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Questions and Answers on Benzyl alcohol 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 benzyl alcohol and why is it used as an excipient?

Benzyl alcohol is an aromatic alcohol with the formula C_7H_8O. In the body, benzyl alcohol is metabolised into benzoic acid.

Benzyl alcohol Benzoic acid

It is used as an excipient for its preservative properties or as a solubilising agent. It is also used as an active ingredient in antiseptic and local anaesthetic products.

[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

3. Which medicinal products contain benzyl alcohol?

Benzyl alcohol is mainly used as an excipient in medicinal products that are administered intramuscularly, such as antibiotics, anti-inflammatory or neuroleptic medicines where its anaesthetic properties reduce pain at the injection site. Benzyl alcohol is also present in medicinal products administered intravenously (anti-cancer drugs, heparins, cardiovascular drugs). Finally, benzyl alcohol is used as a preservative in many topical preparations, such as antifungal and anti-inflammatory products. It is also used as an active ingredient in local antiseptics.

4. What are the safety concerns?

Based on animal toxicity data, the SFC (Scientific Committee on Food) of the European Commission, has reviewed the data on benzyl alcohol in 2002 [1] and has added benzyl alcohol to the ADI group of 0-5 mg/kg bw. This position was based on a previous position given by EPA (the US Environmental Agency) in 1989 [2]. The EPA's review relied on toxicology studies performed by the NTP published in 1989 [3]. Indeed, a subchronic oral reference dose of 1 mg/kg/day for adult was derived based on the NOAEL of 200 mg/kg found in a 13 weeks rat study. A chronic oral reference dose of 0.3 mg/kg/day for adult was derived based on the LOAEL of 200 mg/kg found in a 2 years carcinogenicity study.

There are no animal toxicological data for parenteral or topical use of benzyl alcohol. However, oral absorption is close to 100%, hence recommendations for oral use are considered applicable for other routes of administration. Regarding oral juvenile studies, only one short-term study has been performed in juvenile rats [4], which established a NOAEL of 300 mg/kg/day which is close to the adult. There are no juvenile animal toxicity studies related to long-term use.

The main problem linked to the use of benzyl alcohol concerns newborn babies (pre-term and full-term) due to the immaturity of metabolic enzymes and the risk of accumulation of benzyl alcohol. Benzyl alcohol administered intravenously in the range of 100 to 200 mg/kg/day has been linked to the "gasping syndrome" in several pre-term newborns with metabolic acidosis that resulted in deterioration of the neurological status, cardio-vascular failure and haematological anomalies [5, 6]. This syndrome is associated with the accumulation of benzyl alcohol and the majority of poisonings were fatal.

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

The current recommendations are incomplete and too strict, as they contra-indicate benzyl alcohol for children up to 3 years old. While this excipient should not be used in neonates, it may be used for children aged older than 4 weeks with caution. In addition, the threshold needs to be revised.

The current information for the package leaflet is the following:

71 ***Current information in the package leaflet***

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Benzyl alcohol	Parenteral	Exposures less than 90 mg/kg/day	Must not be given to premature babies or neonates. May cause toxic reactions and allergic reactions in infants and children up to 3 years old.	SPC: 'allergic' should be expressed as 'anaphylactoid' The amount of benzyl alcohol in mg per <volume> should be stated in the package leaflet and SPC.
		90 mg/kg/day	Must not be given to premature babies or neonates. Due to the risk of fatal toxic reactions arising from exposure to benzyl alcohol in excess of 90 mg/kg/day, this product should not be used in infants and children up to 3 years old.	The amount of benzyl alcohol per <volume> should be stated in the package leaflet and SPC.

72 # 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)
Benzyl alcohol	Oral	zero	The amount of benzyl alcohol per each <volume/unit> is xx mg.	The amount of benzyl alcohol in mg per <volume> should be also stated in the SmPC.
			May cause allergic reactions	SmPC: 'allergic' should be expressed as 'anaphylactoid'.
	Parenteral, rectal	Zero	The amount of benzyl alcohol per each <volume/unit> is xx mg.	
			May cause allergic reactions	SmPC: 'allergic' should be expressed as 'anaphylactoid'.
			Should not be used in pre-term or full-term neonates unless strictly necessary because of the risk of severe toxicity including abnormal respiration ("gasping syndrome").	Intravenous administration of benzyl alcohol has been associated with serious adverse events and death in neonates characterized by central nervous system depression, metabolic acidosis, gasping respirations, cardio-vascular failure and haematological anomalies ("gasping syndrome"). Warning in section 4.4 in the SmPC should be given if used in neonates.

Name	Route of Administration	Threshold*	Information for the Package Leaflet	Comments (for health care professionals)
			Talk to your doctor or pharmacist if you have liver or kidney problems or if you are pregnant or breast-feeding as high volumes may lead to toxicity (metabolic perturbation)	The minimum amount of benzyl alcohol at which toxicity may occur is not known. Use only if it is necessary and if there are no alternatives possible. If given in high volumes, should be used with caution and preferably for short term treatment in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis)
	Topical	Zero	The amount of benzyl alcohol per each <volume/unit> is xx mg.	
			May cause allergic reactions.	SmPC: 'allergic' should be expressed as 'anaphylactoid'.
			Should not be used in neonates (pre-term and full-term) unless strictly necessary as benzyl alcohol has been associated with serious adverse events in neonates ("gasping syndrome").	Intravenous administration of benzyl alcohol has been associated with serious adverse events and death in neonates characterized by central nervous system depression, metabolic acidosis, gasping respirations, cardio-vascular failure and haematological anomalies ("gasping syndrome").
			Use with caution and preferably not more than a week in children (more than 4 weeks old), adolescents and adults	
			Mildly irritant to the skin, eyes and mucous membranes.	Cutaneous absorption of benzyl alcohol is significant.

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

1. Opinion of the Scientific Committee on Food on Benzyl alcohol, 2002. Available at: http://ec.europa.eu/food/fs/sc/scf/out138_en.pdf
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