9 October 2017
EMA/CHMP/157147/2015
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on the draft 'Questions & answers on propylene glycol and esters' (EMA/CHMP/704195/2013)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	CEFIC Propylene Oxide/Propylene Glycol Sector Group
2	IFAPP (International Federation of Associations of Pharmaceutical Physicians & Pharmaceutical Medicine
3	AESGP (representing the manufacturers of non-prescription medicines in Europe)
4	European Formulation Initiative (EuPFI www.eupfi.org)
5	Medicines Evaluation Board in the Netherlands

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	The Revision Guideline EMA/CHMP/704195/2013 2, referred hereafter as the Draft, appropriately describes propylene glycol as a commonly used medicinal excipient with a long history of safe use at the normally encountered doses used in medical applications, and extensive toxicological dataset. Indeed, the available safety data support that propylene glycol is safe at the dose levels proposed in the Draft. However, below we present a number of recommended changes to the Draft for consideration by the Agency for clarification of propylene glycol's safety profile and the adjustments to the maximum safe dose for children less than 5 years of age.	No comments.
1	The Draft departs from previous advice in the following specifications for maximum safe doses: 1) The proposed maximum safe dose for adults and children over the age of five is higher than the previous guidance (500 mg/kg BW/day vs. 400 mg/kg BW/day), and, 2) The previous advice for a maximum dose for children (200 mg/kg BW/day) is proposed in the draft to be lowered and partitioned into two groups: children less than 1 month (1 mg/kg BW/day), and children from 1 month to 5 years of age (50 mg/kg BW/day). We have no comments or concerns on the proposed specific guidance doses for adults and children over the age of 5 years. The 500 mg/kg BW/day dose level is expected to be a safe upper limit for propylene glycol doses in adults and older children based on the available toxicity data: Summary of Acute and Repeat-Dose Toxicology Studies on Propylene Glycol	Acknowledged.

<table>
<tr><th>Stakeholder no.</th><th>General comment (if any)</th><th>Outcome (if applicable)</th></tr>
<tr><td></td><td>with Critical Doses and Effects.
<table>
<tr><th>Endpoint</th><th>Species</th><th>Dose</th><th>Effect</th><th>Reference</th></tr>
<tr><td>Acute toxicity (oral)</td><td>Rats, mice, rabbits, guinea pigs</td><td>22 – 33.5 g/kg BW</td><td>Median lethal dose (LD_{50})</td><td>Summarized in Fowles et al., (2013)</td></tr>
<tr><td>Repeat dose toxicity (oral, 2-year)</td><td>Rats, dogs</td><td>Up to 2.1 g/kg BW/day</td><td>No treatment related effects</td><td>Gaunt et al., (1972); Seidenfeld and Hanzlik (1932); Weil et al., (1971);</td></tr>
<tr><td>Reproductive Developmental</td><td>Mice, Rats, Hamsters, Rabbits</td><td>> 10 g/kg BW/day</td><td>No treatment related effects on reproduction or development</td><td>Morrissey et al., 1989; NTP (2004); Kavlock et al., (1987)</td></tr>
</table></td><td></td></tr>
<tr><td>1</td><td>Given that the previous EMA safe dose guidance level for children was 200 mg/kg BW/day, the magnitude of the proposed change implies that the previous dose level was not sufficiently protective. Cefic is not aware of evidence supporting this proposal, nor is there such evidence presented in the Draft.

For younger children less than 5 years of age, it is appropriate to scale the safe adult propylene glycol doses downward, due to their juvenile, immature hepatic alcohol and aldehyde dehydrogenase (ADH) metabolic systems shortly after birth. However, the magnitude of such a reduction should be based on actual clinical experience and/or non-clinical scientific data. Studies have</td><td>The current Guideline on Excipients [1] effectively requires that the warning: “May cause alcohol-like symptoms” is included in the package leaflet of parenteral and oral drugs containing propylene glycol doses in excess of 400 mg/kg if used in adults and 200 mg/kg if used in children. These thresholds were also advised by the Dutch Medicines Evaluation Board as maximum tolerable daily dosages of propylene glycol in cough medicines [2].

In the absence of actual data, the dose of 200 mg/kg was proposed for children as half of the adult dose.</td></tr>
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	found, for example, that rats are born with 53% of adult hepatic ADH activities, increasing to 82% by post-natal day 47 (NTP, 2004; Fowles et al., 2013). Humans similarly develop ADH slowly from pre-term through the first months after birth (NTP, 2004). ADH levels are reported to be up to 10 times lower in infants which would result in prolonged serum levels (half-life) in infants. Fligner et al. (1985) reported a half-life of 16 hours for a premature infant as compared to 5 hours in adults. Glasgow (1983) measured serum half-life in ten infants finding a range of serum values of 0.65–9.5 g/L [8.55–125mM] and calculated the mean half-life of propylene glycol to be 19.3 hours with a range of 10.8–30.5 hours which is about 10 times longer than in adults. Therefore Cefic recommends that 50 mg/kg BW/day safe dose limit be applied for children from birth to 5 years of age. The low value of 1 mg/kg BW/day is recommended as a guidance value for children from birth to 5 years of age whom are suspected of being co-exposed to other medicines or chemicals involved in ADH metabolic processes. **References** Fligner C L, Jack R, Twiggs G A and Raisys V A. (1985) Hyperosmolality induced by propylene glycol. A complication of silver sulfadiazine therapy. *JAMA*. 253: 1606-1609. Fowles J, Banton M, and Pottenger L. (2013). A toxicological review of the propylene glycols. *Crit. Rev. Toxicol.* 43(4):363-390. Glasgow AM, Boeckx RL, Miller MK, MacDonald MG, August GP and Goodman SI. (1983). Hyperosmolality in small infants due to propylene glycol. Pediatrics. 72: 353-355. MacDonald MG, Getson PR, Glasgow AM, et al. (1987). Propylene glycol: Increased incidence of seizures in low birth weight infants. *Pediatrics*, 79, 622–5.	The safety limits of 50 mg/kg for children between 1 month to 5 years of age and of 1 mg/kg for the children under 1 month of age (or 44 weeks gestational age) are based upon nonclinical and clinical data as laid down in the “draft report on propylene glycol published in support to the propylene glycol Q&A document. [3] For information only”. Rationale has been added in the propylene glycol Q&A document. **References** [1] European Commission (2003). Guideline on the excipients in the label and package leaflet of medicinal products for human use. [2] Van der Laan, J. W., De Waal, E. J. and Peters-Volleberg, G. W. M. (1994). Toxicological evaluation of propylene glycol as solvent in cough medecines. Pharm Weekbl 129(27):687–8. [3] Background review for the excipient propylene glycol (draft report EMA/CHMP/334655/2013, pages 36-38) 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)

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Morrissey RE, Lamb IV , JC, Morris RW, et al. (1989). Results and evaluations of 48 continuous breeding reproduction studies conducted in mice. *Fundam Appl Toxicol*, 13, 747–77. NTP. (2004). Center for the Evaluation of Risks to Human Reproduction (CERHR). NTP-CERHR expert panel report on the reproductive and developmental toxicity of propylene glycol. NIH publication No. 04-4482. March 2004. Seidenfeld MA, Hanzlik PJ. (1932). The general properties, actions and toxicity of propylene glycol. *J Pharmacol Exp Therap*, 44, 109. Weil CS, Woodside MD, Smyth HF, Carpenter CP. (1971). Results of feeding propylene glycol in the diet of dogs for two years. *Food Cosmet Toxicol*, 9, 479–90.	
2	IFAPP fully agrees on the document's contents	No comments.
3	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) the labelling of selected excipients, such as propylene glycol (PG), listed in the Annex of the above mentioned EC guideline will be updated.[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', EMA/CHMP/704195/2013.] On 20 Nov 2014 a proposal for updated information in the package leaflet of propylene glycol containing medicinal products was published (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', EMA/CHMP/704195/2013). The proposed information for the package leaflet – depending on the amount of propylene glycol taken per day – differs significantly from the information given to date. Most importantly, there is no	Justification of the safety limits: see above. Route of administration: Rationale has been added in the propylene glycol Q&A document. The same safety limits are considered for IV and oral route because oral bioavailability is closed to 100%. The same safety limits are proposed for topical administration because propylene glycol does not penetrate intact skin but penetrates well injured skin, to a variable extent difficult to predict depending on the severity of the skin damage (from rash to burns).

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	differentiation between oral/parenteral use and topical administration as in the current version.	
4	EuPFI welcomes the opportunity to provide comments on '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'	Acknowledged.
4	The title of the document states that this is an Q&A on propylene glycol and esters. However neither in the Information for the Package Leaflet nor in the Comments (for health care professionals), does it mention "esters". It only mentions propylene glycol. In the background review it states "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". Should we assume that the same labelling would be used for esters? It would be helpful if it's clarified in the document.	Accepted. Esters have been added to the table. The same labelling should indeed be used.
4	The major concern is on the readability of the proposed labelling wording – it is essential that patients are able to understand the safe use of the medicines and why they should talk to doctor before giving the medicine to their child.	Accepted. We believe the amendments made to the wording address the concern of readability.
4	For topical administration, probably there should be warning stating that the medicines contains propylene glycol which may cause skin irritation and should not be applied to impaired/irritated skin.	Accepted.
4	In general, consistency in the wording in needed.	Accepted.
4	For background information (line 75-79) (line 80-81); reference should be provided, probably the reference to the background review of propylene glycol.	Accepted. Reference has been added.
4	Including an additional column for age population next to the safety limit	Not accepted. The structure should remain as in the annex

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	would be helpful (as in; 1 mg/kg -neonates up to 28 days or 44 weeks post menstrual age for pre-terms; 50mg/kg/day – 1 month (29 days) up to 4 years) would be helpful. If not column, insert the age information below the safety limit.	dated 2003 so that the format of the revised excipients is consistent with the format of the excipients for which the label is not being revised. When necessary the age is mentioned in the text of the label.
5	The Medicines Evaluation Board in the Netherlands considers that it should be clear from the revised Guideline on the "Excipients in the label and package leaflet of medicinal products for human use" and its related Questions and Answers that the guideline/Q&As is only intended to provide information to stakeholders on excipients with a relevant safety concern in cases where the acceptability of the excipient in the proposed quantity/concentration has been adequately justified by the company in the MA-dossier i.e. has been found acceptable by the regulatory authorities in view of an overall benefit to risk evaluation of the medicinal product and adequate pharmaceutical development. In order to clearly inform the readers of the guideline/Q&As on this important aspect, this statement should be included at the top of the guideline/Q&As. It is noted that this statement particularly applies to paediatric medicines.	This is explained in the main text of the Guideline (not in the scope of the Annex).
5	It is not clear whether the Q&A will be a stand-alone document or should be read in addition to the current Guideline. In case the Q&A is intended to be a stand-alone document, an explanatory note to clarify the structure of the Table in Section 6 should be included. If it is to be read in conjunction with the current Guideline, this should be clearly mentioned.	Q&A and reports are documents providing a scientific rationale for the updated information in the PL. Clarification has been added on the webpage (www.ema.europa.eu > Human regulatory > Marketing authorisation > Product information > Reference and guidelines > Excipients labelling).
5	The table in section 5 is useful to compare the information in the current document with the proposed text. However in the final document the table in section 5 may cause confusion. There is a risk that the information in this table will be used instead of the proposed information, especially because the table	Accepted. Title changed into "Information in the package leaflet as per the 2003 Guideline".

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	refers to "*current* information in the package leaflet". Therefore, it is advised to delete the table in section 5 in the final document.	
5	The purpose of the last column of the Table included in Section 6 "Comments (for health care professionals)" is not clear. In some occasions it is mentioned that the information should be stated in the SmPC. However, it is not always mentioned to include the information given in the SmPC. In case reference to SmPC is missing, it is assumed the information given is a general clarification not to be included in the SmPC. However, the heading of the column states "comment (for HCPs)". In our opinion the information given in this column is in several cases relevant for health care professionals, and hence reference to include this information in the SmPC should be included. Furthermore, inclusion of information which is considered relevant for health care providers in the SmPC seems logical. One cannot expect health care professionals to read a Q&A document for additional clarification. It is suggested to replace the last column by two other columns; one for information to be included in the SmPC and a second column for additional comments for the benefit of applicants and competent authorities.	The mention in brackets "(for healthcare professionals)" was removed to avoid confusion. The comments column is intended for applicants and competent authorities as stated in the "explanatory notes" of the main text of the guideline. Regarding references to SmPC, SmPC information should always be consistent in both the package leaflet and the SmPC, as mentioned in the main text of the guideline. whether or not it is specified in the "comments". Suggestions for SmPC wording are there to clarify the safety concerns in medical terms where relevant, whereas the exact wording and in which sections of the SmPC it should be placed is a product specific decision out of scope of this guideline.
5	In the title of this document and in the title of the guideline is mentioned '…Excipients in the label and package leaflet…'. However also advice regarding the information to be included in the SmPC is given. Therefore, we propose to change "in the label and package leaflet" into 'in the product information'.	Rejected. The scope of the guideline, defined in the legislation, is the package leaflet and not the SmPC (see above).
5	As propylene glycol is used in dermal, oral and parenteral products, it is suggested to add a paragraph in which the bioavailability of the different routes of administration is summarised.	Accepted. A sentence has been added in section 4 of the Q&A.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
41-43	5	**Comment:** It is assumed that the percentages refer to the concentration propylene glycol in the products, please confirm. **Proposed change:** Please clarify the text	Yes, the % refers to the concentration in PG. The sentence has been clarified.
50 , 54, and 59	5	**Comment:** The systemic exposure is dependent on the route of administration (oral/ parenteral/dermal). **Proposed change:** Please add route of administration (oral/ parenteral/ dermal).	Accepted. Oral route has been added. More details can be found in the report.
53	1	**Comments:** The Draft should make clear that these adverse events are secondary phenomena to the overload effect caused by extreme doses. Rationale: The adverse effects discussed in the Draft only occur at very high doses that can cause blood osmolality changes, with numerous downstream systemic sequelae and are not achievable by the proposed dose levels. These downstream events can involve various organ systems, including the kidney, liver, haematological system, and the central nervous system (CNS),	Change not accepted. It is written that this occurs at high doses. These effects may be reached at lower doses for example in children with immature metabolic/renal clearance.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		none of which represent toxicological target organs *per se*. These effects are essentially the result of a perturbed homeostasis from the high doses of propylene glycol and should be presented as such in the Draft. **Proposed change:** Add the following sentence: *"These adverse effects are secondary phenomena to the overload effect caused by very high doses of propylene glycol".*	
57	1	**Comments:** There are no confirmed human fatalities at any age from propylene glycol toxicity Rationale: Despite the many human exposures to high doses of propylene glycol, there are no confirmed human fatalities at any age from propylene glycol toxicity (Fowles et al., 2013). **Proposed change:** Add the following sentence: *"There are no confirmed human fatalities at any age from propylene glycol toxicity."*	Not accepted. Death and severe toxicities were described in children (see NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Propylene Glycol (May 2003).
59	5	**Comment:** The sentence is unclear: do you mean intoxications due to absorption of propylene glycol after oral intake of consumer products or medicines containing propylene glycol? **Proposed change:** Please rephrase.	Not accepted. The text clearly highlights it is in both cases.

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60-64	5	**Comment:** It is assumed that the mentioned adverse events were attributed to propylene glycol, please confirm. If the adverse events are probably the result of higher bioavailability of the active substance, due to the presence of propylene glycol in the formulation, this should also be clearly mentioned. **Proposed change:** Please clarify and rephrase.	
70	5	**Comment:** Do you have any information on the parenteral or dermal routes of administration? **Proposed change:** Please add if this information is available.	A text has been added explaining the bioavailability/exposure through different routes of administration. More detail are available in the report.
80, 81	1	**Comments:** Recommend adding a statement prior to line 80, page 3 of the draft, to indicate that propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans. Current text: *"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."* Rationale: The Draft recommends case-by-case evaluations of the use of propylene glycol for patients in pregnancy or in	Accepted. The text was rephrased as follows: "While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it is susceptible to reach the foetus and was found in milk. As a consequence administration of propylene glycol to pregnant or lactating patients should be considered on a case by case basis."

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		lactation scenarios. However, the available non-clinical data, including 6 teratology studies and 1 two-generation reproduction study, demonstrate that propylene glycol is not toxic via lactation or *in utero*. Cefic has conducted appropriate literature reviews and is not aware of human epidemiology data nor case reports suggesting that propylene glycol has been associated with any adverse development outcomes. The propylene glycol dataset was reviewed by the National Toxicology Program in 2004, and found it not to constitute a reproductive hazard (NTP, 2004). **Proposed change:** ~~*Because p*~~***P****ropylene glycol* ~~*is susceptible to*~~***can*** *reach the foetus and* ***can be*** *found in milk*~~.~~***.*** ***However,*** ~~*administration of propylene glycol*~~ ***has not been shown to cause reproductive or developmental toxicity in animals or humans.*** ~~*to pregnant or lactating patients should be considered on a case by case basis.*~~	
93-94	5	**Comment:** In the 'proposal for an updated information on the package leaflet' table (section 6 of the Q&A), three routes of administration are considered, oral, parenteral and topical which are treated the same for the 1 mg and 50 mg/kg/day thresholds. In the text in section 4 on the safety concerns, no differentiation is made between the different routes of administration. It would be helpful if in section 4 it is explained why the same thresholds are applied for the different routes. Is e.g. the exposure the same (especially for the topical route) and are the same safety	Accepted. Clarification was added to the text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		issues applicable for all three routes? **Proposed change:** Please mention in the text if the exposure and the safety issues are the same for all three routes of administration.	
93-94	1	**Comments:** Recommend that 50 mg/kg BW/day safe dose limit be applied for children from birth to 5 years of age. The low value of 1 mg/kg BW/day is recommended as guidance value for children from birth to 5 years of age whom are suspected of being co-exposed to other medicines or chemicals involved in ADH metabolic processes. Current text: *"Talk to your doctor or pharmacist before giving this medicine to your baby if she is less than 4 weeks old."* Rationale: The available clinical and analytical data indicate that a maximum safe dosage level 10 fold lower than adults should be protective to infants. The proposed new 500-fold safety factor for exposures to infants less than 1 month old, would constitute an overabundance of precaution, rather than representing a margin of safety based on specific findings. MacDonald et al., (1987) reported an increase in seizures (likely a high dose, hyperosmolality effect) in infants receiving propylene glycol as a carrier vehicle for intravenous vitamins, when propylene glycol i.v. doses were 3 g/day, compared to infants receiving 300 mg/day. A dose of 300 mg/day translates into 100 mg/kg BW/day for an infant of 3 kg. Thus, clinical evidence would tend	Not accepted. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		to support a safe dose of greater than two orders of magnitude more than the proposed 1 mg/kg BW/day limit for infants who are not co-exposed to other chemicals requiring ADH metabolism. **Proposed change:** Talk to your doctor or pharmacist before giving this medicine to your baby if **(**s**)**he **is currently taking other medications and** is less than ~~4 weeks~~**5 years** old.	
93	1	**Proposed change:** If your **child** ~~are pregnant or breastfeeding or if you~~ suffer**s** from a liver or kidney disease, talk to your doctor or pharmacist before ~~taking~~**administering** this medicine because of its content in propylene glycol.	Not accepted. See final text.
93	1	**Proposed change:** The clinical benefit that is expected from this medicine has been considered to ~~overcome~~**outweigh** the risk of those effects.	See change in final wording.
93	1	**Comments:** Based on comments presented, the table with updated information for the package leaflet is proposed to be revised as follows (italics show proposed changes in pertinent table columns):	Not accepted. DD metabolic interaction potential is specifically high during the first weeks of age because GFR is particularly low at birth but increases rapidly after birth: “Due to haemodynamic changes during and just after birth, GFR increases rapidly in the first two weeks of life. Afterwards, GFR corrected for body surface area (BSA) increases more slowly to reach adult levels between 1 to 2 years of age.” (Guideline on the Investigation of Medicinal Products in the Term and Preterm Neonate -

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		1 mg/kg /day	This product contains XXX [concentration] propylene glycol as an ingredient necessary for the medicine to work properly. *This dose is expected to be safe for 5 years old or younger that are taking other medications. However, talk to your doctor or pharmacist before giving this medicine to your child if (s)he is currently taking other medications and is less than 5 years old.*	Content to be also in the SmPC to reflect this PL information. Co-administration with any substrate of alcohol dehydrogenase such as ethanol may induce serious adverse effects in neonates.	EMEA/536810/2008)
		50 mg/kg /day	This product contains XXX [concentration] propylene glycol as an ingredient necessary for the medicine to work properly. *Propylene glycol is expected to be safe for children under 5 years of age at this dose.* *If a child suffers from a liver or kidney disease, talk to your doctor or pharmacist before administering this medicine because of its content in propylene*	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. Propylene glycol administration should be monitored with caution in patients with impaired renal or hepatic functions.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		<table><tr><td></td><td>*glycol.*</td><td></td></tr><tr><td>500 mg/kg /day</td><td>This product contains XXX [concentration] 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 *outweigh* the risk of those effects.</td><td>Various adverse events, sometimes serious, have been reported with high doses or prolonged use of propylene glycol. *The clinical benefit that is expected from this medicine has been considered to outweigh 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.</td></tr></table>	
93-94 **Topical products**	3	**Comments:** While the need for revision of the excipient warnings is acknowledged and the scientific effort of the members of the working group who compiled the excellent background review is highly appreciated, we nevertheless disagree with the conclusions drawn for topical products. Propylene glycol (PG) is a highly water soluble substance and penetration through the intact skin is therefore expected to be very limited. Both an *in vitro* study in rats and one study of human skin biopsy specimens from adults showed no uptake of	

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		PG from intact skin. Therefore, the dermal absorption rate across dermal skin is likely to be slow.[NTP-CERHR Monograph on the potential human reproductive and developemental effects of propylene glycol.] However, when the stratum corneum is impaired PG might cross the skin barrier in larger amounts. Transdermal absorption of PG from topical preparations applied to patients with burns and the associated signs and symptoms of PG toxicity have been reported in some studies.[Bekeris L, Baker C, Fenton J, Kimball D, Bermes E. Propylene glycol as a cause of an elevated serum osmolality. Am J Clin Pathol 1979; 72: 633-636.; Fligner CL, Jack R, Twiggs GA, Raisys VA. Hyperosmolality induced by propylene glycol. A complication of silver sulfadiazine therapy. JAMA 1985; 253: 1606-1609; Kulick MI, Wong R, Okarma TB, Falces E, Berkowitz RL. Prospective study of side effects associated with the use of silver sulfadiazine in severely burned patients. Ann Plast Surg 1985; 14: 407-419] Eklund *et al*. have shown that an increased total surface area affected by severe burns may be a reason for PG leaking into the systemic circulation.[Eklund J. Studies on renal function in burns. 3. Hyperosmolal states in burned patients related to renal osmolal regulation. Acta Chir Scand 1970; 136: 741-751.] Kulick *et al.,* when evaluating a population consisting mainly of adult burn patients, made the observation that PG levels causing hyperosmolality only seem to occur in patients with total burn surface area (TBSA) above 35 %.[Kulick MI, Lewis NS, Bansal V, Warpeha R. Hyperosmolality in the burn patient: analysis of an osmolal discrepancy. J Trauma 1980; 20: 223-228.] This apparent threshold of TBSA > 35 % was also confirmed in other	

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		observations.[Bekeris L, Baker C, Fenton J, Kimball D, Bermes E. Propylene glycol as a cause of an elevated serum osmolality. Am J Clin Pathol 1979; 72: 633-636.; Fligner CL, Jack R, Twiggs GA, Raisys VA. Hyperosmolality induced by propylene glycol. A complication of silver sulfadiazine therapy. JAMA 1985; 253: 1606-1609] These studies were conducted in patients treated with silver sulfadiazine which is only indicated in burns of second and third degree [Willis MS, Cairns BA, Purdy A, Bortsov AV, Jones SW, Ortiz-Pujols SM, Schade Willis TM, Joyner BL. Persistent lactic acidosis after chronic topical application of silver sulfadiazine in a pediatric burn patient: a review of the literature. Int J Burn Trauma 2013;3(1):1-8.] where the skin barrier is severely damaged. However, it is acknowledged that the apparent threshold of TBSA > 35 % has not yet been confirmed in paediatric patients and especially premature babies might be more sensitive to PG toxicity, as discussed by Willis *et al*.[Willis MS, Cairns BA, Purdy A, Bortsov AV, Jones SW, Ortiz-Pujols SM, Schade Willis TM, Joyner BL. Persistent lactic acidosis after chronic topical application of silver sulfadiazine in a pediatric burn patient: a review of the literature. Int J Burn Trauma 2013;3(1):1-8.] Besides the area of damaged skin and the degree of skin barrier disruption, also vasodilatation and the inability to oxidize PG or excrete PG via the kidneys might play a role in the described cases of PG toxicity.[Commens CA. Topical propylene glycol and hyperosmolality. Br J Dermatol. 1990 Jan;122(1):77-80.] It has to be taken into consideration that silver sulfadiazine has been used in high quantities for the adjunctive treatment of burns in the studies cited above, which are not representative	

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		for other topical treatments. In a case series of 45 burn patients, the average amount was 800 g of cream per leg, 400 g per arm and 1200 g for the trunk, applied 2 to 3 times per day.[Kulick MI, Wong R, Okarma TB, Falces E, Berkowitz RL. Prospective study of side effects associated with the use of silver sulfadiazine in severely burned patients. Ann Plast Surg 1985; 14: 407-419.] Because, so far, uptake of larger amounts of PG was nearly exclusively described in patients with large burned areas (TBSA > 35 %) treated with silver sulfadiazine, the proposed labelling information for PG seems inappropriate for the dermal administration in patients with skin diseases in general. This is underlined by a study in which patients suffering from psoriasis and scaling disorders were treated with a PG containing cream (1.5-6.1 g propylene glycol/ kg body weight/ 24 h for 5 days). Serum osmolality and lactate levels did not change after the PG exposure, nor did a significant osmolality gap develop between measured and calculated osmolality. Serum electrolyte levels showed that an anion gap had not developed.[Commens CA. Topical propylene glycol and hyperosmolality. Br J Dermatol. 1990 Jan;122(1):77-80.] Hence using the same labelling information for the dermal application of PG containing medicinal products seems inappropriate, with the exception of topical treatment used on intensively damaged skin, i.e. burned skin. Furthermore, inappropriate labelling (warnings) might even harm patients as exaggerated information on adverse effects can lead to a new and worsening symptoms caused only by negative expectations, anticipations and anxiety (nocebo response).[Colloca L, Miller FG. The nocebo effect and its relevance for clinical practice. Psychoyom Med. 2011; 73(7):	

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		598-603.; Häuser W, Hansen E, Enck P. Nocebo phenomena in medicine: their relevance in everyday clinical practice. Dtsch Arztebl Int 2012; 109(26): 459-65.; Wells RE. To Tell the Truth, the Whole Truth, May Do Patients Harm: The Problem of the Nocebo Effect for Informed Consent. Am J Bioeth 2012; 12(3): 22-29.] Reviews show that nocebo effects have been observed in various medicinal treatments.[Colloca L, Miller FG. The nocebo effect and its relevance for clinical practice. Psychoyom Med. 2011; 73(7): 598-603.; Häuser W, Hansen E, Enck P. Nocebo phenomena in medicine: their relevance in everyday clinical practice. Dtsch Arztebl Int 2012; 109(26): 459-65.] In all these cases the information provided changed the adverse effect profile. Nocebo effect might result in psychological distress, significant excess costs because of increased medication non-adherence, extra-treatment visits and even additional medicines prescribed to treat the nocebo effects.[Barsky AJ, Saintfort R, Rogers MP, Borus JF. Nonspecific medication side effects and the nocebo phenomenon. Journal of American Medical Association. 2002; 287(5):622–7.] Against this background, inappropriate warnings should be avoided. It should be noted that PG is used as an excipient in topical preparations for the treatment of diseases like head lice infections which are usually not associated with a relevant skin barrier dysfunction. The proposed common thresholds for oral, parenteral and topical products are also considered questionable, since it is often difficult to calculate a daily dose of topical preparations due to the varying area of application and amount of product applied to the skin.	

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		Proposed change: Topically administered medicinal products should not be labelled with the same warnings as oral and parenteral medicinal products as uptake of clinically relevant amounts of PG is not likely to occur in patients with skin diseases except those with severely burned skin. Consequently the following proposals are made which should be evaluated as alternatives: Insert the following footnote: The warning statements for topical products are only required for products likely to be applied in conditions where absorption of large quantities of PG is possible, e. g. in patients with open wounds and large areas of burned skin. OR: Route of administration: Topical Threshold: Zero Propylene glycol administration should be monitored with caution in neonates and in conditions where absorption of large quantities of propylene glycol is possible, e. g. in patients with open wounds and large areas of burned skin.	Accepted. A paragraph on dose selection and routes of administration has been added in the text, and a clarification in the table.
93-94 **Paediatric age groups**	3	**Comments:** Whilst we agree that caution is necessary especially in risk patient groups like newborns and little children (particularly if data are scarse), currently the proposed new thresholds for propylene glycol are very conservative for these age groups. This unnecessarily puts at risks some existing paediatric	Not accepted. While it is agreed that the “limits” are conservative for children below 5y of age because of the scarcity of data the following considerations are not in favour of changes: - The proposed limits indicate that special cautious has to be applied, not that higher doses are necessarily toxic.

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		medicines with a well-known safety record. The new thresholds are based on a wide margin of safety due to scarse data and are not based on current proved safety concerns or new data. According to the impurity guideline (IMPURITIES: GUIDELINE FOR RESIDUAL SOLVENTS Q3C (R5)) used for the new calculation of thresholds the solvent propylene glycol was classified as class III residual solvent with low toxicity. The calculation used for the revision of the excipients guideline was only for class II residual solvents with higher toxic effects. The safety margin that is calculated according to class II residual solvents is not applicable for propylene glycol and these low thresholds cannot be justified with this calculation. Furthermore in accordance with this guideline these limits are intended for medicinal products for application duration of more than 30 days and in normal cases not for medicinal product intended for short term use, such as non-prescription medicines which are commonly approved for short-term use. For this reason the duration of treatment needs to be taken into account in the excipients guideline. Non-prescription medicines and medicines indicated for a short term use should be exempted from warnings of the lower thresholds. According to the calculation for class III residual solvents of the above mentioned guideline the very restrictive threshold for newborns of less than 4 weeks includes a risk factor for the short duration of the animal studies. However the duration normally taken into account does not correspond with the juvenile age of a maximum of three weeks (calculation according to background paper of question and answer for propylene glycol). If the	If there is a leaflet, it means that the risk/benefit has been considered positive for the drug product based upon actual data. - For this reason there is no reason to revisit the products on the market, unless new data. Of note it is not obvious that side effects attributable to propylene glycol would always have been detected particularly in severely ill very young patients. - The limit of 25mg/kg is not based upon paediatric data for very young children (less than 4 weeks). - There are new data (even if scare). - There are no data in children discussing the impact of duration of treatment.

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		duration factor is not applied this would lead to a threshold of 10 mg/kg/day. Furthermore as already mentioned above this calculation should not be applicable for propylene glycol as it was already exempted in the guideline. In accordance with the WHO recommendation for the amount of acceptable daily intake for propylene glycol 25 mg/kg/day **is deemed safe considering an everyday intake through the whole lifetime.** Furthermore, clinical data in newborns as cited in the background paper by the EMA did not show any adverse effects in even higher dosages. Glasgow et al. studied a dosage of 3 g/day in children weighing 1 kg up to 4.5 kg. MacDonald et al. studied dosages of 300 mg and 3 g propylene glycol per day which only resulted in a higher incidence of seizures in the highest dose. Allegaert et al. describe dosages of 14-252 mg/kg/day without any biochemical deviations. For this reason, due to missing data about new risks corresponding to such a low dose as recommended for a new threshold of propylene glycol in neonates this threshold should be reconsidered. We recommend 25 mg/kg/day as the lowest threshold. There is no concern that would question the daily safe intake recommendation by the WHO. For this reason an adaptation to the WHO recommendation for the lowest threshold is rational. **Proposed changes:** The low thresholds should be reassessed because the applied guideline does not justify the calculation for propylene glycol. Insert the following note for the lower thresholds calculated by the above mentioned impurity guideline:	

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		"The warning statements for oral products are not required for products that are intended for a treatment not longer than 28 days."	
93-94	4	Comments: The sentence "Content to be also in the SmPC to reflect this PL information" under the comments for healthcare professionals does not read right. Probably the word "mentioned" is missing Proposed change: Content to be also **mentioned** in the SmPC to reflect this PL information.	For consistency with the PL, the amount should also appear in the SmPC. Therefore the sentence is unnecessary and has been removed.
93-94	4	**Comments:** Talk to your doctor or pharmacist before giving this medicine to your baby if she is less than 4 weeks old. A bracket is missing **Proposed change:** Talk to your doctor or pharmacist before giving this medicine to your baby if **(**s**)**he is less than 4 weeks old	Accepted.
93-94	5	**Proposed change:** "she" should be changed into '(s)he'.	Accepted.
93-94	4	**Comments:** The sentence "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" under information for	Agreed. This expression is not anymore in the final text.

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		package leaflet does not read right. Also the patient should be able to understand why to talk to doctor. It's not only that because it contains propylene glycol but because it may cause serious side effects. The patients probably may not know what propylene glycol is and what it does? **Proposed change:** ~~Because of its content in~~ **As the medicine contains** propylene glycol **which may cause serious side effects** talk to your doctor or pharmacist before giving this medicine to your child if (s)he is less than 5 years old.	
93-94	4	**Comment:** The sentence "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" also does not read right. **Proposed change:** 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 **which may cause serious side effects**.	See above
	4	**Comments:** In sentence "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", the word toxic is too harsh. May be worth considering to replacing it by	Partially accepted. See change in final text.

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		serious side effects/adverse effects. To be consistent, the same wordings as used in the other sentence for neonates could be used; “Co-administration with any substrate of alcohol dehydrogenase such as ethanol may induce serious adverse effects in neonates” **Proposed change:** **Co-administration with any substrate of alcohol dehydrogenase such as ethanol may induce serious adverse effects, particularly** ~~Propylene glycol may be toxic~~ in children less than 5 years old.	
	4	**Comment:** The sentence “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” is bit complicated and long. For consistency with other wordings we propose “This medicine contains high amount of Propylene glycol which may cause adverse/side effects. Talk to your doctor before the administration of this medicine.” **Proposed change:** ~~Because of the high content (xxx mg/unit)~~ **This medicine contains high amount** of propylene glycol **which may cause adverse/side effects. Talk to** your doctor ~~needs to supervise the administration of this medicine to prevent adverse effects. Your doctor has considered that the clinical benefit will overcome~~	Partly accepted. See final text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~the risk of those effects~~.	
93-94	5	**Comment:** At the end of the table is mentioned: “The threshold is a value, equal to or above which it is necessary to provide information stated for the package leaflet.” Therefore, it is not necessary to mention “>” before “500”in the third column. **Proposed change:** Delete “>”.	Agreed. The footnote has been removed as the meaning of the threshold is defined in the explanatory notes of the main Guideline.