Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paramol 10mg/500mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredients:	**Per Tablet**
Paracetamol	500.0 mg
Dihydrocodeine Hydrogen Tartrate	10.0 mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
Oval, white uncoated tablets marked ‘PARAMOL’ on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

As an analgesic in the relief of moderate pain. As an antipyretic and antitussive in the treatment of non-productive cough.

4.2 Posology and method of administration

For oral administration.

Adults and Children over 12 years:

Analgesic: The usual dose is one to two tablets every four hours or as directed by the doctor with a maximum of eight tablets in twenty-four hours.

Antitussive and Antipyretic: The usual dose is one tablet every four hours.

Paramol is not recommended for children under 12 years.

4.3 Contraindications

Use in patients with hypersensitivity or idiosyncratic response to the active ingredients.

Use in respiratory depression or in obstructive airways disease.

4.4 Special warnings and precautions for use

This product should be used with great caution in patients with allergic disorders or with a history of asthma, as dihydrocodeine may cause the release of histamine.

Use with caution in patients with a previous history of opioid abuse. See section 4.5 for additional information.

Dosage should be reduced in the elderly, in hypothyroidism and in those with renal or hepatic dysfunction. Overdose

can cause hepatic necrosis.

Opioid analgesics should be avoided in patients with raised intra-cranial pressure or head injury.

CYP2D6 Metabolism:

Dihydrocodeine is a semi-synthetic analogue of codeine. There are similarities between the metabolism of codeine and dihydrocodeine in the formation of (O-demethylated) metabolites catalysed by CYP2D6. There are genetic differences in the expression of the CYP2D6 enzyme. For codeine, this results in a risk of lack of efficacy in poor metabolisers and a risk of opioid toxicity in patients who are ultra rapid metabolisers. The clinical implications of CYP2D6 genetic polymorphisms have not been sufficiently elucidated for dihydrocodeine (see section 5.2).

4.5 Interaction with other medicinal products and other forms of interaction

Dihydrocodeine should only be used with caution in patients who are currently receiving, or have within the previous two weeks received Monoamine Oxidase Inhibitors.

Additive CNS depression may occur with alcohol.

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by colestyramine.

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.

Co-administration of dihydrocodeine in users of opiates/opioids, in particular with heroin/diamorphine, methadone and benzodiazepines, may increase the risk of accidental fatal overdose.

4.6 Fertility, pregnancy and lactation

The frequent use of paracetamol (defined as most days or daily use) in late pregnancy may be associated with an increased risk of persistent wheezing in the infant. Paracetamol also crosses the placenta and is present in breast milk, but not in a clinically significant amount.

Dihydrocodeine should be avoided immediately prior to delivery because of the risk of neonatal respiratory depression. Babies born to opioid-dependent mothers may suffer withdrawal symptoms. All the narcotic analgesics are able to traverse the placenta and are also excreted in milk. They should not be used during pregnancy or lactation unless considered essential by the doctor.

4.7 Effects on ability to drive and use machines

This product may induce drowsiness. Patients receiving it should not drive or operate machinery unless it has been shown not to affect physical or mental ability.

4.8 Undesirable effects

Adverse effects of paracetamol are rare and usually mild, although skin rashes, and other hypersensitivity reactions occur occasionally.
Very rare cases of serious skin reactions have been reported.

This product may cause drowsiness. Patients receiving it should not drive or operate machinery unless it has been shown not to affect physical or mental ability.

Prolonged use of high dosage dihydrocodeine may induce dependence, with a withdrawal syndrome on discontinuation. Repeated use may result in the development of tolerance.

Tachyardia, bradycardia and palpitations have been reported as undesirable effects associated with opioid analgesics in general, but these effects have not been directly attributable to dihydrocodeine. Urinary retention may be experienced following the administration of higher doses of dihydrocodeine.

System Order Class	**Very rare (<1/10,000)**	**Frequency of adverse reactions not known (cannot be estimated from the available data)**
Immune system disorders		Skin rashes and other hypersensitivity reactions
Psychiatric disorders		Dependence, hallucinations, confusion and mood changes
Nervous system disorders		Headache, vertigo and drowsiness
Gastrointestinal disorders		Constipation, nausea and vomiting
Skin and subcutaneous tissue disorders	Serious skin reactions	
Renal and urinary disorders		Urinary retention
General disorders and administration site conditions		Tolerance and withdrawal syndrome

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Paracetamol Overdose

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 carbamazepine, 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 of Paracetamol Overdose

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 of Paracetamol Overdose

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.

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 the National Poisons Information Centre (NPIC) or a liver unit.

Dihydrocodeine Overdose

The effects in overdosage will be potentiated by simultaneous ingestion of alcohol or psychotropic drugs.

Deaths due to multiple drug intoxication may occur at blood dihydrocodeine concentrations below 1000ng/ml, whereas most fatal cases involving dihydrocodeine alone have dihydrocodeine concentrations higher than 1000ng/ml with the exception of naïve users who have no tolerance to dihydrocodeine.

Co-administration of dihydrocodeine in users of opiates/opiods, in particular with heroin/diamorphine, methadone and benzodiazepines may increase the risk of accidental fatal overdose.

Symptoms of Dihydrocodeine Overdose

Nausea and vomiting are common, and pupils may be pinpoint on eye examination. Central nervous system depression, including respiratory depression, may develop, but is unlikely to be severe unless other sedative agents have been co-ingested, including alcohol, or the overdose is very large. Hypotension and tachycardia are possible but unlikely.

Management of Dihydrocodeine Overdose

This should include general symptomatic and supportive measures including maintaining a clear airway and monitoring of vital signs until stable.

The specific opioid antagonist naloxone hydrochloride should be used to treat severe respiratory depression at a dosage of 0.4 - 2.0 mg subcutaneously or intravenously, repeated as required at 2-3 minute intervals or it may be given as a continuous intravenous infusion.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anilides
ATC Code: NO2B E51

Paracetamol has analgesic and antipyretic properties. The exact mode of action is unknown. It inhibits prostaglandin synthesis to some extent and may also have a central action.

Dihydrocodeine tartrate is an opioid analgesic related to codeine, acting mainly on the CNS.

5.2 Pharmacokinetic properties

Paracetamol is readily absorbed following oral administration and peak plasma concentrations are reached within an hour. Paracetamol is distributed into most body tissues. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations. Paracetamol is metabolised predominantly in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unchanged Paracetamol.

The elimination half-life varies from about 1 to 3 hours. A minor hydroxylated metabolite (n-acetyl-x-benzoquinoneimine) which is usually produced in very small amounts by mixed-function oxidases in the liver and kidney and which is usually detoxified by conjugation with glutathione may accumulate following paracetamol overdosage and cause tissue damage.

The pharmacokinetics of dihydrocodeine are similar to those of codeine. Absorption after oral administration may vary because of substantial first pass metabolism in the liver. Peak plasma concentrations are achieved in approximately 2 hours. The elimination half-life varies between 3 and 5 hours. Excretion occurs almost entirely via the kidney as conjugates with glucuronic acid.

The metabolism of dihydrocodeine shows important similarities with metabolism of codeine. Dihydrocodeine is also a substrate of the polymorphic enzyme CYP2D6. This enzyme catalyses the conversion of dihydrocodeine to dihydromorphine by the O-demethylation pathway (see section 4.4).

5.3 Preclinical safety data

Paracetamol and dihydrocodeine tartrate have been used for many years and thus it is not considered necessary to provide information under this section.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose
Magnesium Stearate
Povidone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Polypropylene containers of 4, 100 or 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Galen Limited
Seagoe Industrial Estate
Craigavon
BT63 5UA
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 1329/006/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4 April 1984

Date of last renewal: 15 February 2010

10 DATE OF REVISION OF THE TEXT

August 2014