

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **IBUMEX 200MG TABLETS**

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<b>1. Name of the medicinal product</b>
<b>a) Proprietary name of a medicine</b>
Ibumex 200mg Tablets
<b>b) Approved generic name(s)</b>
Ibuprofen BP
<b>2 Qualitative and quantitative composition</b>
Ibuprofen 200mg
<b>3 Pharmaceutical form Dosage form</b>
Tablet
<b>4 Clinical particulars</b>
<b>4.1 Therapeutic indication(s)</b>
<p>Ibuprofen is a non-steroidal anti-inflammatory drug with analgesic, anti-inflammatory and antipyretic actions. Ibuprofen tablets are used for the relief of pain associated with low backache, tendinitis and frozen shoulder. It can also be used in soft tissue injuries like sprains and strains. The analgesic effect of ibuprofen makes it of use to relieve pain associated with mild to moderate toothache and headache.</p>
<b>4.2 Posology and method of administration</b>
<p>The treatment should start with the lowest dose anticipated to be effective, which can subsequently be adjusted, depending on the therapeutic response and any undesirable effects. In long-term treatment a low maintenance dose should be the aim</p> <p>Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptom</p> <p>Method of administration</p> <p>For oral use.</p> <p>It is recommended that patients with sensitive stomachs take ibuprofen tablet with food. If taken shortly after eating, the onset of action of ibuprofen tablet may be delayed. To be taken preferably with or after food, with plenty of fluid. Ibuprofen tablets should be swallowed whole and not chewed, broken, crushed or sucked on to avoid oral discomfort and throat irritation.</p>
<b>4.3 Contra-indications</b>
<p>Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.</p> <p>Active gastric or duodenal ulcer or a history of recurrent gastrointestinal ulcer/bleeding (two or more clear episodes of demonstrable ulceration or bleeding).</p> <p>Severe hepatic failure.</p> <p>Severe heart failure (NYHA Class IV) or coronary heart disease.</p> <p>Severe renal failure (glomerular filtration below 30 mL/min).</p> <p>Conditions involving an increased tendency to bleeding.</p> <p>Gastrointestinal bleeding or perforation in connection with previous treatment with NSAIDs.</p>

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The third trimester of pregnancy (see section 4.6).

Because of cross-reactions, ibuprofen should not be given to patients who have developed hypersensitivity reactions, including symptoms of asthma, rhinitis or urticaria after taking acetylsalicylic acid or other NSAIDs.

In patients with cerebrovascular or other acute bleeding

Hematologic diseases (e.g. hemorrhagic diathesis, hematopoietic disorder)

In patients with severe dehydration (caused by vomiting, diarrhoea or insufficient fluid intake),

Colitis ulcerosa

#### **4.4 Special warnings and precautions for use**

##### General precautions

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

As with other NSAIDs, ibuprofen may mask the signs of infection.

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

Ibuprofen tablets contain lactose monohydrate and should not be given to patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. 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 headache medications.

##### Cardiovascular effects

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate heart failure as fluid retention and oedema have been reported in association with NSAID therapy. NSAIDs might decrease the effect of diuretics and other antihypertensive agents (see section 4.5).

Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/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.  $\leq$  1200 mg/day) 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.

##### Gastrointestinal bleeding, ulceration and perforation

There is a strong link between the dose and severe gastrointestinal bleeding. The concomitant administration of ibuprofen and other NSAIDs, including selective cyclooxygenase-2 (COX-2) inhibitors should be avoided.

Elderly patients are at greater risk of experiencing undesirable effects when treated with an NSAID, especially gastrointestinal bleeding and perforation, which may be fatal.

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Potentially fatal gastrointestinal bleeding, ulceration and perforation have been reported in connection with treatment with all types of NSAID and have occurred at any time during treatment, with or without warning symptoms or previous episodes of severe gastrointestinal events.

The risk of gastrointestinal bleeding, ulceration or perforation is higher at increased doses of NSAIDs in patients with a history of ulcer, especially if complicated with bleeding or perforation (see section 4.3), and in the elderly. Patients with the above-mentioned risk factors should commence treatment at the lowest possible dose.

Treatment with mucosa-protective drugs (e.g. misoprostol or proton pump inhibitors) should be considered for these patients as well as for patients on low doses of an acetylsalicylic acid or other drugs that may increase the risk of undesirable gastrointestinal effects

#### 4.5 Interactions

The following combinations with Ibuprofen should be avoided:

*The dicumarol group:* NSAIDs may increase the effect of anticoagulants such as warfarin. Experimental studies show that ibuprofen reinforces the effects of warfarin on bleeding time. NSAIDs and the dicumarol group are metabolised by the same enzyme, CYP2C9.

*Anti-platelet agent:* NSAIDs should not be combined with antiplatelet agents such as ticlopidine due to the additive inhibition of the platelet function (see below).

*Methotrexate:* NSAIDs inhibit the tubular secretion of methotrexate and some metabolic interaction with reduced clearance of methotrexate may also occur as a result. Accordingly, in high-dose treatment with methotrexate one should always avoid prescribing NSAIDs (see below).

*Acetylsalicylic acid:* Concomitant administration of ibuprofen and acetylsalicylic acid 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 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 acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

*Cardiac glycosides:* NSAIDs can exacerbate heart failure, reduce glomerular filtration and increase plasma cardiac glycoside (e.g. digoxin) levels.

*Mifepristone:* A decrease in the efficacy of the medicinal product can theoretically occur due to the antiprostaglandin properties of non-steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid. Limited evidence suggests that co-administration 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 medical termination of pregnancy

*Sulfonylureas:* NSAIDs may potentiate the effects of sulfonylurea medications. There are rare reports of hypoglycaemia in patients on sulfonylurea medications receiving ibuprofen.

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

The following combinations with Ibuprofen may require dose adjustment:

*Antihypertensives:* NSAIDs can reduce the effect of diuretics and other antihypertensive agents.

*Aminoglycosides:* NSAIDs may reduce the excretion of aminoglycosides. *Children:* Care should be taken during concomitant treatment with ibuprofen and aminoglycosides.

*Lithium:* Ibuprofen reduces the renal clearance of lithium, as a result of which serum lithium levels may rise. The combination should be avoided unless frequent checks of serum lithium can be

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carried out and a possible reduction in the dose of lithium made.

*ACE inhibitors and angiotensin-II antagonists:*

There is an increased risk of acute renal failure, usually reversible, in patients with renal impairment (e.g. dehydrated and/or elderly patients) when treatment with ACE inhibitors or angiotensin-II antagonists is given at the same time as NSAIDs, including selective cyclooxygenase-2 inhibitors. The combination should, therefore, be given with care to patients with renal impairment, especially elderly patients. Patients should be adequately hydrated and a check of renal function should be considered after the initiation of combination treatment and at regular intervals during treatment (see section 4.4).

*Beta-blockers:* NSAIDs counteract the antihypertensive effect of beta-adrenoceptor blocking drugs.

*Selective serotonin re-uptake inhibitors (SSRIs):*

SSRIs and NSAIDs each entail an increased risk of bleeding, e.g. from the gastrointestinal tract. This risk is increased by combination therapy. The mechanism may possibly be linked to reduced uptake of serotonin in the platelets (see section 4.4).

*Cyclosporine:* The concomitant administration of NSAIDs and cyclosporine is thought to be capable of increasing the risk of nephrotoxicity due to decreased synthesis of prostacyclin in the kidney. Accordingly, in the event of combination treatment, renal function must be monitored closely.

*Captopril:* Experimental studies indicate that ibuprofen counteracts the effect of captopril on sodium excretion.

*Colestyramine:* The concomitant administration of ibuprofen and colestyramine retards and reduces (by 25%) the absorption of ibuprofen. These drugs should be given at an interval of at least 2 hours.

*Thiazides, thiazide-related preparations and loop diuretics:* NSAIDs can counteract the diuretic effect of furosemide and bumetanide, possibly through inhibition of prostaglandin synthesis. They can also counteract the antihypertensive effect of thiazides.

#### 4.6 Pregnancy and lactation

##### *Pregnancy*

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 gastroschisis after the use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk of cardiovascular malformation was increased from less than 1% up to approximately 1.5%. 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/foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, has also been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimesters of pregnancy, ibuprofen should not be given unless clearly necessary. If ibuprofen is used by a woman attempting to conceive or during the first and second trimester, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester, all prostaglandin synthesis inhibitors may expose the foetus to:

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

The mother and the neonate, at the end of pregnancy, to:

- Prolongation of bleeding time,
- Inhibition of uterine contractions, resulting in delayed or prolonged labour.

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Consequently ibuprofen is contraindicated during the last trimester of pregnancy.

**Breast-feeding**

Ibuprofen is excreted in breast milk, but with therapeutic doses during short term treatment the risk for influence on infant seems unlikely. If, however, longer treatment is prescribed, early weaning should be considered.

**Fertility**

The use of ibuprofen may impair 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 ibuprofen should be considered.

**4.7 Effects on the ability to drive and operate machinery**

Following treatment with ibuprofen, the reaction time of certain patients may be affected. This should be taken into account where increased vigilance is required. Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

**4.8 Undesirable effects**

The undesirable effects are mainly associated with the pharmacological effect of ibuprofen on prostaglandin synthesis. The most common effects are dyspepsia and diarrhoea, which are estimated to occur in about 10–30% of treated patients.

System organ class	Frequency	Adverse reaction
Infections and infestations	Uncommon	Rhinitis
	Rare	Aseptic meningitis
Blood and lymphatic system disorders	Uncommon	Leukopenia, thrombocytopenia, agranulocytosis, neutropenia, aplastic anaemia and haemolytic anaemia
Immune system disorders	Rare	Anaphylactic reaction
Psychiatric disorders	Uncommon	Insomnia, anxiety
	Rare	Depression, confusional state
Nervous system disorders	Common	Headache, dizziness
	Uncommon	Paraesthesia, somnolence
	Rare	Optic neuritis
Eye disorders	Uncommon	Visual impairment
	Rare	Toxic optic neuropathy
Ear and labyrinth disorders	Uncommon	Hearing impaired
	Rare	Tinnitus, vertigo
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, 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, abnormal hepatic function
	Rare	Liver injury
	Very rare	Hepatic failure
Skin and subcutaneous tissue disorders	Common	Rash

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	Uncommon	Urticaria, pruritus, 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)
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)

#### 4.9 Overdose

##### *Toxicity*

Risk of symptoms at doses >80–100 mg/kg. At doses >200 mg/kg there is a risk of severe symptoms, though with considerable variations between individuals. A dose of 560 mg/kg in a child aged 15 months gave severe intoxication, 3.2 g in a 6-year-old mild to moderate intoxication, 2.8–4 g in a 1½-year-old and 6 g in a 6-year-old severe intoxication even after gastric lavage, 8 g in an adult moderate intoxication and >20 g in an adult very severe intoxication. 8 g administered to a 16-year-old affected the kidney and 12 g in combination with alcohol administered to a teenager resulted in acute tubular necrosis.

##### *Symptoms*

Most patients who have ingested significant amounts of ibuprofen will manifest symptoms within 4 to 6 hours.

The predominant symptoms of overdose are ones from the gastrointestinal tract, e.g. nausea, abdominal pain and vomiting (possibly blood-streaked). Central nervous system effects include headache, tinnitus, confusion and nystagmus. At high doses loss of consciousness and convulsions (mainly in children) may occur. Cardiovascular toxicity, including bradycardia, tachycardia and hypotension have been reported. Hypernatraemia, kidney effects and haematuria may occur. In serious poisoning metabolic acidosis may occur. In significant overdose, renal failure and liver damage are possible. Hypothermia and ARDS have occasionally been reported.

##### *Treatment*

Management should be symptomatic and supportive 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.

### 5 Pharmacological properties

#### 5.1 Pharmacodynamic properties

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

ATC code: M01AE01

##### *Mechanism of action*

Ibuprofen belongs to the group of non-steroidal anti-inflammatory drugs (NSAIDs). It contains the propionic acid derivative p-isobutyl-hydrothropic acid. Ibuprofen has anti-inflammatory, analgesic and antipyretic effects. The anti-phlogistic effect is comparable with that of acetylsalicylic acid and indometacin. The pharmacological effect of ibuprofen is probably associated with its ability to inhibit prostaglandin synthesis. Ibuprofen prolongs bleeding time through reversible inhibition of platelet aggregation.

##### *Clinical efficacy and safety*

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that when single doses of ibuprofen 400 mg were taken within 8 h

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before or within 30 min after immediate release acetylsalicylic acid dosing (81 mg), a decreased effect of acetylsalicylic acid 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 cardio protective 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).

Ibuprofen inhibits renal prostaglandin synthesis. In patients with normal renal function this effect is of no particular significance. In patients with chronic renal insufficiency, decompensated heart or liver insufficiency as well as conditions involving changes in plasma volume, the inhibited prostaglandin synthesis can lead to acute renal insufficiency, fluid retention and heart failure (see section 4.3).

## 5.2 Pharmacokinetic properties

### *Absorption*

Ibuprofen is rapidly absorbed from the gastrointestinal tract with a bioavailability of 80-90%. Peak serum concentrations occur one to two hours after administration. If administered with food, peak serum concentrations are lower and achieved more slowly than when taken on an empty stomach. Food does not affect markedly total bioavailability.

### *Distribution*

Ibuprofen is extensively bound to plasma proteins (99%). Ibuprofen has a small volume of distribution being about 0.12-0.2 L/kg in adults.

### *Biotransformation*

Ibuprofen is rapidly metabolized in the liver through cytochrome P450, preferentially CYP2C9, to two primary inactive metabolites, 2-hydroxyibuprofen and 3-carboxyibuprofen. Following oral ingestion of the drug, slightly less than 90% of an oral dose of ibuprofen can be accounted for in the urine as oxidative metabolites and their glucuronic conjugates. Very little ibuprofen is excreted unchanged in the urine.

### *Elimination*

Excretion by the kidney is both rapid and complete. The elimination half-life is approximately 2 hours. The excretion of ibuprofen is virtually complete 24 hours after the last dose.

### *Special populations*

#### *Elderly*

Given that no renal impairment exists, there are only small, clinically insignificant differences in the pharmacokinetic profile and urinary excretion between young and elderly.

#### *Children*

The systemic exposure of ibuprofen following weight adjusted therapeutic dosage (5mg/kg to 10 mg/kg bodyweight) in children aged 1 year or over, appears similar to that in adults.

Children 3 months to 2.5 years appeared to have a higher volume of distribution (L/kg) and clearance (L/kg/h) of ibuprofen than did children >2.5 to 12 years of age.

#### *Renal impairment*

For patients with mild renal impairment increased unbound (S)-ibuprofen, higher AUC values for (S)-ibuprofen and increased enantiomer AUC (S/R) ratios as compared with healthy controls have been reported.

In end-stage renal disease patients receiving dialysis the mean free fraction of ibuprofen was about 3% compared with about 1% in healthy volunteers. Severe impairment of renal function may result in accumulation of ibuprofen metabolites. The significance of this effect is unknown. The metabolites can be removed by haemodialysis (see sections 4.2, 4.3 and 4.4).

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### *Hepatic impairment*

Alcoholic liver disease with mild to moderate hepatic impairment did not result in substantially altered pharmacokinetic parameters.

In cirrhotic patients with moderate hepatic impairment (Child Pugh's score 6-10) treated with racemic ibuprofen an average 2-fold prolongation of the half-life was observed and the enantiomer AUC ratio (S/R) was significantly lower compared to healthy controls suggesting an impairment of metabolic inversion of (R)-ibuprofen to the active (S)-enantiomer (see sections 4.2, 4.3 and 4.4).

### **5.3 Preclinical safety data**

There are no preclinical data of relevance for the safety assessment, apart from what has already been taken into account in this summary of product characteristics.

## **6 Pharmaceutical particulars**

### **6.1 List of excipients:**

Starch  
Povidone  
Sodium Benzoate  
Potassium Sorbate  
Purified Water  
Magnesium Stearate

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### **6.2 Incompatibilities - None known.**

### **6.3 Shelf-life -**

- **In the original unopened container; 48 months**
- **After reconstitution (where appropriate) NA**
- **Shelf-life after first opening: Not applicable**

### **6.4 Special precautions for storage:**

Ibumex should be stored below 25°C, in a dry and dark place.

Keep out of the reach of children

### **6.5 Nature and composition of containers**

Pack Size: 10x10, 100x10 and 1000s; Aluminium Foil ,Ibumex Suspension/Tablet Leaflets, Ibumex Tablet unit cartons,

### **6.6 Instruction for use/handling**

For internal use only

#### **Restriction on sale / distribution:**

Prescription only medicine (POM)

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**7 Administrative data**

**i. Name and address of holder of a registration.**

**Regal Pharmaceuticals Limited**

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**8. Registration number. – H88/171**

**ii. Date of first registration- 23/09/1988**

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