Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Buplex Rx 800 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film−coated tablet contains 800 mg ibuprofen.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film−coated tablet.

White, oval, biconvex film−coated tablets with a score on one face.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Rheumatic conditions such as arthritic diseases (e.g. rheumatoid arthritis including juvenile rheumatoid arthritis), degenerative arthritic conditions (e.g. osteoarthritis), non-articular rheumatic conditions, other muscular and joint disorders, and soft tissue injuries.

4.2 Posology and method of administration

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

The ibuprofen dose depends on the patient's age and body weight. The maximum single daily dose for adults should not exceed 800 mg of ibuprofen.

The tablet should be swallowed with a glass of water during or after a meal.

Rheumatic diseases
Adults:
The usual dose is 400−600 mg 3 times a day. Maintenance doses of 600 mg−1200 mg daily may be effective in some patients. In acute and severe conditions the dose may be increased to a maximum of 2400 mg in 3 or 4 divided doses.

Adolescents over 12 years of age (>40 kg):
The recommended dose is 20 mg/kg to a maximum of 40 mg/kg body weight daily in 3 to 4 divided doses.
There are other dosage forms which may be more suitable to attain the required posology in this age and body weight group.

Elderly
NSAIDs should be used with particular caution in elderly patients who are more prone to adverse events and are at increased risk of potentially fatal gastrointestinal haemorrhage, ulceration or perforation (see section 4.4). If treatment is considered necessary, the lowest dose for the shortest duration necessary to control symptoms should be used. Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs.

Impaired renal function
In patients with mild or moderate reduction of renal function, the dose should be kept as low as possible for the shortest duration necessary to control symptoms and renal function monitored. (For patients with severe renal failure see section 4.3).

Impaired liver function
In patients with mild or moderate reduction of liver function the dose should be kept as low as possible for the shortest duration necessary to control symptoms and renal function monitored. (For patients with severe liver failure see section 4.3).

4.3 Contraindications

Buplex Rx is contraindicated in patients with:
- hypersensitivity to the active substance or to any of the excipients of Buplex Rx
- previous hypersensitivity reactions (e.g. asthma, rhinitis, urticaria or angioedema) in response to acetylsalicylic acid or other NSAIDs
- history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy
- active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
- severe hepatic or severe renal insufficiency
- severe heart failure or coronary heart disease
- last trimester of pregnancy (see section 4.6)
- significant dehydration (caused by vomiting, diarrhoea or insufficient fluid intake)
- cerebrovascular or other active bleeding
- dishaematopoiesis of unknown origin
- children younger than 12 years of age.

4.4 Special warnings and precautions for use

The use of Buplex Rx with concomitant NSAIDs including cyclooxygenase−2 selective inhibitors should be avoided.

Asthmatic patients are to seek their doctor’s advice before using ibuprofen (see below).

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below). Patients treated with NSAIDs long term should undergo regular medical supervision to monitor for adverse events.

Buplex Rx should only be administered under strict consideration of the benefit-risk ratio in the following conditions:
- Systemic Lupus Erythematosus (SLE) or other autoimmune diseases.
- Congenital disturbance of porphyrin metabolism (e.g. acute intermittent porphyria)
- The first and second trimester of pregnancy
- Lactation

Special care has to be taken in the following cases:
- Gastrointestinal diseases including chronic inflammatory intestinal disease (ulcerative colitis, Crohn's disease)
- Cardiac insufficiency and hypertension
- Reduced renal function
- Hepatic dysfunction
- Disturbed haematopoiesis
- Blood coagulation defects
- Allergies, hay fever, chronic swelling of nasal mucosa, adenoids, chronic obstructive airway disease or bronchial asthma
- Immediately after major surgical interventions

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.

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 acetylsalicylic acid, or other medicinal products likely to increase gastrointestinal risk. (See below and section 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 or heparin, selective serotonin-reuptake inhibitors or anti-platelet agents such as acetylsalicylic acid (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving Buplex Rx, 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 their condition may be exacerbated. (See section 4.8).

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).

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, hypertension and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of ibuprofen, particularly at high doses (2400 mg daily) and in long−term treatment, may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low-dose ibuprofen (e.g. $\leq$ 1200 mg daily) is associated with an increased risk of myocardial infarction.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking).

Skin reactions
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. Buplex Rx should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Renal effect
Ibuprofen may cause the retention of sodium, potassium and fluid in patients who have not previously suffered from renal disorders because of its effect on renal perfusion. This may cause oedema or even lead to cardiac insufficiency or hypertension in predisposed patients.

As with other NSAIDs, the prolonged administration of ibuprofen to animals has resulted in renal papillary necrosis and other pathological renal changes. In humans, there have been reports of acute interstitial nephritis with haematuria, proteinuria and occasionally nephrotic syndrome. Cases of renal toxicity have also been observed in patients in whom prostaglandins play a compensatory role in the maintenance of renal perfusion. In these patients, administration of NSAIDs may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of suffering this reaction are those with renal dysfunction, heart failure, hepatic dysfunction, those taking diuretics and ACE inhibitors and the elderly. Discontinuation of NSAID treatment is generally followed by recovery to the pre-treatment state.

Other precautions
Bronchospasm, urticaria or angioedema may be precipitated in patients suffering from or with a previous history of bronchial asthma, chronic rhinitis, sinusitis, nasal polyps, adenoids or allergic diseases.

Ibuprofen may mask the signs or symptoms of an infection (fever, pain and swelling).

During the long−term, high−dose use of analgesics headaches may occur which should not be treated with elevated doses of the medicinal product. In general the habitual intake of analgesics, particularly the combination use of different analgesic substances, may cause permanent renal damage and a risk of renal failure (analgesics nephropathy).

During treatment with ibuprofen, some cases with symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed in patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease).

Ibuprofen may temporarily inhibit platelet aggregation and prolong the bleeding time. Therefore, patients with coagulation defects or on anticoagulant therapy should be observed carefully.

In case of long−term treatment with ibuprofen a periodical monitoring of hepatic and renal function as well as the blood count is necessary, especially in high risk patients.

Consumption of alcohol should be avoided since it may intensify side effects of NSAIDs, especially if affecting the gastrointestinal tract or the central nervous system.

Patients on ibuprofen should report to their doctor signs or symptoms of gastro-intestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain or oedema.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of ibuprofen and the following substances should be avoided:

Acetylsalicylic acid, low dose: Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1)

Other NSAIDs: As a result of synergistic effects, the concurrent use of several NSAIDs can increase the risk of gastrointestinal ulcers and haemorrhage. Co−administration of ibuprofen with other NSAIDs should therefore be avoided (see section 4.4).

Anti-coagulants: NSAIDs may enhance the effects of anticoagulants, such as warfarin or heparin (see section 4.4). In case of simultaneous treatment, monitoring of the coagulation state is recommended.

Ticlopidin: NSAIDs should not be combined with ticlopidine due to a risk of an additive effect in the inhibition of the platelet function.

Methotrexate: NSAID inhibits the tubular secretion of methotrexate and certain metabolic interactions can occur resulting in decreased clearance of methotrexate. The administration of Buplex Rx within 24 hours before or after the administration of methotrexate can lead to an elevated concentration of methotrexate and an increase in its toxic effects. Therefore, concomitant use of NSAIDs and high doses of methotrexate should be avoided. Also, the potential risk of interactions in low dose treatment with methotrexate should be considered, especially in patients with impaired renal function. In combined treatment, renal function should be monitored.

Ibuprofen (like other NSAIDs) should be taken only with caution in combination with the following substaces:

Moclobemide: Enhances the effect of ibuprofen.

Phenytoin, lithium: Co−administration of Buplex Rx with phenytoin or lithium preparations can increase the serum level of these medicinal products. Checking the serum lithium level is necessary and it is recommended to check the serum phenytoin levels.

Cardiac glycosides (e.g digoxin): NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma levels of cardiac glycosides. Monitoring of serum digoxin is recommended.

Diurectis and antihypertensives: Diuretics and ACE-inhibitors can increase the nephrotoxicity of NSAIDs. NSAIDs can reduce the effect of diuretics and antihypertensives, including ACE-inhibitors and beta-blockers. In patients with reduced kidney function (e.g. dehydrated patients or elderly patients with reduced kidney function), the concomitant use of an ACE inhibitor and angiotension II antagonist with a cyclooxygenase-inhibiting medicinal product can lead to further impairment of kidney function and through to acute renal failure. This is usually reversible. Such combination should therefore only be used with caution, especially in elderly patients. The patients have to be instructed to drink sufficient liquid and periodic monitoring of the kidney values should be considered for the time immediately after the start of the combination therapy.
The concomitant administration of Buplex Rx and potassium−sparing diuretics or ACE-inhibitors can result in hyperkalaemia. Careful monitoring of potassium levels is necessary.

Captopril: Experimental studies indicate that ibuprofen counteracts the effect of captopril of increased sodium excretion.

Aminoglycosides: NSAIDs can slow down the elimination of aminoglycosides and increase their toxicity.

Selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see section 4.4).

Ciclosporine: The risk of kidney damage by ciclosporin is increased by the concomitant administration of certain NSAIDs. This effect can not be ruled out for the combination of ciclosporine and ibuprofen, either.

Cholestyramine: Concomitant treatment with cholestyramine and ibuprofen results in prolonged and reduced (25%) absorption of ibuprofen. The medicinal products should be administered with at least one hour interval.

Tacrolimus: Elevated risk of nephrotoxicity.

Zidovudine: There is evidence of an increased risk of haemarthrosis and haematoma in HIV positive haemophilia patients receiving concurrent treatment with zidovudine and ibuprofen. There may be an increased risk of haematotoxicity during concomitant use of zidovudine and NSAIDs. Blood counts 1−2 weeks after starting use together are recommended.

Ritonavir: May increase the plasma concentrations of NSAIDs.

Mifepristone: If NSAIDs are used within 8−12 days after mifepristone administration they can reduce the effect of mifepristone.

Probenecid or sulfinpyrazone: May cause a delay in the elimination of ibuprofen. The uricosuric action of these substances is decreased.

Quinolone antibiotics: Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Sulphonylureas: NSAIDs can increase the hypoglycemic effect of sulphonylureas. In the case of simultaneous treatment, monitoring of blood glucose levels is recommended.

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

Anti-platelet aggregation agents (e.g. clopidogrel and ticlopidine): Increase the risk of gastrointestinal bleeding (see section 4.4).

Alcohol, bisphosphonates and oxpentifylline (pentoxyflline): May potentiate the GI side-effects and the risk of bleeding and ulceration.

Baclofen: Elevated baclofen toxicity.

4.6 Fertility, pregnancy and lactation

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, Buplex Rx should not be given unless clearly necessary. If Buplex Rx 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-hydramniosis;

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 Buplex Rx is contraindicated during the last trimester of pregnancy.

Lactation
Ibuprofen is excreted in breast milk, but with therapeutic doses during short term treatment the risk for influence on infant seems unlikely. If, however, longer treatment is prescribed, early weaning should be considered.

Fertility
The use of ibuprofen may impair 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 ibuprofen should be considered.

4.7 Effects on ability to drive and use machines

Ibuprofen generally has no adverse effects on the ability to drive and use machinery. However since at high dosage side effects such as fatigue, somnolence, vertigo (reported as common) and visual disturbances (reported as uncommon) may be experienced, the ability to drive a car or operate machinery may be impaired in individual cases. This effect is potentiated by simultaneous consumption of alcohol.

4.8 Undesirable effects

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, heamatemesis, ulcerative stomatits, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration. Less frequently, gastritis has been observed.

Undesirable effects are mostly dose-dependent. Especially the risk for the occurrence of gastrointestinal bleedings depends on the dosage range and duration of the treatment. Other known risk factors, see section 4.4.

Clinical trial and epidemiological data suggest that use of ibuprofen, particularly at high dose (2400 mg daily) and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

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

The undesirable effects are less frequent when the maximum daily dose is 1200 mg.

Assessment of adverse reactions is normally based on the following occurrence frequency:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000), not known (cannot be estimated from the available data)

Investigations
Rare: increase of blood urea nitrogen, serum transaminases and alkaline phosphatase, decrease in haemoglobin and haematocrit values, inhibition of platelet aggregation, prolonged bleeding time, decrease of serum calcium, increase in serum uric acid

Cardiac disorders
Very rare: palpitations, heart failure, myocardial infarction, acute pulmonary oedema, oedema,

Blood and lymphatic system disorders
Very rare: haematopoietic disorders (anaemia, leucopoenia, thrombocytopenia, pancytopenia, agranulocytosis). The first symptoms or signs may include: fever, sore throat, surface mouth ulcers, flu-like symptoms, severe fatigue, nasal and skin bleeding

Nervous system disorders
Common: headache, somnolence, vertigo, fatigue, agitation, dizziness, insomnia, irritability
Very rare: aseptic meningitis

Eye disorders
Uncommon: visual disturbances
Rare: toxic amblyopia

Ear and labyrinth disorders
Very rare: tinnitus

Respiratory, thoracic and mediastinal disorders
Uncommon: rhinitis, bronchospasm

Gastrointestinal disorders
Very common: gastrointestinal disorders, such as heartburn, dyspepsia, abdominal pain and nausea, vomiting, flatulence, diarrhoea, constipation
Common: gastrointestinal ulcers, sometimes with bleeding and perforation (see section 4.4), occult blood loss which may lead to anaemia, melaena, haematemesis, ulcerative stomatitis, colitis, exacerbation of inflammatory bowel disease, complications of colonic diverticula (perforation, fistula)
Uncommon: gastritis
Very rare: oesophagitis, pancreatitis, intestinal strictures

Renal and urinary disorders
Uncommon: development of oedema especially in patients with arterial hypertension or renal insufficiency, nephrotic syndrome, interstitial nephritis which can be associated with renal failure
Very rare: renal papillary necrosis in long−term use (see section 4.4)

Skin and subcutaneous tissue disorders
Uncommon: photosensitivity
Very rare: severe forms of skin reactions (erythema multiforme, exfoliative dermatitis, bullous reactions including Stevens−Johnson syndrome and toxic epidermal necrolysis, alopecia, necrotising fascitis

Vascular disorder
Very rare: hypertension

Immune system disorders
Uncommon: hypersensitivity reactions such as urticaria, pruritus, purpura and exanthema as well as asthma attacks (sometimes with hypotension)
Rare: lupus erythematosus syndrome
Very rare: severe hypersensitivity reactions. The symptoms may include: facial oedema, swelling of the tongue, internal laryngeal swelling with constriction of the airways, dyspnoea, tachycardia, fall of blood pressure to the point of life-threatening shock

Hepatobiliary disorders
Very rare: liver dysfunction, liver damage, especially in long−term use, liver failure, acute hepatitis, jaundice

Psychiatric disorder
Rare: depression, confusion, hallucinations

4.9 Overdose

Symptoms
Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely, diarrhoea. Tinnitus, headache, dizziness, vertigo and gastrointestinal bleeding may also occur. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. Children may also develop myoclonic cramps. In serious poisoning metabolic acidosis may occur and the prothrombin time/INR may be prolonged, probably due to the actions of circulating clotting factors. Acute renal failure, liver damage, hypotension, respiratory depression and cyanosis may occur. Exacerbation of asthma is possible in asthmatics.

Treatment
Treatment should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Gastric emptying or oral administration of activated charcoal is indicated if the patient presents within one hour of ingestion of more than 400 mg per kg of body weight. If Buplex Rx has already been absorbed, alkaline substances should be administered to promote the excretion of the acid ibuprofen in the urine. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Bronchodilators should be given for asthma. No specific antidote is available.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids; propionic acid derivatives.
ATC code: M01AE01

Ibuprofen is a NSAID that possesses anti-inflammatory, analgesic and antipyretic activity. Animal models for pain and inflammation indicate that ibuprofen effectively inhibits the synthesis of prostaglandins. In humans, ibuprofen reduces pain possibly caused by inflammation or connected with it, swelling and fever. Ibuprofen exerts an inhibitory effect on prostaglandin synthesis by inhibiting the activity of cyclo-oxygenase. In addition ibuprofen has an inhibitory effect on ADP (adenosine diphosphate) or collagen-stimulated platelet aggregation.

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400 mg was taken within 8 hour before or within 30 min after immediate release acetylsalicylic acid dosing (81 mg), a decreased effect of ASA on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

Ibuprofen inhibits prostaglandin synthesis in the uterus, thereby reducing intrauterine rest and active pressure, the periodic uterine contractions and the amount of prostaglandins released into the circulation. These changes are assumed to explain the alleviation of menstrual pain. Ibuprofen inhibits renal prostaglandin synthesis which can lead to renal insufficiency, fluid retention and heart failure in risk patients (see section 4.3).
Prostaglandins are connected with ovulation and the use of medicinal products inhibiting prostaglandin synthesis may therefore affect the fertility of women (see section 4.4, 4.6 and 5.3).

5.2 Pharmacokinetic properties

Absorption
Ibuprofen is rapidly absorbed from the gastrointestinal tract, peak serum concentrations occurring 1−2 hours after administration.

Distribution
Ibuprofen is rapidly distributed throughout the whole body. The plasma protein binding is approximately 99%.

Metabolism
Ibuprofen is metabolised in the liver (hydroxylation, carboxylation).

Elimination
The elimination half-life is approximately 2.5 hours in healthy individuals. Pharmacologically inactive metabolites are mainly excreted (90%) by the kidneys but also in bile.

5.3 Preclinical safety data

As a well established and widely used product, the pre-clinical safety of ibuprofen is well documented.

Ibuprofen's subchronic and chronic toxicity was mainly shown by animal tests as gastric tract damage and ulcers.

The vitro and in vivo tests have not shown any clinically significant signs about ibuprofen's mutagenicity. Furthermore no carcinogenic effects have been observed in mice and rats.
Ibuprofen inhibits ovulation in rabbits and impairs implantation in various animal species (rabbit, rat, and mouse). In reproduction tests undertaken with rats and rabbits, ibuprofen passed across the placenta. When using doses toxic to the mother, malformations occur more frequently (i.e. ventricular septum defects).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Cellulose, microcrystalline
Silica, colloidal anhydrous
Hydroxypropylcellulose
Sodium laurylsulfate
Croscarmellose sodium
Talc

Film coating (Opadry (white) 06B28499)
Hypromellose
Macrogol 400
Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Opaque PVC/Aluminium blister packs.
Clear PVC/Aluminium blister packs.
Tablet containers (polyethylene) with polypropylene caps.

Pack sizes:

Blisters: 6, 10, 12, 20, 24, 30, 50, 60, 90, 100 and 250 film−coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf
Reykjavikurvegi 76-78
220 Hafnarfjordur
Iceland

8 MARKETING AUTHORISATION NUMBER

PA 1380/088/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd July 2009

10 DATE OF REVISION OF THE TEXT

April 2012