IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA1424/001/001
Case No: 2046816

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

BioAlliance Pharma SA

49 Boulevard du GÃ©nÃ©ral Martial Valin, **75015 Paris**, **France**

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

SITAMIC 50 mg muco-adhesive buccal tablets

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 **25/04/2008** until **10/04/2013**.

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

SITAMIC 50 mg, muco-adhesive buccal tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg of miconazole.

Excipients: lactose monohydrate, milk protein concentrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Muco-adhesive buccal tablet.

White to slightly yellow tablets with a rounded side and a flat side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of oropharyngeal candidiasis (OPC) in immunocompromised patients (See Section 5.1)

4.2 Posology and method of administration

Gingival use.

For adults only.

Application of one muco-adhesive buccal tablet once a day for 7 to 14 days depending on the patient's clinical response. It is preferable to apply the tablet in the morning, after brushing of the teeth, as during the night the salivary flow is less important. SITAMIC can be administered with food and drinks.

In case of failure to improve after 7 days, the treatment should be continued for 7 additional days.

In the event of complete clinical response (defined as complete resolution of disease signs and symptoms) after 7 days of treatment, the use of SITAMIC can be stopped.

Method of administration:

SITAMIC should be applied to the upper-gum just above the incisor tooth:

- Once the tablet is removed from the bottle, it should be used immediately. It should be noted that the tablet has a rounded side and a flat side.
- The rounded side of the tablet should be applied on the upper gum above an incisor tooth. Hold the tablet in place for 30 seconds with a slight pressure of the finger over the upper lip.
- If the tablet does not adhere properly, it should be repositioned.
- If the tablet falls off within the first 6 hours but is not swallowed, it should be replaced immediately.
- If SITAMIC is accidentally swallowed it is recommended to drink a glass of water. If swallowed within the first 6 hours after application, the tablet should be replaced only once.
- With each application of SITAMIC , the tablet should be applied to alternate sides of the upper-gum.

Elderly population: SITAMIC can be used by the elderly.

There is no experience in children.

4.3 Contraindications

- Hypersensitivity to the active substance and to any of the excipients
- Allergy to milk or milk derivatives.
- In patients with liver dysfunction.
- Concomitant administration of oral anticoagulants, hypoglycaemic sulfonamides, cisapride, pimozide, ergot alkamoids: ergotamine, dihydroergotamine (See Section 4.5).

4.4 Special warnings and precautions for use

Co-administration with halofantrine is not recommended (see section 4.5).

SITAMIC should not be given to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

Local irritation after the application of SITAMIC has rarely been observed. As with all drugs, hypersensitivity reactions may occur.

As SITAMIC should be applied to the upper gum just above the incisor tooth:

- All situations that could interfere with adhesion of the tablet should be avoided including touching or pressing the tablet already placed. Chewing gum should also be avoided.
- The tablet should not be sucked, chewed or swallowed.
- If teeth brushing occur during the day, the tablet should not be touched, and the mouth should be rinsed with caution.
- If the mouth is dry, it is recommended to drink a lot.
- Accidental ingestion of SITAMIC may occur. If SITAMIC is accidentally swallowed it is recommended to drink a glass of water.

4.5 Interaction with other medicinal products and other forms of interaction

Miconazole is an inhibitor of CYP2C9 and CYP3A4. No interaction studies have been performed with SITAMIC. Even if the systemic absorption observed with SITAMIC has been insufficiently evaluated, administration of medicinal products with narrow therapeutic index and which are metabolised by CYP2C9 and CYP3A4 are contraindicated because of an increased exposure (see section 4.3).

<u>Concomitant use contraindicated</u>

- Oral anticoagulants

  Unforeseeable bleeding that could eventually be severe

- Cisapride

  Increased risk of ventricular arrhythmia, e.g. torsades de pointes

- Pimozide

  Increased risk of ventricular arrhythmia, e.g. torsades de pointes

- Ergot alkaloids: ergotamine, dihydroergotamine

Risk of ergotism with necrosis of extremities

- Hypoglycaemic sulfonamides

Potential occurrence of hypoglycaemic symptoms, even coma

Concomitant use not recommended

- Halofantrine

Increased risk of ventricular arrhythmia, e.g. torsades de pointes

Concomitant use requiring precautions for use:

- Phenytoin (and fosphenytoin by extrapolation)

Increased phenytoin plasma concentrations that may reach toxic levels, due to an inhibition of the hepatic metabolism of phenytoin.

A close clinical monitoring is recommended.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data from the use of miconazole in pregnant women. Animal studies do not indicate teratogenic effects but other effects on reproduction were recorded (see section 5.3). The risk for humans is unknown. Miconazole should be used during pregnancy only if necessary.

Lactation

There are no available data on the excretion of miconazole in human milk. Therefore, caution should be exercised when prescribing to breastfeeding mothers.

If the new-born baby or the breastfed infant takes cisapride, the administration of miconazole to the mother is contraindicated as a safety measure, due to the potential risk of drug interaction in the child (torsades de pointes).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed with SITAMIC. Nevertheless miconazole is known not to affect the alertness or driving ability.

4.8 Undesirable effects

The safety profile of SITAMIC is based on 2 clinical trials (172 patients including 25 HIV infected patients and 147 patients with head and neck cancer receiving radiotherapy).
Adverse reactions by system organ and frequency are listed below (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).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The most commonly reported adverse reactions (ADRs) are gastrointestinal disorders.

Gastrointestinal disorders
Common: abdominal pain, nausea, oral discomfort
Uncommon: vomiting

Nervous system disorders
Common: dysgeusia

Skin and subcutaneous tissue disorders
Common*:* pruritus
Uncommon: dermatitis, rash

General disorders and administration site conditions
Common: burning sensation at the site of application of the tablet
Uncommon: oedema

4.9 Overdose

Symptoms

In the event of accidental overdosage, vomiting and diarrhoea may occur.

Treatment

There is no known antidote to miconazole: Overdose should be treated symptomatically.

In the event of accidental ingestion of large quantities of SITAMIC an appropriate method of gastic emptying may be used, if considered necessary.

No case of overdose has been reported with SITAMIC.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-infective and Antiseptics for Local Oral Treatment

ATC code: A01AB09

Microbiology:

Miconazole displays broad-spectrum antifungal activity against *Candida* species, including *C. albicans*, and also non *albicans* species such as *C. glabrata*, *C. krusei*, *C. parapsilosis, C. tropicalis*, and *C. pseudotropicalis.*

Miconazole also displays antibacterial activities against Gram-positive bacteria (including *Streptococcus pyogenes*, *Staphylococcus aureus*, and *Erysipelothrix insidiosa*).

Candida species most often involved in buccal candidiasis (*C. albicans, C. glabrata, C. krusei and C. tropicalis*) are susceptible or moderately susceptible to miconazole.

Mechanism of action

Miconazole exerts its antifungal activity by inhibition of ergosterol biosynthesis in the cell membrane of the pathogen. At low concentration, it interacts with fungal cytochrome P450, which results in inhibition of 14-α-demethylation, a step in ergosterol biosynthesis. The depletion of ergosterol and concomitant accumulation of lanosterol lead to some membrane-related disorders. Miconazole displays a fungistatic activity due to the inhibition of membrane sterol synthesis and a fungicidal activity by change in the barrier function of the fungal membrane.

Clinical Experience

In the study conducted in patients with head and neck cancer having undergone radiotherapy (n=282), the response rate at Day 14 was 56% and the relapse rate at Day 30 was 19% (CI_{95}: [10.7; 29.7]). Due to a limited number of HIV-positive patients (n=26) treated with SITAMIC in the study (non-comparative open-label), the demonstration of efficacy cannot be considered robust. The response rate at Day 15 was 84% and the relapse rate at Day 45 in this study was 32% (CI_{95}: [14.9; 53.5]).

5.2 Pharmacokinetic properties

The oral bioavailability of miconazole is low (25-30%) because miconazole is poorly absorbed in the gastrointestinal tract. Most of the absorbed miconazole is metabolised by the liver. Less than 1% of the administered dose is found unchanged in urine.

In case of renal impairment the pharmacokinetics of miconazole is not significantly affected. There are no active metabolites and the terminal half-life is about 20 hours.

The single dose of SITAMIC containing 50 mg of miconazole administered to healthy volunteers provides a maximum mean salivary concentration of 15µg/mL 7 hours after application of the tablet with an area under the curve (AUC_{0-24h}) of 55.23 µg.h/mL. Miconazole salivary concentrations above 1 µg/mL, the lower limit of the minimum inhibitory concentration (MIC) range for *C. albicans* strains, were measured. This threshold is achieved 1 hour after the application of the tablet. The mean duration of miconazole exposure above the MIC was 13 hours obtained with the application of a single tablet of 50 mg.

Plasma concentrations of miconazole were below the limit of quantification (0.4 µg/mL) in most of healthy volunteers, confirming the poor absorption of miconazole through the buccal mucosa or in the gastrointestinal tract after the saliva is swallowed.

After 7 days of treatment, all plasma concentrations of miconazole were below the limit of quantification (0.1 µg/mL).

5.3 Preclinical safety data

In the toxicology studies after single-dose and repeated-dose administration, and in the pre and postnatal development studies, toxic effects have been observed in animals (mouse, rat, rabbit, dog) at doses 30 to 900-fold higher than the maximal recommended dose in humans (0.7mg/kg). Embryotoxic effects but not teratogenic effects of miconazole have been observed in the reprotoxicity studies.

Conventional studies of genotoxicity (Ames, chromosomal aberration, micronucleus) did not reveal any potential genotoxicity.

Local tolerance studies (jugal mucosa of hamster and sensitization LLNA assay in mice) did not show any toxicity.

No carcinogenicity studies have been conducted with miconazole.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose 2208
Milk protein concentrate
Maize starch
Lactose monohydrate
Sodium laurilsulfate
Magnesium stearate
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

18 months.

6.4 Special precautions for storage

Store below 30°C.

Keep in the original bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

14 tablets in a bottle (HDPE) with a child-resistant cap (polypropylene) which contains a desiccant.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

BioAlliance Pharma
49 Boulevard du Général Martial Valin
75015 Paris
France

8 MARKETING AUTHORISATION NUMBER

PA 1424/1/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 11th April 2008

10 DATE OF REVISION OF THE TEXT

April 2008