All redactions under Section 41 and Section 43 of the Freedom of Information Act.

# KETOCONAZOLE

## shampoo 2%

# 2.7.4 Summary of clinical safety

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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).

The following table displays ADRs that have been reported with the use of Ketoconazole 2% Shampoo from either clinical trial or postmarketing experiences.

The displayed frequency categories use the following convention:
Very common (≥1/10); Common (≥1/100 to <1/10); ;Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000). Not known (cannot be estimated form the available clinical trial data).

| **System Organ Class** | **Adverse Drug Reactions** | | |
|---|---|---|---|
| | **Frequency Category** | | |
| | **Uncommon**<br>(1/1,000 to <1/100) | **Rare**<br>(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<br>Dry skin (Sinawe and Casadesus, 2022)<br>Hair texture abnormal (Sinawe and Casadesus, 2022)<br>Rash<br>Skin burning sensation (Kaur and Kakkar, 2010; Dias, et al, 2013). | Acne<br>Dermatitis contact (Dias, et al, 2013; Sinawe and Casadesus, 2022)<br>Skin disorder<br>Skin exfoliation | Angioedema (Sinawe and Casadesus, 2022)<br>Urticaria<br>Hair colour changes (Sinawe and Casadesus, 2022; Kubicki, et al 2020) |

| | | | |
|---|---|---|---|
| **General Disorders and Administration Site Conditions** | Application site erythema<br>Application site irritation (Kaur and Kakkar, 2010; Dias, et al, 2013)<br>Application site pruritus (Sinawe and Casadesus, 2022)<br>Application site reaction (Sinawe and Casadesus, 2022; Dias, et al, 2013) | Application site hypersensitivity (Sinawe and Casadesus, 2022)<br>Application site pustules | |

**Safety studies**

Pityriasis versicolor is a common superficial fungal infection caused by lipophilic yeast. The topical short-term application of ketoconazole 2% shampoo may provide effective and safe therapy for tinea versicolor. 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).

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).

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).

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 analyzed.

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).

Ketoconazole and zinc pyrithione are compounds active against the Malassezia spp. yeasts, which are believed to play a major role in dandruff and seborrheic dermatitis. 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).