Panafen* Plus
Product Information

COMPOSITION

Actives: Ibuprofen 200 mg, codeine phosphate 12.8 mg

Inactives: cellulose-microcrystalline, vegetable oil-hydrogenated, sodium starch glycollate, silica-colloidal anhydrous, lactose, cellulose-powdered, hypromellose, macrogol 400.

DESCRIPTION

Ibuprofen

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

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

MW: 206.3

CAS: 15687-27-1

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.

Codeine phosphate.

Chemical name: (5R,6S)-7, 8-didehydro-4,5- epoxy-3-methoxy-N-methylmorphinan-6-ol dihydrogen orthophosphate hemihydrate

Molecular formula: $C_{18}H_{21}NO_3H_3PO_4.½H_2O$

MW: 406.4

CAS: 41444-62-6

Codeine phosphate is a small, colourless, odourless crystal or a white, odourless crystalline powder. It is soluble in four parts water, slightly soluble in ethanol (96%), practically insoluble in chloroform and ether.

PHARMACOLOGY

It is thought that ibuprofen produces an anti-inflammatory effect at least in part by inhibiting prostaglandin synthetase. Ibuprofen has shown anti-inflammatory, analgesic and antipyretic activity in both animal and human studies.

Codeine phosphate is a narcotic analgesic acting on central opiate receptors, although its pharmacological effects are thought to be largely due to its biotransformation to morphine.

Pharmacokinetics

Absorption: Ibuprofen is well absorbed after oral administration with peak serum levels occurring after one to two hours.

Codeine is well absorbed from the gastrointestinal tract and peak plasma concentrations are reached one hour after oral administration. Onset of action occurs in 15 to 30 minutes and analgesia is maintained for four to six hours.

Distribution: The apparent volume of distribution for ibuprofen is 0.14 L/kg. Ibuprofen and its metabolites readily cross the placental barrier in pregnant rabbits and rats. It is not known if the drug enters the cerebrospinal fluid. 99% of ibuprofen is protein bound. The high protein binding of the drug should be borne in mind when prescribing ibuprofen together with other protein bound drugs that bind to the same site on human serum albumin.

Codeine is rapidly distributed to skeletal muscles, kidneys, liver, gastrointestinal tract, lungs, spleen and brain. It crosses the placenta and is distributed in low levels in breast milk.

Metabolism: 90% of ibuprofen is metabolised in the liver to produce two major metabolites, a hydroxylated and carboxylated compound.

Codeine is metabolised mainly in the liver. The major metabolic pathway involves glucuronidation of codeine to codeine-6-glucuronide. Codeine can also undergo O- and N-demethylation catalysed by CYP2D6 and CYP3A4 respectively. About 10% of an administered dose of codeine is converted by O-demethylation to morphine, which subsequently undergoes glucuronidation to morphine-3 or morphine-6 glucuronide, or N-demethylation to normorphine. Approximately 5 to 10% of the Caucasian population cannot convert codeine to morphine as they are deficient in the CYP2D6 enzyme. These patients are likely to obtain reduced pain relief from codeine. Codeine is also converted by N-demethylation to norcodeine, which subsequently undergoes glucuronidation to norcodeine glucuronide or O-demethylation to normorphine.

Excretion: Both the inactive metabolites of ibuprofen 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 1.9 to 2.2 hours.

Codeine is excreted mainly by the kidneys. Of the excreted material in the urine, 40 to 70% is free or conjugated codeine, 5 to 15% is free or conjugated morphine and 10 to 20% is free or conjugated norcodeine. The plasma half-life of codeine is two to four hours. Only traces of codeine and its metabolites are found in the faeces.

INDICATIONS

The temporary relief of strong pain and discomfort associated with migraine headache, tension headache, period pain, toothache, cold & flu symptoms, back or muscular pain, arthritis and neuralgia. Reduces fever.

CONTRAINDICATIONS

Known hypersensitivity to ibuprofen, codeine or other opioid analgesics or any of the excipients.

Hypersensitivity (e.g. asthma, rhinitis or urticaria) to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs).

As with other NSAIDs, ibuprofen should not be used in active gastrointestinal bleeding or in the presence of peptic ulceration.

Respiratory depression, chronic constipation and active alcoholism.

Diarrhoea caused by pseudomembranous colitis or poisoning (until the causative organism or toxin has been eliminated from the gastrointestinal tract, since codeine may slow down the elimination and thereby prolonging the diarrhoea).

PRECAUTIONS

Panafen Plus should be administered with caution, and at the lowest effective dose, to patients with a history of gastrointestinal haemorrhage or ulcer.

Panafen Plus should be administered with caution to patients with asthma, and especially those patients who have not taken an NSAID before.

Panafen Plus should be administered with caution to patients with cardiac impairment.

As with other drugs of this class, ibuprofen may mask the usual signs of infection. Codeine may also obscure the diagnosis or the course of gastrointestinal diseases. Panafen Plus should therefore be administered with caution in such situations.

Panafen Plus should be administered with caution to patients who have recently had gastrointestinal surgery, as codeine may reduce gastrointestinal motility.

Panafen Plus should be administered with caution to those with hypotension and/or hypothyroidism. The caplets should be used with caution in patients with CNS depression, raised intracranial pressure or head injury, since codeine may increase the risk of respiratory depression and further elevate intracranial pressure.

Physical and/or psychological dependence may occur following prolonged administration of codeine. Tolerance may also develop following prolonged administration.

Panafen Plus should be administered with caution to patients with prostatic hypertrophy since codeine may cause urinary retention.

Panafen Plus should be administered with caution to patients with renal impairment. In patients with renal impairment, renal function should be monitored since it may deteriorate following the use of any NSAID.

Panafen Plus should be administered with caution to patients with hepatic impairment.

Use in the elderly
Adverse effects may have more serious consequences in the elderly and they may be more susceptible to the CNS depressant effects of opioids.

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. Continuous treatment with NSAIDs during the last trimester of pregnancy should only be given on sound indications. During the last few days before expected birth, agents with an inhibitory effect on prostaglandin synthesis should be avoided.

Based on animal studies and limited clinical experience, there is no evidence to suggest foetal abnormalities associated with the use of codeine. However, Panafen Plus caplets should be avoided during pregnancy.

Use in lactation
In limited studies, ibuprofen appears in breast milk in very low concentrations and is unlikely to affect the breastfed infant adversely. Codeine is excreted in breast milk. The use of Panafen Plus caplets should be avoided if possible during lactation.

Effect on ability to drive or operate machinery
Codeine may cause drowsiness. Those affected should not drive or operate machinery.

Interactions

ACE inhibitors, beta-blockers and diuretics: Ibuprofen, like other NSAIDs, can reduce the antihypertensive effect of ACE inhibitors and beta-blockers with possible loss of blood pressure control and can attenuate the natriuretic effects of diuretics.

Anticholinergics: Concurrent use of codeine and anticholinergic agents may increase the risk of severe constipation and/or urinary retention.

Anticoagulants: Concurrent use of NSAIDs and warfarin has been associated with severe, sometimes fatal, haemorrhage. The mechanism of this interaction is not known but may involve increased bleeding from NSAID-induced gastrointestinal ulceration or an additive effect of NSAID inhibition of platelet function with the anticoagulant effect of warfarin. Panafen Plus should only be used in patients taking warfarin if absolutely necessary. Patients taking this combination must be closely monitored.

Antihypertensives: Hypotensive effects of antihypertensive agents may be potentiated when used concurrently with codeine and lead to orthostatic hypotension.

Antiperistaltic antidiarrhoeals (including kaolin, pectin, loperamide): Concurrent use of these agents with codeine may increase the risk of severe constipation.

Cardiac glycosides: NSAIDs may increase plasma glycoside levels. Care should therefore be taken in patients treated with cardiac glycosides.

Central nervous system depressants: Codeine may potentiate the effects of CNS depressants.

Corticosteroids: An increased risk of gastrointestinal bleeding may occur with corticosteroids.

Lithium: Ibuprofen has been shown to decrease the renal clearance and increase plasma concentrations of lithium. Lithium plasma concentrations should be monitored in patients on concurrent ibuprofen therapy.

Metoclopramide: Codeine may antagonise the effects of metoclopramide on gastrointestinal motility.

Methotrexate: NSAIDs inhibit tubular secretion of methotrexate in animals. As a result, reduction in the clearance of methotrexate may occur. Use of high doses of methotrexate concomitantly with NSAIDs should be avoided. At low doses of methotrexate, caution should be used if ibuprofen is administered concomitantly.

Monoamine oxidase inhibitors (MAOIs): Concurrent administration or use within 14 days of ceasing monoamine oxidase inhibitors may enhance the potential respiratory depressant effects of codeine.

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

Ibuprofen may inhibit the antiplatelet effect of low dose aspirin. Patients on low dose aspirin should be instructed to consult their doctor or pharmacist before taking ibuprofen.

Opioid analgesics: Concurrent use of codeine and other opioid receptor agonists is usually inappropriate as additive CNS depression, respiratory depression and hypotensive effects may occur.

Probenecid and phenytoin: Interactions may also occur with probenecid, antidiabetic medications and phenytoin.

Quinidine: Interferes with the metabolism of codeine to morphine, lowering the analgesic effect of codeine.

Tranquillisers, sedatives and hypnotics: Codeine may potentiate the effects of these drugs.

Zidovudine: Concurrent administration with ibuprofen may prolong bleeding time in patients.

It is possible that interactions could occur between drugs that can inhibit CYP2D6 (such as quinidine, phenothiazines and antipsychotic agents) and codeine.

ADVERSE REACTIONS

Gastrointestinal: Abdominal pain, nausea, dyspepsia, diarrhoea, constipation and vomiting.

Skin: Skin rash and itching. Rarely, exfoliative dermatitis and epidermal necrolysis have been reported with ibuprofen.

Renal: Papillary necrosis, which can lead to renal failure.

Central nervous system: Cough suppression, respiratory depression, dizziness and drowsiness.

Other: Hepatic dysfunction, headache, dizziness, hearing disturbance. Rarely allergic reactions, such as swelling of the face or breathing difficulties and, rarely, thrombocytopenia.

DOSAGE AND ADMINISTRATION

Adults and children 12 years and over
Initial dose two caplets taken with fluid, then one or two caplets every four hours when necessary. Maximum six caplets in a 24 hour period.

Children
Not recommended for children under 12 years.

OVERDOSAGE

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. Large overdoses are generally well tolerated when no other drugs are involved. No specific antidote is available. All patients should be treated symptomatically as required, using supportive care where appropriate. Activated charcoal can be used within one hour of ingestion.

Codeine
Nausea and vomiting are prominent features of codeine overdose. Respiratory depression, excitability, convulsions, hypotension and loss of consciousness may occur with large codeine overdose.

The stomach should be emptied and activated charcoal may be given within one hour of ingestion. If severe CNS depression has occurred, artificial respiration, oxygen and parenteral naloxone may be needed. Imbalance of electrolyte levels should be considered.

Naloxone hydrochloride is given subcutaneously, intramuscularly or intravenously, with a usual adult dose of 0.4 to 2 mg repeated at intervals of two to three minutes if necessary. Intravenous administration is the preferred route for naloxone to achieve the most rapid onset of action and is recommended in emergency situations. If no response is observed after naloxone hydrochloride 10 mg has been administered, the diagnosis of opioid induced toxicity should be questioned.

Children may receive an initial dose of 0.01 mg/kg; if this dose does not produce the desired degree of response, a subsequent dose of 0.1 mg/kg may be administered. Since the duration of action of codeine may be longer than that of naloxone, the patient should be kept under surveillance and doses of naloxone repeated as needed.

The Poisons Information Centre can also be contacted (telephone 13 11 26) for current information on the treatment of oral overdoses.

PRESENTATION

Caplets (white, capsule shaped tablets, marked with a “+” sign surrounded by an oval): 24's, 48's and 75’s.

POISONS SCHEDULE

24's: S2
48's: S3, except NSW: S2.
75's: S3, except NSW: S2.

SPONSOR

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