IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0823/011/001
Case No: 2043984

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

McNeil Healthcare (Ireland) Ltd

Airton Road, **Tallaght**, **Dublin 24**, **Ireland**

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

Benylin with Codeine Syrup

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 **31/10/2008** until **03/03/2010**.

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

BENYLIN with Codeine Syrup

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Benylin with Codeine contains Diphenhydramine Hydrochloride 14 mg, Codeine Phosphate Hemihydrate 5.7 mg and Levomenthol 1.1 mg in each 5 ml.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Syrup
Clear red syrup with a taste of menthol.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Benylin with Codeine is indicated for the relief of persistent, dry, irritating cough.

4.2 Posology and method of administration

For oral use.

Adults and children over 12 years:
10 ml three to four times daily.

Children aged 6 to 12 years:
One teaspoonful (5 ml) three to four times daily.

Benylin with Codeine is not recommended for children under 6 years.

The Elderly:
Experience suggests that normal adult dosage is appropriate (see Pharmacokinetics – The Elderly).

Renal dysfunction:
It may be prudent to increase the dosage interval in subjects with moderate to severe renal failure (see Pharmacokinetics – Renal dysfunction).

4.3 Contraindications

Benylin with Codeine is contra-indicated in individuals with known hypersensitivity to the product or any of its constituents.

Benylin with Codeine is contra-indicated in individuals with hepatic or respiratory failure.

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

4.4 Special warnings and precautions for use

This product may cause drowsiness. If affected, individuals should not drive or operate machinery.

Subjects with moderate to severe renal dysfunction should exercise caution when using this product (see Pharmacokinetics – Renal dysfunction).

This product should not be taken by individuals with narrow-angle glaucoma or symptomatic prostatic hypertrophy.

This product contains codeine which is a narcotic analgesic. Tolerance, psychological dependence and constipation may occur at high doses. This should be borne in mind when prescribing for patients with a propensity for addiction to drugs, including alcohol.

Benylin with Codeine should not be administered to patients with chronic or persistent cough, such as occurs with asthma, or where cough is accompanied by excessive secretions, unless directed by a physician.

This product may act as a cerebral stimulant in children and occasionally in adults.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase - isomaltase insufficiency should not take this medicine.

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

This product contains diphenhydramine and therefore may potentiate the effect of alcohol and other CNS depressants.

As diphenhydramine possesses some anticholinergic activity, the effects of anticholinergics (e.g. some psychotrophic drugs and atropine) may be potentiated by this product. This may result in tachycardia, dry mouth, gastrointestinal disturbances (e.g. colic) urinary retention and headache.

4.6 Pregnancy and lactation

Although diphenhydramine and codeine have been in widespread use for many years without ill consequence, both are known to cross the placenta and have also been detected in breast milk. Benylin with Codeine should therefore only be used when the potential benefit of treatment to the mother exceeds any possible hazards to the developing foetus or suckling 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, 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 treatments 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 opoid toxicity as well. Should such signs be noted in mothers 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

This product may cause drowsiness. If affected, individuals should not drive or operate machinery.

4.8 Undesirable effects

Side effects associated with the use of Benylin with Codeine are uncommon.

Diphenhydramine may cause drowsiness, dizziness, gastrointestinal disturbance, dry mouth, nose and throat, difficulty in urination or blurred vision, skin rash.

Codeine may cause constipation, nausea, dizziness and drowsiness.

Adverse reactions to menthol at the low concentration present in Benylin with Codeine are not anticipated.

4.9 Overdose

Symptoms and signs
The symptoms and signs of Benylin with Codeine overdose may include drowsiness, hyperpyrexia and anticholinergic effects.
With higher doses, and particularly in children, symptoms of CNS excitation including hallucinations and convulsions may appear. With massive doses, coma or cardiovascular collapse may follow. Codeine may cause respiratory depression.

Treatment
Treatment of overdose should be symptomatic and supportive. Measures to promote rapid gastric emptying (with syrup of ipecac-induced emesis or gastric lavage) and in cases of acute poisoning, the use of activated charcoal, may be useful. The intravenous use of physostigmine may be efficacious in antagonising severe anticholinergic symptoms. Administration of naloxone is recommended if adverse effects due to codeine overdose are evident.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Diphenhydramine possesses antitussive, antihistaminic and anticholinergic properties. Experiments have shown that the antitussive effect (resulting from an action on the brainstem) is discrete from its antihistaminic effect. The duration of activity is between 4 and 8 hours.

Codeine is an opiate agonist, having narcotic antitussive and analgesic properties.

Menthol has mild local anaesthetic and decongestant properties.

5.2 Pharmacokinetic properties

Absorption
Diphenhydramine, codeine and menthol are well absorbed from the gut following oral administration. Peak serum levels of diphenhydramine following a 50 mg oral dose are reached at between 2 and 2.5 hours. Peak plasma levels of codeine phosphate are attained within 2 hours following an oral dose.

Distribution
Diphenhydramine is widely distributed throughout the body, including the CNS. Following a 50 mg oral dose of diphenhydramine, the volume of distribution is in the range 3.3-6.8 L/kg and it is some 78% bound to plasma proteins. Codeine is widely distributed throughout the body and is some 25 % bound to plasma proteins.

Metabolism and elimination
Diphenhydramine undergoes extensive first pass metabolism. Two successive N-demethylations occur, with the resultant amine being oxidised to a carboxylic acid. Values for plasma clearance of a 50 mg oral dose of diphenhydramine lie in the range 600-1300 ml/min and the terminal elimination half-life lies in the range 3.4-9.3 hours. Little unchanged drug is excreted in the urine.

The plasma half-life of codeine has been reported to be between 3 and 4 hours. Metabolism takes place in the liver by O-demethylation to form morphine (approx 10%), N-demethylation to form norcodeine and conjugation to form glucuronides and sulphates of both unchanged drug and its metabolites. Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid. Menthol is conjugated in the liver and excreted both in urine and bile as the glucuronide.

Menthol is hydroxylated in the liver by microsomal enzymes to p-methane-3,8 diol. This is then conjugated with glucuronide and excreted both in urine and bile as the glucuronide.

The Elderly
Pharmacokinetic studies indicate no major differences in distribution or elimination of diphenhydramine compared to younger adults. There is insufficient information to determine the effects of old age on the pharmacokinetics of codeine (see Pharmacokinetics – Hepatic dysfunction).

Renal Dysfunction
The results of a review on the use of a variety of drugs in renal failure suggest that, for diphenhydramine, in moderate to severe renal failure, the dose interval should be extended by a period dependent on glomerular filtration rate (GFR). No dosage adjustments are suggested when administering codeine.

Hepatic Dysfunction
After intravenous administration of 0.8 mg/kg diphenhydramine, a prolonged half-life was noted in patients with chronic liver disease which correlated with the severity of the disease. However, the mean plasma clearance and apparent volume of distribution were not significantly affected. As codeine is metabolised in the liver, hepatic dysfunction may affect the pharmacokinetics of codeine.

5.3 Preclinical safety data

Mutagenicity
The results of a range of tests suggest that neither diphenhydramine nor menthol have mutagenic potential. There is insufficient information available to determine if codeine has mutagenic potential.

Carcinogenicity
There is insufficient information to determine the carcinogenic potential of diphenhydramine, menthol, or codeine, although such effects have not been associated with these drugs in animal studies.

Teratogenicity
The results of a number of studies suggest that the administration of either diphenhydramine or menthol does not produce any statistically significant teratogenic effects in rats, rabbits and mice. There is insufficient information to determine whether codeine has teratogenic potential.

Fertility
There is insufficient information to determine whether diphenhydramine, codeine or menthol have the potential to impair fertility, although a diminished fertility rate has been observed in mice administered diphenhydramine in one study.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glucose syrup
Sucrose
Sodium citrate
Ethanol (96%)
Citric acid monohydrate
Glycerol
Saccharin sodium
Sodium benzoate (E211)
Ponceau 4R (E124)
Caramel T12 (E150)
Raspberry essence
Purified water

6.2 Incompatibilities

None known.

6.3 Shelf Life

3 years unopened.

6.4 Special precautions for storage

Do not store above 30°C. Keep the bottle tightly closed.

6.5 Nature and contents of container

125ml amber glass bottle with a ROPP aluminium cap or a 3 piece plastic child resistant, tamper evident closure fitted with a PE- Alu- PET or polyethylene/expanded polyethylene laminated wad or with a HDPE plastic cap fitted with a PE-Alu-PET wad.

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

McNeil Healthcare (Ireland) Ltd.
Airton Road
Tallaght
Dublin 24

8 MARKETING AUTHORISATION NUMBER

PA 823/11/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 March 1975

Date of last renewal: 04 March 2005

10 DATE OF REVISION OF THE TEXT

October 2008