# NONCLINICAL OVERVIEW

of:

# KETOCONAZOLE

## shampoo 2%

**Non-clinical overview on the medicine**

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

**KETOCONAZOLE shampoo 2%**

The request for preparing the non-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

**CONTENT**

**Introduction**

**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

- **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.

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**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 form 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 non-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:**

***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.

## 2.4.1 OVERVIEW OF THE NON-CLINICAL TESTING STRATEGY

**General information**

Ketoconazole is an imidazole antifungal agent. Ketoconazole has a potent antimycotic action 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

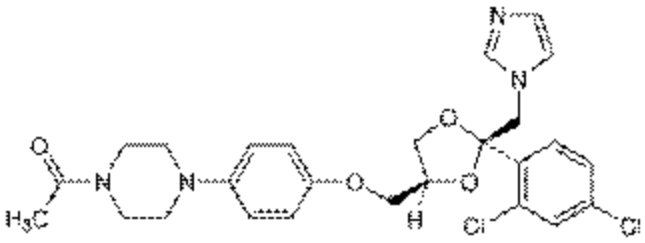
**INN:** Ketoconazole [rINN (en)]

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

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

**Molecular structure:** 531.4

**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.

## 2.4.2 PHARMACOLOGY

### 2.4.2.1 Pharmacology written summary

Ketoconazole is an imidazole antifungal agent (Roy, et al 2023; Buxton, 1988; Van Tyle, et al 1984; Sohn, 1982). Ketoconazole exhibits antifungal activity, similar to its predecessors clotrimazole and miconazole, by inhibition of uptake of precursors of RNA and DNA, synthesis of oxidative and peroxidative enzymes and increasing membrane permeability.
Ketoconazole has a potent antimycotic action against yeasts, including Malassezia and dermatophytes. Its broad spectrum of activity is already well known (Roy, et al 2023; Domosławska and Zduńczyk, 2021; Moriello, 2017; Jiang, et al. 2005; Hay, 1985; Van Tyle, et al 1984; Borgers, et al. 1983; Nagpal, et al. 2003; Kyle and Dahl, 2004). 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; Van Tyle, et al 1984; Fromtling, 1988; Strippoli, et al 1997).
The shampoo is intended for topical application. It contains the active ingredient, ketoconazole, which is a potent antifungal agent with broad spectrum of activity against yeasts, including Malassezia and dermatophytes. It's broad spectrum of activity is already well known.

### 2.4.2.2 Primary Pharmacodynamics

Ketoconazole is an antifungal medication that works primarily by inhibiting the synthesis of ergosterol, an essential component of fungal cell membranes. Ergosterol is crucial for maintaining the integrity and function of fungal cell membranes, and its inhibition disrupts the fungal cell membrane structure, leading to cell death (Sinawe and Casadesus, 2022; Ankley, et al. 2007).
The primary pharmacodynamic effect of ketoconazole is its inhibition of the enzyme lanosterol 14α-demethylase, which is a key enzyme involved in the synthesis of ergosterol from lanosterol in fungal cells. This inhibition disrupts the synthesis of ergosterol, leading to the accumulation of toxic sterol intermediates and impairing fungal membrane function (Daneshmend and Warnock, 1988).
Ketoconazole appears to block enzymes in the steroid biosynthetic pathway (Daneshmend and Warnock, 1988). Their data indicates that ketoconazole primarily inhibits C-17, 29-desmolase, the enzyme responsible for androstenedione biosynthesis. Fungi often infect the skin surface and subsequently invade the stratum corneum to avoid being shed from the skin surface by desquamation. Pharmacologic agents applied to the surface of the skin in the form of creams, lotions, or sprays, readily penetrate into the stratum corneum to kill the fungi (fungicidal agents), or at least render them unable to grow or divide (fungistatic agents). Thus, topical therapies work well to rid the skin of topical fungi and yeasts. Azole drugs such as miconazole, clotrimazole, and ketoconazole are fungistatic, limiting fungal growth but depending on epidermal turnover to shed the still-living fungus from the skin surface (Kyle and Dahl, 2004).

<u>Spectrum of activity</u>
Ketoconazole has a potent antimycotic action against yeasts, including Malassezia and dermatophytes. Its broad spectrum of activity is already well known (Roy, et al 2023; Domosławska

and Zduńczyk, 2021; Moriello, 2017; Jiang, et al. 2005; Hay, 1985). 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; Van Tyle, et al 1984; Fromtling, 1988; Strippoli, et al 1997). The antifungal potency of ketoconazole in vitro was studied in Sabouraud's broth for 715 fungal strains belonging to 85 species and several strains were tested in other media, including Eagle's minimal essential medium. Ketoconazole is highly active in vitro and possesses broad spectrum of activity including the following organisms: dermatophytes (Microsporum, Trichophyton, Epidermophyton), fungi (Candida, Cryptococcus, Torulopsis, Pityrosporum), dimorphic fungi (Histoplasma capsulatum, Coccidiodes, Paracoccidiodes) and eumycetes (Van den Bossche, et al. 1980; Dixon, et al. 1978; Ishibashi and Kaufman, 1986; Kaur and Kakkar, 2010; Fromtling, 1988).

Synergism

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 (Borgers, et al. 1983).

### 2.4.2.3 Secondary Pharmacodynamics

Ketoconazole is primarily used as an antifungal medication, but it also exhibits secondary pharmacological effects due to its interaction with various enzymes and receptors in the body. Some of the secondary pharmacological effects of ketoconazole include i**nhibition of steroid synthesis** by inhibiting of the enzyme cytochrome P450 14α-demethylase, which is involved in the synthesis of ergosterol, an essential component of fungal cell membranes (Sinawe and Casadesus, 2022; Ankley, et al. 2007). This same enzyme also plays a role in the synthesis of steroid hormones in humans, including cortisol and testosterone (English, et al. 1986). Therefore, ketoconazole can inhibit the synthesis of these hormones, leading to effects such as decreased cortisol levels and decreased testosterone levels (Kyle and Dahl, 2004; Sinawe and Casadesus, 2022; Van Tyle, et al 1984). Consequently, because ketoconazole inhibits testosterone synthesis, it can have anti-androgenic effects (English, et al. 1986) which can be used in the treatment of conditions such as hirsutism (excessive hair growth) and androgenic alopecia (male pattern baldness) in certain cases (Pont, et al. 1982). Ketoconazole can inhibit various cytochrome P450 enzymes involved in drug metabolism, such as CYP3A4. This inhibition can lead to increased plasma concentrations of drugs metabolized by these enzymes, potentially resulting in drug interactions and increased risk of adverse effects (Sinawe and Casadesus, 2022; Ankley, et al. 2007). It's important to note that while these secondary pharmacological effects of ketoconazole can be beneficial in certain clinical contexts, they can also contribute to its potential for adverse effects and drug interactions (Micromedex_Ketoconazole, 2024; Van Tyle, et al 1984). However, Ketoconazole in a form of shampoo intended for topical application has negligible systemic absorption. Therefore, no drug interactions or adverse effects are expected.

### 2.4.2.4 Safety Pharmacology

Ketoconazole shampoo is generally considered safe when used as directed. It's important to understand its safety profile, particularly regarding local irritation or sensitization reactions. Nonclinical study performed on rabbits eye's shows that topical ketoconazole does not influence closure of experimentally produced corneal epithelial defects in rabbits and is well tolerated in the eye (Ishibashi and Kaufman, 1986).
The safety of ketoconazole 2% shampoo was evaluated in 2890 subjects who participated in 22 clinical trials. Ketoconazole2% 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% (SmPC Nizoral SmPC Nizoral 2% shampoo, Thornton & Ross Ltd. UK, 23/10/2020).

### 2.4.2.5 Pharmacodynamic Drug Interactions

Ketoconazole shampoo is primarily used to treat fungal infections of the scalp, such as dandruff or seborrheic dermatitis. As for pharmacodynamic interactions, these occur when drugs affect the same physiological or biochemical pathways, potentially leading to additive or antagonistic effects. However, since ketoconazole shampoo is primarily applied topically to the scalp and has negligible systemic absorption, it's less likely to cause pharmacodynamic interactions with other drugs compared to oral medications. Drug interactions of theoretical, if not practical significance include warfarin, chlordiazepoxide, methylprednisolone, cyclosporin and drugs known to induce microsomal enzymes (Mayer, et al 2008; Dahlinger, et al 1998). In each case. some dosage adjustment for ketoconazole or the interacting drug may be required (Daneshmend and Warnock, 1988). Additionally, in accordance with SmPC of Nizoral 2% shampoo, (Thornton & Ross Ltd. UK), which is used as parallel product for development of [redacted] shampoo [redacted] no interaction studies have been performed (SmPC Nizoral 2% shampoo, Thornton & Ross Ltd. UK, 23/10/2020).

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

### 2.4.2.6 Discussion and Conclusions

Ketoconazole is an imidazole antifungal agent (Roy, et al 2023; Buxton, 1988; Van Tyle, et al 1984; Sohn, 1982). Ketoconazole exhibits antifungal activity, similar to its predecessors clotrimazole and miconazole, by inhibition of uptake of precursors of RNA and DNA, synthesis of oxidative and peroxidative enzymes and increasing membrane permeability (Martindale, Ketoconazole 2007). Ketoconazole differs from miconazole in that it can be given orally (Sohn, 1982). Ketoconazole has a potent antimycotic action against dermatophytes and yeasts (Van Tyle, et al 1984; Borgers, et al. 1983; Nagpal, et al. 2003; Kyle and Dahl, 2004).
The primary pharmacodynamic effect of ketoconazole is its inhibition of the enzyme lanosterol 14α-demethylase, which is a key enzyme involved in the synthesis of ergosterol from lanosterol in fungal cells. This inhibition disrupts the synthesis of ergosterol, leading to the accumulation of toxic sterol intermediates and impairing fungal membrane function (Daneshmend and Warnock, 1988). Ketoconazole has a potent antimycotic action against yeasts, including Malassezia and dermatophytes. Its broad spectrum of activity is already well known (Roy, et al 2023; Domosławska

and Zduńczyk, 2021; Moriello, 2017; Jiang, et al. 2005; Hay, 1985). 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; Van Tyle, et al 1984; Strippoli, et al 1997).

Ketoconazole is primarily used as an antifungal medication, but it also exhibits secondary pharmacological effects due to its interaction with various enzymes and receptors in the body. Some of the secondary pharmacological effects of ketoconazole include **inhibition of steroid synthesis** by inhibiting of the enzyme cytochrome P450 14α-demethylase, which is involved in the synthesis of ergosterol, an essential component of fungal cell membranes (Sinawe and Casadesus, 2022; Ankley, et al. 2007).

It's important to note that while these secondary pharmacological effects of ketoconazole can be beneficial in certain clinical contexts, they can also contribute to its potential for adverse effects and drug interactions (Micromedex_Ketoconazole, 2024; Van Tyle, et al 1984).

However, Ketoconazole in a form of shampoo intended for topical application has negligible systemic absorption. Therefore, no drug interactions or adverse effects are expected.

Ketoconazole in a form of shampoo primarily exerts its pharmacodynamic effect through its antifungal properties (Van Tyle, et al 1984; Borgers, et al. 1983; Nagpal, et al. 2003; Kyle and Dahl, 2004). In the context of ketoconazole shampoo, this mechanism of action allows it to effectively target and eliminate fungi that cause conditions such as dandruff (caused by Malassezia yeasts) and seborrheic dermatitis (Jiang, et al. 2005). By controlling fungal overgrowth on the scalp, ketoconazole shampoo helps alleviate symptoms associated with these conditions, including itching, flaking, and inflammation (Jiang, et al. 2005; Van Cutsem, et al. 1991). It's important to note that while ketoconazole shampoo primarily acts as an antifungal agent, it may also have additional effects, such as anti-inflammatory properties, which can contribute to its therapeutic efficacy in conditions like seborrheic dermatitis (Van Cutsem, et al. 1991; Marsella, et al 1997). However, the primary pharmacodynamic action of ketoconazole shampoo remains its antifungal activity targeting the fungal pathogens responsible for scalp-related conditions (Jiang, et al. 2005).

## 2.4.3 PHARMACOKINETICS

### 2.4.4.1 Brief Summary

Ketoconazole is not absorbed systemically after topical administration (Daneshmend and Warnock, 1988). Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use (Schäfer-Korting, 1989).

Plasma concentrations of ketoconazole were not detectable after topical administration of Nizoral 2%shampoo on the scalp. Plasma levels were detected after topical administration of Nizoral 2% shampoo on the whole body (SmPC Nizoral 2% shampoo, Thornton & Ross Ltd. UK, 23/10/2020 – used as parallel product during development of [redacted] 2% shampoo).

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

### 2.4.4.2 Methods of Analysis

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

[redacted] Method for determination of assay of ketoconazole, provided in part 3.2.P.5.2, is used for quantification of its content in final dosage form. [redacted]

### 2.4.4.3 Absorption

Ketoconazole applied topically as shampoo or cream, has negligible systemic absorption. Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use (Schäfer-Korting, 1989).

### 2.4.4.4 Distribution

Following chronic or single application with 2% ketoconazole shampoo, plasma concentrations of ketoconazole were undetectable with no hepatic function test abnormalities.

### 2.4.4.5 Metabolism

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. Ketoconazole is not absorbed systemically after topical administration (Daneshmend and Warnock, 1988).

### 2.4.4.6 Excretion

Not applicable.

### 2.4.4.7 Pharmacokinetic Drug Interactions

Van Tyle, et al investigated drug interactions of ketoconazole, and concluded that Ketoconazole has several reported drug interactions, including lower bioavailability with cimetidine, accumulation of cyclosporin during concurrent therapy and a possible disulfiram-like reaction with alcohol (Van Tyle, et al 1984).
Since Ketoconazole is not absorbed systemically after topical administration (Daneshmend and Warnock, 1988), no drug interactions or adverse effects are expected.

### 2.4.4.8 Other Pharmacokinetic Studies

Not applicable.

### 2.4.4.9 Discussion and Conclusions

Ketoconazole shampoo is designed to act primarily locally on the scalp to treat fungal infections such as dandruff or seborrheic dermatitis. The absorption of ketoconazole from shampoo applied topically to the scalp is minimal compared to oral formulations (Daneshmend and Warnock, 1988). Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use (Schäfer-Korting, 1989).
Plasma concentrations of ketoconazole were not detectable after topical administration of Nizoral 2%shampoo on the scalp. Plasma levels were detected after topical administration of Nizoral 2% shampoo on the whole body (SmPC Nizoral 2% shampoo, Thornton & Ross Ltd. UK, 23/10/2020 – used as parallel product during development of [redacted] 2% shampoo).

Overall, while some absorption of ketoconazole from shampoo can occur, it is typically minimal and primarily localized to the scalp. This localized action makes ketoconazole shampoo an effective and safe treatment option for scalp fungal infections, with a reduced risk of systemic side effects compared to oral formulations.

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## 2.4.4 TOXICOLOGY

### 2.4.6.1 Brief Summary

Ketoconazole shampoo is an effective and generally safe treatment for fungal scalp infections when used as directed. Topically applied ketoconazole appears to have a low order of toxicity and is generally well tolerated. Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

### 2.4.6.2 Single-Dose Toxicity

Studies on the single-dose toxicity of ketoconazole shampoo in various animal models have been conducted to assess its safety profile . After oral administration toxicity was manifested in mice, rats and guinea pigs by sedation, catalepsy, ataxia, tremors, convulsions and pre-lethal loss of the righting reflex at doses >320 mg/kg. In dogs, toxicity was manifested by diarrhea and vomiting at doses >80 mg/kg (Product Monograph Ketoconazole, Teva). Here's a general overview of the findings:

**Rats and Mice**: Research on rats and mice has shown that acute oral doses of ketoconazole can cause toxicity, including symptoms such as lethargy, decreased activity, and gastrointestinal distress. The severity of toxicity typically depends on the dose administered (PubChem_Ketoconazole; Product Monograph Ketoconazole, Teva).

**Dogs**: Dogs are more sensitive to ketoconazole compared to some other species. Studies have demonstrated that single doses of ketoconazole in dogs can result in symptoms such as vomiting, diarrhea, and neurological effects (Mayer, et al. 2008).
The severity of toxicity in these animals can vary based on factors such as the dosage administered, the route of administration (oral, dermal, etc.), and individual sensitivity. It's important to note that these studies provide valuable insights into the potential risks associated with ketoconazole exposure in animals, but the findings may not directly translate to human toxicity.

### 2.4.6.3 Repeat-Dose Toxicity

Repeat-Dose use of ketoconazole shampoo has not been associated with significant adverse effects. However, prolonged exposure to high concentrations may cause irritation or sensitization of the scalp.

**Rats and mice**: prolonged treatment with oral ketoconazole in rats may lead to hepatic side-effects as well as interactions with mammalian. The prediction of these side-effects is difficult but the potential to interact with mammalian cytochrome P-450 enzymes is considered to be important (Van Cauteren, et al. 1989).
Chronic administration of ketoconazole to male rats and mice resulted in steroid levels comparable with those of control animals. Epididymal sperm motility was only slightly reduced in male mice 4

hours after administration of the drug. No effect on sperm motility was noted after chronic administration in either species studied. In vitro exposure of epididymal sperm to ketoconazole resulted in a significant reduction of sperm motility. Breeding trials after ketoconazole administration resulted in normal fertility and fecundity even at the highest dosage studied (Heckman, et al 1992).
Preclinical studies performed on rats concluded that Ketoconazole treated animals (adult male albino rats) showed distortion of hepatic architecture increase size of hepatocytes, decrease nuclear diameter and necrosis of hepatocytes within hepatic lobule as compared to control group-A animals. It was concluded from this study that ketoconazole induced injury is dose and duration of therapy dependent and due to its cost-effective frequent use needs further research in humans (Shaikh, et al 2010). Slight pathological changes in the kidney, adrenals and ovaries were noted in an 18-month repeated dose rat study. No toxicity has been noted to date in these human studies (Borelli, et al. 1979).
Repeated doses of oral Ketoconazole may cause endocrine disruption (Kang, et al 2003). The endocrine-related effects of ketoconazole could be detected by the parameters examined in the present study based on the Organization for Economic Cooperation and Development (OECD) protocol, suggesting that the Enhanced TG407 protocol should be a suitable screening test for detection of endocrine-mediated effects of chemicals (Shin, et al. 2006).

**Dogs:**
Ketoconazole toxicosis was first recognized in 1982 in a nonclinical experimental study involving Beagles. This study investigated the usefulness and hazards of ketoconazole treatment for mycotic infections in dogs with escalated supratherapeutic dosages. Hyporexia, weight loss, variable emesis, and increases in serum ALT and ALP activities occurred when administered at 40 and 60 mg/kg/d (18 and 27 mg/lb/d), PO, for 1 year and 20 weeks, respectively. In addition to these signs, jaundice, gastritis, and lethal toxicosis were noted after 2 to 4 weeks of ketoconazole administration at 80 mg/kg/d (36 mg/lb/d), PO. Adverse clinical reactions to ketoconazole (2.6 to 33.6 mg/kg/d [1.2 to 15.3 mg/lb/d], PO) have been retrospectively characterized in 15% (92/632) of dogs treated at 3 specialty dermatology practices (Mayer, et al 2008). In that study, (Mayer, et al 2008) suspected adverse drug reactions were identified by use of the Naranjo adverse reaction probability scale. An adverse drug reaction was considered to have occurred if clinical signs, clinicopathologic markers, or hepatic histologic abnormalities developed after drug exposure and subsequently improved with drug discontinuation or dose reduction, in the absence of alternative plausible causes (Arimone , et al 1992). Observed adverse effects included vomiting (7%), anorexia (5%), lethargy (2%), and diarrhea (1%) and, less frequently, cutaneous erythema, trembling, and weakness; some dogs had > 1 complication (Mayer, et al 2008).
Three studies performed on Beagle dogs were enclosed in Product Monograph Ketoconazole, Teva. Studies were performed with different doses in a period of 6 months and 12 months.
Repeated doses of oral shows changes in high dose group in haematological parameters, urinalyses and serum analyses and marginally low haemoglobin value during the entire dosing period. Behaviour was normal in the 0, 2.5 and 10mg/kg/day groups; however, at 40 mg/kg decreased appetite and sporadic emesis were noted in all animals during the entire study. No drug-related mortality was observed; however, body weight gain was significantly lower in the high-dose group

during the entire experimental period. Gross pathology was normal in all groups except the high-dose group, where all dogs exhibited dark coloured livers, brownish discoloured pancreas, thymus, adrenals, thyroid, testes, ovaries, lymph nodes and fatty tissue and gray coloured ovaries. In the high-dosed group, the absolute weight of several organs decreased with an increase of the relative organ weight. Absolute and relative liver weight increased in the high-dose group. Histology revealed deposition and marked accumulation of a granular yellowish pigment in macrophages in various tissues (in the ovaries, in the hepatocytes, in the fasciculata and glomerulosa zones of the adrenals, in the biliary epithelium and in the interstitial tissue and Leydig cells of the testis) in a dose-related fashion at 10 and 40 mg/kg/day. The livers of the 40 mg/kg dosed males were devoid of glycogen. Large vacuolated cells were seen in the fasciculata zone of the adrenals of the high dosed animals of both sexes. Desquamation and spermatid giant cells were conspicuous in some 40 mg/kg dosed dogs and one dog showed reduced spermatogenic activity. Many macrophages with yellowish pigment were seen in the 40 mg/kg dosed dogs and in 2/3 female dogs dosed at 10 mg/kg (Product Monograph Ketoconazole, Teva).

In another experiment, Beagle dogs were orally dosed with gelatin capsules containing increasing doses of ketoconazole (20, 40, 60 mg/kg/day) for a period of 6 months. One animal (60 mg/kg) died of gastroenteritis and nephritis during week 12. A dose-related body weight loss was seen above 20 mg/kg/day coincident with reduced appetite. There was no effect on the ECG at any dose and serum analyses and haematology were normal during the 20 and 40 mg/kg dosage periods. At 60 mg/kg/day an increase in SGOT and haptoglobin, a slight decrease of total protein and albumin and a pronounced increase of alkaline phosphatase and SGPT were seen. Decreases of haematocrit, haemoglobin and RBC were seen in most animals during the 60 mg/kg dosage period. Both serum analyses and haematology normalized during the withdrawal period. Gross pathology revealed a small sized thymus (decreased absolute and relative weight) and swollen liver (increased relative and absolute weight) at 60 mg/kg; however, these effects were reversible since they normalized during the withdrawal period. Histology indicated the presence of macrophages loaded with lipofuscin in the gallbladder, liver, ileum, spleen, lymph nodes, testes, ovaries, adrenals and prostate gland. In the liver, lipo-pigment also accumulated in the hepatocytes. Interstitial parotitis with reduced zymogen storage was seen in one dog. No spermatogenic activity was noted in 2/3 dogs - one having an immature aspect and the other a degenerated germinal epithelium. Lipofuscin loaded Leydig cells were noted in 2/3 dogs. An increase of clear replacement cells and reduced amount of secretion of the prostate was noted in the dogs with no spermatogenic activity (Product Monograph Ketoconazole, Teva).

In another study, at a dose of 80 mg/kg/day, performed on six Beagle dogs, four animals died during the second week of the study, one died at 3 weeks and one during the fourth week. Anorexia with progressive weight loss and exhaustion was seen in all animals. All animals had an increased heart rate, severe gastroenteritis and clinical icterus haematology demonstrated an increase of segmented heterophils and decrease of lymphocytes and platelets. Alkaline phosphatase, SGPT and haptoglobin showed marked increases with increases of SGOT and bilirubin less pronounced. Total protein, albumin and glucose were decreased. Absolute and relative weight increases of the liver and adrenals and a decreased absolute and relative weight of the thymus were observed at necropsy (Product Monograph Ketoconazole, Teva).

### 2.4.6.4 Genotoxicity

No evidence of mutagenicity was found with ketoconazole in *in vitro* and *in vivo* studies (Product Monograph_Ketoconazole, Teva; PubChem_Ketoconazole).

### 2.4.6.5 Carcinogenicity

No evidence of carcinogenicity was found with ketoconazole in studies of rats and mice (Contrera, et al 1996). Four groups of 50 male and 50 female albino Swiss mice received doses of 0, 5, 20 and 80 mg/kg/day of ketoconazole administered via the diet for 18 months. There were no significant differences between groups on overall mortality or on the time of death. There were no statistically significant differences between groups in the incidence or type of tumours (Product Monograph_Ketoconazole, Teva).

### 2.4.6.6 Reproductive and Developmental Toxicity

Imidazoles inhibit testicular and male reproductive function by inhibiting testosterone secretion, testicular interstitial fluid production and luteinising hormone (LH) secretion regulatory systems (Adams et al. 1998; Shin et al. 2006).
Ketoconazole may have effects on the endocrine system and liver (Gupta, et al 1994b). Animal tests show that this substance possibly causes toxicity to human reproduction or development (PubChem_Ketoconazole). At high doses (0, 6.25, 25 or 100 mg/kg/day), ketoconazole blocks testicular and adrenal biosynthesis. A repeated 28-day oral toxicity study of ketoconazole in rats showed a decrease in testosterone and an increase in oestradiol, luteinising hormone, and follicle stimulating hormone (Shin et al. 2006). Ketoconazole adversely affects spermatogenesis in rodents, but knowledge on adverse effects of prolonged administration of ketoconazole on the fertility of male dogs is lacking. A case of reversible infertility with azoospermia in a male American Stafordshire terrier treated with ketoconazole is reported here. A seven-year old male American Stafordshire terrier treated for 3 months with ketoconazole for a persistent Malassezia dermatitis displayed reduced libido and mating of 3 bitches had been unsuccessful. The dog was presented at the clinic 40 days after the treatment had been stopped. At first presentation, low libido and complete absence of sperm in the ejaculate (azoospermia) associated with low testosterone level were found. Repeated examinations revealed that sperm quality and testosterone level had restored 100 days after ketoconazole had been withdrawn. Thereafter, the dog successfully mated 2 bitches. Conclusion: The treatment with ketoconazole for 3 months may have led to reversible infertility characterized by azoospermia. Therefore, owners of stud dogs should be informed of this risk prior to initiating such treatment and in case of infertility, previous treatment with ketoconazole should be considered as a possible cause. (Domosławska and Zduńczyk, 2021).
In developmental studies in rats the incidence of stillborn foetuses increased from a control value of 0.5% to 32.7% in rats dosed with 40 mg/kg and cannibalization of young occurred in two litters. In mice a significant decline in sperm motility and density in cauda epididymis was noted. A sharp

decline in fertility (50% negative) in ketoconazole treated mice was observed. A significant reduction in the total protein and sialic acid contents of testes, epididymis, seminal vesicle and ventral prostate were noticed. The cholesterol contents of testes were raised while fructose contents of seminal vesicle were reduced significantly. The ketoconazole treatment altered the biochemical milieu of the reproductive tract. In the rabbit, ketoconazole produces evidence of maternal toxicity, embryotoxicity and teratogenicity at a high dose of 40 mg/kg/day (PubChem_Ketoconazole).

### 2.4.6.7 Local Tolerance

Local tolerance studies for ketoconazole shampoo would assess its safety and potential for irritation or sensitization when applied to the scalp and skin. These studies are important for ensuring that the shampoo is well-tolerated by users and does not cause adverse reactions when used as directed. Sung, et al conducted a case study on female cocker spaniel dog and provide evidence suggesting that ketoconazole shampoo-triggered pemphigus-like reactions most probably represent a unique contact drug-triggered PF, which has never been described in veterinary medicine. The case also highlights the need for clinicians to understand the mechanism of contact drug-triggered PF in order to ensure appropriate diagnosis and treatment. Furthermore, this report emphasizes that a careful topical medication history, including shampoo, is essential in the workup of cases of pemphigus (Sung, et al 2017).

Ketoconazole is a widely used imidazole antifungal agent. True contact allergy to topical ketoconazole is rare, and few cases of patients with contact allergy to ketoconazole have been reported. Allergies to inactive ingredients, especially vehicles and preservatives, are more common than allergies to ketoconazole itself (Warsaw, 2014).

Ketoconazole shampoo has an excellent safety profile, with mild adverse events occurring in only 1% to 7% of patients. The most common side effects are dryness of the scalp and hair, and application site reaction. Kubicki, et al presented case of ketoconazole shampoo-induced hair discoloration (Kubicki, et al 2020).

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### 2.4.6.8 Other Toxicity Studies (if available)

[redacted]. Method for determination of assay of ketoconazole, provided in part 3.2.P.5.2, is used for quantification of its content in final dosage form. [redacted]

[redacted]

### 2.4.6.9 Discussion and Conclusions

Topically applied ketoconazole appears to have a low order of toxicity and is generally well tolerated. Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Studies on the single-dose toxicity of ketoconazole shampoo in various animal models have been conducted to assess its safety profile. After oral administration toxicity was manifested in mice, rats and guinea pigs by sedation, catalepsy, ataxia, tremors, convulsions and pre-lethal loss of the righting reflex at doses >320 mg/kg. In dogs, toxicity was manifested by diarrhea and vomiting at doses >80 mg/kg.
Chronic administration of ketoconazole to male rats and mice resulted in steroid levels comparable with those of control animals. Prolonged treatment with oral ketoconazole in rats may lead to hepatic side-effects as well as interactions with mammalian. Repeated doses of oral Ketoconazole may cause endocrine disruption. Ketoconazole may have effects on the endocrine system and liver. The ketoconazole treatment altered the biochemical milieu of the reproductive tract. In the rabbit, ketoconazole produces evidence of maternal toxicity, embryotoxicity and teratogenicity at a high dose of 40 mg/kg/day Animal tests show that this substance possibly causes toxicity to human reproduction or development. No evidence of carcinogenicity and mutagenicity were found with ketoconazole.
Repeat-Dose use of ketoconazole shampoo has not been associated with significant adverse effects. However, prolonged exposure to high concentrations may cause irritation or sensitization of the scalp.

## 2.4.5 INTEGRATED OVERVIEW AND CONCLUSION

Ketoconazole is an imidazole antifungal agent. Ketoconazole has a potent antimycotic action against dermatophytes and yeasts. Ketoconazole exhibits antifungal activity, similar to its predecessors clotrimazole and miconazole, by inhibition of uptake of precursors of RNA and DNA, synthesis of oxidative and peroxidative enzymes and increasing membrane permeability.
The antifungal properties of ketoconazole were investigated both in vitro and in vivo. The antifungal potency of ketoconazole in vitro was studied in Sabouraud's broth for 715 fungal strains belonging to 85 species and several strains were tested in other media, including Eagle's minimal essential medium. Ketoconazole is highly active in vitro and possesses broad spectrum activity.
Ketoconazole is very potent in the topical treatment of skin dermatophytosis, skin candidiasis, and in vaginal candidiasis of laboratory animals.
Ketoconazole blocks testosterone synthesis during long-term oral administration. The drug may find usefulness given in high doses to suppress steroid synthesis in conditions such as prostatic carcinoma, Cushing's syndrome, or hirsutism. Ketoconazole appears to block enzymes in the steroid biosynthetic pathway. Their data indicates that ketoconazole primarily inhibits C-17, 29-desmolase, the enzyme responsible for androstenedione biosynthesis.

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.

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.
Animal studies have shown reproductive toxicity at doses that are not relevant to the topical administration of ketoconazole. 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.
Ketoconazole did not show any signs of mutagenic potential when evaluated using the dominant lethal mutation test or the Ames Salmonella microsomal activator assay.

It can be concluded that topically applied ketoconazole have a low order of toxicity and is generally well tolerated.

Redacted under Section 40 of the FOI Act.

**The overview was prepared by:**

[redacted]

**September, 2024**

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