Froben/Transact (Flurbiprofen)

RECOMMENDED CHANGES TO THE PRODUCT INFORMATION

The following changes to the product information of medicinal products containing the active substance flurbiprofen are recommended:

Summary of product characteristics

Indications (4.1 section of SmPC)

The therapeutic indications in all MSs should be put in line with the CCDS version 2009, in particular, reference to antipyretic and paediatric indication should be deleted.

For paediatric indications see above comments.

Posology (4.2 section of SmPC)

Maximum duration of treatment for local on mucosae (spray, lozenges, mouthwash, etc.) use should not exceed three days: "It is recommended that this product should be used for a maximum of three days" should be added in section 4.2.

Children:

Not recommended for use in children under 12 years.

Contraindications (4.3 section of SmPC)

The contra-indications in the last trimester of pregnancy and in case of severe cardiac failure should be added.

"Severe heart failure, renal failure or hepatic failure (see section 4.4)"

"Last trimester of pregnancy"

Special warnings and precautions for use (4.4 section of SmPC)

Cardiovascular, renal and hepatic impairment

"The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients (see also section 4.3)"

Flurbiprofen should be given with care to patients with a history of heart failure or hypertension since oedema has been reported in association with flurbiprofen administration."

Cardiovascular and cerebrovascular effects

Appropriate monitoring and advice are required for 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 flurbiprofen administration and NSAID therapy.

SLE and mixed connective tissue disease

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis (see section 4.8).

Impaired female fertility

The use of flurbiprofen 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 flurbiprofen should be considered.

Interactions (4.5 section of SmPC)

Diuretics, ACE inhibitors and Angiotensin II Antagonists: NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking flurbiprofen concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Pregnancy and lactation (4.6 section of SmPC)

Pregnancy

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, flurbiprofen should not be given unless clearly necessary. If flurbiprofen 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, flurbiprofen is contraindicated during the third trimester of pregnancy.

Lactation

In the limited studies so far available, NSAIDs can appear in the breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breastfeeding.

See section 4.4 Special warnings and precautions for use, regarding female fertility.

Driving and machineries (4.7 section of SmPC)

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

Undesirable effects (4.8 section of SmPC)

Immune system disorders: Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of (a) non-specific allergic reactions and anaphylaxis, (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and, more rarely exfoliative and bullous dermatoses (including toxic epidermal necrolysis and erythema multiforme).

Cardiac disorders and Vascular disorders: Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.

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).

Blood and lymphatic system disorders: neutropenia, haemolytic anaemia.

Psychiatric disorders: Depression, confusional state, hallucination

Nervous system disorders: Cerebrovascular accident, optic neuritis, headache, paraesthesia, dizziness, and somnolence.

Aseptic meningitis (especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus and mixed connective tissue disease) with symptoms of stiff neck, headache, nausea, vomiting, fever or disorientation) (see section 4.4).

Eye disorders: Visual disturbance

Ear and labyrinth disorders: Tinnitus, vertigo

Hepatobiliary disorders: Abnormal liver function, hepatitis and jaundice.

Skin and subcutaneous tissue disorders: photosensitivity reaction.

Renal and urinary disorders: Toxic nephropathy in various forms, including interstitial nephritis, nephrotic syndrome and renal failure.

General disorders and administration site conditions: Malaise, fatigue

Package leaflet

The MAH should provide a proposal of PIL to include the information above requested

[Add sections as relevant, ensuring that the above proposed changes to the SmPC are adequately reflected, in lay terms, in the package leaflet]