

IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0540/032/005

Case No: 2072051

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

Batrafen 10mg/g Shampoo

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 **05/11/2009** until **25/08/2010**.

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

Batrafen 10mg/g Shampoo

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One gram shampoo contains 10 mg ciclopirox.

For excipients see section 6.1.

3 PHARMACEUTICAL FORM

Shampoo

Almost colourless to yellowish, translucent solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Batrafen 10mg/g Shampoo is indicated for the treatment of seborrhoeic dermatitis of the scalp.

4.2 Posology and method of administration

For cutaneous use.

For the initial treatment of the symptoms of seborrhoeic dermatitis Batrafen 10mg/g Shampoo is applied on the scalp once or twice a week, depending on severity, for four weeks.

For subsequent prophylaxis of symptoms, the treatment may be continued for a further 12 weeks.

The contents of one sealing cup (about 5 ml) Batrafen 10mg/g Shampoo are applied to the wet hair and scalp and worked to a lather. This is then thoroughly massaged on the scalp. If the hair has more than shoulder length, up to two capful (about 10 ml) are used. Batrafen 10mg/g Shampoo is left to take effect for 3 minutes and is then rinsed off with water.

The product has not been tested in children.

The use of Batrafen 10mg/g Shampoo is limited to a maximum of 16-weeks of continuous use.

4.3 Contraindications

Batrafen 10mg/g Shampoo should not be used in known hypersensitivity to ciclopirox, ciclopirox-olamine, parabens or to any of the excipients.

4.4 Special warnings and precautions for use

When using Batrafen 10mg/g Shampoo, patients should be advised to avoid contact with eyes. If accidental contact occurs, rinse eyes with copious amounts of water.

This medicinal product contains Parabens and their esters, and can therefore may cause immediate or delayed hypersensitivity reactions. Benzoic acid can cause mild irritation of skin, eyes and mucosae.

In case of irritation or sensitisation after prolonged use of the product, the therapy should be stopped and another appropriate treatment initiated.

4.5 Interaction with other medicinal products and other forms of interaction

There are no known reports of interactions between ciclopirox and other medicinal products.

4.6 Pregnancy and lactation

Pregnancy:

No clinical data on exposed pregnancies are available for ciclopirox. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development and parturition. However, there are no sufficient data concerning possible long term effects on postnatal development (see section 5.3).

As a precautionary measure, invented name should therefore not be used in pregnancy.

Lactation:

The excretion of ciclopirox in human milk is unknown. Therefore, breast-feeding women should not use Batrafen 10mg/g Shampoo.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Immune System Disorders

Rare (> 1/10,000 and <1/1000): Allergic contact dermatitis may occur.

Skin And Subcutaneous Disorders

Uncommon (>1/1000; <1/100): Hair disorders, like matted and dull hair, mild dry hair, mild hair loss or discoloration and skin reactions at the application site such as irritation and eczema and subjective discomfort such as burning and itching. Parabens may cause hypersensitivity reactions, including delayed reactions.

4.9 Overdose

No experience with ciclopirox containing preparations overdose is available. However too frequent use of Batrafen 10mg/g Shampoo should not be expected to lead to any major systemic effects.

In case of accidental ingestion, adequate treatment should be initiated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antifungal agents.

ATC code: D01A E14 (other antifungals for topical use).

Ciclopirox is a broad spectrum N-hydroxypyridone antifungal agent with fungicidal action against pathogenic dermatophytes, moulds and yeasts including *Pityrosporum ovale* which is regarded as principal cause of seborrhoeic dermatitis.

Preclinical studies a steep dose-response curve indicating not only fungistatic but also fungicidal activity, a favourable pH-optimum, a long duration of action, a low influence of protein on the inhibiting concentrations, a good penetration into the deeper layers of the epidermis, and an additional antibacterial activity against Gram-positive as well as against Gram-negative aerobic bacteria.

The influence of ciclopirox medicinal shampoo on the viability of *Pityrosporum ovale* was studied in a model of excised back skin of pigs indicating that the shampoo is active even after short periods of treatment. Penetration experiments into the stratum corneum of excised pig skin showed that a short contact time of ciclopirox medicinal shampoo is sufficient to achieve active drug concentrations even in deeper layers of the stratum corneum. *In vivo* experiments confirmed the efficacy of ciclopirox using experimental dermatophytosis in guinea pigs. Ciclopirox demonstrated a clear dose-response efficacy against infections with *Microsporum canis* and *Trichophyton mentagrophytes*.

A quick onset of action was observed.

The mode of action is very complex by targeting a variety of metabolic processes in the fungal cell. Unlike most antifungal agents, ciclopirox does not affect sterol biosynthesis. The basis of the main mechanism in fungal cells is the high affinity of ciclopirox for trivalent metal cations such as Fe^{3+} . The trapping of this essential enzymatic co-factor causes an inhibitory effect on enzymes such as cytochromes, which are involved in mitochondrial electron transport processes in the course of energy production. In addition, the activity of catalase and peroxidase, which are responsible for the intracellular degradation of toxic peroxides is strongly reduced in the presence of the drug. As a consequence, ciclopirox impairs the fungal metabolism by affecting transport mechanisms, which are located in the fungus cell membrane. This particular mode of action of ciclopirox suggests that there is a low risk for the development of resistance and minimises the risk of cross-resistance with other antimycotic agents such as azoles and allylamines. Ciclopirox has anti-inflammatory properties. *In vitro* studies have shown that ciclopirox inhibits the production of cyclooxygenase and 5-lipoxygenase inflammatory mediators. Ciclopirox shows also *in vivo* anti-inflammatory effects in animals, which were confirmed in UV-erythema in human volunteers. The inflammation-inhibiting activity can promote healing in certain fungal skin infections, such as seborrhoeic dermatitis.

A total of 1189 patients with seborrhoeic dermatitis were treated over a 4-week period in three vehicle-controlled double-blind studies using four disease's signs and symptoms (status, scaling, inflammation, itching) as efficacy variables which were combined to two derived main response criteria: "effectively treated" and "cleared". After using the shampoo, 17.2 % (application once a week) and 21.3 % (application twice a week) of the patients became completely cleared. Cleared or effectively treated were 44.2 % (application once a week), and 52.5 % (application twice a week).

As an extension of the above results for the acute treatment of the disease, a clinical study has shown that a maintenance treatment once a week led to a re-occurrence of the disease in only 16 % of the patients compared to 36 % if a shampoo without active substance was used.

A total of 737 subjects were randomised in a double-blind study comparing the efficacy of a twice weekly application of the shampoo containing ciclopirox 1 % to another with ketoconazole 2 % using analogous response criteria. After the 4-week treatment period, about 74% of the patients responded in the ciclopirox group and 78,7 % in the ketoconazole group respectively. The similar response to both treatments gave in the statistical test for non-inferiority a p-value of 0.047 for the ITT population and $p=0.061$ for the VC population. When account is taken of the greater number of more severe cases at baseline in the 1-% ciclopirox group, the p-values for non-inferiority were 0.014 (VC) and 0.021 (ITT).

5.2 Pharmacokinetic properties

In three clinical trials of the 1% shampoo formulation, ciclopirox serum and urine concentrations were measured in patients with seborrhoeic dermatitis of the scalp. In the first study, patients were treated twice weekly for 4 weeks. In the second study, patients were treated under exaggerated use conditions, i.e. the patients washed their hair with ciclopirox shampoo every day for 29 days, increasing the contact time from 3 min to 6 min after 15 days. In one Phase III trial, ciclopirox serum and urine levels were measured after 4 weeks of once- or twice-weekly treatment and again after an additional 12 weeks of prophylactic treatment used once a week or once every 2 weeks. After four weeks of treatment, serum levels were detected in 21 of 293 patients, with maximum serum levels ranging between 13.2 and 39.0 microgram/L. After another 12 weeks of prophylactic treatment, ciclopirox levels were detected in 2 of 94 patients (max. 14.4 microgram/L).

In chronic oral toxicity studies, the no-toxic-effect levels of ciclopirox and its main metabolites were 2210 – 2790 microgram/L in rats and 1500 – 3500 microgram/L in dogs, indicating high safety margins.

When urinary output of ciclopirox was measured, excretion peaks were produced within the first 4 hours of administration which fell off rapidly thereafter. Since the kidney eliminates more than 98% of absorbed ciclopirox, urinary excretion is a reliable measure of the amount of drug absorbed during shampooing. In these studies, the median urinary excretion of ciclopirox ranged between 0.42 and 1.36% of the administered dose.

5.3 Preclinical safety data

Preclinical data reveal no evidence of toxicity up to a daily oral dose of 10mg/kg based on conventional studies of repeated dose toxicity, and no evidence of genotoxicity and carcinogenicity. A reduced fertility index was found with 5mg/kg bw ciclopirox in rats. No embryo/foetotoxicity or teratogenicity was observed in rats and rabbits. There was no evidence of peri/postnatal toxicity, however possible long-term effects on offspring have not been investigated.

In a cutaneous tolerance study in rabbits, Batrafen shampoo showed no irritant effect.

In a mucosal tolerance study in rabbits, undiluted Batrafen shampoo produced ocular irritation. To date, no studies have investigated irritation after repeated local administration, or evaluated sensitisation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium dodecyl- di(oxyethylene) sulphate , 27 % solution¹⁾

Disodium dodecyl- poly(oxyethylene)-3-2-sulphosuccinate, 33 % solution²⁾

Macrogol lauryl ether

Sodium chloride

Purified water

¹⁾ consisting of: sodium dodecyl- di(oxyethylene) sulphate; purified water; benzoic acid (E210).

²⁾ consisting of: disodium dodecyl poly(oxyethylene)-3-2-sulphosuccinate; phenoxyethanol; isobutyl (4-hydroxybenzoate); butyl (4-hydroxybenzoate); purified water; methyl parahydroxybenzoate (E218); ethyl parahydroxybenzoate (E214); propyl parahydroxybenzoate (E216).

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

After first opening the bottle, the shampoo may be used for up to 8 weeks.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

This medicinal product is supplied in low density polyethylene (LDPE) bottles with polypropylene (PP) hinged closure in:

30ml bottle, box of 1.

60ml bottle, box of 1 or 2.

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

Sanofi-Aventis Ireland Ltd
Citywest Business Campus
Dublin 24

8 MARKETING AUTHORISATION NUMBER

PA 540/32/5

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 August 2005

10 DATE OF REVISION OF THE TEXT

April 2007