SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rupan 400mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400 mg ibuprofen.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

Pink, round, convex, scored, film-coated tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

As an anti-inflammatory, analgesic and antipyretic for short term management of mild to moderate pain, fever and inflammation such as is associated with headache, dental pain, period pain, muscular strain, neuralgia, rheumatic pain and migraine and for the management of the symptoms of head colds and influenza.

4.2. Posology and method of administration

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

The patient should consult a doctor if symptoms persist or worsen, or if the product is required for more than 3 days.

Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs.

Posology

Adults, the elderly and children over 12 years

400mg taken with water up to three times a day as required. Leave at least four hours between doses with a maximum of 1200mg in any 24 hour period. If in adolescents this medicinal product is required for more than 3 days or if symptoms worsen a doctor should be consulted.

Pediatric population
Not for use by children under 12 years of age.

Elderly
NSAIDs 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).

Method of administration
For oral administration and short term use only. Do not chew.

4.3. Contraindications

Hypersensitivity to ibuprofen, acetylsalicylic acid (Aspirin), or other NSAIDs or to any of the excipients listed in section 6.1.
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 or other gastrointestinal disorders).
Patients who have previously shown hypersensitivity (e.g. bronchospasm, asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, acetylsalicylic acid (Aspirin) or other non-steroidal anti-inflammatory drugs (NSAIDs).
Use in children under 12 years of age.
Patients with severe hepatic failure or severe renal failure (see section 4.4).
Severe heart failure (NYHA Class IV).
During the third trimester of pregnancy (see section 4.6).

4.4. Special warnings and precautions for use

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).
If symptoms persist for more than 3 days, patients should be advised to consult their doctor.

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).
Prolonged use of NSAIDs in the elderly is not recommended. Where prolonged therapy is required, patients should be reviewed regularly.

Other NSAIDs

The use of this product with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

Respiratory

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

Renal

Caution is required in patients with renal impairment since renal function may deteriorate (see section 4.3 and 4.8). The dose should be as low as possible and renal function should be monitored.
There is a risk of renal impairment in dehydrated adolescents.

Hepatic

Hepatic impairment (see section 4.8).

Gastrointestinal effects

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8).
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 GI events.
When GI bleeding or ulceration occurs in patients receiving ibuprofen, the treatment should be withdrawn.
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 4.5).
Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (see section 4.5).

Cardiovascular and cerebrovascular effects

Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with a history of hypertension and/or heart failure as fluid retention, hypertension and oedema have been reported in association with NSAID therapy.

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. ≤ 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.

Blood effects

As NSAIDs can interfere with platelet function, they should be used with caution in patients with idiopathic thrombocytopenia purpura (ITP), intracranial haemorrhage and bleeding diathesis.

Severe skin reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Acute generalised exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing products. Ibuprofen should be discontinued, at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.

Masking of symptoms of underlying infections

Ibuprofen 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 ibuprofen is

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

Exceptionally, varicella can be at the origin of serious cutaneous and soft tissue infectious complications. It advisable to avoid use of ibuprofen in cases of varicella.

SLE and mixed connective tissue disease

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

Impaired female fertility

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

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' should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

4.5. Interactions with other medicinal products and other forms of interaction

Ibuprofen should be avoided in combination with:

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).

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

Ibuprofen (like other NSAIDs) should be used with caution in combination with Anti-coagulants: NSAIDs may enhance the effects of anticoagulants, such as warfarin (see section 4.4). It is considered

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

Anti-hypertensives (ACE inhibitors and Angiotensin II Antagonists) and diuretics: NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ace inhibitor or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking ibuprofen concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Corticosteroids: as these may increase the risk of gastrointestinal ulceration or bleeding (see Section 4.4).

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

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

Aminoglycosides: reduction in renal function in susceptible individuals, decreased elimination of aminoglycoside and increased plasma concentrations.

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

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

Ciclosporin: Increased risk of nephrotoxicity.

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

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

Probenecid: reduction in metabolism and elimination of NSAID and metabolites.

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

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

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

4.6. Fertility, pregnancy and lactation

Pregnancy:

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for 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, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryfoetal 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, ibuprofen 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 and 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 ibuprofen for several days from gestational week 20 onward. Ibuprofen 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:

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

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

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

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

Breastfeeding:

In limited studies, ibuprofen and its metabolites appear in the breast milk in very low concentration (0.0008% of the maternal dose) and is unlikely to affect the breast-fed infant adversely.

Fertility

There is some evidence that medicinal products which inhibit cyclo-oxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment (see Section 4.4 regarding female fertility).

4.7. Effects on ability to drive and use machines

None expected at recommended doses and duration of therapy.

4.8. Undesirable effects

Possible side effects are those experienced with ibuprofen acid (maximum 1200mg Ibuprofen per day), in short-term use. In the treatment of chronic conditions, under long-term treatment, additional adverse events may occur.

Adverse events which have been associated with Ibuprofen are given below, tabulated by system organ class and frequency.

Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and < 1/1000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

Within each frequency grouping adverse events are presented in order of decreasing seriousness.

System Organ Class	*Frequency*	*Adverse Event*
Blood and Lymphatic System Disorders	Very rare:	Haematopoietic disorders1
Immune System Disorders	Uncommon	Hypersensitivity with urticaria and pruritus2
	Very rare	Swelling face, swollen tongue, pharyngeal oedema, dyspnoea, tachycardia, and hypotension (anaphylaxis, angioedema or severe shock)2
Nervous System Disorders	Uncommon	Headache
	Very rare	Aseptic meningitis3
Ear and Labyrinth Disorders	Not Known	Hearing Impaired
Cardiac Disorders	Not Known	Cardiac failure andoedema4
Vascular Disorders	Not Known	Hypertension4
Respiratory, Thoracic and Mediastinal Disorders	Not Known	Respiratory tract reactivity comprising asthma, bronchospasmordyspnoea2
Gastrointestinal Disorders	Uncommon	Abdominal pain, nausea and dyspepsia5
	Rare	Diarrhoea, flatulence, constipation and vomiting

	Very rare	Peptic ulcer, gastrointestinal perforation or gastrointestinal haemorrhage, melaena, and haematemesis6. Mouth ulceration and gastritis
	Not Known	Exacerbation of colitis and Crohn'sdisease7
Hepatobiliary Disorders	Very rare	Liver disorders
	Not Known	Hepatic function abnormal
Skin and Subcutaneous Tissue Disorders	Uncommon	Skin rash2
	Very rare	Bullous reactions, including Stevens-Johnson syndrome, erythema multiforme and toxic epidermal necrolysis2
	Not Known	Rash maculo-papular, erythema. Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome). Acute generalised exanthematous pustulosis (AGEP) Photosensitivity reactions
Renal and Urinary Disorders	Very rare	Acute renal failure8
Investigations	Very rare	Haemoglobin decreased
Infections and infestations	Very rare	Exacerbation of infections related inflammation (e.g. development of necrotizing fasciitis), in exceptional cases, severe skin infections and soft-tissue complication may occur during a varicella infection.

Description of Selected Adverse Reactions

1 Examples include anaemia, leucopenia, thrombocytopenia, pancytopenia and agranulocytosis. First signs are fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.

2 Hypersensitivity reactions: These may consist of (a) non-specific allergic reactions and anaphylaxis, (b) respiratory tract reactivity, including asthma, aggravated asthma, bronchospasm, and dyspnoea or (c) various skin reactions, including pruritus, urticaria, purpura, angioedema and, more rarely, exfoliative and bullous dermatoses, including toxic epidermal necrolysis, Stevens-Johnson Syndrome and erythema multiforme.

3 The pathogenic mechanism of drug-induced aseptic meningitis is not fully understood. However, the available data on NSAID-related aseptic meningitis points to a hypersensitivity reaction (due to a temporal relationship with drug intake, and disappearance of symptoms after drug discontinuation). Of note, single cases of symptoms of aseptic meningitis (such as stiff neck, headache, nausea,

vomiting, fever or disorientation) have been observed during treatment with ibuprofen in patients with existing auto-immune disorders (such as systemic lupus erythematosus and mixed connective tissue disease).

4 Clinical trial and epidemiological studies suggest that use of Ibuprofen (particularly at high doses 2400mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke), (see section 4.4).

5 The most commonly observed adverse events are gastrointestinal in nature.

6 Sometimes fatal, particularly in the elderly.

7 See Section 4.4.

8 Especially in long term use, associated with increased serum urea and oedema. Also includes papillary necrosis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions is an important way to gather more information to continuously monitor the benefit / risk balance of the medicinal product. Any suspected adverse reactions should be reported via the national reporting system.

4.9. Overdose

In adults the dose response effect is less clear cut than in children where ingestion of more than 400mg/kg may cause symptoms. The half- life in overdose is 1.5-3 hours.

Symptoms

Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, abdominal pain, or more rarely diarrhoea. Tinnitus, headache, dizziness and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, nystagmus, blurred vision, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning metabolic acidosis may occur and the prothrombin time/INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure, loss of consciousness, hypotension and liver damage may occur. Exacerbation of asthma is possible in asthmatics. A dose in excess of 200mg/kg carries a risk of causing toxicity.

Treatment

No specific antidote is available. Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal if the patient presents within one hour of ingestion of a

potentially toxic amount. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, propionic acid derivatives, ATC code: M01AE01.

Ibuprofen is a propionic acid derivative NSAID that has demonstrated its efficacy by inhibition of prostaglandin synthesis. In humans, ibuprofen reduces inflammatory pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation.

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).

5.2. Pharmacokinetic properties

Ibuprofen is rabidly absorbed following administration and is rapidly distributed throughout the whole body. The excretion is rapid and complete via the kidneys.
Maximum plasma concentrations are reached 45 minutes after ingestion if taken on an empty stomach. When taken with food, peak levels are observed after 1 to 2 hours. These times may vary with different dosage forms.
Elimination half-life is approximately 2 hours.
Following hepatic metabolism (hydroxylation, carboxylation, conjugation), the pharmacologically inactive metabolites are completely eliminated, mainly renally (90%), but also with the bile. The elimination half-life in healthy individuals and those with liver and kidney diseases is 1.8 to 3.5 hours.
Plasma-protein binding is about 99%.
No significant differences in pharmacokinetic profile are observed in the elderly.

5.3. Preclinical safety data

No relevant information, additional to that contained elsewhere in the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Microcrystalline cellulose
Sodium lauryl sulphate
Colloidal anhydrous silica
Sodium starch glycolate
Powdered cellulose
Magnesium stearate
Titanium dioxide (E171)
Purified talc
Erythrosine aluminium lake (E127)
Polyethylene glycol

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store below 30°C in the original package.

6.5. Nature and contents of container

Tablets are packed in combination blisters of polyvinylchloride film and aluminium foil and in PVC securitainers.
Blisters: packs of 10, 20, 30 or 100 tablets are available.

PVC securitainers: packs of 100, 500 and 1000 tablets are available.
Not all pack sizes may be marketed.

6.6. Special precautions for disposal

No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

MEDOCHEMIE LTD, 1-10 Constantinoupoleos street, 3011 Limassol, Cyprus

8. MARKETING AUTHORISATION NUMBER

05746/07484/REN/2020

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26/10/2016
Date of latest renewal: 09/03/2021

10. DATE OF REVISION OF THE TEXT

07/2023