SCHEDULING STATUS

S1

PROPRIETARY NAME (and dosage form)

BRUFEN® 200 (Film-coated tablets)

COMPOSITION

BRUFEN® 200: Each film-coated tablet contains 200 mg ibuprofen

Excipients: Microcrystalline cellulose, croscamellose sodium, lactose monohydrate, colloidal anhydrous silica, sodium laurilsulfate, magnesium stearate, hypromellose, titanium dioxide, purified water, industrial methylated spirit, dry color dispersion, white 06A28611 and opaspray white M-1-7111B,

Contains lactose monohydrate

PHARMACOLOGICAL CLASSIFICATION

A 2.7 Antipyretic or antipyretic and anti-inflammatory analgesics

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Chemically, ibuprofen is described as 2-(4-isobutylphenyl) propionic acid and is a non-steroidal compound, which exhibits anti-inflammatory, analgesic and anti-pyretic activities.

Pharmacokinetic properties

Ibuprofen is well absorbed on oral administration. An oral dose taken on an empty stomach by human volunteers produced peak serum levels after three quarters of an hour. Absorption was slower and peak serum levels lower after food.

Excretion is rapid with no evidence of accumulation. Two major metabolites of ibuprofen have been isolated from human urine. They are (+)2-4'hydroxy-2-methylpropyl) phenylpropionic acid (metabolite A) and (+)2,4'(2-carboxylpropyl) phenylpropionic acid (metabolite B).

The levels in human serum of both metabolites have been measured after single and repeated doses. About 60 % of a dose is excreted in the urine, and the excretory products are in the form of either free or conjugated metabolites A and B. No ibuprofen is found.

INDICATIONS

BRUFEN® 200 is indicated for the treatment of mild to moderate pain of inflammatory origin and fever, including:

- Soft tissue injuries such as sprains and strains
- headache
- back pain of musculo-skeletal origin
- fever
- muscular aches and pain
- menstrual pain
- dental pain
- pain associated with migraine
- earache

CONTRA-INDICATIONS

BRUFEN® 200 should not be given to patients with:

- peptic ulceration
- History of gastrointestinal perforation, ulceration or bleeding (PUB) related to previous NSAID's use.
- Active or history of recurrent ulcer, haemorrhage or perforations.
- Third trimester of pregnancy and during labour. (see PREGNANCY AND LACTATION)

- **BRUFEN® 200** is contraindicated in patients who are hypersensitive to ibuprofen, aspirin or any other non-steroidal anti-inflammatory agent. Because of the possibility of cross-sensitivity due to structural relationships which exist among non-steroidal anti-inflammatory medicines, acute allergic reactions may be more likely to occur in patients who have exhibited allergic reactions to these compounds.
- **BRUFEN® 200** is contraindicated in patients with heart failure.
- **BRUFEN® 200** is contraindicated in patients with renal failure

WARNINGS and SPECIAL PRECAUTIONS

- 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 **BRUFEN® 200** therapy. In view of the **BRUFEN® 200**'s inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.
- Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs including **BRUFEN® 200**, especially gastrointestinal perforation, ulceration and bleeding (PUBs) which may be fatal.
- The risk of gastrointestinal perforation, ulceration or bleeding (PUBs) is higher with increasing doses of **BRUFEN® 200**, in patients with a history of ulcers, and the elderly.
- When gastrointestinal bleeding or ulceration occurs in patients receiving **BRUFEN® 200**, treatment with **BRUFEN® 200** should be stopped.
- **BRUFEN® 200** should be given with caution to patients with a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as the condition may be exacerbated.
- Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolyis have been reported. **BRUFEN® 200** should be

discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

- Regular use of NSAIDs such as **BRUFEN® 200** during the third trimester of pregnancy, may result in premature closure of the foetal ductus arteriosus *in utero*, and possibly, in persistent pulmonary hypertension of the new-born. The onset of labour may be delayed and its duration increased. (see PREGNANCY AND LACTATION)
- **BRUFEN® 200** contains lactose monohydrate and should not be given to patients with rare hereditary problems or a history of galactose intolerance, lapp lactase deficiency or glucose-galactose malabsorption.

BRUFEN® 200 should be given with care to the elderly, to patients with asthma or bronchospasm, bleeding disorders, cardiovascular disease, a history of peptic ulceration, and in liver or renal failure. Patients with congestive heart failure, cirrhosis, diuretic-induced volume depletion, or renal insufficiency require local synthesis of vasodilating prostaglandins to maintain renal perfusion, and therefore these patients are at greater risk of developing renal dysfunction due to NSAID- induced inhibition of renal prostaglandin synthesis.

Care is required in those who are also receiving warfarin and other anti-coagulants. Patients who are sensitive to aspirin or other NSAIDs should generally not be given ibuprofen.
Ibuprofen should be discontinued in patients who experience blurred or diminished vision, or changes in colour vision. Patients with collagen disease may be at increased risk of developing aseptic meningitis.

Effects on ability to drive and use machines

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking **BRUFEN® 200**. If affected, patients should not drive or operate machinery.

INTERACTIONS

- Antihypertensives, beta-blockers and diuretics: **BRUFEN® 200** may reduce the effect of anti-hypertensives, such as ACE inhibitors, beta-blockers and diuretics.
- NSAIDs: use of two or more NSAIDs concomitantly could result in an increase in side effects
- Corticosteroids: increased risk of gastrointestinal perforation, ulceration or bleeding (PUBs)
- Anti-coagulants: **BRUFEN® 200** may enhance the effects of anti-coagulants such as warfarin
- Anti-platelet medicines and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding.
- Diuretics can also increase the risk of nephrotoxicity of **BRUFEN® 200**.
- Digoxin: **BRUFEN® 200** may exacerbate cardiac failure, reduce GFR and increase plasma digoxin levels.
- Lithium: Decreased elimination of lithium.
- Ciclosporin: Increased risk of nephrotoxicity.
- Mifepristone: A decrease in the efficacy of the medicinal product can theoretically occur due to the antiprostaglandin properties of **BRUFEN® 200**. Limited evidence suggests that coadministration of **BRUFEN® 200** on the day of prostaglandin administration does not adversely influence the effects of mifepristone or the prostaglandin on cervical ripening or uterine contractility and does not reduce the clinical efficacy of medicinal termination of pregnancy
- Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking **BRUFEN® 200**and quinolones may have an increased risk of developing convulsions.
- Aminoglycosides: **BRUFEN® 200** may decrease the excretion of aminoglycosides.
- Herbal extracts: Ginkgo biloba may potentiate the risk of bleeding with **BRUFEN® 200**.

PREGNANCY AND LACTATION

BRUFEN® 200 should not be used in third trimester of pregnancy and during labour. (see CONTRAINDICATIONS)

Regular use of NSAIDs such as **BRUFEN® 200** during the third trimester of pregnancy, may result in premature closure of the foetal ductus arteriosus *in utero*, and possibly, in persistent pulmonary hypertension of the new-born. The onset of labour may be delayed and its duration increased.(see WARNINGS AND SPECIAL PRECAUTIONS)

DOSAGE AND DIRECTIONS FOR USE

Adults:

Use the lowest effective dose for the shortest possible duration of treatment.

The recommended dosage of **BRUFEN® 200** is 1,200 mg daily in divided doses (1 to 2 tablets every four hours) for the relief of:

1) mild to moderate pain of

- Soft tissue injuries such as sprains and strains
- Dental pain
- Back pain of musculo-skeletal origin
- Earache
- Pain associated with migraine
- Muscular ache and pains

2) Fever

3) Menstrual pain

The total daily dose of **BRUFEN® 200** should not exceed 1,200 mg. Once the acute phase has been brought under control, it is normal practice to revert to a maintenance dosage.

Children:

Not to be given to children under 12 years of age.

SIDE-EFFECTS

The following side-effects have been reported:

Gastrointestinal system disorders:

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal. Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease, gastritis.

Less frequent: abdominal discomfort or pain, nausea, vomiting, gastro-intestinal ulcers, sometimes with bleeding

Nervous system disorder:

Frequent: Dizziness, nervousness, tinnitus, drowsiness, insomnia

Psychiatric disorder:

Frequent: Depression

Eye disorders:

Visual impairment, changes in visual colour perception, toxic amblyopia

Renal and Urinary disorders:

Less frequent: Acute renal failure, cystitis, haematuria, interstitial nephritis, nephrotic syndrome

Hepatobiliary syndrome:

Less frequent: Hepatotoxicity, abnormalities in liver function tests

Blood and lymphatic system disorders:

Less frequent: Anaemia, thrombocytopenia, neutropenia, eosinophilia, agranulocytosis

Immune disorders:

Less frequent: Aseptic meningitis, angioedema and anaphylaxis

Hypersensitivity disorders:

Less frequent: Fever, rashes, exacerbation of asthma and bronchospasm

Cardiovascular disorders:

Frequency unknown: Oedema, hypertension and cardiac failure.

Skin and subcutaneous tissue disorders:

Frequency unknown: Bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

The most likely symptoms of overdosage are epigastric pain and nausea. If recently taken, gastric lavage will remove any unabsorbed ibuprofen. Electrolytes may be corrected by intravenous infusions, if necessary. There is no specific antidote to **BRUFEN® 200**. Treatment is symptomatic and supportive

IDENTIFICATION

A white, pillow-shaped, film-coated tablet.

PRESENTATION

PVC/Aluminium or PVC/PVDC/Aluminium blister strips of 10 or 20 tablets per pack

STORAGE INSTRUCTIONS

Store at or below 25 ºC

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER

BRUFEN 200 mg Tablets: A/3.1/0727

NAME AND BUSINESS ADDRESS OF THE APPLICANT

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CONSTANTIA KLOOF

1709

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