CLINICAL OVERVIEW

of:

KETOCONAZOLE

shampoo 2%

Clinical overview on the medicine

KETOCONAZOLE shampoo 2%

Redacted under Section 41 and Section 43 of the Freedom of the Freedom of Information Act.

The request for preparing the clinical overview on the preparation KETOCONAZOLE shampoo 2%; 120 ml was submitted by [redacted]

[redacted]

The Expert overview, as intended for obtaining Marketing Authorisation in other countries is prepared under the international non-proprietary name (INN) of the medicine.

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2.5. INTRODUCTION TO APPLICATION TYPE

2.5.1 General information

Application type: Well established medicine

The Marketing Application is based on the relevant sections of Annex 1 analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of medicinal products (as amended) to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

Ketoconazole (INN, USAN, BAN, JAN) is a synthetic imidazole antifungal drug used primarily to treat fungal infections. Ketoconazole is sold commercially as a tablet for oral administration, and in a variety of formulations for topical administration, such as creams (used to treat tinea; cutaneous candidiasis, including candidal paronychia; and pityriasis versicolor) and shampoos (used primarily to treat dandruff—seborrhoeic dermatitis of the scalp). Topically administered ketoconazole is usually prescribed for fungal infections of the skin and mucous membranes, such as athlete's foot, ringworm, candidiasis (yeast infection or thrush), jock itch, and tinea versicolor.
Topical ketoconazole is also used as a treatment for dandruff (seborrheic dermatitis of the scalp) and for seborrheic dermatitis on other areas of the body, perhaps acting in these conditions by suppressing levels of the fungus *Malassezia furfur* on the skin.

Ketoconazole was discovered in 1976 at Janssen Pharmaceuticals. International "birth date", is 02.12.1983. It followed griseofulvin as one of the first available oral treatments for fungal infections. It is marketed under the trademark name Nizoral by Ortho-McNeil Pharmaceutical in the United States, Australia and Canada, as Sebizole by Douglas Pharmaceuticals in Australia and New Zealand and as Ketomed in Latin America. In Spain, products with ketoconazole as main agent include Ketoisdin gel (gel) and Fungarest (cream). In India, ketoconazole is sold as keton (tablets, soap & cream) by Green Apple Lifesciences Limited.

According to Article 10a of directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, by way of derogation from Article 8(3)(i), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of pre-clinical tests or clinical trials if he can demonstrate that the active substances of the medicinal product have been in well-established medicinal use within the Community for at least ten years, with recognized efficacy and an acceptable level of safety in terms of the conditions set out in the Annex. In that event, the test and trial results shall be replaced by appropriate scientific literature.

2. Well established medicinal use

Definition of well-established medicinal use
'Well established medicinal use' is the reference to the constituent(s) of a medicinal product that has/have a historically proven acceptable level of safety and with recognised efficacy based on the following criteria:

2.1 The time over which a substance has been used with regular application in patients

Ketoconazole, was discovered in 1976, and the international "birth date", is 02.12.1983. It is used to prevent and treat fungal skin infections. Ketoconazole is present in different pharmaceutical formulations: an anti-dandruff shampoo, topical cream, and oral tablet.
Actually, the active substance with generic name: ketoconazole with ATC code: D01AC08 and Chemical name: (±)-*cis*-1-Acetyl-4-{4-[2-(2,4-dichlorophenyl)-2-imidazol-1-ylmethyl-1,3-dioxolan -4-ylmethoxy] phenyl} piperazine is longer than 10 years at the market.

Ketoconazole shampoo 2% is available on the market across Europe as:

SmPC from EMC medicines (www.medicines.org.uk/emc):

- **Boots Anti-Dandruff Ketoconazole 2% w/w Shampoo** (Manufactured for The Boots Company PLC, by MAH Pinewood Laboratories Limited, Ireland).
  Date of first authorisation/renewal of the authorisation: 10.10.2003 / 26.03.2009;
  MA No. PL 04917/0063.

- **Dandrazol 2% Shampoo** (Transdermal Limited UK);
  Date of first authorisation/renewal of the authorisation: 30/01/2009;
  MA No. PL 14308/0004;

- **Dandrazol Anti-Dandruff Shampoo** (Transdermal Limited UK);
  Date of first authorisation/renewal of the authorisation: 30/01/2009;
  MA No. PL 14308/0006;

- **Ketoconazole 2% w/w Shampoo** (MAH Pinewood Laboratories Limited, trading as Pinewood Healthcare, Ireland); Date of first authorisation/renewal of the authorisation: 09/02/2009 ; MA No. PL PL 04917/0039;

- **Nizoral 2% Shampoo** (Thornton & Ross Ltd, UK)
  Date of first authorisation/renewal of the authorisation: 24.06.2008;

MA No PL 00240/0451 Date of first authorization/renewal of the authorization: 24/06/200823/10/2020. Date of revision of the text: 23/10/2020

- **Nizoral Antidandruff Shampoo** (Thornton & Ross Ltd, UK)
  Date of first authorisation/renewal of the authorisation: 10.12.2010;
  MA No PL 00240/0453

- **Nizoral Dandruff Shampoo** (Thornton & Ross Ltd, UK)
  Date of first authorisation/renewal of the authorisation: 10.12.2010
  MA No PL 00240/0452

SmPC from MHRA *(www.mhra.gov.uk/):

- **Dandrazol 2% Shampoo** (Transdermal Limited UK);
  Date of first authorisation/renewal of the authorisation: 30/01/2009; MA No. PL 14308/0004);

- **Dandrazol Anti-Dandruff Shampoo** (Transdermal Limited UK);
  Date of first authorisation/renewal of the authorisation: 30/01/2009; MA No. PL 14308/0006;

- **Ketoconazole 2% w/w Shampoo** (MAH Pinewood Laboratories Limited, trading as Pinewood Healthcare, Ireland); Date of first authorisation/renewal of the authorisation: 09/02/2009 ; MA No. PL 00327/0178;

- **Ketopine Dandruff Shampoo Boots Anti-Dandruff Ketoconazole 2% w/w Shampoo (MAH** Pinewood Laboratories Limited, Ireland); Date of first authorisation/renewal of the authorisation: 10.10.2003 / 26.03.2009; MA No. PL 04917/0063;

- **Merazol 2% Shampoo** (Noumed Life Sciences Limited, Noumed House, UK);
  Date of first authorisation/renewal of the authorisation: 24/06/2008; MA No. PL 44041/0121;

- **Nizoral 2% shampoo** (MAH Thornton & Ross Ltd., UK)
  Date of first authorisation/renewal of the authorisation: 24/06/2008; MA No. PL 00240/0451

- **Nizoral™ Anti-Dandruff Shampoo** (MAH: Thornton & Ross Ltd, UK);
  Date of first authorisation/renewal of the authorisation: 10/12/2010; MA No. PL 00240/0453.

- **Nizoral™ Dandruff Shampoo** (MAH: Thornton & Ross Ltd, UK);

Date of first authorisation/renewal of the authorisation: 10/12/2010; MA No. PL 00240/0452.

* MHRA means The Medicines and Healthcare Products Regulatory Agency, UK (www.mhra.gov.uk/)

2.2 Quantitative aspects of the use of the substance, taking into account the extent to which the substance has been used in practice, the extent of use on a geographical basis and the extent to which the use of the substance has been monitored by pharmacovigilance or other valid methods

Quantitative aspects of the active substance ketoconazole in [redacted] (ketoconazole) shampoo 2% from [redacted] and in the products registered on the market across Europe are the same.

2.3 The degree of scientific interest in the use of the substance (reflected in the published scientific literature) and the coherence of scientific assessments

Considering the fact that Ketoconazole was presented in 1981, there is a lot of published scientific literature. The coherence of scientific assessments is proved throughout available bibliographic literature.

2.4 The period of time required for establishing a well-established medicinal use of a constituent of a medicinal product must not be less than ten years from the first systematic and documented use of that substance as a medicinal product or thirty years in the case of herbal medicinal products.

Ketoconazole was first registered as tablets and oral suspension in December 1980. This was followed by the registration of topical pharmaceutical forms such as cream /ointment/shampoo. The use of ketoconazole has been monitored by the WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre, (UMC), in Sweden, so the relevant safety profile is presented in PSUR (Periodic Safety Update Report), and the adverse drug reactions are listed in updated SmPC as part of this application.

Ketoconazole is used in many countries, as listed below (Martindale: The Complete Drug Reference 2007). The medicinal product has been introduced on the market more than ten years. On the former Yugoslavia (SFRJ) market, the product was introduced in 1990 (Unique classification of medicinal products with Marketing authorisations in SFRJ) with DDD and ATC classification, Federal Institute for Health Protection, Belgrade 1990).

Conclusion

Based on the presented data it can be concluded that Ketoconazole is in human use for more than 10 years periods of time (actually more than 40 years), period of time which is enough for establishing well-established use of Ketoconazole substance.

In any case, however, the period of time required for establishing a well-established medicinal use of a constituent of a medicinal product must not be less than one decade from the first systematic and documented use of that substance as a medicinal product in the Community- the condition that Ketoconazole comply.

This clinical overview is covering the recent data for medicinal product Ketoconazole in a form of shampoo. In order to provide concise and up-to-date information, this overview refers to drugs containing Ketoconazole as active ingredient. In particular, the overview will address the recently published literature so that any new information on the safety and efficacy of the drug can be taken into account.

Preparations (as listed in Martindale: The Complete Drug Reference 2007)

List of preparations:

Europe

Austria: Fungoral; Nizoral; ***Belgium***: Nizoral; ***Czech Republic***: Nizoral; Orozanol; ***Denmark***: Kezoral; Nizoral; ***Finland***: Nizoral; ***France***: Ketoderm; Nizoral; ***Germany***: Nizoral; Terzolin; ***Greece***: Abba; Adenosan; Aquarius; Botaderm; Cezolin; Ebersept; Fungoral; Ilgem; Mycofebrin; Neo-egmol; Scalpin; Sostatin; ***Hungary***: Nizoral; ***Ireland***: Nizoral; ***Israel***: Nizoral; ***Italy***: Nizoral; Triatop; ***Netherlands***: Nizoral; ***Norway***: Fungoral; ***New Zealand***: Daktagold; Ketopine; Nizoral; Sebizole; ***Portugal***: Frisolac; Nizale; Nizoral; Rapamic; Tedol; ***Russia***: Livarole (Ливарол); Mycosoral (Микозорал); Nizoral (Низорал); ***Spain***: Fungarest; Fungo Farmasierra; Fungo Zeus; Keto-Cure; Ketoisdin; Medezol; Micoticum; Panfungol; ***Sweden***: Fundan; Fungoral; Ketoson; ***Switzerland***: Ketozol; Nizoral; Terzolin; ***United Kingdom***: Daktarin Gold; Dandrazol; Dandrid; Nizoral.

Worldwide

Argentina: C-86; Cetonil; Eumicel; Faction; Fangan; Fitonal; Fungicil; Grenfung; Keduo; Ketonazol; Ketozol; Micoespec K; Micoral; Orifungal; Perative; Quadion; Socosep; Tikl; Triatop; - ***Australia***: Hexal Konazol Shampoo; Nizoral; Sebizole; ***Brazil***: Aciderm; Arcolan; Candiderm; Candoral; Cetocona; Cetoconalab; Cetohexal; Cetomed; Cetomicoss; Cetomizol; Cetonax; Cetoneo; Cetonil; Cetonin; Cetozan; Cetozaz; Cetozol; Fungoral; Ketomicol;

Ketonan; Ketonazol; Lozan; Miconan; Micoral; Nizoral; Nizoretic; Noriderm; Noronal; Sioconazol; Tonazox; Zanoc; Zolmicol;
Canada: Ketoderm; Nizoral; ***Chile***: Arcolane; Biogel; Eprofil; Fungarest; Fungium; Ketonil; Soridermal; TKC; ***Hong Kong***: Diazon; Fluzoral; Fungazol; Ketozol; Ketozole; Larry; Nizoral; Pristine; Pristinex; Stada K; Synizoral; ***India***: Arcolane; Danfree; Danruf; Funazole; Fungicide; Hyphoral; Keto; ***Malaysia***: Dezor; Fungazol; Funginox; Ketozole; Kezoral; Nizoral; Pristine; Pristinex; Sebizole; Sunazol; Yucomy; ***Mexico***: Akorazol; Apo-Kesol; Biozoral; Conazol; Cremosan; Ergomicon; Eurolat; Fungipar; Fungoral; Fungosine; Honzil; Ketofar; Ketomed; Ketomizol; Ketoril; Konaderm; Konaturil; Lemyken; Lizovag; Luminovag; Mi-Ke-Sons; Micoser; Micozol; Mycodib; Nastil; Nazolfarm; Nazoltec; Nizoral; Onofin-K; Prenalon; Remecon; Strizole; Termizol; Tiniazol; Tocomizol; Toconal; Tolcrem; Tomiko; Triatop; ***South Africa***: Adco-Dermed; Ketazol; Kez; Nizcreme; Nizoral; Nizorelle; Nizovules; Nizshampoo; ***Singapore***: Antanazol; Beatoconazole; Dezor; Diazon; Ketozole; Nizoral; Pristine; Pristinex; Sebizole; ***Thailand***: AC-FA; Chintaral; Diazon; Fungazol; Fungiderm-K; Funginox; Kara; Katsin; Kazinal; Kenalyn; Kenazol; Kenazole; Kenoral; Ketazol; Ketazon; Ketocine; Ketolan; Ketomed; Ketonazole; Ketosil; Kezon; Lama; Larry; Manoketo; Masarol; Mizoron; Mycella; Mycoral; Ninazol; Nizoral; Nora; Pasalen; Sporoxyl; Triatop; ***United States***: Nizoral; ***Venezuela***: Arcolane; Danfree; Freetop; Kenazol; Ketazol; Ketocoval; Ketomed; Napox; Nizoral; Noractin; Topstar.

2.5.1 PRODUCT DEVELOPMENT RATIONALE

General information

Ketoconazole is an imidazole-dioxolane antimycotic, active against yeasts, including Malassezia and dermatophytes. Its broad spectrum of activity is already well known.

Name: KETOCONAZOLE

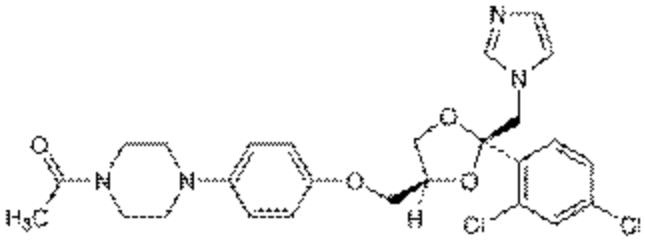
Synonyms: Ketoconazol; Ketoconazolum; Ketokonatsoli; Ketokonazol; Ketokonazolas; R-41400

INN: Ketoconazole [rINN (en)]

Chemical name: (±)-cis-1-Acetyl-4-{4-[2-(2,4-dichlorophenyl)-2-imidazol-1-ylmethyl-1,3-dioxolan-4-ylmethoxy] phenyl} piperazine

Molecular formula: $C_{26}H_{28}Cl_2N_4O_4$

Chemical Structure:



Pharmacopoeias: In **Chin.**, **Eur.**, **Int.**, **Pol.**, and **US.**

Ph. Eur. 5.5 (Ketoconazole).

A white or almost white powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane; soluble in methyl alcohol. Protect from light.

2.5.2 OVERVIEW OF BIOPHARMACEUTICS

Not applicable.

2.5.3 OVERVIEW OF CLINICAL PHARMACOLOGY

2.5.3.1 Pharmacodynamic properties

Ketoconazole is an imidazole-dioxolane antimycotic, active against yeasts, including Malassezia and dermatophytes. (Van Tyle, et al 1984; Buxton, 1988; Sohn, 1982). Its broad spectrum of activity is already well known. (Van Tyle, et al 1984; Borgers, et al. 1983; Nagpal, et al. 2003; Kyle and Dahl, 2004).

Ketoconazole works as an antifungal agent by inhibiting the cytochrome P450 14α-demethylase enzyme. This enzyme is responsible for inhibiting the biosynthesis of triglycerides and phospholipids by fungi (Van Tyle, et al 1984). More specifically, ketoconazole inhibits the synthesis of lanosterol, a necessary precursor for ergosterol biosynthesis. Ergosterol is needed to maintain the integrity of the membrane of fungi. Without ergosterol, the fluidity of the membrane increase, which in turn prevents fungal growth (Van Tyle, et al 1984; Borgers, et al. 1983; Van den Bossche, 1980). Ketoconazole inhibits the activity of the enzyme 21-hydroxylase. This enzyme is essential for synthesizing mineralocorticoids and glucocorticoids, such as cortisol, in the adrenal cortex. By inhibiting enzymes involved in cortisol synthesis, ketoconazole can be a treatment option for Cushing syndrome (Sinawe and Casadesus, 2022).

Spectrum of Activity

Ketoconazole is active against yeasts, including Malassezia and dermatophytes. (Van Tyle, et al 1984; Buxton, 1988; Sohn, 1982). Its broad spectrum of activity is already well known The antifungal properties of ketoconazole were investigated both in vitro and in vivo (Odds, et al 1980; Van Cutsem J 1983; Van den Bossche, et al. 1980, Graybill, et al. 1980; Fernández-Torres, et al 2000).

2.5.3.2 Pharmacokinetic properties

Plasma concentrations of ketoconazole were not detectable after topical administration of ketoconazole 2% shampoo on the scalp (Chowdhry and Gupta, 2016).

Plasma levels were detected after topical administration of ketoconazole 2% shampoo on the whole body (SmPC Nizoral 2% shampoo, Thornton & Ross Ltd. UK, 23/10/2020; Mitu MA et al 2011).

2.5.4. OVERVIEW OF EFFICACY

2.5.4.1 Therapeutic indications

Ketoconazole shampoo is indicated for:

- **Prevention and treatment of infections in which the yeast Malassezia (previously called Pityrosporum) is likely to be involved, such as dandruff and seborrhoeic dermatitis** (Borda and Wikramanayake, 2015; Schwartz, et al 2006; Chowdhry and Gupta, 2016; Borgers, et al 2007; Goldenberg, 2013; Mokos, et al 2012; Herrera-Arellano, et al., 2004; Okokon, et al, 2015; Kastarinen, et al 2014; Manríquez and Uribe, 2007; Marconi and Powell, 1992; Green, et al. 1987; Aly and Berger, 1996; Chatzikokkinou, et al., 2008; Piérard-Franchimont et al 1997; Stefanaki and Katsambas, 2010; Squire and Goode, 2002; Ashtiani et al 2013; Peter and Richarz-Barthauer, 1995; Piérard-Franchimont, et al. 2002).

- **Treatment of tinea (pityriasis) versicolor** (Gupta AK, et al 2004; Hald, et al., 2015; Rathi, 2003; Lange, et al. 1998; Marais and Osuch, 2017; Aggarwal, et al 2003; Straten Vander, et al., 2003; Kakourou, et al 2010; Marais and Osuch, 2017; Kaul, et al 2017; Greer, 2000; Bookstaver, et al 2011).

2.5.4.2 Clinical studies (literature data)

Prevention and treatment of Malassezia (previously called Pityrosporum) yeast infections

Seborrheic Dermatitis and Dandruff

Seborrheic Dermatitis (SD) and dandruff are of a continuous spectrum of the same disease that affects the seborrheic areas of the body. Dandruff is restricted to the scalp, and involves itchy, flaking skin without visible inflammation. SD can affect the scalp as well as other seborrheic areas, and involves itchy and flaking or scaling skin, inflammation and pruritus. It is estimated that SD and dandruff combined affect half of the adult population. Despite such high prevalence, their etiology is not well understood. Various intrinsic and environmental factors, such as sebaceous secretions, skin surface fungal colonization, individual susceptibility, and interactions between these factors, all contribute to the pathogenesis of SD and dandruff (Borda and Wikramanayake, 2015). Multiple topical agents are effective therapies for the treatment of dandruff. These agents include pyrithione zinc, selenium sulfide, salicylic acid, sulfur, coal tar, hydrocortisone and ketoconazole. A common mechanism of most effective actives is their antifungal activity against *Malassezia.* In vitro fungistatic and fungicidal tests of ketoconazole, pyrithione zinc, and selenium disulfide have demonstrated low inhibitory concentrations of growth (MICs) against *Malassezia furfur* (Schwartz, et al 2006; Waldroup and Scheinfeld, 2008).

Both systemic and topical applications of ketoconazole have been found effective in seborrhoeic dermatitis (Chowdhry and Gupta, 2016; Borgers, et al 2007; Goldenberg, 2013; Mokos, et al 2012; Herrera-Arellano, et al., 2004).

The Cochrane Skin Group recently conducted a meta-analysis for studies published so far on the use of topical antifungals for SD. They concluded that as compared to placebo group, participants taking ketoconazole were 31% less likely to have symptoms persisting at four weeks of follow-up (Okokon, et al, 2015).

To assess the effects of topical pharmacological interventions with established anti-inflammatory action for seborrheic dermatitis occurring in adolescents and adults, the investigators searched the databases up to September 2013: the Cochrane Skin Group Specialised Register, CENTRAL in The Cochrane Library (2013, Issue 9), MEDLINE (from 1946), Embase (from 1974), LILACS (from 1982), and the GREAT database. Investigators searched five trials databases and checked the reference lists of included studies for further references to relevant randomised controlled trials (RCTs). 36 RCTs (2706 participants) were included. At the end, authors concluded that ttreatment with azoles seems as effective as steroids concerning short-term total clearance, but in other outcomes, strong steroids were more effective (Kastarinen, et al 2014).

In adults with seborrhoeic dermatitis of the scalp, antifungal preparations containing ketoconazole improve symptoms compared with placebo. Ketoconazole shampoo is more effective than placebo at improving scalp symptoms such as scaling, itching, redness, and dandruff at 4 weeks in people with seborrhoeic dermatitis of the scalp (moderate quality evidence). Five randomized control trials (RCTs) ranging in size from 20 to 246 participants found improvements in symptoms with ketoconazole 2% shampoo after 4 weeks compared with placebo. Four of the five RCTs reported that there were no adverse effects of treatment. The fifth RCT reported one instance of scalp tenderness that was probably related to ketoconazole treatment (Manríquez and Uribe, 2007). In the only placebo-controlled trial of seborrhoea treatment, it was demonstrated a significantly higher cure rate in adults with seborrhoea and cultures positive for M. furfur who were treated for 4 weeks with a twice-weekly ketoconazole shampoo (Marconi and Powell, 1992).

A randomized, double-blind, placebo-controlled study was made of 2% ketoconazole shampoo and cream in 20 patients with seborrheic dermatitis of the face. Sixteen also had seborrheic dermatitis of the scalp and five had seborrheic dermatitis of the chest or back. Responses were measured by clinicians and patients independently using a grading system and linear analogue scales, respectively. Face and scalp lesions, assessed by both patient and clinician, showed a significant improvement or complete clearance in the group treated with ketoconazole. The patients who had seborrheic dermatitis of the chest or back and were treated with ketoconazole also improved. There was no improvement with placebo. This study provides further evidence for the aetiological role of pityrosporon yeasts in seborrheic dermatitis and of the efficacy of topical ketoconazole in its treatment (Green, et al. 1987).

Superficial mycotic infections such as seborrheic dermatitis, tinea pedis, tinea corporis, and onychomycosis are common in patients infected with human immunodeficiency virus (HIV). In communities where HIV infections are frequent, some of these clinical presentations serve as markers of the stage of HIV infection. The diagnosis of superficial fungal infection in

HIV-positive patients may be difficult because of atypical clinical manifestations. Therefore, to ensure a correct diagnosis, skin scrapings should be collected for potassium hydroxide preparations and cultures. Most forms of dermatophytosis in HIV-positive patients respond well to many topical antifungal agents, such as azoles, terbinafine, and ciclopirox olamine. If the disease is chronic and extensive, then ketoconazole, fluconazole, and itraconazole are each effective (Aly and Berger, 1996).

In the general population, the prevalence of seborrheic dermatitis varies between 3% and 5%, while in HIV positive patients there is an increased prevalence of seborrheic dermatitis ranging between 30% and 83%. Seborrheic dermatitis occurs early in the course of HIV disease and may be an initial clinical marker of HIV infection. Antimycotics remain a popular treatment for SD, in the form of shampoos or creams. Many double-blind studies have documented the efficacy of ketoconazole 2% in reducing flaking and *Malassezia* counts; furthermore, ketoconazole 2% shampoo has been shown to have a significant prophylactic effect when used once weekly. Nevertheless, low potency topical corticosteroids (e.g., hydrocortisone) and emollients have been used in the initial stages of treatment (Chatzikokkinou, et al., 2008).

The clinical efficacy of antidandruff shampoos is correlated with both their anti-Malassezia and their squamolytic acctivities. The sebum flow nourishing the lipophilic yeasts is another actor on the scene fueling the skin disorder. This study was conducted in 120 men in order to quantify the effect of eight proprietary antidandruff shampoos on sebum flow dynamics.

Evaluation were made using the Lipometer©. Two shampoos exhibited a significant effect upon the sebum follicular reservoir, steadily increasing the sebum excretion race in time. One other product induced a significant decrease in sebum output. Present data give insight into the distinct effects of shampoos on the follicular reservoir function in androgenic alopecia. The resulting sebum flow dynamics may be significantly increased or decreased by proprietary products (Piérard-Franchimont C et al 1997).

A randomized, double-blind, placebo-controlled trial was conducted in order to evaluate the safety and effectiveness of ketoconazole 2% shampoo versus selenium sulfide 2.5% shampoo and placebo shampoo in patients with moderate to severe dandruff. Features assessed included adherent and loose dandruff scores, presence or absence of irritation, itching, yeast cells, and global improvement rating by the investigator. A total of 246 patients were included. Mean total adherent dandruff score declined throughout the treatment period with both ketoconazole 2% and selenium sulfide 2.5% shampoos significantly better than placebo at all visits. Ketoconazole was statistically superior to selenium sulfide at day 8 only ($p = 0.0026$). Both medicated shampoos were significantly better than placebo for reducing irritation and itching. Of the nine adverse experiences reported during the treatment phase, all involved patients treated with selenium sulfide 2.5% shampoo. It was concluded that both ketoconazole 2% shampoo and selenium sulfide 2.5% shampoo are effective in the treatment of moderate to severe dandruff; however, ketoconazole 2% shampoo appears to be better tolerated (Danby, et al 1993).

In a randomized double-blind trial, selenium sulfide 2.5% was tested against ketoconazole 2% and placebo in 246 patients with moderate to severe dandruff. Both ketoconazole and selenium sulfide shampoos were effective, but ketoconazole was better tolerated.

Ketoconazole shampoo 2% is superior to 1% and can be used once-weekly as maintenance therapy for scalp seborrheic dermatitis. Zinc pyrithione 1% shampoo in comparison with ketoconazole 2% shampoo has produced inferior results, whereas selenium sulphide exhibited similar efficacy (Stefanaki and Katsambas, 2010).

To compare the therapeutic efficacy of a shampoo containing 1.5% ciclopirox olamine and 3% salicylic acid (CPO/SA) with Nizoral (2.0% ketoconazole shampoo) in a study involving 154 subjects with dandruff - 70 of whom also had seborrheic dermatitis of the scalp. The shampoos were used three times week for 4 weeks, with 2-week washout and follow-up periods. Clinical and self-assessments were made throughout treatment and after follow-up (day 43). Within and between-treatment assessments of signs and symptoms were analysed.

In the two groups, seborrheic dermatitis and dandruff improved significantly throughout treatment, with lower clinical and self-assessment scores at both the end of treatment (day 29) and follow-up (day 43). Only the subjects treated with CPO/SA shampoo showed a significant reduction in the itching of seborrheic dermatitis at these times. The study demonstrated that both CPO/SA and Ketoconazole 2 % shampoo (Nizoral) were safe and effective in the treatment of dandruff and seborrheic dermatitis (Squire and Goode, 2002).

In another study, 120 volunteers, who suffered from dandruff, were recruited into the study in 3 groups. The first group used Cepigene shampoo, the second group used Ketoconazole shampoo and the third group used vehicle. The samples were also cultured for fungi detection. For isolating the fungi and evaluating the rate of Dandruff and Seborrheic dermatitis, the subjects were sampled from their scalp in zero day of the study. Trypan blue assay was used to study the antifungal effects of cepigen and ketoconasole. There was a remarkable decrease in the scaling and itching of scalp after a weeklong treatment by Cepigene and Ketoconazole shampoo. Indeed, both products delivered a reduction in ASF scores in comparison with those of controls. Trypane blue assay showed a dose-dependent decrease in the M. furfur and M. globosa viability following exposure to cepigen and ketoconazole. This study supports the efficacy in treating Dandruff and Seborrheic Dermatitis with Cepigene shampoo enriched in appropriate chemical and herbal compounds (Ashtiani et al 2013).

Ketoconazole 2% shampoo was effective not only in treating seborrheic dermatitis, but also in preventing relapse when used once weekly as prophylaxis. An 88% response rate was achieved among 575 ketoconazole-treated patients with moderate to severe seborrheic dermatitis. A 6-month prophylactic treatment phase comprised 312 of the responding patients, 102 of whom were randomized to once weekly treatment with placebo shampoo, 121 who used ketoconazole shampoo once weekly, and 100 who alternated ketoconazole and placebo once weekly. Relapse occurred in only 19% of the active treatment group, compared with 47% of the placebo group and 31% of the ketoconazole/placebo group (Peter and Richarz-Barthauer, 1995).

The efficacy and safety of Ketoconazole 2% and zinc pyrithione 1% in shampoo formulations were compared for the alleviation of severe dandruff and seborrheic dermatitis. This open randomized, parallel-group trial began with a 2-week run-in phase during which subjects applied a neutral non-antidandruff shampoo. It was followed by a 4-week randomized treatment phase and a subsequent 4-week follow-up phase without treatment. Shampooing

during the treatment period was carried out twice weekly for the Ketoconazole group and at least twice weekly for the zinc pyrithione group in accordance with the label instructions. A total of 343 subjects were recruited to enter the trial. Of the 331 eligible volunteers, 171 were randomized to Ketoconazole 2% and 160 to zinc pyrithione 1%. Clinical assessments were performed. Beneficial effects were evidenced for both medicated shampoos, but the effect was significantly better for Ketoconazole 2%, which achieved a 73% improvement in the total dandruff severity score compared with 67% for zinc pyrithione 1% at week 4 ($p < 0.02$). The recurrence rate of the disease was also significantly lower following Ketoconazole 2% treatment than following zinc pyrithione 1% treatment. As a consequence, the overall clearing of the skin condition at the end of treatment and follow-up phase was in favor of the Ketoconazole 2% formulation ($p = 0.004$). Side effects were minimal. It is concluded that after a 4-week treatment, Ketoconazole 2% shampoo was significantly superior to zinc pyrithione 1% shampoo in the treatment of subjects with severe dandruff or seborrheic dermatitis of the scalp. It is our assumption that this difference is noticeable for the patient and as a consequence relevant. Both formulations were well tolerated (Piérard-Franchimont, et al. 2002).

Treatment of tinea (pityriasis) versicolor

Yeasts of the genus, Malassezia, formerly known as Pityrosporum, are lipophilic yeasts, which are a part of the normal skin flora (microbiome). Malassezia colonize the human skin after birth and must therefore, as commensals, be normally tolerated by the human immune system. The Malassezia yeasts also have a pathogenic potential where they can, under appropriate conditions, invade the stratum corneum and interact with the host immune system, both directly but also through chemical mediators. The species distribution on the skin and the pathogenetic potential of the yeast varies between different Malassezia related diseases such as head and neck dermatitis, seborrheic dermatitis, pityriasis versicolor, and Malassezia folliculitis. Skin diseases caused by Malassezia are usually treated with antifungal therapy and if there are associated inflammatory skin mechanisms this is often supplemented by anti-inflammatory therapy (Saunte, et al 2020). Many studies have been published after the taxonomic revision carried out in 1996 in which 7 species were recognized. Two new species have been recently described, one of which has been isolated from patients with atopic dermatitis (Gupta AK, et al 2004).

Main recommendations in most cases of pityriasis versicolor and seborrheic dermatitis include topical treatment which has been shown to be sufficient. As first choice, treatment should be based on topical antifungal medication. A short course of topical corticosteroid or topical calcineurin inhibitors has an anti-inflammatory effect in seborrheic dermatitis. Systemic antifungal therapy may be indicated for widespread lesions or lesions refractory to topical treatment. Maintenance therapy is often necessary to prevent relapses. In the treatment of Malassezia folliculitis systemic antifungal treatment is probably more effective than topical treatment but a combination may be favourable (Hald, et al., 2015).

The aim of one study was to evaluate the efficacy of ketoconazole 2% shampoo in the treatment of pityriasis versicolor, for which thirty patients were included. The shampoo was

applied daily for 3 days and found to be very effective in clearing the signs and symptoms of the disease. There were no serious adverse effects (Rathi, 2003).
Another study was performed in order to evaluate the efficacy and safety of a single application (1 day) versus three daily applications (3 days) of ketoconazole 2% shampoo versus placebo shampoo in the treatment of mycologically confirmed tinea versicolor. Three hundred twelve patients were included in the primary analyses for this 31-day study. Global evaluation scores were measured on days 10 and 31 with a 5-point scale (1 = healed to 5 = worsening), and a cellophane tape test was done at baseline and days 3, 10, and 31. Efficacy was assessed by clinical response, defined as both a global evaluation score of 1 (healed) and a negative cellophane tape test on day 31. Signs and symptoms of tinea versicolor (scaling, itching, erythema, hypopigmentation, hyperpigmentation) also were evaluated at baseline, day 10, and day 31 with a 4-point scale (0 = absent to 3 = severe). Both regimens of ketoconazole shampoo were significantly ($P < .001$) more effective than placebo for rate of clinical response, global evaluation scores, and mycologic outcomes (cellophane tape test). The clinical response rates at day 31 were 73%, 69%, and 5% for the 3-day ketoconazole, 1-day ketoconazole, and placebo groups, respectively. The difference in the efficacy of the two ketoconazole treatment regimens was not statistically significant. There were no significant differences between any of the treatment groups in the number of patients who experienced adverse events. No serious adverse events occurred and no patient withdrew from the trial prematurely because of an adverse event. At the end of the study, it was concluded that Ketoconazole 2% shampoo, used as a single application or daily for 3 days, is safe and highly effective in the treatment of tinea versicolor (Lange, et al. 1998).

Tinea corporis responds well to topical antifungal agents from the imidazole (clotrimazole, econazole, ketoconazole) and allylamine (terbinafine, tolnaftate) groups, where it is administered once or twice per day for one to three weeks. Treatment is continued for at least one week after clinical resolution has been achieved (Marais and Osuch, 2017).
Forty patients suffering from pityriasis versicolor were treated with either 2% ketoconazole shampoo (20 patients) or 2.5% selenium sulphide shampoo (20 patients), once a week for three weeks. On global assessment after one month of start of therapy, 19 (95%) out of 20 patients treated with ketoconazole shampoo were cured while one case had mild residual disease. In selenium sulphide shampoo group, 17 (85%) out of 20 patients were cured, one had mild residual disease and two had considerable residual disease. No significant difference was observed in the response rates in the two groups. Relapse occurred in one patient of ketoconazole group and two patients of selenium sulphide group during the follow-up period of three months (Aggarwal, et al 2003).
Topical treatments can be effective, including econazole cream, ketoconazole cream or shampoo, or selenium sulfide lotion or shampoo. Econazole and ketoconazole creams may be used every day for 2 weeks. Ketoconazole shampoo may be used every day (lather, rinse, and repeat) for 3 days; selenium sulfide can be used every day (left on the skin for 10 to 15 minutes and then rinsed off) for 10 to 14 days, then one night per month to prevent recurrence. Recurrences may occur less frequently if treated orally for a short time:

itraconazole, 200 mg every day for 5 to 7 days; fluconazole, 400 mg single dose; or ketoconazole 200 mg every day for 5 to 10 days. Oral terbinafine is ineffective in treatment of tinea versicolor, although a spray preparation (used topically) seems to be effective (Straten Vander, et al., 2003).

Tinea capitis

Topical treatment for Tinea capitis is only used as adjuvant therapy to systemic antifungals. Adjunctive topical therapies such as Selenium sulfide (Grade of recommendation B; strength of evidence II a) or ketoconazole (Grade of recommendation B; strength of evidence III) shampoos as well as fungicidal creams or lotions have been shown to decrease the carriage of viable spores responsible for the disease contagion and reinfection and may shorten the cure rate with oral antifungal. The topical fungicidal cream/ lotion should be applied to the lesions once daily for a week (Grade of recommendation C; strength of evidence IV). The shampoo should be applied to the scalp and hair for 5 minutes twice weekly for 2–4 weeks or three times weekly until the patient is clinically and mycologically cured (Grade of recommendation C; strength of evidence IV). The latter in conjunction with 1 week of topical fungicidal cream or lotion application is recommended by the authors. Clinical and mycologic examinations of the children should be conducted at regular intervals (2–4 weeks). The treatment may be stopped after the culture becomes negative or when hair regrowth is clinically evident; consequently, the duration of treatment can be individualized according to the response (Kakourou, et al 2010).

Current guidelines for treating Tinea capitis recommend washing the hair with shampoos containing 2.5% selenium sulfide or 2% ketoconazole two to three times per week for a period of 4–8 weeks (Marais and Osuch, 2017).

To prevent the transmission of spores, 2–4 times weekly use of 1% selenium sulphide, 1% or 2% zinc pyrithione, 2.5% povidone–iodine, and 2% ketoconazole shampoos have been shown to be effective (Kaul, et al 2017). The purpose of one open study was to evaluate ketoconazole 2% shampoo as a monotherapy for the treatment of tinea capitis. A total of 16 black children, aged 3-6, all with proven tinea capitis caused by Trichophyton tonsurans, were treated daily for 8 weeks with 2% ketoconazole shampoo for a total of 56 treatments. Clinical and mycologic examinations were performed every 2 weeks and again at 4 weeks following treatment. The number of colonies were counted on each plate after each visit. Patients with positive cultures after 8 weeks were placed on oral griseofulvin; those with negative cultures were followed monthly by culture for an additional 12 months. Marked clinical improvement occurred in all patients within 2 weeks and absence of pruritus was noted by the patients as early as 2-6 days. After 8 weeks of shampoo, 14 of the 15 (93%) children were clinically healed. Mycologically, the cultures dropped from a confluent growth of T. tonsurans to less than 100 colonies within 2 weeks; fewer than 50 at week 4 and 20 colonies or fewer after week 6. At 8 weeks of treatment the number of colonies remained at 20 or fewer. Six of the 15 children (40%) had negative cultures after 2, 4, and 6 weeks. One child relapsed at the first 4-week follow-up visit. Five of 15 (33%) of the children remained culturally negative for 12 months post-treatment. It was concluded that Ketoconazole 2% shampoo alone reduces the number of viable arthroconidia in children with tinea capitis thus

reducing the transmissibility and contagious nature of the disease. Unexpectedly, complete cure was obtained in 5/15 (33%) of the children. The children remained clinically and mycologically clear as long as one year after treatment (Greer, 2000).
A retrospective analysis was performed in order to evaluate the efficacy of prophylactic ketoconazole shampoo for tinea capitis in a high-risk paediatric population**.** Patients at high risk for tinea capitis received twice-weekly ketoconazole shampoo. The primary outcome of the study was a reduction in the number of documented tinea capitis infections between the 12-month preprotocol and 12-month postprotocol periods. A secondary outcome included the evaluation of predisposing risk factors for acquiring tinea infections. Ninety-seven patients, with a mean age of 8.06 years, were included. Most patients (78%) were African American. There were a total of 13 tinea capitis infections during the 12-month preprotocol period. During the 12-month postprotocol period, 41 infections were documented: 37 (90.2%) in the prophylaxis group and 4 (9.8%) in the nonprophylaxis group. The average numbers of per-patient infections in the postprotocol period were 0.79 and 0.08 in the prophylaxis and nonprophylaxis groups, respectively. Initiation of prophylaxis did not reduce tinea capitis infections (p=NS). Previous history of infection and a high level of care were significant predictors of infections ($p<0.05$). It was concluded that improved hygiene, adherence to prescribed treatment regimens, and prevention of recurrent environmental exposure to surviving fomites should be stressed in high-risk patients and supersede the need for an antifungal (ketoconazole shampoo) prophylaxis protocol (Bookstaver, et al 2011).

2.5.4.3 Posology and method of administration

Ketoconazole shampoo is intended for topical administration.
Ketoconazole shampoo 2% is for use in adolescents and adults: Wash affected areas and leave for 3-5 minutes before rinsing.

Treatment:
Dandruff and seborrhoeic dermatitis: Wash hair twice weekly for 2-4 weeks (Kaur, et al, 2010).

Tinea versicolor: Once daily for 1-5 days (Kaur, et al, 2010; Straten, et al., 2003).

Prophylaxis:
Dandruff and seborrhoeic dermatitis: Use once every 1-2 weeks.

2.5.5. OVERVIEW OF SAFETY

2.5.5.1 Undesirable effects

The safety of ketoconazole 2% shampoo was evaluated in 2890 subjects who participated in 22 clinical trials. Ketoconazole 2% shampoo was administered topically to the scalp and/or skin. Based on pooled safety data from these clinical trials, there were no ADRs reported with an incidence ≥1% (Product Monograph Nizoral 2% shampoo, 2019).

System Organ Class	**Adverse Drug Reactions**		
	Frequency Category		
	Uncommon (1/1,000 to <1/100)	**Rare** (1/10,000 and <1/1,000)	**Not Known**
Immune System disorders		Hypersensitvity	
Nervous System Disorders		Dysgeusia	
Infections and Infestations	Folliculitis		
Eye Disorders	Increased lacrimation	Eye irritation	
Skin and Subcutaneous Tissue Disorders	Alopecia Dry skin (Sinawe and Casadesus, 2022) Hair texture abnormal (Sinawe and Casadesus, 2022) Rash Skin burning sensation (Kaur and Kakkar, 2010; Dias, et al, 2013).	Acne Dermatitis contact (Dias, et al, 2013; Sinawe and Casadesus, 2022) Skin disorder Skin exfoliation	Angioedema (Sinawe and Casadesus, 2022) Urticaria Hair colour changes (Sinawe and Casadesus, 2022; Kubicki, et al 2020)
General Disorders and Administration Site Conditions	Application site erythema Application site irritation (Kaur and Kakkar, 2010; Dias, et al, 2013) Application site	Application site hypersensitivity (Sinawe and Casadesus, 2022) Application site pustules	

	pruritus (Sinawe and Casadesus, 2022) Application site reaction (Sinawe and Casadesus, 2022; Dias, et al, 2013)		

2.5.5.2 Special warnings and precautions for use

In patients who have been on prolonged treatment with topical corticosteroids, it is recommended that the steroid therapy be gradually withdrawn over a period of 2 to 3 weeks, while using Ketoconazole 2% shampoo, to prevent any potential rebound effect (Product Monograph Nizoral 2% shampoo, 2019). Keep out of the eyes. If the shampoo should get into the eyes, they should be bathed with water (Sinawe and Casadesus, 2022).

2.5.5.3 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. The potential for drug-drug interactions is minimal for topical antifungals as opposed to oral antifungals as they have minimal exposure to other co-administered medications (Gupta, et al, 2018). Since Ketoconazole is not absorbed systemically after topical administration (Daneshmend and Warnock, 1988), no drug interactions or adverse effects are expected after topical application (Gupta, et al, 2018).

2.5.5.4 Contraindications

Known hypersensitivity to ketoconazole or any of the excipients (Sinawe and Casadesus, 2022; Micromedex_Ketoconazole, 2024; Calogiuri, et al, 2019).

2.5.5.5 Pregnancy and lactation

There are no adequate and well-controlled studies in pregnant or lactating women (Product Monograph Nizoral 2% shampoo, 2019; Kaul, et al., 2017). Data on a limited number of exposed pregnancies indicate no adverse effects of topical ketoconazole on pregnancy or on the health of the foetus/newborn child (Patel, et al 2021). Animal studies have shown reproductive toxicity at doses that are not relevant to the topical administration of ketoconazole (King, et al 1998; Adams et al. 1998; Gupta, et al 1994b; Shin et al. 2006; Maretta, et al 2023). No effects on the breastfed newborn/infant are anticipated. Plasma concentrations of ketoconazole were not detectable after topical administration of ketoconazole 2% shampoo to the scalp of non-pregnant humans. Plasma levels were detected after topical administration of ketoconazole 2% shampoo on the whole body. There are no known risks associated with the use of ketoconazole 2% shampoo in pregnancy or lactation.

2.5.5.6 Effects on ability to drive and use machines

Not relevant.

2.5.5.7 Overdose

In the event of accidental ingestion, supportive and symptomatic measures should be carried out. In order to avoid aspiration, neither emesis nor gastric lavage should be instigated.

2.5.6 BENEFITS AND RISKS CONCLUSIONS

Ketoconazole is an imidazole-dioxolane antimycotic, active against yeasts, including Malassezia and dermatophytes. Its broad spectrum of activity is already well known.
Ketoconazole is present in a variety of formulations for topical administration, such as creams (used to treat tinea; cutaneous candidiasis, including candidal paronychia; and pityriasis versicolor) and shampoos (used primarily to treat dandruff—seborrhoeic dermatitis of the scalp). In vitro, ketoconazole has a relatively broad spectrum of antifungal activity including the following organisms: dermatophytes (Microsporum, Trichophyton, Epidermophyton), fungi (Candida, Cryptococcus, Torulopsis, Pityrosporum), dimorphic fungi (Histoplasma capsulatum, Coccidiodes, Paracoccidiodes) and eumycetes. There is synergistic action between ketoconazole and host defense cells. This synergism may explain, in part, the effectiveness of ketoconazole in eradicating deep fungal infections secondary to continuous active blood levels achieved after a single daily dose which inhibits growth and transformation of deep fungal infections.

In a form of shampoo intended for topical application, ketoconazole is used for prevention and treatment of infections in which the yeast Malassezia (previously called Pityrosporum) is likely to be involved, such as dandruff, seborrhoeic dermatitis and tinea (pityriasis) versicolor. It is very important to emphasis the fact that plasma concentrations of ketoconazole were not detectable after topical administration of ketoconazole 2% shampoo on the scalp. Plasma levels were detected after topical administration of ketoconazole 2% shampoo on the whole body. Also, data on a limited number of exposed pregnancies indicate no adverse effects of topical ketoconazole on pregnancy or on the health of the foetus/newborn child. There are no known risks associated with the use of ketoconazole shampoo 2% in pregnancy or lactation.

Recent literature data confirms the efficacy and safety of ketoconazole shampoo in the proposed indications. Presented scientific literature and results of clinical trials provides further evidences for efficacy and safety of ketoconazole shampoo. Since ketoconazole shampoo has been present on market for more than 20 years, there is a lot of bibliographic data and post marketing studies. The safety of ketoconazole 2% shampoo was also evaluated in a great number of clinical trials, in which Ketoconazole 2% shampoo was administered topically to the scalp and/or skin. Based on pooled safety data from these clinical trials, there were no ADRs reported with an incidence ≥1%.

Based on the presented evidence it can be concluded that clinical experience confirms the ketoconazole shampoo as safe and well tolerated medicine.

The overview was prepared by:

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