1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S2

PROPRIETARY NAME AND DOSAGE FORM

IBUMOL GRAPE (suspension)

COMPOSITION

Each 10 ml of IBUMOL GRAPE contains 200 mg of ibuprofen and 250 mg of paracetamol.

Excipients:

Brilliant blue (C.I. 42090), carbopol, carmoisine (C.I. 14720), flavour grape, flavour tutti-frutti, glycerol, polysorbate, purified water, saccharin sodium, sodium benzoate, sodium cyclamate, sodium metabisulphite, sorbitol (70 %) solution

Preservative:

Sodium benzoate 0,1 % *m/v*

Contains sugar: Sorbitol 3,26 g, glycerol 630,5 mg

Contains sweetener: Sodium cyclamate 50 mg, saccharin sodium 7 mg

CATEGORY AND CLASS

A 2.8 Analgesic combinations

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Ibuprofen has analgesic, antipyretic and anti-inflammatory activities. Ibuprofen inhibits platelet aggregation.

Paracetamol has analgesic and antipyretic effects.

Pharmacokinetic properties

Ibuprofen:

Well absorbed after oral administration. Onset of action for pain relief is 30 minutes and the time for peak effect for fever is 2 to 4 hours. The half-life of ibuprofen is about 2 hours and the duration of action for fever is 6 to 8 hours or more and is 4 to 6 hours for pain. More than 90 % of an ingested dose is excreted in the urine as metabolites or their conjugates. Protein binding of ibuprofen is more than 95 %.

Paracetamol:

Absorption following oral administration is well and almost complete. Paracetamol is metabolised in the liver primarily by conjugation. Paracetamol has half-life of 1 to 4 hours, time to peak concentration of 0,5 to 2 hours, time to peak effect of 1 to 3 hours and the duration of action of 3 to 4 hours. Paracetamol is renally excreted primarily as metabolites and 3 % of a dose may be excreted unchanged.

INDICATIONS

IBUMOL GRAPE is indicated for the short-term treatment of mild to moderate pain of inflammatory origin or non-inflammatory origin with or without fever.

CONTRAINDICATIONS

- Hypersensitivity to any of the ingredients of IBUMOL GRAPE.

Ibuprofen:

- History of gastrointestinal bleeding, ulceration or perforation (PUBs) related to previous NSAIDs.
- Active or history of recurrent gastrointestinal ulcer or haemorrhage or perforations.
- Cardiovascular diseases, heart failure, hepatic failure and renal failure.
- IBUMOL GRAPE should not be used in patients sensitive to aspirin or another non-steroidal anti-inflammatory medicines.
- Uncontrolled asthma or bronchospasm.
- Nasal polyps associated with aspirin-induced bronchospasm.
- IBUMOL GRAPE is contraindicated during the last trimester of pregnancy (see HUMAN REPRODUCTION).
- Patients who are receiving coumarin anticoagulants.

Paracetamol:

Severe liver impairment.

WARNINGS AND SPECIAL PRECAUTIONS

Ibuprofen:

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

Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding, ulceration and perforation (PUBs) which may be fatal. These patients are more likely to develop adverse hepatic or renal effects and if gastrointestinal ulceration or bleeding occurs is more likely to cause serious consequences.

The risk of gastrointestinal bleeding, ulceration or perforation (PUBs) is higher with increasing doses of IBUMOL GRAPE, in patients with a history of ulcers, and the elderly.

When gastrointestinal bleeding or ulceration occurs in patients receiving IBUMOL GRAPE, treatment with IBUMOL GRAPE should be stopped. IBUMOL GRAPE can interfere with platelet aggregation and has been shown to prolong bleeding time in normal subjects.

In view of the product's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

IBUMOL GRAPE should be given with caution to patients with a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as the condition may be exacerbated.

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported. IBUMOL GRAPE should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Anaemia may be exacerbated.

Hepatic function impairment which may increase risk of hepatotoxicity.

Renal function impairment where renal failure may be provoked, especially in patients with pre-existing renal impairment.

Allergic conditions with a possibility of cross sensitivity.

The antipyretic, analgesic and anti-inflammatory action of IBUMOL GRAPE may mask symptoms of the occurrence of worsening of infection.

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis.

Paracetamol:

IBUMOL GRAPE contains paracetamol which may be fatal in overdose. In the event of overdosage or suspected overdose and notwithstanding the fact that the person may be asymptomatic, the nearest doctor, hospital or poison centre must be contacted immediately.

Dosages of IBUMOL GRAPE in excess of those recommended may cause severe liver damage.

IBUMOL GRAPE should be given with care to patients with impaired kidney or liver function. Large doses should be avoided in patients with hepatic impairment. IBUMOL GRAPE should

also be given with care to patients with alcohol dependence.

If taken for pain, including arthritic pain, and the pain persists for longer than 10 days, or if taking for fever and the fever persists for longer than 3 days or if the condition deteriorates or new symptoms develop, the doctor needs to be contacted as additional treatment may be necessary.

Avoid alcohol: There is an increased risk of liver toxicity, especially in alcoholics with high doses and prolonged use of IBUMOL GRAPE.

Diabetic patients may experience false results with blood glucose tests.

Effects on ability to drive and use machines

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking IBUMOL GRAPE. If affected, patients should not drive or operate machinery.

Excipients

Patients with the rare hereditary condition of sorbitol intolerance should not take IBUMOL GRAPE.

INTERACTIONS

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

Ibuprofen:

- *NSAIDs:* Use of two or more NSAIDs including, cyclooxygenase-2 selective inhibitors and aspirin, concomitantly could result in an increase in side effects.
- *Corticosteroids:* Increased risk of gastrointestinal perforation, ulceration or bleeding (PUBs).
- *Anticoagulants:* IBUMOL GRAPE may enhance the effects of anticoagulants such as warfarin.
- *Antiplatelet medicines and selective serotonin reuptake inhibitors (SSRIs):* Increased risk of gastrointestinal bleeding, ulceration and perforation.
- *Antihypertensives, beta-blockers:* NSAIDs such as IBUMOL GRAPE may reduce the effect of antihypertensives. There may be an increased risk of hyperkalaemia.
- *Aminoglycosides:* NSAIDs such as IBUMOL GRAPE may decrease the excretion of aminoglycosides.
- *Antidiabetic medicines:* Hypoglycaemic effects of these medicines may be increased.
- *Digoxin:* NSAIDs such as IBUMOL GRAPE may exacerbate cardiac failure, reduce GFR and increase plasma digoxin levels.
- *Ciclosporin and tacrolimus:* Increased risk of nephrotoxicity.
- *Lithium:* Increase in the steady-state concentration, and therefore elimination, of lithium.
- *Herbal extracts:* Ginkgo biloba may potentiate the risk of bleeding.
- *Methotrexate:* Increased and prolonged methotrexate plasma concentration and an increased risk of methotrexate toxicity.
- *Diuretics:* can also increase the risk of nephrotoxicity of IBUMOL GRAPE.
- *Mifepristone:* A decrease in the efficacy of mifepristone can theoretically occur due to the antiprostaglandin properties of NSAIDs including IBUMOL GRAPE. Evidence

suggests that coadministration of IBUMOL GRAPE on the day of prostaglandin administration does not adversely influence the effects of mifepristone or the prostaglandin on cervical ripening or uterine contractility. IBUMOL GRAPE should therefore not be used for 8 to 12 days after mifepristone administration.

- *Quinolone antibiotics:* NSAIDs such as IBUMOL GRAPE can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs such as IBUMOL GRAPE and quinolones may have an increased risk of developing convulsions.
- *SSRIs:* Increased risk of gastrointestinal bleeding.
- *Zidovudine:* Increased risk of haematological toxicity when NSAIDs such as IBUMOL GRAPE are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and IBUMOL GRAPE.
- *Bone marrow depressants:* The leucopenic and/or thrombocytopenic effects of these medicines may be increased.
- The risk of gastrointestinal bleeding ulceration and perforation is increased when used with alcohol, bisphosphonates or oxypentifylline.

Paracetamol:

- *Enzyme inducing and hepatotoxic medicines:* Increased risk of hepatoxicity. Possible decrease in therapeutic effects of paracetamol.
- *Metoclopramide:* Absorption of paracetamol may be accelerated.
- *Cholestyramine:* Absorption of paracetamol is reduced if given within one hour of cholestyramine.
- *Probenecid:* Excretion of paracetamol may be affected and plasma concentrations

altered.

HUMAN REPRODUCTION

Safety and efficacy in pregnancy and lactation has not been established (see CONTRAINDICATIONS).

Pregnancy

Ibuprofen

Regular use of non-steroidal anti-inflammatory medicines during the third trimester of pregnancy, may result in premature closure of the fetal ductus arteriosus *in-utero*, and possibly, in persistent pulmonary hypertension of the new-born. The onset of labour may be delayed and its duration increased.

Consequently, IBUMOL GRAPE is contraindicated during the third trimester of pregnancy.

Lactation

Ibuprofen

IBUMOL GRAPE can appear in breast milk in very low concentrations and should be avoided when breastfeeding.

DOSAGE AND DIRECTIONS FOR USE

DO NOT EXCEED THE RECOMMENDED DOSE.

SHAKE THE BOTTLE BEFORE USE.

Adults and children over twelve years:

One to two medicine measurefuls (5 ml to 10 ml) four hourly if necessary and not more than six medicine measurefuls in twenty four hours.

Children six to twelve years old:

One to two medicine measurefuls (5 ml to 10 ml) three to four times daily.

Children two to five years old:

Half to one medicine measurefuls (2,5 ml to 5 ml) three to four times daily.

Safety in children under two years of age has not been proven.

IBUMOL GRAPE should be taken with or after food.

SIDE EFFECTS

Ibuprofen

Infections and infestations

Less frequent: Rhinitis, 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

Blood and the lymphatic system disorders

Less frequent: Leukopenia, thrombocytopenia with or without purpura, agranulocytosis, anaemias (aplastic anaemia and haemolytic anaemia)

Frequency unknown: Eosinophilia

Immune system disorders

Frequency unknown: Hypersensitivity reactions have been reported following treatment with IBUMOL GRAPE. 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, more rarely, exfoliative and bullous dermatoses

Psychiatric disorders

Less frequent: Nervousness, insomnia

Frequency unknown: Confusion, anxiety, depression, hallucination

Nervous system disorders

Frequent: Dizziness

Less frequent: Drowsiness, headache

Frequency unknown: Optic neuritis, paraesthesia, somnolence

Eye disorders

Less frequent: Blurred vision and other ocular reactions

Frequency unknown: Visual impairment, toxic optic neuropathy

Ear and labyrinth disorders

Less frequent: Tinnitus

Frequency unknown: Impaired hearing, and vertigo

Cardiac disorders

Less frequent: Hypertension

Frequency unknown: Oedema, cardiac failure

Gastrointestinal disorders

The most commonly observed adverse events are gastrointestinal in nature.

Frequent: Nausea, abdominal cramps and pain

Less frequent: Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal, particularly in the elderly, bloating, constipation, decreased appetite, diarrhoea, melaena, haematemesis, pancreatitis

Frequency unknown: Gastrointestinal perforation, dyspepsia, ulcerative stomatitis, exacerbation of colitis and Crohn's disease, gastritis (see WARNINGS AND SPECIAL PRECAUTIONS)

Hepatobiliary disorders

Less frequent: Hepatitis and jaundice

Frequency unknown: Abnormalities of liver function test, hepatic failure

Skin and subcutaneous tissue disorders

Frequent: Skin rash, pruritus

Less frequent: Bullous reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis

Frequency unknown: Photosensitivity reaction

Renal and urinary disorders

Less frequent: Impaired renal functions, acute reversible renal failure, toxic nephropathy in various forms, including interstitial nephritis, nephrotic syndrome

Paracetamol

Blood and the lymphatic system disorders

Less frequent: Haematological reactions (including agranulocytosis, thrombocytopenia, neutropenia, pancytopenia, leukopenia)

Hepatobiliary disorders

Less frequent: Hepatitis

Skin and subcutaneous tissue disorders

Frequency unknown: Sensitivity reactions resulting in reversible skin rash (which may be accompanied by fever and mucosal lesions) or blood disorders

Renal and urinary disorders

Frequency unknown: Renal failure, renal colic

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS

Ibuprofen

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 of ibuprofen overdose

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, apnoea, diarrhoea and depression of the CNS and respiratory system have also been rarely reported. Disorientation, excitation, fainting and cardiovascular toxicity, including hypotension, bradycardia and tachycardia have been reported. In cases of significant overdose, renal failure and liver damage are possible. Large overdoses are generally well tolerated when no other medicines are being taken.

Therapeutic measures

Patients should be treated symptomatically 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.

Good urine output should be ensured. Renal and liver function should be closely monitored. Patients should be observed for at least four hours after ingestion of potentially toxic amounts.

Frequent or prolonged convulsions should be treated with intravenous diazepam.

Other measures may be indicated by the patient's clinical condition.

Paracetamol

Prompt treatment is essential. In the event of an overdosage, consult a doctor immediately, or take the person to a hospital directly. A delay in starting treatment may mean that the antidote is given too late to be effective. Evidence of liver damage is often delayed until after the time for effective treatment has lapsed.

Susceptibility to paracetamol toxicity is increased in patients who have taken repeated high doses (greater than 5 g/day to 10 g/day) of paracetamol for several days, in chronic alcoholism, chronic liver disease, AIDS, malnutrition, and with the use of drugs that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine.

Symptoms of paracetamol overdose: In the first 24 hours include pallor, nausea, vomiting, anorexia and possibly abdominal pain. Mild symptoms during the first two days of acute poisoning do not reflect the potential seriousness of the overdosage.

Liver damage may become apparent 12 to 48 hours, or later after ingestion of paracetamol, initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentrations and prolongation of the prothrombin time. Liver damage may lead to encephalopathy, coma and death.

Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Abnormalities of glucose metabolism and metabolic acidosis may occur.

Cardiac arrhythmias have been reported.

Treatment of paracetamol overdose:

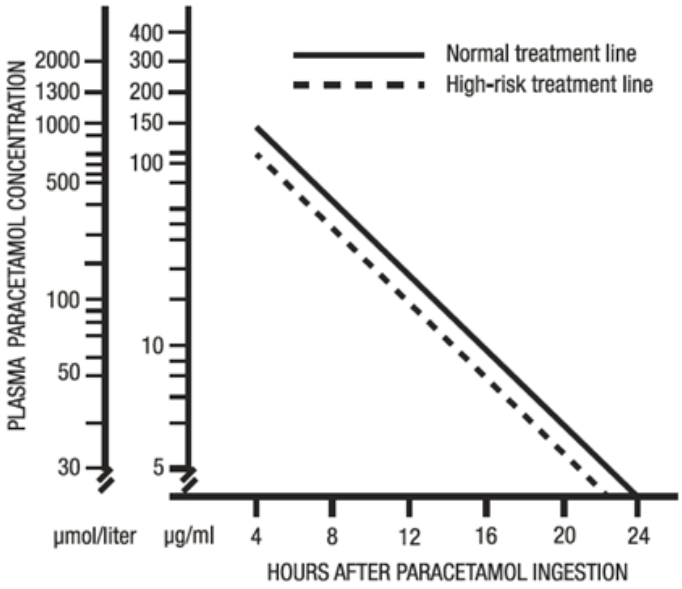
Although evidence is limited it is recommended that an adult who has ingested 5 g to 10 g or more of paracetamol (or a child who has had more than 140 mg/kg) within the preceding four hours, should have the stomach emptied by lavage (emesis may be adequate for children) and a single dose of 50 g activated charcoal given via the lavage tube. Ingestion of amounts of paracetamol smaller than this may require treatment in patients susceptible to paracetamol poisoning (see above). In patients who are stuperose or comatose, endotracheal intubation should precede gastric lavage in order to avoid aspiration.

N-acetylcysteine should be administered to all cases of suspected overdose as soon as possible preferably within eight hours of overdosage, although treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken. An initial dose of 150 mg/kg N-acetylcysteine in 200 ml dextrose injection given **intravenously** over 15 minutes, followed by an infusion of 50 mg/kg in 500 ml dextrose injection over the next four hours, and then 100 mg/kg in 1 000 ml dextrose injection over the next sixteen hours. **The volume of intravenous fluid should be modified for children.**

Although the oral formulation is not the treatment of choice, 140 mg/kg dissolved in water as a 5 % solution may be administered initially, followed by 70 mg/kg every four hours for seventeen doses.

A plasma paracetamol level should be determined four hours after ingestion in all cases of suspected overdosage. Levels done before four hours, unless high, may be misleading.

Patients at risk of liver damage, and hence requiring continued treatment with N-acetylcysteine, can be identified according to their 4-hour plasma paracetamol level. The plasma paracetamol level can be plotted against time since ingestion in the nomogram below. The nomogram should be used only in relation to a single acute ingestion.



Those, whose plasma paracetamol levels are above the “Normal treatment line”, should continue N-acetylcysteine treatment with 100 mg/kg IV over sixteen hours repeatedly until recovery. Patients with increased susceptibility to liver damage as identified above, should continue treatment if concentrations are above the “High-risk treatment line”.

Prothrombin time/INR correlates best with survival.

Monitor all patients with significant ingestions for at least ninety-six hours.

IDENTIFICATION

A homogenous, purple suspension with a sweet, fruity grape odour and flavour and a bitter aftertaste.

PRESENTATION

100 ml is packed into a round, amber glass bottle sealed with a white, tamper evident polypropylene duet screwcap with an expanded polyethylene liner. The bottle is placed in an outer cardboard carton.

100 ml is packed into a natural brown, round, high density polyethylene bottle sealed with a white, low density polyethylene (LDPE), snap-cap closure. The bottle is placed in an outer cardboard carton.

Not all packs and pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS

Store at or below 25 °C in well-closed containers.

Protect from light.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

A39/2.8/ 0229

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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