



Scientific Committee on Consumer Safety

SCCS

ADDENDUM to the Opinion SCCS/1506/13

On

Climbazole

Cosmetics Europe: P64

The SCCS adopted this addendum at its Plenary of
26 February 2013

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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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http://ec.europa.eu/health/scientific_committees/consumer_safety/index_en.htm

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This opinion has been subject to a commenting period of four weeks after its initial publication. Comments received during this time have been considered by the SCCS and discussed in the subsequent plenary meeting. Where appropriate, the text of the relevant sections of the opinion has been modified or explanations have been added. In the cases where the SCCS after consideration and discussion of the comments, has decided to maintain its initial views, the opinion (or the section concerned) has remained unchanged. Revised opinions carry the date of revision.

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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 2005, the SCCP adopted a scientific opinion (SCCP/0918/05) on climbazole in which the SCCP recommended a complete re-evaluation of the safety of this compound.

In 2009, the SCCP adopted a scientific opinion (SCCP/1204/08) on climbazole with the following conclusion:

Question 1: Does the SCCP consider with the scientific data provided that climbazole is safe for the consumers, when used as a preservative in cosmetic products up to a maximum concentration of 0.5%?

The SCCP is of the opinion 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.

Question 2: Does the SCCP consider with the scientific data provided that climbazole is safe for the consumers, when used for non-preservative purposes as an anti-dandruff active ingredient in hair care formulations up to a maximum concentration of 2.0% in rinse-off products?

The SCCP is of the opinion that the 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.

Question 3: Does the SCCP consider with the new scientific data provided that climbazole is safe for the consumers, when used for non-preservative purposes as an anti-aging ingredient in leave-on products up to a maximum concentration of 0.5%, even though this application might already be covered by Question 1?

The SCCP is of the opinion that 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.

The inhalation exposure to climbazole from spray products was not assessed in this opinion.

Based on the above opinion, the Commission prepared a draft Cosmetic Directive to implement the restriction, which was submitted to a public consultation. The current mandate is the consequence of that consultation as a company applied to extend the group of face and hair products with the foot care products in which climbazole could be safely used as a preservative in a concentration up to 0.5%.

2. TERMS OF REFERENCE

Does the SCCS consider that climbazole is safe for the consumers, when used as a preservative in cosmetic products up to a maximum concentration of 0.5% if the product categories face and hair products, as recommended by the former SCCP opinion (SCCP/1204/08) are extended to include foot care products?

3. DISCUSSION

3.1 Relevant Information out of SCCP/1204/08 (Ref. 1)

3.1.1 General toxicological profile of Climbazole

Irritation / sensitisation

The previous results of an old Draize eye test and a combination of two newly carried out *in vitro* screening tests for eye irritation (HET-CAM and CEET) suggest that Climbazole is not an eye irritant. Its potential to cause skin irritation is assessed through a human single patch test and shows only mild to no skin irritation. Considering the results of the above studies and considering the dilution of the compound in its intended use, there appears to be no reason to suspect any irritation problems with the use of Climbazole in cosmetic products.

As far as its sensitising potential is concerned, a well-performed LLNA shows Climbazole to be non-sensitising in the performed mouse assay

Dermal absorption

A well-performed dermal absorption study for Climbazole contained at 2% in a shampoo formulation is available and reveals a dermal absorption value of **0.297 µg/cm²** or 0.150%. As far as application under leave-on conditions and a Climbazole concentration of 0.5% is concerned, a recent *in vitro* dermal absorption study reveals absorption levels of **1.10 µg/cm²** (2.23%) and **1.25 µg/cm²** (3.46%) for an aqueous hair lotion and a water-in-oil skin preparation, respectively.

General toxicity

Several subacute and subchronic studies with rodents and non-rodents were available, though were performed before the introduction of GLP. Based upon the available test descriptions and raw data, the SCCP deduced a **conservative NOEL** value of **5 mg/kg bw/day** from the presented 90-day study with the rat.

Mutagenicity / genotoxicity

Climbazole showed to be negative in the Ames test, in the *in vitro* micronucleus test and in the *in vitro* mammalian cell gene mutation test (with the exception of the prolonged exposure scheme, where some mutagenic potential was apparent).

The *in vivo* micronucleus test and the *in vivo* UDS assay with Climbazole showed the substance to be negative, meaning that no mutagenic/genotoxic effects are to be expected.

Reproduction toxicity

Climbazole was tested in a 1-generation reproductive toxicity test which was considered questionable as far as its overall scientific validity is concerned, and in well-performed teratogenicity study, leading to a NOAEL (embryotoxicity) of 30 mg/kg bw/day and a NOAEL (maternal toxicity) of 15 mg/kg bw/day.

Toxicokinetics

A newly performed oral bioavailability assay of ¹⁴C Climbazole in mice confirms the results that were described earlier, namely that Climbazole is rapidly absorbed and excreted and that its maximum concentration in plasma is reached after approximately 8 hours.

3.1.2 MoS calculations and SCCP conclusions

Calculation for the use of Climbazole at 2% as an anti-dandruff agent in shampoo

Dermal absorption through human skin	A ($\mu\text{g}/\text{cm}^2$)	=	0.297 $\mu\text{g}/\text{cm}^2$
Skin Area surface (area hand + $\frac{1}{2}$ area head)	SAS (cm^2)	=	1440 cm^2
Typical human body weight		=	60 kg
Systemic exposure dose (SED)	$A \times (10^{-3}\text{mg}/\mu\text{g}) \times \text{SAS} / 60 \text{ kg}$	=	0.007 mg/kg bw
No observed effect level (90 day, oral, rat)	NOEL	=	5 mg/kg bw/day

Margin of Safety	NOEL / SED	=	701
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Calculation for the use of Climbazole as preservative at 0.5% in aqueous hair lotions

Dermal absorption through human skin	A ($\mu\text{g}/\text{cm}^2$)	=	1.10 $\mu\text{g}/\text{cm}^2$
Skin Area surface (area hand + $\frac{1}{2}$ area head)	SAS (cm^2)	=	1440 cm^2
Typical human body weight		=	60 kg
Systemic exposure dose (SED)	$A \times (10^{-3}\text{mg}/\mu\text{g}) \times \text{SAS} / 60 \text{ kg}$	=	0.026 mg/kg bw
No observed effect level (90 day, oral, rat)	NOEL	=	5 mg/kg bw/day

Margin of Safety	NOEL / SED	=	189
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Calculation for the use of Climbazole as preservative at 0.5% in a cosmetic face cream

Dermal absorption through human skin	A ($\mu\text{g}/\text{cm}^2$)	=	1.25 $\mu\text{g}/\text{cm}^2$
Skin Area surface (1/2 area head female)	SAS (cm^2)	=	565 cm^2
Typical human body weight		=	60 kg
Systemic exposure dose (SED)	$A \times (10^{-3}\text{mg}/\mu\text{g}) \times \text{SAS} / 60 \text{ kg}$	=	0.012 mg/kg bw
No observed effect level (90 day, oral, rat)	NOEL	=	5 mg/kg bw/day

Margin of Safety	NOEL / SED	=	425
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Calculation for the use of Climbazole as preservative at 0.5% in leave-on body lotion

Dermal absorption through human skin	A ($\mu\text{g}/\text{cm}^2$)	=	1.25 $\mu\text{g}/\text{cm}^2$
Skin Area surface (whole body)	SAS (cm^2)	=	18,000 cm^2
Typical human body weight		=	60 kg
Systemic exposure dose (SED)	$A \times (10^{-3}\text{mg}/\mu\text{g}) \times \text{SAS} / 60 \text{ kg}$	=	0.38 mg/kg bw
No observed effect level (90 day, oral, rat)	NOEL	=	5 mg/kg bw/day

Margin of Safety	NOEL / SED	=	13
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Based upon the above calculations, the SCCP considered the following uses of climbazole in cosmetic products as safe:

- as an anti-dandruff agent up to 2% in cosmetic shampoos (MoS = 701),
- as preservative up to 0.5% in an aqueous hair lotion (MoS = 189),
- as preservative up to 0.5% in a face cream (MoS = 425).

The use of Climbazole as preservative up to 0.5% for whole body applications, however, could not be considered as safe (MoS = 13). To generate an acceptable MoS (≥ 100), the SCCP concluded that the treated surface area for leave-on products containing up to 0.5% Climbazole as preservative should not exceed 2400 cm².

3.2 Current Request

In a letter, dated 16 February 2010, the applicant requests the extension of the use of Climbazole as preservative to foot care products. The following calculation of the MoS for that particular application is as follows:

Calculation for the use of Climbazole as preservative up to 0.5% in foot care products

Dermal absorption through human skin	A ($\mu\text{g}/\text{cm}^2$)	=	1.25 $\mu\text{g}/\text{cm}^2$
Skin Area surface (feet, Ref. 2)	SAS (cm^2)	=	1170 cm^2
Typical human body weight		=	60 kg
Systemic exposure dose (SED)	$A \times (10^{-3}\text{mg}/\mu\text{g}) \times \text{SAS} / 60 \text{ kg}$	=	0.024 mg/kg bw
No observed effect level (90 day, oral, rat)	NOEL	=	5 mg/kg bw/day

Margin of Safety	NOEL / SED	=	205
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The applicant proposes to use the same dermal absorption value as found for a leave-on body lotion, as foot care products have a closely related composition. In addition, it is pointed out that the MoS is further enhanced by differences between body areas like the volar forearm, scalp and face and the plantar region of the feet. The relation regarding percutaneous penetration of hydrocortisone through human skin is stated to be typically 1.0 for the volar forearm and 0.14 for the plantar sole/arch (Ref. 3).

Calculation for the combined use of Climbazole at the requested maximum concentration as preservative (0.5%) in leave-on and rinse-off cosmetic products and as an anti-dandruff agent in shampoo (2%)

Combination of 2 cosmetic products	SED (mg/kg bw/d)	MOS
Preservative and anti-dandruff use in shampoo		
Shampoo + hair lotion	0.033	151
Shampoo + face cream	0.019	263
Shampoo + foot care	0.041	121
Preservative use		
Hair lotion + face cream	0.038	131
Hair lotion + foot care	0.051	98
Face cream + foot care	0.036	139

Table 1: Safety data for the simultaneous use of two cosmetic products containing climbazole at the requested maximum concentration

In Table 1, the SED and MOS for all possible combinations of 2 cosmetic products, containing Climbazole at the requested maximum concentration, are shown. Only the products that are, when individually used, safe for the consumer, are taken up. From this table it appears that all combinations considered provide an acceptable MOS.

Combination of 3 cosmetic products	SED (mg/kg bw/d)	MOS
Preservative in leave-on cosmetics and anti-dandruff use in shampoo		
Shampoo + hair lotion + face cream	0.045	111
Shampoo + hair lotion + foot care	0.057	88
Shampoo + face cream + foot care	0.043	116
Combination of these 4 products above	0.069	72
Preservative use (0.5%)		
Face cream + hair lotion + foot care	0.062	81

Table 2: Safety data for the simultaneous use of three and four cosmetic products containing Climbazole at the requested maximum concentration.

In Table 2, the SED and MOS for all possible combinations of 3 and 4 cosmetic products all containing Climbazole at the requested maximum concentration, are shown. Only the products that are, when individually used, safe for the consumer, are taken up. It seems that not all combinations provide an acceptable MOS. Only the combination of a rinse-off (shampoo) with face cream and either a hair lotion or a foot care product can be considered safe for the consumer when the maximum requested concentration of Climbazole is present.

3.3 Discussion

In its opinion SCCP/1204/08 on Climbazole (Ref. 1), the SCCP concluded that, to ensure the safe use of Climbazole as preservative at a concentration of up to 0.5% in cosmetic leave-on products, the treated surface area should not exceed 2400 cm². The requested use in foot care products as a preservative to a maximum concentration of up to 0.5% involves a skin surface area of 1170 cm², of which a large part (i.e. the foot soles) is expected to show a lower dermal absorption due to increased skin thickness. On the other hand, the dermal absorption between the toes may be higher due to potential occlusion and sweating effects. The SCCS is therefore of the opinion that, taking both types of areas on the foot into consideration, the above calculation for the preservative use of Climbazole at a concentration of 0.5% in a foot care product can be accepted. Its single use as a foot product is safe for the consumer.

As it is possible that different cosmetic products containing Climbazole at the highest requested concentration, which are safe for the consumer when used individually, are applied simultaneously, their combination should also be considered. In order to obtain a sufficiently high MOS, the systemic exposure after combined use should be ≤ 0.05 mg/kg bw/d. This is the case for all combinations of 2 products of the cosmetics taken up in table 1 (shampoo, hair lotion, face cream, foot care product). The combination hair lotion, foot care gives a MOS of 98, which is considered to be acceptable as all products are considered to contain the highest allowed concentration of Climbazole.

Combined use of 3 cosmetic products (table 2), only provides for 2 combinations (Shampoo + hair lotion + face cream and Shampoo + face cream + foot care) an acceptable MOS when the maximum requested concentration of Climbazole is present.

The simultaneous use of either shampoo, hair lotion and a foot care product, or the combination of hair lotion, foot care and face cream products all containing Climbazole at the maximum concentration requested, cannot be considered safe for the consumer.

Body lotion containing Climbazole at a maximum concentration of up to 0.5% is excluded from this table as the SCCS already earlier considered it as not being safe for the consumer, even when used as a single product containing this anti-fungal agent.

4. CONCLUSION

Does the SCCS consider that Climbazole is safe for the consumers, when used as a preservative in cosmetic products up to a maximum concentration of 0.5% if the product categories face and hair products, as recommended by the former SCCP opinion (SCCP/1204/08) are extended to include foot care products?

The SCCS is of the opinion that the use of Climbazole as a preservative at a maximum concentration of 0.5% either in a foot care cosmetic and used alone, or in combination with a 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 the case of combination of the 3 products (foot care cosmetic, face cream and hair lotion), each containing Climbazole at the maximum requested concentration (0.5%, safe when used separately) applied simultaneously, this combination cannot be considered safe for the consumer.

As Climbazole can also be used in cosmetics as an anti-dandruff agent in shampoo (rinse-off) up to a maximum concentration of 2%, the use of shampoo alone or in combination with face cream or hair lotion or foot care cosmetic does not pose any risk. However, when anti-dandruff shampoo is used together with hair lotion and foot care cosmetic this combined use cannot be considered safe for the consumer.

When the 4 different types of products (shampoo, hair lotion, foot care cosmetic and face care cosmetic), all containing Climbazole at the maximum allowed concentration, are simultaneously topically applied, this combination cannot be considered safe for the consumer.

This opinion does not address the possible environmental concerns of the use of Climbazole in cosmetic products.

5. MINORITY OPINION

Not applicable.

6. REFERENCES

1. SCCP/1204/08. Opinion on Climbazole (Colipa n° P64), adopted by the SCCP during the 19th plenary meeting of 21 January 2009.
2. SCCNFP/0690/03. Notes of Guidance for the testing of cosmetic ingredients and their safety evaluation, adopted by the SCCNFP during the 25th plenary meeting of 20 October 2003.
3. Niedner R, Ziegenmeyer J (Eds). Biopharmazeutische Aspekte. In: Dermatika – Therapeutischer Einsatz, Pharmakologie und Pharmazie. Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, Germany (1992).