IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0979/003/001
Case No: 2057368

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

Reckitt Benckiser Ireland Ltd

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

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

Codis Dispersible Tablets, 500mg Aspirin, 8mg Codeine phosphate

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 **28/04/2009**.

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

Codis Dispersible Tablets
500mg Aspirin
8mg Codeine phosphate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substances	mg/tablet
Aspirin	500.0
Codeine phosphate*	8.0

*Equivalent to 6.2 mg codeine.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Dispersible tablet.
White, flat, bevel-edged dispersible tablet with ‘C on Sword’ motif engraved on one face and ‘Plain’ on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the relief of moderate pain such as is associated with headache, toothache, neuralgia, period pains, muscular aches and pains.

Symptomatic relief in upper respiratory tract infections (such as feverishness, colds and flu, sore throat).

Reduction of inflammation such as in lumbago.

4.2 Posology and method of administration

For oral administration, after dissolution in water.

Adults only: One tablet every 3 hours if required up to a maximum of eight doses per 24 hours or as directed by the physician.

Elderly: Non-steroidal anti-inflammatory drugs should be used with particular caution in elderly patients who are more prone to adverse events. The lowest dose compatible with adequate safe clinical control should be employed.

Do not give to children and adolescents aged under 16 years, except on medical advice, where the benefit outweighs the risk.

4.3 Contraindications

Severe heart failure.

History of gastrointestinal bleeding or perforation related to previous NSAIDs therapy. Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding

Not to be given to patients hypersensitive (e.g. bronchospasm, rhinitis, urticaria) to aspirin or to other non-steroidal anti-inflammatory drugs. Do not use in patients suffering from peptic ulceration or coagulation disorders.

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

4.4 Special warnings and precautions for use

The use with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms (See section 4.2, and GI and cardiovascular risks below).

Gastrointestinal bleeding, ulceration and perforation: GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without any warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and 4.5).

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors or anti-platelet agents such as aspirin (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving Codis Tablets, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's Disease) as their condition may be exacerbated (see section 4.8 – undesirable effects).
Cardiovascular and cerebrovascular effects: Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for aspirin when given at a daily dose of ≤4000mg .

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Codis Tablets should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

There is some evidence that drugs which inhibit cyclo-oxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2)

Elderly patients are particularly susceptible to the adverse effects of non-steroidal anti-inflammatory drugs. Unsupervised prolonged use of non-steroidal anti-inflammatory drugs in the elderly is not recommended.

The product should be taken only when necessary.

Prolonged use except on medical advice can be harmful.

Undesirable effects may be reduced by using the minimum effective dose for the shortest possible duration.

The doctor should be consulted if there is no improvement on 24 hours.

If the patient is on any medication consult the doctor or pharmacist before using.

If the patient suffers from asthma, has renal or hepatic impairment, or a history of peptic ulceration or inflammatory bowel disease, then a doctor should be consulted before taking the product.

Do not take if you have or have ever had a stomach ulcer or other gastrointestinal disease or if you have worsening of asthma, urticaria or rhinitis associated with aspirin or other non-steroidal anti-inflammatory drugs or are allergic to any of the ingredients.

Do not take with other aspirin or non-steroidal anti-inflammatory drugs.

There is 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 and adolescents aged under 16 years unless specifically indicated.

Prolonged regular use, except under medical supervision, may lead to physical and psychological dependence (addiction) and result in withdrawal symptoms, such as restlessness and irritability, once the drug is stopped.

4.5 Interaction with other medicinal products and other forms of interaction

Anti-coagulants: NSAIDs may enhance the effects of anticoagulants, such as warfarin (see section 4.4).

It is considered unsafe to take NSAIDs in combination with warfarin or heparin unless under direct medical supervision.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section4.4).

Aspirin may enhance the effects of anticoagulants, inhibit the effects of uricosurics and reduce the excretion of methotrexate (increasing its toxicity).

Diuretics: Reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Other non-steroidals: Avoid concomitant use of two or more non-steroidal anti-inflammatory drugs.

Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

Antihypertensives: Reduced antihypertensive effect.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels.

Lithium: Decreased elimination of lithium.

Cyclosporin: Increased risk of nephrotoxicity with NSAIDs.

Aminoglycosides: Reduction in renal function in susceptible individuals, decreased elimination of aminoglycoside and increased plasma concentrations.

Methotrexate: Decreased elimination of methotrexate.

Probenecid: Reduction in metabolism and elimination of NSAID and metabolites.

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

4.6 Pregnancy and lactation

As with all other drugs, aspirin should be taken during pregnancy only after strict risk-benefit evaluation.

In the last three months of pregnancy, the prolonged administration of aspirin (>300 mg/day) can lead to delayed onset and increased duration of labour, premature closure of the ductus arteriosus and inhibition of uterine contractions. An increased haemorrhagic tendency has been observed in both the mother and child. Administration of aspirin in high doses shortly before birth can lead to intracranial haemorrhages, particularly in premature babies.

Salicylates pass into breast milk in small quantities. As no adverse effects on the infant have been observed after occasional use, interruption of breast feeding is usually unnecessary. However, if high doses (>300 mg/day) are used regularly, breast feeding should be discontinued, as toxicity to the new-born cannot be ruled out.

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

None known.

4.8 Undesirable effects

Adverse effects occurring with aspirin include gastro-intestinal disturbance, peptic ulceration and gastro-intestinal bleeding. Other less frequent adverse effects to aspirin include headache, skin rash, oedema, blurred vision, hypersensitivity, thrombocytopenia, abnormal liver function and impaired renal function.

Gastrointestinal: The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea,

flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4 –Special warnings and precautions for use) have been reported following administration. Less frequently, gastritis has been observed. Gastrointestinal blood losses leading to anaemia have been reported with non-steroidal anti-inflammatory drugs such as aspirin.

Cardiovascular: Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. Cardiovascular and cerebrovascular effects: Clinical trial and epidemiological data suggest that use of some NSAIDs, (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Skin reactions: Bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (very rare).

Non-steroidal anti-inflammatory drugs including aspirin may precipitate bronchospasm, rhinitis or urticaria, or induce attacks of asthma in susceptible subjects.

Isolated cases of liver (increased transaminases) and kidney dysfunction and severe skin reactions have been described.

4.9 Overdose

Acute salicylate poisoning is usually manifested with hypokalaemia with metabolic acidosis and respiratory alkalosis. Nausea, vomiting, tinnitus, hyperpnoea, hyperpyrexia confusion, disorientated, dizziness, coma and/or convulsions are common. Gastrointestinal haemorrhage is frequent. However, alkalaemia or acidaemia, alkaluria or aciduria, hyperglycaemia or hypoglycaemia, and water and electrolyte imbalances, can occur.

Chronic salicylate intoxication is commonly associated with daily headaches, nausea, tinnitus, dizziness, lethargy and confusion; coma may occur. The symptoms can mimic those resulting from illness for which the drug was given. Irritability, lethargy, delayed unresponsiveness and encephalopathy may be seen one to three days following withdrawal of aspirin. At the same time, the concentration of salicylate in the CNS may be high, with non-toxic values in the serum.

Serum salicylate levels above 3.6 mmol/l in adults (2.2 mmol/l in children) are likely to be toxic and levels of 54.4 mmol/l can be fatal.

Treatment: Fluid and electrolyte management is the mainstay of therapy; the immediate aim is to correct acidosis, hyperpyrexia, hypokalaemia and dehydration. Drug absorption can be arrested by induction of emesis or gastric lavage within an hour of ingestion. Drug excretion is enhanced by forced alkaline diuresis and by the early use of activated charcoal. Rarely, haemodialysis is necessary. Delayed encephalopathy may respond to the administration of mannitol.

For respiratory depression caused by the codeine, nalorphine or naloxone should be given by injection. It is advisable for the patient to be sent to hospital for appropriate biochemical assessment and treatment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Aspirin

Aspirin inhibits the cyclo-oxygenase enzyme involved in conversion of phospholipids to prostaglandins and its effect on the body is believed to result primarily from prevention of prostaglandin production. These effects include peripheral analgesia, fever reduction, reduction in inflammation and inhibition of platelet aggregation.

Experimental data suggests that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400mg was taken within 8 h before or within 30 min after immediate release aspirin dosing 81mg, a decreased effect of ASA on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no

clinically relevant effect is considered to be likely for occasional ibuprofen use.

Codeine

Codeine is an opioid analgesic structurally related to morphine which acts upon the central nervous system and the bowel through specific binding sites. Its actions include analgesia, inhibition of the cough reflex and reduction in gastrointestinal motility.

5.2 Pharmacokinetic properties

Aspirin

Aspirin is rapidly absorbed from the stomach and upper gastrointestinal tract with peak levels after around 20-30 minutes following dissolution. It is subject to first-pass metabolism with an overall bioavailability of around 70%. Metabolism is by conversion to salicylic acid and then further to other metabolites. These are excreted both free and conjugated mainly by the kidneys. The plasma half-life of aspirin is around 15-20 minutes and of salicylic acid is 2-3 hours.

Codeine

Codeine is well absorbed from the gastrointestinal tract with peak concentrations occurring after around 1 hour. Absorption is rapid and virtually complete with a bioavailability of around 60%. It is metabolised in the liver and excreted mainly in the urine as free and conjugated metabolites. The half-life of codeine in plasma is 2.5-4 hours.

5.3 Preclinical safety data

No preclinical findings of relevance have been reported.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium carbonate
Maize starch
Citric acid Anhydrous
Talc
Sodium laurilsulphate
Saccharin

6.2 Incompatibilities

Not Applicable

6.3 Shelf Life

Three years.

6.4 Special precautions for storage

Do not store above 30°C. Keep in original package in order to protect from light.

6.5 Nature and contents of container

Strips of aluminium foil in cartons containing 24 tablets.

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.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Reckitt Benckiser Ireland Limited
7 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 979/3/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1978

Date of last renewal: 01 April 2008

10 DATE OF REVISION OF THE TEXT

April 2009