Approved Professional Information for Medicines for Human Use: IBROFEX 400

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

IBROFEX 400 film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

IBROFEX 400 mg film-coated tablets.

Each film-coated tablet contains ibuprofen 400 mg.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

IBROFEX 400 mg film-coated tablets.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IBROFEX 400 is indicated as an anti-inflammatory and analgesic in the treatment of rheumatoid arthritis (including Still's disease or juvenile rheumatoid arthritis), osteoarthritis, acute gouty arthritis and ankylosing spondylitis; the treatment of non-articular rheumatism, including fibrositis; the treatment of periarticular conditions such as bursitis, capsulitis, synovitis, tendonitis and lower back pain and the treatment of soft-tissue injuries (strains and sprains).

IBROFEX 400 is also indicated as an analgesic in the relief of mild to moderate pain such as, dental, post episiotomy- and post-partum pain, dysmenorrhoea, headache and pain associated with

Austell Pharmaceuticals (Pty) Ltd, 561085, IBROFEX 400, Film-coated tablets and 400 mg migraine. IBROFEX 400 may be used as an antipyretic.

4.2 Posology and method of administration

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

Adults:

Recommended dose:

1200 mg per day in divided doses.

This equals 3 x 400 mg tablets.

Acute dose:

In severe cases until the acute phase is under control - 2 400 mg per day in divided doses. This equals 6 x 400 mg tablets.

Early morning stiffness can be relieved by taking the first dose of the day immediately after waking up. The following doses are recommended for mild and moderate pain: Dysmenorrhoea - 1200 mg per day in 3 divided doses. For dental pain or post-episiotomy pain, an initial dose of 800 mg may be given. The total daily dose of IBROFEX 400 should not be more than 2400 mg. A maintenance dose should be followed once the acute phase is under control.

Maintenance dose:

600 mg to 1200 mg per day in divided doses.

Acute gout:

2400 mg daily (800mg 8 hourly or 600mg 6 hourly) until the acute phase has relieved. Consult a medical practitioner if acute symptoms do not resolve within 3 days.

Children

Juvenile rheumatoid arthritis - 20 mg/kg of body mas in divided doses daily. Safety in children under one year of age has not been established.

Pain:

Initial dose of 5 mg/kg of body weight. After 2 hours a second dose of 5 mg/kg may be given and thereafter. If pain is not controlled 5 mg/kg every 4-6 hours.

Do not exceed 20 mg/kg of bodyweight per day. Consult a medical practitioner if pain persists more than 7 days.

Fever:

5 mg/kg of body weight every 4-6 hours. Do not exceed 20 mg/kg of bodyweight per day.

Consult medical practitioner if fever persists more than 3 days.

Method of administration

For oral use.

IBROFEX 400 tablets may be taken with food to minimize gastro-intestinal side-effects. If gastrointestinal disturbances occur, IBROFEX 400 should be given with food or milk.

4.3 Contraindications

- Hypersensitivity to the ibuprofen or to any of the excipients listed in section 6.1.
- Pregnancy and during breastfeeding (see sections 4.6).
- History of gastrointestinal bleeding (PUBs) or perforation related to previous nonsteroidal anti-inflammatory (NSAID) use (see section 4.4).
- Patients with active or a history of recurrent ulcer/haemorrhage/perforations
- Heart failure
- Caution is advised in those patients who are receiving coumarin anticoagulants such as warfarin (see section 4.5).
- Hypersensitivity to aspirin.
- IBROFEX 400 should be prescribed with caution for those with asthma and especially for patients who have developed bronchospasm with other non-steroidal medicines.

- When IBROFEX 400 is taken together with antiplatelet medicines and selective serotonin reuptake inhibitors (SSRIs), there may be an increased risk of gastrointestinal bleeding.

4.4 Special warnings and precautions for use

Caution is required in patients with certain conditions:

Systemic lupus erythematosus as well as those with mixed connective tissue disease due to increased risk of aseptic meningitis (see section 4.8).

Gastrointestinal disorders and chronic inflammatory intestinal disease as these conditions may be exacerbated (ulcerative colitis, Crohn's disease) (see section 4.8).

Caution is required prior to starting treatment in patients with a history of hypertension and/or heart failure. Oedema, hypertension and/or cardiac impairment as renal function may deteriorate and/or fluid retention occur (see section 4.5).

Renal impairment as renal function may deteriorate (see section 4.3 and 4.8).

Renal tubular acidosis and hypokalaemia may occur following acute overdose and in patients taking ibuprofen products over long periods at high doses (typically greater than 4 weeks), including doses exceeding the recommended daily dose.

Hepatic dysfunction (see section 4.3 and 4.8).

Undesirable effects may be minimised by using the minimum effective dose for the shortest possible duration to control symptoms (see GI and cardiovascular risks below).

The elderly are at increased risk of the serious consequences of adverse reactions.

Bronchospasms may be precipitated in patients suffering from or with a previous history of bronchial asthma or allergic disease.

Use with concomitant NSAIDs including cyclo-oxygenase-2 specific inhibitors (See section 4.5).

Cardiovascular and cerebrovascular effects

Clinical studies suggest that use of ibuprofen, particularly at high doses (2400mg/day) 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. ≤1200mg daily) is associated with an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure (NYHA 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 (2400 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 ibuprofen (2400 mg/day) are required.

There is some evidence that medicines which inhibit cyclo-oxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

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 (including ulcerative colitis, Crohn's disease).

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.

Patients with a history of GI toxicity, particularly the 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 gastrotoxicity or bleeding, such as corticosteroids, or anticoagulants such as warfarin, selective serotonin re-uptake inhibitors or anti-platelet medicines such as aspirin (see section 4.5).

Where GI bleeding or ulceration occurs in patients receiving ibuprofen, the treatment should be withdrawn immediately.

Severe 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 NSAIDSs (see section 4.8). Patients appear to be at highest risk for 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.

Acute generalised exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing products.

Ibuprofen should be discontinued at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.

Masking of symptoms of underlying infections

IBROFEX 400 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 IBROFEX 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 medical practitioner if symptoms persist or worsen.

Risk of foetal renal dysfunction

The use of nonsteroidal anti-inflammatory medicines (NSAIDs), including ibuprofen such as in IBROFEX 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 IBROFEX 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 IBROFEX 400 treatment extends beyond 48 hours. Discontinue IBROFEX 400 if

oligohydramnios occurs and follow up according to clinical practice (see sections 4.3 and 4.6).

Medicine Reaction with Eosinophillia and Systemic Symptoms (DRESS)

DRESS has been reported in patients taking NSAIDs such as ibuprofen, the active ingredient contained in IBROFEX 400. Some of these events have been fatal or life-threatening. 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. Eosinophillia 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 IBROFEX 400 and evaluate the patient immediately.

Elderly

The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation, which may be fatal.

Paediatric population

There is a risk of renal impairment in dehydrated children and adolescents, between the ages of 12-18 year olds.

Excipient sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicines and other forms of interaction

Ibuprofen should not be used in combination with:

Aspirin (Acetylsalicylic acid)

Concomitant administration of ibuprofen and aspirin (acetylsalicylic acid) is not generally recommended (unless low dose aspirin (not above 75mg daily) has been advised by a medical practitioner), as this combination may increase the incidence of adverse reactions (see section 4.4)

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose aspirin (acetylsalicylic acid) 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 aspirin (acetylsalicylic acid) cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

Other NSAIDs including cyclooxygenase-2 selective inhibitors as these may increase the incidence of adverse effects (see section 4.4)

Ibuprofen should be used in caution in combination with:

Corticosteroids: May increase the risk of adverse reactions, especially the gastrointestinal tract (see section 4.4).

Antihypertensives and diuretics: NSAIDs may diminish the effects of these medicines. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Anticoagulant: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4).

Anti-platelet medicines and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4).

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

Lithium: There is evidence for the potential increase in plasma levels of lithium.

Methotrexate: There is evidence for the potential increase in plasma levels of methotrexate.

Ciclosporin: Increased risk of nephrotoxicity.

Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

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

Zidovudine: There is evidence for an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

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.

IBROFEX 400 may enhance the effects of phenytoin and sulphonylurea antidiabetics.

Alcohol may increase the risk of gastrointestinal side effects, including ulceration or haemorrhage.

Ginkgo biloba may potentiate the risk of bleeding with IBROFEX 400.

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

IBROFEX 400 should not be used in pregnancy or by breastfeeding mothers (see section 4.4).

The use of NSAIDs, such as IBROFEX 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).

Breastfeeding

In limited studies, ibuprofen appears in the breast milk in very low concentrations, and is unlikely to affect the breast fed infant adversely.

Fertility

There is some evidence that medicines, which inhibit cyclooxygenase/ prostaglandin synthesis, may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

4.7 Effects on ability to drive and use machines

No studies on the effect of ability to drive or use machines have been performed.
IBROFEX 400 may cause side effects such as dizziness, drowsiness. fatigue and visual disturbances which can affect the ability to drive a vehicle and use machines (see section 4.8).
Caution is advised before driving a vehicle or operating machinery until the effects of IBROFEX 400 are known.

4.8 Undesirable effects

a) Summary of the safety profile

Hypersensitivity reactions have been reported and these may consist of:

a) Non-specific allergic reactions and anaphylaxis,

b) Respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea,

c) Various skin reactions, e.g. pruritus, urticaria, angioedema and more rarely, exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

The list of the following adverse effects relates to those experienced with ibuprofen at OTC doses, from short-term use. In chronic conditions, under long-term treatment, additional adverse effects may occur.

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

Clinical studies suggest that use of ibuprofen, (particularly at a high dose (2400mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

b) Tabulated list of adverse reactions

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

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**

Blood and lymphatic system disorders	--	Haematopoietic disorders (anaemia, hemolytic anemia, aplastic anemia, leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, nose and skin bleeding.	--
Immune system disorders	--	Hypersensitivity reactions with urticaria and pruritus. In patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease) during treatment with ibuprofen, single cases of symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed. Severe hypersensitivity reactions. Symptoms could be: facial, tongue and larynx swelling, dyspnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock). Exacerbation of asthma and bronchospasm.	--
Psychiatric disorders	--	Nervousness, Insomnia, Anxiety, Depression, Confusional state	--

Nervous system disorders	--	Headache, aseptic meningitis, Paraesthesia, somnolence	--
Eye disorders	--	Visual impairment, toxic amblyopia blurred vision and other visual field detects	--
Ear and labyrinth disorders	--	Tinnitus, vertigo, hearing impaired	--
Cardiac disorders	--	Cardiac failure, angina pectoris	--
Vascular disorders	--	Hypertension	--
Respiratory, thoracic and mediastinal disorders	--	Asthma, bronchospasm, dyspnoea and wheezing	--
Gastrointestinal disorders	--	Abdominal pain, abdominal distension, dyspepsia and nausea. Diarrhoea, flatulence, constipation and vomiting. Peptic ulcer, perforation or gastrointestinal haemorrhage, melaena, haematemesis sometimes fatal, particularly in the elderly (see section 4.4). Exacerbation of ulcerative colitis and Crohn's disease (see section 4.3). Mouth ulceration.	--

Hepatobiliary disorders	--	Liver disorders, especially in long-term treatment, hepatitis and jaundice, abnormalities of liver function tests	--
Skin and subcutaneous tissue disorders	--	Various skin rashes Severe forms of skin reactions such as bullous reactions, including Stevens-Johnson Syndrome, erythema multiforme and epidermal necrolysis can occur.	Medicine reaction with eosinophilia and systemic symptoms (DRESS syndrome), Acute generalised exanthematous pustulosis (AGEP). Photosensitivity reactions.
Renal and urinary disorders	--	Acute renal failure, papillary necrosis, especially in long-term use, associated with increased serum urea and oedema. Haematuria, tubulointerstitial nephritis, nephritic syndrome, proteinuria.	Ureteric colic, dysuria, renal tubular acidosis*
Metabolism and Nutrition Disorders	--	--	Decreased Appetite, Hypokalaemia*
*Renal tubular acidosis and hypokalaemia have been reported in the post-marketing setting typically following prolonged use of the ibuprofen component at higher than recommended doses.			

General disorders and administration site conditions	--	Oedema, peripheral oedema	--
Investigations	--	Decreased hematocrit and hemoglobin levels	--

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. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Suspected adverse reactions can also be reported directly to the HCR via medsafety@austell.co.za

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 and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation, hypotension and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning, metabolic acidosis may occur and the prothrombin time/INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur.

Exacerbation of asthma is possible in asthmatics.

In serious poisoning metabolic acidosis may occur and the prothrombin time/INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur.

Prolonged use at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalised weakness (see section 4.4 and section 4.8).

Management

Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal if the patient presents within 1 hour of ingestion of a potentially toxic amount. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 3.1 Antirheumatics (anti-inflammatory medicines)

Pharmacotherapeutic group: Propionic acid derivatives

ATC Code: M01AE

IBROFEX 400 contains ibuprofen, a propionic acid derivative, which is a non-steroidal compound. Ibuprofen is an anti-inflammatory medicine and also has analgesic and antipyretic properties. The medicine'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.

5.2 Pharmacokinetic properties

Absorption

Ibuprofen is absorbed following oral administration, and peak serum concentrations are observed after to 2 hours.

Distribution

Ibuprofen is extensively bound to plasma proteins (99 %). It passes
slowly into the synovial spaces and remains there in higher concentrations as the concentrations in plasma decline.

Elimination

The excretion of ibuprofen is rapid and complete. Greater than 90 % of an ingested dose is excreted in the urine as metabolites or their conjugates, and no ibuprofen by itself is found in the urine. The major metabolites are hydroxylated and carboxylated compounds.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tables core

Colloidal silicon dioxide

Maize starch

Magnesium stearate

Purified talc

Sodium lauryl sulfate

Sodium starch glycolate (type A)

Film-coating

Instacoat-pink (A05R03211) consisting of:

- Hypromellose
- Lake erythrosine
- Propyl glycol
- Sodium acetate
- Titanium dioxide.

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

48 months for HDPE bottle pack

24 months for PRP pouch and Blister pack

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 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

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8. REGISTRATION NUMBER

56/3.1/1085

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 November 2024.

10. DATE OF REVISION OF THE TEXT