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Questions and answers on benzalkonium chloride used as an excipient in medicinal products for human use

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This document should be read in the context of the revision of the Annex of the European Commission guideline 'Excipients in the labelling and package leaflet of medicinal products for human use' (EMA/CHMP/302620/2017) [1].

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1. 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 1950's 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.

2. 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 [6].

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 inhalation use are authorised on EU markets based on the additional survey performed amongst a limited number of member states. 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.

3. What are the safety concerns?

Repeated dose oral toxicity studies have shown that within 2 days of dosing benzalkonium chloride is lethal in mice and rats at concentrations of approximately 500 mg/kg/day (dietary administration) 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 and chronic toxicity studies have only shown changes in body weight and other general responses [7].

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 [12].

In vitro studies have suggested that benzalkonium chloride (0.001–0.05%) may cause ciliary beat stasis [11] as well as nasal lesions in rats when applied eight times daily [10].

Available experimental data indicate that benzalkonium chloride is neither genotoxic nor carcinogenic nor a reproductive toxicant [4, 7].

Clinically, benzalkonium chloride may cause eye irritation and is known to discolour soft contact lenses. Benzalkonium chloride in eye drops has also been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy, especially in frequent or prolonged use or in conditions where the cornea is compromised. However, 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 [6]). Some clinical studies showed that benzalkonium chloride may increase conjunctival inflammation and may affect the cornea but these results were not consistent across studies. As a precaution, in long-term use (e.g. glaucoma patients) and in subpopulations with abnormal tearing and/or ocular surface diseases, alternative preservative compounds or preservative-free formulations have been proposed [13].

Where data is available, no significant difference in adverse event profile in children compared to adults was found [6].

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 [5] and has been associated with the precipitation of respiratory arrest [3].

Ototoxicity can occur when benzalkonium chloride is applied to the ear [8].

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 specify 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 [6].

4. 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 nasal use as no specific information was included in the guideline dated 2003 (see Annex 1).
- The threshold should be zero for all routes of administration.

5. Updated information in the package leaflet

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Benzalkonium chloride	All routes of administration	Zero	This medicine contains x mg benzalkonium chloride in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>.	
	Ocular	Zero	Benzalkonium chloride may be absorbed by soft contact lenses and may change the colour of the contact lenses. You should remove contact lenses before using this medicine and put them back 15 minutes afterwards. Benzalkonium chloride may also cause eye irritation, especially if you have dry eyes or disorders of the cornea (the clear layer at the front of the eye). If you feel abnormal eye sensation, stinging or pain in the eye after using this medicine, talk to your doctor.	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. Irritation may have an effect on treatment adherence in children. Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. Should be used with caution in dry eye patients and in patients where the cornea may be compromised. Patients should be monitored in case of prolonged use.
	Nasal	Zero	Benzalkonium chloride may cause irritation or swelling inside the nose, especially if used for a long time.	Long-term use may cause oedema of the nasal mucosa.

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
	Inhalation	Zero	Benzalkonium chloride may cause wheezing and breathing difficulties (bronchospasm), especially if you have asthma.	
	Cutaneous	Zero	Benzalkonium chloride may irritate the skin. You should not apply this medicine to the breasts if you are breast feeding because the baby may take it in with your milk.	Use during pregnancy and lactation is not expected to be associated with harmful effects to the mother as cutaneous absorption of benzalkonium chloride is minimal. Not for application to mucosa.
	Oromucosal, rectal and vaginal	Zero	Benzalkonium chloride may cause local irritation.	

Further scientific background is available in the report entitled 'Benzalkonium chloride used as an excipient' [2].

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Annex 1 - Information in the package leaflet as per 2003 Guideline [8]

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.	