ANNEX III

AMENDMENTS TO THE SUMMARY OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLET

AMENDMENTS TO BE INCLUDED IN THE RELEVANT SECTIONS OF THE SUMMARY OF PRODUCT CHARACTERISTICS OF NIMESULIDE CONTAINING MEDICINAL PRODUCTS (SYSTEMIC FORMULATIONS)

Additions appear in italics and underlined deletions in ~~italics and strikethrough~~

4.1 Therapeutic indications

Treatment of acute pain *(see section 4.2).*
Symptomatic treatment of painful osteoarthritis *(see section 4.2).*
Primary dysmenorrhoea.

Nimesulide should only be prescribed as second line treatment.
The decision to prescribe nimesulide should be based on an assessment of the individual patient's overall risks (see sections 4.3 and 4.4).

4.2 Posology and method of administration

The minimum effective dose should be used for the shortest duration to reduce the undesirable effects.

The maximum duration of a treatment course with nimesulide is 15 days.
Nimesulide 100mg Tablets/granules should be used for the shortest possible duration, as required by the clinical situation.
Adults**:**
100mg bid after meal.

Elderly: In elderly patients there is no need to reduce the daily dosage (see section 5.2).

Children (< 12 years): Nimesulide 100mg Tablets/granules is contraindicated in these patients (see also section 4.3).

Adolescents (from 12 to 18 years): on the basis of the kinetic profile in adults and on the pharmacodynamic characteristics of nimesulide, no dosage adjustment in these patients is necessary.

Impaired renal function: on the basis of pharmacokinetics, no dosage adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance of 30-80 ml/min), while Nimesulide 100mg Tablets/granules is contraindicated in case of severe renal impairment (creatinine clearance < 30ml/min) (see sections 4.3 and 5.2).

Hepatic impairment: the use of Nimesulide 100mg Tablets/granules is contraindicated in patients with hepatic impairment (see section 5.2).

4.3 Contraindications

Known hypersensitivity to nimesulide or to any of the excipients of the products.
History of hypersensitivity reactions (e.g. bronchospasm, rhinitis, urticaria) in response to acetylsalicylic acid or other non-steroidal anti-inflammatory drugs.
History of hepatotoxic reactions to nimesulide
Concomitant exposure to other potentially hepatotoxic substances.
Alcoholism, drug addiction.
Active gastric or duodenal ulcer, a history of recurrent ulceration or gastrointestinal bleeding, cerebrovascular bleeding or other active bleeding or bleeding disorders.
Severe coagulation disorders.
Severe heart failure
Severe renal impairment.
Hepatic impairment.

Patients with fever and/or flu-like symptoms.
Children under 12 years.
The third trimester of pregnancy and breastfeeding (see sections 4.6 and 5.3).

4.4 Special warnings and special precautions for use

The risk of undesirable effects may be reduced by using Nimesulide 100mg Tablets/granules for the shortest possible duration (see section 4.2)
Treatment should be discontinued if no benefit is seen.

Rarely Nimesulide 100mg Tablets/granules has been reported to be associated with serious hepatic reactions, including very rare fatal cases (see also section 4.8). Patients who experience symptoms compatible with hepatic injury during treatment with Nimesulide 100mg Tablets/granules (e.g. anorexia, nausea, vomiting, abdominal pain, fatigue, dark urine) or patients who develop abnormal liver function tests should have treatment discontinued. These patients should not be rechallenged with nimesulide. Liver damage, in most cases reversible, has been reported following short exposure to the drug.
~~*Concomitant administration with known hepatotoxic drugs, and alcohol abuse must be avoided during treatment with Nimesulide 100mg tablets/granules treatment, since either may increase the risk of hepatic reactions.*~~
During therapy with Nimesulide 100mg Tablets/granules, patients should be advised to refrain from other analgesics. Simultaneous use of different NSAIDs is not recommended.

Patients receiving nimesulide who develop fever and/or flu-like symptoms should discontinue treatment
Gastrointestinal bleeding or ulceration / perforation can occur at any time during treatment with or without warning symptoms or a previous history of gastrointestinal events. If gastrointestinal bleeding or ulceration occurs, nimesulide should be discontinued. Nimesulide should be used with caution in patients with gastrointestinal disorders, including history of peptic ulceration, history of gastrointestinal haemorrhage, ulcerative colitis or Crohn's disease.

In patients with renal or cardiac impairment, caution is required since the use of Nimesulide 100mg Tablets/granules may result in deterioration of renal function. In the event of deterioration, the treatment should be discontinued (see also section 4.5).

Elderly patients are particularly susceptible to the adverse effects of NSAIDs, including gastrointestinal haemorrhage and perforation, impaired renal, cardiac and hepatic function. Therefore, appropriate clinical monitoring is advisable.

As nimesulide can interfere with platelet function, it should be used with caution in patients with bleeding diathesis (see also section 4.3).
However, Nimesulide 100mg Tablets/granules is not a substitute for acetylsalicylic acid for cardiovascular prophylaxis.

~~*NSAIDs may mask the fever related to an underlying bacterial infection.*~~

The use of Nimesulide 100mg Tablets/granules 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 Nimesulide 100mg Tablets/granules should be considered (see section 4.6).

AMENDMENTS TO BE INCLUDED IN THE RELEVANT SECTIONS OF THE PACKAGE LEAFLET OF NIMESULIDE CONTAINING MEDICINAL PRODUCTS (SYSTEMIC FORMULATIONS)

Additions appear in italics and underlined deletions in ~~italics and strikethrough~~

1. WHAT TRADEMARK IS AND WHAT IT IS USED FOR

TRADEMARK is a non-steroidal anti-inflammatory drug ("NSAID"), with pain-killing ~~*and fever-lowering*~~ properties. It is used for treatment of acute pain, for the treatment of symptoms of painful osteoarthritis, and for the treatment of period pains.

Before prescribing TRADEMARK your doctor will assess the benefits this medicine may give you against your risks of developing side effects.

2. BEFORE YOU TAKE TRADEMARK

Do not use TRADEMARK if you:

- are hypersensitive (allergic) to nimesulide or any of the other ingredients of TRADEMARK;
- have had allergic reactions (e.g. wheezing, runny or blocked nose, hives or nettle rash) after aspirin or other non-steroidal anti-inflammatory drugs;
- had a reaction to nimesulide affecting the liver in the past;
- *are taking other medicines that are known to affect the liver, e.g. paracetamol or any other pain-killers or NSAID treatment*
- *are taking drugs of addiction, or have developed a habit that makes you dependent on drugs or other substances*
- *are a regular heavy drinker (alcohol),*
- if you have liver disease or increased liver enzymes
- have a peptic ulcer (stomach or duodenal ulcer) now or had one in the past;
- have had bleeding from the stomach or bowel;
- have had bleeding into the brain (a stroke);
- have any other problem with bleeding or any problems due to your blood not clotting;
- have heart failure or a kidney disorder (poor kidney function) or any liver disorder;
- *are suffering from fever or flu (feeling generally achy, unwell, chills or shivering or have a temperature);*
- are in the last 3 months of pregnancy;
- are breastfeeding.
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Do not give TRADEMARK to a child aged less than 12.

3. HOW TO TAKE TRADEMARK

Always take TRADEMARK exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. The usual dose is 1 <unit> of 100 mg twice a day after a meal. Use TRADEMARK for as short a period of time as possible *and for not more than 15 days in any single course of treatment*.

Take special care with TRADEMARK

- If you have an intolerance to some sugars, you should contact your doctor before taking this medicine.

- If you are taking any of the following as they may interact with TRADEMARK:
  - medicine to thin the blood (anti-coagulants, aspirin or other salicylates)
  - water tablets (diuretics) used for heart failure or blood pressure
  - lithium which is used to treat depression and similar conditions
  - methotrexate
  - cyclosporin

  make sure that your doctor or pharmacist knows that you are taking these medicines before taking TRADEMARK.
- ~~*Do not take other medicines that are known to affect the liver, e.g. paracetamol or any other pain killers or NSAID treatment*~~
- ~~*Avoid excess alcohol during treatment with TRADEMARK*~~
- If during nimesulide treatment you develop symptoms that suggest a liver condition, you should stop taking nimesulide and inform your doctor immediately. Symptoms suggesting a liver condition include loss of appetite, nausea, vomiting, abdominal pain, persistent tiredness or dark urine. If you have ever suffered from peptic ulcers, bleeding from the stomach or bowel, ulcerative colitis or Crohn's disease, you should tell your doctor before taking TRADEMARK.
- *If during treatment with TRADEMARK, you develop fever and/or flu-like symptoms (feeling generally achy, unwell and chills or shivering) you should stop taking the product and inform your doctor.*
- If you suffer from heart or kidney disease, you should tell your doctor before taking TRADEMARK; kidney function may become worse on TRADEMARK.
- If you are elderly, your doctor may want to see you at intervals to make sure that TRADEMARK is not causing stomach, kidney, heart or liver problems.
- If you are planning a pregnancy, you should inform your doctor since TRADEMARK may decrease fertility.