



Scientific Committee on Consumer Safety

SCCS

OPINION on

**Climbazole regarding potential development of (cross)-
resistance**

Cosmetics Europe: P64

The SCCS adopted this opinion at its 18th plenary meeting
of 26 February 2013

About the Scientific Committees

Three independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

They are: the Scientific Committee on Consumer Safety (SCCS), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) and are made up of external experts.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Agency (EMA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCCS

The Committee shall provide opinions on questions concerning all types of health and safety risks (notably chemical, biological, mechanical and other physical risks) of non-food consumer products (for example: cosmetic products and their ingredients, toys, textiles, clothing, personal care and household products such as detergents, etc.) and services (for example: tattooing, artificial sun tanning, etc.).

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TABLE OF CONTENTS

ACKNOWLEDGMENTS	3
1. BACKGROUND	5
2. TERMS OF REFERENCE.....	5
3. OPINION.....	6
4. CONCLUSION	9
5. MINORITY OPINION.....	10
6. REFERENCES	10

1. BACKGROUND

Climbazole, with the chemical name 1-(4-chlorophenoxy)-1-imidazol-1-yl-3,3-dimethyl-2-butanone, is currently regulated in the Cosmetics Directive as a preservative in Annex VI, entry 32, with a maximum authorized concentration of 0.5%.

In opinion SCCP/1204/08, adopted on 21 February 2009, the SCCP concluded that:

- "The use of Climbazole as a preservative at a maximum concentration of 0.5% in all cosmetic products cannot be considered safe. However, when used as a preservative in hair cosmetics and face cosmetics at 0.5%, climbazole does not pose a risk to the health of the consumer";
- "the (non-preservative) use of Climbazole in rinse-off hair cosmetics up to a maximum concentration of 2.0% does not pose a risk to the health of the consumer";
- "The non-preservative use of Climbazole in hair cosmetics and face cosmetics at 0.5% does not pose a risk to the health of the consumer. The use of Climbazole at 0.5% in leave-on products other than those mentioned above, however, is not considered safe".

In this opinion, the SCCP also remarked that no specific information regarding the potential development of (cross-) resistance had been provided.

A working document proposing to restrict the use of Climbazole as suggested by the SCCP was put forward by the Commission in October 2009. Member States declared concerns in relation to possible induction by climbazole of antimicrobial resistance and cross-resistance to antimicrobial medicinal products and asked the Commission to consult EMA on the issue.

In addition, at the time of the public consultation to evaluate the economic impact of the restriction, one company claimed use of climbazole in an additional type of products (i.e. foot care).

The Commission subsequently consulted EMA and issued a mandate to the SCCS to evaluate the safety of the additional use in foot care products. The CHMP/EMA Innovation Task Force (ITF) concluded in its scientific opinion that *'in view of its mechanism of action, the use of climbazole in cosmetic products may increase the risk of cross-resistance to other azole antifungals used as medicinal products, the greatest concern being the possible effect of climbazole on microbiota on the human skin and the possibility for development of cross-resistance for other azole antifungals, especially in immune-compromised individuals.'*

2. TERMS OF REFERENCE

The SCCS is asked to answer the following questions:

1. *In light of the EMA opinion and the information contained therein, can climbazole still be considered safe for use as an ingredient in cosmetic products?*
2. *If the answer to question 1 is yes, does the SCCS consider that any aspects of the previous assessment of climbazole needs to be revised on the basis of the dossier produced by EMA on this ingredient?*
3. *If the answer to question 1 is yes, does the SCCS consider that Climbazole is safe for the consumers, when used up to a concentration of 0.5% in foot care products in*

addition to the previous evaluated uses (i.e. hair cosmetics and face cosmetics up to 0.5%, rinse-off hair cosmetics up to 2.0%)

4. *Does the SCCS have any further scientific concern with regard to the use of climbazole in cosmetic products?*

3. OPINION

3.1. Actual status of the opinion on Climbazole

In its opinion of September 2005 on Climbazole (SCCP/0918/05), the SCCP formulated a list of shortcomings related to the submitted dossier. These comments were taken up in submissions II and III, which resulted in opinion SCCP/1204/08, adopted on 21 January 2009 by the SCCP.

This opinion contained the full toxicological profile of Climbazole with all references included from the different submissions.

It was concluded that Climbazole may be used as a preservative (or non-preservative) ingredient up to a maximum concentration of 0.5% in leave-on hair and face cosmetics.

Its non-preservative use in rinse-off hair cosmetics up to a maximum concentration of 2% was also considered to be safe. Its use in leave-on products other than those mentioned above was, however, not considered safe. The SCCP made the remark that no specific information regarding the potential development of (cross-) resistance was provided. Also no data were available on possible bio-persistence.

The Commission prepared a draft Cosmetic Directive to implement the above restriction, which was submitted to a public consultation. As a consequence, a company applied to extend the group of leave-on face and hair products with foot care products in which Climbazole would be used in a concentration of up to 0.5%. The SCCS performed a risk assessment and came to the conclusion that the non-preservative use of Climbazole at a maximum concentration of 0.5% either in foot care cosmetics and used alone, or in combination with either shampoo (at a maximum concentration of 2%) or face cream (at a maximum concentration of 0.5%) or hair lotion (at a maximum concentration of 0.5%) does not pose a risk to the health of the consumer. In case 3 products, each containing Climbazole at the maximum concentration requested (being safe when used separately) are simultaneously applied, the combinations of either shampoo, hair lotion and a foot care product, or hair lotion, face cream and a foot care product cannot be considered safe for the consumer. Also the topical use of the 4 types of products together cannot be considered safe when the maximum requested concentration of Climbazole is present.

3.2. Information provided by CHMP/EMA innovation task force (ITF) on Climbazole

EMA (European Medicines Agency) was asked whether the structural similarities between Climbazole and the pharmaceutically active substance Ketoconazole poses a potential risk of cross-resistance with other azoles used as medicinal products. In the scientific opinion of 25 October 2011 (EMA/CHMP/618632/2011), the ITF considered the information by DG Sanco, the properties of both Climbazole and Ketoconazole, an earlier CHMP scientific opinion on Ketoconazole (EMA/CHMP62096/2005) and the scientific literature available on Climbazole. Background information (edited from information submitted to the Agency) was provided which emphasized that:

- 1) *the use of ketoconazole in any product including cosmetic products is by nature related to a risk of resistance development against the azole antifungals;*

- 2) *the occurrence of inherently ketoconazole-resistant and other azole cross-resistant fungi might increase in the environment due to selective pressure.*
"Multidrug-resistant" human pathogenic mould has already been isolated from the environment and an increased number of infections due to those fungi have been demonstrated during the last decade.

Going in more detail on the issue of azoles cross-resistance as applicable to Climbazole, a number of arguments were given of which most are mentioned here:

- All azoles have the same action mechanism of inhibition of lanosterol demethylase and consequently of the ergosterol production.
- Resistance, however, to antifungal agents has gained in importance as being implicated in the treatment of life-threatening mycoses involving *Candida* species and increasingly non-*Candida* (e.g. aspergillosis) invasive fungal infections.
- Exposure to any antifungal agent, thus also to Climbazole, poses a risk of resistance development (microbiological and clinical) against the azole antifungals having potential consequences for the treatment of patients.
- A number of molecular mechanisms of resistance to azoles is already well-known.
- Resistance, however, could be linked to an individual compound, rather than to the whole class.
- Proof exists in agriculture that acquired fungus resistance after azole treatment may lead to cross-resistance to other azoles. Not enough evidence, however, exists to support the hypothesis that azole resistance in medicine is linked to the use of azoles in agriculture.
- Non-medical use of Ketoconazole increases the environmental load of active compound and includes accumulation and potential interference with hormonal metabolism of different species, including man.
- Azoles and triazoles act additively and could have neurotoxic consequences.
- No database concerned with the surveillance of fungal susceptibility to azoles is available for consultation in the public domain and data for Climbazole are scarce and of limited quality (in vivo and in vitro).
- Climbazole is claimed to act against *Malassezia* yeasts but could also inhibit other species such as *Aspergillus*, *Penicilium*, *Candida* and others.

The CHMP opinion (EMA/CHMP/618632/2011) concluded that in view of the arguments mentioned above, the use of Climbazole in cosmetic products may increase the risk of cross-resistance to other azole antifungals used as medicinal products, the greatest concern being the possible effect on microbiota on the human skin and the possibility of cross-resistance especially in immune-compromised individuals.

It was further concluded that, seen the lack of data for Climbazole, it is not possible to exclude a relationship between the use of Climbazole and the development of resistance in the different fungi causing invasive fungal infections in humans.

Generation of data on the activity of all medically important azoles on the different relevant fungal species, including clinical isolates either harbouring various resistance mechanisms and showing resistance to Climbazole, would be needed to make such an exclusion.

3.3. Argumentation provided by Cosmetics Europe as a response to the CHMP/EMA opinion on Clotrimazole

The European Commission received a letter on 14 November 2012 containing the following argumentation:

- The EMA opinion does not provide scientific evidence that the use of Clotrimazole in cosmetics increases the risk of cross resistance to other azoles
- In the EMA opinion, assumptions are made by extrapolating study results on the medical use of Ketoconazole in immune-compromised patients to the general population. The appropriateness of these is questioned (as also done by EMA themselves) and reference is made to studies showing that the fungal resistance is linked to an individual azole compound rather than to the azole group.
- Long-term efficacy studies of Clotrimazole and Ketoconazole as anti-dandruff agents do not show any development of fungal resistance at the application site.
- The environmental exposure to Clotrimazole caused by cosmetic use is very small in comparison with its use in agriculture and therefore has no significance in contributing to environmental resistance.
- Clotrimazole is an important cosmetic anti-dandruff agent among a limited number of other allowed substances. Consequently its prohibition will increase the exposure to the few other actives in this field.
- It is proposed to consider for the time being the SCCS safety assessment to human health of Clotrimazole (opinion SCCS/1506/13) and further to monitor the potential anti-fungal resistance and re-evaluate the situation with respect to fungal resistance when scientific evidence in this field becomes available.

3.4. Discussion

The CHMP/EMA ITF report could not directly show that there exists a Clotrimazole-related increased risk of cross-resistance to other azole antifungals used as medicinal products. Hypothetical data, however, point to the possibility of cross-resistance, in particular in immune-compromised persons and concern was expressed for possible effects of Clotrimazole on human skin microbiota.

- Cosmetics Europe expressed its concern with respect to the lack of scientific evidence of the statement in the CHMP/EMA ITF report concerning the use of Clotrimazole in cosmetics and the increasing risk of cross resistance to other azoles.
- As the limited number of *in vitro* and *in vivo* data on Clotrimazole, available in the public domain with respect to fungal resistance, are of a rather poor quality and susceptibility breakpoints for Clotrimazole are lacking, the SCCS felt that it was not in a position to exclude a potential relationship between the use of Clotrimazole and the development of (cross)-resistance. Therefore the opinion of an external internationally recognised authority in this field was asked. The following arguments were provided by the expert:
 - (i) The mechanisms of resistance of fungi to azole antifungals vary across different species and with route of infection and administration. (ii) There is no precedent described in the peer reviewed literature where a topically applied azole has been shown to induce cross resistance to either skin organisms or internal pathogenic fungi. (iii) Fungi differ from bacteria in that exchange of genetic material responsible

for drug resistance between different organisms is not known to occur, reducing the facility to spread resistance between microflora, including commensal organisms.(iv) Resistance to azoles amongst *Malassezia* species is rare although differences in treatment responses may be due to the documented variations in “*in vitro*” drug sensitivities, but these values only rarely reach break point levels accepted under laboratory standards as indicative of microbiological resistance. (v) Resistance to Climbazole has not been reported in the scientific literature.

In the expert opinion it was concluded that the mechanism described in the analysis by the EMA is rather a theoretical possibility, not backed up by scientific observations and therefore that from the view point of resistance, Climbazole remains a safe product to apply to the skin. It was further emphasized that from the point of antimicrobial resistance, there is no difference between its use as a leave-on and rinse-off application versus a rinse-off application only.

4. CONCLUSION

Question 1: In light of the EMA opinion and the information contained therein, can Climbazole still be considered safe for use as an ingredient in cosmetic products?

The SCCS is of the opinion that in light of the EMA opinion, providing only indirect arguments of concern with respect to the use of Climbazole and the development of resistance in the different fungi causing invasive fungus infections in humans, and on the other hand the clear opinion of an internationally famed expert in the field, that actually Climbazole can be considered as a safe ingredient with respect to antimicrobial resistance, in rinse-off as well as in leave-on cosmetic products.

Question 2: If the answer to question 1 is yes, does the SCCS consider that any aspects of the previous assessment of climbazole needs to be revised on the basis of the dossier produced by EMA on this ingredient?

In the light of the opinion provided by the external expert with respect to (cross-) resistance, the dossier of Climbazole contains the necessary elements to allow risk assessment for human health according to the SCCS's Notes of Guidance for the testing of cosmetic ingredients and their safety evaluation.

Question 3: If the answer to question 1 is yes, does the SCCS consider that Climbazole is safe for the consumers, when used up to a concentration of 0.5% in foot care products in addition to the previous evaluated uses (i.e. hair cosmetics and face cosmetics up to 0.5%, rinse-off hair cosmetics up to 2.0%)

In the risk assessment (opinion on P64) of December 2012 the SCCS came to the conclusion that the non-preservative use of Climbazole either in foot care cosmetics alone at a concentration of up to 0.5% or in combination with either shampoo (at a maximum concentration of 2%) or face cream (at a maximum concentration of up to 0.5%) or with hair lotion (at a maximum concentration of up to 0.5%), does not pose a risk to the health of the consumer. In the case, however, that 3 products, although each safe when used separately, are combined, the combinations of either shampoo, hair lotion and a foot care product or face cream, hair lotion and a foot care product (all containing Climbazole at the maximum requested concentration) cannot be considered safe for the consumer.

Question 4: Does the SCCS have any further scientific concern with regard to the use of Climbazole in cosmetic products?

The SCCS is of the opinion that the scientific literature should be carefully followed with respect to potential (cross-) resistance of Clotrimazole and related compounds. When new information with respect to (cross)-resistance development becomes available, re-evaluation of the situation with respect to fungal resistance might be necessary.

5. MINORITY OPINION

Not applicable

6. REFERENCES

- Schmidt-Rose T, Braren S, Fölster H, et al Efficacy of a piroctone olamine/clotrimazole shampoo in comparison with a zinc pyrithione shampoo in subjects with moderate to severe dandruff. *Int J Cosmet Sci.* 2011; 33:276-282
- Mayser P, Argembeaux H, Rippke F. The hair strand test – a new method for testing antifungal effects of antidandruff preparations. *J Cosmet Sci.* 2003 ;54:263-270
- Schmidt A. In vitro activity of clotrimazole, miconazole and silver-sulphadiazine against isolates of *Malassezia pachydermatis*. *Zentralbl Veterinarmed B.* 1997 ;44:193-7
- Pfaller MA. Antifungal drug resistance: mechanisms, epidemiology and consequences for treatment. *Am J Med .* 2012. 125, Issue 1, supplement S3-S13
- Johnson E, Davey KG, Szekely A et al. Itraconazole susceptibilities of fluconazole sensitive and resistant isolates of five *Candida* species. *J Antimicrob Ther* 1995; 36; 787-793
- Snelders E., Camps SM., Karawajczyk A, et al. Triazole fungicides can induce cross-resistance to medical triazoles in *Aspergillus fumigatus*. *PLoS One.* 2012;7:e31801
- Yamaguchi H, Uchida K, Watanabe S, et al. Preclinical and clinical studies on the efficacy of bifonazole in patients with tinea pedis at 10 years after approval. Part 1. Susceptibility to bifonazole of clinical isolates of dermatophytes. *Jpn J Antibiot.* 1996 ;49:1085-94
- Miranda KC, de Araujo CR, Costa CR, et al Antifungal activities of azole agents against the *Malassezia* species. *Int J Antimicrob Agents.* 2007;29:281-4
- Schmidt A, Rühl-Hörster B. In vitro susceptibility of *Malassezia furfur* against azole compounds. *Mycoses.* 1996;39:309-12
- Jesus FP, Lautert C, Zanette RA, et al In vitro susceptibility of fluconazole-susceptible and -resistant isolates of *Malassezia pachydermatis* against azoles. *Vet Microbiol.* 2011 26;152:161-4
- Lynch ME, Sobel JD, Fidel PR . Role of antifungal drug resistance in the pathogenesis of recurrent vulvovaginal candidiasis. *J Med Vet Mycol.* 1996;34:337-339