SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

IBOFLAM, 200 mg coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg Ibuprofen.

Contains sugar: Sucrose 35,424 mg per tablet

Lactose 112,08 mg per tablet

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Coated tablets (tablets)

Pink, round, biconvex, sugar-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IBOFLAM is indicated in adults and children over 12 years of age for the treatment of:

- Rheumatoid arthritis
- Ankylosing spondylitis
- Osteoarthritis
- Acute gouty arthritis
- Non-articular rheumatism including fibrositis.

4.2 Posology and method of administration

Posology

Adults

The recommended dosage of IBOFLAM is 400 – 600 mg (2 – 3 tablets) 6 to 8-hourly.

The total daily dose of IBOFLAM should not exceed 2 400 mg (12 tablets).

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

Children

This dosage form is not suitable for children younger than 12 years of age.

Method of administration

For oral administration with food to minimize gastro-intestinal side-effects.

Special populations

Elderly

The elderly are at increased risk of serious consequences of adverse reactions. If IBOFLAM is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during IBOFLAM therapy. If renal or hepatic function is impaired, dosage should be assessed individually.

Renal impairment

Patients with mild to moderate renal impairment, (see section 4.4) and patients with severe renal insufficiency (see section 4.3).

Hepatic impairment

For patients with mild to moderate hepatic impairment (see section 4.4) and patients with severe hepatic dysfunction (see section 4.3).

4.3 Contraindications

- Hypersensitivity to ibuprofen or to any of the excipients listed in section 6.1.
- Peptic ulcer disease or gastrointestinal bleeding.
- Patients sensitive to aspirin or another nonsteroidal anti-inflammatory drugs (NSAIDs).
- History of severe allergic reactions such as anaphylaxis or angioedema, induced by aspirin or other NSAIDs because of the possibility of cross-sensitivity (due to structural relationships) which exist among non-steroidal anti-inflammatory medicines, acute allergic reactions are likely to occur in patients who have exhibited allergic reactions to these compounds.
- Nasal polyps and bronchospasm.
- Children under the age of 12 years.
- The last trimester of pregnancy (see section 4.6).
- Heart failure, hepatic failure and renal failure (see section 4.4).
- History of gastrointestinal ulceration, bleeding or perforation (PUBs) related to previous NSAIDs.
- Active or history of recurrent ulcer/haemorrhage/perforations.

4.4 Special warnings and precautions for use

Masking of symptoms of underlying infections

The antipyretic, analgesic, and anti-inflammatory action of IBOFLAM may mask symptoms of the occurrence or worsening of infection.

Cardiovascular and cerebrovascular effects

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 IBOFLAM therapy.

Elderly

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

Gastrointestinal effects

The risk of gastrointestinal bleeding or perforation (PUBs) is higher with increasing doses of IBOFLAM, in patients with a history of ulcers, and the elderly.

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

IBOFLAM 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.

Severe skin reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported. IBOFLAM should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Cardiac, renal, and hepatic impairment

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.

Haematological effects

IBOFLAM can interfere with platelet aggregation and prolong bleeding time in normal subjects.

Visual impairment

IBOFLAM should be discontinued in patients who experience blurred or diminished vision, or changes in colour vision (see section 4.8).

SLE and mixed connective tissue disease

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

Respiratory disorders and hypersensitivity reactions

Caution is required if IBOFLAM is administered to patients suffering from, or with a previous history of, bronchial asthma, chronic rhinitis, or allergic diseases since NSAIDs as in IBOFLAM have been reported to precipitate bronchospasm, urticaria or angioedema in such patients. [(1)]

Medication overuse headache (MOH)

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.

Hypokalaemia and renal tubular acidosis

Severe hypokalaemia and renal tubular acidosis have been reported due to prolonged use of ibuprofen as in IBOFLAM at higher than recommended doses. This risk is increased with the use of codeine/ ibuprofen as patients may become dependent on the codeine component (section 4.8 c. Description of selected adverse reactions and section 4.9). Presenting signs and symptoms included reduced level of consciousness and generalised weakness. Ibuprofen induced renal tubular acidosis should be considered in patients with unexplained hypokalaemia and metabolic acidosis.

Excipients with known effect

IBOFLAM contains sucrose: Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take IBOFLAM.

IBOFLAM contains lactose: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take IBOFLAM.

4.5 Interactions with other medicines and other forms of interaction

- *Alcohol, corticosteroids, clopidogrel, ticlopidine, bisphosphonates, pentoxifylline:* Increased risk of gastrointestinal bleeding and ulceration.
- *Antidiabetic medicines, e.g., sulfonylureas:* Hypoglycaemic effects of these medicines may be increased.
- *Digoxin:* Increase in serum digoxin concentrations.
- *Lithium:* Increase in the steady-state concentration of lithium.
- *Methotrexate:* Increased and prolonged methotrexate plasma concentration and an increased risk of methotrexate toxicity.
- *Nephrotoxic medicines e.g., ciclosporin and tacrolimus:* Increased risk of nephrotoxicity.
- *Antihypertensives or diuretics:* Reduction or reversal of the antihypertensive effect may occur. Diuretics can also increase the risk of nephrotoxicity of NSAIDs.
- *Bone marrow depressants:* The leukopenia and/or thrombocytopenic effects of these medicines may be increased.
- *Non-Steroidal Anti-Inflammatory Drugs (NSAIDs):* Use of two or more NSAIDs concomitantly could result in an increase in side effects.
- *Anticoagulants:* IBOFLAM may enhance the effects of anti-coagulants such as warfarin.
- *Antiplatelet medicines and selective serotonin reuptake inhibitors (SSRIs):* Increased risk of gastrointestinal bleeding.
- *Quinolone antibiotics:* Patients taking IBOFLAM, and quinolones may have an increased risk of developing convulsions.
- *Aminoglycosides:* IBOFLAM may decrease the excretion of aminoglycosides.
- *Herbal extracts:* Ginkgo biloba may potentiate the risk of bleeding with IBOFLAM.
- *Zidovudine:* Increased risk of haematological toxicity when IBOFLAM are given with zidovudine. There is evidence of an increased risk of haemarthrosis and haematoma in

HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

- *CYP2C9 Inhibitors:* Concomitant administration of IBOFLAM 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 – 100 % has been shown. Reduction of the IBOFLAM dose should be considered when potent CYP2C9 inhibitors are administered concomitantly, particularly when high-dose IBOFLAM is administered with either voriconazole or fluconazole.

4.6 Fertility, pregnancy, and lactation

Fertility

Women of childbearing potential: IBOFLAM may cause impairment of female fertility by an effect of ovulation. This is reversible upon withdrawal of treatment.

Pregnancy

IBOFLAM is contraindicated during the third trimester of pregnancy (see section 4.3). IBOFLAM is not recommended for use by pregnant women.

First and second trimester

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or embryo/foetal 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.

Third trimester

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus 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.

Breastfeeding

Patients using IBOFLAM should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

IBOFLAM may interfere with the daily activities of a patient, such as dizziness, drowsiness, fatigue and visual disturbances (see section 4.8). Patients should ensure that they do not engage in the above activities until they are aware of the measure to which IBOFLAM affects them.

4.8 Undesirable effects

a. Summary of the safety profile

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 have been reported.

Immune system disorders: Hypersensitivity reactions have been reported consisting 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 (2400 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).

Skin and subcutaneous tissue disorders: In exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection (see section 4.4).

b. Tabulated summary of adverse reactions

System Organ Class	**Frequency**	**Adverse reactions**
Infections and infestations	Less frequent	Rhinitis, meningitis aseptic (see section 4.4)
Blood and lymphatic system disorders	Less frequent	Leukopenia, thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia, haemolytic anaemia
Immune system disorders	Less frequent	Hypersensitivity, anaphylactic reaction
Metabolism and nutrition disorders	Frequency unknown	Hypokalaemia *
Psychiatric disorders	Less frequent	Insomnia, anxiety, depression, confusional state
Nervous system	Frequent	Headache, dizziness

System Organ Class	Frequency	Adverse reactions
disorders	Less frequent	Paraesthesia, somnolence, optic neuritis
Eye disorders	Less frequent	Visual impairment, toxic optic neuropathy
Ear and labyrinth disorders	Less frequent	Hearing impaired, tinnitus, vertigo
Cardiac disorders	Less frequent	Cardiac failure, myocardial infarction (see section 4.4)
Vascular disorders	Less frequent	Hypertension
Respiratory, thoracic and mediastinal disorders	Less frequent	Asthma, bronchospasm, dyspnoea
Gastrointestinal disorders	Frequent	Dyspepsia, diarrhoea, nausea, vomiting, abdominal pain, flatulence, constipation, melaena, haematemesis, gastrointestinal haemorrhage
	Less frequent	Gastritis, duodenal ulcer, gastric ulcer, mouth ulceration, gastrointestinal perforation, pancreatitis
	Frequency unknown	Exacerbation of colitis and Crohn's disease
Hepato-biliary disorders	Less frequent	Hepatitis, jaundice, hepatic function abnormal, hepatic failure
Skin and subcutaneous tissue disorders	Frequent	Rash
	Less frequent	Urticaria, pruritus, purpura, angioedema, photosensitivity reaction,

System Organ Class	Frequency	Adverse reactions
		severe forms of skin reactions (e.g., Erythema multiforme, bullous reactions, including Stevens-Johnson syndrome, and toxic epidermal necrolysis)
	Frequency unknown	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), acute generalised exanthematous pustulosis (AGEP)
Renal and urinary disorders	Less frequent	Nephrotoxity in various forms e.g., tubulointerstitial nephritis, nephrotic syndrome and renal failure
	Frequency unknown	Renal tubular acidosis *
General disorders and administrative site conditions	Frequent	Fatigue
	Less frequent	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.

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).

Symptoms

Most patients who have ingested significant amounts of ibuprofen will manifest symptoms within 4 to 6 hours. The most likely symptoms of overdosage are epigastric pain, nausea and gastrointestinal bleeding and perforation (PUBs). 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 drugs are being taken.

Management

There is no specific antidote for IBOFLAM. Treatment is symptomatic and supportive.
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

Ibuprofen has analgesic, antipyretic and anti-inflammatory activities.

5.2 Pharmacokinetic properties

Ibuprofen is well-absorbed after oral administration. The onset of action for pain relief is 30 minutes and the time for peak effect for fever is 2 to 4 hours. The half-life of ibuprofen is about 2 hours. More than 90 % of an ingested dose is excreted in the urine as metabolites or their conjugates.

Ibuprofen inhibits platelets aggregation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Ludipress® (contains lactose, Kollidon® 30 (povidone), Kollidon® CL (crospovidone))

Magnesium stearate

Microcrystalline cellulose

Starch

Coating

Wax formula

Carnauba wax, Chloroform, White beeswax

Opalux pink colour

Mastercoat pink DSP0091 (FD&C Red No. 40 Al. Lake, Eurolake Erythrodine, Titanium Dioxide)

Sucrose

White smoothing cream

Calcium carbonate, Gum acacia powder, Sucrose, Talc, purified Titanium dioxide

Sealing solution

Ethanol 96,4 % (*v/v*), Opadry® OY-28-0200 (polyvinyl acetate phthalate, stearic acid), Talc

Gelatin

Gelatin, Sucrose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

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

Protect from light.

6.5 Nature and contents of container

1 000 tablets in amber PVC bottles.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACORP (PTY) LTD

29 Victoria Link

Route 21 Corporate Park

Irene, 0178, RSA

8. REGISTRATION NUMBER(S)

Z/3.1/377

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 April 2012

10. DATE OF REVISION OF THE TEXT

30 September 2023