For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

ZUPAR TABLETS

Ibuprofen and Paracetamol Tablets IP

Taking more than daily dose may cause serious liver damage or allergic reactions (e.g. swelling of the face, mouth and throat, difficulty in breathing, itching or rash)

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:
Ibuprofen IP 400 mg
Paracetamol IP 325 mg

PHARMACEUTICAL FORM

Uncoated Tablets.

CLINICAL PARTICULARS

Therapeutic Indications

ZUPAR Tablets are indicated for the temporary relief of mild to moderate pain associated with: rheumatoid arthritis,

- osteoarthritis,
- cervical spondylosis,
- ankylosing spondylitis,
- bursitis sciatica,
- low back pain,
- strains,
- sprains,
- sports injuries,
- dysmenorrhea,
- infective inflammation such as: tonsillitis, pharyngitis, sinusitis, etc.,
- dental conditions such as alveolar abscess, periodontitis, following dental extractions.

Posology and Method of Administration

For short term-use only.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms *(*see Section *Special Warnings and Special Precautions for Use)*. Ibuprofen/ paracetamol, 400 mg/ 325 mg, tablet should not be used with other paracetamol, ibuprofen or NSAID containing products.

Route of Administration

For oral use.

Adults

Normal recommended dosage is 1 tablet with water every 6 hours, preferably with or after meals to minimise side effects.

If the one tablet dose does not control symptoms, a maximum of two tablets may be taken up to three times a day.

Do not take more than 6 tablets in 24 hours and do not take tablets more frequently than every 6 hours. Maximum daily dose of paracetamol is 4000 mg. Do not exceed the stated dose.

The patient should consult a doctor if the symptoms persist for more than 2 days.

Children

Not for use by children under 18 years.

Elderly

No special dosage modifications are required *(*see Section *Special Warnings and Special Precautions for Use).* Non-steroidal anti-inflammatory drugs (NSAIDs) should be used with particular caution in elderly patients who are more prone to adverse events. The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used for the shortest possible duration. The patient should be monitored regularly for gastrointestinal bleeding during NSAID therapy.

Renal impairment

ZUPAR is contraindicated in patients with severe renal failure.

Hepatic impairment

ZUPAR is contraindicated in patients with severe hepatic failure. *(*see Section *Special Warnings and Special Precautions for Use).*

Contraindications

ZUPAR is contraindicated in:

- patients with a known hypersensitivity to ibuprofen, paracetamol or any excipients,
- patients with a history of hypersensitivity reactions (e.g. bronchospasm, angioedema, asthma, rhinitis, or urticaria) associated with acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs),
- patients with active, or a history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding), including that associated with NSAIDs *(*see Section *Special Warnings and Special Precautions for Use),*
- patients with defects in coagulation,
- patients with severe hepatic failure or severe renal failure
- patients with severe heart failure (NYHA Class IV) *(*see Section *Special Warnings and Special Precautions for Use),*
- concomitant use with other NSAID containing products, including cyclo-oxygenase-2 (COX-2) specific inhibitors and doses of acetylsalicylic acid above 75 mg daily – increased risk of adverse reactions *(*see Section *Interaction with Other Medicaments and Other Forms of Interaction),*
- concomitant use with other paracetamol-containing products – increased risk of serious adverse effects *(*see Section *Interaction with Other Medicaments and Other Forms of Interaction),*
- the last trimester of pregnancy due to risk of premature closure of the foetal ductus arteriosus with possible pulmonary hypertension *(*see Section *Pregnancy and Lactation).*

Special Warnings and Special Precautions for Use

Paracetamol

Risk of overdose in patients with non-cirrhotic alcoholic liver disease.

The concomitant use with other products containing paracetamol may lead to an overdose.

The hazard of paracetamol overdose is greater in patients with non-cirrhotic alcoholic liver disease. Immediate medical advice should be sought in the event of an overdose, even if the patient feels well, because of the risk of delayed, serious liver damage.

Paracetamol overdose may cause liver failure which may require liver transplant or lead to death.

Underlying liver disease increases the risk of paracetamol-related liver damage. Patients who have been diagnosed with liver or kidney impairment must seek medical advice before taking this medication.

Cases of hepatic dysfunction/failure have been reported in patients with depleted glutathione levels, such as those who are severely malnourished, anorexic, have a low body mass index or are chronic heavy users of alcohol or have sepsis.

In patients with glutathione depleted states, the use of paracetamol may increase the risk of metabolic acidosis.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see *Cardiovascular effects* and *Gastrointestinal effects* below) and by patients taking the dose with food. The concomitant use of ibuprofen with other systemic NSAIDs, including cyclooxygenase-2 selective inhibitors, should be avoided due to the potential for additive undesirable effects.

Elderly

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

Respiratory disorders
In patients suffering from, or with a history of, bronchial asthma, allergic disease or nasal polyps NSAIDs have been reported to precipitate bronchospasm.

Renal impairment

The use of non-steroidal anti-inflammatory drugs (NSAIDs) may result in deterioration of renal function.

As with other NSAIDs, long-term administration of ibuprofen has resulted in renal papillary necrosis and other renal pathologic changes.

Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and secondarily, in renal blood flow, which may precipitate overt renal decompensation.

As fluid retention and oedema have been reported in association with NSAIDs, including ibuprofen, caution is required in patients with impaired cardiac or renal function, history of hypertension, the elderly, patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and in those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery.

Monitoring of renal function is recommended as a precautionary measure when using ibuprofen in such cases.

Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state. Renal function should be monitored in these patients *(*see Section *Contraindications).*

Cardiovascular and cerebrovascular effects

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

Clinical trial and epidemiological data suggest that use of ibuprofen, particularly at high doses (2400 mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤1200mg daily) 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 be also exercised before initiating long-term treatment for 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 effects

Gastrointestinal (GI) bleeding, ulceration and perforation, which can be fatal, has been reported with all NSAIDs at anytime 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 *Contraindications)* 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 acetylsalicylic acid, or other drugs likely to increase gastrointestinal risk *(see below and* see Section *Interaction with Other Medicaments and Other Forms of Interaction).*

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 antiplatelet agents such as acetylsalicylic acid *(*see Section *Interaction with Other Medicaments and Other Forms of Interaction).*

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

NSAIDs should be given with care to patients with a history of GI disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated *(*see Section *Undesirable Effects).*

SLE and mixed connective tissue disease

In patient with systemic lupus erythematosus (SLE) and mixed connective tissue disease disorders there may be an increased risk of aseptic meningitis *(*see Section *Undesirable Effects).*

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

Dermatological effects

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs *(*see Section *Undesirable Effects).* Patients appear to be at highest risk of 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. Use of this product should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Infections

Like other NSAIDs, ibuprofen may mask the signs and symptoms of infection due to its anti-inflammatory, analgesic and anti-pyretic properties.

Impaired female fertility

There is limited evidence that drugs which inhibit cyclooxygenase/ prostaglandin synthesis may impair female fertility by an effect on ovulation and is not recommended in women attempting to conceive. This is reversible on withdrawal of treatment. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of the product should be considered *(*see Section *Pregnancy and Lactation).*

Interaction with Other Medicaments and Other Forms of Interaction

This product (like any other paracetamol containing products) is contraindicated in combination with other paracetamol containing products – increased risk of serious adverse effects *(*see Section *Contraindications).*

<u>This product (like any other paracetamol containing products) should be used with caution in combination with:</u>

Cholestyramine

The speed of absorption of paracetamol is reduced by cholestyramine. Therefore, cholestyramine should not be taken within one hour if maximal analgesia is required.

Metoclopramide and domperidone

The absorption of paracetamol is increased by metoclopramide and domperidone. However, concurrent use need not be avoided.

Warfarin

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

This product (like any other ibuprofen containing products and NSAIDs) is contraindicated in combination with:

Acetylsalicylic acid

Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects, unless low-dose acetylsalicylic acid (not above 75 mg daily) has been advised by a doctor *(*see Section *Contraindications).*

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelets 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 *Pharmacodynamic Properties).*

Other NSAIDs

Other NSAIDs including cyclo-oxygenase-2 selective inhibitors as these may increase the risk of adverse effects *(*see Section *Contraindications).*

This product (like any other ibuprofen containing products and NSAIDs) should be used with caution in combination with:

Anticoagulants

NSAIDs may enhance the effects of anticoagulants, i.e. warfarin *(*see Section *Special Warnings and Special Precautions for Use).*

Antihypertensives (ACE inhibitors and Angiotensin II Antagonists)

NSAIDs may reduce the effects of these 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 cyclooxygenase 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 cyclooxygenase inhibitors 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.

Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs)

Increased risk of gastrointestinal bleeding (see Section *Special Warnings and Special Precautions for Use).*

Aminoglycosides

Reduction in renal function in susceptible individuals, decreased elimination of aminoglycoside and increased plasma concentrations.

Cardiac glycosides

NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels. Monitoring of the serum glycoside levels is recommended.

Ciclosporin

Increased risk of nephrotoxicity.

Corticosteroids

Increased risk of gastrointestinal ulceration or bleeding *(*see Section *Special Warnings and Special Precautions for Use).*

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.

Diuretics

Reduced diuretic effect. Diuretics may increase the risk of nephrotoxicity of NSAIDs.

Oral hypoglycemic agents

Inhibition of metabolism of sulfonylurea drugs, prolonged half-life and increased risk of hypoglycaemia. In case of concomitant use with ibuprofen, monitoring of the blood glucose level is recommended.

Lithium

Decreased elimination of lithium. Monitoring of the serum lithium level is recommended.

Methotrexate

Decreased elimination of methotrexate. In case of concomitant use with ibuprofen, renal function should be monitored.

Mifepristone

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

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.

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.

Pregnancy and Lactation

Fertility

There is limited evidence that drugs which inhibit cyclooxygenase/ prostaglandin synthesis may impair female fertility by an effect on ovulation and is not recommended in women attempting to conceive. This is reversible on withdrawal of treatment.

In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of the product should be considered *(*see Section *Special Warnings and Special Precautions for Use).*

Pregnancy

The use of this product should be avoided in the first six months of pregnancy and contraindicated in the last three months of pregnancy *(*see Section *Contraindications).*

There is no experience of use of this product in humans during pregnancy.

Congenital abnormalities have been reported in association with NSAID administration in man; however these are low in frequency and do not appear to follow any discernible pattern. In view of the known affects of NSAIDs on the foetal cardiovascular system (risk of closure of ductus arteriosus with possible persistent pulmonary hypertension) and also a risk of fetal renal impairment with subsequent oligohydramnios, use in the last trimester is contraindicated.

The onset of labour may be delayed and duration increased with an increased bleeding tendency in both mother and child *(*see Section *Contraindications).* NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol use at the recommended dosage.

Lactation

It is not necessary to interrupt breastfeeding for short-term treatment with the recommended dose of this product.

Ibuprofen and its metabolites can pass in very small amounts (0.0008% of the maternal dose) into the breast milk. No harmful effects to infants are known.

Paracetamol is excreted in breast milk but not in a clinically significant amount.

Available published data do not contraindicate breastfeeding.

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.

Undesirable Effects

Clinical Trial and Post Marketing Data

Clinical trials with this product have not indicated any other undesirable effects other than those for ibuprofen or paracetamol alone.

Adverse reactions are ranked under headings of frequency using the following convention:
Very common ≥1/10
Common ≥1/100 to <1/10
Uncommon ≥1/1000 to <1/100
Rare ≥1/10000 to <1/1000
Very rare <1/10000
Not known (cannot be estimated from the available data).

Clinical studies suggest that use of ibuprofen, particularly at high doses (2400 mg daily) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).

Blood and lymphatic system disorders

Very rare: haematopoietic disorders[1].

Immune system disorders

Uncommon: hypersensitivity with urticaria and pruritus[2].
Very rare: severe hypersensitivity reactions. Symptoms can include facial, tongue and throat swelling, dyspnoea, tachycardia, hypotension (anaphylaxis, angioedema or severe shock)[2].

Psychiatric disorders

Very rare: confusion, depression, hallucinations.

Nervous system disorders

Uncommon: headache, dizziness.
Very rare: paraesthesia, optic neuritis, somnolence, aseptic meningitis[3].

Eye disorders

Very rare: visual disturbance.

Ear and labyrinth disorders

Very rare: tinnitus, vertigo.

Cardiac disorders

Very rare: oedema and cardiac failure[4].

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) *(*see Section *Special Warnings and Special Precautions for Use).*

Vascular disorders

Very rare: hypertension[4].

Respiratory, thoracic and mediastinal disorders

Very rare: respiratory reactivity including: asthma, exacerbation of asthma, bronchospasm, /dyspnoea[2].

Gastrointestinal disorders

Common: abdominal pain, diarrhoea, dyspepsia, nausea, abdominal discomfort and vomiting[5].

Uncommon: flatulence, constipation; peptic ulcer, gastrointestinal perforation or gastrointestinal haemorrhage, melaena, haematemesis[6], mouth ulceration, exacerbation of colitis, and Crohn's disease[7], gastritis, pancreatitis.

Not known: intestinal diaphragm disease

Hepatobiliary disorders

Very rare: abnormal liver function, hepatitis, jaundice[8].

Skin and subcutaneous tissue disorders

Common: hyperhidrosis.

Uncommon: various skin rashes[2].

Very rare: purpura, photosensitivity, exfoliative dermatoses, bullous reactions including erythema multiforme, Stevens Johnson Syndrome, Toxic Epidermal Necrolysis[2].

Not known: Drug reaction with eosinophilia and systemic symptoms (*DRESS syndrome)*

Renal and urinary disorders

Very rare: nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome, acute and chronic renal failure[9].

General disorders and administration site conditions

Very rare: fatigue, malaise.

Investigations

Common:	alanine aminotransferase increased, gamma-glutamyltransferase increased and liver function tests abnormal with paracetamol; blood creatinine increased, blood urea increased.
Uncommon:	aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatine phosphokinase increased, haemoglobin decreased, platelet count increased.

Description of Selected Adverse Reactions

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

[2]Very rare cases of serious skin reactions have been reported. Hypersensitivity reactions have been reported. These may consist of (a) non-specific allergic reactions and anaphylaxis, (b) respiratory tract activity, e.g. asthma, aggravated asthma, bronchospasm (in patients sensitive to aspirin and other NSAIDs) or dyspnoea, or (c) various skin reactions, including rashes of various types, 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 aseptic meningitis in patients with existing autoimmune disorders (such as systemic lupus erythematosus and mixed connective tissue disease) during treatment with ibuprofen, with symptoms such as: stiff neck, headache, nausea, vomiting, fever or disorientation have been observed (see Section *Special Warnings and Special Precautions for Use*).

[4]Clinical trial and epidemiological data 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 (for example myocardial infarction or stroke) (see Section *Special Warnings and Special Precautions for Use*).

[5]The adverse events observed most often are gastrointestinal in nature.

[6]Sometimes fatal, particularly in the elderly.

[7]see Section *Special Warnings and Special Precautions for Use*.

[8]In overdose Paracetamol can cause acute hepatic failure, hepatic failure, hepatic necrosis and liver injury (see Section *Overdose*).

[9]Especially in long-term use, associated with increased serum urea and oedema.
Also includes papillary necrosis.

Overdose

Symptoms and signs

Ibuprofen

In children ingestion of more than 400 mg/kg of ibuprofen may cause symptoms. In adults the dose response effect is less clear cut.

The half-life in overdose is 1.5 - 3 hours.

Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, 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 and liver damage may occur if there is a co-incident of dehydration. Exacerbation of asthma is possible in asthmatics.

Paracetamol

PARACETAMOL OVERDOSE MAY BE INJURIOUS TO LIVER.

Paracetamol overdose may cause liver failure which may require to liver transplant or lead to death.

Acute pancreatitis has been observed, usually with hepatic dysfunction and liver toxicity.

Liver damage is possible in adults who have taken 10 g or more of paracetamol. Ingestion of 5 g or more of paracetamol may lead to liver damage if the patient has one or more of the risk factors below:

- is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes,
- regularly consumes alcohol in excess of recommended amounts,
- is likely to be glutathione depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms of paracetamol overdose in the first 24 hours include pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion as liver function tests become abnormal. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Treatment

Ibuprofen

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 1 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.

Paracetamol

Immediate medical management is required in the event of overdose, even if symptoms of overdose are not present. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable).

Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol however; the maximum protective effect is obtained up to 8 hours post ingestion. The effectiveness of the antidote declines sharply after this time.

If required the patient should be given intravenous-N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital. Patients who present with serious hepatic dysfunction beyond 24 hours from ingestion should be managed in accordance with established guidelines.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group

Musculoskeletal system, anti-inflammatory and antirheumatic products, non-steroids, propionic acid derivatives. Ibuprofen combinations. (ATC Code: M01AE51).

Mechanism of Action and Pharmacodynamic Effects

The pharmacological actions of ibuprofen and paracetamol differ in their site and mode of action. These complementary modes of action are synergistic which results in greater antinociception and antipyresis than the single actives alone.

Ibuprofen is an NSAID that has demonstrated its efficacy in the common animal experimental inflammation models by inhibition of prostaglandin synthesis. Prostaglandins sensitise nociceptive afferent nerve terminals to mediators such as bradykinin.

Ibuprofen therefore elicits an analgesic effect through peripheral inhibition of the cycloxygenase-2 (COX-2) isoenzyme with a subsequent reduction in sensitisation of nociceptive nerve terminals. Ibuprofen has also been shown to inhibit induced-leucocyte migration into inflamed areas. Ibuprofen has a pronounced action within the spinal cord due, in part, to the inhibition of COX.

Ibuprofen's antipyretic effects are produced by the central inhibition of prostaglandins in the hypothalamus. Ibuprofen reversibly inhibits platelet aggregation. In humans, ibuprofen reduces inflammatory pain, swellings and fever.

Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelets aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400mg was taken within 8 hours before or within 30 min after immediate release acetylsalicylic acid (81mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred.

However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

Paracetamol's exact mechanism of action is still not completely defined; however there is considerable evidence to support the hypothesis of a central antinociceptive effect. Various biochemical studies point to inhibition of central COX 2 activity. Paracetamol may also stimulate the activity of descending 5-hydroxytryptamine (serotonin) pathways that inhibit nociceptive signal transmission in the spinal cord. Evidence has shown that paracetamol is a very weak inhibitor of peripheral COX-1 and 2 isoenzymes.

The clinical efficacy of ibuprofen and paracetamol has been demonstrated in pain associated with headache, toothache and dysmenorrhoea, and fever; furthermore efficacy has been shown in patients with pain and fever associated with cold and influenza and in pain models such as sore throat, muscular pain or soft tissue injury and backache.

This product is especially suitable for pain which requires stronger pain relief than ibuprofen 400 mg or paracetamol 1000 mg alone, and faster pain relief than ibuprofen.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelets aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400 mg was taken within 8 h before or within 30 min after immediate release acetylsalicylic acid (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 *Interactions with Other Medicaments and Other Forms of Interaction).*

Pharmacokinetic Properties

Ibuprofen

Ibuprofen is well absorbed from the gastrointestinal tract and is extensively bound to plasma proteins. Ibuprofen diffuses into the synovial fluid. Plasma levels of ibuprofen from this product are detected from 5 minutes with peak plasma concentrations achieved within 1-2 hours after ingestion on an empty stomach. When this product was taken with food peak ibuprofen plasma levels were lower and delayed by a median of 25 minutes, but overall extent of absorption was equivalent.

Ibuprofen is metabolised in the liver to two major metabolites with primary excretion via the kidneys, either as such or as major conjugates, together with a negligible amount of unchanged ibuprofen. Excretion by the kidney is both rapid and complete. The elimination half-life is approximately 2 hours.

In limited studies, ibuprofen appears in the breast milk in very low concentrations.

No significant differences in ibuprofen pharmacokinetic profile are observed in the elderly.

Paracetamol

Paracetamol is readily absorbed from the gastrointestinal tract. Plasma protein binding is negligible at usual therapeutic concentrations, although this is dose-dependent. Plasma levels of

paracetamol from this product are detected from 5 minutes with peak plasma concentrations occurring at 0.5-0.67 hours after ingestion on an empty stomach. When this product was taken with food peak paracetamol plasma levels were lower and delayed by a median of 55 minutes, but overall extent of absorption was equivalent.

Paracetamol is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates, with about 10% as glutathione conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life is approximately 3 hours.

A minor hydroxylated metabolite, which is usually produced in very small amounts by mixed function oxidases in the liver and detoxified by conjugation with liver glutathione, may accumulate following paracetamol overdose and cause liver damage. No significant differences in the paracetamol pharmacokinetic profile are observed in the elderly.

Clinical Studies

A randomized, double-blind placebo-controlled studies were conducted with the combination using the acute pain model of post-operative dental pain. The studies show that:

- This product provides more effective pain relief than paracetamol 1000 mg ($p<0.0001$) and ibuprofen 400 mg ($p< 0.05$) which are clinically and statistically significant.
- This product has a fast onset of action with 'confirmed perceptible pain relief' achieved in a median of 18.3 minutes. The onset of action was significantly more rapid than for ibuprofen 400 mg (23.8 minutes, $p=0.0015$). 'Meaningful pain relief' for this product was achieved in a median of 44.6 minutes, which was significantly faster than for ibuprofen 400 mg (70.5 minutes, $p<0.0001$).
- Duration of analgesia was significantly longer for this product (9.1 hours) compared to paracetamol 500 mg (4 hours) or 1000 mg (5 hours).
- The global evaluation of the study medication by the subjects showed high levels of satisfaction with 93.2% rating the product as 'good', 'very good' or 'excellent' in achieving pain relief. The fixed combination product performed significantly better than paracetamol 1000 mg ($p<0.0001$).

A randomised, double-blind controlled clinical study was conducted with the product in the treatment of chronic knee pain. The study showed that:

- The product provides more effective pain relief than paracetamol 1000 mg in short-term treatment ($p<0.01$) and long term treatment ($p<0.01$).
- The global evaluation of the product by the subjects showed high levels of satisfaction with 60.2% rating the product as 'good' or 'excellent' as a long term treatment for a painful knee. The product performed significantly better than paracetamol 1000 mg ($p<0.001$).

Preclinical Safety Data

The toxicological safety profile of ibuprofen and paracetamol has been established in animal experiments and in humans from extensive clinical experience.

PHARMACEUTICAL PARTICULARS

List of Excipients

Starch Maize, Polyvinyl Pyrrolidone K-30, Disodium Edetate, Methyl Paraben, Propyl Paraben, Talc Purified, Magnesium Stearate, Sodium Lauryl Sulphate, Sodium Starch Glycollate and Colloidal Silicon Dioxide.

Incompatibilities

There are no relevant data available.

Shelf Life

The expiry date is indicated on the label and packaging.

Special Precautions for Storage

Store protected from moisture, at a temperature not exceeding 30°C.

Keep out of reach of children.

Nature and Specification of Container

Blister foil strips in a carton.

Instructions for Use/Handling

There are no special requirements for use and handling of this product.

For further information please contact:
GlaxoSmithKline Pharmaceuticals Limited.
Registered Office:
Dr. Annie Besant Road, Worli,
Mumbai 400 030, India.

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Adapted from Ibuprofen/ Paracetamol Non-Central Data sheet (NCDS) version 04 dated 03 December 2018.