

Panafen[®] Plus

Data Sheet

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: C₁₃H₁₈O₂

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: C₁₈H₂₁NO₃H₃PO₄·½H₂O

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

Panafen Plus should not be taken in patients with:

- 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).
- gastrointestinal bleeding or with an active or previous peptic ulcer.
- a history of upper gastrointestinal bleeding or perforation, related to previous NSAIDs therapy
- severe hepatic, renal or heart failure.
- Obstructive airway disease and acute asthma attack
- paralytic ileus

Panafen Plus should not be taken in those using concomitant NSAIDs including cyclo-oxygenase-2 (Cox-2) specific inhibitors (see Drug Interactions).

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Panafen Plus should not be used in pregnancy or breastfeeding unless it has been prescribed by a doctor.

WARNINGS AND PRECAUTIONS

Panafen Plus should be used with caution in patients with the following conditions:

- history of hypertension or heart failure should seek medical advice before use as fluid retention, hypertension and oedema have been reported with NSAID therapy.
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- gall bladder disease or gall stones
- Reduced respiratory function
- Patients with asthma and especially those who have not taken an NSAID before
- chronic inflammatory intestinal disease (ulcerative colitis, Crohn's Disease), obstructive bowel disorders or acute abdominal conditions, as these conditions may be exacerbated.
- patients with a history of cholecystectomy as Panafen Plus may cause acute pancreatitis in some patients.
- patients with renal impairment. In patients with renal impairment, renal function should be monitored since it may deteriorate following the use of any NSAID.
- patients with hepatic impairment.
- patients who have recently had gastrointestinal surgery, as codeine may reduce gastrointestinal motility.
- Obstructive and inflammatory bowel disease – codeine reduces peristalsis, increases tone and segmentation in the bowel and can raise colonic pressure
- Patients taking monoamine oxidase inhibitors or within 14 days of stopping such treatment
- SLE and mixed connective tissue disease due to an increased risk of aseptic meningitis

Undesirable effects may be minimised by using the minimum effective dose for the shortest possible duration.

Gastrointestinal (GI) bleeding, ulceration or 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. When GI bleeding or ulceration occurs in patients receiving ibuprofen, the treatment should be withdrawn and patients should consult a doctor (see Adverse Reactions)

Discontinue at the first appearance of skin rash, mucosal -lesions, or any other sign of hypersensitivity. As serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs

Clinical trial and epidemiological data suggest that the 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 (for example 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.

Gastrointestinal – NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated.

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly. These patients should commence treatment on the lowest dose available.

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of gastrotoxicity or bleeding, such as corticosteroids or anticoagulants such as warfarin or anti-platelet agents such as aspirin.

Bronchospasm may be precipitated by ibuprofen in patients suffering from or with previous history of asthma or allergic disease.

Skin reactions – Serious skin reaction, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs. 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. PANAFEN PLUS should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Dependence – taking codeine regularly for a long time can lead to addiction. Stopping treatment can result in withdrawal symptoms. Codeine is not a satisfactory substitute for patients dependent on morphine. Regular use of analgesics for headache can result in an overuse syndrome.

Tolerance diminishes rapidly after withdrawal so a previously tolerated dose may prove fatal.

Withdrawal – abrupt withdrawal precipitates a withdrawal syndrome. Symptoms may include tremor, insomnia, restlessness, irritability, anxiety, depression, anorexia, nausea, vomiting, diarrhoea, sweating, lacrimation, rhinorrhoea, sneezing, yawning, piloerection, mydriasis, weakness, pyrexia, muscle cramps, dehydration and increase in heart rate, respiratory rate and blood pressure. These effects can also occur in neonates exposed to codeine in utero (see use in pregnancy).

Genetic polymorphism – Codeine is metabolised to morphine by cytochrome P450 2D6.

Some patients are ultra-rapid metabolisers and are at higher risk of toxic opioid effects.

Some patients are slow metabolisers and these patients may not experience adequate analgesic effect with codeine.

Use in the elderly

NSAIDs should be used with particular caution in elderly patients who are more prone to adverse events.

Effect on female fertility

There is some evidence that drugs which inhibit cyclo-oxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible upon withdrawal of treatment.

Use in pregnancy (Category C)

This product should not be used during pregnancy. The safety of codeine during pregnancy has not been established relative to the possible adverse effect on foetal development. Maternal use of codeine during labour may cause respiratory depression in the child. There is an ibuprofen-related risk of premature closure of the foetal ductus arteriosus with possible persistent pulmonary hypertension during the third trimester of pregnancy. The onset of labour may be delayed and its duration increased, with an increased risk of bleeding tendency in both mother and child.

Regular use during pregnancy may cause physical dependence in the foetus, leading to withdrawal symptoms (convulsions, irritability, excessive crying, tremors, hyperactive reflexes, fever, vomiting, diarrhoea, sneezing and yawning) in the neonate. Prolonged high dose use of Codeine prior to delivery may produce Codeine withdrawal symptoms in the neonate.

Use in lactation

Panafen Plus should be used while breastfeeding unless prescribed by a doctor.

Codeine is excreted into breast milk. However with usual analgesic doses, concentrations are generally low. However, infants of nursing mothers taking

codeine may have an increased risk of morphine overdose if the mother is an ultra-rapid metaboliser of codeine. Nursing mothers taking codeine, who are ultra-rapid metabolisers, may have higher morphine levels in this breast milk, which may lead to life-threatening or fatal side effects in nursing babies. Signs of high morphine levels in a mother are extreme sleepiness and trouble caring for the baby.

Breastfed babies usually nurse every two or three hours and should not sleep more than four hours at a time. If the baby shows signs of increased sleepiness (more than usual), difficulty in breastfeeding, breathing difficulties, or limpness, the mother should immediately seek medical advice.

The lowest effective dose should be used, for the shortest period of time. Nursing mothers should be informed about carefully monitoring the infant during treatment for any sign and symptom of morphine toxicity.

Effect on ability to drive or operate machinery

Codeine may cause dizziness or drowsiness. Those affected should not drive or operate machinery.

Interactions

Ibuprofen-containing products should not be used in combination with other NSAIDs including aspirin and cyclo-oxygenase-2 (Cox-2) specific inhibitors as these may increase the risk of adverse effects (see Contraindications)

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.

Ibuprofen-containing products should be used with caution in combination with the following drugs as interactions have been reported:

Antihypertensives & diuretics: Ibuprofen, like other NSAIDs, can reduce the antihypertensive effect with possible loss of blood pressure control and can attenuate the natriuretic effects of diuretics.

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.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels. Care should therefore be taken in patients treated with cardiac glycosides.

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.

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.

Cyclosporin: Increased risk of nephrotoxicity.

Hypoglycemic agents (oral): Inhibition of metabolism of sulfonylurea drugs, prolonged half-life and increased risk of hypoglycaemia.

Quinolones: NSAIDs can increase the risk of convulsions associated with quinolone antibiotics.

Zidovudine: Increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs.

Aminoglycosides: Reduction in renal function in susceptible individuals, decreased elimination of aminoglycoside and increased plasma concentration.

Selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding.

Codeine-containing products should be used with caution in combination with the following drugs as interactions have been reported.

Central nervous system depressants: Codeine may potentiate the effects of CNS depressants including alcohol, anaesthetics, hypnotics, sedatives, tricyclic antidepressants and phenothiazines.

Metoclopramide & domperidone: Codeine may antagonise the effects of these antiemetics gastrointestinal motility.

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.

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.

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

ADVERSE REACTIONS

Adverse reactions reported from extensive post-marketing experience are listed below by System Organ Class and frequency. The following convention has been utilised for the classification of undesirable effects: very common ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1000$ and $< 1/100$), rare ($\geq 1/10,000$ and $< 1/1000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Ibuprofen

The following list of adverse effects related to those experienced with ibuprofen at OTC doses, for short term use. The treatment of chronic conditions, under long-term treatment, additional adverse effects may occur.

Gastrointestinal disorders: Uncommon: abdominal pain, nausea, dyspepsia. Rare: diarrhoea, flatulence, constipation and vomiting. Very rare: peptic ulcer, perforation or gastrointestinal haemorrhage, sometimes fatal, particularly in the elderly. Exacerbation of ulcerative colitis and Crohn's disease.

Nervous system disorders: Common: headache, dizziness, hearing disturbance (tinnitus).

Skin and subcutaneous tissue disorders: Uncommon: skin rashes and itching. Very rare: severe forms of skin reactions, exfoliative and bullous dermatitoses such as Stevens-Johnson syndrome, erythema multiforme and toxic epidermal necrolysis can occur.

Renal and urinary disorders: Very rare: acute renal failure, papillary necrosis, especially in long-term use, associated with increased serum urea and oedema.

Hepatobiliary disorders: Very rare: liver disorders.

Blood and lymphatic system disorders: Very rare: haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). First signs are fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.

Immune system disorders: Uncommon: hypersensitivity reactions including urticaria and pruritus. Very rare: severe hypersensitivity reactions. Symptoms could be: facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension (anaphylaxis, angioedema or severe shock), exacerbation of

asthma and bronchospasm.

Others with unknown frequency: Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment. In patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease) during treatment with ibuprofen, single cases of symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed.

Codeine

Psychiatric disorders: Not known: drug dependency can occur after prolonged use of codeine at higher doses.

Gastrointestinal disorders: Not known: constipation, nausea, vomiting, dyspepsia, dry mouth, acute pancreatitis in patients with a history of cholecystectomy.

Nervous system disorder: Not known: tiredness, vertigo, dizziness, worsening of headache with prolonged use and drowsiness.

Skin and subcutaneous tissue disorder: Pruritus and sweating

Withdrawal effects – abrupt withdrawal of codeine precipitates a withdrawal syndrome.

Symptoms may include tremor, insomnia, restlessness, irritability, anxiety, depression, nausea, vomiting, diarrhoea, sweating, lacrimation, rhinorrhoea, sneezing, yawning, piloerection, mydriasis, weakness, pyrexia, muscle cramps, dehydration and increase in heart rate, respiratory rate and blood pressure.

Tolerance diminishes rapidly after withdrawal so a previously tolerated dose may prove fatal.

Regular prolonged use of codeine is known to lead to addiction and tolerance. Prolonged use of a painkiller for headache can make them worse.

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. Do not use for more than three days.

Children

Not recommended for children under 12 years.

OVERDOSAGE

Ibuprofen

In children ingestion of more than 400mg/kg may cause symptoms. In adults the dose response effect is less clear cut. The half-life in overdose is 1.5 – 3 hours.

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 severe 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 the prothrombin time/INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur. Exacerbation of asthma is possible in asthmatics.

Treatment should be symptomatic and supportive including the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Activated charcoal may reduce absorption of the drug if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.

Codeine

An overdose of codeine is characterised, in the first phase, by nausea and vomiting. An acute depression of the respiratory centre can cause cyanosis, slower breathing, drowsiness, ataxia and, more rarely, pulmonary oedema. Respiratory pauses, miosis, convulsion, collapse and urine retention as well as signs of histamine release have been observed as well.

Treatment should include general symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. Activated charcoal may reduce absorption of the drug if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected. Give naloxone if coma or respiratory depression is present. Observe for at least four hours after ingestion.

The National Poisons Centre can also be contacted (telephone 0800 764 766) for current information on the treatment of oral overdoses.

PRESENTATION

Caplets (white, capsule shaped tablets, marked with a “+” sign surrounded by an oval):

Pack sizes: 15 and 30.

POISONS SCHEDULE

S3: Pharmacist Only Medicine

SPONSOR

GlaxoSmithKline (NZ) Ltd
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