PROFESSIONAL INFORMATION

SCHEDULING STATUS: S2

1. NAME OF THE MEDICINE

Ibupain® (capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each IBUPAIN capsule contains: 200 mg ibuprofen and 250 mg paracetamol.

Sugar free.

3. PHARMACEUTICAL FORM

Size 0 capsule with opaque white body and opaque dark green cap containing a free flowing white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IBUPAIN is indicated for the treatment of mild to moderate pain of inflammatory origin or non-inflammatory origin with or without fever.

4.2 Posology and method of administration

For oral administration and short term use only.

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

DO NOT EXCEED THE RECOMMENDED DOSE.

Not recommended for children under 12 years of age.

Adults and children over 12 years: 2 capsules every 4 hours when necessary. Do not exceed 6 capsules in 24 hours.

IBUPAIN should be taken with or after food.

If taking IBUPAIN for pain and the pain persists for longer than 7 days, or if taking IBUPAIN for fever and the fever persists for longer than 3 days or if the condition deteriorates or new symptoms develop, a re-evaluation of the condition is required by the doctor.

4.3 Contraindications

- Hypersensitivity to ibuprofen or paracetamol or to any of the excipients of IBUPAIN in section 6.1.
- Patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema, or urticaria) in response to aspirin or other non-steroidal anti-inflammatory medicines.
- Patients with bleeding disorders.
- History of gastrointestinal Perforation, Ulceration or Bleeding (PUBs) related to previous NSAIDs, including IBUPAIN.
- Active or history of recurrent peptic ulcer/haemorrhage/perforations (two or more distinct episodes of proven ulceration or bleeding).
- Heart failure (NYHA Class IV).
- Uncontrolled asthma or bronchospasm.

- Nasal polyps associated with aspirin-induced bronchospasm.
- Cardiovascular diseases.
- Severe liver impairment.
- Renal impairment.
- Lactation (see section 4.6).
- Pregnancy - risk of foetal renal dysfunction (see section 4.4 and 4.6).
- Patients who are receiving coumarin-anticoagulants.

4.4 Special warnings and precautions for use

This product 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 paracetamol in excess of those recommended may cause severe liver damage.

IBUPAIN is for short term use only.

The use of IBUPAIN with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Patients should be warned not to take other medicines containing paracetamol concurrently due to the risk of severe liver damage in case of overdose (see section 4.9).

Undesirable effects may be minimised by using the lowest effective dose for the shortest possible duration necessary to control symptoms (see section 4.2, GI and cardiovascular risks below).

Elderly

The elderly have an increased frequency of adverse reactions to NSAIDs, including IBUPAIN, especially gastrointestinal Perforation, Ulceration or Bleeding (PUBs), which may be fatal.

IBUPAIN 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 IBUPAIN 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.

Respiratory disorders

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

Cardiovascular, renal and hepatic impairment

The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure.

The habitual concomitant intake of various similar painkillers further increases this risk.

Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients (see section 4.3).

Caution is advised in the administration of paracetamol to patients with renal and hepatic insufficiency.

Dose reduction is recommended in patients showing signs of worsening hepatic function. Treatment should be stopped in those patients who develop severe liver failure (see section 4.3).

Treatment should be stopped in those patients who develop severe renal failure (see section 4.3).

The hazards of paracetamol overdose are greater in those with non-cirrhotic alcoholic liver disease. Caution should be exercised in cases of chronic alcoholism. Alcohol should not be used during the treatment with paracetamol.

Cardiovascular and cerebrovascular effects

Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with a history of heart failure and/or hypertension as fluid retention and oedema has been reported in association with IBUPAIN therapy. In view of IBUPAIN's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

Clinical studies suggest that the 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.

Gastrointestinal effects

Gastrointestinal (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 gastrointestinal perforation, ulceration or bleeding (PUBs) is higher with increasing doses of IBUPAIN, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and 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 medicines likely to increase gastrointestinal risk (see below and section 4.5).

Patients with a history of GI toxicity, 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 anti-platelet agents such as aspirin (see section 4.5).

When gastrointestinal bleeding or ulceration occurs in patients receiving IBUPAIN, treatment with IBUPAIN should be stopped.

IBUPAIN 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 (see section 4.8).

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 4.8). 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. Acute Generalised Exanthematous Pustulosis (AGEP) has been reported in relation to ibuprofen-containing products. IBUPAIN should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

SLE and mixed connective tissue disease

In patients with Systemic Lupus Erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis (see section 4.8).

Haematological effects

Ibuprofen, like other NSAIDs, can interfere with platelet aggregation and prolong bleeding time in normal subjects.

Surgery – possible enhanced bleeding if surgery is required.

Paediatric population

There is a risk of renal impairment in dehydrated children and adolescents.

Regular use of NSAIDs such as IBUPAIN during the third trimester of pregnancy, may result in premature closure of the foetal ductus arteriosus *in utero*, and possibly, in persistent

pulmonary hypertension of the newborn. The onset of labour may be delayed and its duration increased.

During 20 weeks gestation or later in pregnancy may cause a rare but serious foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Complications of prolonged oligohydramnios include limb contractures and delayed lung maturation, which may require invasive procedures such as exchange transfusion or dialysis, in some cases.

Diabetic patients may experience false results with blood glucose tests.

4.5 Interaction with other medicines and other forms of interaction

Ibuprofen and paracetamol

Other analgesics including cyclooxygenase-2 selective inhibitors

IBUPAIN should not be taken with other medicines containing paracetamol, ibuprofen, acetylsalicylic acid, salicylates or with any other anti-inflammatory drugs (NSAIDs) unless under a doctor's instruction.

Ibuprofen

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

The use of two or more NSAIDs concomitantly could result in an increase in side effects (see section 4.4).

Anticoagulants

IBUPAIN may enhance the effects of anticoagulants, such as warfarin (see section 4.4). This may increase risk of severe bleeding and sometimes fatal haemorrhage, especially from the gastrointestinal tract. IBUPAIN should only be used in patients taking warfarin if absolutely necessary and they must be closely monitored.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs)

Increased risk of gastrointestinal bleeding with NSAIDs (see section 4.4).

Anti-hypertensives and diuretics

IBUPAIN may reduce the anti-hypertensive effect of ACE inhibitors, betablockers and diuretics, and may cause natriuresis and hyperkalemia. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Corticosteroids

Increased risk of gastrointestinal perforation, ulceration or bleeding (PUBs) (see section 4.4).

Cardiac glycosides

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

Lithium

There is evidence for potential increases in plasma levels of lithium.

Methotrexate

There is a potential for an increase in plasma methotrexate.

Ciclosporin

Increased risk of nephrotoxicity.

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.

Quinolones 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.

Mifepristone

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

Probenecid

IBUPAIN may interact with probenecid.

Phenytoin

IBUPAIN may interact with phenytoin.

Sulphonylureas

IBUPAIN may interact with sulphonylureas.

Antidiabetic medicines

Hypoglycaemic effects of these medicines may be increased.

Bone marrow depressants

The leucopenic and/or thrombocytopenic effects of these medicines may be increased.

Paracetamol

Hepatotoxic medicines

Hepatotoxic substances may increase the possibility of paracetamol accumulation and overdose. The risk of hepatotoxicity of paracetamol may be increased by medicines which induce liver microsomal enzymes such as anticonvulsants and alcohol.

Anticoagulants

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. Dosage may require reduction if paracetamol and anticoagulants are taken for a prolonged period of time.

Metoclopramide and domperidone

Accelerate absorption of paracetamol.

Cholestyramine

Reduces the absorption of paracetamol if given within one hour of paracetamol.

Probenecid

Paracetamol excretion may be affected and plasma concentrations altered when given with probenecid.

Medicines which decrease gastric emptying

Paracetamol absorption is decreased by substances that decrease gastric emptying, e.g. propantheline, antidepressants with anticholinergic properties, and narcotic analgesics.

Chloramphenicol

Paracetamol may increase chloramphenicol plasma concentrations.

Isoniazid and medicines for tuberculosis

Severe hepatotoxicity at therapeutic doses or moderate overdoses of paracetamol has been reported in patients receiving isoniazid alone or with other medicines for tuberculosis.

Zidovudine and co-trimoxazole

Severe hepatotoxicity has occurred after use of paracetamol in a patient taking zidovudine and co-trimoxazole.

4.6 Fertility, pregnancy and lactation

Safety and efficacy in pregnancy and lactation have not been established.

Pregnancy

During the second or third trimester of pregnancy, NSAIDs including celecoxib/ibuprofen may cause foetal renal dysfunction which may result in reduction of amniotic fluid volume or oligohydramnios in severe cases.

Non-steroidal anti-inflammatories are not recommended during pregnancy and is contraindicated in the third trimester because of possible adverse effects on the foetus, such as premature closure of the ductus arteriosus *in utero*, and possibly, in persistent pulmonary hypertension. The onset of labour may be delayed and duration of labour increased, with increased bleeding tendency in both mother and child. IBUPAIN is contraindicated during pregnancy (see section 4.3).

Breastfeeding

IBUPAIN should not be used during breastfeeding (see section 4.3).

Fertility

The use of IBUPAIN 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 IBUPAIN should be considered.

4.7 Effects on ability to drive and use machines

No studies on the effect of ability to drive or use machines have been performed. Undesirable effects such as dizziness, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

Ibuprofen:

Infections and infestations:

Less frequent: Meningitis aseptic.

Aseptic meningitis (especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus and mixed connective tissue disease) with symptoms of stiff neck, headache, nausea, vomiting, fever or disorientation (see section 4.4).

Blood and lymphatic system disorders:

Less frequent: Haematopoietic disorders (anaemia, haemolytic anaemia, aplastic anaemia), leukopenia, pancytopenia, agranulocytosis, thrombocytopenia, bleeding episodes (e.g. epistaxis, menorrhagia).

Immune system disorders:

Less frequent: Hypersensitivity reactions including skin rashes, urticaria and pruritus as well as asthmatic attacks. Severe hypersensitivity reactions where symptoms can include: facial, tongue and larynx swelling, dyspnoea, tachycardia, hypotension up to life-threatening shock. Exacerbation of asthma and bronchospasm. Serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis, angioedema.

Metabolic and nutrition disorders:

Less frequent: Gynaecomastia, hypoglycaemic reaction.

Psychiatric disorders:

Frequent: Nervousness.

Less frequent: Depression, confusion, emotional lability, hallucinations, dream abnormalities.

Nervous system disorders:

Frequent: Dizziness, headache.

Less frequent: Paraesthesias, drowsiness, insomnia, somnolence, paradoxical stimulation, optic neuritis, psychomotor impairment, extrapyramidal effects, tremor and convulsions.

Eye disorders:

Less frequent: Visual impairment, blurred vision and other ocular reactions.

Ear and labyrinth disorders:

Less frequent: Tinnitus, vertigo.

Cardiac disorders:

Less frequent: Cardiac failure may be precipitated in compromised patients, angina pectoris, cardiac arrhythmias, palpitations.

Vascular disorders:

Less frequent: Hypertension.

Respiratory, thoracic and mediastinal disorder:

Less frequent: Asthma, bronchospasm, dyspnoea, wheezing, thickened respiratory tract secretions.

Gastrointestinal disorders:

Frequent: Dyspepsia, nausea, vomiting, diarrhoea, abdominal pain, constipation.

Less frequent: Gastrointestinal ulcers, potentially with bleeding and perforation with symptoms of melaena haematemesis sometimes fatal, particularly in the elderly. Ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4), gastritis, pancreatitis, flatulence.

The most commonly observed adverse events are gastrointestinal in nature.

Hepatobiliary disorders:

Less frequent: Liver function tests abnormal, hepatic damage, particularly in long-term therapy, acute hepatitis, jaundice.

Skin and subcutaneous tissue disorders:

Less frequent: Skin rash, pruritus, exfoliative dermatoses and bullous reaction including Stevens-Johnson syndrome and toxic epidermal necrolysis.
Not known: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome). Acute Generalised Exanthematous Pustulosis (AGEP).

Renal and urinary disorders:

Less frequent: Nephrotic syndrome; interstitial nephritis that may be accompanied by acute renal insufficiency; renal tissue damage (papillary necrosis) with increased serum urea, oedema, haematuria, tubulointerstitial nephritis, nephritic syndrome, proteinuria, urinary retention.

General disorders and administration site conditions:

Less frequent: Oedema, peripheral oedema, fatigue, malaise.

Investigations:

Frequent: Alanine aminotransferase increased, gamma-glutamyltransferase increased, blood creatinine increased and blood urea increased.
Less frequent: Decreased haematocrit and haemoglobin levels, aspartate aminotransferase increased, bloodalkaline phosphatase increased, blood creatine phosphokinease increased, platelet count increased.

Paracetamol:

Blood and lymphatic system disorders:

Less frequent: Agranulocytosis, thrombocytopenia, leucopenia, pancytopenia, neutropenia.

Immune system disorders:

Less frequent: Hypersensitivity, angioedema, anaphylactic reaction.

Very rare cases of serious skin reactions have been reported (including medicine-induced Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and Acute Generalised Exanthematous Pustulosis (AGEP)).

Respiratory, thoracic and mediastinal disorders:

Less frequent: Bronchospasm*.

* There have been cases of bronchospasm with paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs.

Hepatobiliary disorders:

Less frequent: Hepatitis, hepatic dysfunction.

Skin and subcutaneous tissue disorders:

Less frequent: Sensitivity reactions resulting in reversible skin rash (which may be accompanied by fever and mucosal lesions).

Renal and urinary disorders:

Less frequent: Renal colic, renal failure.

Investigations:

Frequent: Liver function tests abnormal.

4.9 Overdose

Prompt treatment is essential

In the event of an overdosage, consult a doctor immediately, or take the person directly to a hospital. 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.

Paracetamol

Symptoms

Susceptibility to paracetamol toxicity is increased in patients who have taken repeated high doses (greater than 5 to 10 g/day) of paracetamol for several days, elderly subjects, young children, in patients with hepatopathy, in chronic alcoholism, chronic liver disease, AIDS, malnutrition, eating disorder, cystic fibrosis and with the use of medicines that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, St John's Wort, phenytoin and carbamazepine. In these cases, overdose may lead to death.

Symptoms usually occur within 24 hours: pallor, nausea, vomiting, anorexia and possibly abdominal pain. Afterwards, the subjective condition may improve, however, mild abdominal pain indicating liver damage persists. Mild symptoms during the first two days of acute poisoning do not reflect the potential seriousness of the overdosage.

Overdose leads to liver cell necrosis which may result in total irreversible necrosis and later in hepatocellular insufficiency, metabolic acidosis and encephalopathy. These in turn may lead to coma, even with lethal outcome. Clinical symptoms of hepatotoxicity are usually visible after 2 days. Even if there is no severe hepatotoxicity, acute renal failure with acute tubular necrosis may occur.

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. Cerebral oedema and non-specific myocardial depression have occurred.

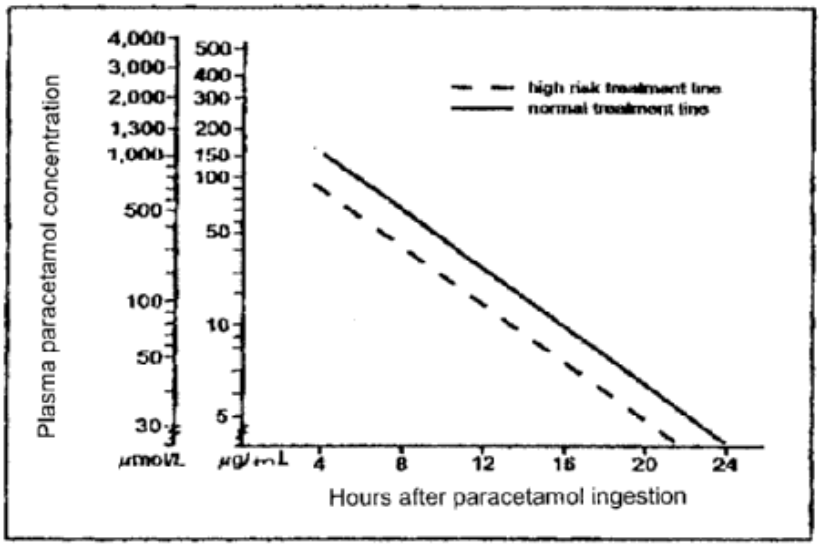
Treatment:

Although evidence is limited, it is recommended that an adult who has ingested 5 to 10 g or more of paracetamol (or a child who has had more than 140 mg/kg) within the preceding 4 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 8 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 4 hours, and then 100 mg/kg in 1000 ml dextrose injection over the next 16 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 4 hours for seventeen doses. If activated charcoal is used then it should be removed by gastric lavage as it may interfere with absorption of orally administered N-acetylcysteine and decrease its efficacy.

A plasma paracetamol level should be determined 4 hours after ingestion in all cases of suspected overdosage. Levels done before 4 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 plasma paracetamol level. The plasma paracetamol level can be plotted against time since ingestion.



Adapted from Smilkstein *et al*., Ann. Emerg.Med., 1991, 20, 1059

Those whose plasma paracetamol levels are above the “normal treatment line”, should continue N-acetylcysteine treatment with 100 mg/kg IV over 16 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 index correlates best with survival.

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

Ibuprofen:

Symptoms

Most patients who have ingested clinically important amounts of NSAIDs will develop no more than epigastric pain, nausea, vomiting, 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 vertigo, headache, respiratory depression, dyspnoea, drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning, hypotension, hyperkalaemia, and 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. Exacerbation of asthma is possible in asthmatics.

Treatment

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.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A 2.8 Analgesic combinations

5.1 Pharmacodynamic properties

Paracetamol has analgesic and antipyretic effects. Ibuprofen has analgesic, antipyretic and anti-inflammatory activities. Ibuprofen 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).

The exact mechanism of action of ibuprofen is thought to be through peripheral inhibition of cyclooxygenases and subsequent prostaglandin synthesis inhibition.

5.2 Pharmacokinetic properties

Paracetamol:

Absorption following oral administration is well and almost complete. Paracetamol is metabolised in the liver primarily by conjugation. Paracetamol has a 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.

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 %.

5.3 Preclinical safety data

The toxicological safety profile of ibuprofen and paracetamol has been established in animal experiments. There are no new preclinical data of relevance which are additional to the data already presented in this Summary of Product Characteristics.

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatine capsules (brilliant blue FCF, erythrosin, gelatine, quinolone yellow, titanium dioxide), microcrystalline cellulose, pregelatinised starch, purified talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Keep in a dry place below 25 °C. Protect from light.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Sealed aluminium layflat patient ready bags with LDPE ribbed zipper with 30, 60 or 100 capsules.

PVC/Tristar/Aluminium foil blisters packed into printed cardboard boxes together with the package leaflet with 10, 30, 60, 100 or 500 capsules.

Opaque white polypropylene securitainers with clip-on, low density or medium density or high density polyethylene pilfer proof seals with 10, 30, 60, 100 or 500 capsules.

Amber glass containers with black, hard plastic (polypropylene) screw caps with expanded LDPC inner seals with 30, 60 or 100 capsules.

Not all packs are necessarily marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Waterfall 5-Ir

Magwa Crescent West

Waterfall City

Jukskei View

2090

8. REGISTRATION NUMBER

37/2.8/0133

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03 June 2005

10. DATE OF REVISION OF THE TEXT

25 August 2021

Additional country registration details:

Country	*Product name*	*Scheduling status (or Category of distribution)*	*Registration number*
Namibia	Ibupain	NS1	12/2.8/0065

Name and address of manufacturer:

Kiara Health (Pty) Ltd.

72 Steel Road, Spartan
Kempton Park, Johannesburg
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[1]Company Reg. No.: 1990/001979/07