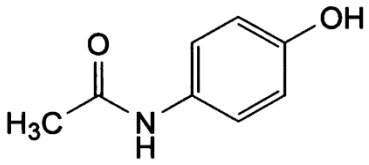
NAME OF THE MEDICINE

Paracetamol and Ibuprofen

Paracetamol:



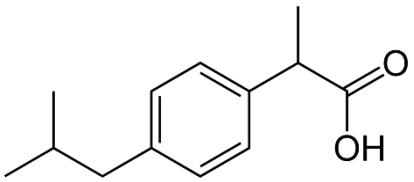
Molecular Formula: $C_8H_9NO_2$

Molecular weight: 151.2

CAS: 103-90-2

Ibuprofen:

Structure



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

Molecular weight: 206.3

CAS: 15687-27-1

DESCRIPTION

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 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.

Actives: Each tablet contains Paracetamol 500mg and Ibuprofen 200mg

Excipients: pregelatinised maize starch, povidone, crospovidone, microcrystalline cellulose, colloidal anhydrous silica, magnesium stearate, hypromellose, purified talc, titanium dioxide and Opadry FX silver.

PHARMACOLOGY

Pharmacodynamics

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.

Pharmacokinetics

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.

CLINICAL TRIALS

Not available

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.

CONTRAINDICATIONS

- Known hypersensitivity or idiosyncratic reaction to ibuprofen, paracetamol, or any other ingredients in the product listed in the description section above
- Hypersensitivity to aspirin or other NSAIDs or analgesic drugs
- Asthma
- Pregnancy
- History of, or active gastrointestinal bleeding or peptic ulceration, or other stomach disorder
- Impaired hepatic function, impaired renal function or heart failure
- Conditions that predispose to renal failure
- Taking other products containing ibuprofen, paracetamol, aspirin, salicylates or with other anti-inflammatory medicines (see section on **Interactions with Other Medicines**)
- Children under 12 years

Refer to Interactions with Other Medicines for additional information.

PRECAUTIONS

IBUPANE tablets should be administered with caution in patients with:

- Diabetes
- Respiratory disorders: NSAIDs have been reported to precipitate bronchospasm. This product is contraindicated in patients with asthma (see **CONTRAINDICATIONS**)
- Renal and hepatic impairment: NSAIDs may cause dose-dependent reduction in prostaglandin formation and precipitate renal failure. Excessive or prolonged use of ibuprofen may increase the risk of heart attack, stroke or liver damage. The product is contraindicated in patients with impaired renal or liver function or heart failure.

The hazard of paracetamol overdose is greater in patients with non-cirrotic 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 minimized by using the lowest effective dose for the short duration necessary to control symptoms.

- Cardiovascular and cerebrovascular effects

As with other NSAIDs, excessive or prolonged use of ibuprofen may increase the risk of heart attack or stroke.

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. The product is contraindicated in patients with heart failure (see **CONTRAINDICATIONS**).

Clinical data suggest that the use of ibuprofen, particularly at high doses (2400mg 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. < 1200mg 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. hypertensions, hyperlipidaemia, diabetes mellitus and smoking). The product is contraindicated in heart failure (see **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 advises 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 **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.

- 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 t 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.

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

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.

Refer to 'Interactions with other medicines' for additional information.

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.

Further, there is insufficient experience with the safety of use of ibuprofen in humans during pregnancy.

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.

There is inadequate information regarding the use of IBUPANE tablets in pregnancy. Therefore this medicine should not be used during pregnancy or in patients planning to become pregnant.

Use in lactation

Paracetamol appears in breast milk in low concentrations (<0.2%). Maternal ingestion of paracetamol in recommended doses does not appear to present a risk to breastfed infants. Ibuprofen appears in breast milk in very low concentrations and is unlikely to affect the breast fed infant adversely.

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.

Use in the elderly

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

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

INTERACTIONS WITH OTHER MEDICINES

This product is contraindication 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.

Paracetamol. The following interactions have been noted

- Anticoagulant drugs (warfarin) - dosage may require reduction if this medication and anticoagulants are taken for a prolonged period of time.
- Paracetamol absorption is increased by drugs which increase gastric emptying, e.g. metoclopramide, and decreased by drugs which decrease gastric emptying, e.g. propantheline, antidepressants with anticholinergic properties and narcotic analgesics.
- Paracetamol may increase chloramphenicol concentrations.
- The likelihood of paracetamol toxicity may be increased by the concomitant use of other hepatotoxic drugs or liver microsomal enzyme inducing agents, such as alcohol or antiepileptic drugs.
- Paracetamol excretion may be affected and plasma concentrations altered when given with probenecid.
- Cholestyramine reduces the absorption of paracetamol if given within 1 hour of paracetamol.

Ibuprofen. The following interactions have been noted

- 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
- 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

- Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce glomerular filtration rate (GFR) and increase plasma glycoside levels.
- Corticosteroids: An increased risk of gastrointestinal bleeding may occur with corticosteroids.
- 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.
- Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs): Concurrent administration with ibuprofen may prolong bleeding time in patients.
- Cyclosporin: increased risk of nephrotoxicity
- Mifepristone; NSAIDs should not be used for 8 – 12 days after mifepristone administration as NSAIDs cane 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 increase in nephrotoxicity
- Zidovudine: increased risk of heamatological toxicity. There is evidence of an increased risk of haemarthroses and haematoma in HIV + haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

ADVERSE EFFECTS

Paracetamol: Reports of adverse reactions are rare. Although the following reactions have been reported, a causal relationship to the administration of paracetamol has been neither confirmed nor refuted: dyspepsia, nausea, allergic and hematological reactions.

Ibuprofen: Report of adverse reactions 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 - – increased risk of myocardial infarction or stroke, particularly with higher doses and longer duration of use, and in the elderly. Fluid retention and in some cases oedema. 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: Take 1 tablet three times a day when necessary (every 8 hours).

Keep to the recommended dose. Do not take for more than 3 days at a time (2 days for adolescents aged 12 to 17 years).

Do not give to children under 12 years of age.

OVERDOSAGE

Symptoms

Paracetamol: Toxic symptoms include vomiting, abdominal pain, hypotension, sweating, central stimulation with exhilaration and convulsions in children, drowsiness, respiratory depression, cyanosis and coma. The most serious adverse effect of acute overdosage of paracetamol is a dose dependent, potentially fatal hepatic necrosis.

In adults, hepatotoxicity may occur after ingestion of a single dose of paracetamol 10 to 15 g; a dose of 25 g or more is potentially fatal.

Symptoms during the first two days of acute poisoning by paracetamol do not reflect the potential seriousness of the intoxication.

Major manifestations of liver failure, such as jaundice, hypoglycaemia and metabolic acidosis, may take at least three days to develop.

Ibuprofen: Symptoms of overdose with ibuprofen include nausea, vomiting, abdominal pain, dizziness, drowsiness, nystagmus, blurred vision, tinnitus and rarely, metabolic acidosis and loss of consciousness.

Treatment:

If an overdose is taken or suspected, immediately contact the Poisons Information Centre (in Australia, call 131 126; in New Zealand call 0800 764 766) for advice, or go to a hospital straight away even if you feel well because of the risk of delayed, serious liver damage.

For information on the management of overdosage, contact the Poison Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Ibupane	:	Tablets are white to off white, oval shaped, biconvex, film-coated pearlescent tablets plain on both side. The products are available in blister packs of 4, 5, 6, 8, 10, 12, 16, 20, 24 and 30 tablets.* Not all pack sizes are marketed. Store below 25°C

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Schedule 3.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

19/01/2016

DATE OF MOST RECENT AMENDMENT

Aug2016

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