

PRODUCT INFORMATION

Maxigesic[®]

Product Description

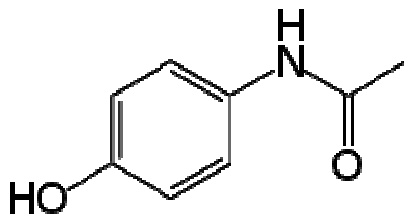
Each capsule shaped film coated tablet contains Paracetamol 500 mg and Ibuprofen 150 mg. Other ingredients are maize starch, microcrystalline cellulose, crosscarmellose sodium, magnesium stearate, opadry white and talc.

Paracetamol:

Chemical Name: N-acetyl-p-aminophenol

CAS number: 103-90-2

Structural Formula:

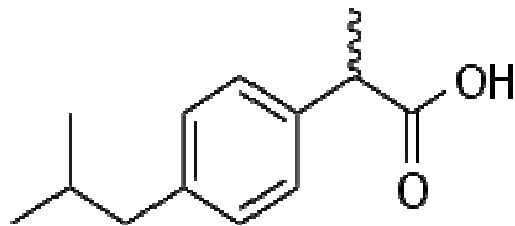


Ibuprofen:

Chemical Name: (±) - 2 - (p - isobutylphenyl) propionic acid.

CAS number: 15687-27-1

Structural Formula:



Pharmacology

Pharmacokinetics:

Paracetamol:

Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentration occurring about 10 to 60 minutes after oral administration. Paracetamol is distributed into most body tissues. The elimination half-life varies from about 1 to 3 hours.

Paracetamol is metabolised extensively in the liver and excreted in the urine, mainly as inactive glucuronide and sulphate conjugates. Less than 5% is excreted unchanged. The metabolites of paracetamol include a minor hydroxylated intermediate which has hepatotoxic activity. This active intermediate is detoxified by conjugation with glutathione, however, it can accumulate following paracetamol overdose and if left untreated has the potential to cause irreversible liver damage.

Paracetamol is metabolised differently by premature infants, newborns, and young children compared with adults, the sulphate conjugate being most predominant.

Ibuprofen:

Ibuprofen is well absorbed from the gastrointestinal tract. It is highly bound (90-99%) to plasma proteins and is extensively metabolised to inactive compounds in the liver, mainly by glucuronidation. Both the inactive metabolites and a small amount of unchanged ibuprofen are excreted rapidly and completely by the kidney, with 95% of the administered dose eliminated in the urine within four hours of ingestion. The elimination half-life of ibuprofen is in the range of 1.9 to 2.2 hours.

The Fixed Dose Combination:

Pharmacokinetics

A specific study to investigate possible effects of paracetamol on the plasma clearance of ibuprofen and vice versa did not identify any drug interactions.

Metabolism

The metabolic pathways of paracetamol and ibuprofen are distinct and there should be no drug interactions where the metabolism of one affects the metabolism of the other. A formal study to investigate such a possibility failed to find any potential drug interaction on the metabolic pathways.

Pharmacodynamics/Mechanism of action:

Paracetamol:

Although the exact site and mechanism of analgesic action is not clearly defined, paracetamol appears to produce analgesia by elevation of the pain threshold. The potential mechanism may involve inhibition of the nitric oxide pathway mediated by a variety of neurotransmitter receptors including N-methyl-D-aspartate and substance P.

Ibuprofen:

Ibuprofen possesses analgesic, antipyretic and anti-inflammatory properties, similar to other non-steroidal anti-inflammatory drugs (NSAIDs). Its mechanism of action is unknown, but is thought to be through peripheral inhibition of cyclooxygenases and subsequent prostaglandin synthesis inhibition.

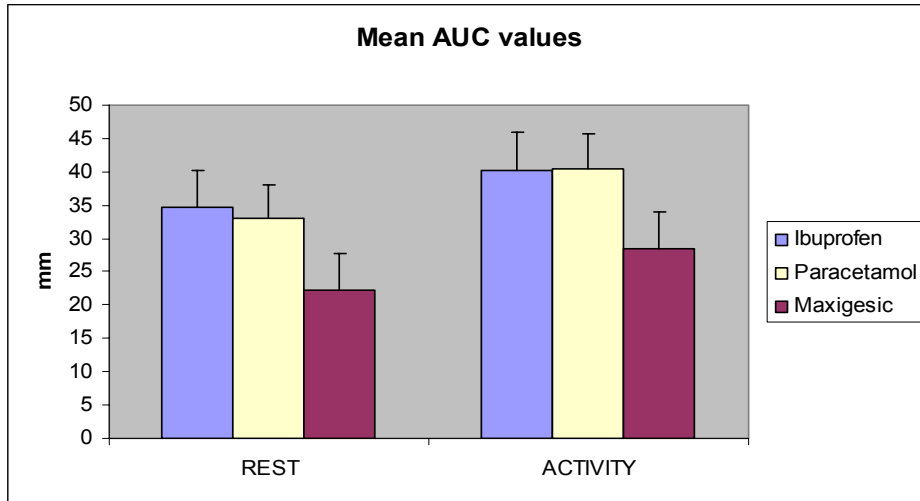
Clinical Trials

A prospective, Parallel Group, Double-Blind Comparison of the Analgesic Effect of Maxigesic[®], Paracetamol alone, or Ibuprofen alone in Patients with Post-Operative dental pain for 48 hours following oral surgery was conducted. Total dose in the 24 hours were paracetamol 4000mg, ibuprofen 1200mg and Maxigesic[®]. Analgesia, the primary efficacy end point was a time-corrected AUC (Area under the Curve) calculated from 100mm VAS (Visual Analogue Scale) pain scores over 48 hours at both rest and on activity.

The primary end points, assessed on the Intent to Treat (ITT) population, showed the mean time-adjusted AUCs over 48 hours calculated from the VAS pain scores for Maxigesic[®] were significantly lower than for paracetamol at rest (22.344 [SE 3.2] and 33.016 [3.005] respectively (p=0.007), and on activity 28.377 [SE 3.396] and 40.364 [SE 3.271] respectively (p=0.006).

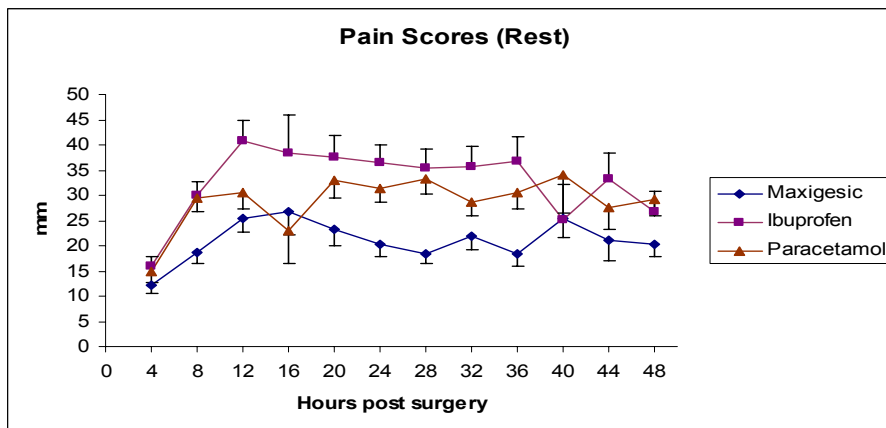
A similar outcome is seen for the Maxigesic® comparison where the AUCs over 48 hours showed the VAS for the combination drug were significantly lower than for ibuprofen at rest, 22.344 [SE 3.2] and 34.78 [SE 3.22] respectively (p=0.003) and during activity 28.377 [SE 3.396] and 40.217 [SE 3.418] respectively (p=0.007).

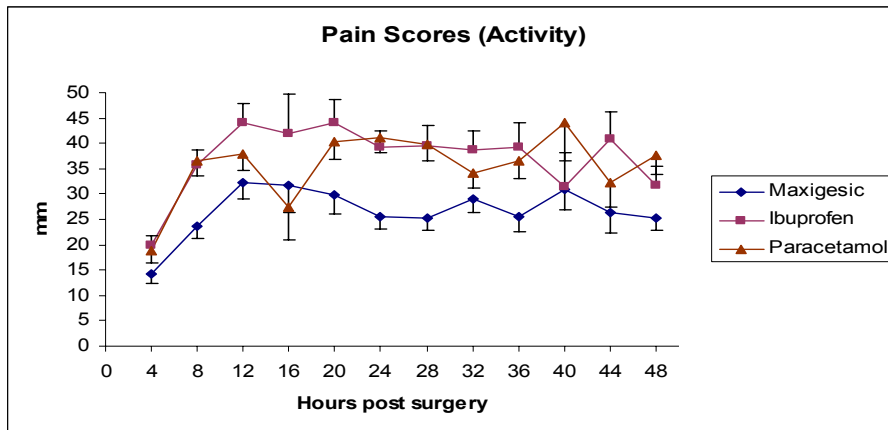
Figure 1: Means of Time-adjusted AUC at rest and on activity by treatment groups



A presentation of the pain records during the 48 hours also shows the Maxigesic® analgesic effect showed a faster onset than either of its two active ingredients, and exhibited superior analgesia at almost all time points at both rest and during activity (Fig 2).

Figure 2: Pain Score Plot-- Scores Given Are Those Rated During Each 4-Hour Period Post Surgery





Indications

Maxigesic[®] tablets are indicated for relief of pain and reduction of fever and inflammation.

Contraindications

Maxigesic[®] is contraindicated for use in patients with known hypersensitivity reaction to paracetamol, ibuprofen, other NSAIDs or any other ingredients in the product.

Paracetamol

Paracetamol should not be used in patients with active alcoholism as chronic excessive alcohol ingestion may predispose patients to paracetamol hepatotoxicity.

Ibuprofen

Ibuprofen should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see Precautions, Pre-existing Asthma).

Ibuprofen is contraindicated for use in patients with active gastrointestinal bleeding or peptic ulceration. Use of ibuprofen is contraindicated during the third trimester of pregnancy (see Use in pregnancy).

Maxigesic[®] should not be taken with other products containing ibuprofen, aspirin, salicylates or with any other anti-inflammatory medicines unless under a doctor's instruction. Refer to 'Interactions with other medicines' for additional information.

Precautions

Use in Chronic Liver Disease or a History of Liver Disease

Paracetamol:

Paracetamol at higher than recommended doses can lead to hepatotoxicity and even hepatic failure and death. Paracetamol can be used in patients with liver disease and has been studied in both one-time single (1500 mg) and multiple doses (4000 mg/d) in adult patients with chronic stable liver disease. A double-blind, two-period, crossover study was conducted to evaluate the use of 4000 mg/d of paracetamol for 13 days in patients with stable chronic liver disease. There were no abnormalities indicative of an adverse reaction to paracetamol. The metabolism following a single 1500-mg dose was compared in normal subjects, patients with mild liver disease, and patients with severe liver disease. There were no significant differences in overall 24-hour urinary excretion of paracetamol and glucuronide, cysteine, and mercapturic acid conjugates of paracetamol. Following a single (10 mg/kg) dose of paracetamol, the pharmacokinetic profiles in patients with mild, moderate, or severe liver disease were not significantly different. Although the plasma half-life of paracetamol was prolonged in patients with severe liver disease, there were no significant differences in the 24-hour (adult) and 36-hour (children) urinary excretion of paracetamol or its conjugates (glucuronide, cysteine, mercapturic acid).

Ibuprofen:

Patients with impaired liver function or a history of liver disease who are on long term ibuprofen therapy should have hepatic function monitored at regular intervals. Ibuprofen has been reported to have a minor and transient effect on liver enzymes.

Severe hepatic reactions, including jaundice and cases of fatal hepatitis, though rare, have been reported with ibuprofen as with other NSAIDs . If abnormal liver tests persist or worsen, or if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), ibuprofen should be discontinued

Use in Renal Disease

Paracetamol:

Paracetamol can be used in patients with chronic renal disease without dosage adjustment. In a single-dose study, the disposition and metabolite kinetics of 1000 mg of paracetamol were compared in patients with renal disease and in healthy volunteers. The fractional urinary recovery of paracetamol and its conjugates (e.g., glucuronide, sulphate, cysteine, mercapturate) was similar in healthy volunteers and in patients with moderate renal failure. In a 10-day, multi-dose study, the disposition of paracetamol 3000 mg daily in healthy volunteers was compared with patients with chronic renal failure. A slight increase in predose trough paracetamol levels was noted in patients with renal failure (3.1 µg/mL) compared with controls (1.1 µg/mL), but there was no evidence of accumulation of the glutathione-derived metabolites of paracetamol (e.g., cysteine, mercapturate). Although mean daily predose plasma concentrations of sulphate and glucuronide conjugates were higher in patients with chronic renal disease, these conjugates disappeared rapidly when paracetamol was discontinued. There is no significant risk of paracetamol toxicity in patients with moderate to severe renal failure.

Ibuprofen:

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

The two major metabolites of ibuprofen are excreted mainly in the urine and impairment of renal function may result in their accumulation. The significance of this is unknown.

NSAIDs have been reported to cause nephrotoxicity in various forms; interstitial nephritis, nephritic syndrome and renal failure. In patients with renal, cardiac or hepatic impairment, those taking diuretics and ACE Inhibitors, and the elderly, caution is required since the use of nonsteroidal anti-inflammatory drugs may result in deterioration of renal function. The dose should be kept as low as possible and renal function should be monitored in these patients.

Use in Older Patients

Paracetamol:

No adjustment in labelled dosage is necessary for older patients who require paracetamol therapy. Those who require therapy for longer than 10 days should consult their physician for condition monitoring; however, no reduction in recommended dosage is necessary.

Ibuprofen:

Ibuprofen should not be taken by adults over the age of 65 without consideration of co-morbidities and co-medications because of an increased risk of adverse effects, in particular heart failure, gastrointestinal ulceration and renal impairment.

Haematological Effects

Paracetamol:

Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

In therapeutic doses, paracetamol does not shorten the lifespan of red blood cells and does not produce any clinically perceptible destruction of circulating red blood cells. It can alter the metabolism of oral anticoagulants (see Interactions with Other Medicines).

Ibuprofen:

Haematological Monitoring

Blood dyscrasias have been rarely reported. Patients on long-term therapy with ibuprofen should have regular haematological monitoring.

Coagulation Defects

Like other NSAIDs, ibuprofen can inhibit platelet aggregation. Ibuprofen has been shown to prolong bleeding time (but within the normal range), in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying haemostatic defects, ibuprofen should be used with caution in persons with intrinsic coagulation defects and those on anti-coagulation therapy.

Carcinogenicity/Mutagenicity

Paracetamol:

Various animal bioassays on a weight-of-evidence basis have demonstrated no evidence of carcinogenic potential for paracetamol.

Carcinogenicity (Human)

Although it has been hypothesized that long-term use of analgesics may be associated with a slight increase in urinary tract tumours and renal cell cancer in man, a number of population-based, case-controlled studies have shown that it is unlikely that paracetamol use plays a major role in renal cell cancer.

A comprehensive and conclusive review, accepted by the Committee for Proprietary

Medicinal Products (CPMP) of the European Union, considered the genotoxic and carcinogenic properties of paracetamol. This review concluded that genotoxic effects of paracetamol are not reached at therapeutic dosage.

Reproductive and Teratogenic Effects (Animal)

There was no effect on pregnancy or offspring when paracetamol was given at dose levels of 600 mg/kg/d in the diet of male rats for 60 days prior to mating and to female rats from 14 days before mating to the end of pregnancy. An oral dose of 600 mg/kg/d produced no teratogenicity or embryotoxicity when given from days 6 through 15 of pregnancy. When paracetamol was given from day 16 of pregnancy through a 3-week lactation period, no deleterious effect was noted on pregnancy rate or on percent of live births, but a decrease in body weight gain and survival rate was noted among offspring of drug-treated females. In another study, paracetamol 250 mg/kg/d did not affect foetal length or weight, incidence of resorptions, or placental weight.

Potential Laboratory Test Interferences

Paracetamol:

Using current analytical systems, paracetamol does not cause interference with laboratory assays. However, there are certain methods with which the possibility of laboratory interference exists, as described below:

Blood Tests:

Paracetamol at recommended doses does not appear to interfere with glucose analysis using currently marketed blood glucose meters. For further detail, it may be advisable to contact the specific laboratory instrumentation manufacturer.

Urine Tests:

Paracetamol in therapeutic doses may interfere with the determination of 5-hydroxyindoleacetic acid (5HIAA), causing false-positive results. False determinations may be eliminated by avoiding paracetamol ingestion several hours before and during the collection of the urine specimen.

Gastrointestinal Events

Ibuprofen:

Upper GI ulcers, gross bleeding or perforation have been described with NSAIDs. The risks increase with dose and duration of treatment and are more common in patients over the age of 65 years. Some patients will experience dyspepsia, heartburn, nausea, stomach pain or diarrhoea. These risks are minimal when Maxigesic[®] is used at the prescribed dose for a few days.

Ibuprofen should be used with extreme caution, and at the lowest effective dose for the shortest duration, in patients with a history of gastrointestinal haemorrhage or ulcer since their condition may be exacerbated.

Maxigesic[®] should be discontinued if there is any evidence of gastrointestinal bleeding.

The concurrent use of aspirin and NSAIDs also increases the risk of serious gastrointestinal adverse events.

Cardiovascular Thrombotic Events

Ibuprofen:

Observational studies have indicated that non-selective NSAIDs may be associated with an increased risk of serious cardiovascular events, including myocardial infarction and stroke, which may increase with dose or duration of use. The risks are described as minimal at maximum daily doses which include ibuprofen at 1200 mg, the recommended maximum dose in Maxigesic[®].

Patients with cardiovascular disease or cardiovascular risk factors may also be at greater risk. To minimise the potential risk of an adverse cardiovascular event in patients taking an NSAID, especially in those with cardiovascular risk factors, the lowest effective dose should be used for the shortest possible duration.

There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAIDs use.

Hypertension:

NSAIDs may lead to onset of new hypertension or worsening of pre-existing hypertension and patients taking antihypertensive medicines with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

Heart failure

Fluid retention and oedema have been observed in some patients taking NSAIDs; therefore caution is advised in patients with fluid retention or heart failure.

Severe Skin Reactions

Ibuprofen:

NSAIDs may very rarely cause serious cutaneous adverse events such as exfoliative dermatitis, toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), which can be fatal and occur without warning. These serious adverse events are idiosyncratic and are independent of dose or duration of use. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of a skin rash or any other sign of hypersensitivity.

Pre-existing asthma

Ibuprofen:

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and NSAIDs has been reported in such aspirin-sensitive patients, ibuprofen tablets should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with pre-existing asthma

Ophthalmological effects

Ibuprofen:

Adverse ophthalmological effects have been observed with NSAIDs; accordingly, patients who develop visual disturbances during treatment with ibuprofen should have an ophthalmological examination.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics

Ibuprofen:

The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID or COX-2 inhibitor) and thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Aseptic Meningitis

Ibuprofen:

Aseptic meningitis has been reported only rarely, usually but not always in patients with systemic lupus erythematosus (SLE) or other connective tissue disorders.

Masking Signs of Infection

Ibuprofen:

As with other drugs of this class, ibuprofen may mask the usual signs of infection.

Special Precautions

Ibuprofen:

In order to avoid exacerbation of disease or adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

Use in pregnancy

Paracetamol:

Category A: Paracetamol has been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.

Ibuprofen:

Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Ibuprofen inhibits prostaglandin synthesis and, when given during the latter part of pregnancy, may cause closure of the foetal ductus arteriosus, foetal renal impairment, inhibition of platelet aggregation and may delay labour and birth.

Thus, using Maxigesic[®] which contains ibuprofen is contraindicated during the third trimester of pregnancy, especially over the last few days before expected birth.

Further, there is insufficient experience with the safety of use of ibuprofen in humans during pregnancy. Therefore, Maxigesic[®] should not be used during the first 6 months of pregnancy unless the potential benefits to the patient outweigh the possible risk to the foetus.

Use in lactation

Maxigesic® is not recommended for nursing mothers.

Interaction with other medicines

Paracetamol

The following interactions have been noted:

- anticoagulant drugs (warfarin) - dosage may require reduction if paracetamol and anticoagulants are taken for a prolonged period of time
- paracetamol absorption is increased by substances that increase gastric emptying, e.g. metoclopramide
- paracetamol absorption is decreased by substances that decrease gastric emptying, e.g. propantheline, antidepressants with anticholinergic properties, and narcotic analgesics
- paracetamol may increase chloramphenicol plasma concentrations
- the risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes such as alcohol and anticonvulsant agents
- paracetamol excretion may be affected and plasma concentrations altered when given with probenecid
- cholestyramine reduces the absorption of paracetamol if given within 1 hour of paracetamol.
- Severe hepatotoxicity at therapeutic doses or moderate overdoses of paracetamol has been reported in patients receiving isoniazid alone or with other drugs for tuberculosis.
- Severe hepatotoxicity has occurred after use of paracetamol in a patient taking zidovudine and co-trimoxazole.

Ibuprofen

The following interactions have been noted:

- anticoagulants, including warfarin – ibuprofen interferes with the stability of INR and may increase risk of severe bleeding and sometimes fatal haemorrhage, especially from the gastrointestinal tract. Ibuprofen should only be used in patients taking warfarin if absolutely necessary and they must be closely monitored.
- Ibuprofen may decrease renal clearance and increase plasma concentration of lithium
- Ibuprofen may reduce the anti-hypertensive effect of ACE inhibitors, beta-blockers and diuretics and may cause natriuresis and hyperkalemia in patients under these treatments
- Ibuprofen reduces methotrexate clearance
- Ibuprofen may increase plasma levels of cardiac glycosides
- Ibuprofen may increase the risk of gastrointestinal bleeding especially if taken with corticosteroids
- Ibuprofen may prolong bleeding time in patients treated with zidovudine
- Ibuprofen may also interact with probenecid, antidiabetic medicines and phenytoin.

Adverse reactions

Paracetamol

Side effects of paracetamol are rare and usually mild, although haematological reactions have been reported. Skin rashes and hypersensitivity reactions occur occasionally. Overdosage with paracetamol if left untreated can result in severe, sometimes fatal liver damage and rarely, acute renal tubular necrosis.

Ibuprofen

Adverse effects with non-prescription (OTC) or short-term use ibuprofen are rare and may include:

- gastrointestinal – gastrointestinal bleeding, dyspepsia, heartburn, nausea, loss of appetite, stomach pain, diarrhoea
- central nervous system (CNS) – dizziness, fatigue, headache, nervousness
- hypersensitivity reactions - skin rashes and itching. Rarely exfoliative dermatitis and epidermal necrolysis have been reported with ibuprofen.
- rare cases of photosensitivity
- cardiovascular – risks of myocardial infarct and stroke. These risks are minimal at Maxigesic[®] recommended maximum daily doses but increase with longer duration of treatment, and in the elderly. Fluid retention and in some cases oedema have been reported with all NSAIDs. These effects are rare at non-prescription doses.

Allergic reactions such as skin rash, itching, swelling of the face or breathing difficulties may also occur. These are usually transient and reversible on cessation of treatment.

Dosage

Adults and Children over 12 years: The usual dosage is 1-2 tablets taken every four to six hours, up to a maximum of eight tablets in 24 hours.

Children under 12 years: Maxigesic[®] is not recommended for children under 12 years.

Overdosage

Symptoms

Paracetamol:

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may proceed to encephalopathy, coma and death. Acute renal failure with acute tubular necrosis may develop in the absence of severe liver damage. Cardiac arrhythmias have been reported. Liver damage is likely in adults who have taken 10 g or more of paracetamol, due to excess quantities of a toxic metabolite becoming irreversibly bound to liver tissue.

Ibuprofen

Symptoms include nausea, abdominal pain and vomiting, dizziness, convulsion and rarely, loss of consciousness. Clinical features of overdose with ibuprofen which may

result are depression of the central nervous system and the respiratory system.

Treatment

Paracetamol:

Prompt treatment is essential in the management of paracetamol overdosage even when there are no obvious symptoms, and should not be delayed while waiting for laboratory results. Any patient who has ingested 7.5 g or more of paracetamol in the preceding 4 hours should undergo gastric lavage. Specific therapy with an antidote such as acetylcysteine (intravenous) or methionine (oral) should be instituted as soon as possible.

Acetylcysteine is most effective when administered during the first 8 hours following ingestion of the overdose and the effect diminishes progressively between 8 and 16 hours. It used to be believed that starting treatment more than 15 hours after overdosage was of no benefit and might possibly aggravate the risk of hepatic encephalopathy. However, late administration has now been shown to be safe, and studies of patients treated up to 36 hours after ingestion suggest that beneficial results may be obtained beyond 15 hours. Furthermore, administration of intravenous acetylcysteine to patients who have already developed fulminant hepatic failure has been shown to reduce morbidity and mortality.

An initial dose of 150 mg/kg of acetylcysteine in 200 mL 5% glucose is given intravenously over 15 minutes, followed by an I.V. infusion of 50 mg/kg in 500 mL 5% glucose over 4 hours and then 100 mg/kg in 1 litre 5% glucose over 16 hours. The volume of I.V. fluids should be modified for children.

Methionine is given orally as 2.5 g every 4 hours up to 10 g. Methionine treatment must be started within 10 hours after ingestion of paracetamol; otherwise it will be ineffective and may exacerbate liver damage.

Evidence of serious symptoms may not become apparent until 4 or 5 days following overdosage and patients should be carefully observed for an extended period.

Ibuprofen:

In cases of acute overdosage, the stomach should be emptied by vomiting or lavage, though little drug will likely be recovered if more than an hour has elapsed since ingestion. Because the drug is acidic and is excreted in the urine, it is theoretically beneficial to administer alkali and induce diuresis. In addition to supportive measures, the use of oral activated charcoal may help to reduce the absorption and reabsorption of ibuprofen tablets.

Presentation

A white coloured, capsule shaped, film coated tablet with breakline on one side and plain on the other side.

Available in blister pack containing 16, 50, and 100 tablets

Store below 30 °C in a dry place, protected from light.

Poisons Schedule in Australia: PHARMACY ONLY MEDICINE-Schedule 2.

Medicine classification in New Zealand:

16 tablets pack: General sale medicine

32, 50 and 100 tablets pack: Pharmacy only medicine

Name and address of Sponsor:

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Date of preparation

April 2011