Submission date: 31 May 2019

Submission of comments on Information for the package leaflet regarding lactose used as an excipient in medicinal products for human use (EMA/CHMP/186428/2016)

Comments from:

Name of organisation or individual
EFA - European Federation of Allergy and Airways Diseases Patients' Associations. Submitted by Panagiotis Chaslaridis (info@efanet.org) in coordination with EFA Food Allergy Working Group and EFA Allergy and Asthma Working Group

Please note that comments will be sent to the **ICH M10 EWG** for consideration in the context of Step 3 of the ICH process.

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)
	The European Federation of Allergy and Airways Diseases Patients' Associations (EFA) welcomes the initiative of the European Medicines Agency to revise the European Commission Guideline Annex on 'Excipients in the labelling and package leaflet of medicinal products for human use'. The provisions included in the Draft Paper of this public consultation are in line with EFA's long-standing position in favour of transparent, accurate and safe information about medicines for patients. EMA's revision proposal comes in an appropriate and timely fashion as it suggests to update the Guideline Annex with specific lactose information on the package leaflet relevant to medicines administered through the parenteral and inhaled routes, something that currently only applies to the oral route. We believe allergen/intolerance information should be included in any package leaflet, independently of its use and route of administration, when it poses a risk to patients, and therefore this consultation addresses a crucial element for the intolerance/allergy community of patients, filling the current gap of the Guideline Annex and thereby protecting patients with intolerance who are commonly using inhaled and intravenous-administered medicines as long-term treatments. While EFA welcomes EMA's proposal and not being a scientific organisation, has no comment on the proposed thresholds and the accompanying leaflet information, we believe that several points remain to be addressed, on the basis of the published Draft Paper. Please find these and the proposed changes in the specific comments below.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes
177-358		Comment: The clinical manifestations cited in the sub-sections 4.1 and 4.2 seem to only consider immediate or recognisable reactions (e.g. anaphylactic/respiratory reactions) to medicines containing lactose among patients with diagnosed or undiagnosed intolerance. EFA suggests to also consider **potential long-term or accumulating (in case of multiple medicines) adverse health effects of a lactose-containing medicine**, that in some cases are difficult to detect because of their internal nature. (e.g. eosinophilic esophagitis). Proposed change (if any): Extend the evidence basis with reports and data from cases of cumulative or long-term effects provoking organ inflammation due to allergy to milk, affected by lactose and lactose intolerance.
177-358		Comment: The current text seems to be focusing only on proteins that might be contained in the lactose derived from cow's milk, as the cause of allergic or intolerance reactions. However, according to the Annex VII of the Regulation (EU) 1308/2013, milk refers to the normal mammary secretion obtained from one or more milkings. Accordingly, the European Commission Notice 2017/C 428/01 clarifies the definition of milk in the Annex II of the Regulation (EU) 1169/2011 as the as the product coming 'from the mammary gland of farmed animals'. This means that an updated Guidance should take other milk into account as well, such as **bovine milk** which also contains lactose and is often linked to lactose intolerance. In this context, it would be helpful for clarity in order to differentiate between synthetic lactose and lactose from bovine sources so a risk-based assessment and clinical decisions can be made by the prescribing healthcare professional based upon the patient's allergy or intolerance severity and risks, versus benefits of the medication to their health. Proposed change (if any): In addition to cow's milk, cite also other lactose-containing milk, showcasing the need to take respective action by setting the equivalent thresholds.
221-297		Comment: With regard to inhalers used as a form of preventing and relieving asthma symptoms, in cases where food allergy and asthma co-exist there is an increased risk of more severe allergic reactions with respiratory symptoms due to hypersensitive airways.

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		Proposed change (if any): Consideration should be given to lactose/milk protein content in dry powder inhalers and relevant warnings in the packaged leaflet.
298-321		Comment: As for oral medicines, members of the public in some countries (e.g. the United Kingdom) have made public concerns over the possible effects of symptoms following ingestion of lactose. These concerns are linked with the **limited support and information available on medication containing lactose**, which is causing high levels of anxiety, especially among parents. Proposed change (if any): Where the suggestion is made on packaging to 'talk to your doctor or pharmacist' it should be noted that the advice given will be subject to variance, depending on the clinician's awareness and understanding of food allergy.
426-464		Comment: Although EMA addresses the issue correctly by proposing a threshold of zero for parenteral administration of lactose-containing medicines in milk-allergic patients, EFA thinks that **allergy should be given greater priority** within the section 5 on 'Safety information relevant for the package leaflet'. Prioritisation of cow's milk protein allergy in the safety section is recommended because of the complex nature of this type of food allergy and the possible severe consequences specifically in infants and children where cow's milk allergy has the highest prevalence compared to the adults (1% versus 0,5% in the EU). Furthermore, in light of the increase in the overall number of people allergic to food (including in lactose-containing dairy products), we think that milk allergy should top the list of safety concerns and be supported by stronger statements and scientific data, but this need to **pragmatic and science-based and should in no case lead to unnecessary further restrictions for people with allergy/intolerance while protecting health. This can be done with appropriate, transparent and nuanced package information**. Proposed change (if any): Move the reference to allergy safety concerns up at the beginning of the section, explaining the need for such a revision for patients who are typically using inhaled and parenteral medicines, while also adding elements that highlight the increasing prevalence of the disease, especially among children. Accordingly, make reference to accompanying evidence supporting serious allergic reactions versus mild.
All		Comment: A key point that is not addressed in the draft paper relates to the **impact of new leaflet rules in different countries**. As a result of the different national standards, limits in the content of lactose in medicines may differ considerably

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		across the EU. For example, in some Member States lactose presence in medicines is not understood as a problem among populations of concern, as medicinal products normally contain milk that is pure i.e. protein-free and therefore does not pose a problem and overlabelling can lead to unnecessary restrictions. One such case is Denmark who uses a pragmatic approach, while as we understand from our members, Sweden uses the precautionary principle. In some other cases, patients perceive that not mentioning lactose in the package leaflet constitutes a safety issue, as they think that "cheaper" or "generic" medicines may not be produced with such lactose purity (e.g. Sweden). EFA would wish to see how the EMA addresses the issue of different national standards, and what it expects from a potential harmonisation of limit values. Proposed change (if any):

Please add more rows if needed.