



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 October 2017
EMA/CHMP/273718/2014
Committee for Human Medicinal Products (CHMP)

Information for the package leaflet for fragrances containing allergens used as excipients in medicinal products for human use

Draft agreed by Excipients Drafting group	19 April 2016
Adopted by CHMP for release for consultation	28 April 2016
Start of public consultation	4 May 2016
End of consultation (deadline for comments)	3 August 2016
Agreed by Excipients Drafting group	8 November 2016
Adopted by CHMP	15 December 2016
Date of publication	9 October 2017

Keywords	<i>Excipients, Package leaflet, Fragrances, Allergens</i>
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Executive summary

This document has been written in the context of the revision of the Annex of the European Commission Guideline on 'Excipients in the label and package leaflet of medicinal products for human use' [1, 2].

The European Commission (EC) designated 26 fragrances as allergens requiring labelling in cosmetic and detergent products if the concentration of the designated ingredient exceeds 100 parts per million (ppm) for a rinse-off product and 10 ppm for a leave-on product. Some of these allergens are also used in topically applied medicinal products. Hence, it was considered necessary to also request labelling for these 26 fragrances if contained in topically applied medicinal products. However, since topically applied medicinal products may be applied on a more sensitive skin (if damaged), a zero threshold should be applied instead.

It is noted that benzyl alcohol, which is among the 26 fragrance allergens, is also addressed separately in the excipients guideline, and hence, reference is made to the separate document for benzyl alcohol [3].

New information in the package leaflet

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Fragrances containing allergens* (See appendix)	Topical	Zero	This medicine contains fragrance with <allergen(s)>*. <Allergen(s)>* may cause allergic reactions.	* < >: fragrance allergens listed in appendix. In addition to allergic reactions in sensitised patients, non-sensitised patients may become sensitised. Benzyl alcohol is listed as one of the 26 fragrance allergens but can also be used as an excipient. When benzyl alcohol is used as an excipient (in addition to a fragrance or not), the label of this excipient applies.

Scientific background

1. Use in medicinal products

Fragrances are added in order to obtain an acceptable or even pleasant over-all odour to medicinal products in which some active ingredients carry an unpleasant smell, which may hinder its use by the patient.

Fragrances are used as excipients in some topically applied medicinal products, e.g. various approved ointments and creams.

2. Safety concerns

In Germany, approximately 7% of the population experience an acute contact dermatitis within a year and about 15–20% of the population is sensitised to at least one common allergen. With regard to fragrance allergens, in the European population there is an estimated frequency of contact allergy to fragrances of 1–3% [5, 6].

In Regulation 1223/2009 on cosmetic products [Article 19 (1) g in combination with Annex III: labelling of substances of fragrances in cosmetics] [4] and former Directive 76/768/EEC, amended, 26 fragrances are currently designated by the EC as allergens requiring labelling in cosmetic and detergent products if the concentration of the designated ingredient exceeds 100 parts per million (ppm) for a rinse-off product and 10 ppm for a leave-on product. Some of these allergens are also used in medicinal products.

The 26 fragrance allergens if contained in topically applied medicinal products may

- a) Cause severe allergic reactions in sensitised patients. Information of patients before the use of the medicinal product containing these allergens is the adequate prevention.
- b) Sensitise fragrance allergen naïve patients to these allergens (e.g. patients in particular prone to develop sensitisation).

3. Safety information relevant for the package leaflet

Fragrance allergens requiring labelling in cosmetics should also be labelled in the product information of topically applied drug products if contained in these. However, in contrast to cosmetics a zero threshold should be applied since topically applied medicinal products may be used on a more sensitive skin (if damaged). The International Nomenclature of Cosmetic Ingredients (INCI) is also considered to be applicable to medicines.

Inclusion of these allergens in the excipients guideline is therefore proposed as an appropriate approach to solve this issue.

The information on the allergens in the excipients guideline will be ensured by a cross-reference to Annex III of the Regulation 1223/2009 on cosmetic products [4]. Table 1 in the appendix lists all the 26 fragrance allergens designated by the EC and refers to the respective Annex III (items #67 to #92 in annex III).

However, the Annex III reflects the status at the time of the adoption of the Regulation on 30 November 2009. Therefore, the reader should check periodically whether amendments of the Annex III

with regard to the fragrance allergens requiring labelling have been introduced in the meantime since any amendments would then also apply to the excipients guideline.

It is pointed out that benzyl alcohol – although among the 26 fragrance allergens listed in Annex III (i.e. #45) of Regulation 1223/2009 on cosmetic products – is already addressed separately in the excipients guideline and by a specific Q&A, and hence, reference is made to the separate document for benzyl alcohol [3].

1

References – Bibliography

1. Annex of the European Commission guideline 'Excipients in the labelling and package leaflet of medicinal products for human use' (EMA/CHMP/302620/2017).
2. Guideline on excipients in the label and package leaflet of medicinal products for human use (CPMP/463/00 Rev.1). July 2003.
3. Questions and answers on benzyl alcohol used as an excipient in medicinal products for human use (EMA/CHMP/508188/2013).
4. Regulation 1223/2009 on cosmetic products [Article 19 (1) g in combination with Annex III: labelling of substances of fragrances in cosmetics].
5. Schnuch, A. et al., Bundesgesundheitsbl, Vol. 55, 2012, p. 329–37.
6. Scientific Committee on Consumer Safety (SCCS) OPINION on Fragrance allergens in cosmetic products. June 2012.

Appendix

Table 1: European Union List of Fragrance Allergens Requiring Labelling on Cosmetic and Detergent Products [3]

Substance	CAS No
3-Methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-one	127-51-5
Amyl cinnamal	122-40-7
Amylcinnamyl alcohol	101-85-9
Anisyl alcohol	105-13-5
Benzyl alcohol	100-51-6
Benzyl benzoate	120-51-4
Benzyl cinnamate	103-41-3
Benzyl salicylate	118-58-1
Cinnamal	104-55-2
Cinnamyl alcohol	104-54-1
Citral	5392-40-5
Citronellol	106-22-9
Coumarin	91-64-5
d-Limonene	5989-27-5
Eugenol	97-53-0
Farnesol	4602-84-0
Geraniol	106-24-1
Hexyl cinnamaldehyde	101-86-0
Hydroxycitronellal	107-75-5
Hydroxymethylpentyl-cyclohexenecarboxaldehyde	31906-04-4
Isoeugenol	97-54-1
Lilial	80-54-6
Linalool	78-70-6
Methyl heptine carbonate	111-12-6
Oak moss	90028-68-5
Tree moss	90028-67-4