AUSTRALIAN PRODUCT INFORMATION

IBUPANE®

(paracetamol / ibuprofen) tablet

1 NAME OF THE MEDICINE

Paracetamol and ibuprofen

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg paracetamol and 200 mg ibuprofen as the active ingredients.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Tablets are white to off white, oval shaped, biconvex, film-coated pearlescent tablets plain on both sides.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

The lowest effective dose should be used for the shortest duration necessary to relieve symptoms (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Adults under 65 years of age and children over 12 years: Take 1 tablet three times a day when necessary (every 8 hours).

Keep to the recommended dose. IBUPANE should not be used for more than 3 days at a time (or not more than 2 days at a time for adolescents aged 12 to 17 years) unless on medical advice, in which case the patient should be reviewed regularly with regard to efficacy, risk factors and ongoing need for treatment.

Do not give to children under 12 years of age.

Elderly: do not give to adults aged 65 years and over.

Pregnancy: see Section 4.3 CONTRAINDICATIONS and Section 4.6 FERTILITY, PREGNANCY, AND LACTATION.

Monitoring advice: if symptoms persist please consult your healthcare professional.

4.3 CONTRAINDICATIONS

This product is contraindicated in patients with:

- Known hypersensitivity or idiosyncratic reaction to ibuprofen, paracetamol or any other ingredients in the medicinal product
- History of hypersensitivity reactions (e.g. bronchospasm, angioedema, rhinitis or urticaria) associated with aspirin or other NSAIDs or analgesic drugs
- Asthma

- Pregnancy (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION)
- History of, or an existing gastrointestinal ulceration / perforation or bleed, or other stomach disorder
- Impaired hepatic function, impaired renal function or heart failure
- Conditions that predispose to renal failure
- Taking other products containing ibuprofen or other NSAID-containing products including cyclooxygenase-2 (COX-2) specific inhibitors and aspirin or other anti-inflammatory medicines as there is an increased risk of adverse reactions
- Taking other paracetamol-containing products as there is an increased risk of serious adverse effects; patients should be advised not 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.
- Aged 65 years and over and in children under 12 years
- Undergoing treatment of perioperative pain in setting of coronary artery bypass surgery (CABG).

Refer to Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS for additional information.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The hazard of paracetamol overdose is greater in patients with non-cirrhotic 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. This product is contraindicated in patients with asthma (see Section 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 Section 4.3 CONTRAINDICATIONS). Renal function should be monitored in other at risk patients.

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 clinical 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, pruritus, jaundice, abdominal tenderness in the right upper quadrant and “flu-like” symptoms).

Cardiovascular and cerebrovascular effects

As with other NSAIDs, excessive or prolonged use of ibuprofen may increase the risk of serious cardiovascular events, including myocardial infarction and stroke. Patients with cardiovascular disease, history of atherosclerotic cardiovascular disease or cardiovascular risk factors may also be at greater risk.

Appropriate monitoring and advice are required for patients with a history of hypertension as fluid retention and oedema have been reported in associated with NSAID therapy. Patients taking antihypertensives with NSAIDs may have an impaired antihypertensive response. The product is contraindicated in patients with heart failure (see Section 4.3 CONTRAINDICATIONS).

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.

Clinical 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 ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with this product 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 Section 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 is 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 Section 4.3 CONTRAINDICATIONS).

Treatment with this product should be stopped if GI bleeding or ulceration occurs.

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.

Skin and subcutaneous tissue disorders

Dermatological serious skin reactions, some of them fatal including exfoliative dermatitis, Stevens Johnson syndrome, Drug Reaction with Eosinophilia with Systemic Symptoms (see DRESS) 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.

Severe skin reactions

Severe skin reactions such as acute generalised exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing products. The acute pustular eruption may occur with ibuprofen-containing products. The acute pustular eruption may occur within the first 2 days of treatment, with fever, and numerous, small, mostly non-follicular pustules arising on a widespread oedematous erythema and mainly localised on the skin folds, trunk, and upper extremities. Patients should be carefully monitored. If signs and symptoms such as pyrexia, erythema, or many small pustules are observed, administration of IBUPANE tablets should be discontinued and appropriate measures taken if needed.

Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS)

DRESS has been reported in patients using NSAIDs. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue the NSAID and evaluate the patient immediately.

Masking of symptoms of underlying infections

As with other drugs of this class, ibuprofen can mask the symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When IBUPANE tablet is administered for fever or pain relief in relation to infection, monitoring the infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.

IBUPANE tablets 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.

Use in the Elderly

Ibuprofen is contraindicated in adults aged 65 years and over because of an increased risk of adverse effects, in particular heart failure, gastro-intestinal ulceration and renal impairment.

The elderly is also more likely to have age related renal impairment.

Paediatric Use

The product is contraindicated in children under 12 years of age since no investigations have been carried out with this product in this age group.

Effects on Laboratory Tests

No data available.

Refer to Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS for additional information.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

This product is contraindicated in combination with:

- Aspirin
- Other paracetamol containing products
- Other NSAIDs including cyclo-oxygenase-2 selective inhibitors
- Other anti-inflammatories and analgesics

As concomitant use may increase the risk of adverse reactions.

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

- Chloramphenicol: increased plasma concentration of chloramphenicol.

- Colestyramine: the speed of absorption of paracetamol is reduced by colestyramine. Therefore colestyramine should not be taken within 1 hour if maximal analgesia is required.

- Flucloxacillin: Concurrent use of paracetamol and with flucloxacillin is associated with an increased risk of metabolic acidosis especially in patients with severe renal impairment, sepsis, malnutrition and chronic alcoholism

- Isoniazid may increase paracetamol toxicity

- Liver enzyme-inducing drugs: Drugs which induce or regulate liver microsomal enzymes (cytochrome p-450 isoenzyme 2E1), such as anticonvulsants (including phenytoin, barbiturates, carbamazepine) and alcohol, may increase the hepatoxic potential of paracetamol.

- Paracetamol absorption is increased by drugs which increase gastric emptying, e.g. metoclopramide and domperidone, and decreased by drugs which decrease gastric emptying, e.g. propantheline, antidepressants with anticholinergic properties and narcotic analgesics.

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

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

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

- Anticoagulants: Ibuprofen interferes with the stability of INR and may increase the 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

- Antihypertensives: Ibuprofen, like other NSAIDs may reduce the antihypertensive effect of ACE inhibitors and beta-blockers and diuretics and may cause natriuresis and hyperkalemia in patients under these treatments

- Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding

- Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce glomerular filtration rate (GFR) and increase plasma glycoside levels

- Ciclosporin: increased risk of nephrotoxicity

- Corticosteroids: an increased risk of gastrointestinal ulceration or bleeding

- Diuretics: reduced diuretic effect. Diuretics may increase the risk of nephrotoxicity of NSAIDs

- Lithium: Ibuprofen may decrease the renal clearance and increase plasma concentrations of lithium. Lithium plasma concentrations should be monitored in patients on concurrent ibuprofen therapy.

- Methotrexate: Ibuprofen reduces methotrexate clearance. Use of high doses of methotrexate concomitantly with NSAIDs should be avoided and caution should be used if low doses of methotrexate are administered concomitantly with ibuprofen.

- Aspirin and other NSAIDs: Concurrent use of ibuprofen with aspirin or other NSAIDs can lead to increased gastrointestinal adverse effects.

- 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 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 (Category C)

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.

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 malformation. These effects may be reversible.

Further, there is insufficient experience with the safety 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.

Oligohydramnios and Neonatal Renal Impairment:

Use of NSAIDs from about 20 weeks gestation may cause neonatal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment.

These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some post-marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required. If, after careful consideration of alternative treatment options for pain management, NSAID treatment is necessary from about 20 weeks, limit use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if treatment extends beyond 48 hours. Discontinue treatment with NSAIDs if oligohydramnios occurs.

Use in Lactation

Paracetamol appears in breast milk but not in a clinically significant amount. Available published data do not contraindicate breastfeeding. Maternal ingestion of paracetamol in recommended doses does not appear to present a risk to breastfed infants. Ibuprofen and its metabolites can appear in breast milk in very low concentrations and is unlikely to affect the breast fed infant adversely.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients experiencing dizziness or drowsiness while taking IBUPANE tablets should refrain from driving a vehicle or operating machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

In clinical trials, the product administered in 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 minimized 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, gamma glutamyl transferase increased and liver function tests abnormal with paracetamol. Blood creatinine increased and blood urea increased.
- Skin and subcutaneous tissue disorders: hyperhidrosis

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 face. Acute generalised exanthematous pustulosis (AGEP).
- 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.
- Immune system disorders: Hypersensitivity with urticaria and pruritus

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 non-specific 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 (2400 mg 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: 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.

Unknown frequency (cannot be estimated from the available data)

- Pregnancy, puerperium and perinatal conditions: Oligohydramnios, neonatal renal impairment

- Skin and subcutaneous tissue disorders: Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP) and photosensitivity reactions

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

- Non-specific allergic reactions and anaphylaxis.

- Respiratory tract reactivity e.g. asthma, aggravated asthma, bronchospasm and dyspnoea.

- 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 information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

Paracetamol:

Liver damage is possible in adults who have taken 10 g (equivalent to 20 tablets) or more of paracetamol. Ingestion of 5 g (equivalent to 10 tablets) or more of paracetamol may lead to liver damage if the patient has one or more of the risk factors 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. CNS stimulation and delirium may occur initially, followed by CNS depression, stupor, hypothermia, rapid shallow breathing, hypotension and circulatory failure. Shock may also develop, as well as seizures and coma. Cardiac arrhythmias and pancreatitis have been reported.

Additional information on special patient populations

An increased risk of liver damage from paracetamol overdosing has been associated with:

- Patients taking isoniazid

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 concentration 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 post-ingestion. The effectiveness of the antidote declines sharply 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 co-incident 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

Paracetamol's analgesic mechanism of action has not been fully elucidated, but may involve blocking impulse generation at the bradykinin sensitive chemoreceptors that evoke pain.

The antipyretic effect of paracetamol rises from its ability to block the action of prostaglandin synthetase and so prevent the synthesis of prostaglandins in response to the pyrogen stimulus in the region of the anterior hypothalamus.

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 synthetase inhibition.

Clinical Trials

Not data available.

5.2 PHARMACOKINETIC PROPERTIES

Paracetamol: After oral administration, paracetamol is absorbed rapidly and completely from the small intestine; peak plasma levels occur 30 to 120 minutes after administration. 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. Paracetamol is metabolised by the hepatic microsomal enzyme system. In adults, at therapeutic doses, paracetamol is mainly conjugated with glucuronide (45 to 55%) or sulfate (20 to 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.

A minor hydroxylated metabolite, which is usually produced in very small amounts by mixed function oxidases in the liver and detoxified by conjugation with liver glutathione, may accumulate following paracetamol overdose and cause liver damage.

Paracetamol is excreted in the urine mainly as the glucuronide and sulfate conjugates. Less than 5% is excreted as unchanged paracetamol, with 85 to 90% of the administered dose eliminated in the urine within 24 hours of ingestion. The elimination half-life varies from one to four hours. Food intake delays paracetamol absorption.

Ibuprofen: It is well absorbed from the gastrointestinal tract after oral administration with peak serum levels occurring after 1-2 hours. It is highly bound (90-99%) to plasma proteins and consequently, this characteristic of the drug should be considered when prescribing ibuprofen together with other drugs that bind to the same site on human serum albumin.

Apparent volume of distribution is 0.14L/kg. Ibuprofen and its metabolites readily cross the placental barrier in pregnant animals (rabbits & rats). It is not known if ibuprofen enters the cerebrospinal fluid.

90% of ibuprofen is metabolised to inactive compounds in the liver, mainly by glucuronidation, to produce two metabolites - a hydroxylated compound and a carboxylated compound. 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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Pregelatinised maize starch, povidone, crospovidone, microcrystalline cellulose, colloidal anhydrous silica, magnesium stearate, hypromellose, purified talc, titanium dioxide and OPADRY fx special effects film coating system 63F97546 SILVER (ARTG PI No: 106945).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine. See Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**.**

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

The products are available in PVC/PVDC/Al blister packs of 4, 5, 6, 8, 10, 12, 16, 20, 24 and 30 tablets.

Not all pack sizes are marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 267396 – IBUPANE paracetamol 500 mg and ibuprofen 200 mg film coated tablet blister

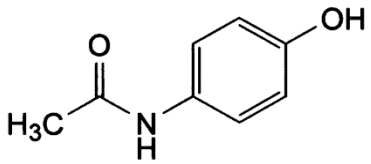
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Paracetamol:



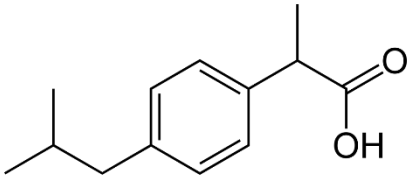
Chemical name: *N*-(4-Hydroxyphenyl)acetamide

Molecular Formula: $C_8H_9NO_2$

Molecular weight: 151.2

Paracetamol is a white or almost white crystalline powder. It is sparingly soluble in water, freely soluble in alcohol, very slightly soluble in methylene chloride. Paracetamol is an analgesic and antipyretic.

Ibuprofen:



Chemical name: 2-(4-Isobutylphenyl) propionic acid

Molecular Formula: $C_{13}H_{18}O_2$

Molecular weight: 206.3

Ibuprofen is a white or almost white powder or crystals with a characteristic odour. Practically insoluble in water, soluble 1 in 1.5 of alcohol, 1 in 1 of chloroform, 1 in 2 of ether and 1 in 1.5 of acetone; soluble in aqueous solutions of alkali hydroxides and carbonates.

CAS Number

Paracetamol: 103-90-2

Ibuprofen: 15687-27-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

S3 (Pharmacist Only Medicine): 16, 20, 24 and 30 tablet pack sizes

S2 (Pharmacy Medicine): 4, 5, 6, 8, 10 and 12 tablet pack sizes

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

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Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

19/01/2016

10 DATE OF REVISION

12/09/2023

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial change
4.2	Additional dosage information
4.5	Additional of drug interaction with diuretics
4.8	Additional adverse events for unknown frequency

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