1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC) In English

Name of the medicine

MARCPROFEN (Ibuprofen Tablets 400 MG)

Qualitative / quantitative composition of the active substance (s) (in the form of a table)

Each Film coated Tablet contains

Ibuprofen BP…….. 400 MG

Excipients …….Q.S.

Colour: Erythrosine

List of excipients

Croscarmellose sodium

Starch

MCC p-[ph102]

Colloidal silicon dioxide

Purified talc

Magnesium stearate

Erythrosine

Pharmaceutical form and its contents by weight, volume or number of units Oral Dosage Form

Film coated Tablets

Shelf life / storage conditions

36 months

Store at controlled room temperature 20°C to 25°C

Therapeutic indications

Symptomatic treatment of pain and inflammation in rheumatoid arthritis (including systemic Juvenile Idiopathic Arthritis [sJIA]), osteoarthritis, seronegative arthropathies and in painful swelling and inflammation after soft tissue injuries.

Posology and method of administration

Posology

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.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

Adults and adolescents (12 years and older, >40kg):

Rheumatic diseases

One 400 MG tablet three times daily, an interval of at least 4-6 hours should be allowed between doses. Some patients can be maintained on 600-1200mg daily. In severe or acute conditions, it can be advantageous to increase the dosage until the acute phase is brought under control, provided that the total daily dose does not exceed 2400mg in divided doses. This tablet cannot be halved and in some instances a different strength or formulation of ibuprofen must be used.

Juvenile Rheumatoid Arthritis

Adolescents over 12 years of age (>40 kg): The recommended dose is 20-30mg/kg body weight daily in 3 to 4 divided doses up to a maximum of 40 mg/kg body weight daily in severe cases. Ibuprofen 600mg tablet is not suitable for children and adolescents younger than 12 years of age as correct dosing is not possible.

Elderly

The elderly are at increased risk of serious consequences of adverse reactions. If an NSAID 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 NSAID therapy. If renal or hepatic function is impaired, dosage should be assessed individually.

Renal impairment

Caution should be taken with ibuprofen dosage in patients with renal impairment. The dosage should be assessed individually. The dose should be kept as low as possible and renal function should be monitored.

Hepatic impairment

Caution should be taken with dosage in patients with hepatic impairment. The dosage should be assessed individually and the dose should be kept as low as possible

Method of administration

For oral use

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.

Contraindications

Hypersensitivity to the active substance or to any of the excipients

Active gastric or duodenal ulcer or a history of recurrent gastrointestinal ulcer/bleeding (two or more clear episodes of demonstrable ulceration or bleeding)

Severe hepatic failure

Severe heart failure (NYHA Class IV) or coronary heart disease

Severe renal failure (glomerular filtration below 30 ml/min)

Conditions involving an increased tendency to bleeding

Gastrointestinal bleeding or perforation in connection with previous treatment with NSAIDs

The third trimester of pregnancy

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, hematopoetic disorder)

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

The 400 MG tablets are contraindicated in children aged less than 12 years.

Drug 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 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.

***Tacrolimus*:** Concomitant administration of NSAIDs and tacrolimus 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 should be monitored closely.

***Methotrexate*:** The risk of a potential interaction between an NSAID and methotrexate should also be taken into account in connection with low-dose treatment with methotrexate, especially in patients with renal impairment. Whenever combination treatment is given, renal function should be monitored. Caution should be exercised if both an NSAID and methotrexate are given within 24 hours, as the plasma levels of methotrexate can increase, resulting in increased toxicity (see above).

Corticosteroids: Concomitant treatment gives rise to an increased risk of gastrointestinal ulceration or bleeding.

Antiplatelet drugs: Increased risk of gastrointestinal bleeding (see above).

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.

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).

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.

Ritonavir: It is a possible increase in the concentration of NSAIDs.

Probenecid: It slows the excretion of NSAIDs, with possible increase of their plasma concentrations.

Pemetrexed: An interaction with pemetrexed as there is an increased risk of its toxicity by decreased renal clearance. In patients with an impaired renal function displaying a creatinine clearance between 45-80 ml/min, this combination is to be avoided. In patients with normal renal function, a precaution for use is sufficient based on laboratory tests of the renal function.

Interaction studies have only been performed on adults.

Use in 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.

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.

Effects on ability to drive and use machines

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.

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.

Adverse events at least possibly related to ibuprofen are displayed by MedDRA frequency convention and system organ class database. The following frequency groupings are used: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon

(≥1/1000 to <1/100), Rare (≥1/10000 to <1/1000), Very rare (<1/10,000) and Not known (cannot be estimated from the available data).

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
	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)
Renal and urinary disorders	Uncommon	Nephrotoxity in various forms e.g. tubulointerstitial nephritis, nephrotic syndrome and renal failure
General disorders and administration site conditions	Common	Fatigue
	Rare	Oedema
Cardiac disorders	Not known	Cardiac failure, myocardial infarction (also see section 4.4)
Vascular disorders	Not known	Hypertension

Cardiac disorders and vascular disorders: Oedema, hypertension and heart failure have been reported in association with NSAID treatment. 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 such as myocardial infarction or stroke (see section 4.4).

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).

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).

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 (e.g. development of necrotising fasciitis) 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").

Ibuprofen can cause prolongation of bleeding time through reversible inhibition of platelet aggregation.

Deterioration of ulcerative colitis and Crohn's disease have been reported in connection with NSAID treatment.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard

Overdose, symptoms, emergency measures and antidotes

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.

In the event of gastrointestinal problems, administer antacids. In the event of hypotension, intravenous fluid and, if required, inotropic support. Ensure adequate diuresis. Correct acid-base and electrolyte disorders.

Patients should be observed for at least four hours after ingestion of potentially toxic amounts.

Pharmacological Properties

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 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 cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 4.5).

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).

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 enantiomeric 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).

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 enantiomeric 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).

Pre-clinical Safety:

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.

Marketing Authorization Holder

MARC-OLIVIA HEALTHCARE LIMITED

Address:
Marcolivia House
143/145, Broad Street,
By Apogbon Bridge, Lagos.

Name of the manufacturer of the finished product

KESAR PHARMA (P) LIMITED

Address:
Plot Survey No.50-P/2,
At Village, Bileshwarpura,
Po Chhatral-382729.
Tal.Kalol,
Dist. Gandhinagar INDIA

Date of text revision

11/10/2022