders and administration site conditions

- uncommon: oedema

Investigations

- rare: weight increased (*applies only to solids and syrup*)

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

*applies to solids only*

General disorders and administration site conditions

- not known: fatigue

*applies to IV and IM only*

Gastrointestinal disorders: gastrointestinal discomfort, gastric pain, and rare cases of colitis

Renal and urinary disorders:

- water/sodium retention with possible edema, hyperkalemia (see section 4.4 and section 4.5).
- organic renal damage that could cause acute renal insufficiency: isolated cases of acute tubular necrosis and renal papillary necrosis have been reported.

Blood and lymphatic system disorders: rare cases of leukopenia

General disorders and administration site conditions: some cases of pain and a burning sensation at the injection site have been reported.

## 4.9 Overdose

### applies to solid forms only

Cases of overdose have been reported with doses up to 2.5 g of ketoprofen. In most instances, the symptoms observed have been benign and limited to lethargy, drowsiness, nausea, vomiting and epigastric pain.

There are no specific antidotes to ketoprofen overdosages. In cases of suspected massive overdosages, a gastric lavage is recommended and symptomatic and supportive treatment should be instituted to compensate for dehydration, to monitor urinary excretion and to correct acidosis, if present.

If renal failure is present, haemodialysis may be useful to remove circulating medicinal product.

### applies to syrup only

In the event of massive overdosage, the patient should be transferred immediately to hospital. Gastric contents must be rapidly evacuated.

Symptomatic treatment should be instituted.

### applies to IV and IM only

In adults, the principal signs of overdose are headache, dizziness, drowsiness, nausea, vomiting, diarrhea and abdominal pain. During severe intoxication, hypotension, respiratory depression and gastrointestinal bleeding have been observed.

The patient must be transferred immediately to a specialized hospital setting where symptomatic treatment can begin.

There is no specific antidote.

\* gemäß Key element

Oben angeführte Textabschnitte stellen eine **Mindestanforderung** dar, zusätzliche nationale Hinweise in diesen Abschnitten sind zu belassen.