Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Brupro Max 400mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400 mg of ibuprofen.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film–coated tablet.

White, oblong, biconvex film-coated tablets with a score notch on both sides (length approx. 16.1mm, width approx. 7.1mm) The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the management of muscular pain, backache, dental pain and dysmenorrhoea.

4.2 Posology and method of administration

The lowest effective dose should be used for the shortest duration necessary to control symptoms (*see section 4.4*).

Adults and children over the age of 12 years only: The usual dose is 400mg and subsequently if necessary 400mg every 4-6 hours with a maximum of 1200mg in a 24 hour period.

Children under the age of 12 years: Not recommended.

Elderly: No specific dosage modifications are required for elderly patients, unless renal or hepatic function is impaired, in which case, dosage should be assessed individually.

NSAIDs (Nonsteroidal anti-inflammatories) should be used with particular caution in elderly patients who are more prone to adverse events. The lowest dose compatible with adequate safe clinical control should be employed. (*See section 4.4, special warnings and special precautions for use*). Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs.

Take ibuprofen tablets with a glass of water. Ibuprofen tablets should be swallowed whole and not chewed, broken, crushed or sucked on to avoid oral discomfort and throat irritation.

For oral administration. To be taken preferably with or after food.

4.3 Contraindications

Ibuprofen is contraindicated in patients with known hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Ibuprofen is contraindicated in patients with a history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy. Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

Ibuprofen is contraindicated in patients with severe heart failure (NYHA Class IV).

Ibuprofen is contraindicated in patients with severe liver failure.

Ibuprofen is contraindicated in patients with severe renal failure (glomerular filtration below 30ml/min).

Ibuprofen should not be given to patients with conditions involving an increased tendency to bleeding.

Ibuprofen should not be used in patients with known hypersensitivity or who have experienced asthma, urticaria, or allergic-type reactions after taking ibuprofen, aspirin or other NSAIDs.

Ibuprofen is contraindicated during the third trimester of pregnancy (see section 4.6).

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 GI and cardiovascular risks below). Patients treated with NSAIDs long term should undergo regular medical supervision to monitor for adverse events.

Caution is required if ibuprofen is administered to patients suffering from, or with a previous history of, bronchial asthma since ibuprofen has been reported to cause bronchospasm in such patients.

Caution is required in patients with renal, hepatic or cardiac impairment since the use of NSAIDs may result in deterioration of renal function. The dose should be kept as low as possible and assessment of renal function should occur prior to the initiation of therapy and regularly thereafter.

Caution is required in patients with a history of heart failure and/or hypertension as fluid retention and oedema has been reported in association with NSAID therapy.

The use of ibuprofen may impair female 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.

Elderly: the elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (*see section 4.2*).

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

The use of ibuprofen with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided due to the potential for additive effects.

Gastrointestinal bleeding, ulceration and perforation:

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events.
The risk of GI bleeding, ulceration or perforation is higher with increasing 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. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin or other drugs likely to increase gastrointestinal risk (*See below and section 4.5*).

The concomitant administration of ibuprofen and other NSAIDs, including cyclooxygenase-2 (Cox-2) selective inhibitors, should be avoided due to the increased risk of ulceration or bleeding (see below and section 4.5).

Patients with a history of GI disease, particularly when 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 ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or antiplatelet agents such as aspirin (See section *4.5*).

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

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated (*See section 4.8*).

Cardiovascular and cerebrovascular effects

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

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). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤ 1200mg day) is associated with an increased risk of myocardial infarction.

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 (2400mg/day) should be avoided.

Careful consideration should also be exercised before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking), particularly if high doses of ibuprofen (2400mg/day) are required.
Cases of Kounis syndrome have been reported in patients treated with Brupro Max. Kounis syndrome has been defined as cardiovascular symptoms secondary to an allergic or hypersensitive reaction associated with constriction of coronary arteries and potentially leading to myocardial infarction.

Renal Effects

Caution should be used when initiating treatment with ibuprofen in patients with considerable dehydration.

As with other NSAIDs, long-term administration of ibuprofen has resulted in renal papillary necrosis and other renal pathological changes. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependant reduction in prostaglandins formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those who are taking diuretics and ACE inhibitors and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state.

Haematological Effects

As NSAIDs can interfere with platelet function and may prolong bleeding time, ibuprofen should be used with caution in patients with intercranial haemorrhage and bleeding diathesis.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs), including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome), and acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with the use of ibuprofen (see section 4.8). Most of these reactions occurred within the first month. If signs and symptoms suggestive of these reactions appearIbuprofen should bewithdrawn immediately and an alternative treatment considered (as appropriate).

Exceptionally, varicella can be at the origin of serious cutaneous and soft tissue infectious complications. To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of Brupro Max in case of varicella.
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Masking of symptoms of underlying infections

Brupro Max 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 Brupro Max is administered for fever or pain relief in relation to infection, monitoring of infection is advised. In nonhospital settings, the patient should consult a doctor if symptoms persist or worsen.

Aseptic Meningitis

Aseptic meningitis has been observed on rare occasions in patients with ibuprofen therapy. Although it is probably more unlikely to occur in patients with systematic lupus erythematosus and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease.

Brupro Max contains 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 medicinal products and other forms of interaction

It is considered unsafe to take NSAIDs in combination with warfarin or heparin unless under direct medical supervision.

Care should be taken in patients treated with any of the following drugs as interactions have been reported:

Antihypertensives, beta-blockers and diuretics: NSAIDs may reduce the effect of antihypertensives, such as ACE inhibitors, beta-blockers and diuretics.

Diuretics can also increase the risk of nephrotoxicity of NSAIDs.

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

Lithium: NSAIDs may decrease elimination of lithium.

Methotrexate: NSAIDs may inhibit the tubular secretion of methotrexate and reduce clearance of methotrexate.

Cyclosporin: increased risk of nephrotoxicity with NSAIDs.

Other analgesics including cyclooxygenase-2 selective inhibitors:avoid concomitant use of two or more NSAIDs, (including aspirin) as this may increase the risk of adverse effects (see section 4.4).

Corticosteroids: increased risk of gastrointestinal ulceration or bleeding with NSAIDs (*see section 4.4*).

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

Acetylsalicylic acid: Concomitant administration of ibuprofen and acetylsalicylic 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 use (see section 5.1).

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding with NSAIDs (*see section 4.4, Special warnings and precautions for use*).

Aminoglycosides: NSAIDs may decrease the excretion of aminoglycosides.
Cholestyramine: The concomitant administration of ibuprofen and cholestyramine may reduce the absorption of ibuprofen in the gastrointestinal tract. However, the clinical significance is unknown.

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

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

Probenecid: there have been no reports of interactions between probenacid and ibuprofen. However, probenacid produces a reduction in metabolism and elimination of some NSAIDs and metabolites.

Oral hypoglycaemic agents: inhibition of metabolism of sulfonylurea drugs, prolonged half-life and increased risk of hypoglycaemia.

Mifepristone: A decrease in the efficacy of the medicinal product can theoretically occur due to the antiprostaglandin properties of NSAIDs. Limited evidence suggests that coadministration of NSAIDs on the day of prostaglandin administration does not adversely influence the effects of mifepristone or the prostaglandin on cervical ripening or uterine contractility.

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

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

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.

Ginkgo biloba may potentiate the risk of bleeding with NSAIDs.

4.6 Fertility, pregnancy and lactation

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. 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, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. From the 20th week of pregnancy onward, Brupro Max use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore during the first and second trimester of pregnancy, ibuprofen should not be given unless clearly necessary. If ibuprofen is used by a woman attempting to conceive, or during the first or second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to Brupro Max for several days from gestational week 20 onward. Brupro Max should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

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

- Cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension)
- Renal dysfunction (see above);

At the end of pregnancy, prostaglandin synthesis inhibitors may expose the mother and the neonate to the following:

- Possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
- Inhibition of uterine contractions, which may result in delayed or prolonged labour.

Consequently, ibuprofen is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Labour and delivery: Administration of ibuprofen is not recommended during labour and delivery. The onset of labour may be delayed and the duration increased with a greater bleeding tendency in both mother and child.

In the limited studies to date, ibuprofen appears in breast milk in very low concentrations, brupro is not recommended for use in nursing mothers.

Female Fertility: The use of ibuprofen may impair female 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 ability to drive and use machines

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

Immune system disorders: Hypersensitivity reactions have been reported following treatment with ibuprofen. These may consist of (a) nonspecific 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, bullous dermatoses (including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme).

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, exacerbation of colitis and Crohn's disease (*See section 4.4,)* have been reported following administration. Less frequently, gastritis has been observed. Pancreatitis has been reported very rarely.

Cardiac disorders and vascular disorders: Kounis syndrome (frequency *Not Known),* 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,*).

Other adverse events reported include

Infections and infestations: rhinitis and meningitis aseptic.

Blood and lymphatic system disorders: leukopenia, thrombocytopenia, neutropenia, agranulocytosis, aplastic anemia and haemolytic anaemia.

Psychiatric disorders: insomnia, anxiety, depression, confusional state, hallucinations Nervous system disorders: headaches, paraesthesia, dizziness, somnolence
Eye disorders: visual impairment, optic neuritis, toxic optic neuropathy Ear and labyrinth disorders: hearing impaired, vertigo, tinnitus
Hepatobiliary disorders: abnormal hepatic function, hepatic failure, hepatitis, jaundice

Skin and subcutaneous tissue disorders**:** severe cutaneous adverse reactions (SCARs), (including erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis) bullous reactions including Steven's Johnson syndrome toxic epidermal necrolysis (very rare), drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) (frequency not known), acute generalised exanthematous pustulosis (AGEP) (frequency not known), photosensitivity reaction (frequency unknown

General disorders and administration site conditions: malaise, fatigue.

Renal and urinary disorders: impaired renal function, toxic nephropathy in various forms, including interstitial nephritis, nephrotic syndrome and renal failure.

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 HPRA Pharmacovigilance, Website: www.hpra.ie

4.9 Overdose

Toxicity:
Signs and symptoms of toxicity have generally not been observed at doses below 100 mg/kg in children or adults. However, supportive care may be needed in some cases. Children have been observed to manifest signs and symptoms of toxicity after ingestion of 400 mg/kg or greater.

Symptoms:
Most patients who have ingested significant amounts of ibuprofen will manifest symptoms within 4 to 6 hours. The most frequently reported symptoms of overdose include nausea, vomiting, abdominal pain, lethargy and drowsiness. Central nervous system (CNS) effects include headache, tinnitus, dizziness, convulsion, and loss of consciousness. Nystagmus, metabolic acidosis, hypothermia, renal effects, gastrointestinal bleeding, coma, apnea and depression of the CNS and respiratory system have also been rarely reported. Cardiovascular toxicity, including hypotension, bradycardia and tachycardia, has been reported. In cases of significant overdose, renal failure and liver damage are possible. In serious poisoning metabolic acidosis may occur. Large overdoses are generally well tolerated when no other drugs are being taken.

Treatment:
There is no specific antidote for ibuprofen overdose. Gastric emptying followed by supportive measures is recommended if the quantity ingested exceeds 400 mg/kg within the previous hour. For the most current information, contact the local poison control center.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: M01AE01, ATC code: propionic acid derivatives

Ibuprofen is a phenylpropionic acid derivative with analgesic, anti-inflammatory and antipyretic activity. The drug's therapeutic effects as a NSAID are thought to result from its inhibitory effect on the enzyme cyclo-oxygenase, which results in a marked reduction in prostaglandin synthesis.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Some pharmacodynamics studies show that when single doses of ibuprofen 400mg were taken within 8 h before or within 30 min after immediate release acetylsalicylic acid dosing (81mg), 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).

5.2 Pharmacokinetic properties

Ibuprofen is rapidly absorbed after oral administration, is strongly plasma protein bound, and is excreted mainly in the urine as metabolites. The drug has a plasma half-life of 2 hours.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica
Croscarmellose sodium
Microcrystalline cellulose

Magnesium stearate
Stearic acid
Maize starch

Film-coating
Hypromellose
Talc
Macrogol 400
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister pack comprising of an opaque white polyvinylchloride/polyvinylidene chloride (PVC/PVDC) laminate with aluminium foil base.

Pack size: 12 and 24 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Rowa Pharmaceuticals Limited
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0074/067/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th March 2015

Date of last renewal: 12th March 2020

10 DATE OF REVISION OF THE TEXT

July 2024