IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0007/015/004
Case No: 2066509

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 Syrup 10mg/5ml

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 **29/10/2009**.

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

Alupent Syrup 10mg/5ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains Orciprenaline sulphate 10 mg.

Excipients: Also includes sodium metabisulphite (E223) 500 micrograms/5ml; methyl parahydroxybenzoate (E218) 14mg/5ml; propyl parahydroxybenzoate (E216) 50 micrograms/5ml and sorbitol solution (70 per cent) (non-crystallising) (E420) 2.0g/5ml.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Syrup
Clear, colourless to slightly yellow, brown syrup with a faint odour.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

ALUPENT is indicated as a bronchodilator in the relief of bronchospasm such as occurs in asthma, bronchitis and emphysema.

4.2 Posology and method of administration

Adults:
The usual dose is 2 x 5 ml four times daily. The maximum recommended daily dosage is 8 x 5 ml spoonfuls.

Children 3-12 years:
The usual starting dose is 1 x 5 ml four times daily. This may be increased to 2 x 5 ml three times daily as necessary. The maximum recommended daily dosage is 6 x 5 ml spoonfuls.

Children 1-3 years:
The usual starting dose is ½ x 5 ml four times daily. This may be increased to 1 x 5 ml four times daily as necessary. The maximum recommended daily dosage is 4 x 5 ml spoonfuls.

Children 0-1 year:
The usual starting dose is ½ x 5 ml three times daily. This may be increased to 1 x 5 ml three times daily as necessary. The maximum recommended daily dosage is 3 x 5 ml spoonfuls.

Diluents:

ALUPENT Syrup may be diluted with either Syrup BP or Sorbitol Solution BP.

No specific information on the use of this product in the elderly is available.
Clinical trials have included patients over 65 years and no adverse reactions specific to this age group have been reported.

4.3 Contraindications

Hypertrophic obstructive cardiomyopathy, and tachyarrhythmia. Hypersensitivity to any of the ingredients in ALUPENT Syrup

4.4 Special warnings and precautions for use

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.

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

Other sympathomimetic bronchodilators should only be used with ALUPENT under strict medical supervision. Anticholinergic bronchodilators may, however, be inhaled at the same time.

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

Cardiovascular effects may be seen with sympathicomimetic drugs, including ALUPENT®. There is some evidence from post-marketing data and published literature of rare occurrences of myocardial ischaemia associated with beta-agonists. Patients with underlying severe heart disease (e.g.ischaemic heart disease, arrhythmia or severe heart failure) who are receiving ALUPENT®, should be warned to seek medical advice if they experience chest pain or other symptoms of worsening heart disease. Attention should be paid to assessment of symptoms such as dyspnoea and chest pain, as they may be of either respiratory or cardiac origin.

If bronchial obstruction deteriorates, it is inappropriate and potentially hazardous to simply increase the use of beta-agonists such as ALUPENT beyond the recommended dose over extended periods of time. The use of high amounts of beta-agonist like ALUPENT 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 excessive beta-agonist therapy. Particular caution is advised in severe asthma, as this effect may be potentiated by concomitant treatment with xanthine derivatives, glucocorticosteroids 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.

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. Beta-adrenergics, anticholinergics and xanthine derivatives (such as theophylline) may enhance the bronchodilatory effect of orciprenaline.

The concurrent administration of the 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 ALUPENT. 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 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 sulphate on uterine contraction should be taken into account.

Safety during lactation has not yet been established.

4.7 Effects on ability to drive and use machines

None stated.

4.8 Undesirable effects

The most frequently reported undesirable effects observed with ALUPENT 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.

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

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

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 beta mimetics.

4.9 Overdose

Symptoms:

The expected symptoms of overdosage with ALUPENT 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. Hypokalaemia may occur following overdose with orciprenaline. Serum potassium levels should be monitored.

Therapy:

Treatment of overdosage should primarily be supportive and symptom-oriented. If specific therapy is considered necessary, cardioselective beta-blockers are to be preferred. These should be administered with extreme caution to patients with asthma because of the risk of precipitating severe bronchospasm.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ALUPENT is a synthetic sympathomimetic amine with beta-adrenergic stimulant properties. When administered orally or by inhalation, orciprenaline sulphate decreases reversible bronchospasm. It is thought that beta-adrenergic agonists produce many of their pharmacological effects by activation of adenylcyclase, the enzyme that catalyses the conversion of adenosine triphosphate to adenosine monophosphate.
With ALUPENT it has been possible to inhibit the antigen induced histamine release both in vitro in human lung tissue and in isolated mast cells. In addition, it is known that beta-adrenergic agonists cause an increase in the rate of ciliary movement which enhances mucociliary clearance.

5.2 Pharmacokinetic properties

Following oral administration the effect is usually noted within 30 minutes. The peak effect of bronchodilator activity following ALUPENT generally occurs within 60 to 90 minutes and varies from 1 to 5 hours. Oral administration of ALUPENT is followed by rapid absorption with a maximum plasma level between 0.75 –3 hours, and a half-life of 2.1 hours. Approximately 60% of an orally administered dose is absorbed and is subject to extensive first pass metabolism by the liver. Excretion occurs mainly as the sulphuric acid conjugate, 45% of the oral dose being excreted via the kidneys.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium metabisulphite (E223)
Disodium edetate
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Hydroxyethylcellulose
Saccharin
Sorbitol solution (70%) (Non-Crystallising) (E420)
Woodruff aroma
Sodium hydroxide

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Keep container in the outer carton.

6.5 Nature and contents of container

ALUPENT Syrup is presented in amber glass Type III bottles with tamper-evident, child-resistant polypropylene caps with expanded polyethylene liners.
Registered pack sizes: 50 ml, 250 ml, 300 ml and 2 litres. The current marketed pack size is an original pack of 300 ml.

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 7/15/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1 April 1979

Date of last renewal: 30 June 2007

10 DATE OF REVISION OF THE TEXT

October 2009