AUSTRALIAN PRODUCT INFORMATION

MAXOFEN
tablets

1 NAME OF THE MEDICINE

Ibuprofen and paracetamol

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains ibuprofen 200mg and paracetamol 500mg.

Excipients with known effect: Lactose (as part of the tablet coating).

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Tablets (white coloured, film-coated, capsule shaped, plain on one side and a breakline on the other side).

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

MAXOFEN tablets are used for temporary relief of acute (short term) pain and/or inflammation associated with headache, migraine headache, tension headache, sinus pain, toothache, dental procedures, backache, muscular aches and pains, period pain, sore throat, tennis elbow, rheumatic pain and arthritis, and the aches and pains associated with colds and flu. Reduces fever.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults under 65 years and children over 12 years: Take one tablet with fluid every 8 hours, as necessary. Do not take more than three tablets in 24 hours. Do not use for more than 3 days at a time (adults) or 2 days (adolescents aged 12 to 17 years), except on the advice of a doctor. MAXOFEN tablets are not recommended for children under 12 years of age or adults aged over 65 years.

4.3 CONTRAINDICATIONS

MAXOFEN tablets is contraindicated in:

- Patients with a known hypersensitivity to ibuprofen, paracetamol or any other constituent of the medicinal product,
- Patients with a history of hypersensitivity reactions (e.g. bronchospasm, angioedema, rhinitis or urticaria) associated with aspirin or other anti-inflammatory drugs or analgesic drugs,
- Patients with a history of, or an existing gastrointestinal ulceration/perforation or bleed, or other stomach disorder,
- Patients with impaired hepatic function, impaired renal function or heart failure,
- Patients undergoing treatment of perioperative pain in setting of coronary artery bypass surgery (CABG),
- Patients with asthma,
- Pregnancy,
- Patients with conditions that predispose to renal failure,
- Concomitant use with ibuprofen or other NSAID containing products, including cyclooxygenase-2 (COX-2) specific inhibitors and aspirin or other anti-inflammatories as there is an increased risk of adverse reactions,
- Concomitant use with other paracetamol-containing products as there is an increased risk of serious adverse effects; patients should be advised not to take with any other paracetamol-containing products. Immediate medical advice should be sought if this occurs, even if they feel well as this can result in an overdose,
- Patients aged 65 years and over and in children under 12 years.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The hazard of paracetamol overdose is greater in patients with noncirrhotic alcoholic liver disease. Immediate medical advice should be sought in the event of an overdose, even if the patient feels well, because of the risk of delayed, serious liver damage. Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.

Diabetes:
Caution is required in patients suffering from diabetes. Paracetamol falsely elevates continuous blood glucose monitor (CGM) readings compared to finger stick (BG meter) readings. This is applicable for those using CGM devices with or without an automated insulin delivery pump e.g. in type I diabetes.

Respiratory disorders:
Caution is required in patients with a history of bronchial asthma or allergic disease since NSAIDs have been reported to precipitate bronchospasm. The product is contraindicated in asthma (see *4.3 Contraindications*).

Renal and hepatic impairment:
The administration of NSAIDs may cause a dose dependent reduction in prostaglandin

formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. The product is contraindicated in patients with impaired renal or liver function or heart failure and in patients 65 years of age or older (see *4.3 Contraindications*). Renal function should be monitored in other at risk patients.

Cardiovascular and cerebrovascular effects:
Appropriate monitoring and advice are required for patients with a history of hypertension as fluid retention and oedema have been reported in association with NSAID therapy. The product is contraindicated in patients with heart failure (see *4.3 Contraindications*).

Clinical trial data suggest that the use of ibuprofen, particularly at high doses (2400 mg daily) may be associated with an increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. < 1200 mg daily) is associated with an increased risk of myocardial infarction.

Patients with uncontrolled hypertension, established ischemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with MAXOFEN after careful consideration. Similar consideration should be made before initiating treatment for patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking). The product is contraindicated in heart failure (see *4.3 Contraindications*).

Gastrointestinal bleeding, ulceration and perforation:
Gastrointestinal (GI) bleeding, ulceration and 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.

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 (SSRIs), or antiplatelet agents.

The product is contraindicated in patients with a history of GI toxicity including ulceration (see *4.3 Contraindications*). When GI bleeding or ulceration occurs in patients receiving MAXOFEN, the treatment should be withdrawn.

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

Dermatological:
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN), have been reported very rarely in association with the use of NSAIDs and paracetamol. 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. Use of this product should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Use in the elderly

MAXOFEN tablets are contraindicated in adults over the age of 65.

Paediatric use

MAXOFEN tablets are contraindicated in children under 12 years of age.

Effects on laboratory tests

No data available.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

This product is contraindicated in combination with: aspirin, other paracetamol containing products, other NSAIDs including cyclooxygenase-2 selective inhibitors, other anti-inflammatories and analgesics as concomitant use may increase the risk of adverse reactions (*see 4.8 Adverse Effects*).

This product (like any other paracetamol containing products) should be used with caution in combination with the following:

- **Chloramphenicol**. Increased plasma concentration of chloramphenicol.
- **Cholestyramine**. The speed of absorption of paracetamol is reduced by cholestyramine. Therefore, cholestyramine should not be taken within one hour if maximal analgesia is required.
- **Metoclopramide and domperidone**. The absorption of paracetamol is increased by metoclopramide and domperidone. However, concurrent use need not be avoided.
- **Warfarin**. 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.

This product (like any other ibuprofen containing products and NSAIDs) should be used with caution in combination with the following:

- **Anticoagulants**. NSAIDS may enhance the effects of anticoagulants (i.e. warfarin)
- **Antihypertensives**. NSAIDs may reduce the effects of these medicines.
- **Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs)**. Increased risk of gastrointestinal bleeding.

- **Cardiac glycosides**. NSAIDs may exacerbate cardiac failure, reduce glomerular filtration rate (GFT) and increase plasma glycoside levels.
- **Ciclosporin**. Increased risk of nephrotoxicity.
- **Corticosteroids**. Increased risk of gastrointestinal ulceration or bleeding.
- **Diuretics**. Reduced diuretic effect. Diuretics may increase the risk of nephrotoxicity of NSAIDs.
- **Lithium**. Decreased elimination of lithium.
- **Methotrexate**. Decreased elimination of methotrexate.
- **Mifepristone**. NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.
- **Quinolone 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.
- **Tacrolimus**. Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.
- **Zidovudine**. Increased risk of haematological toxicity when NSAIDs are given concomitantly with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV+ haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The use of the product may impair female fertility and is not recommended in women attempting to conceive.

Use in pregnancy

Australian Pregnancy Category C: Medicines 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.

There is no experience of use of this product in humans during pregnancy. Therefore this product is contraindicated for use during pregnancy.

Congenital abnormalities have been reported in association with NSAID administration in man; however these are low in frequency and do not appear to follow any discernible pattern. Use of NSAIDs during the last trimester of pregnancy may cause effects on the foetal cardiovascular system (risk of closure of ductus arteriosus), and the onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child.

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol use at the recommended dosage.

Use in Lactation

Ibuprofen and its metabolites can pass in very small amounts (0.0008% of the maternal dose) into the breast milk. No harmful effects to infants are known.

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding.

Therefore it is not necessary to interrupt breastfeeding for short-term treatment with the recommended dose of this product.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Following treatment with ibuprofen, the reaction time of patients may be affected. This should be taken into account where increased vigilance is required, e.g. when driving a car or operating machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trials with this combination of active ingredients have not indicated any other undesirable effects other than those for ibuprofen or paracetamol alone.

In clinical trials, administration of single or multiple doses was shown to have a safety profile comparable to that of placebo. The percentage of subjects who experienced side effects, as well as the individual side effects seen, were similar to the well documented profiles of paracetamol and ibuprofen administered alone.

The following is a list of adverse effects from pharmacovigilance data experienced by patients taking ibuprofen alone or paracetamol alone in short-term and long-term use. Adverse events may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms.

Common (occur in >1% and <10%)
Gastrointestinal. Abdominal pain, diarrhoea, dyspepsia, nausea, stomach discomfort and vomiting.
Investigations. Alanine aminotransferase increased, gammaglutamyltransferase increased and liver function tests abnormal with paracetamol. Blood creatinine increased and blood urea increased.

Uncommon (occur in >0.1% and <1%)
Gastrointestinal. Flatulence and constipation, peptic ulcer, perforation or gastrointestinal haemorrhage with symptoms of melaena, haematemesis sometimes fatal particularly in the elderly. Ulcerative stomatitis and exacerbation of ulcerative colitis and Crohn’s disease. Less frequently gastritis has been observed and pancreatitis reported.

Skin and subcutaneous tissue disorders. Rashes of various types (including urticarial) and pruritis. Angioedema and swelling of the face. Acute generalised exanthematous pustulosis.
Investigations. Aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatine phosphokinase increased, blood creatinine increased, haemoglobin decreased and platelet count increased.
Nervous system disorders. Headache and dizziness.

Very rare (occur in <0.01%)
Blood and lymphatic system disorders. Haematopoietic disorders (agranulocytosis, anaemia, aplastic anaemia, haemolytic anaemia, leucopaenia, neutropaenia, thrombocytopaenia and pancytopaenia). First signs are fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising and nose bleeds.
Immune system disorders. Hypersensitivity reactions have been reported. These may consist of nonspecific allergic reactions and anaphylaxis. Symptoms of severe hypersensitivity reactions can include facial, tongue and larynx swelling, dyspnoea, tachycardia, hypotension, anaphylaxis, angioedema or severe shock.
Psychiatric disorders. Confusion, depression and hallucinations.
Nervous system disorders. Paraesthesia, optic neuritis and somnolence. Single cases of aseptic meningitis in patients with existing autoimmune disorders (e.g. systemic lupus erythematosus and mixed connective tissue disease) during treatment with ibuprofen with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed.
Eye disorders. Visual disturbance.
Ear and labyrinth disorders. Tinnitus and vertigo.
Cardiac disorders. Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. Clinical trial and epidemiological data suggest that use of ibuprofen, particularly at high doses (2400mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke).
Respiratory, thoracic and mediastinal disorders. Respiratory reactivity including asthma, exacerbation of asthma, bronchospasm and dyspnoea.
Hepatobiliary disorders. Abnormal liver function, hepatitis and jaundice. In overdose, paracetamol can cause acute hepatic failure, hepatic failure, hepatic necrosis and liver injury.
Skin and subcutaneous tissue disorders. Hyperhidrosis, purpura and photosensitivity. Exfoliative dermatoses. Bullous reactions including bullous erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.
Renal and urinary disorders. Nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome and acute and chronic renal failure.
General disorders and administration site conditions. Fatigue and malaise.

Hypersensitivity reactions have been reported following treatment with both paracetamol and ibuprofen. These may consist of the following:

a) Nonspecific allergic reactions and anaphylaxis

b) Respiratory tract reactivity e.g. asthma, aggravated asthma, bronchospasm and dyspnoea
c) Assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and more rarely bullous dermatoses (including toxic epidermal necrolysis and bullous erythema multiforme).

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at *www.tga.gov.au/reporting-problems*.

4.9 OVERDOSE

For advice on the management of overdose please contact the Poisons Information Centre on 13 11 26 (Australia) or 0800 766 764 (New Zealand).

Paracetamol:
Liver damage is possible in adults who have taken 10g (equivalent to 20 tablets) or more of paracetamol. Ingestion of 5g (equivalent to 10 tablets) or more of paracetamol may lead to liver damage if the patient has one or more of the risk factors listed below:
a) Is on long-term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's wort or other drugs that induce liver enzymes
b) Regularly consumes alcohol in excess of recommended amounts
c) Is likely to be glutathione depleted, e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms. Symptoms of paracetamol overdose in the first 24 hours include pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion as liver function tests become abnormal. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Management. Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines.
Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentrations should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable).

Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol, however the maximum protective effect is obtained up to 8 hours postingestion. The effectiveness of the antidote declines after this time.
If required, the patient should be given intravenous N-acetylcysteine in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas outside hospital.
Patients who present with serious hepatic dysfunction beyond 24 hours from ingestion should be managed in accordance with established guidelines.

Ibuprofen:

Symptoms. Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, 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 drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning, metabolic acidosis may occur and prolong the prothrombin time (PT) and increase the international normalised ratio (INR), probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur if there is coincident dehydration. Exacerbation of asthma is possible in asthmatics.

Management. 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

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action:
The pharmacological actions of ibuprofen and paracetamol differ in their site and mode of action. These complementary modes of action result in greater antinociception than the single actives alone. Ibuprofen possesses analgesic, antipyretic and anti-inflammatory properties, similar to other nonsteroidal anti-inflammatory drugs (NSAID). Its mechanism of action is unknown but it is thought to be through peripheral inhibition of cyclooxygenases and subsequent prostaglandin synthetase inhibition. Paracetamol is a para-aminophenol derivative that exhibits analgesic and antipyretic activity. Paracetamol has minimal anti-inflammatory action. The precise mechanism of action remains uncertain; it is believed to include inhibition of prostaglandin synthesis, primarily within the central nervous system.

Clinical Trials:
No data available.

5.2 PHARMACOKINETIC PROPERTIES

Ibuprofen
Absorption:
Ibuprofen is well absorbed from the gastrointestinal tract.

Distribution:
It is highly bound (90-99%) to plasma proteins.

Metabolism:
It is extensively metabolised to inactive compounds in the liver, mainly by glucuronidation.

Excretion:
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.

Paracetamol
Absorption:
After oral administration paracetamol is absorbed rapidly and completely from the small intestine; peak plasma levels occur 20 to 120 minutes after administration. Food intake delays paracetamol absorption.

Distribution:
Paracetamol is uniformly distributed throughout most body fluids; the apparent volume of distribution is 1 to 1.2 L/kg. Paracetamol can cross the placenta and is excreted in milk. Plasma protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

Metabolism:
Paracetamol is metabolised by the hepatic microsomal enzyme system. In adults at therapeutic doses paracetamol is mainly conjugated with glucuronide (45-55%) or sulfate (20-30%). A minor proportion (less than 20%) is metabolised to catechol derivatives and mercapturic acid compounds via oxidation. Paracetamol is metabolised differently by infants and children compared to adults, the sulfate conjugate being predominant.

Excretion:
Paracetamol is excreted in the urine mainly as the glucuronide and sulfate conjugates. Less than 5% is excreted as unchanged paracetamol with 85-90% of the administered dose eliminated in the urine within 24 hours of ingestion. Excretion is almost complete within 24 hours.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity:
No data available.

Carcinogenicity:
No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

MAXOFEN tablets also contain colloidal anhydrous silica, croscarmellose sodium, magnesium stearate, maize starch, microcrystalline cellulose, povidone, stearic acid, purified water, dichloromethane, isopropyl alcohol and Opadry White OY-LS-58900 coating.

6.2 INCOMPATIBILITIES

Incompatibilities were not assessed as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

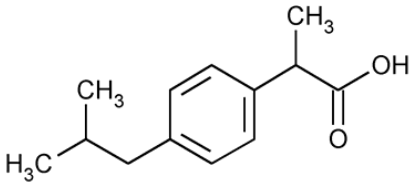
MAXOFEN tablets in PVC/PVDC/Aluminium blisters are registered in packs of 10, 12, 24 and 30 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure - Ibuprofen:

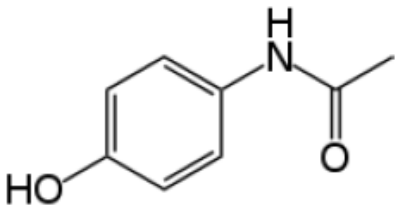


Ibuprofen is (±)-2-(*p*-isobutylphenyl) propionic acid. Ibuprofen is a white crystalline solid with a melting point of 74 - 77ºC and is practically insoluble in water (< 0.1mg/mL) and readily soluble in organic solvents such as ethanol and acetone.

CAS number:

15687-27-1

Chemical structure - Paracetamol:



Paracetamol is *N*-(4-hydroxyphenyl)acetamide. It is sparingly soluble in water, freely soluble in alcohol, and very slightly soluble in ether and methylene chloride.

CAS number:

103-90-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

S3 – Pharmacist Only Medicine (24 and 30 tablet packs)

S2 – Pharmacy Medicine (10 and 12 tablet packs)

8 SPONSOR

Nova Pharmaceuticals Australasia Pty Ltd
Suite 305, 10 Norbrik Drive,
Bella Vista, NSW, 2153
novapharm.com.au.

9 DATE OF FIRST APPROVAL

15 January 2019

10 DATE OF REVISION

Date of this document: 17 January 2020

Summary table of changes

Section Changed	Summary of new information