IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0540/159/002
Case No: 2057612

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

Transferred from PA0077/104/003.

sanofi-aventis Ireland Limited

Citywest Business Campus, **Dublin 24**, **Ireland**

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

Solpadol 500 mg/30 mg Hard Capsules

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 **03/11/2008** until **31/10/2009**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Solpadol 500 mg/30 mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Paracetamol	500.0	mg
Codeine Phosphate Hemihydrate	30.0	mg

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard
Hard gelatin capsule with a light grey opaque body and purple opaque cap, printed with ‘Solpadol’ in black on both body and cap and containing a fine white odourless powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the relief of severe pain.

4.2 Posology and method of administration

Adults: Two capsules not to be taken more frequently than every 4 hours, up to a maximum of 8 capsules in any 24 hour period.

Elderly: The dosage may need to be reduced and should be titrated to the individual’s need and overall medication.

Children: Not recommended for children under 12 years of age.

Solpadol Capsules are for oral administration.

4.3 Contraindications

Use in patients hypersensitive to paracetamol or codeine, or hypersensitivity to any of the other constituents.

Use in patients with acute asthma, respiratory depression, acute alcoholism, head injuries, raised intra-cranial pressure and following biliary tract surgery.

Use in patients currently receiving or within 14 days of stopping monoamine oxidase inhibitor therapy.

Use of codeine containing products is contraindicated in mothers who are breastfeeding unless prescribed by a doctor (see also Section 4.6 Pregnancy and Lactation).

4.4 Special warnings and precautions for use

This product should only be used with great care in any patient whose condition may be exacerbated by opioids, particularly the elderly, who may be sensitive to its central and gastro-intestinal effects, those who are on concurrent CNS depressant drugs, those with prostatic hypertrophy and those with inflammatory or obstructive bowel disorders.

Care should also be observed if prolonged therapy is contemplated.

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

Patients should be advised not to exceed the recommended dose and not take other paracetamol containing products concurrently.

Tolerance and dependence can occur, especially with prolonged high dosage of codeine.

4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol may increase the elimination half-life of chloramphenicol. Oral contraceptives may increase its rate of clearance. 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.

The effects of CNS depressants (including alcohol) may be potentiated by codeine.

4.6 Pregnancy and lactation

This product should not be used during pregnancy.

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, miosis and difficulty breastfeeding or breathing. In severe cases respiratory depression and death can occur. In severe cases, naloxone may be appropriate to reverse the effects. 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 signs and/or symptoms of morphine toxicity such as increased drowsiness or sedation, difficulty breastfeeding, breathing difficulties, miosis and decreased tone, and seeking immediate medical care if such symptoms or signs are noticed. The nursing mother should be informed about monitoring for signs and symptoms of maternal opioid toxicity as well. Should such signs/symptoms be noted in mother or baby, the mother should immediately stop taking all codeine-containing medicines and seek medical advice.

Codeine-containing products must not be used while breastfeeding unless prescribed by a doctor.

4.7 Effects on ability to drive and use machines

Patients receiving this medication should be advised not to drive or operate machinery if affected by dizziness or sedation.

4.8 Undesirable effects

Codeine can produce typical opioid effects including constipation, nausea, vomiting, dizziness, light-headedness, confusion, drowsiness and urinary retention. The frequency and severity are determined by dosage, duration of treatment and individual sensitivity.

Adverse effects of paracetamol are rare but hypersensitivity including skin rash may occur. There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol.

Very rare occurrence of pancreatitis.

4.9 Overdose

Nausea and vomiting are prominent symptoms of codeine toxicity and if there is evidence of circulatory and respiratory depression, suggested treatment is gastric lavage and catharsis. If CNS depression is severe, assisted ventilation, oxygen and parenteral naloxone may be needed.

Patients in whom oxidative liver enzymes have been induced, including alcoholics and those receiving barbiturates and patients who are chronically malnourished, may be particularly sensitive to the toxic effects of paracetamol in 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 and pancreatitis 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 had 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

Pharmacotherapeutic group: Anilides, Paracetamol combinations.
ATC Code: N02B E51.
Paracetamol is an analgesic which acts peripherally, probably by blocking impulse generation at the bradykinin sensitive chemo-receptors which evoke pain. Although it is a prostaglandin synthetase inhibitor, the synthetase system in the CNS rather than the periphery appears to be more sensitive to it. This may explain paracetamol's lack of appreciable anti-inflammatory activity. Paracetamol also exhibits antipyretic activity.
Codeine is a centrally acting analgesic which produces its effect by its action at opioid-binding sites (μ-receptors) within the CNS. It is a full agonist.

5.2 Pharmacokinetic properties

Following oral administration of two capsules (i.e. a dose of paracetamol 1000mg and codeine phosphate 60mg) the mean maximum plasma concentrations of paracetamol and codeine were 17.5 micrograms/ml and 327ng/ml respectively. The mean times to maximum plasma concentrations were 1.03 hours for paracetamol 1.10 hours for codeine phosphate.

The mean AUC for the ten hours following administration was 48.0 micrograms.ml $^{-1}$.h for paracetamol and 1301 ng/ml $^{-1}$.h for codeine.

The bioavailabilities of paracetamol and codeine when given as the combination are similar to those when they are given separately.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Magnesium stearate
Talc

Capsule Shell
Indigo Carmine (E132)
Azorubine (E122)
Titanium dioxide (E171)
Gelatin
Black iron oxide (E172)

Printing Ink
Shellac
Soya lecithin
Dimeticone
Black Iron Oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package.

6.5 Nature and contents of container

White, opaque PVC (250 μm)/aluminium foil (20μm) or White, opaque PVC (250μm)/aluminium foil (20μm)/PVC (15μm) blister packs contained in cardboard cartons. Pack sizes of 10 and 60 capsules.

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

sanofi-aventis Ireland Ltd.
Citywest Business Campus
Dublin 24

8 MARKETING AUTHORISATION NUMBER

PA 540/159/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06 February 1998

Date of last renewal: 01 November 2004

10 DATE OF REVISION OF THE TEXT

November 2008