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# Questions and answers on propylene glycol used as an excipient in medicinal products for human use

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This document should be read in the context of the revision of the Annex of the European Commission guideline 'Excipients in the labelling and package leaflet of medicinal products for human use' (EMA/CHMP/302620/2017) [2].

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# Questions and answers on propylene glycol used as an excipient in medicinal products for human use

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# 1. 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 an excipient for different purposes and at different concentrations (in % hereafter)

- 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 or as solvent in medicinal e-cigarettes.

# 2. Which medicinal products contain propylene glycol?

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,
- topical products such as silver sulfadiazine, and
- inhaled medicines such as e-cigarettes containing nicotine.

# 3. What are the safety concerns?

In toxicological studies after long-term repeat-dose exposure (mainly by oral route), propylene glycol had a rather low systemic toxicity in experimental adult animals at up to 1 to 3g/kg/day. Airway irritation has been seen at lower doses in inhalation studies. At very high doses (8-40 g/kg orally) in short-term studies in rodents, propylene glycol caused CNS, hematologic/hyperosmotic, and perhaps cardiovascular effects, as well as lactic acidosis. Animals lethally intoxicated undergo CNS depression, narcosis, and eventual respiratory arrest. No treatment-related adverse effects were observed up to the highest doses tested (10 g/kg/day) in reproduction toxicity studies. Information in juvenile animals is limited to one single dose juvenile mouse study [10] 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 attributed to propylene glycol 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 hemolysis) and haemoglobinuria; or multisystem organ dysfunction.

In paediatrics, it was demonstrated that the pharmacokinetic parameters of propylene glycol in neonates [4, 5, 9] 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 [6]).

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 [11]) 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 [12].

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 [12].

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.

Esters of propylene glycol (mainly used topically) have not been the subject of a systematic review in the context of this update. Because esters of propylene glycol are broken down into propylene glycol and fatty acids once absorbed in the body, their safety can be based on the content of propylene glycol itself and the same labelling applies [8].

## 4. 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.

Based upon recent data the following safety thresholds have been established:

*Adult patients and children ≥ 5 years of age:*

Papers from Yaucher et al. [16] and Yahwak et al. [15] indicate that doses up to 500 mg of propylene glycol/kg/day could be administered safely to adult patients and children ≥ 5 years of age even for long term periods.

*Children ≥ 1 month and < 5 years of age:*

In children below 5 years down to 1 month of age a dose limit of 50 mg/kg is being proposed based upon the following data:

- Allegaert et al. [1] demonstrated that no short term biochemical impact was detected in neonates during or following a median propylene glycol exposure of 34 mg/kg/24hr (range 14–252). Exposure to propylene glycol seemed well tolerated and did not affect normal postnatal maturational changes in renal, metabolic and hepatic functions.
- The human equivalent dose to the NOAEL of 1000mg/kg in the juvenile mouse [10] was calculated to be 192 mg/kg for a neonate (3.5 kg), 150 mg/kg for a 1-year-old child (9 kg), and 126 mg/kg for a 4-year-old child (15 kg). The proposed dose limit of 50 mg/kg is still 2.5 times lower.
- Model-based simulated concentration-time profiles of propylene glycol in a term neonate (birth weight 3.5 kg) following the administration of 34 mg propylene glycol/kg/day in paracetamol, did not show accumulation (no increase in propylene serum concentration following repeated administration). Therefore the risk of accumulation may be considered limited above the age of 1 month in children administered 50 mg propylene glycol/kg with non-impaired liver and/or renal functions. This is confirmed by data from Chicella et al. [3].

In the absence of additional safety data this threshold is applied to all children below 5 years of age, except neonates.

*Children below 1 month of age*:

In (pre)term neonates De Cock et al. [4] have demonstrated that total body clearance is very low compare to the adult clearance [17], but also that the contribution of renal clearance to the total body clearance is very low. The results of this study [5] may indicate that due to maturational changes, some drug/drug metabolic interactions are more relevant for this specific population. This may explain the toxicities observed in neonates given Kaletra® which contains 356.3 mg ethanol/ml and 152.7 mg propylene glycol/ml.

Considering also the data produced by Shehab [13] and Whittaker [14] showing the multiple sources of propylene glycol and ethanol in neonatalogy units, it is proposed to restrict the safety limit to 1 mg/kg in preterm neonates, or below one month post-natal age for term neonates.

***Routes of administration:*** The same safety limits are considered for the IV and oral routes of administration because the oral bioavailability is closed to 100%. The same safety limits are proposed for topical administration (which includes inhalation). For cutaneous administration, propylene glycol does not penetrate intact skin but well injured skin, to a variable extent difficult to predict depending on the severity of the skin damage (from rash to burns).

## 5. Proposal for updated information in the package leaflet

| Name | Route of Administration | Threshold | Information for the Package Leaflet | Comments |
|---|---|---|---|---|
| **Propylene glycol and esters of propylene glycol** | All routes of administration | 1 mg/kg/day | This medicine contains x mg propylene glycol in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>. | |
| | Oral, parenteral | 1 mg/kg/day | If your baby is less than 4 weeks old, talk to your doctor or pharmacist before giving them this medicine, in particular if the baby is given other medicines that contain propylene glycol or alcohol. | Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce serious adverse effects in neonates. |
| | | 50 mg/kg/day | If your child is less than 5 years old, talk to your doctor or pharmacist before giving them this medicine, in particular if they use other medicines that contain propylene glycol or alcohol. | Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce adverse effects in children less than 5 years old. |
| | | | If you are pregnant or breast-feeding, do not take this medicine unless recommended by your doctor. Your doctor may carry out extra checks while you are taking this medicine. | While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may 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. |
| | | | If you suffer from a liver or kidney disease, do not take this medicine unless recommended by your doctor. Your doctor may carry out extra checks while you are | Medical monitoring is required in patients with impaired renal or hepatic functions because various adverse events attributed to propylene glycol have been reported such as renal |

| Name | Route of Administration | Threshold | Information for the Package Leaflet | Comments |
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| | | | taking this medicine. | dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction. |
| | | 500 mg/kg/day | Propylene glycol in this medicine can have the same effects as drinking alcohol and increase the likelihood of side effects.<br><br>Do not use this medicine in children less than 5 years old.<br><br>Use this medicine only if recommended by a doctor. Your doctor may carry out extra checks while you are taking this medicine. | Various adverse events, such as hyperosmolality, lactic acidosis; renal dysfunction (acute tubular necrosis), acute renal failure; cardiotoxicity (arrhythmia, hypotension); central nervous system disorders (depression, coma, seizures); respiratory depression, dyspnoea; liver dysfunction; haemolytic reaction (intravascular haemolysis) and haemoglobinuria; or multisystem organ dysfunction, have been reported with high doses or prolonged use of propylene glycol.<br><br>Therefore doses higher than 500 mg/kg/day may be administered in children > 5 years old but will have to be considered case by case.<br><br>Adverse events usually reverse following weaning off of propylene glycol, and in more severe cases following hemodialysis.<br><br>Medical monitoring is required. |
| | Cutaneous | 50 mg/kg/day | Propylene glycol may cause skin irritation.<br><br>Do not use this medicine in babies less than 4 weeks old with open wounds or large areas of broken or damaged skin (such as burns) without talking to your doctor or pharmacist. | |

| Name | Route of Administration | Threshold | Information for the Package Leaflet | Comments |
|---|---|---|---|---|
| | | 500 mg/kg/day | Propylene glycol may cause skin irritation.<br><br>Because this medicine contains propylene glycol, do not use it on open wounds or large areas of broken or damaged skin (such as burns) without checking with your doctor or pharmacist. | |

Further scientific background is available in the report entitled ‘Propylene glycol used as an excipient’ [12].

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## Annex 1 - Information in the package leaflet as per 2003 Guideline [7]

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