

IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0385/001/001

Case No: 2030302

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

The Wallis Laboratory Ltd

Ash Road North, Wrexham, LL13 9UF, United Kingdom

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Paracetamol Tablets BP 500 mg

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **29/11/2006** until **29/02/2008**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol Tablets BP 500 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredients:

Each tablet contains 500 mg of Paracetamol.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Tablet

Capsule shaped, plain white, marked with a breakline on one face.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the relief of symptoms of headache, rheumatic pains, colds and influenza.

4.2 Posology and method of administration

DOSE: unless otherwise directed by a Doctor.

Adults and children over 12 years: 1 to 2 tablets to be swallowed with water.

Children 6 years to under 12 years: ½ to 1 tablet. The dose should not be repeated more frequently than at four hourly intervals and not more than 4 times in any 24 hour period.

If symptoms persist for more than 3 days, consult your doctor. Keep all medicines out of the reach of children.

4.3 Contraindications

Hypersensitivity to Paracetamol and/or other constituents.

4.4 Special warnings and precautions for use

Care is advised in the administration of Paracetamol to patients with severe renal or hepatic impairment and in those with non-cirrhotic alcoholic liver disease. The hazards of overdose are greater in those with alcoholic liver disease.

Warning: Do not exceed the stated dose(s).

Patients should be advised not to take any other Paracetamol-containing products concurrently.

Immediate medical advice should be sought in the event of an overdosage, because of the risk of irreversible liver damage.

This product should be used only when clearly necessary.

Prolonged use except under medical supervision may be harmful.

If symptoms persist consult your Doctor.

Keep out of the reach of children.

4.5 Interaction with other medicinal products and other forms of interaction

The speed of absorption of Paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine.

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of Paracetamol with increased risk of bleeding.

Paracetamol may cause a marginal increase in blood levels of chloramphenicol.

4.6 Pregnancy and lactation

Epidemiological studies in human pregnancy have shown no effects due to Paracetamol used at the recommended dosage. However, Paracetamol should be avoided in pregnancy unless considered essential by the physician. Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding.

4.7 Effects on ability to drive and use machines

None reported.

4.8 Undesirable effects

Adverse effects of Paracetamol are rare but hypersensitivity including skin rash may occur. There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis and of acute pancreatitis.

4.9 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, coma and death. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias have been reported.

Liver damage is likely in adults who have taken 10g or more of Paracetamol. It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of Paracetamol are ingested); become irreversibly bound to liver tissue.

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 and any patient who has ingested around 7.5g or more of Paracetamol in the preceding 4 hours should undergo gastric lavage. Administration of oral methionine or intravenous N-acetylcysteine which may have a beneficial effect up to at least 48 hours after the overdose may be required. General supportive measures must be available.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Paracetamol has analgesic and antipyretic properties but no anti-inflammatory properties, except at very high doses. Paracetamol inhibits prostaglandin synthesis, more centrally than peripherally.

5.2 Pharmacokinetic properties

Paracetamol is rapidly absorbed from the upper gastrointestinal tract after oral administration. Peak plasma levels of 15-20 micrograms per ml after 1g oral dose occur within 30-90 mins., depending on dosage form. It is rapidly distributed throughout the body and is primarily metabolised in the liver. About 85% is by conjugation with glucuronide and sulphate and about 10% by conjugation with glutathione.

Excretion of the biotransformation products is via the kidney. The elimination half-life is approximately 2- hours.

In overdose, glucuronide pathways become saturated and excess Paracetamol is metabolised via the glutathione pathway. Hepatic glutathione is rapidly depleted and an intermediate hydroxylamine metabolite accumulates and binds to liver proteins causing irreversible damage.

Acute Toxicity

Paracetamol hepatotoxicity is directly dependent on the plasma concentration related to time. Plasma concentrations above 1.2mmol/l at 4 hours. 0.6mmol/l at 8 hours and 0.3mmol/l at 12 hours are criteria for treatment with acetylcysteine to prevent irreversible liver damage.

Chronic Toxicity

In animal experiments the sub-chronic and chronic toxicity of Paracetamol occurred in rats and mice as lesions in the gastro-intestinal tract, blood-count changes, degeneration and even necrosis of the hepatic and renal parenchyma. The metabolites that are assumed to have the toxic effects and the organic changes associated with them have been proven in humans as well.

Therefore, Paracetamol should not be taken for a long period of time and in excessive doses. Oral daily doses with clearly hepatotoxic effects are around 5.8g for non-alcoholics, symptoms of intoxication can occur as soon as 3 weeks after administration.

Mutagenic and tumorigenic potential

In mammalian cell cultures, Paracetamol induces chromosome mutations depending on its concentration. *In vivo* tests show negative as well as slightly positive results. Due to the insufficient relevance of the most part of the *in vivo* tests, no final evaluation is possible at this time.

Long-term studies in rats and mice have yielded no indications of a carcinogenic effect.

Reproductive Toxicology

Paracetamol passes the placental barrier. Animal studies and experience to date in humans reveal no evidence of embryotoxicity.

5.3 Preclinical safety data

There are no pre - clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Potato starch
Pregelatinised starch
Talc
Povidone
Stearic Acid
Sodium starch glycollate
*Nipasept
Magnesium Stearate

* Nipasept consist of Methyl-p-Hydroxy Benzoate (E218), Ethyl-p-Hydroxy Benzoate (E214) and Propyl-p-Hydroxy Benzoate (E216).

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years – Blister packs.
2 years – Polypropylene/polyethylene containers.

6.4 Special precautions for storage

Store below 25°C.
Keep blister in the outer carton.
Store in the original package (to protect from light).

6.5 Nature and contents of container

Blister packs: 12 as GSL.
16, 20, 24, 28, 30, 32 as pharmacy packs.

Materials:

Aluminium foil:
Hard tempered 20 micron, colour gravure heat sealed lacquer.
PVC Film:
Standard vacuum forming film 250 micron glossy-glossy finish, opaque white.

Polypropylene/polyethylene containers: 100.

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

The Wallis Laboratory Limited
Ash Road North
Wrexham
LL13 9UF
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 385/1/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 March 1988

Date of last renewal: 31 March 2003

10 DATE OF REVISION OF THE TEXT

November 2006