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Questions and Answers on Benzalkonium chloride in the context of the revision of the guideline on 'Excipients in the label and package leaflet of medicinal products for human use' (CPMP/463/00)

Draft

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Comments should be provided using this template. The completed comments form should be sent to excipients@ema.europa.eu

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1. Background

Following the European Commission decision to revise the Annex of the guideline on 'Excipients in the label and package leaflet of medicinal products for human use' (CPMP/463/00)[1], a multidisciplinary group of experts involving SWP (lead), QWP, PDCO, PRAC (ex PVWP), CMD(h), VWP, BWP and BPWP was created in 2011.

The objective of this group is to update the labelling of selected excipients listed in the Annex of the above mentioned EC guideline, as well as to add new excipients to the list, based on a review of their safety. The main safety aspects to be addressed were summarised in a concept paper published in March 2012[2].

Q&A documents on excipients will be progressively released for public consultation. They will include proposals for new or updated information for the labelling and package leaflet. Once a Q&A is finalised, the corresponding background report supporting its review will be also published.

When the Q&As of all the selected excipients have been finalised, they will be grouped in a single Q&A document. This information will be integrated in the updated Annex of the new revised EC guideline.

2. What is benzalkonium chloride and why is it used as an excipient?

Benzalkonium chloride is a quaternary ammonium antiseptic and disinfectant with actions and uses similar to those of other cationic surfactants. It is also used as an antimicrobial preservative for pharmaceutical products. For most multidose aqueous nasal, ophthalmic and otic products, benzalkonium chloride is the preservative of choice. It has been used in eye drops as a preservative since the 1950s and it is still the most common preservative used in ophthalmic solutions at a concentration of 0.01 – 0.02%. It is an effective bactericidal and fungicidal agent that helps to minimise the growth of organisms in multidose containers.

3. Which medicinal products contain benzalkonium chloride?

According to the survey on preservatives in ophthalmic preparations conducted in 2009 and involving 17 member states, benzalkonium chloride appears to be the main preservative in ophthalmic preparations on the EU market, approximately 74% of ophthalmic preparations contain benzalkonium chloride as a preservative [1].

[1] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003412.pdf
[2] Concept paper on the need for revision of the 'Guideline on excipients in the label and package leaflet of medicinal products for human use' (CPMP/463/00) EMA/CHMP/SWP/888239/2011 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/03/WC500123804.pdf

Benzalkonium chloride is further used as a preservative in more than 200 medicinal products for the nasal route of administration and about 10 preparations for nebulisation/inhalation use are authorised on EU markets based on the additional survey performed amongst the limited number of MS. Only a few medicinal products containing benzalkonium chloride are intended for other routes of administrations i.e. cutaneous, oral, oromucosal, rectal, vaginal and parenteral use.

4. What are the safety concerns?

Repeated dose oral toxicity studies have shown that benzalkonium chloride is lethal in mice and rats at concentrations of 500 mg/kg/day and above due to local effects in the gastrointestinal (GI) tract. However, no organ-specific toxicity was observed in these two species at concentrations below those causing direct effects on the GI tract. Results of 90-day chronic toxicity studies have only showed changes in body weight and other general responses [2].

Substantial literature data indicate that benzalkonium chloride may induce ocular damage. *In vivo* studies have been mainly performed in rabbits and, therefore, careful extrapolation to humans is required due to the differences between these two species. A recent study of the toxicity of ophthalmological solutions containing 0,005% and 0,01% of benzalkonium chloride applied twice daily in rabbits and monkeys for up to 52 weeks did not show ophthalmological changes of irritation or corneal damage [3].

In vitro studies have suggested that benzalkonium chloride may cause ciliary beat stasis [4] as well as nasal lesions in rats when applied eight times daily [5].

Available experimental data indicates that benzalkonium chloride is neither genotoxic nor carcinogenic nor toxic for the reproduction [2, 6].

When used clinically in eye drops, benzalkonium chloride has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. In addition benzalkonium chloride may cause eye irritation and is known to discolour soft contact lenses. Consistent evidence of benzalkonium chloride - related toxicity did not emerge from a review of dedicated clinical investigations, (CHMP ad-hoc group on preservatives in eye drops, 2009 [1]). Some clinical studies showed that benzalkonium chloride may increase conjunctival inflammation and may affect the cornea but these results were not consistent across studies. However, especially for long term use (e.g. glaucoma patients), subpopulations with abnormal tearing and/or ocular surface diseases, alternative preservative compounds or preservative-free formulations have been proposed as a precaution [7].

Where data is available, no significant difference in adverse event profile in children compared to adults was found.

Benzalkonium chloride used as a preservative in nebulised solutions of anti-asthma drugs has been reported to cause dose-related bronchoconstriction especially in asthmatic patients [8] and has been associated with the precipitation of respiratory arrest [9].

Although some reports indicate an increased incidence of adverse effects after long term use of products containing benzalkonium chloride as a preservative it is not possible to recommend any safety limit for the general population of patients.

When present in medicinal products, the concentration of benzalkonium chloride is optimised so that the minimum sufficient amount is present to achieve compliance with the Ph. Eur. test for efficacy of antimicrobial preservation [1].

5. What are the reasons for updating the information in the package leaflet?

- It is proposed to harmonise the wording in line with the currently authorised product information (in particular for ocular use and topical use) and to add a comment with regard to children / breastfeeding when necessary.
- The respiratory and topical routes of administration should be corrected in line with the current Ph. Eur. standard terms.
- Information should be added for oral, oromucosal, rectal and vaginal use as well as for nasal use as no specific information is included in the current guideline.

96 ***Current information in the package leaflet***

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Benzalkonium chloride	Ocular	Zero	May cause eye irritation. Avoid contact with soft contact lenses. Remove contact lenses prior to application and wait at least 15 minutes before reinsertion. Known to discolour soft contact lenses.	
	Topical		Irritant, may cause skin reactions.	
	Respiratory	10 micrograms / delivered dose	May cause bronchospasm.	

97 # 6. Proposal for an updated information in the package leaflet

Name	Route of Administration	Threshold*	Information for the Package Leaflet	Comments (for health care professionals)
Benzalkonium chloride	Ocular use	Zero	/name of product/ contains the preservative benzalkonium chloride (… mg/ml), which may be absorbed by soft contact lenses and may discolour them. Contact lenses should be removed prior to instillation and may be reinserted 15 minutes following administration. Benzalkonium chloride has been reported to cause eye irritation, dry eyes and may affect the corneal surface. /name of product/ should be used with caution in dry eye patients and in patients where the cornea may be compromised. In addition, monitoring is required with prolonged use in such patients.	From the limited data available, there is no difference in the adverse event profile in children compared to adults. Generally, however, eyes in children show a stronger reaction for a given stimulus than the adult eye. If eye drops cause stinging and pain (potentially due to preservatives) this may have an effect on compliance in children.
	Nasal use	Zero	/name of product/ contains the preservative benzalkonium chloride (…mg/ml). May cause irritation and, especially on long term use, oedema of the nasal mucosa.	
	Nebulisation and inhalation use	Zero	/name of product/ contains the preservative benzalkonium chloride (…mg/ml). May cause bronchospasm especially in asthmatic	

Name	Route of Administration	Threshold*	Information for the Package Leaflet	Comments (for health care professionals)
			patients.	
	Cutaneous use	Zero	/name of product/ contains benzalkonium chloride as preservative, which may cause skin irritation.	
			In order to avoid ingestion by a breast fed child, application to the breasts during lactation is not advised.	Use during pregnancy and lactation is not expected to be associated with harmful effects as cutaneous absorption is minimal. Not for application to mucosa.
	Oral, oromucosal, rectal and vaginal use	Zero	/name of product/ contains benzalkonium chloride, which may cause mucosal irritation.	

Note:
* This threshold will trigger the inclusion in the package leaflet of the corresponding safety statements (provided in the column “information for the Package Leaflet”).

References

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