PHARMADEX

(Paracetamol, Aspirin & Caffeine Caplets)

INSERT:

For the use of Registered Medical Practitioner, Hospital or a Laboratory only.

PHARMADEX

Paracetamol , Aspirin & Caffeine Caplets

Composition :
Each caplet contains:
Paracetamol BP 325 mg
Aspirin BP 400 mg
Caffeine BP 30 mg
Excipients Q S
DOSAGE FORM:
Solid, Tablet/ caplet
THERAPEUTIC INDICATIONS :
Pharmadex caplets are used for relief from mild to moderate pain including headache, migraine, neuralgia, toothache, sore throat, period pains; and symptomatic relief of sprains, strains, rheumatic pain, sciatica, lumbago, fibrositis, muscular aches and pains, joint swelling and stiffness, influenza, feverishness and feverish colds.

POSOLOGY & METHOD OF ADMINISTRATION :
Posology
Adult : 1 to 2 caplets
Children : 12 years & Over : 1 Caplet
Repeat dosage three or four times a day if necessary or
As directed by the physician.
Method of Administration
Oral
CONTRAINDICATIONS:
Peptic ulceration and those with a history of peptic ulceration; haemophilia; concurrent anti-coagulant therapy; hypersensitivity to aspirin, paracetamol and/or other constituents; children under 16 years and when breast feeding because of possible risk of Reye's Syndrome.

WARNINGS AND PRECAUTIONS :
Hypersensitivity – asthma – aspirin may provoke or worsen asthma. There is a possible association between aspirin and Reye's syndrome when given to children. Reye's syndrome is a very rare disease, which affects the brain and liver and can be fatal. For this reason aspirin should not be given to children under 16 years unless specifically indicated (e.g. for Kawasaki's disease).
CONTAINS ASPIRIN AND PARACETAMOL.
Do not exceed the stated dose.
"Do not take any other paracetamol-containing products whilst taking this product" and
"Immediate medical advice should be sought in the event of an overdose, even if you feel well."
Care is advised in the administration of paracetamol to patients with severe renal or hepatic impairment. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

INTERACTIONS WITH OTHER MEDICAMENTS :
The following are noted, but are unlikely to apply when the product is used for a short-term **symptomatic relief, as directed:-**
ASPIRIN
Antacids and Adsorbents: Increase excretion of aspirin in alkaline urine.
Mifepristone: Increased risk of bleeding – avoid use of aspirin for 8-12 days after administration of mifepristone.
Spironolactone: Antagonism of diuretic effect. Heparin: Increased risk of bleeding.
Pheninclone: Increased risk of bleeding.
Warfarin & other coumarins: Increased risk of bleeding.
Domperidone & Metoclopramide: Enhance the effect of aspirin.
Phenytoin & valproate: Enhance the effect of phenytoin and valproate.
Methotrexate: Delayed excretion and increased toxicity of
Methotrexate Uricosurics: Inhibition of uricosurics.
PARACETAMOL
The speed of absorption of paracetamol may be increased by metoclopramide or domperidone.
Colestyramine may reduce the absorption of paracetamol.
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.

PREGNANCY & LACTATION:
Pregnancy
There is clinical and epidemiological evidence of safety of aspirin in pregnancy but it may prolong labour and contribute to maternal and neonatal bleeding, and so is best discontinued in late pregnancy. Aspirin appears in breast milk, and regular high doses may affect neonatal clotting. Not recommended with breast feeding due to possible risk of Reye's Syndrome as well as neonatal bleeding due to hypoprothrombinaemia. Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage, but patients should follow the advice of their doctor regarding its use.
Breast-feeding
Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding. Caffeine appears in breast milk. Irritability and poor sleeping pattern in the infant have been reported.
EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
None Stated.
UNDESIRABLE EFFECTS
Side effects are mild and infrequent, but there is a high incidence of gastro-intestinal irritation with slight asymptomatic blood loss. Increased bleeding time. Bronchospasm and skin reactions in hypersensitive patients. Aspirin may induce gastro-intestinal haemorrhage, occasionally major. It may precipitate gout in susceptible individuals. Possible risk of Reye's Syndrome in children.
Adverse effects of paracetamol are rare but hypersensitivity including skin rash may occur. There have been rare reports of blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol.
OVERDOSE :
PARACETAMOL
Liver damage is possible in adults who have taken 10g or more of paracetamol. Ingestion of 5g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).
Risk factors
If the patient
A, Is on long term treatment with carbamezepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
Or B, Regularly consumes ethanol in excess of recommended amounts.
Or C, Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.
Symptoms
Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. 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. Cardiac arrhythmias and pancreatitis have been reported.
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, see BNF overdose section.
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. Management of patients who present with serious hepatic dysfunction beyond 24h from ingestion should be discussed with a liver unit.
SALICYLATES/ASPIRIN
Salicylate poisoning is usually associated with plasma concentrations >350 mg/L (2.5 mmol/L). Most adult deaths occur in patients whose concentrations exceed 700 mg/L (5.1 mmol/L). Single
doses less than 100 mg/kg are unlikely to cause serious poisoning.
Symptoms
Common features include vomiting, dehydration, tinnitus, vertigo, deafness, sweating, warm extremities with bounding pulses, increased respiratory rate and hyperventilation. Some degree of acid-base disturbance is present in most cases.
A mixed respiratory alkalosis and metabolic acidosis with normal or high arterial pH (normal or reduced hydrogen ion concentration) is usual in adults and children over the age of four years. In children aged four years or less, a dominant metabolic acidosis with low arterial pH (raised hydrogen ion concentration) is common. Acidosis may increase salicylate transfer across the blood brain barrier.
Uncommon features include haematemesis, hyperpyrexia, hypoglycaemia, hypokalaemia, thrombocytopaenia, increased INR/PTR, intravascular coagulation, renal failure and non-cardiac pulmonary oedema.
Central nervous system features including confusion, disorientation, coma and convulsions are less common in adults than in children.
Management
Give activated charcoal if an adult presents within one hour of ingestion of more than 250 mg/kg.
The plasma salicylate concentration should be measured, although the severity of poisoning cannot be determined from this alone and the clinical and biochemical features must be taken into account.
Elimination is increased by urinary alkalinisation, which is achieved by the administration of 1.26% sodium bicarbonate. The urine pH should be monitored. Correct metabolic acidosis with intravenous 8.4% sodium bicarbonate (first check serum potassium). Forced diuresis should not be used since it does not enhance salicylate excretion and may cause pulmonary oedema.
Haemodialysis is the treatment of choice for severe poisoning and should be considered in patients with plasma salicylate concentrations >700 mg/L (5.1 mmol/L), or lower concentrations associated with severe clinical or metabolic features. Patients under ten years or over 70 have increased risk of salicylate toxicity and may require dialysis at an earlier stage.
PHARMACODYNAMICS :
ASPIRIN
Mechanism of action:
Salicylate inhibit the activity of the enzyme cyclo-oxygenase to decrease the formation of precursors of prostaglandin's and thromboxanes from arachidonic acid. Although many of the therapeutic effects may result from inhibition of prostaglandin synthesis (and consequent reduction of prostaglandin activity) in various tissues, other actions may also contribute significantly to the therapeutic effects.
Analgesic:
Produces analgesia through a peripheral action by blocking pain impulse generation and via a central action, possibly in the hypothalamus.
Anti-inflammatory (non-steroidal):
Exact mechanisms have not been determined. Salicylates may act peripherally in inflamed tissue probably by inhibiting the synthesis of prostaglandins and possibly by inhibiting the synthesis and/or actions of other mediators of the inflammatory response.
PARACETAMOL
Analgesic:
The mechanism of analgesic action has not been fully determined. Paracetamol may act predominantly by inhibiting a prostaglandin synthesis in the central nervous system (CNS) and to a lesser extent through a peripheral action by blocking pain-impulse generation. The peripheral action may also be due to inhibition of prostaglandin synthesis or to inhibition of the synthesis or actions of other substances that sensitise pain receptors to mechanical or chemical stimulation.
Antipyretic:
Paracetamol probably produces antipyresis by acting centrally on the hypothalamic heat-regulating centre to produce peripheral vasodilation resulting in increased blood flow through the skin, sweating and heat loss. The central action probably involves inhibition of prostaglandin synthesis in the hypothalamus.
CAFFEINE
Central nervous system stimulant – Caffeine stimulates all levels of the CNS, although its cortical effects are milder and of shorter duration than those of amfetamines.
Analgesia Adjunct:
Caffeine constricts cerebral vasculature with an accompanying decrease in cerebral blood flow and in the oxygen tension of the brain. It is believed that caffeine helps to relieve headache by providing a more rapid onset of action and/or enhanced pain relief with lower doses of analgesic. Recent studies with ergotamine indicate that the enhancement of effect by the addition of caffeine may also be due to improved gastrointestinal absorption of ergotamine when administered with caffeine.

ATC code: R05X

PHARMACOKINETICS :
Acetaminophen; aspirin and caffeine combination products are administered orally. The pharmacokinetics of this drug combination have not been studied. The systemic pharmacokinetic information below is based on administration of each agent alone.
Paracetamol:
Paracetamol is metabolized in the liver via glucuronidation and sulfate conjugation and is excreted in the urine as glutathione and sulfate conjugates. However, about 10—15% of the acetaminophen dose undergoes oxidative metabolism via cytochrome P450 isoenzymes (CYP) 2E1 and 1A2 and then glucuronidation to cysteine and mercapturic acid conjugates. In cases of glucuronide depletion, such as acetaminophen overdose, a hepatotoxic metabolite is formed. The half-life of acetaminophen in patients with normal hepatic function is 2—4 hours.
Aspirin :
Aspirin is hydrolyzed to salicylic acid by the liver and is widely distributed into most body tissues. Aspirin is poorly bound to plasma proteins, but it should be used cautiously in patients already receiving other highly protein-bound drugs dua to high protein binding of salicylic acid. Aspirin is 99% metabolized to salicylic acid and other metabolites. The elimination half-life of aspirin in plasma is about 15—20 minutes. Salicylic acid, but not aspirin itself, undergoes saturable kinetics. At low doses, the elimination is first-order and the half-life remains constant at 2—3 hours; however, at higher doses, the enzymes responsible for metabolism become saturated and the apparent half-life can increase to 15—30 hours. Because of this, 5—7 days may be required before a steady-state concentration is reached. Salicylic acid and its metabolites are excreted primarily by the kidneys. The excretion of salicylic acid is enhanced by alkalinization of the urine.
Caffeine:
Caffeine undergoes hepatic metabolism to paraxanthine, theobromine, and theophylline. Elimination of caffeine is renal as inactive metabolites. The elimination half-life of caffeine in adults is 3-7 hours.
STORAGE:
Store below 30°C.
Protect from light and moisture.
Keep medicine out of reach of children.