IRISH MEDICINES BOARD ACT 1995, as amended

Medicinal Products (Control of Placing on the Market) Regulations, 2007, as amended

PA0540/120/001
Case No: 2083927

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

Pentacarinat Ready-To-Use 300mg/5ml Nebuliser Solution

the particulars of which are set out in 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 **23/08/2010**.

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

Pentacarinat Ready-To-Use 300mg/5ml Nebuliser Solution.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml bottle contains 300mg Pentamidine Isethionate (60mg/ml), equivalent to 172.4 mg pentamidine base per 5ml.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nebuliser solution.

A clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Pentacarinat Ready-to-Use Solution is indicated in the treatment of Pneumocystis carinii pneumonia (PCP).

Pentacarinat Ready-to-Use Solution is also indicated in the prevention of Pneumocystis carinii pneumonia (PCP) in patients infected by the human immunodeficiency virus (HIV) who have experienced a previous episode of PCP.

4.2 Posology and method of administration

Adults

Treatment of Pneumocystis carinii pneumonia (PCP)
600mg, (two bottles) given once daily for 3 weeks, administered by a suitable nebuliser.

Prevention of Pneumocystis carinii pneumonia
300mg given once a month or 150mg given every two weeks, administered using a suitable nebuliser.

Elderly

There are no specific dosage recommendations for the elderly.

Hepatic failure

No information is available.

The optimal particle size for alveolar deposition is between 1 and 2 microns.

The solution containing the required dosage should be administered by inhalation using a suitable nebuliser such as a Respirgard II (trade mark of Marquest Medical Products Inc.), Modified acorn system 22 (trade mark of Medic-aid) or an equivalent device with either a compressor or piped oxygen at a flow rate of 6 to 10 litres/minute.

Dosage equivalence: 4mg pentamidine isethionate contain 2.3mg pentamidine base. 1mg pentamidine base is equivalent to 1.74mg pentamidine isethionate.

4.3 Contraindications

The drug should not be administered to patients with a known hypersensitivity to pentamidine.

4.4 Special warnings and precautions for use

Severe reactions, sometimes fatal due to severe hypotension, hypoglycaemia, acute pancreatitis and cardiac arrhythmias have been reported in patients treated with pentamidine isethionate, by both the intramusclar and intravenous routes. Baseline blood pressure should be established and patients should receive the drug lying down. Blood pressure should be closely monitored during administration and at regular intervals until treatment is concluded. Therefore patients receiving pentamidine by inhalation should be closely monitored for the development of severe adverse reactions.

Pentamidine Isethionate should be used with particular caution in patients with a history of, or existing hepatic and/or renal dysfunction, hypertension or hypotension, hyperglycaemia or hypoglycaemia, diabetes mellitus, cystic fibrosis or blood dyscrasias (leucopenia, thrombocytopenia or anaemia).

The benefit of aerosolised pentamidine therapy in patients at high risk of a pneumothorax should be weighed against the clinical consequences of such an occurrence.

Pentamidine isethionate may prolong the QT interval. Cardiac arrhythmias indicative of QT prolongation, such as Torsades de Pointes, have been reported in isolated cases with administration of pentamidine isethionate. Therefore, pentamidine isethionate should be used with care in patients with coronary heart disease, a history of ventricular arrhythmias, uncorrected hypokalaemia and or hypomagnesaemia, bradycardia (<50 bpm), or during concomitant administration of pentamidine isethionate with QT prolonging agents.

Particular caution is necessary if the QTc exceeds 500 msec whilst receiving pentamidine isetionate therapy, continuous cardiac monitoring should be considered in this case.

Should the QTc-interval exceed 550 msec then an alternative regimen should be considered.

Laboratory monitoring: The following test should be carried out before during and after therapy by the parenteral route:
I) Blood urea, nitrogen and serum creatinine daily during therapy.
II) Complete blood and platelet counts daily during therapy.
III) Fasting blood glucose measurements daily during therapy, and at regular intervals after completion of therapy. Hyperglycaemia and diabetes mellitus, with or without preceding hypoglycaemia have occurred up to several months after cessation of therapy.
IV) Liver function tests (LFTs) including bilirubin, alkaline phosphatase, aspartate aminotransferase (AST/GOT) and alkanine aminotransferase (ALT/GPT). If baseline measurements are normal and remain so during therapy, test weekly. When there is baseline elevation in LFTS and/or LFTS increase during therapy, continue monitoring weekly unless the patient is on other hepatotoxic agents, when monitoring every 3-5 days is appropriate.
V) Serum calcium, test weekly. Serum magnesium, test twice weekly.
VI) Urine analysis and serum electrolytes daily during therapy.
VII) Electrocardiograms at regular intervals.

The benefit of aerosolised pentamidine therapy in patients at high risk of pneumothorax should be weighed against the clinical consequences of such a manifestation.

4.5 Interaction with other medicinal products and other forms of interaction

Caution is advised when pentamidine isethionate is concomitantly used with drugs that are known to prolong the QT interval such as phenothiazines, tricyclic antidepressants, terfenadine and astemizole, IV erythromycin, halofantrine,

and quinolone antibiotics (see Special Precautions and Warnings section).

Foscarnet: risk of hypocalcaemia

4.6 Pregnancy and lactation

There is no evidence of the safety of pentamidine isethionate in human pregnancy. A miscarriage within the first trimester of pregnancy has been reported following aerosolised prophylactic administration. There is some evidence of transplacental passage but none related to elimination in breast milk. Pentamidine isethionate should not be administered to pregnant patients unless considered essential.

Lactation: The use of pentamidine isethionate is contra-indicated in breast feeding mothers unless considered essential by the physician.

4.7 Effects on ability to drive and use machines

Pentamidine has no known effect on the ability to drive and use machines. Considering the risk of dizziness, one should be careful.

4.8 Undesirable effects

Adverse reactions frequency is defined using the following convention:
Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

Inhalation Route:

Metabolism and nutrition disorders
Frequency not known: hypoglycaemia

Nervous system disorders
Frequency not known: light-headedness

Vascular disorders:
Frequency not known: hypotension

Respiratory, thoracic and mediastinal disorders:
Common: local reactions ranging in severity from cough, shortness of breath, wheezing, bronchospasms, particularly in patients with a history of smoking or asthma, which can usually be controlled by prior use of bronchodilators
Rare: eosinophilic pneumonia
Frequency not known: pneumothorax in patients presenting a history of Pneumocystis carinii pneumonia.

Gastrointestinal disorders:
Common: taste disturbance, nausea
Frequency not known: acute pancreatitis

Skin and subcutaneous tissue disorders:
Frequency not known: rash

Renal and urinary disorders:
Frequency not known: renal insufficiency

General disorders and administration site conditions:
Frequency not known: fever, decrease in appetite, fatigue

4.9 Overdose

Cardiac rhythm disorders, including Torsades de Pointes, have been reported following overdose of pentamidine isethionate.

Should overdosage occur, treatment is symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pentamidine isethionate is an aromatic diamidine. It is an antiprotozoal agent, which acts by interfering with DNA and folate transformation, and by the inhibition of RNA and protein synthesis.

5.2 Pharmacokinetic properties

Pentamidine isethionate has a short half-life in plasma with rapid liver distribution to liver, kidney, lung and pancreas. Routes of metabolism are uncertain, excretion is via bile and urine with T½ of between 5 and 10 days.

When administered by the use of a nebuliser, human kinetic studies revealed significant differences when compared to parenteral administration. Aerosol administration resulted in a 10-fold increase in bronchial alveolar lavage (BAL) supernatant fluid and an 80-fold increase in BAL sediment concentrations in comparison with those seen with equivalent parenteral doses.

Limited data suggests that the half-life of pentamidine in BAL fluid is greater than 10-14 days. Peak plasma concentrations after inhalation therapy were found to be approximately 10% of those observed with equivalent intramuscular doses and less than 5% of those observed following intravenous administration. This suggests that systemic effects by the inhalation route are less likely.

Long term pulmonary parenchymal effects of aerosolised pentamidine are not known. Lung volume and alveolar capillary diffusion, however, have not been shown to be affected by high doses of pentamidine administered by inhalation to AIDS patients.

5.3 Preclinical safety data

No additional data of relevance to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glucose monohydrate
Sodium acetate
Glacial acetic acid
Water for injections

6.2 Incompatibilities

Pentamidine nebuliser solution should not be mixed with any other solution.

6.3 Shelf Life

12 months.

Once opened, use immediately.

6.4 Special precautions for storage

Do not store above 25°C.

Do not refrigerate.

6.5 Nature and contents of container

10 ml low density polyethylene bottles and plug with yellow high density polyethylene tamper evident caps packed in single unit cartons.

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 optimal particle size for alveolar deposition is between 1 and 2 microns. The solution containing the required dosage should be administered by inhalation using a suitable nebuliser such as a Respirgard II (trade mark of Marquest Medical Products inc.), modified Acorn System 22 (trade mark of Medic-Aid) or an equivalent device with either a compressor or piped oxygen at a flow rate of 6 to 10 litres/minute.

The nebuliser should be used in a vacated well ventilated room. Only staff wearing adequate protective clothing (mask, goggles, gloves) should be in the room when nebulisers are being used.

A suitable well fitted one way system should be employed such that the nebuliser stores the aerosolised drug during exhalations and disperses exhaled pentamidine into a reservoir. A filter should be fitted to the exhaust line to reduce atmospheric pollution.

It is advisable to use a suitable exhaust tube which vents directly through a window to the external atmosphere. Care should be taken to ensure that passers-by will not be exposed to the exhaust. All bystanders including medical personnel, women of child bearing potential, pregnant women, children and people with a history of asthma should avoid exposure to atmospheric pentamidine resulting from nebuliser usage.

Dosage equivalence: 4 mg pentamidine isethionate contain 2.3 mg pentamidine base. 1 mg pentamidine base is equivalent to 1.74 mg pentamidine isethionate.

Any solid material evident in the polyethylene bottle should be re-dissolved by gentle warming in the hand before use. The solution placed in the nebuliser reservoir should be visually inspected prior to use. Any solution containing particulate matter should be discarded and the nebuliser reservoir rinsed with sterile water prior to re-use.

All materials that have been utilised for dilution and administration should be disposed of according to standard procedure.

7 MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Ireland Ltd.
Citywest Business Campus
Dublin 24

8 MARKETING AUTHORISATION NUMBER

PA 0540/120/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th October 1991

Date of last renewal: 14th October 2006

10 DATE OF REVISION OF THE TEXT

August 2010