



London, 26 September 2006
EMA/CHMP/381615/2006

Key elements* for the summaries of product characteristics of the non-selective NSAIDs piroxicam, ketoprofen and ketorolac adopted by the CHMP

GASTROINTESTINAL SAFETY OF NSAIDS

Section 4.1 Therapeutic indications

(Wording to supplement existing indications):

Piroxicam: Treatment should only be initiated by specialist clinicians *[to be defined nationally]*

Ketorolac: Treatment should be only be initiated in hospitals. The maximum duration of treatment is x days *[national wording may apply, treatment duration should be specified for both parenteral and oral forms]*

Section 4.2 Posology and method of administration

Ketoprofen: The maximum daily dose is 200mg. The balance of risks and benefits should be carefully considered before commencing treatment with 200mg daily, and higher doses are not recommended (see also section 4.4)

Section 4.3 Contra-indications

Active peptic ulcer, or any history of gastrointestinal bleeding, ulceration or perforation

Section 4.4 Special Warnings and Precautions for Use

The use of <Invented name> with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided. *[note: ketorolac SPCs already contraindicate concomitant NSAIDs in many Member States]*

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

Piroxicam: Epidemiological evidence suggests that piroxicam may be associated with a high risk of serious gastrointestinal toxicity, relative to other NSAIDs (see also section 4.1 and 4.3).

Ketoprofen: 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).

Ketorolac: Epidemiological evidence suggests that ketorolac may be associated with a high risk of serious gastrointestinal toxicity, relative to some other NSAIDs, especially when used outside the licensed indications and/or for prolonged periods (see also section 4.1, 4.2 and 4.3).

* Unless otherwise specified the changes pertain to all 3 products; ketoprofen, ketorolac and piroxicam

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).

Section 4.5 Interactions with other medicaments and other forms of interaction

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

Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4).

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4).

Section 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.

CARDIOVASCULAR SAFETY OF NSAIDS

Section 4.3 Contraindications

Piroxicam: Moderate or severe heart failure.

Ketoprofen and Ketorolac: Severe heart failure.

Section 4.4 Special Warnings and precautions for Use

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

Section 4.8 Undesirable effects

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.

SKIN REACTIONS OF PRESCRIPTION NSAIDS

Section 4.4 Special Warnings and precautions for Use

Piroxicam:

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). Epidemiological evidence suggests that piroxicam may be associated with a higher level of risk of serious skin reactions than some other NSAIDs. Patients appear to be at highest risk for 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. Piroxicam should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Ketoprofen and Ketorolac:

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 for 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. <Invented name> should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Section 4.8 Undesirable effects

Bullous reactions including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis (very rare).