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Questions and Answers on Benzoic acid and Benzoates 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 are benzoic acid and benzoates and why are they used as excipients?

Benzoic acid (and its Na or K salts) is a bacteriostatic antiseptic that is only active in an acidic environment (pH 2.5 to 4.5).

In mammals, benzoic acid is primarily metabolized to its glycine conjugate, hippuric acid, which is readily excreted via the renal organic anion transport system. Moreover, benzoic acid is also found as a metabolite of benzyl alcohol.

Benzoic acid is mainly used as preservative at levels from 0.01 to 0.2% and at levels from 2 to 73% as active principle.

3. Which medicinal products contain benzoic acid or benzoates?

Benzoic acid is rarely used as such in medicines whereas its salts (benzoates) are more commonly used. Sodium benzoate is found as excipients in some medicinal products administered orally, topically

[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

(e.g. antifungals) or injected. Sodium benzoate is also administered intravenously and orally as an active substance to infants and children for the treatment of hyperammonaemia related to urea cycle disorders.

4. What are the safety concerns?

The main safety concern with benzoic acid is its ability to displace bilirubin from albumin. This is of particular concern in pre-term and full-term neonates where immaturity of metabolic enzymes [1] until 8 weeks of age, may result in an accumulation of benzoic acid. Neonatal unconjugated hyperbilirubinemia and resultant clinical jaundice affect up to 85% of newborns, usually this condition is benign. However, the displacement of bilirubin from albumin leads to hyperbilirubinaemia which may cause a serious concern of brain injury in some neonates with jaundice. Thus, acute bilirubin encephalopathy may evolve to kernicterus (bilirubin-induced brain dysfunction) if left untreated. This risk exists with oral, parenteral and also cutaneous preparations, as the cutaneous absorption of benzoic acid is significant, in particular for neonates. Moreover this threat of developing a kernicterus for neonates is also to be considered when benzyl alcohol [2, 3] is used since benzoic acid is one of its metabolites as previously mentioned.

Co-administration of products containing either excipient must be used with caution in paediatrics since both share similar metabolic pathways and may accumulate.

The multigenerational study in rats using dietary administration of benzoic acid, found no effects on birth weight, postnatal growth or survival up to 750 mg/kg bw/day [4]. In the mouse, oral gavage studies with benzyl alcohol, a lowest–observed-adverse-effect level (LOAEL) of 750 mg/kg bw/day for effects on pup weight and a no-observed-adverse-effect level (NOAEL) of 550 mg/kg bw/day were identified [5].

In a dietary study on sodium benzoate, adverse effects on the foetuses and delivered offspring of Wistar rats were seen at very high doses, but a NOAEL of 1310 mg/kg bw/day was identified [6].

NOAELs from gavage administration were slightly lower than those from dietary administration. The exact mechanism of the foetal and offspring toxicity, seen at high doses in some studies, cannot be determined from the data available; it could be secondary to maternal toxicity.

However, identifying the mechanism of toxicity is not critical to the evaluation since there are adequate data to establish an overall NOAEL of 500 mg/kg bw/day.

According to the opinion of the Scientific Committee on Consumer Products (SCCP) in 2005 [7] the acceptable daily intake (ADI) for benzoic acid and its salts has been established to 0-5 mg/kg bw in agreement with the WHO/JECFA report of 1996 [8].

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

The current information for the package leaflet needs to be further expanded regarding the risk to neonates and the route of administration.

81 ***Current information in the package leaflet***

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Benzoic acid and benzoates: **for example:** **E210 benzoic acid** **E211 sodium benzoate** **E212 potassium benzoate**	Topical	Zero	Mildly irritant to the skin, eyes and mucous membranes.	
	Parenteral	Zero	May increase the risk of jaundice in newborn babies.	

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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)
Benzoic acid and benzoates: **for example:** **E210 benzoic acid** **E211 sodium benzoate** **E212 potassium benzoate**	Parenteral, oral	Zero	The amount of <benzoic acid /benzoate salt> per each <volume/unit> is xx mg.	The amount of <benzoic acid /benzoate salt> in mg per <volume> should be also stated in the SmPC.
			May increase jaundice (yellowing of the skin and eyes) in pre-term and full-term jaundiced neonates.	Increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).
	Topical	Zero	The amount of <benzoic acid /benzoate salt> per each <volume/unit> is xx mg.	
			May increase jaundice (yellowing of the skin and eyes) in pre-term and full-term jaundiced neonates because of its absorption through the skin.	Absorption through the immature skin of neonates is significant. Increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).
			May be irritant to the skin, eyes and mucous membranes.	May cause non-immunologic immediate contact reactions by a possible cholinergic mechanism.

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”).

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