IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0007/015/002
Case No: 2053944

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

Boehringer Ingelheim Limited

Ellesfield Avenue, **Bracknell**, **Berkshire RG12 8YS**, **United Kingdom**

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

Alupent Expectorant Mixture

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 **11/08/2008** until **31/03/2009**.

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

Alupent Expectorant Mixture

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains orciprenaline sulphate 10 mg and bromhexine hydrochloride 4 mg.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Syrup
Clear, colourless syrup with an odour of cocoa.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Alupent Expectorant Mixture is indicated for conditions in which both bronchospasm and sputum are present, e.g. in asthma or bronchitis. During infective episodes a suitable antibiotic should also be given.

4.2 Posology and method of administration

Dosage and administration orally:

Adults	*Children (5 - 10 years)*	*Children (2 - 5 years)*
2 x 5 ml four times daily	1 x 5 ml three or four times daily	1 x 5 ml twice daily

Diluent: Alupent Expectorant may be diluted with Syrup BP or Sorbitol BP.

4.3 Contraindications

Hypertrophic obstructive cardiomyopathy and tachyarrhythmia. Known hypersensitivity to orciprenaline, bromhexine or any other excipient in this product.
In cases of rare hereditary conditions that may be incompatible with an excipient of the product (please refer to 'Special warnings and precautions') the use of the product is contraindicated.

4.4 Special warnings and precautions for use

Patients requiring long-term management with bronchodilators should be kept under regular surveillance.

Other sympathomimetic bronchodilators should only be used with Alupent Expectorant Mixture under strict medical supervision. Anti-cholinergic bronchodilators may, however, be inhaled at the same time.

In the following conditions Alupent Expectorant Mixture should be used after careful risk/benefit assessment, especially when doses higher than recommended are used:
insufficiently controlled diabetes mellitus, recent myocardial infarction and/or severe organic heart or vascular disorders, hyperthyroidism, pheochromocytoma, and in patients who are unusually responsive to sympathomimetic amines.

Patients must be warned not to exceed the prescribed dose. In the case of acute, rapidly worsening dyspnoea, a doctor should be consulted immediately.

If bronchial obstruction deteriorates, it is inappropriate and possibly hazardous to simply increase the use of beta-agonists beyond the recommended dose over extended periods of time. The use of high amounts of beta-agonists like orciprenaline on a regular basis to control symptoms of bronchial obstruction may suggest declining disease control. In this situation, the patient's therapy plan, and in particular the adequacy of anti-inflammatory therapy should be reviewed to prevent potentially life-threatening deterioration of disease control.

Potentially serious hypokalaemia may result from $beta_2$-agonist therapy. Particularly caution is advised in severe asthma, as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics. Additionally, hypoxia may aggravate the effects of hypokalaemia on cardiac rhythm. It is recommended that serum potassium levels are monitored in such situations.

Bromhexine should be used with caution in patients with a history of, or existing, peptic ulceration.

There have been very rare reports of severe skin lesions such as Stevens Johnson syndrome and Lyell's syndrome in temporal association with the administration of mucolytic substances such as bromhexine. Mostly these could be explained by the severity of the underlying disease or concomitant medication. If new skin or mucosal lesions occur, medical advice should be sought immediately and treatment with bromhexine discontinued as a precaution.

On demand treatment (symptom orientated) may be preferable to regular use in patients on long-term treatment. In addition, these patients should be re-evaluated for the addition or the increase of anti-inflammatory therapy (e.g. inhaled corticosteroids) to control airway inflammation, and to prevent long-term damage.

As the product contains sorbitol, patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

In view of the possible interaction between beta-adrenergics and monoamine oxidase inhibitors or tricyclic anti-depressants, care should be exercised if it is proposed to administer these compounds concurrently with Alupent Expectorant Mixture. Beta-adrenergics, anticholinergics and xanthine derivatives (such as theophylline) may enhance the bronchodilatory effect of orciprenaline.

The concurrent administration of other beta-adrenergics, systemically absorbed anticholinergics and xanthine derivatives (e.g. theophylline) may increase the frequency and severity of unwanted effects.

$Beta_2$-receptor blockers counteract the action of orciprenaline. Potentially serious bronchospasm may occur during concurrent administration of beta-blockers to patients with reversible airways obstruction.

Inhalation of halogenated hydrocarbon anaesthetics such as halothane, trichloroethylene and enflurane may increase the susceptibility to the cardiovascular effect of beta-agonists.

4.6 Pregnancy and lactation

In some pre-clinical studies at high doses, orciprenaline has shown the potential to cause foetal abnormalities. The significance to humans is not known. There are no adequate and well controlled studies in pregnant women. Alupent Expectorant Mixture should only be used during pregnancy, especially the first trimester, if the potential benefit outweighs the potential risk to the foetus. The inhibitory effect of orciprenaline on uterine contraction should be taken into account.

Safety during lactation has not yet been established although as bromhexine is expected to enter breast milk the product should be avoided during lactation.

4.7 Effects on ability to drive and use machines

None stated.

4.8 Undesirable effects

The most frequently reported undesirable effects observed with orciprenaline are tremor and nervousness, headache, dizziness, tachycardia, palpitations, gastro-intestinal discomfort, nausea and vomiting. Some patients have experienced a feeling of tightness in the chest.

In rare cases, local irritation, skin reactions or allergic reactions have been reported. There have been isolated cases of anaphylactic or anaphylactoid reactions. In individual cases psychological alterations have been reported under inhalational therapy with betamimetics.

Potentially serious hypokalemia may result from $beta_2$-agonist therapy.

As with other beta-mimetics, sweating, weakness and myalgia/muscle cramps may occur. In rare cases decrease in diastolic blood pressure, increase in systolic blood pressure, arrhythmias, particularly after higher doses may occur.

Diarrhoea, nausea, vomiting and other mild gastro-intestinal side effects have been reported with bromhexine hydrochloride. Allergic reactions including skin rashes, urticaria, bronchospasm, angio-oedema and anaphylaxis have been reported rarely.

In a very few patients a transitory rise in serum transaminase levels may be seen during treatment with bromhexine hydrochloride. With continuation of the drug, transaminases return to pre-treatment levels, even in those patients in whom there was pre-existing impairment of hepatic function.

4.9 Overdose

Symptoms: The expected symptoms of overdosage with orciprenaline are those of excessive beta-stimulation such as flushing, tremor, nausea, restlessness, tachycardia, palpitation, dizziness, headache, hypotension, hypertension, a feeling of pressure in the chest, excitation, angina, increased pulse pressure and arrhythmia. Hypokalemia may occur following overdose with orciprenaline. Serum potassium levels should be monitored.

Toxic effects following overdosage with bromhexine hydrochloride have not been reported, but animal studies suggest that these may include listlessness, anorexia, ataxia, cyanosis, pulmonary rales, hypothermia, diuresis, respiratory failure, convulsions or coma.

Therapy: Treatment consists of discontinuation of the product together with appropriate symptomatic therapy. Should the administration of a beta-adrenergic blocking agent be necessary to counteract the effects of overdosage, its use in a patient liable to bronchospasm should be carefully monitored.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Alupent Expectorant Mixture provides the dual action of the bronchodilator orciprenaline sulphate and the mucolytic agent bromhexine hydrochloride. Orciprenaline sulphate is a sympathomimetic amine with bronchodilator properties. Bromhexine is a synthetic derivative of the herbal active ingredient vasicine. Preclinically, it has been shown to increase the proportion of serous bronchial secretion. Bromhexine enhances mucus transport by reducing mucus viscosity and by activating the ciliated epithelium (mucociliary clearance.)

In clinical studies, bromhexine showed a secretolytic and secretomotor effect in the bronchial tract area, which facilitates expectoration and eases cough.

Following the administration of bromhexine antibiotic concentrations (amoxicillin, erythromycin, oxytetracycline) in the sputum and bronchopulmonary secretions are increased.

5.2 Pharmacokinetic properties

Following oral administration orciprenaline is absorbed from the GI tract and undergoes extensive first pass metabolism; about 40% of an oral dose is reported to reach the circulation unchanged. It is excreted in the urine primarily as glucuronide conjugates.

Bromhexine shows dose proportional pharmacokinetics. It is rapidly and completely absorbed from the gastrointestinal tract. After administration of radiolabelled bromhexine about 97.4 ± 1.9 % of the dose were recovered as radioactivity in urine, with less than 1 % as parent compound. Bromhexine is a high clearance drug (CL ~ 843-1073 mL/min) resulting in high inter- and intraindividual variability (CV > 30%).

After oral administration solid and liquid formulations show similar bioavailability. The absolute bioavailability of bromhexine hydrochloride was about 22.2 ± 8.5 % up to 26.8 ± 13.1 % for BISOLVON® tablets and solution, respectively.

Intravenous administrations showed a mean volume of distribution (Vss) of up to 1209 ± 206 L. The distribution in lung tissue (bronchial and parenchymal) was investigated after i.v. (8 mg, 16 mg) and oral (32 mg, 64 mg) administration. Bromhexine tissue concentrations two hours post dose were three to four times higher in lung tissue compared to plasma. Parenchymal tissue seemed to show a higher enrichment of bromhexine than bronchial tissue especially after oral absorption.
Unchanged bromhexine is bound to plasma proteins by 95 % (non-restrictive binding).

Bromhexine is almost completely metabolised to a variety of hydroxylated metabolites and to dibromanthranilic acid. All metabolites and bromhexine itself are conjugated most probably in form of N-glucuronides and O-glucuronides. A minor part of bromhexine is metabolised to dibromanthranilic acid most probably via cytochrome P450 3A4. There are no substantial hints for a change of the metabolic pattern by a sulphonamide or oxytetracyclin. There is a insufficient pharmacokinetic data to evaluate a possible drug-drug interaction between bromhexine and erythromycin.

Bromhexine plasma concentrations showed a multiexponential decline. The relevant half-life to predict the multiple dose pharmacokinetics is about 1 hour, thus no accumulation was seen after multiple dosing (accumulation factor 1.05).

There are no data for bromhexine pharmacokinetics in the elderly or in patients with renal or liver insufficiency.

Concomitant food leads to an increase of bromhexine plasma concentrations.

Bromhexine pharmacokinetics is not relevantly affected by co-administration of ampicillin or oxytetracycline.

Interaction studies with oral anticoagulants or digoxin were not performed.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethylenediamine tetraacetate disodium salt
Methylparahydroxybenzoate (E218)
Propylparahydroxybenzoate (E216)
Hydroxyethylcellulose
Sorbitol solution 70 % (E420)
Artificial cocoa aroma
Hydrochloric acid 25 %
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years.

6.4 Special precautions for storage

Store below 25°C.
Store in the original container.

6.5 Nature and contents of container

250 ml, 300 ml and 2 L amber glass bottles with tamper-evident, child-resistant polypropylene caps with expanded polyethylene liners. The current marketed pack is 300ml.

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

Boehringer Ingelheim Limited
Ellesfield Avenue
Bracknell
Berkshire
RG12 8YS
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 7/15/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1979

Date of last renewal: 01 April 2004

10 DATE OF REVISION OF THE TEXT

July 2008