Approved Professional Information for Medicines for Human Use: BREN-400

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

BREN-400 film-coated tablets (tablets).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Ibuprofen 400 mg.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets (tablets).

Pink coloured, circular, slightly biconvex film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BREN-400 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,
- osteoarthritis,
- acute gouty arthritis,

- non-articular rheumatism including fibrositis,
- peri-articular conditions such as frozen shoulder (capsulitis), bursitis, tendonitis, tenosynovitis and low-back pain,
- soft-tissue injuries such as sprains and strains.

BREN-400 is also indicated for its analgesic effect in the relief of mild to moderate pain such as:

- dysmenorrhoea,
- dental pain,
- post-episiotomy pain,
- post-partum pain.

BREN-400 may also be used as an antipyretic.

4.2 Posology and method of administration

Posology

Adults

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

The recommended dosage of BREN-400 is 1 200 mg daily in divided doses.

In severe conditions it can be advantageous to increase the dosage until the acute phase has been brought under control.

To relieve early morning stiffness, the first dose of the day can be given immediately after the patient awakes.

For the relief of mild to moderate pain the following doses are recommended:

Dysmenorrhoea

1 200 mg per day in three divided doses. In cases of dental or post-episiotomy pain, an initial dose of 800 mg may be given. The total daily dose of BREN-400 should not exceed 2 400 mg. Once the acute phase has been brought under control, it is normal practice to revert to a maintenance dosage.

Acute gout

2 400 mg daily, given as 800 mg 8 hourly, until the acute symptoms have been relieved. If the acute symptoms do not resolve within three days, consult a doctor.

Pain

Initial dose 5 mg/kg of bodyweight. A second dose of 5 mg/kg may be given after 2 hours if pain is not controlled, thereafter 5 mg/kg every 4 – 6 hours. DO NOT EXCEED 20 mg/kg of bodyweight per day. If pain persists for more than 7 days, consult your doctor.

Fever

5 mg/kg of bodyweight every 4 – 6 hours. DO NOT EXCEED 20 mg/kg of body weight per day. If fever persists for more than 3 days, consult your doctor.

Children

In Juvenile Rheumatoid Arthritis, the total daily dosage of BREN-400 is 20 mg/kg of body mass given in divided doses.

Paediatric population

Safety in children under one year of age has not been proven.

Method of administration

BREN-400 is for oral administration.

4.3 Contraindications

- Hypersensitivity to the ibuprofen or to any of the excipients listed in section 6.1.
- Hypersensitivity to aspirin or any other non-steroidal anti-inflammatory drugs (NSAIDs). Because of the possibility of cross-sensitivity due to structural relationships which exists 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 NSAID's use (see section 4.4).
- Active or history of recurrent ulcer, haemorrhage or perforations.
- Third trimester of pregnancy and during labour (see sections 4.4 and 4.6).
- BREN-400 is contraindicated in patients with heart failure (see section 4.4).
- BREN-400 is contraindicated in patients with renal failure (see section 4.4).

4.4 Special warnings and precautions for use

Undesirable effects

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).

Concomitant use with other NSAIDs

Use of BREN-400 with concomitant NSAIDs including cyclo-oxygenase-2 specific inhibitors should be avoided due to the increased risk of ulceration or bleeding (see section 4.5).

Medicine overuse headache

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

Concomitant use of alcohol

The concomitant consumption of excessive alcohol with NSAIDs, including ibuprofen 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.

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 BREN-400 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

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 medicines which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or antiplatelet medicines such as aspirin (see section 4.5).

When gastrointestinal bleeding or ulceration occurs in patients receiving BREN-400, treatment with BREN-400 should be stopped.

BREN-400 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 these conditions may be exacerbated (see section 4.8).

Respiratory disorders and hypersensitivity reactions

Caution is required if BREN-400 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.(see also section 4.3).

Oedema has been reported in association with ibuprofen administration. In view of BREN-400's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients (see section 4.3).

Cardiovascular and cerebrovascular effects

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.

Renal effects

Caution should be used when initiating treatment with ibuprofen 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, such as in BREN-400 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 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. Other patients at risk include those taking ACE inhibitors and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state.

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).

Acute reversible renal failure has been reported. BREN-400 should be used with care in patients with impaired renal function.

Risk of foetal renal dysfunction

The use of nonsteroidal anti-inflammatory drugs (NSAIDs), including ibuprofen such as in BREN-400 around 20 weeks gestation or later in pregnancy may cause foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Oligohydramnios is often, but not always, reversable with treatment discontinuation. Complications of prolonged oligohydramnios may include limb contractures and delayed lung maturation (see sections 4.3 and 4.6). Invasive procedures such as exchange transfusion or dialysis may be required. If BREN-400 treatment is deemed necessary between 20 to 30 weeks of pregnancy, limit use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if BREN-400 treatment extends beyond 48 hours. Discontinue BREN-400 if oligohydramnios occurs and follow up according to clinical practice (see sections 4.3 and 4.6).

Closure of foetal ductus arteriosus

Regular use of NSAIDs such as BREN-400 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 section 4.6).

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 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 within the first month of treatment in the majority of cases. Acute generalised exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing medicines. BREN-400 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 tissues 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 BREN-400 in case of *varicella*.
Also see DRESS below.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

DRESS has been reported in patients taking NSAIDs such as ibuprofen, the active ingredient contained in BREN-400. Some of these events have been fatal or life-threatening (see section 4.8). DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy,

may be present even though rash is not evident. If such signs or symptoms are present, discontinue BREN-400 and evaluate the patient immediately.

Masking of symptoms of underlying infections

The antipyretic, analgesic and anti-inflammatory action of ibuprofen may mask symptoms of the occurrence or worsening 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 bacteria complications to *varicella*.

When BREN-400 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.

Changes in vision

BREN-400 should be discontinued in patients who experience blurred or diminished vision, or changes in colour vision.

Haematological effects

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

Aseptic meningitis

Aseptic meningitis has been observed in patients on ibuprofen therapy, such as BREN-400 (see section 4.8). 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.

Impaired female fertility

The use of BREN-400 may impair female fertility (see section 4.6).

Monitoring of patients

Patients undergoing therapy with BREN-400 may need to be monitored for the development of blood, kidney, liver or eye disorders.

Elderly

The elderly have an increased frequency of adverse reactions to NSAIDs including BREN-400, especially gastrointestinal perforation, ulceration and bleeding (PUBs) which may be fatal.

BREN-400 should be given with care to the elderly.

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

NSAIDs 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 NSAIDs.

There may also be an increased risk of hyperkalaemia with angiotensin-converting enzyme (ACE) inhibitors and potassium-sparing diuretics.

Cardiac glycosides

NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels.

Cholestyramine

The concomitant administration of ibuprofen and cholestyramine 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 anti-prostaglandin properties of NSAIDs. Limited evidence suggests that coadministration of NSAIDs 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.

Other analgesics and cyclooxygenase-2 selective 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 ibuprofen 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 (see section 5.1).

Corticosteroids

Increased risk of gastrointestinal ulceration or bleeding with NSAIDs (see section 4.4).

Alcohol

Alcohol may increase the risk of gastrointestinal side-effects, including ulceration or haemorrhage (see section 4.4).

Anticoagulants

NSAIDs may enhance the effects of anticoagulants, such as warfarin (see section 4.4).

Quinolone antibiotics

Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Phenytoin

NSAIDs may potentiate the effects of phenytoin.

Sulfonylureas

NSAIDs may potentiate the effects of sulfonylurea medicines. There have been rare reports of hypoglycaemia in patients on sulfonylurea medicines receiving ibuprofen.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs)

Increased risk of gastrointestinal bleeding with NSAIDs (see section 4.4).

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 ibuprofen.

Aminoglycosides

NSAIDs may decrease the excretion of aminoglycosides.

Herbal extracts

Ginkgo biloba may potentiate the risk of bleeding with NSAIDs.

CYP2C9 inhibitors

Concomitant administration of ibuprofen 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 ibuprofen dose should be considered when potent CYP2C9 inhibitors are administered concomitantly, particularly when high-dose ibuprofen is administered with either voriconazole or fluconazole.

4.6 Fertility, pregnancy and lactation

Pregnancy

BREN-400 should not be used in third trimester of pregnancy and during labour (see section 4.3).

Regular use of NSAIDs 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 newborn. The onset of labour may be delayed and its duration increased (see section 4.4).

The use of NSAIDs, such as BREN-400 used at 20 weeks gestation or later may cause serious kidney problems in an unborn baby. After around 20 weeks of pregnancy, the unborn babies' kidneys produce most of the amniotic fluid. Amniotic fluid provides a protective cushion and helps the unborn babies' lungs, digestive system, and muscles develop. Foetal renal dysfunction can lead to oligohydramnios due to the low levels of amnionic fluid. Complications of prolonged oligohydramnios may include limb contractures and delayed lung maturation (see section 4.4).

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.

Fertility

The use of BREN-400 may impair female fertility (see section 4.4) and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of BREN-400 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 BREN-400 (see section 4.8). If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

a) Summary of the safety profile

Gastrointestinal disorders

It is reported that 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 Ibuprofen 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").

b) Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and post-market spontaneous reports with ibuprofen.

System Organ Class	Frequency		
	Frequent	**Less Frequent**	**Not known**
Infections and infestations		rhinitis, meningitis aseptic (see section 4.4)	
Blood and lymphatic system disorders		leukopenia, thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia, haemolytic anaemia, eosinophilia	
Immune system disorders		hypersensitivity, anaphylactic reaction	
Psychiatric disorders		insomnia, anxiety, depression, confusional state	
Nervous system disorders	headache, dizziness	paraesthesia, somnolence, optic neuritis	
Eye disorders		visual impairment,	

		toxic optic neuropathy	
Ear and labyrinth disorders		hearing impaired, tinnitus, vertigo	
Cardiac disorders		cardiac failure, myocardial infarction (also see section 4.4)	
Vascular disorders		hypertension	
Respiratory, thoracic and mediastinal disorders		asthma, bronchospasm, dyspnoea	
Gastrointestinal disorders	dyspepsia, diarrhoea, nausea, vomiting, abdominal pain, flatulence, constipation, melaena, haematemesis,	gastritis, duodenal ulcer, gastric ulcer, mouth ulceration, gastrointestinal perforation, pancreatitis	exacerbation of colitis and Crohn´s disease (see section 4.4)

	gastrointestinal haemorrhage		
Hepatobiliary disorders		hepatitis, jaundice, hepatic function abnormal, hepatic failure	
Skin and subcutaneous tissue disorders	rash	urticaria, pruritus, purpura, angioedema, photosensitivity reaction, severe forms of skin reactions (e.g., erythema multiforme, bullous reactions, including Stevens-Johnson syndrome, and toxic epidermal necrolysis) (see section 4.4)	drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) (see section 4.4), acute generalised exanthematous pustulosis (AGEP) (see section 4.4)
Renal and urinary disorders		nephrotoxicity in various forms e.g., tubulointerstitial	

		nephritis, nephrotic syndrome and renal failure (see section 4.4)	
General disorders and administration site conditions	fatigue	oedema	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Toxicity

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.

Symptoms

Most patients who have ingested significant amounts of ibuprofen will manifest symptoms within 4 to 6 hours. The most frequently reported symptoms of overdose 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 less frequently 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.

Therapeutic measures

There is no specific antidote to BREN-400.

Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 3.1 Antirheumatics (anti-inflammatory agents)

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

ATC Code: M01AE01

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.

5.2 Pharmacokinetic properties

Absorption

Ibuprofen is rapidly absorbed after oral administration, and peak concentrations in plasma are observed after 1 to 2 hours. Absorption was slower and peak serum levels lower after food. The half-life in plasma is about 2 hours.

An oral dose taken on an empty stomach by human volunteers produced peak serum levels after three quarters of an hour.

Distribution

Ibuprofen is extensively (99 %) bound to plasma proteins, but the drug occupies only a fraction of the total drug-binding sites at usual concentrations. Ibuprofen passes slowly into the synovial spaces and may remain there in higher concentration as the concentrations in plasma decline. In experimental animals, ibuprofen and its metabolites pass easily across the placenta.

Biotransformation

Ibuprofen is metabolised in the liver to two inactive metabolites, i.e., a hydroxylated and a carboxylated compound, and these, together with unchanged ibuprofen, are excreted by the kidney either as such or as conjugates.

Elimination

The excretion of ibuprofen is rapid and complete. More than 90 % of an ingested dose is excreted in the urine as metabolites or their conjugates.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Colloidal silicon dioxide

Maize starch

Magnesium stearate

Purified talc

Sodium lauryl sulfate

Sodium starch glycolate (type A)

Film-coating

Hypromellose

Lake erythrosine

Propyl glycol

Sodium acetate

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Store in a cool dry place at or below 25 °C.

Protect from light.

Keep the blister in the carton until required for use.

6.5 Nature and contents of container

Blister packs (composed of colourless PVC and aluminium foil) of 10 tablets, 15 tablets or 84 tablets per carton.

Opaque white High Density Polyethylene (HDPE) containers containing 1 000 tablets.

White Low Density Polyethylene (LDPE) plastic Patient Ready Packs (PRPs) containing different pack sizes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Shanur Healthcare (Pty) Ltd.,

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3A Eton Road,

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8. REGISTRATION NUMBER

36/3.1/0041

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 November 2002.

10. DATE OF REVISION OF THE TEXT