PRODUCT INFORMATION

DYMADON FORTE

COMPOSITION:

Paracetamol 500 mg, codeine phosphate 30 mg (each tablet contains sodium metabisulphite 0.3 mg).

ACTIONS:

Analgesic, antipyretic.
Paracetamol relieves pain peripherally by blocking impulse generation at the bradykininsensitive chemo-receptors which evoke pain. The antipyretic effect of paracetamol is due to a direct action on the hypothalamus, by reducing the pyrogen induced release of prostaglandins. While paracetamol inhibits prostaglandin synthetase it is not anti-inflammatory. Paracetamol is non-ulcerogenic and may be a suitable alternative in cases where aspirin is contraindicated eg dyspepsia, gastro-intestinal ulcers, aspirin sensitivity.

Codeine is morphine methyl ether. It produces analgesia by altering the patients perception of the pain stimulus. The effect may be due to its conversion to morphine. About 10% of the total dose of codeine is demethylated to morphine. Other effects on the central nervous system and the bowel include drowsiness, changes in mood, respiratory depression, inhibition of the cough reflex, decreased gastro-intestinal motility, nausea, vomiting and alternations of the endocrine and autonomic nervous system.

The analgesic effects of paracetamol and codeine are additive.

PHARMACOKINETICS:

After oral administration, paracetamol is absorbed rapidly and completely from the small intestine; peak plasma levels occur 30 to 60 minutes after administration. Peak levels are reduced and delayed by food intake. Oral bioavailability is reduced by the first pass elimination of about 10% of the administered dose.

Paracetamol is uniformly distributed throughout most body fluids, can cross the placenta and is excreted in breast milk. Protein binding is insignificant at therapeutic doses.

At normal adult therapeutic doses, paracetamol is metabolised by the liver, mainly in conjunction with glucuronide or sulphate, and a minor proportion by oxidation.

85-90% of the administered dose is eliminated in the urine mainly as glucuronide and sulphate conjugates within the first 24 hours. Up to 4% of the dose is excreted unchanged in the urine.

Codeine is well absorbed from the gastro-intestinal tract with peak plasma levels occurring in about one hour. First pass metabolism reduces oral bioavailability to approximately 60% of the administered dose.

At therapeutic blood levels about 30% of codeine is protein bound.

Metabolism:
Codeine is metabolised in the liver, mainly to the glucuronide conjugate and excreted in the urine. Approximately 10% is demethylated to morphine. Patients who metabolise drugs poorly via CYP2D6 are likely to obtain reduced benefit from codeine due to reduced formation of the active metabolite.

In a randomised crossover bioequivalence study in healthy volunteers, the following pharmacokinetic parameters were calculated for Dymadon Forte tablets, after a single dose of 2 tablets.

	Paracetamol	Codeine
C_{max} (µg/mL)	16.9 ± 6.5	0.113 ± 0.032
t_{max} (h)	0.8 ± 0.6	1.1 ± 0.7
t½ (h)	6.2 ± 2.5	2.4 ± 0.4
Cl/F (L/h)	21.0 ± 5.8	165.0 ± 51.6
V/F (L/kg)	2.66 ± 1.31	7.97 ± 2.26

INDICATIONS:

Relief of moderate to severe pain which does not respond to milder analgesics such as paracetamol or aspirin alone, but does not require use of morphine or morphine substitutes, eg pain in neoplastic disease, orthopaedic or musculo-skeletal trauma, acute arthritic pain, migraine, dysmenorrhoea, post surgical pain, pleurisy and pain resulting from burns.

CONTRAINDICATIONS:

Hypersensitivity to paracetamol and opiate narcotics; acute asthma or other obstructive airway disease, and acute respiratory depression; cor pulmonale; cardiac arrythmias; acute alcoholism; delirium tremens; severe CNS depression; convulsive disorders; increased cerebrospinal or intracranial pressure; head injury; brain tumour, suspected surgical abdomen; concomitant MAOIs (or within 14 days of such therapy).

Dymadon Forte is not for use by children under 12 years.

Use of codeine containing products is contraindicated in mothers who are breastfeeding unless prescribed by a doctor.

PRECAUTIONS:

Dymadon Forte should be used with caution in patients with renal or hepatic impairment.

Due to its codeine content, Dymadon Forte may cause constipation. Codeine should not be used in diverticulitis, following bowel surgery or in ulcerative colitis or Crohn's disease. Codeine may exacerbate the pain of biliary colic in some patients. The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury.

Caution is advised in the administration of products containing paracetamol to patients with Gilbert's Syndrome.

Prolonged administration of large doses of Dymadon Forte is undesirable. The maximum recommended daily dose is 8 tablets in 24 hours.

WARNINGS:

Codeine should be used with great caution in patients with decreased respiratory reserve, eg patients with emphysema, chronic bronchial asthma.

Codeine should be avoided in intestinal obstruction.

Drug Dependence:
Codeine can produce drug dependence of the morphine type, and therefore has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of this drug and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications.

Dymadon Forte tablets contain sodium metabisulphite, which may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in susceptible people. The overall prevalence of sulphite sensitivity in the general population is unknown and probably low. Sulphite sensitivity is seen more frequently in asthmatic than non asthmatic people.

Use in Pregnancy (Category A):
Drugs which have been taken by a large number of pregnant women and women of child bearing age without any proven increase in the frequency of malformations or direct or indirect harmful effects on the foetus having been observed.

The maternal use of codeine during labour may cause respiratory depression in the neonate.

Use in Lactation:
Both codeine and paracetamol are excreted in breast milk. When Dymadon Forte is administered to a nursing mother, alternative arrangements should be made for feeding the infant.

In nursing mothers, who are ultra-rapid metabolisers of codeine, higher than expected serum and breast milk morphine levels can occur. Morphine toxicity in babies can cause excessive somnolence, hypotonia and difficulty breastfeeding or breathing. In severe cases respiratory depression and death can occur. The lowest effective dose should be used, for the shortest possible time. Nursing mothers should be informed about carefully monitoring the infant during treatment for any sign and symptoms of morphine toxicity such as increased drowsiness or sedation, difficulty breastfeeding, breathing difficulties, and decreased tone, and seeking immediate medical care if such symptoms or signs are noticed. Codeine-containing products must not be used while breastfeeding unless prescribed by a doctor.

ADVERSE REACTIONS:

The most common side-effects attributed to codeine are constipation, nausea, vomiting, dizziness and drowsiness. Skin rashes have been reported rarely in patients hypersensitive to codeine. Prolonged use of codeine may result in dependence of the morphine type - see **WARNINGS, Drug Dependence**.

Reports of adverse reactions to paracetamol are rare. Rash, methaemoglobinaemia, thrombocytopenia, haemolytic anaemia, pancytopenia, decreased accommodation, mydriasis, decreased pupillary light reflex and cross sensitivity with aspirin have been reported.

OVERDOSAGE SYMPTOMS:

Toxic symptoms of paracetamol overdose include vomiting, hypotension and sweating. Liver damage is unlikely to occur after ingestion of less than 15 g and death is unlikely from less than 25 g as a single dose.

Jaundice, hypoglycaemia and metabolic acidosis are major manifestations of liver failure which may take at least three days to develop.

Acute overdosage with codeine may result in coma, pulmonary oedema and respiratory depression. Central nervous system excitation can also occur, including convulsions. Hypotension may be noted. Pinpoint pupils are characteristic of opioid overdosage, but they may be dilated in the presence of severe acidosis, hypoxia or respiratory depression. Gastro-intestinal motility is reduced, which can cause faecal impaction. The delay in gastric emptying can result in cyclical onset of symptoms, as each time partial recovery is achieved more drug can be released from the stomach, and be absorbed. Ingestion of more than 5 mg/kg has caused respiratory arrest. The estimated lethal dose in adults is 7-14 mg/kg.

Treatment:
Methods of reducing the absorption of the ingested drug are important. Induce emesis unless the patient if comatose, convulsing or has lost the gag reflex. If any of these contraindications are present, endotracheal intubation should precede gastric lavage. Administer activated charcoal 60-100 g.

If 15 g or more of paracetamol has been ingested, administer intravenously, 20% acetylcysteine immediately without waiting for positive urine test or plasma level results; initial dose 150 mg/kg over 15 minutes followed by continuous infusion of 50 mg/kg in 500 mL 5% glucose over 4 hours and 100 mg/kg in 1 L 5% glucose over 16 hours.

Alternatively, administer methionine or 5% acetylcysteine orally according to the following dosage regimen:

Methionine: 2.5 g immediately followed by three further doses of 2.5 g every four hours. Acetylcysteine 5%: 140 mg/kg as a loading dose, then 70 mg/kg every four hours for a total of 17 maintenance doses. If patient vomits within 1 hour of administration of any dose, repeat dose.

If more than 10 hours have elapsed since the overdosage was taken, the antidote may be ineffective.

The narcotic antagonist naloxone is a specific antidote for respiratory depression which may result from codeine overdose. An initial dose of 0.4 to 2 mg may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions is not obtained, it may be repeated at 2-3 minute intervals. Naloxone may be diluted for intravenous infusion in normal saline or 5% glucose solutions. Since the duration of action of Dymadon Forte may exceed that of naloxone, the patient should be kept under continued surveillance.

Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

DOSAGE AND ADMINISTRATION:

Adults and children over 12 years:
1-2 tablets, repeated as required, with a maximum of 8 tablets in 24 hours.

Dymadon Forte is not suitable for use by children under 12 years.

PRESENTATION:

Tablets (white capsule shaped, marked “F3B” on one face and ‘WELLCOME” on the other): 20s, 50s.

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Poisons Schedules: S4

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