IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0540/103/002
Case No: 2068748

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

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

Intal CFC-Free Inhaler 5mg pressurised inhalation suspension

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 **12/08/2009** until **12/03/2014**.

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

Intal CFC-Free Inhaler 5mg pressurised inhalation suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Sodium cromoglicate 5 mg per metered dose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Pressurised inhalation, suspension

Pressurised container fitted with a metering valve containing a white pressurised inhalation suspension

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Intal CFC-Free is indicated for the preventative treatment of bronchial asthma, in adults and children.

4.2 Posology and method of administration

Intal CFC-Free is for inhalation use only. It is essential to instruct the patient how to use the inhaler correctly. Intal CFC-Free therapy is preventative, it is therefore important that regular dosing should be maintained. The patient should also be advised that because several doses may be needed to establish benefit, relief may not be apparent immediately, but may take some weeks to develop.

Adults and Children
The recommended dosage is two metered doses of the aerosol four times daily. Once adequate control of the symptoms has been achieved it may be possible to reduce the dosage to one metered dose four times daily. In more severe cases, during periods of severe antigen challenge or exercise the dose may be increased to two metered doses six or eight times daily.

Elderly
No specific dosage recommendations.

For protection against bronchospasm induced by exercise or other known trigger factors, Intal CFC-Free should be used 15-30 minutes before exposure to the factor concerned.

In patients currently treated with steroids, the addition of Intal CFC-Free to the regimen may make it possible to reduce the maintenance dose, or discontinue the steroid therapy. The patient must be carefully supervised while the steroid dose is reduced in a step-wise fashion.

If the inhaler is new, it should be primed by actuating 4 times prior to inhalation. If not used for more than 3 days, additional priming with 1-2 actuations is advised.

The inhaler should be well shaken and the dustcap removed. The patient should be instructed to breathe in slowly and deeply and as inhalation begins the aerosol should be actuated by pressing the can down firmly with the first finger whilst continuing to breathe in. The breath should then be held for several seconds before exhaling into the air. To avoid condensation of moisture in the inhaler and blocking of the spray, exhalation through the inhaler should be avoided. The plastic mouthpiece cover should be replaced following use. To prevent excessive accumulation of powder the plastic body and mouthpiece cover should be washed twice a week and then thoroughly dried.

Detailed instructions for the inhalation of Intal CFC-Free is provided in the Package leaflet supplied with the pack.

4.3 Contraindications

Intal CFC-Free is contraindicated in patients with known hypersensitivity to sodium cromoglicate or to any of the other constituents.

4.4 Special warnings and precautions for use

Intal CFC-Free should be discontinued if an eosinophilic pneumonia appears (See section 4.8 Undesirable Effects).

Intal CFC-Free should not be used for relief of an acute attack of bronchospasm.

In those cases where reduction of steroid treatment is attempted in patients receiving sodium cromoglicate, the patient must be carefully supervised while the steroid dose is reduced in a step-wise fashion. If possible, peak flow monitoring should be continued during such reductions and patients should be given instructions about what action to take is deterioration of asthma symptoms occurs.

Withdrawal of INTAL CFC-Free therapy
If it is necessary to withdraw treatment, it should be done progressively over a period of one week. Symptoms of asthma may recur following withdrawal of treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Sodium cromoglicate has been used for the treatment of a variety of indications in man for many years and no evidence of clinically significant drug interactions has been detected in post-marketing surveillance, nor are expected for sodium cromoglicate, due to its pharmacokinetic properties (no metabolism, moderate plasma protein binding, low plasma concentrations) and its high safety profile.

4.6 Pregnancy and lactation

As with all medication, caution should be exercised especially during the first trimester of pregnancy. There are no adequate and well-controlled studies in pregnant women. Cumulative post-marketing experience with sodium cromoglicate does not suggest that an association between the drug and congenital defects. It should be used in pregnancy only if the benefits to the mother outweighs the potential risk to the foetus.

It is unknown if the drug is excreted in human milk. Cumulative post-marketing experience with sodium cromoglicate used by nursing mothers does not suggest an adverse effect on the infant. It should be used in nursing mothers only if the benefit to the mother outweighs the potential risk to the infant.

4.7 Effects on ability to drive and use machines

Intal CFC-Free has no known effect on ability to drive or operate machinery.

4.8 Undesirable effects

Mild throat irritation; coughing and transient bronchospasm may occur. Hypersensitivity reactions, including angioedema, bronchospasm, hypotension and collapse, have been reported extremely rarely, in patients using inhaled sodium cromoglicate.

As with other inhalation therapy, paradoxical bronchospasm may occur immediately after administration: in such cases the product should be discontinued and alternative treatment instituted.

Very rare cases of eosinophilic pneumonia have been reported (See Section 4.4 Special Warnings and Precautions for Use).

4.9 Overdose

Animal studies have shown that sodium cromoglicate has a very low local or systemic toxicity and extended human studies have not revealed any safety hazard with products containing sodium cromoglicate. Overdosage is therefore unlikely to cause problems, but, if suspected, treatment should be supportive and directed to the control of the relevant symptoms.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Sodium cromoglicate inhibits the activation of many of the cell types involved in the development and progression of asthma. Thus, sodium cromoglicate inhibits the release of inflammatory mediators including cytokines from mast cells and reduces the chemotactic activity of eosinophils and neutrophils. Activation of and mediator release from monocytes and macrophages in vitro is also reduced by sodium cromoglicate.

Sodium cromoglicate inhibits antigen-induced early and late phase airway obstruction in conscious animals and reduces the influx of inflammatory cells into airways. The drug also inhibits sensory nerve (C fibre) activation in the dog lung and inflammatory responses induced by neuronal stimulation in the airways of animals.

The diverse range of activities of the drug may be explained by the ability of sodium cromoglicate to block chloride channels in different cell types which are important in cell activation.

In acute bronchial provocation tests in humans, sodium cromoglicate has been shown to inhibit or diminish the asthmatic reaction to antigen, exercise and to a range of non-specific triggers including cold air, sulphur dioxide, hypertonic saline and bradykinin. Antigen-induced increased bronchial hyperactivity to histamine is prevented and a reduction in bronchial mucus eosinophils and antigen-specific IgE occurs after 4 weeks treatment of asthmatic subjects with sodium cromoglicate.

5.2 Pharmacokinetic properties

After inhalation in man via a metered dose inhaler approximately 10% of a dose of sodium cromoglicate is absorbed from the respiratory tract. The remainder is either exhaled or deposited in the oropharynx, or swallowed and eliminated via the alimentary tract, as only a small amount (1%) of the dose is absorbed from the gastrointestinal tract. The rate of absorption of sodium cromoglicate from the respiratory tract is slower than the elimination rate ($t_{½}$ of 1.5-2h). Hence, the drug remains effectively in the lungs to produce its local therapeutic effect and is then cleared rapidly from the systemic circulation. No substantial increase in plasma concentration occurs during repeated dose therapy.

Sodium cromoglicate is moderately and reversibly bound to plasma proteins (≈ 65%) and is not metabolised in humans. It is excreted unchanged in both urine and bile in approximately equal proportions.

5.3 Preclinical safety data

Sodium cromoglicate is not carcinogenic, mutagenic or teratogenic in animals. No evidence of impaired fertility was shown in laboratory animal reproduction studies. By inhalation, even in long-term studies, it proved impossible to achieve toxic dose levels of sodium cromoglicate in a range of mammalian species. Sodium cromoglicate is non-irritating to the eye and nasal mucosa in animal tests.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone K30
Macrogol 600
Apaflurane (HFA 227)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

30 months.

6.4 Special precautions for storage

The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C. Do not pierce the canister.

6.5 Nature and contents of container

Aluminium can fitted with a metering valve which delivers a minimum of 112 metered doses.
Intal 5 Inhaler CFC - Free Inhaler: The cartoned pack consists of an aerosol canister and a plastic adaptor with a dustcap.

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

The patient should be instructed in the correct use of the inhaler. See section 4.2.

7 MARKETING AUTHORISATION HOLDER

sanofi-aventis Ireland Ltd.
Citywest Business Campus
Dublin 24

8 MARKETING AUTHORISATION NUMBER

PA 540/103/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 13th March 2009

10 DATE OF REVISION OF THE TEXT

July 2009