SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

BRUFEN® RETARD 800 mg sustained-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 800 mg of ibuprofen in a sustained release form.

Sugar free.

For the full list of excipients, see section 6 .1.

3. PHARMACEUTICAL FORM

Sustained-release tablets.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BRUFEN® RETARD is indicated for its analgesic and anti-inflammatory effect in the treatment of rheumatoid arthritis (including juvenile rheumatoid arthritis or Still's disease), ankylosing spondylitis, and osteo-arthritis. BRUFEN® RETARD is indicated in the treatment of non-articular rheumatism including fibrositis.

BRUFEN® RETARD is indicated in periarticular conditions such as frozen shoulder (capsulitis), bursitis, tendinitis, tenosynovitis and low-back pain. BRUFEN® RETARD can also be used in soft-tissue injuries such as sprains and strains.

BRUFEN® RETARD is also indicated for its analgesic effect in the relief of mild to moderate pain such as dysmenorrhoea, dental, post episiotomy pain and post-partum pain.

4.2 Posology and method of administration

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

BRUFEN® RETARD is not recommended in children under 12 years.

Adults: The recommended daily dosage is two (2) tablets taken as a single dose, preferably in the early evening. In severe or acute conditions, the total daily dosage may be increased to three (3) tablets taken in two divided doses.

Elderly: No special dosage modifications are required for elderly patients, unless renal or hepatic function is impaired, in which case dosage should be assessed individually.

Method of administration

The tablets should be swallowed whole with plenty of fluid.

4.3 Contraindications

BRUFEN® RETARD should not be given to patients with:

- A hypersensitivity to ibuprofen or any of the excipients listed in section 6.1, aspirin or any other nonsteroidal anti-inflammatory drug. 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.
- Peptic ulceration.
- History of gastrointestinal perforation, ulceration or bleeding (PUB) related to previous nonsteroidal anti-inflammatory drugs (NSAID's) use.
- Active or history of recurrent ulcer, haemorrhage or perforations.
- Third trimester of pregnancy and during labour (see section 4.6).
- Bronchospasm may be precipitated in patients suffering from, or with a previous history of bronchial asthma. BRUFEN® RETARD should not be given to patients in whom aspirin and

other non-steroidal anti-inflammatory drugs induce the symptoms of asthma, rhinitis or urticaria.

- Severe heart failure (NYHA Class IV).
- Severe hepatic failure or severe renal failure (see section 4.4).

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, GI and cardiovascular risks below).

As with other NSAIDs, BRUFEN® RETARD may mask the signs of infection.

The use of BRUFEN® RETARD with concomitant NSAIDs, including cyclooxygenase-2 selective (COX-2) inhibitors, should be avoided due to the increased risk of ulceration or bleeding (see section 4.5).

The diagnosis of medication overuse headache (MOH) should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of analgesic medication. Patients with medication overuse headache should not be treated by increasing the dose of the analgesic. In such cases the use of analgesics should be discontinued.

The concomitant consumption of excessive alcohol with NSAIDs, including BRUFEN® RETARD, may increase the risk of adverse effects on the gastrointestinal tract, such as GI haemorrhage or the central nervous system, possibly due to an additive effect.

Elderly

The elderly have an increased frequency of adverse reaction to NSAIDs including BRUFEN® RETARD, especially gastrointestinal bleeding, ulceration and perforation, which may be fatal.

Gastrointestinal (GI) bleeding, ulceration and perforation

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time 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 doses of BRUFEN® RETARD, in patients with a history of ulcers, particularly if complicated with haemorrhage or perforation (see section 4.3) and the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective medicines (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other medicines likely to increase gastrointestinal risk (see below and section 4.5).

Patients with a history of gastrointestinal disease, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal 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 medicines, such as aspirin (see section 4.5).

When gastrointestinal bleeding or ulceration occurs in patients receiving BRUFEN® RETARD, treatment with BRUFEN® RETARD should be stopped.

BRUFEN® RETARD 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 (see section 4.8).

Respiratory disorders and hypersensitivity reactions

Caution is required if BRUFEN® RETARD is administered to patients suffering from, or with a previous history of, bronchial asthma, chronic rhinitis or allergic diseases since NSAIDs have been reported to precipitate bronchospasm, urticaria or angioedema in such patients.

Cardiac, renal and hepatic impairment

The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. The habitual concomitant intake of various similar painkillers further increases this risk. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. For these patients, use the lowest effective dose, for the shortest possible duration and monitor renal function especially in long-term treated patients (see also section 4.3).

Cardiovascular and cerebrovascular effects

Appropriate monitoring and caution are required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with BRUFEN® RETARD therapy. In view of the BRUFEN® RETARD's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

Clinical studies suggest that use of ibuprofen, particularly at a high dose (2 400 mg/day) may be associated with a small increased risk of arterial thrombotic events such as myocardial infarction or stroke. Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤ 1 200 mg/day) is associated with an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure (NYHA Class II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2 400 mg/day should be avoided). Careful consideration should also be exercised before initiating long-term treatment of

patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking), particularly if high doses of BRUFEN® RETARD (2 400 mg/day) are required (see section 4.3).

Renal effects

Caution should be used when initiating treatment with BRUFEN® RETARD in patients with considerable dehydration. There is a risk of renal impairment especially in dehydrated children, adolescents and the elderly.

As with other NSAIDs, long-term administration of ibuprofen, as in BRUFEN® RETARD, has resulted in renal papillary necrosis and other renal pathologic changes. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependant reduction in prostaglandin formation and, secondarily, in renal blood flow, which may cause renal failure. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and angiotensin converting enzyme (ACE) inhibitors and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state.

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 below and section 4.8).

Severe skin reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported (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 within the first month of treatment in the majority of cases. Acute generalised exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing products.

BRUFEN® RETARD should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

In exceptional cases, varicella can be at the origin of serious cutaneous and soft tissue infectious complications. To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of BRUFEN® RETARD in case of varicella.

Haematological effects

BRUFEN® RETARD, like other NSAIDs, can interfere with platelet aggregation and prolong bleeding time in normal subjects.

Aseptic meningitis

Aseptic meningitis has been observed on rare occasions in patients on ibuprofen therapy. Although it is probably more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease.

Masking of symptoms of underlying infections

As with other NSAIDs, BRUFEN® RETARD can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When BRUFEN® RETARD is administered for fever or pain relief in relation to infection, monitoring of infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.

Pregnancy

Around 20 weeks or later in pregnancy, NSAIDs such as BRUFEN® RETARD may cause fetal renal dysfunction leading to oligohydramnios and in some cases neonatal renal impairment.

Regular use of NSAIDs, such as BRUFEN® RETARD during third trimester of pregnancy, may result in premature closure of the fetal ductus arteriosus *in utero*, and possible, in persistent pulmonary hypertension of the new-born. The onset of labour may be delayed, and its duration increased (see section 4.6).

Use with care in patients with bleeding disorders, cardiovascular disease, patients using anticoagulant medicines and in elderly patients. Use with care in patients with impaired renal function.

Paediatric population

There is a risk of renal impairment in dehydrated children and adolescents.

4.5 Interaction with other medicines and other forms of interaction

Care should be taken in patients treated with any of the following medicines as interactions have been reported in some patients.

Antihypertensives, beta-blockers and diuretics: BRUFEN® RETARD may reduce the effect of anti-hypertensives, such as ACE inhibitors, angiotensin-II receptor antagonists, beta-blockers and diuretics. Diuretics can also increase the risk of nephrotoxicity of BRUFEN® RETARD.

Other analgesics and cyclooxygenase-2 selective (COX-2) inhibitors: Avoid concomitant use of two or more NSAIDs, including COX-2 inhibitors, as this may increase the risk of adverse effects (see section 4.4).

Aspirin (acetylsalicylic acid): As with other products containing NSAIDs, concomitant administration of BRUFEN® RETARD and aspirin is not generally recommended because of the potential of increased adverse effects.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional use.

Corticosteroids: Increased risk of gastrointestinal perforation, ulceration or bleeding with NSAIDs (see section 4.4).

Anticoagulants: BRUFEN® RETARD may enhance the effects of anticoagulants, such as warfarin (see section 4.4).

Anti-platelet medicine and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding with NSAIDs (see section 4.4).

Cardiac glycosides: BRUFEN® RETARD may exacerbate cardiac failure, reduce glomerular filtration rate (GFR) and increase plasma cardiac glycoside levels.

Colestyramine: The concomitant administration of BRUFEN® RETARD and colestyramine may reduce the absorption of ibuprofen in the gastrointestinal tract. However, the clinical significance is unknown.

Lithium: Decreased elimination of lithium.

Methotrexate: NSAIDs may inhibit the tubular secretion of methotrexate and reduce clearance of methotrexate.

Ciclosporin: Increased risk of nephrotoxicity.

Mifepristone: A decrease in the efficacy of the medicine can theoretically occur due to the antiprostaglandin properties of BRUFEN® RETARD. Limited evidence suggests that co-administration of BRUFEN® RETARD 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 convulsion associated with quinolone antibiotics. Patients taking BRUFEN® RETARD and quinolones may have an increased of developing convulsions.

Sulfonylureas: NSAIDs may potentiate the effects of sulfonylurea medications. There have been rare reports of hypoglycaemia in patients on sulfonylurea medications receiving ibuprofen, as in BRUFEN® RETARD.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and BRUFEN® RETARD.

Aminoglycosides: BRUFEN® RETARD may decrease the excretion of aminoglycosides.

Herbal extracts: Ginkgo biloba may potentiate the risk of bleeding with BRUFEN® RETARD.

CYP2C9 Inhibitors: Concomitant administration of BRUFEN® RETARD with CYP2C9 inhibitors may increase the exposure to ibuprofen (CYP2C9 substrate). In a study with voriconazole and

fluconazole (CYP2C9 inhibitors), an increased S(+)-ibuprofen exposure by approximately 80 to 100 % has been shown.
Reduction of the BRUFEN® RETARD dose should be considered when potent CYP2C9 inhibitors are administered concomitantly, particularly when high-dose ibuprofen is administered with either voriconazole or fluconazole.

Use with care together with other protein-bound medicines (e.g. tolbutamide, coumarin and hydantoin).

4.6 Fertility, pregnancy and lactation

Pregnancy

Consider ultrasound monitoring of amniotic fluid if BRUFEN® RETARD treatment extends beyond 48 hours and discontinue the BRUFEN® RETARD if oligohydramnios is found.

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or embryo/fetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after the use of a prostaglandin synthesis inhibitor in early pregnancy. The risk is believed to increase with dose and duration of therapy. In animals, the administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation losses and embryo/fetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

If BRUFEN® RETARD is used by a woman attempting to conceive, or during the first or 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 fetus to the following:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension)
- renal dysfunction, which may progress to renal failure with oligohydramnios.

At the end of pregnancy, prostaglandin synthesis inhibitors may expose the mother and the neonate to the following:

- possible prolongation of bleeding time
- inhibition of uterine contractions, which may result in delayed or prolonged labour.

Consequently, ibuprofen is contraindicated during the third trimester of should be avoided.

Breastfeeding

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

Fertility

The use of BRUFEN® RETARD 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 BRUFEN® RETARD should be considered.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adverse reactions are listed below as MedDRA preferred term by system organ class and frequency. Frequencies are defined as: very common (> 1/10), common (≥ 1/100 and < 1/10), uncommon (≥ 1/1 000 and < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000) and not known (cannot be estimated from the available data).

Infections and infestations

Uncommon: rhinitis

Rare: aseptic meningitis

Blood and [~~the~~] lymphatic system disorders

Rare: leukopenia, thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia, haemolytic anaemia

Immune system disorders

Uncommon: hypersensitivity

Rare: anaphylactic reaction

Psychiatric disorders

Uncommon: insomnia, anxiety

Rare: depression, confusional state

Nervous system disorders

Common: headache, dizziness, nervousness, drowsiness

Uncommon: paraesthesia, somnolence

Rare: optic neuritis

Eye disorders

Uncommon: visual impairment, toxic amblyopia, blurred vision

Rare: toxic optic neuropathy

Ear and labyrinth disorders

Uncommon: hearing imparied, tinnitus, vertigo

Cardiac disorders

Very rare: cardiac failure, myocardial infarction

Vascular disorders

Very rare: hypertension

Respiratory, thoracic and mediastinal disorders

Uncommon: asthma, bronchospasm, dyspnoea

Gastrointestinal disorders

Common: dyspepsia, diarrhoea, nausea, vomiting, abdominal pain, flatulence, constipation, melaena, haematemesis, gastrointestinal haemorrhage

Uncommon: gastritis, abdominal discomfort, duodenal ulcer, gastric ulcer, mouth ulceration, gastrointestinal perforation

Very rare: pancreatitis

Not known: exacerbation of colitis and Crohn's disease

Hepatobiliary disorders

Uncommon: hepatitis, jaundice, hepatic function abnormal

Very rare: hepatic failure

Skin and subcutaneous tissue disorders

Common: rash

Uncommon: urticaria, pruritis, purpura, angioedema photosensitivity reaction

Very rare: severe forms of skin reactions, e.g. erythema multiforme, bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis

Renal and urinary disorders

Uncommon: nephrotoxicity in various forms, e.g. tubulointerstitial nephritis, nephrotic syndrome and renal failure

General disorders and administration site conditions

Common: fatigue

Rare: oedema.

Description of selected adverse reactions

Gastrointestinal disorders

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, gastrointestinal haemorrhage and exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following ibuprofen administration. Less frequently, gastritis, duodenal ulcer, gastric ulcer and gastrointestinal perforation have been observed.

Immune system disorders

Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of (a) non-specific allergic reaction 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 very rarely, erythema multiforme, bullous dermatoses (including Stevens-Johnson syndrome and toxic epidermal necrolysis).

Cardiac disorders and vascular disorders

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. Clinical studies suggest that use of ibuprofen, particularly at high dose (2 400 mg/day) may be associated with a small increased risk of arterial thrombotic events such as myocardial infarction or stroke (see section 4.4).

Infections and infestations

Rhinitis and 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). Exacerbation of infection-related inflammations coinciding with the use of NSAIDs has been described. If signs of an infection occur or get worse during use of BRUFEN® RETARD, the patient is therefore recommended to go to a doctor without delay.

Skin and subcutaneous tissue disorders

In exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection (see also "Infections and infestations").

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of BRUFEN® RETARD is important. It allows continued monitoring of the benefit/risk balance of BRUFEN® RETARD. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Signs and symptoms of toxicity have generally not been observed at doses below 100 mg/kg in children or adults. However, supportive care may be needed in some cases. Children have been observed to manifest signs and symptoms of toxicity after ingestion of 400 mg/kg or greater.

Most patients who have ingested significant amounts of ibuprofen will manifest symptoms within 4 to 6 hours. The most frequently reported symptoms of overdosage include nausea, vomiting, abdominal pain, lethargy and drowsiness. Central nervous system (CNS) effects include headache, tinnitus, dizziness, convulsion, and loss of consciousness. Nystagmus, metabolic acidosis, hypothermia, renal effects, gastrointestinal bleeding, coma, apnoea, diarrhoea and depression of the CNS and respiratory system have also been rarely reported. In serious poisoning metabolic acidosis may occur. Disorientation, excitation, fainting and cardiovascular toxicity, including hypotension, bradycardia and tachycardia have been reported. In cases of significant overdose, renal failure and liver damage are possible. Large overdoses are generally well tolerated when no other medicines are being taken.

Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered.

Good urine output should be ensured. Renal and liver function should be closely monitored. Patients should be observed for at least four hours after ingestion of potentially toxic amounts. Frequent or prolonged convulsions should be treated with intravenous diazepam. Other measures may be indicated by the patient's clinical condition. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 3.1 Antirheumatics (Anti-inflammatory agents)

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, nonsteroidal; propionic acid derivatives.

ATC code: M01AE01

Mechanism of action

Chemically, ibuprofen is described as 2-(4-isobutylphenyl) propionic acid and is a propionic acid derivative non-steroidal compound, which exhibits anti-inflammatory, analgesic and anti-pyretic activities necessary for the effective treatment of rheumatoid arthritis and osteo-arthritis. The drug's therapeutic effects as an NSAID is thought to result from its inhibitory effect on the enzyme cyclo-oxygenase, which results in a marked reduction in prostaglandin synthesis.

Specific studies confirm that BRUFEN® RETARD possesses anti-inflammatory, analgesic and antipyretic properties in animal tests. Glucocorticoid activity is absent.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that when single doses of ibuprofen 400 mg were taken within 8 hours before or within 30 minutes after immediate release aspirin dosing (81 mg), a decreased effect of aspirin on the formation of thromboxane or platelet aggregation occurred. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 4.5).

5.2 Pharmacokinetic properties

BRUFEN® RETARD tablets are specifically formulated to allow the gradual release of active substance giving stable serum levels and a prolonged duration of effect over the dosage interval. The pharmacokinetic profile of BRUFEN® RETARD compared with that of conventional release 400 mg tablets showed that the sustained release formulation reduced peaks and troughs characteristic of the conventional release tablets and gave higher levels at 5, 10, 15 and 24 hours. Compared with conventional release tablets the area under the plasma concentration time curve for sustained tablets was almost identical.

Absorption

Both mean plasma profiles and the pre dose plasma levels showed no major difference between the young and elderly age groups. In several studies, BRUFEN® RETARD produced a double peak plasma profile when taken under fasting conditions. The rate of absorption may be delayed by food and higher plasma concentrations (C_{max}) may also be obtained when taken with food.

Distribution

Ibuprofen is extensively bound to plasma proteins.

Biotransformation

Ibuprofen is metabolised in the liver to two inactive metabolites.
The levels in human serum of both metabolites have been measured after single and repeated doses.

Elimination

Excretion by the kidney is both rapid and complete. Two major metabolites of ibuprofen have been isolated from human urine. They are (+)2,4(2-hydroxy-2- methylpropyl) phenylpropionic acid (metabolite A) and (+)2,4(2-carboxylpropyl) phenylpropionic acid (metabolite B).
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. There is no evidence of accumulation. The elimination half-life of ibuprofen is approximately 2 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Colloidal anhydrous silica

Hypromellose

Povidone

Stearic acid

Talc

Titanium dioxide (E171)

Xanthan gum.

Tablet coating:

Opaspray White M-1-7111B (containing hypromellose and titanium dioxide (E171)).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

BRUFEN® RETARD is packed in cartons containing 60 tablets in blister strips.

6.6 Special precautions for disposal and other handling

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Abbott Laboratories S.A. (Pty) Ltd

Abbott place, 219 Glof Club Terrace

Constantia Kloof 1709

South Africa

8. REGISTRATION NUMBER

Y/3.1/13

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 June 1990

10. DATE OF REVISION OF THE TEXT

20 January 2023

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