PRODUCT INFORMATION

APOHEALTH IBUPROFEN PLUS CODEINE Ibuprofen 200mg/Codeine 12.8mg tablets

Composition:
A white to off-white capsule-shaped, biconvex tablet, containing ibuprofen 200mg and codeine phosphate 12.8mg. It also contains, Cellulose-microcrystalline, Starch - pregelatinised maize, croscarmellose sodium, silica-colloidal anhydrous, Opadry complete film coating system OY-58900 white.

APOHEALTH IBUPROFEN PLUS CODEINE tablets do not contain gluten or preservatives.

Description:
Ibuprofen:
Chemical name: 2-(4-Isobutylphenyl) propionic acid.
Molecular formula: $C_{13}H_{18}O_2$.
MW:206.3.
CAS: 15687-27-1.
It 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: $C_{18}H_{21}NO_3.H_3PO_4 \bullet ½\ H2O$.
MW:406.4.
CAS: 41444-62-6. It is a small, colourless, odourless crystal or a white, odourless crystalline powder. Codeine phosphate is soluble in four parts water, slightly soluble in ethanol (96%), practically insoluble in chloroform and ether.

Pharmacology:
Actions:**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.

Codeine acts centrally on opiate receptors. Its analgesic effect is thought to be due mainly to its partial metabolic conversion to morphine. Codeine has about one-sixth the analgesic activity of morphine.

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

Metabolism: 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.
Excretion: Both the inactive metabolites and a small amount of unchanged ibuprofen are excreted rapidly and completely by the kidney, with 95% of the administered dose eliminated in the urine within four hours of ingestion.
Half-life: The elimination half-life of ibuprofen is in the range of 1.9 to 2.2 hours.

Codeine:
Absorption: Codeine and its salts are well absorbed from the gastrointestinal tract: peak plasma-codeine concentrations occur at about one hour after ingestion of codeine phosphate. Analgesic action occurs in 15 to 30 minutes and analgesia is maintained up to 4- 6 hours.
Distribution: After ingestion 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: Codeine is metabolised by O- and N-demethylation in the liver (by CYP2D6 and CYP3A4 respectively) to morphine (about ten percent of a codeine dose is demethylated to morphine), norcodeine and other metabolites including normorphine and hydrocodone. The major metabolic pathway involves glucuronidation of codeine to codeine-6-glucuronide. About 8% of the general Australian population cannot convert codeine to to its active metabolite morphine as they are deficient in the CYP2D6 enzyme. These persons are likely to obtain reduced pain relief from codeine.
Excretion: Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid. Of the excreted material in the urine 40-70% is free or conjugated codeine, 5-15% is free or conjugated morphine, and 10-20% is free or conjugated norcodeine. Excretion is almost complete within 24 hours. The plasma half-life of codeine has been reported to be between 2 and 4 hours after oral administration.Only traces of codeine and its metabolites are found in the faeces.

Indications:

APOHEALTH IBUPROFEN PLUS CODEINE is used for temporary relief of strong pain and/or inflammation associated with headache (including migraine and tension headache), period pain, dental pain, back pain, neuralgia, rheumatic and arthritic pain, and muscular pain.

Contra-indications:

- Known hypersensitivity or idiosyncratic reaction to ibuprofen, codeine or other opioid analgesics, or any other ingredients in the product listed in the description section above,
- hypersensitivity to aspirin or other NSAIDs
- acute respiratory depression.
- active alcoholism
- active gastrointestinal bleeding or peptic ulceration.
- chronic constipation.
- diarrhoea caused by pseudomembranous colitis or poisoning (until the cause organism or toxin has been eliminated from the gastrointestinal tract, since codeine may slow down the elimination, thereby prolonging the diarrhoea).
- taking other products containing ibuprofen or with other anti-inflammatory medicines (see section on ‘interactions with other medicines’)

Precautions:

APOHEALTH IBUPROFEN PLUS CODEINE should be administered with caution and at lowest effective dose in patients

- with decreased respiratory reserve e.g. asthma or COPD or pre-existing respiratory depression.
- with asthma, especially those patients who have not taken an NSAID.
- who are taking other respiratory depressants or sedatives, including alcohol
- with hepatic, renal or cardiac impairment
- with hypotension
- with previous history of gastrointestinal haemorrhage or ulcers
- who have had recent gastrointestinal tract surgery
- with hypothyroidism
- with prostatic hypertrophy; codeine may cause urinary retention
- with raised intracranial pressure or head injury
- who are pregnant (see use in pregnancy and lactation)
- who are over the age of 65 (see use in the elderly)

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

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.

Physical and/or psychological dependence, including drug tolerance, may occur following prolonged administration of codeine. Codeine may cause drowsiness; those affected should not drive or operate machinery.

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. Use of ibuprofen is thus contraindicated during the third trimester of pregnancy, including the last few days before expected birth.

Further, there is insufficient experience with the safety of use of ibuprofen in humans during pregnancy. Ibuprofen should therefore not be used during the first 6 months of pregnancy unless the potential benefits to the patient outweigh the possible risk to the foetus.

Based on animal studies and limited clinical experience there is no evidence to suggest foetal abnormalities associated with the use of codeine. However, *APOHEALTH IBUPROFEN PLUS CODEINE* tablets should be avoided during pregnancy.

Australian categorisation definition of:

Category C:

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 malformations. These effects may be reversible. Accompanying text above should be consulted for further details.

Use in Lactation:

Ibuprofen appears in breast milk in very low concentrations and is unlikely to affect the breast fed infant adversely. Codeine is excreted in breast milk. The use of *APOHEALTH IBUPROFEN PLUS CODEINE* tablets should be avoided, if possible during lactation.

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 and may be more susceptible to the respiratory depressant effects of codeine.

Interactions with other drugs:

The following interactions with ibuprofen and codeine have been noted:

- *ACE inhibitors, beta-blockers and diuretics*: 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
- *Anticholinergics*: Simultaneous use of codeine and anticholinergic agents may increase the risk of severe constipation and/or urinary retention.
- *Anticoagulant-including warfarin*: 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*: Hypotensive effects of antihypertensive agents may be potentiated when used simultaneously 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.
- *Central nervous system depressants*: Concomitant use of codeine with central nervous system depressants (e.g. barbiturates, chloral hydrate, sedatives, alcohol and centrally acting muscle relaxants) can cause addictive CNS depression.
- *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.
- *Metoclopramide*: Codeine may antagonise the effects of metoclopramide on gastrointestinal motility.
- *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.

- *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.
- *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.
- *Antidiabetic medicines, Probenecid and phenytoin*: Interactions may also occur with probenecid and phenytoin.
- *Drugs that inhibit CYP2D6:* Quinidine, phenothiazines can interfere with the metabolism of codeine to morphine, reducing the analgesic effect of codeine.
- *Tranquillizers, sedatives and hypnotics*: Codeine may potentiate the effects of these preparations.
- *Zidovudine*: Concurrent administration with ibuprofen may prolong bleeding time in patients.

Adverse Reactions:

Adverse effects with non-prescription (OTC) or short-term use of ibuprofen and codeine phosphate may include:

- *Gastro-intestinal*: dyspepsia, heartburn, nausea, vomiting, loss of appetite, diarrhoea, stomach pain, and constipation.
- *Skin*: hypersensitivity reactions-skin rash and itching. Rarely exfoliative dermatitis and epidermal necrolysis have been reported with ibuprofen.
- *Renal*: Papillary necrosis, which can lead to renal failure.
- *Cardiovascular*: At OTC doses fluid retention and in some cases oedema occur rarely.
- *Other*: Hepatic dysfunction, headache, dizziness, hearing disturbance. Rarely, allergic reactions such swelling of the face, or breathing difficulties and rarely thrombocytopenia
- *CNS*: cough suppression, respiratory depression, dizziness and drowsiness.

DOSAGE:

Adults and children 12 years and over: Initial dose two tablets taken with fluid, then one or two tablets every 4 hours when necessary. Maximum dose is 6 tablets in a 24-hour period.

Children: Not recommended for children under 12 years.

Overdosage:
In case of overdose, immediately contact the Poisons Information Centre (in Australia call 13 11 26 and in New Zealand call 0800 764 766) for advice.

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.

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.

Presentation:

APOHEALTH IBUPROFEN PLUS CODEINE: White to off-white capsule-shaped, biconvex, film-coated tablet.

Available in the following pack sizes:
S3 - 20s and 30s.

Storage:
Store below 30ºC.

Sponsor:
Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park, NSW, 2113

AUST R 227876

TGA approval date: 11/9/2014