



Scientific Committee on Consumer Safety

SCCS

OPINION ON

Polidocanol

ADDENDUM to the SCCP opinion on polidocanol (SCCP/1130/07)



The SCCS adopted this opinion at its 13th plenary meeting
of 13-14 December 2011

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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1. BACKGROUND

Polidocanol (CAS 3055-99-0) with the INCI-name laureth-9 is a polyethylene glycol ether of lauryl alcohol, where the average value of ethylene oxide units is 9. The chemical name of polidocanol is 3,6,9,12,15,18,21,24,27-nonaoxanonatriacontan-1-ol according to ECB ¹.

The first opinion (SCCP/1130/07) on the substance was adopted by the SCCP the 2nd October 2007 with the conclusion:

"The data included in this dossier demonstrate that polidocanol is of low toxicity and does not pose a risk to the health of the consumer when used up to 3% in leave-on and up to 4% in rinse-off cosmetic products.

Recent scientific evidence does not confirm the assumed local-anaesthetic effect of polidocanol. Thus, its presence in cosmetics and skin care products will not affect cutaneous sensation".

According to the applicant the substance is used in rinse-off products as a non-ionic emulsifier and co-surfactant, particularly in shampoos and hair conditioners in concentrations from 1 to 4%. It is also used in leave-on products, such as body and face creams, up to a concentration of 3%.

At least one Member State has authorized polidocanol for use in a topical drug formulation at a concentration of 2%. A drug for injection has been approved in concentrations as from 0.5%.

Meanwhile more data was submitted by Member States in order to ensure that all available documentation of the inherent local anaesthetic effects and the ability to curb pruritus that polidocanol possesses have been properly assessed by the Scientific Committee, and especially the use of polidocanol in leave-on products should be revisited.

Furthermore, Member States are asking whether adverse effects have been considered like bradycardia/hypotension and sensitisation reactions.

At the same time, the Commission was asked to request the SCCS to evaluate the homologue substance Laureth-7 together with polidocanol, as this substance is considered to be even more potent than polidocanol with respect to the local anaesthetic properties. However, not much data was submitted to support that purpose.

2. TERMS OF REFERENCE

1. *Does the SCCS see it necessary to change its conclusion on the safe use of polidocanol, especially its safe use in leave-on products or other use conditions taken into account the documentation provided?*
2. *And/or does the SCCS have any further concerns regarding the use of polidocanol in cosmetic products?*
3. *On the available data provided can the SCCS express an opinion on the safe use of laureth-7 in cosmetic products?*

¹ ECB – European Chemicals Bureau (ECB)

3. Opinion

The mandate is based on a document from the Norwegian Food Safety Authority, which the Commission received after the proposal to implement the earlier polidocanol opinion, i.e. inclusion in Annex III of Directive 76/768/EEC with a concentration limit of 3% in cosmetic products. In this addendum to its previous opinion SCCP/1130/07 the SCCS identified and addressed the issues and questions raised in this document.

Concerns were raised in particular about possible local anaesthetic effects and an anti-pruritic effect of polidocanol (Laureth-9) when applied topically. This exposure situation is relevant for use of cosmetic products as well as application of medicinal products for treatment of dermatological conditions such as dry and itchy skin. This scenario differs considerably from uses for medical treatments such as sclerotherapy, treatment of varicosities, etc., where polidocanol is injected intravenously. Nonetheless, the SCCS has also considered literature on this particular use of polidocanol in its re-evaluation of possible adverse side effects from the use in cosmetic products.

3.1. Local anaesthetic properties of polidocanol when applied topically

Numerous studies, mostly old ones, clearly document anaesthetic properties of polidocanol. However, the data were obtained in animals (and volunteers) with injection of the test agents (intracutaneous, subcutaneous, intravenous, peridural, paravertrebral [Soehring et al. 1952; Siems & Soehring 1952; Zipf et al. 1957]).

Two papers describe also local anaesthesia in the rabbit cornea reflex test with polidocanol [Zipf & Dittmann 1964; Ansmann et al. 1997]. The latter, a patent document without any methodological descriptions, states shorter chain alkoxyethylates (Laureth-7) to be more potent than polidocanol (Laureth-9).

The above data document anaesthetic properties, but the application modes clearly differ from topical application of polidocanol containing consumer products. In this situation the efficacy of any local anaesthetic will strongly depend upon its dermal penetration. According to human studies, dermal penetration of polidocanol is rather limited with about 2% [opinion SCCP/1130/07; BfR 2003; Drotman et al. 1980].

When local anaesthetic drugs are applied, various effects may be observed, such as a decrease in pricking pain and a change in burning, itch, and thermal sensations. These effects occur after skin penetration and may be attributed to the action of the anaesthetics on nociceptors and thermoreceptors, i.e., on C and A-delta nerve fibres respectively [Leopold & Maibach 1999].

It is worth noting that well established local anaesthetics do not penetrate readily through human skin. EMLA[®] cream (a 1:1 mixture of lidocaine and prilocaine), widely used as analgesic to decrease venipuncture pain in children, is applied under occlusive dressing to facilitate absorption [Rogers & Ostrow 2004].

Indeed, local anaesthetic drugs differ considerably in percutaneous absorption as measured *in vitro* and also in efficacy when assessed in human volunteers by suitable methods such as pin pricking [McCafferty et al. 1988; McCafferty et al. 1989] or thermal sensory analysis [Leopold & Maibach 1999; 2004]. For instance, in line with their higher permeability *in vitro*, local anaesthesia was demonstrated in pinpricking tests for amethocaine, lignocaine, amylocaine, fomocaine and benzocaine whereas bupivacaine, cinchocaine and mepivacaine (with low apparent permeability *in vitro*) were not active *in vivo* [McCafferty et al. 1988; McCafferty et al. 1989]. In principal similar results were reported by Leopold and Maibach (1999) who assessed percutaneous penetration of local anaesthetics and thermal thresholds over time (3 hours) with a thermal sensory analyzer in human volunteers. In this study, lidocaine, prilocaine, their 1:1 mixture (EMLA) as well as a triple mixture of lidocaine,

prilocaine and tetracaine (1:1:1) clearly affected the threshold for cold and warm sensation whilst bupivacaine and mepivacaine were inactive in this respect.

A recent study with topic application of polidocanol, some other non-ionic surfactants and five conventional local anaesthetics [Leopold & Maibach 2004] confirmed that lidocaine, prilocaine, the 1:1 mixture and the triple mixture of lidocaine, prilocaine and tetracaine are potent local anaesthetics. In contrast, none of the investigated surfactants nor bupivacaine and mepivacaine affected thermal thresholds under the same conditions.

The lack of an anaesthetic effect for topically applied polidocanol is a relevant finding for the overall evaluation, since results for active and inactive local anaesthetics (bupivacaine and mepivacaine) in the thermal sensory analysis [Leopold & Maibach 1999 and 2004] are in accord with negative results for these agents in previous studies with pinpricking [McCafferty et al. 1988; McCafferty et al. 1989].

In the SCCP opinion (SCCP/1130/07), the study by Leopold and Maibach (2004) has been considered as evidence for the absence of local anaesthetic effects with topical application of polidocanol. The SCCS in its re-evaluation endorses this position.

The SCCS sees no need to supplement the study of Leopold and Maibach with additional studies, as there are no scientific arguments against thermal threshold analysis when compared to other methodology, e.g. pin pricking (see above).

3.2. Antipruritic effects of polidocanol containing products

With regard to possible antipruritic effects, the SCCP has quoted Weisshaar et al. (1996), a well controlled clinical study: The effects of a polidocanol containing medicinal product (Optiderm with 5% urea and 3% polidocanol) and of other creams (EMLA® and xylocaine) were evaluated in volunteers who received a focal histamine stimulus. The results were compared to pre-treatment with the corresponding placebo creams. Itching was significantly reduced by all active substances, including the placebo cream corresponding to Optiderm. Therefore it was concluded that antipruritic effects may be due to the presence of urea.

As urea-containing products improve moisture in the skin and can reduce itch, such products are highly regarded in dermatological practice as basic and intermittent therapies for topical treatment of dry skin diseases [Freitag & Hoppner, 1997; Twycross et al. 2003; Weisshaar 2010]. Although polidocanol is often called a 'local anaesthetic' in the literature [e.g. Ring & Frohlich 1985; Ständer et al. 2005], the exact mechanism of an antipruritic effect remains to be defined. It is worth noting that alleviation of symptoms such as itch by means of creams and emollient bath products with polidocanol is not necessarily related to a local anaesthetic effect, but rather to additives such as oils and urea which improve skin conditions.

This view based on the results of Weisshaar et al. (1996) is supported by further experimental studies in humans. Fearfield et al. (2000) investigated whether the use of topical polidocanol containing products could influence cutaneous innervation: They compared in randomized double-blind studies the effects of Balneum® and Balneum Plus® bath oils as well as Optiderm® cream and placebo cream (i.e. the same formulations without and with polidocanol) with regard to treatment differences in weal, flare and blood flow (measured by laser Doppler flowmetry) following challenge with histamine, calcitonin-related peptide (CRGP) and other stimuli. In study I which compared Balneum® and Balneum Plus® bath oils, a significantly smaller mean flare size was observed following challenge with CRPG, not with the other stimuli. In study II which compared Optiderm® and placebo cream, the only treatment difference that achieved statistical significance was a reduced flare size in favour of placebo after intradermal injection of one stimulus (compound 48/80, provokes histamine release). Thus, the authors conclude that the

antipruritic effect claimed for Optiderm® does not appear to be due to cutaneous neuronal or microvasculature influences [Fearfield et al. 2000].

Thereby, this study confirms the findings of Weisshaar et al. (1996) who observed also no superior effects for polidocanol containing creams versus cream base.

3.3. Use of polidocanol in sunscreens

According to the Norwegian document [Enclosure Talberg; Appendix 1 on a search in the EWG database] there are 131 products containing Laureth-9 (polidocanol) none of which are sun protection products. Laureth-7 is used in many more (1702) products, also in several (78) sun protection products. Although this is based on the US market, there are no indications that polidocanol has a widespread use in sun protection products in Europe.

The SCCS has no concerns about possible anaesthetic effects of polidocanol containing products applied with leave-on products to skin that is exposed to UV radiation from the sun. Local increased blood flow to the skin enhances *systemic* delivery but decreases *local* availability of a topically applied drug [Hull 2002]. Under conditions of UV-induced erythema the expectation for polidocanol is that rapid clearance occurs.

3.4. Sensitisation potential of topically applied polidocanol

Human studies listed in the SCCP opinion and reviews on topically applied products with polidocanol – mostly for treatment of pruritus – do not indicate sensitization as an issue of concern [Fruitjer-Pölloth 2005; Twycross et al. 2003; Weisshaar 1996, 2010; Ständer et al. 2006]. In a large survey of clinical patch test populations, patients with atopic dermatitis (which is often treated with polidocanol-containing emollients) was not a significant risk factor for contact allergy to polidocanol [Uter et al. 2000] whilst elderly patients with lower leg dermatitis were at risk, a phenomenon well known for a number of other topical drugs and cosmetic ingredients also.

When polidocanol is injected, mainly for sclerotherapy, allergic and anaphylactic reactions are infrequent with a reported incidence of 0.01 to 0.3 % [Conrad et al. 1995; Feied et al. 1994; Goldman & Bergan 2001; Mimura et al. 2009].

Serious allergic reactions are rare upon injection of polidocanol, and the SCCS sees no risk of sensitisation from topical application of cosmetic products containing it.

3.5. Bradycardia/hypotension side effects

There are only rare reports on bradycardia/hypotension as side effect when polidocanol is injected for medicinal reasons, mainly sclerotherapy [Marrocco-Trishitta et al. 2002; Mimura et al. 2009]. This may occur if maximum doses are exceeded, due to intrinsic negative inotropic effects of polidocanol [Oexle et al. 1988]. Rather large studies [Conrad et al. 1995] report complications such as “fainting on injection” only in 4 of 16,804 treated legs.

This side effect of polidocanol is only seen at high systemic doses, and thus not a relevant issue with topical application. According to literature [e.g. Hyodoh et al. 2005] and the information from Norway, the maximum recommended daily dose for injection of polidocanol is 2 mg/kg bw, while the SCCS calculated a systemic exposure dose from cosmetic use of 0.132 mg/kg bw/day.

3.6. Safety of Laureth-7

According to the limited information available, Laureth-7 seems to have stronger local anaesthetic effects than polidocanol. At least on the US market, it is used more widely, and also in sun protection products. As no data on the pharmacological and toxicological

properties of Laureth-7 is available, the SCCS is presently not in the position to evaluate its safe use in cosmetic products. For the assessment of Laureth-7, a complete safety dossier, including data on dermal penetration and anaesthetic properties, would be required.

4. Conclusions

1. *Does SCCS foresees it necessary to change its conclusion on the safe use of polidocanol, especially its safe use in leave-on products or other use conditions taken into account the documentation provided?*

The SCCS, in a re-evaluation of the earlier SCCP opinion (SCCP/1130/07), taking into account the documentation provided, does not find it necessary to change its conclusions on the safe use of polidocanol in consumer products.

2. *And/or does the SCCS have any further concerns regarding the use of polidocanol in cosmetic products?*

The SCCS has no further concerns regarding the topical use of polidocanol in cosmetic products.

3. *On the available data provided can the SCCS express an opinion on the safe use of laureth-7 in cosmetic products?*

The data presently available indicate that Laureth-7 is used in numerous cosmetic products and in sun protection products. Laureth-7 seems to have stronger local anaesthetic effects than polidocanol. As no other data on the pharmacological and toxicological properties of Laureth-7 is available, the SCCS is presently not in the position to evaluate its safe use in cosmetic products.

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