

## PRODUCT INFORMATION

### Name of the medicine

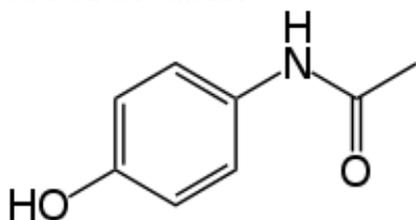
**Maxigesic<sup>®</sup>**

#### Paracetamol:

Chemical Name: N-acetyl-p-aminophenol

CAS number: 103-90-2

Structural Formula:

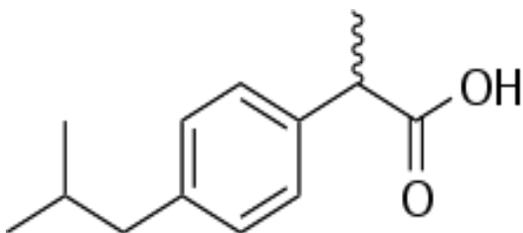


#### Ibuprofen:

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 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 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.

In another study, the effect of ibuprofen on the oxidative metabolism of paracetamol was evaluated in healthy volunteers under fasting conditions. The study results indicated that ibuprofen did not alter the amount of paracetamol undergoing oxidative metabolism, as the amount of paracetamol and its metabolites (glutathione-, mercapturate-, cysteine-, glucuronide- and sulfate-paracetamol) were similar when administered alone, as paracetamol, or with the concomitant administration of ibuprofen (as a fixed combination Maxigesic®).

#### 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.

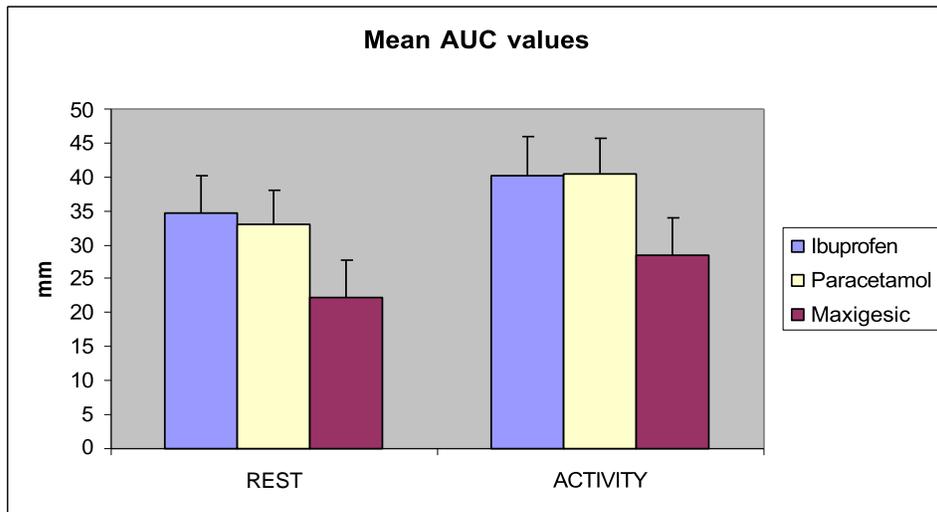
#### **Clinical Trials**

A prospective, Parallel Group, Double-Blind Comparison of the Analgesic Effect of Maxigesic<sup>®</sup>, 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 300mg or Maxigesic<sup>®</sup>) given pre-operatively. Total dose in the 24 hours were paracetamol 4000mg, ibuprofen 1200mg and Maxigesic<sup>®</sup>. 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<sup>®</sup> 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).

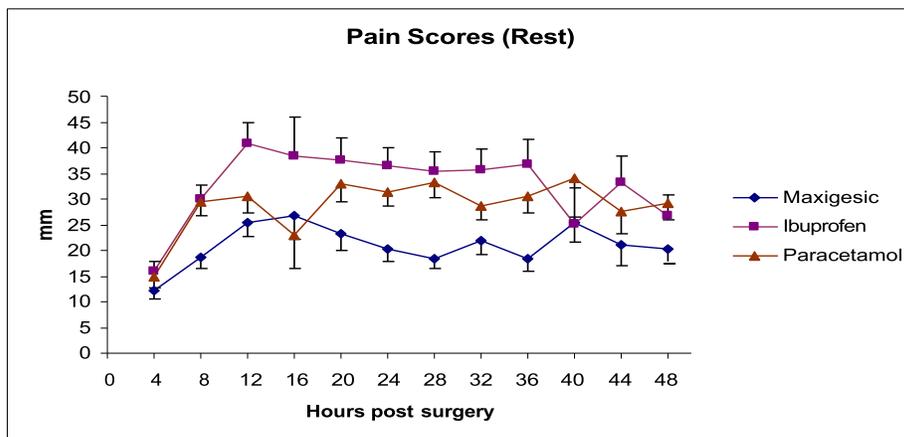
A similar outcome is seen for the Maxigesic<sup>®</sup> comparison where the AUCs over 48 hours showed the VAS for the combination drug were significantly lower than for ibuprofen at rest, 22.344 [SE 3.2] and 34.78 [SE 3.22] respectively (p=0.003) and during activity 28.377 [SE 3.396] and 40.217 [SE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

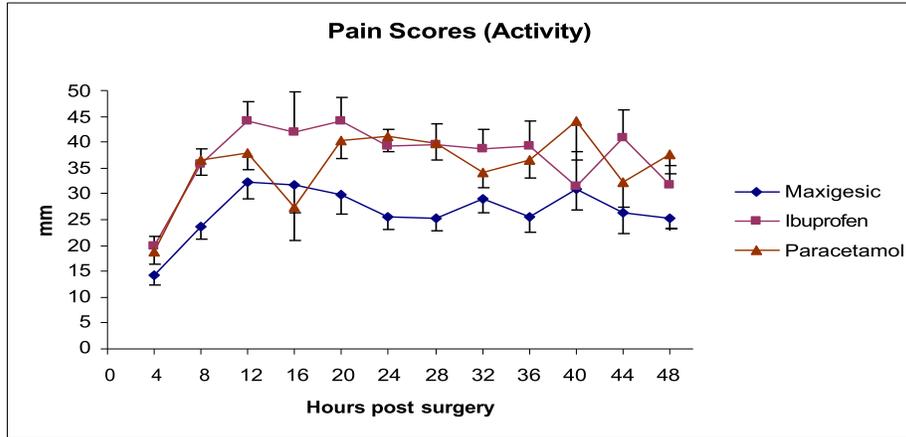
**Figure 1: Means of Time-adjusted AUC at rest and on activity by treatment groups**



A presentation of the pain records during the 48 hours also shows the Maxigesic<sup>®</sup> 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**





A double-blind, placebo-controlled, randomised, parallel group comparison trial was conducted in 159 participants experiencing pain from removal of 2-4 molars. Three different possible doses of Maxigesic<sup>®</sup> were evaluated and compared with that of placebo [N=49]. The doses corresponded to half [N=46], one [N=34] or two tablets [N=30] of Maxigesic<sup>®</sup> given four times a day for 24 hours.

The mean-adjusted Sum of Pain Intensity Difference [SPID] in all the Maxigesic<sup>®</sup> doses were significantly [p=0.004-0.002] higher than placebo consistent with each possible dose of Maxigesic<sup>®</sup> being more effective than placebo.

The results demonstrating the SPID, response rate, maximum VAS pain scores and percentage of patients requiring rescue medication for all four study groups (placebo, half, one and two tablet doses) are presented in the table below:

	Maxigesic <sup>®</sup> (two tablets) N=30	Maxigesic <sup>®</sup> (one tablet) N=34	Maxigesic <sup>®</sup> (half tablet) N=46	Placebo N=49
SPIDs (mm)				
<b>Mean (SD)</b>	<b>20.12(18.01)</b>	<b>20.44(20.78)</b>	<b>19.25(19.99)</b>	<b>6.63(19.79)</b>
<b>P value</b>	<b>0.004</b>	<b>0.002</b>	<b>0.002</b>	-
Response Rate* (%)				
<b>Yes (%)</b>	50.00%	44.10%	45.70%	18.4%
<b>P value</b>	<b>0.003</b>	<b>0.011</b>	<b>0.008</b>	-
Maximum VAS Pain Scores (mm)				
<b>Mean (SD)</b>	<b>51.13(13.22)</b>	<b>55.38(17.61)</b>	<b>54.98 (15.92)</b>	<b>61.20 (18.34)</b>
<b>P value</b>	<b>0.009</b>	<b>0.063</b>	<b>0.062</b>	-
Percentage of Participants Requiring Rescue Medication (%)				
<b>Yes (%)</b>	53.30%	61.80%	56.50%	81.60%
<b>P value</b>	<b>0.007</b>	<b>0.044</b>	<b>0.008</b>	-

\* Response rate = percentage of patients with a decrease of at least 50% in VAS pain score within 6 hours after the first dose

## Indications

Maxigesic<sup>®</sup> tablets are indicated for temporary relief of pain associated with: headache, migraine headache, tension headache, sinus pain, toothache, dental procedures, backache, sore throat, arthritis, tennis elbow, period pain, muscular pain, rheumatic pain, aches and pains associated with colds and flu. Reduces fever.

## Contraindications

Maxigesic<sup>®</sup> 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 hepatotoxicity (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 active gastrointestinal bleeding, peptic ulceration or other stomach disorders.
- during pregnancy or in patients planning to become pregnant
- during breastfeeding
- in patients with impaired kidney function, impaired liver function or heart problems
- in patients with heart failure
- in patients undergoing treatment of perioperative pain in setting of coronary artery bypass surgery (CABG).

## Precautions

Maxigesic<sup>®</sup> should not be taken with other products containing ibuprofen, paracetamol, 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 (see also Contraindications – renal impairment, heart failure).

### ***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 organogenesis, 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<sup>®</sup>.

#### ***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.

Maxigesic® should be used with caution, and at the lowest effective dose for the shortest duration, in patients with a history of gastrointestinal haemorrhage or a history of peptic ulcers since their condition may be exacerbated. It is contraindicated in patients with active gastrointestinal bleeding and in those with peptic ulcers or other stomach disorders.

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 Thrombotic 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. Patients with cardiovascular disease, history of atherosclerotic cardiovascular disease or cardiovascular risk factors may also be at greater risk. Maxigesic® is contraindicated in patients with heart problems.

Patients should be advised to remain alert for such cardiovascular events, even in the absence of previous cardiovascular symptoms. Patients should be informed about signs and/or symptoms of serious cardiovascular toxicity and the steps to take if they occur.

### ***Hypertension:***

Fluid retention, hypertension and oedema have been reported in association with NSAID therapy. 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 (see also Contraindications – heart failure). Blood pressure should be monitored closely during initiation of treatment with Maxigesic® and at regular intervals thereafter.

## ***Hepatic Effects***

As with other NSAIDs elevations of one or more liver function tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may resolve with continued therapy. Meaningful elevations (three times the upper limit of normal) of ALT or AST occurred in controlled trials in less than 1% of patients.

Patients should be advised to remain alert for hepatotoxicity and be informed about the signs and/or symptoms of hepatotoxicity (e.g. nausea, fatigue, lethargy, pruritis, jaundice, abdominal tenderness in the right upper quadrant and “flu-like” symptoms). Excessive use can be harmful and increase the risk of liver damage.

*Combination use of ACE inhibitors or angiotensin receptor antagonist, 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 (see also Contraindications – 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.

**Severe Skin Reactions**

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**

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.

**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 containing ibuprofen, by reducing fever this may mask the usual signs of infection.

**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.

**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<sup>®</sup> in pregnancy. Therefore Maxigesic<sup>®</sup> should not be used during pregnancy or in patients planning to become pregnant.

### **Use in lactation**

Maxigesic<sup>®</sup> 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 a 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

## 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.

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.

Maxigesic® should not be used for more than a few days at a time unless on medical

advice, in which case the patient should be reviewed regularly with regards to efficacy, risk factors and ongoing need for treatment.

## **Overdosage**

If an overdose is taken or suspected, ring the Poisons Information Centre (Australia 13 11 26, New Zealand 0800 764 766) for the most up-to date treatment recommendations. Excessive use can be harmful and increase the risk of heart attack, stroke or liver damage.

### **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.

## **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 8, 10, 12, 16, 20, 24, 30 tablets.

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

## **Name and address of the sponsor:**

AFT Pharmaceuticals Pty Ltd.  
113 Wicks Road  
North Ryde  
NSW 2113  
AUSTRALIA

Freephone 1800-097639 Free Fax: 1800-097810

## **Poisons Schedule of the medicine**

Pharmacy Medicine – S2  
Packs of  
8's  
10's  
12's

Pharmacist Only Medicine - S3  
Packs of  
16's  
20's  
24's  
30's

**Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG)**

23 December 2013

**Date of Most Recent Amendment**

3 August 2016