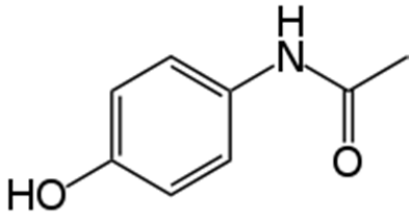
PRODUCT INFORMATION

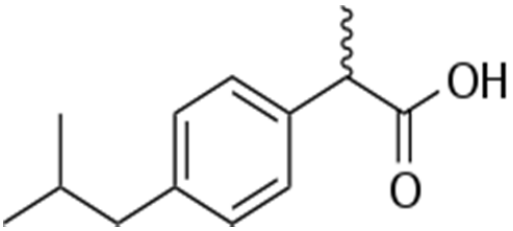
Name of the medicine

Maxigesic® Tablet 500mg/150mg

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:



Description

Each capsule shaped film coated tablet contains Paracetamol 500 mg and Ibuprofen 150 mg. Other ingredients are maize starch, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, opadry white (HMPC 2910/Hypromellose 15cP (E464), Lactose Monohydrate, Titanium Dioxide (E171),Trisodium citrate (E331) Macrogol/PEG 4000) and talc.

Pharmacology

Pharmacokinetics:

Absorption

Paracetamol is absorbed from the gastrointestinal tract with peak plasma concentration occurring about 10 to 60 minutes after oral administration.

Ibuprofen is absorbed following oral administration with maximum plasma concentrations usually achieved in 60 to 120 minutes.

Distribution

Paracetamol is distributed into most body tissues. Ibuprofen is highly protein bound.

Metabolism

Paracetamol is metabolised extensively in the liver and excreted in the urine, mainly as inactive glucuronide and sulphate conjugates. Less that 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 overdosage and if left untreated has the potential to cause severe and even irreversible liver damage.

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

Ibuprofen is highly bound (90-99%) to plasma proteins and is extensively metabolised to inactive compounds in the liver, mainly by glucuronidation.

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 using human liver enzymes to investigate such a possibility failed to find any potential drug interaction on the metabolic pathways.

Elimination

Paracetamol elimination half-life varies from about 1 to 3 hours.
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.

Pharmacokinetic/pharmacodynamic relationship(s)

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

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.

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.

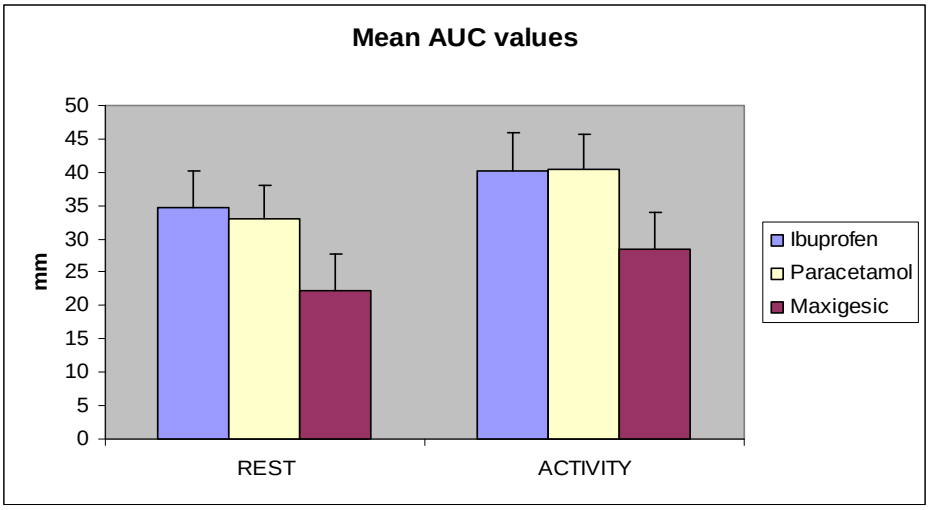
Clinical Trials

A prospective, Parallel Group, Double-Blind Comparison of the Analgesic Effect of Maxigesic®, Paracetamol alone, or Ibuprofen alone in 135 Patients with Post-Operative dental pain for 48 hours following oral surgery was conducted. The oral surgery was conducted under local or general anaesthetic with one dose of oral analgesic (2 tablets of paracetamol 500mg or ibuprofen 150mg or Maxigesic®) given pre-operatively. Total doses administered per 24 hours were paracetamol 4000mg, ibuprofen 1200mg and Maxigesic® (paracetamol 4000mg and ibuprofen 1200mg). 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 [SE3.055] respectively (p=0.007), and on activity 28.377 [SE 3.396] and 40.364 [SE 3.271] respectively (p=0.006).

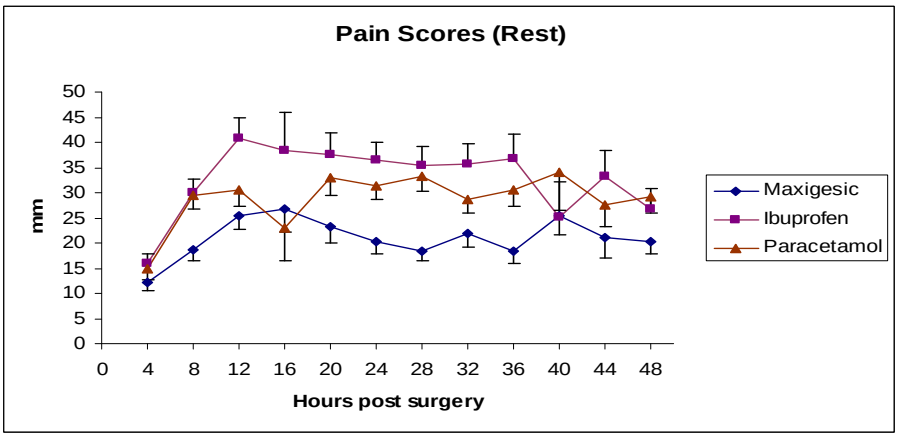
A similar outcome is seen for the Maxigesic® comparison where the AUCs over 48 hours showed the VAS for the combination drug were significantly lower than for ibuprofen at rest, 22.344 [SE 3.2] and 34.78 [SE 3.22] respectively (p=0.003) and during activity 28.377 [SE 3.396] and 40.217 [SE 3.418] respectively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

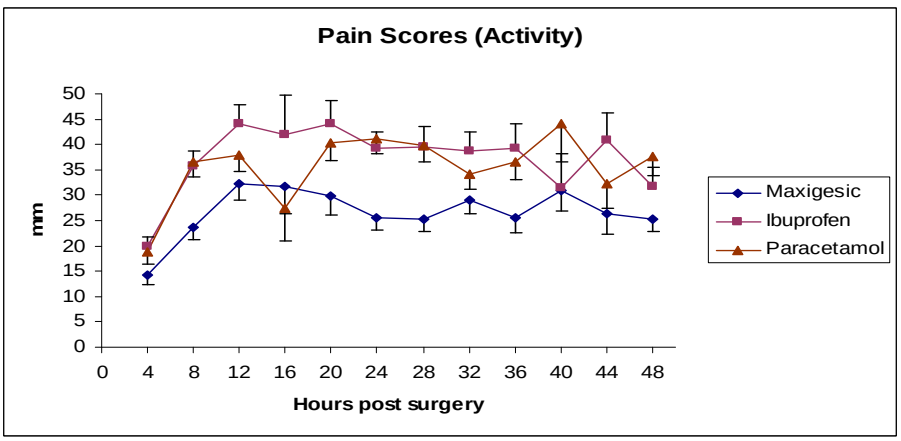
Figure 1: Means of Time-adjusted AUC at rest and on activity by treatment groups



A presentation of the pain records during the 48 hours also shows the Maxigesic® analgesic effect showed lower mean pain scores than either of its two active ingredients 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 temporary relief of mild to moderate pain associated with headache, dental pain, period pain, migraine, backache, rheumatic pain, muscular pain, pain after vaccination and sore throat, and reduction of fever. This product is especially suitable for pain which requires stronger analgesia than ibuprofen or paracetamol alone.

Contraindications

Maxigesic® is contraindicated for use:

- in patients with known hypersensitivity reaction to paracetamol, ibuprofen, aspirin, other NSAIDs or any other ingredients in the product.
- in patients with active alcoholism as chronic excessive alcohol ingestion may predispose patients to paracetamol hepatoxicity (due to the paracetamol component)
- in patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin, ibuprofen or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see Precautions, Pre-existing Asthma).
- in patients with a history of gastrointestinal bleeding or perforation, related to previous NSAID therapy. Ibuprofen should not be used in patients with active, or a history of, ulcerative colitis, Crohn's disease, recurrent peptic ulceration or gastrointestinal haemorrhage (defined as two or more distinct episodes of proven ulceration or bleeding).
- during the third trimester of pregnancy (see Use in pregnancy).
- in patients planning to become pregnant.
- during breastfeeding
- in patients with impaired kidney function, impaired liver function or heart problems
- in patients with conditions involving a tendency to bleed.

Precautions

Maxigesic® should not be taken with other products containing paracetamol, 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.

Use in Older Patients

No adjustment in labelled dosage is necessary for older patients who require paracetamol therapy. Those who require therapy for longer than a few days should consult their physician for condition monitoring; however, no reduction in recommended dosage is necessary. However, caution should be taken with regard to the use of ibuprofen as it 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
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

There is nothing in the available information on ibuprofen and paracetamol to suggest an increased or novel risk of genotoxicity or carcinogenicity with co-administration of ibuprofen and paracetamol.

Reproductive and Teratogenic Effects

No information was found about the potential effects of ibuprofen on mating behavior, or early embryonic development in animals. Paracetamol reportedly does not affect reproductive performance in mice.

When administered to pregnant rats and rabbits during the period of organogensis, ibuprofen reportedly does not affect fetal development in either species. When administered to pregnant mice throughout gestation, paracetamol reportedly results in reduced birth weights.

No information was found about the potential effects of ibuprofen on peri-/post-natal development in animals. When administered to mice throughout gestation and lactation, paracetamol reportedly resulted in reduced pup growth.

Reversible infertility has been reported in women on long-term NSAIDs.

There is nothing in the available information on ibuprofen and paracetamol to suggest an increased or novel risk of reproductive or developmental toxicity with co-administration of the two drugs in the form of Maxigesic®.

Potential Laboratory Test Interferences
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

Upper gastro-intestinal 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 this product is used at the prescribed dose for a few days.

This product 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 and Cerebrovascular Events

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. Maxigesic® is contraindicated in patients with heart problems.

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 Maxigesic® to patients with hypertension. Blood pressure should be monitored closely during initiation of treatment with Maxigesic® and at regular intervals thereafter.

All NSAIDs should not be used perioperatively in patients who have recently undergone coronary artery bypass graft (CABG) surgery and revascularisation procedures.

All NSAIDs should be prescribed at the lowest effective dose and the duration of treatment should be periodically reviewed and kept as short as possible.

Severe Skin Reactions

The active ingredients of this product may 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 discontinue the drug and consult their doctor at the first appearance of a skin rash or any other sign of hypersensitivity.

Pre-existing asthma

Products containing ibuprofen should not be administered to patients with aspirin sensitive asthma and should be used with caution in patients with pre-existing asthma.

Ophthalmological effects
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
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.

Aseptic Meningitis
For products containing 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
As with other drugs of this class, ibuprofen may mask the usual signs of infection by reducing fever.

Special Precautions
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.

Female Fertility
Ibuprofen:
The use of ibuprofen 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 the product should be considered.

Use in pregnancy

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.
NSAIDs inhibit 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 delay labour and birth.

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.

Further, there is inadequate information regarding the use of Maxigesic® in pregnancy. Therefore Maxigesic® should not be used during pregnancy or in patients planning to

become pregnant.

Use in lactation
Maxigesic® is not recommended for nursing mothers.

Interaction with other medicines

Paracetamol
The following interactions have been noted:

- anticoagulant drugs (e.g.warfarin):dosage may require reduction if paracetamol and anticoagulants are taken for a prolonged period of time
- antiepileptic medications: the likelihood of toxicity may be increased by the concomitant use of enzyme inducing agents
- 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
- hepatotoxic drugs or drugs that induce liver microsomal enzymes such as alcohol and anticonvulsant agents: the risk of paracetamol toxicity may be increased in patients receiving these drugs
- probenecid: may affect paracetamol excretion and plasma concentrations
- cholestyramine: reduces the absorption of paracetamol if given within 1 hour of paracetamol.
- isoniazid alone or combined with other drugs for tuberculosis: in patients receiving these drugs severe hepatotoxicity at therapeutic doses or moderate overdoses of paracetamol has been reported
- zidovudine and co-trimoxazole : severe hepatotoxicity has occurred after use of paracetamol in patients taking these drugs.

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.
- lithium: ibuprofen may decrease renal clearance and increase plasma concentration of lithium
- ACE inhibitors, beta-blockers and diuretics: ibuprofen may reduce the anti-hypertensive effect of these drugs and may cause natriuresis and hyperkalemia in patients under these treatments
- methotrexate: ibuprofen reduces methotrexate clearance
- cardiac glycosides: ibuprofen may increase the plasma levels of these drugs
- corticosteroids: the risk of ibuprofen-induced gastrointestinal bleeding may be

increased with concomitant use of oral corticosteroids
- zidovudine: ibuprofen may prolong bleeding time in patients treated with this drug
- probenecid, antidiabetic medicine and phenytoin: these medicines may interact with ibuprofen
- anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs) may increase the risk of gastrointestinal bleeding with ibuprofen.
- ibuprofen may decrease the excretion of aminoglycosides.
- concomitant administration of ibuprofen and aspirin is not generally recommended because of the potential of increased adverse effects. Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. 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.
- cyclosporine may increase risk of nephrotoxicity with ibuprofen.
- ibuprofen may increase the risk of nephrotoxicity when give with tacrolimus.
- concomitant administration of ibuprofen with CYP2C9 inhibitors may increase the exposure to ibuprofen (CYP2C9 substrate).

Adverse effects

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

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.

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.
- stomach ulcer
- ringing in the ears
- impaired kidney and liver function

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 and administration

Adults and Children over 12 years: The usual dosage is one to two tablets taken every six hours, as required, up to a maximum of eight tablets in 24 hours.

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

Do not break the tablet when taking the medicine.

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 and storage conditions

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

Available in blister pack containing 10, 16, 32, 50, 100 tablets.

Store below 30 °C.

Name and address of the Product Owner:

AFT Pharmaceuticals Ltd.
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Date of revision

9 October 2014