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Questions & answers on propylene glycol and esters 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 Rev.1)

Draft

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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 Rev. 1) [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].

Draft Q&A documents on excipients are progressively released for public consultation. They include proposals for new or updated information for the labelling and package leaflet. The corresponding background report supporting the review is published for information only.

When one or several Q&As have been finalised, the Annex of the guideline is revised, including the new information and a timeframe for implementation.

2. What is propylene glycol and why is it used as an excipient?

Propylene glycol, also referred to as 1,2-propanediol or propane-1,2-diol, is an organic compound (diol or double alcohol) with formula $C_3H_8O_2$. It is a clear, colorless, viscous liquid, hygroscopic and miscible with water.

Propylene glycol is used as humectant, solvent and preservative in a wide range of medicinal products.

Propylene glycol and esters are also used in food products and cosmetics.

3. Which medicinal products contain Propylene glycol?

Propylene glycol is used as a humectant in topicals (15%), as a preservative in solutions (15–30%) or as a co-solvent in aerosols (10–25%), parenterals (10–60%), oral solutions (10–25%) and topicals (5–80%). It is also used as plasticiser in aqueous film-coating formulations.

Examples reported in literature of the use of propylene glycol in medicines on the European market are parenteral products containing lorazepam, diazepam, or etomidate, oral products containing lopinavir/ritonavir or phenytoin, and silver sulfadiazine in topical use.

4. What are the safety concerns?

In toxicological studies after repeat-dose exposure, propylene glycol has a rather low systemic toxicity in experimental adult animals. No treatment-related adverse effects were observed up to the highest doses tested (between 1 to 10 g/kg/day in different species) in repeat-dose toxicity studies and reproduction studies with the exception of inhalation studies where airway irritation is seen at lower doses. Based on the results of safety pharmacology studies, high doses of propylene glycol may cause CNS, hematologic, hyperosmotic, and perhaps cardiovascular effects, as well as lactic acidosis. Information in juvenile animals is limited to one single dose juvenile mouse study [3] showing that propylene glycol produces ethanol-like apoptotic neurodegeneration in the developing central nervous system of the mouse, starting at doses of 2 g/kg.

Clinically, the use of propylene glycol as an excipient in marketed products is generally well tolerated. However, adverse effects have been described in the literature in association with intoxications due to consumer products absorption or medicines containing propylene glycol when administered as a prolonged treatment and/or at very high doses in patients. Various adverse events have been reported such as hyperosmolality, lactic acidosis; renal dysfunction (acute tubular necrosis), acute renal failure; cardiotoxicity (arrhythmia, hypotension); central nervous system (depression, coma, seizures); respiratory depression, dyspnoea; liver dysfunction; haemolytic reaction (intravascular haemolysis) and haemoglobinuria; or multisystem organ dysfunction.

In paediatrics, it was demonstrated that the pharmacokinetic parameters of propylene glycol in neonates [4–6] differ significantly from adult values leading to its accumulation following repeated administration (longer elimination half-life, limited renal and metabolic clearances) or when administered in combination with another substrate of alcohol dehydrogenase (limiting step of metabolism) such as ethanol (e.g. toxicity of some anti-viral treatments in neonates [7]).

The WHO has set a maximum permissible daily intake of propylene glycol as a food additive at 25 mg/kg [8].

Permitted daily exposures (PDE) calculated on the basis of more recent animal data (in line with the note for guidance on impurities: Residual Solvents – ICH, 1998 [9]) were of the same order of magnitude.

Nevertheless, clinical data showed that in children from the age of 5 years and adult patients, up to 500 mg/kg/day of propylene glycol could generally be considered safe. In the absence of compelling data this safety threshold is decreased to 50 mg/kg/day in children less than 5 years old, and even to 1 mg/kg/day in pre-term and term neonates due to known immaturity of both metabolic and renal clearances of propylene glycol in these populations.

Because propylene glycol is susceptible to reach the foetus and found in milk, administration of propylene glycol to pregnant or lactating patients should be considered on a case by case basis.

Minute amounts of propylene glycol giving rise to less than 1 mg/kg/day may enter in the composition of other excipients such as flavours or colouring agents and would not produce any detectable increase in propylene glycol serum concentration. They are not of concern and do not have to be reported.

As there is limited data available on esters of propylene glycol, information on propylene glycol will apply also by default to its esters for the relevant route of administration.

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

The main reasons for updating the information in the package leaflet are to update the thresholds and toxicological profile following a review of the published safety data and to adjust them in relation to different age groups.

Current information in the package leaflet (2003 guideline)

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Propylene glycol and esters	Topical	Zero	May cause skin irritation.	
	Oral Parenteral	400mg/kg: Adults 200mg/kg: Children	May cause alcohol-like symptoms.	

93 # 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)
Propylene glycol	Oral, parenteral, topical	1 mg/kg/day	This product contains XXX [concentration] propylene glycol as an ingredient necessary for the medicine to work properly.	Content to be also in the SmPC to reflect this PL information.
			Talk to your doctor or pharmacist before giving this medicine to your baby if she is less than 4 weeks old.	Co-administration with any substrate of alcohol dehydrogenase such as ethanol may induce serious adverse effects in neonates.
		50 mg/kg/day	This product contains XXX [concentration] propylene glycol as an ingredient necessary for the medicine to work properly.	Various adverse events, sometimes serious, have been reported with high doses or prolonged use of propylene glycol. Adverse events usually reverse following weaning off propylene glycol, and in more severe cases following hemodialysis.
			Because of its content in propylene glycol talk to your doctor or pharmacist before giving this medicine to your child if (s)he is less than 5 years old.	Propylene glycol may be toxic in children less than 5 years old in particular when co-administrated with any substrate of alcohol dehydrogenase such as ethanol.
			If you are pregnant or breastfeeding or if you suffer from a liver or kidney disease, talk to your doctor or pharmacist before taking this medicine because of its content in propylene glycol.	Propylene glycol administration should be monitored with caution in patients with impaired renal or hepatic functions.
	Oral, parenteral	> 500	This product contains XXX [concentration]	Various adverse events, sometimes serious, have

Name	Route of Administration	Threshold*	Information for the Package Leaflet	Comments (for health care professionals)
		mg/kg/day	propylene glycol as an ingredient necessary for the medicine to work properly. Because of the high content (xxx mg/unit) of propylene glycol your doctor needs to supervise the administration of this medicine to prevent adverse effects. Your doctor has considered that the clinical benefit will overcome the risk of those effects.	been reported with high doses or prolonged use of propylene glycol. The clinical benefit that is expected from this medicine has been considered to overcome the risk of those effects. Nevertheless this medicine should be administered together with medical monitoring. Adverse events usually reverse following weaning off propylene glycol, and in more severe cases following hemodialysis.

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95 Note:

96 * The threshold is a value, equal to or above which it is necessary to provide the information stated for the package leaflet. This threshold is not a highest acceptable limit. A
97 threshold of 'zero' means that it is necessary to state the information in all cases where the excipient is present in the medicinal product [1].

References

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7. FDA Drug Safety Communication: Serious health problems seen in premature babies given Kaletra (lopinavir/ritonavir) oral solution http://www.fda.gov/drugs/drugsafety/ucm246002.htm

8. Joint FAO/WHO Expert Committee on Food Additives, 1974.

9. Note for guidance on impurities: Residual Solvents – ICH, 1998.