9 October 2017
EMA/CHMP/601508/2014
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on the draft 'Questions and Answers on Benzalkonium chloride' (EMA/495737/2013)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	IFAPP (International Federation of Associations of Pharmaceutical Physicians)
2	NPPG (Neonatal and Paediatric Pharmacists Group)
3	AESGP, Brussels
4	AstraZeneca
5	SciencePharma (Poland)
6	GSK
7	ECI-EEIG (Eye-Care Industries EEIG)
8	Alcon Eye Care U.K. Ltd
9	SANOFI
10	Medicines Evaluation Board, the Netherlands

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	We agree on the proposed rewording of labels and package leaflets.	No action needed
2	Overall the proposal to provide guidance on the use of benzalkonium chloride in medicines used in children is to be welcomed. We agree with the proposals suggested.	General principles with regard the inclusion of antimicrobial preservatives or antioxidants in a medicinal product is included in CHMP Guideline on Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product. Specific provisions for development of paediatric medicines are outlined in Guideline on pharmaceutical development of medicines for paediatric use. In addition as no significant difference in adverse event profile in children compared to adults was found no further guidance on the use of benzalkonium chloride in medicines for children is considered relevant.
5	It would be recommended that the research cited in the guideline (concerns especially section 4 “What are the safety concerns?”) include data on the used benzalkonium chloride concentrations. It would be more informative and provide information to better estimate the risk connected with the use of particular benzalkonium chloride concentration.	Partly agreed. Some further information about durations and concentrations used has been included in section “What are the safety concerns?”. Further information could be found in the Report on Benzalkonium chloride prepared in parallel.
7	The ECI-EEIG appreciates the preparation of common wordings for package leaflets of ophthalmic preparations containing benzalkonium chloride as a preservative. Our members noted that the use of benzalkonium chloride is not questioned and that the currently used concentrations of the preservative are generally acceptable. The proposal for updated information in the package leaflet includes phrases that may not be easily understood by patients. In particular, the text should be phrased in active sentences and some medical terms	Partly agreed. General principles with regard the inclusion of antimicrobial preservatives or antioxidants in a medicinal product is included in CHMP Guideline on Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product. The wordings have been revised to be better understood by patients.

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	translated into layman's language.	
8	Alcon considers that there is insufficient evidence to support inclusion into the excipient guideline concerning ophthalmic products containing BAC of a broad "dry eye" warning statement or a purely hypothetical statement that children might show a stronger reaction. *See specific comments.*	Partly accepted. The information for the PL has been revised and the additional statement included under comments.
9	The information contains in the Package Leaflet should also be implemented in the SPC. *See comments on line 97.*	Not accepted. The issue is covered in the main guideline text and the consistent information should be reflected in SPC and PL.
10	The Medicines Evaluation Board in the Netherlands considers that it should be clear from the revised Guideline on the "Excipients in the label and package leaflet of medicinal products for human use" and its related Questions and Answers that the guideline/Q&As is only intended to provide information to stakeholders on excipients with a relevant safety concern in cases where the acceptability of the excipient in the proposed quantity/concentration has been adequately justified by the company in the MA-dossier i.e. has been found acceptable by the regulatory authorities in view of an overall benefit to risk evaluation of the medicinal product and adequate pharmaceutical development. In order to clearly inform the readers of the guideline/Q&As on this important aspect, this statement should be included at the top of the guideline/Q&As. It is noted that this statement particularly applies to paediatric medicines.	General comment not specifically related to the excipient under discussion. The issue should be solved during the revision of the core guideline.
10	It is not clear whether the Q&A will be a stand alone document or should be read in addition to the current Guideline. In case the Q&A is intended to be a stand alone document, an explanatory note to clarify	General comment not specifically related to the excipient under discussion. The new information in the package leaflet will be implemented stepwise and included in a revised annex of the

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	the structure of the Table in Section 6 should be included. If it is to be read in conjunction with the current Guideline, this should be clearly mentioned.	guideline.
10	Line 96: The table in section 5 is useful to compare the information in the current document with the proposed text. However in the final document the table in section 5 and also the heading of this table may cause confusion. There is a risk that the information in this table will be used instead of the newly proposed information from section 6, especially because the table refers to and is entitled "*current* information in the package leaflet". Therefore, it is advised to delete the table in section 5 in the final document.	Not agreed. The copy of current warnings has been retained in the Q&A document as Annex 1 - Information in the package leaflet as per 2003 Guideline.
10	Line 97: The purpose of the last column of the table included in Section 6 "Comments (for health care professionals)" is not clear. It is not clear when information is to be included in the SmPC, or when the information is included for the benefit of applicant's and competent authorities. Any information considered relevant for health care professionals should be included in the SmPC, and hence reference to the SmPC should be included. It is suggested to replace the last column by two other columns; one for information to be included in the SmPC and a second column for additional comments for the benefit of applicants and competent authorities.	Not accepted. The issue is covered in the main guideline text and the consistent information should be reflected in SPC and PL.
10	In the title of this document and in the title of the guideline is mentioned '…Excipients in the label and package leaflet…'. However also advice regarding the information to be included in the SmPC is given. Therefore, we propose to change "in the label and package leaflet" into 'in the product information'.	General comment not specifically related to the excipient under discussion. Please see the comments above, however widening of the scope of the current guideline should be solved during the revision of the core guideline.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
52	9	**Comment:** It should be specified that studies in rodents were performed using dietary administration (according to EPA document put in reference N°2, see page 115), that do not allow an accurate calculation of the actual dose received. **Proposed change:** Repeated dose oral toxicity studies have shown that 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.	Accepted, text revised.
52-53	9	**Comments:** It is unclear whether the repeated dose oral toxicity studies mentioned are the same that the 90-day chronic toxicity studies mentioned in line 55. **Proposed change:** Repeated dose oral toxicity studies **[indicate duration?]** 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	Partly accepted. Duration is added (within 2 days of dosing). The statement with regard 90-day and chronic studies is in line with the wording of EPA report, hence not corrected.

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		the GI tract. **Lesser concentrations** ~~Results of 90-daychronic toxicity studies have~~ only showed changes in body weight and other general responses.	
64	4	**Comment:** Would be useful to state concentration(s)/doses at which ciliary beat stasis and nasal lesions in rats occurred.	Accepted, text revised.
65	9	**Comment:** Since Benzalkonium Chloride is used in otic formulations, propose to add assessment of potential ototoxicity with reference to publication "Barlow DW, Duckert LG, Kreig CS, Gates GA. Ototoxicity of topical otomicrobial agents. Acta Otolaryngol (Stockh) 1995; 115: 231-235." **Proposed change:** To add before line 65: **"Cochlear and middle ear toxicity of benzalkonium solution was evaluated in juvenile guinea pigs. Juvenile guinea pigs were instilled daily for 7 days with benzalkonium solution into the bullae and sacrificed on the 4th day. Tympanic membranes with 0.05% concentration of benzalkonium solution group were twice as thick compared to those of the 0.026% group (NS significant). Benzalkonium 0.026% showed no evidence of cochlear toxicity, mild middle ear mucosal thickening (similar to**	Partly accepted. Ototoxicity aspects have not been clearly reflected in the Q&A document, but the proposed wording is too detailed and is inserted in the report on BAC. However general statement: Ototoxicity can occur when benzalkonium chloride is applied to the ear is included in the Q&A document with the according reference.

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		normal saline), and mild tympanic membrane thickening. The clinical significance of these changes remains unknown."	
66	4	**Comment:** Propose alternative to 'nor toxic for the reproduction'. **Proposed change:** Available experimental data indicates that benzalkonium chloride is neither genotoxic nor carcinogenic nor ~~toxic for the reproduction~~**a reproductive toxicant**.	Accepted, text revised.
97, column "Comments (for health care professionals)	10	**Comment:** In the excipients guideline it is currently stated that only those excipients that are known to have a recognised action or effect, and that are included in the Commission's guideline, should be declared on the products' labelling. For the excipients that are mentioned in the annex of the guideline, the name should be printed on the product label, including a statement that states: see leaflet for further information. For example: List of excipients: Benzalkonium chloride, see leaflet for further information. However, in a recent Dutch application a parallel imported product, the product was conserved with benzalkonium chloride, while the reference product	Not agreed. BAC may not be the only excipient that needs additional warnings on labelling, hence the issue should be solved during the revision of the core guideline. However this kind of information must not be made obligatory as it may affect the availability of medicines as the text might not fit on the multilingual packages intended for small size markets.

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		contained POLYQUATERNIUM-1 as the preservative. The MEB considered that this difference should be clearly indicated to the user on the product label, as patients that are using the reference products for many years may not read the package label when the product is interchanged with the parallel imported product. If so, they might experience discoloration of soft contact lenses. From the Dutch point of view we would propose that the Q&A clearly indicates that competent authorities may require a more detailed product label because of national substitution practices. **Proposed change, to add:** **Additional warning to be added to the Label (if required):** **Remove contact lenses prior to instillation as Benzalkonium chloride may discolour them.**	
97 Ocular use	6	**Comment:** Current wording could be made more patient friendly. **Proposed change:** /name of product/ contains ~~the preservative~~ **X mg/ml** benzalkonium chloride (**a preservative**~~... mg/ml~~), which may ~~be absorbed by~~**cause eye irritation and may discolour** soft contact lenses~~and~~	Partly agreed. Wording revised to be more patient friendly and warnings on tear film and corneal surface moved to comments section.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~may discolour them~~. ~~Contact lenses should be removed prior to instillation and may be reinserted 15 minutes following administration.~~ **Remove contact lenses prior to application and wait at least 15 minutes before reinsertion.** ~~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.~~	
97 Ocular use	7	**Comment:** While benzalkonium chloride may disrupt the tear film, we would like the agency to reconsider whether the substance causes “dry eyes” on its own. Dry eyes are a multi-factorial disease, which is probably not meant in this context. **Proposed change:** Benzalkonium chloride has been reported to cause eye irritation~~, dry eyes~~ and may affect the corneal surface. **Patients may experience the feeling of dry eyes”**.	Partly accepted. Please see the previous comment.
97	8	**Comment:** While Alcon acknowledges that there is some evidence	Partly agreed.

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Ocular use		supporting that BAC may disrupt the tear film, and that effect could promote evaporative dry eye and tear hyperomolarity, the “dry eye” effect that has been included in CHMP’s proposal has a wider meaning. Dry eye is recognized as a disturbance of the Lacrimal Functional Unit which comprises the lacrimal glands, ocular surface and lids, and sensory and motor nerves. This is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance and tears film instability with potential damage to the ocular surface. **Proposed change:** BAK has been reported to cause eye irritation, ~~dry eyes~~ and may affect the corneal surface **and tear film function.** /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.	Please see the previous comments.
97 Ocular use, column “comments”	8	**Comment:** Alcon respectfully disagrees with the implementation into the guideline of the following warning for HCP: “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	Not agreed. The statement is included in line with Position Paper on Antimicrobial Preservatives in Eye Drops (Human) in the EU. Preservative free formulations should be preferred in children, especially for chronic diseases as the child will potentially be exposed to preservatives for longer period of life than adults. The pharmaceutical companies should be encouraged to develop ophthalmic formulations without preservatives for use

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		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." Alcon bases its comment on the fact that the vast majority of the data are pre-clinical in nature. As mentioned in the Q&A document (EMA/CHMP/495737/2013), consistent evidence of BAC related toxicity did not emerge from a review of dedicated clinical investigations and, specifically, where data are available, no significant difference in the adverse event profile in children compared to adults was found.	in paediatrics.
97 Ocular use, column "comments"	9	**Comment:** For clarity and avoid off label use, the comments for health care professionals concerning children is proposed to be taken into account only if the medicinal product is indicated in children. Add also information for health care professional to be consistent with the proposed statements for the "Information for the Package Leaflet". **Proposed change, to add:** "**As /name of product/ contains the preservative benzalkonium chloride, this may cause eye irritation and is known to discolour soft contact lenses. Avoid contact with soft contact lenses.**	Not accepted. Please see the previous comments. The products may be developed to be used mainly for adults with some restrictions for pediatric population, hence the statement should remain general. The consistency issue is covered in the main guideline text.

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		Therefore, patients must remove contact lenses prior to application of /name of product/ and be instructed to wait 15 minutes after instillation of /name of product/ before inserting contact lenses."	
97 Nasal use	3	**Comment:** We suggest distinguishing two thresholds based on Kuboyama et al., 1997 (cited in Q&A as reference No. 5, line 112): "Rats receiving the lowest concentration, 0.01w/v%, had no light microscopic evidence of BZC-induced lesions in Level 1, 2 or 3 of the nasal cavity. However, rats exposed to 0.05 or 0.10 w/v% BZC had lesions in the anterior nasal cavity (i.e., Level 1 or 2). The BZC-induced lesions were characterized by desquamation, inflammatory cell infiltration and oedema in respiratory epithelium. (…)." **Proposed change:** Nasal use **-** Zero **to 0.01 w/v%** /name of product/ contains the preservative benzalkonium chloride (…mg/ml). May cause irritation ~~and, especially on long term use, oedema~~ of the nasal mucosa.	Not accepted. The preclinical data show that benzalkonium chloride produces not only a concentration dependent but also time depending toxic effects on cilia. So long term use of solutions containing low level of preservative may also cause oedema of nasal mucosa.

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		- Above 0.01 w/v% **/name of product/ contains the preservative benzalkonium chloride (…mg/ml).** **May cause irritation and, especially on long term use, oedema of the nasal mucosa**	
97 Nasal use	6	**Comment:** Current wording could be made more patient friendly. **Proposed change:** /name of product/ contains ~~the preservative~~ **X mg/ml** benzalkonium chloride (**a preservative**~~…mg/ml~~). May cause **eye** irritation and, ~~especially~~ on long term use ~~oedema of the nasal mucosa~~ **swelling of the lining of your nostril**.	Partly agreed. Eye irritation in case of products for nasal use is considered insignificant and general wording for irritation is preferred in order to avoid confusion. Still the information for PL has slightly been changed and additional warning on long term uses included in the comments section.
97 Nasal use	9	**Comment:** Recommended treatment duration for products containing benzalkonium is generally of short duration. **Proposed change:** May cause irritation and, **[**especially on long term use**]**, oedema of the nasal mucosa.	Partly agreed. OTC products are intended for short term use, but the prescription drugs can be used long term and frequently, wording has been slightly changed.
97 Nasal use, column	9	**Comment:** Add also information for health care professional to be consistent with the proposed statements for the	Partly agreed. The consistency issue is covered in the main guideline text and additional warning on long term use is included in the

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"comments"		"Information for the Package Leaflet". **Proposed change, to add:** **As /name of product/ contains the preservative benzalkonium chloride, this may cause irritation and, especially on long term use, oedema of the nasal mucosa.**	comments column.
97 Nebulisation and inhalation use	6	**Comment:** Current wording could be made more patient friendly. **Proposed change:** /name of product/ contains ~~the preservative~~**X mg/ml** benzalkonium chloride (**a preservative**~~... mg/ml~~). May cause **wheezing (**bronchospasm**)** especially in asthmatic patients.	Partly accepted. The term "wheezing" is added and the warning slightly modified, however the proposal to include "preservative" within brackets has no added value.
97 Nebulisation and inhalation use, column "comments"	9	**Comment:** Add also information for health care professional to be consistent with the proposed statements for the "Information for the Package Leaflet". **Proposed change, to add:** **As /name of product/ contains the preservative benzalkonium chloride, this may cause bronchospasm especially in asthmatic patients.**	Not agreed. The consistency issue is covered in the main guideline text.

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97 Cutaneous use	6	**Comment:** Current wording could be made more patient friendly. **Proposed change:** /name of product/ contains ~~the preservative~~ benzalkonium chloride (**a preservative**~~… mg/ml~~), which may cause skin irritation. ~~In order to avoid ingestion by a breast fed child, application to the breasts during lactation is not advised.~~ **To avoid a breastfed child swallowing /name of product/, application to the breasts before breast feeding is not advised.**	Partly agreed. The warning has been rephrased to be more patient friendly.
97 Cutaneous use	9	**Comment:** The propose statement for health care professionals do not make a distinction between benzalkonium chloride and the medicinal product. **Proposed change:** Use during pregnancy and lactation is not expected to be associated with harmful effects as cutaneous absorption **of benzalkonium chloride** is minimal.	Agreed, text revised.
97 Cutaneous use, column	9	**Comment:** Add also information for health care professional to be consistent with the proposed statements for the	Partly agreed. The consistency issue is covered in the main guideline text. The wording for PL has been slightly modified.

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"comments"		"Information for the Package Leaflet" **Proposed change, to add:** **As /name of product/ contains the preservative benzalkonium chloride, this may cause skin irritation.**	
97 Oral, oromucosal, rectal and vaginal use	6	**Comment:** Current wording could be made more patient friendly. **Proposed change:** /name of product/ contains benzalkonium chloride, which may cause ~~mucosal irritation.~~**irritation to the mucous membranes.**	Partly accepted. The wording has been changed from "mucosal irritation" to "local irritation" which is in line with the warnings for other excipients.
97 Oral, oromucosal, rectal and vaginal use	9	**Comment:** Term "Mucosal irritation" could be more friendly. **Proposed change:** /name of product/ contains benzalkonium chloride, which may cause ~~mucosal~~ **local** irritation.	Agreed
97 Oral, oromucosal, rectal and vaginal use, column	9	**Comment:** Add also information for health care professional to be consistent with the proposed statements for the "Information for the Package Leaflet" **Proposed change:** **As /name of product/ contains the preservative**	Not agreed. The consistency issue is covered in the main guideline text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
“comments”		**benzalkonium chloride, this may cause mucosal irritation.**	