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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Propylene glycol in medicinal products for children

International non-proprietary name: PROPYLENE GLYCOL

Article 5(3) of Regulation (EC) No 726/2004

Procedure No. EMEA/H/A-5(3)/1317

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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1. Background information on the procedure

On 9 September 2011, the Paediatric Committee (PDCO) brought to the attention of the Agency an issue regarding formulations containing propylene glycol in medicines for children.

This issue followed a Paediatric Investigation Plan (PIP) opinion ([EMA-000130-PIP01-07](#)) issued on 3 November 2008 for Paracetamol intravenous (IV) infusion, which contained propylene glycol. The PIP included a waiver for patients older than 28 days and a deferral for a pharmacokinetic/pharmacodynamic study ("*Single and multiple dose trial to evaluate pharmacokinetics/pharmacodynamic, safety and efficacy of paracetamol in children from preterm to less than 28 days of age*").

Propylene glycol is known to be potentially toxic in some patients that are not able to adequately metabolise and eliminate this excipient. These patients are mainly infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole. Further to extensive discussions, the PDCO concluded that considering the product (Paracetamol IV infusion) was intended for short term use and since the daily dose of propylene glycol administered to neonates and infants would not exceed the limit of 25 mg/kg/day recommended by the WHO as maximum oral daily intake, the proposed formulation could be acceptable if further supported by analysis of pharmacokinetic and safety data of propylene glycol as considered in the clinical study design.

On 23 January 2009 a decentralised marketing authorisation application for the above medicinal product was submitted for "*short-term treatment of moderate pain, especially following surgery, and for the short-term treatment of fever, when administration by the intravenous route is clinically justified by an urgent need to treat pain or hyperthermia and/or when other routes of administration are not possible*" in the age group 0 – 18 years.

During the assessment of the application a prospective study of short-term propylene glycol tolerance in neonates by Allegaert K et al. was presented. This study was designed in accordance with the agreed PIP and was based on 5566 observations collected from 69 neonates (following median propylene glycol exposure of 34 mg/kg). The authors concluded that propylene glycol administration (34 mg/kg) for a maximum of 48 h seemed to be tolerated in (pre) term neonates and did not affect short-term postnatal adaptations.

As the marketing authorisation application was withdrawn during the procedure it was considered that a scientific evaluation of the data generated in accordance with the agreed PIP and its relevance in relation to safety of IV formulations for short-term use in children less than 4 years of age is relevant.

Therefore, in view of the above and in accordance with Article 5(3) of Regulation (EC) No. 726/2004, on 21 September 2011 the European Medicines Agency (EMA) requested the CHMP to give an opinion on the following aspects:

1. *Based on the data generated from this agreed PIP can the CHMP determine the safety of the excipient propylene glycol in IV formulations for short term use, and comment on what impact this data has on its potential use in the less than 4 years old?*
2. *Based on data of propylene glycol exposure in currently authorised products can the CHMP advice the PDCO on exposure levels that could be considered acceptable in future products containing propylene glycol?*

3. In the possibility that the CHMP is not able to issue an opinion on the safe use of propylene glycol according to exposure limits, could the CHMP advice which additional data would be required to facilitate this decision making process?

2. Scientific Discussion

2.1. Introduction

Propylene glycol (PG) is a clear, colourless, water-soluble alcohol (1,2-propanediol) used as a co-solvent¹ in parenteral and non-parenteral pharmaceutical formulations containing active substances that are not highly soluble in water, for example as phenobarbital, phenytoin and diazepam (EMA/CHMP/PEG/194810/2005²).

It is also used in cosmetics products and in the food industry as a humectant (E1520), preservative in food and as a vehicle for flavours in preference to ethanol. It is included in the list of food additives generally regarded as safe (GRAS) by the US Food and Drug Agency (NTP-CERHR, 2004).

The World Health Organisation (WHO) has set a maximum permissible daily intake of PG as a food additive at 25 mg/kg bodyweight (FAO/WHO, 1974). While its use is generally considered safe as a food additive, concerns with regard to potential toxicity of PG (alcohol effect/accumulation) and its acidic metabolites in young children in cases of pharmacologic exposure, have been reported³.

In adults, the low potential for systemic toxicity has been challenged due to the following adverse events reported in association with the use of PG when administered as excipient^{4,5}:

- Hyperosmolality, lactic acidosis, osmolar gap;
- Renal dysfunction, acute renal failure;
- Cardiotoxicity (arrhythmia, hypotension, cardiorespiratory arrest);
- Central nervous system toxicity (depression, coma, seizures);
- Respiratory depression, dyspnoea;
- Liver dysfunction;
- Haemolytic reaction and haemoglobinuria.

In adults, the kidneys eliminate approximately 45% of the PG and 55% is metabolised by the liver to lactic acid, pyruvic acid, or acetone. The mean elimination half-life in adults is 2.3 ± 0.7 h. Patients with impaired liver and/or kidney function are at an increased risk for developing PG toxicity. PG can also be absorbed through the skin and mucous membrane when administered topically⁵. Due to the lack of significant protein binding, PG can be removed by haemodialysis.

Due to the immature hepatic and renal function in young children the potential for PG toxicity might be aggravated in this population. Children below the age of 4 years have limited metabolic capacity (alcohol dehydrogenase) and therefore accumulation of PG can occur. It is known that neonates have a longer PG half-life (16.9 hours) compared to 5 hours in adults (EMA/CHMP/PEG/194810/2005).

¹ *Arbour R, Esparis B.*, "Osmolar Gap Metabolic Acidosis in a 60-Year-Old Man Treated for Hypoxemic Respiratory Failure", *Chest* 2000; 118; p545-546;

² CHMP Reflection Paper on Formulations of Choice for the Paediatric Population (EMA/CHMP/PEG/194810/2005), 28 July 2008;

³ *Rowe R et al.* Handbook of pharmaceutical excipients, 6th edition

⁴ *Wilson KC, Reardon C, Theodore AC, Farber HW*, "Propylene Glycol Toxicity: A Severe Iatrogenic Illness in ICU Patients Receiving IV Benzodiazepines: A Case Series and Prospective, Observational Pilot Study" *Chest* 2005; 128; 1674-1681

⁵ *Zar T, Graeber C, Perazella MA.* "Recognition, treatment, and prevention of propylene glycol toxicity." *Semin Dial.* 2007, May-Jun; 20(3):217-9.

Administration of large volumes of PG has been associated with adverse events most commonly on the central nervous system, especially in neonates and children⁶.

Pharmacokinetic models for PG have been published and expected to allow predictions of individual pharmacokinetics and in this way provide a better understanding of the potential risk of PG accumulation/toxicity, taking into account patient characteristics such as age⁷. However, at the moment, no limit of acceptable exposure has been defined for PG use as an excipient in medicinal product formulations, neither for the adult nor for the paediatric population⁵.

Nevertheless, various recommendations on the use of PG are delivered in guidelines:

The Guideline on Excipients in the Label and Package Leaflet of Medicinal Products for Human Use (Notice to Applicants, Vol.3B, Guidelines, July 2003) requires the inclusion of the following warning: "May cause alcohol-like symptoms" in the package leaflet of parenteral and oral medicinal products that contain PG daily doses in excess of 200 mg/kg if for used in children and 400 mg/kg if for used in adults. However, these thresholds that except otherwise stated, are expressed as maximum daily doses of the excipient in question, taken as part of a medicinal product. The threshold is a value, equal to or above which it is necessary to provide the information stated.

The reflection paper: Formulations of Choice for the Paediatric Population (EMA/CHMP/PEG/194810/2005) recommends "Products containing high levels of propylene glycol should not be administered to paediatric patients below the age of 4 years". Depression of the central nervous system is considered the main toxic action. Limited metabolic capacity and, following from that, potential PG accumulation in young children is the justification on which this recommendation is based. No specification of "high levels of PG" is given, however.

In 2000 the Safety Working Party (SWP) of the EMA was asked by the CHMP to give its view on the safety of Agenerase oral solution containing 550 mg PG/ml. Referring to the maximum daily dose of Agenerase oral solution recommended for children from 4 years old (2400 mg/day) and of the amprenavir solution (15 mg/ml, containing 550 mg/ml PG), a total of 88 g PG per day would be administered concomitantly (CPMP/SWP/123/00).

The SWP advised that the amount of PG should be substituted or reduced as much as possible or its safety justified.

In the same context, the FDA contraindicated the use of Agenerase, oral solution in children below 4 years of age because of a potential risk of PG toxicity. The maximum recommended Agenerase dose for children aged 4-12 years (as well as 13-16 years if below 50 kg bodyweight) according to the product information is 1650 mg PG /kg per day.

Only recently, the safety of Kaletra (lopinavir/ritonavir) oral solution containing ethanol and PG, has been scrutinised by the US and European regulatory authorities because of the questionable safety-profile and potential serious adverse events in (small) children.

In order to address the questions posed, the CHMP performed an in depth review of quality, clinical and non-clinical data available in the literature. In addition, the final analysis on the study performed in accordance with the PIP was shared by the study investigator for consideration within this scientific assessment. A summary of the review performed and discussion on each question is hereafter presented.

⁶ Nelsen J, Haas C, Habtemariam B, Kaufman D, Partridge A, Welle S and Forrest A: "A Prospective Evaluation of Propylene Glycol Clearance and Accumulation During Continuous-Infusion Lorazepam in Critically Ill Patients" *J Intensive Care Med* 2008 23: 184

⁷ De Cock RFW, Knibbe CAJ, Kulo A, de Hoon J, Verbesselt R, Danhof M, Allegaert K. "Developmental pharmacokinetics of propylene glycol in preterm and term neonates." *Br J Clin Pharmacol.* 2013 Jan; 75(1): 162-71.

2.2. Discussion

Question 1

Based on the data generated from the agreed PIP, can the CHMP determine the safety of PG in i.v. formulations for short term use, and comment on what impact this data has on its potential use in the less than 4 year old?

The data generated from the PIP, which included a waiver for patients older than 28 days and a deferral for a pharmacokinetic/pharmacodynamic study (“Single and multiple dose trial to evaluate pharmacokinetics/pharmacodynamic, safety and efficacy of paracetamol in children from preterm to less than 28 days of age”) concerns a study performed by Allegaert K et al on the developmental pharmacokinetics of PG in preterm and term neonates.

This study included 69 (pre) term neonates with a total of 372 PG serum concentrations performed. The patients were administered either intravenous infusion of paracetamol containing 800 mg PG per 1000 mg paracetamol solution (n=34) or intravenous phenobarbital in which 700 mg PG was necessary to dissolve 200 mg phenobarbital (n=25). Three patients received a combination of both preparations. For paracetamol, a loading dose of 20 mg/kg was given, followed by a maintenance dose of 10 mg/kg every 6 hours. For phenobarbital, a loading dose of 20 mg/kg phenobarbital was given, followed by a maintenance dose of 5 mg/kg.

The pharmacokinetics model used a one and two-compartment model considering that one compartment best describes the pharmacokinetics of propylene glycol and the residual variability was best described by a proportional error model.

Results showed that birth weight was found to be the most important covariate for clearance while bodyweight was found to be the most important covariate for volume of distribution. Postnatal age was also introduced on clearance. Other covariates (gestational age and postmenstrual age) did not reduce the objective function significantly.

Overall, the submitted pharmacokinetic modeling study generated from the PIP data gives a robust estimation of PG clearance and volume of distribution in neonates. From the model and subsequent simulations it can be concluded that both birth weight and postnatal age have an effect on clearance in neonates, with clearance being higher as weight and age increase.

However as stated by the authors, the pharmacokinetic model assumes linearity of PG pharmacokinetics. It is to be noted that there is some evidence in adults that with very high doses of PG, pharmacokinetic becomes non-linear, with a more than dose-proportional increase in exposure. If this non-linearity would be valid for children as well, the exposure of PG would be higher and possibly resulting in more toxicity.

Therefore, a PG dose limit applicable to all age groups under 4 years old cannot be established based on the currently submitted pharmacokinetic modeling study as the clearance is highly dependent on birth weight and post-natal age in neonates, the only studied population. Extrapolation of the results to other age groups up to 4 years of age is difficult. Furthermore, doses in the most fragile patients, i.e. preterm neonates, should be even lower than in term neonates.

In summary, the submitted pharmacokinetic modelling study gives a robust estimation of PG clearance and volume of distribution in neonates but is of less value for addressing a PG dose limit applicable to all age groups under 4 years.

Question 2

Based on data of PG exposure in currently authorised products, can the CHMP advise the PDCO on exposure levels that could be considered acceptable in future products containing PG?

An overview of the medicinal products authorised in the Netherlands and for which the propylene glycol (PG) amount is known, revealed that 3 out of 9 age relevant products, the calculated exposure levels of PG were above the current higher limit level of 200mg/kg: Bactrimel IV (calculated exposure 41 g), Urapidil Nordic (calculated exposure 28 g), and Normosang (calculated exposure 3.4 g).

Bactrimel IV (although indicated for children older than 12 years of age) is the only sulfamethoxazol + trimethoprim IV authorised product in the Netherlands. Urapidil Nordic is authorised for severe hypertensive crisis, which can be considered a life-threatening condition, and Normosang is authorised for porphyria, a rare disease.

No specific safety issues are known for both of these two products approved for used in children.

In view of the above, it seems premature to consider an increase of the acceptable level of 200 mg/kg for PG because of a short duration of use in all three clinical settings, one of which is rare and the other one only relevant to critically ill patients.

When considering lowering the acceptable level of 200 mg/kg, potentially justified by the lack of specific safety concerns of these products, it should be clear whether this measure would be specific enough for the entire paediatric population.

In addition, the question whether specific limits for different age groups should be more appropriate has to be considered, in view of the potential high risk for safety concerns in the lower age groups (i.e. neonates, infants, children below the age of 4) and the fewer experience in these age groups.

Based on the clinical literature available, no recommendation on a safe/acceptable PG dose for the paediatric population can be formulated. Definite correlations between PG exposure, patient characteristics and reported adverse events are not established. While there is a trend of increasing safety concerns with PG doses in excess of several hundred mg PG /kg/day in infants, data limitations do not allow for a more precise statement. Furthermore, there is a lack of data on long-term use.

When setting safe limits for PG amount in paediatric formulations, it should be also taken into account what other excipients are present in the formulation, e.g. excipients that may affect the metabolism of PG, ethanol or other potentially toxic excipients. Neither the proposed maximum plasma concentration of 608 mg/l, nor the 20 mg/kg/day or 200 mg/kg/day levels mentioned in guidelines appear to have a firm basis for determining a reliable maximal daily PG dose.

A broader question to be considered is whether it is absolutely necessary to include this excipient in the paediatric formulations or whether this excipient is avoidable.

From a quality perspective, the use of PG in the formulation of a medicinal product may be essentially critical, but only after sound justification by the applicant. The justification for using PG in a formulation should take into account the following criteria i.e. formulation aspects, safety aspects, disease aspects, duration of use and presence (i.e. acceptance) of the excipient(s) in already marketed products, in line with the guideline on the pharmaceutical development of Paediatric Formulations.

In conclusion, at this point and based on the available evidence it is not possible to advise on a revised exposure level with respect to PG. Further studies are needed to establish whether the current limit requiring labelling (200 mg/kg) is specific enough for the entire paediatric population or specific limits (i.e. lower limits) for different age groups are required. Furthermore, PG should only be used in

paediatric formulations when it has been justified that no other alternative excipient can be used, otherwise said if it is demonstrated that the use of PG is absolutely necessary in the formulation. Scientific advice at an early stage of product development is highly recommended.

Question 3

In the possibility that the CHMP is not able to issue an opinion on the safe use of PG according to exposure limits, could the CHMP advise which additional data would be required to facilitate this decision making process?

Non-clinical safety data assessing the potential toxicity of propylene glycol (PG) in children under 4 years of age (in particular patients older than 28 days) is currently very scarce.

Reproduction and developmental toxicity studies (oral administration of doses up to 1,000 mg/kg PG to pregnant females during the organogenesis period), revealed lack of potential adverse events on embryo-foetal development in rat and rabbit studies. However, a study⁸ in newborn and juvenile C57BL/6 mice of several ages (P4-P30) exposed to a single i.v. dose of PG showed induction of widespread apoptotic neurodegeneration in the brain, with greater damage at the age group of postnatal Day 7, with doses from 2 ml/kg (human equivalent dose of PG 1 ml/kg is 84.23 mg/kg). However, no extrapolation can be made with regards to safety of repeated use of PG in children, particularly in the younger age group.

The scarcity of non-clinical data adds to the difficulty of identifying potential toxic effects associated with the PG exposure particularly in developing organs and systems which are relevant for safety prediction in the paediatric population under 4 years of age. Additionally for this aged group, maturational aspects related to PG metabolism (ADH ontogeny) and renal clearance capacity (glomerular filtration rate vs post conceptional age) should be considered to assess the variability of systemic exposure levels in neonates, and corresponding potential to promote toxic effects (as central nervous system depression, hyperosmolality, renal toxicity and haemolysis).

Clinical data identified for the safety and quantification of the PG exposure in paediatric population include a total of 22 publications. These comprised of 12 individual case reports, 4 comparative studies and the remaining 6 non-comparative studies. An overview of all 22 publications is found in table 1. None of these publications provided information on long-term follow-up.

Three prospective studies compared different medicinal products containing PG with reference products containing mannitol instead of PG as an excipient. One retrospective study compared two different product formulations leading to an exposure of either 300 mg or 3000 mg PG per day. All of the comparative studies were non-randomised and relied on historical controls.

The 6 non-comparative included prospective and retrospective observational studies and all but one were conducted with very limited sample sizes ($n \leq 11$). Two did not assess outcomes other than PG-exposure in excess of generally recommended levels.

Overall, these 22 publications provide data on 385 children exposed to PG with the vast majority (>90%) being younger than 14 days and many delivered pre-term. Three hundred and seventy seven (~98%) were younger than four years. Three hundred and sixty nine (>95%) of the children were administered PG intravenously.

⁸ Karen Lau, Brand S. Swinney, Nick Reeves, Kevin Nogushi, Nuri Farber, "Propylene glycol produces excessive apoptosis in developing mouse brain, alone and in combination with phenobarbital." *Pediatric Research*, 2012, January, 71(1) (54-62).

PG dose, as well as duration of exposure, were highly variable between studies and also within the investigated populations and ranged from 14 mg/kg/day (*Allegaert et al., 2010*⁹) to 9472.7 mg/kg/day (*Shehab et al. 2009*¹⁰) and from a single administration to several weeks of exposure. Observed plasma levels of PG ranged from 21 mg/l (*Yorgin et al. 1997*¹¹) up to 10590 mg/l (*Fligner et al. 1985*¹²). In several studies, the time points at which the PG plasma concentration was measured were not reported, as well as the information whether it was the peak level.

The comparative studies in neonates (*Allegaert et al. 2010* and its update by *Kulo et al. 2012*¹³) with a short-term exposure (max. 48h) and relatively low doses of PG (14-252 mg/kg/day; median 34mg/kg/day) administered intravenously showed no postnatal effect renal, hepatic and metabolic adaptation. At these low PG doses, hepatic and renal parameters did not differ from a historical control that had received reference products containing mannitol instead of PG as an excipient. No adverse events were reported in this study.

Serum hyperosmolality was frequently observed in neonates upon administration of PG doses in excess of 200 mg/kg/day over at least two weeks (*MacDonald, Fletcher et al. 1987*¹⁴; *MacDonald, Getson et al. 1987*¹⁵) and was prolonged in some patients receiving PG as compared to the control group receiving mannitol (*MacDonald, Fletcher et al. 1987*).

Neonates receiving PG in doses exceeding 2000 mg/kg/day exhibited significantly higher degrees of hyperosmolality and higher BUN levels than their counterparts receiving >200 mg/kg/day (*MacDonald, Getson et al. 1987*). Importantly, among the children in the high-dose cohort of the same study, incidence of seizures and intraventricular haemorrhage was significantly increased compared to the low-dose cohort; the death rate in the high-dose group was increased as well, however without reaching significance levels (*MacDonald, Getson et al. 1987*).

The four non-comparative studies, investigating a total of 31 infants up to 15 months of age (*Chicella et al. 2002*¹⁶; *Glasgow et al. 1983*¹⁷; *Sabel & Brandberg 1975*¹⁸) and 4 children 5-12 years of age, PG was given rectally (*Kollöffel et al. 1996*¹⁹).

In the three studies in younger children, PG exposure ranged from 150 mg/kg/day to 3000 mg/kg/day. At a PG exposure of 1008-3288 mg/kg/day over three days to two weeks, *Chicella et al.* reported PG accumulation without significant laboratory abnormalities. *Glasgow et al.* (1983) reported hyperosmolality associated with an administration of 667-3000 mg/kg/day of PG for at least five days. *Sabel & Brandberg* described a case of a haemolytic reaction that occurred in connection with the

⁹ *Allegaert K, Vanhaesebrouck S, Kulo A, Cosaert K, Verbesselt R, Debeer A, de Hoon J.* "Prospective assessment of short-term propylene glycol tolerance in neonates." *Arch Dis Child.* 2010 Dec;95(12):1054-8. Epub 2010 Oct 19.

¹⁰ *Shehab N, Lewis CL, Streetman DD, Donn SM.* "Exposure to the pharmaceutical excipients benzyl alcohol and propylene glycol among critically ill neonates." *Pediatr Crit Care Med.* 2009 Mar;10(2):256-9.

¹¹ *Yorgin PD, Theodorou AA, Al-Uzri A, Davenport K, Boyer-Hassen LV, Johnson MI.* "Propylene glycol-induced proximal renal tubular cell injury." *Am J Kidney Dis.* 1997 Jul;30(1):134-9.

¹² *Fligner CL, Jack R, Twiggs GA, Raisys VA.* "Hyperosmolality induced by propylene glycol. A complication of silver sulfadiazine therapy." *JAMA.* 1985 Mar 15;253(11):1606-9.

¹³ *Kulo A, Smits A, Naulaers G, de Hoon J and Allegaert K.* "Biochemical tolerance during low dose propylene glycol exposure in neonates: A formulation-controlled evaluation." *Daru.* 2012;20(1):5. doi: 10.1186/1560-8115-20-5. Epub 2012 Jul 19.

¹⁴ *MacDonald MG, Fletcher AB, Johnson EL, Boeckx RL, Getson PR, Miller MK.* "The potential toxicity to neonates of multivitamin preparations used in parenteral nutrition". *JPEN J Parenter Enteral Nutr.* 1987 Mar-Apr; 11(2): 169-71.

¹⁵ *MacDonald MG, Getson PR, Glasgow AM, Miller MK, Boeckx RL, Johnson EL.* "Propylene glycol: increased incidence of seizures in low birth weight infants." *Pediatrics.* 1987 Apr; 79(4):622-5.

¹⁶ *Chicella M, Jansen P, Parthiban A, Marlowe KF, Bencsath FA, Krueger KP, Boerth R.* "Propylene glycol accumulation associated with continuous infusion of lorazepam in pediatric intensive care patients." *Crit Care Med.* 2002 Dec; 30(12):2752-6.

¹⁷ *Glasgow AM, Boeckx RL, Miller MK, MacDonald MG, August GP, Goodman SI.* "Hyperosmolality in small infants due to propylene glycol." *Pediatrics.* 1983 Sep;72(3):353-5.

¹⁸ *Sabel KG, Brandberg A.* "Treatment of meningitis and septicemia in infancy with a sulphamethoxazole/trimethoprim combination." *Acta Paediatr Scand.* 1975 Jan;64(1):25-32.

¹⁹ *Kollöffel WJ, Weekers LE, Goldhoorn PB.* "Pharmacokinetics of propylene glycol after rectal administration." *Pharm World Sci.* 1996 Jun; 18(3): 109-13.

administration of approximately 150-225 mg PG /kg/day for 10 days. No adverse effects were reported after a single administration of 173 mg/kg of PG rectally in four children (*Kollöffel et al.*).

The 12 case reports provided data on children of a broad age spectrum, various administration routes and in some cases, very high PG dose levels. Hyperosmolality after PG administration was frequently reported in line with the results of the larger studies. Additionally, several other adverse events have been linked to PG exposure by study authors. These include renal failure, central nervous system depression, acidosis and diarrhoea among others.

Overall, considering that the main toxicological aspects of PG are identified in qualitative terms, it is agreed that a better understanding of the potential risks associated with its use in neonates and younger age will be derived from clinical data, as animal studies will not be sufficient in this context.

From a clinical view point the potential toxicity of PG used in paediatric formulations for less than 4 years old children, particularly in the very low ages (newborns, pre-term) will be more adequately assessed in well-designed clinical studies investigating the safety of PG exposure, reflective of common clinical use in terms of duration and quantity. The available evidence suggests that studies on excipient safety in children are possible. Future studies should specifically address the following points:

- Comparator products containing the same active substance, but varying by PG content or substituting PG with a well-characterised excipient;
- Predefined broad range of safety outcomes to be investigated, including laboratory as well as clinical parameters;
- Observational and follow-up periods should be of sufficient duration to monitor possible long-term effects of PG;
- Different age groups and patients from non-ICU settings should be included to account for differences in maturation of metabolism and baseline health status.

In addition, from a **quality** viewpoint further data on the safe use of PG is required which should allow clear conclusion on whether one single limit (e.g. 200 mg/kg) is specific enough for the entire paediatric population or whether specific limits (i.e. lower limits) for different age groups are required.

It is suggested that a research similar to the one conducted in the Netherlands for authorised medicines is also performed in other European Member States to allow collection of information on dose, dose range, amount of PG in the medicinal products, as well as to determine the exposure to PG for the age appropriate products. In addition, a more in depth calculation on the exposure of PG should be performed which also considers indication and duration of use in the different target age groups.

The quality information resulting from the above research should be put in the perspective of safety information on the specific age groups.

Table 1 Overview of all 22 publications

Study	Design	Patients	N (PG)	Age	via	PG Dose	PG Plasma Levels	Exposure Duration	PG excipient for	Relevant Outcomes
<i>Allegaert et al., 2010</i> Prospective assessment of short-term PG tolerance in neonates	prosp, historical control, PG vs. mannitol	Neonatal intensive care patients, extremely low BW infants 0.5-4.3 kg BW	69	(pre)term newborns (median 2 d)	i.v.	14-252 mg/kg/24h median 34 mg/kg/24h	n.i.	max. 48h	phenobarbital, digoxin, phenytoin, paracetamol	Short-term postnatal renal, hepatic and metabolic adaptation not affected by the administered PG doses No differences observed in renal & hepatic parameters between PG and control group
<i>Kulo et al., 2012</i> Biochemical tolerance during low dose PG exposure in neonates: A formulation-controlled evaluation	prosp, historical control, PG + paracetamol vs. PG + other source vs. mannitol	see above	89 (69 above +20 new)	see above	i.v.	14-252 mg/kg/24h median 34.1 mg/kg/24h	n.i.	see above	paracetamol, phenobarbital, digoxin & diphantoine, phenytoin	See above Findings apply irrespective of PG source
<i>MacDonald, Fletcher et al., 1987</i> The potential toxicity to neonates of multivitamin preparations used in parenteral nutrition	prosp, historical control, PG vs. mannitol	Infants with less than 1500 g BW at birth	30	infants < 48 h	i.v.	300 mg/day (>200mg/kg/day)	400 mg/l-1089 mg/l; (n=14)	up to 40 days	MVI-Concentrate (multivitamin preparation)	Hyperosmolality in both study cohorts Serum hyperosmolality prolonged for low birth weight infants in the PG group

Study	Design	Patients	N (PG)	Age	via	PG Dose	PG Plasma Levels	Exposure Duration	PG excipient for	Relevant Outcomes
<i>MacDonald, Getson et al., 1987</i> PG: increased incidence of seizures in low birth weight infants	retrosp, historical control, PG low dose vs. PG high dose	infants ≤ 1500g BW at birth, admitted to nursery	127 (A: n=78; B: n=49)	1-7 d	i.v.	Cohort A: 300 mg/day (≥200mg/kg/day); Cohort B: 3000 mg/day (≥2000 mg/kg/day)	n.i.	at least 14 days	MVI-12 (multivitamin preparation), maybe other PG-containing drugs (no exposure details)	BUN and serum hyperosmolality significantly higher in high-dose cohort Seizures and intraventricular haemorrhage incidence significantly higher in high-dose cohort Non-significantly increased death rate for high-dose cohort
<i>Chicella et al., 2002</i> PG accumulation associated with continuous infusion of lorazepam in pediatric intensive care patients	prosp	pediatric intensive care patients, mean 5.4 kg BW	11	1-15 m	i.v.	approx. 42-137 mg/kg/h (1008 – 3288 mg/kg/day)	At end of infusion: 165mg/l - 2258 mg/l; mean: 763 (+/- 660) mg/l	3-14 days; (mean 8 days)	lorazepam	PG accumulation No significant laboratory abnormalities
<i>Glasgow et al., 1983</i> Hyperosmolality in small infants due to PG	case report	premature infant, 890 g BW	1	3 d (born at 27 weeks gestation)	i.v.	3000 mg/day (3371 mg/kg/day)	9300 mg/l when initially measured	9 days	MVI-12 (multivitamin preparation)	Acute renal failure Hyperosmolality
	retrosp	infants in nursery, 1000-4500g BW	10	infants	i.v.	3000 mg/day = 667 – 3000 mg/kg/day	650-9500 mg/l " just prior to discontinuation of MVI-12"	at least 5 days	MVI-12 (multivitamin preparation)	Hyperosmolality
<i>Kollöffel et al., 1996</i> Pharmacokinetics of propylene glycol after rectal administration	prosp	healthy, to be operated for inguinal hernia, mean BW 26 kg	4	5-12 y	rectal	173mg/kg	Peak: 146-190 mg/l; mean: 171mg/l	single administration	paracetamol	No side effects detected.

Study	Design	Patients	N (PG)	Age	via	PG Dose	PG Plasma Levels	Exposure Duration	PG excipient for	Relevant Outcomes
<i>Sabel & Brandberg, 1975</i> Treatment of meningitis and septicemia in infants with a sulphamethoxazole/ trimethoprim combination	prosp	infants with septicemia and/or meningitis	10	8 d-10 m (75% < 1 m)	i.v.	approx. 150-225mg/kg/24h (divided into 2 doses daily)	n.i.	10 days	solution of sulphamethoxazole 80 mg/ml and trimethoprim 16 mg/ml in 40% PG	One hemolytic reaction reported as possibly PG-associated
<i>Shehab et al., 2009</i> Exposure to the pharmaceutical excipients benzyl alcohol and PG among critically ill neonates	retrosp	critically ill neonates, 2679 g (+/- 1065 g) BW	82	5.9 d (+/- 6.2 d)	i.v.	median 204.9 mg/kg/day (17.3-9472.7 mg/kg/day)	n.i.	Median 6 days (1-54 days)	diazepam, lorazepam, phenobarbital, phenytoin, digoxin	None assessed
<i>Whittaker et al., 2009</i> Toxic additives in medication for preterm infants	retrosp	Infants with chronic lung disease, 813 g (+/- 205g) BW	7	born at or < 30 wks gestation	oral (liquid)	in excess of 175mg/kg/week at least temporarily	n.i.	Mean: 3.3 weeks	dexamethasone	None assessed
<i>Bekeris et al., 1979</i> PG as a cause of an elevated serum osmolality	case report	boy with second- and third-degree burns (90% of body surface)	1	14 y	topical	"large amounts"	0.04 mol/l 3040mg/l time of measurement : unknown	19 days	cream containing silver sulfadiazine	Hyperosmolality Death (unrelated to PG)
<i>Cady et al., 1994</i> Detection of propan-1,2-diol in neonatal brain by in vivo proton magnetic resonance spectroscopy	case report	infant with hypoxic-ischemic encephalopathy, 2.72 kg BW	1	39 week gestation	i.v.	approx. 4 mmol/kg (= 304mg/kg)	n.i.	Reported dose: 4 d. (14 days of total exposure)	phenobarbiton, phenytoin	PG accumulation in cerebral tissue assumed

Study	Design	Patients	N (PG)	Age	via	PG Dose	PG Plasma Levels	Exposure Duration	PG excipient for	Relevant Outcomes
<i>Fligner et al., 1985</i> Hyperosmolality induced by PG. A complication of silver sulfadiazine therapy	case report	burn and toxic epidermal necrolysis of 78% of body surface, 9.3kg BW	1	8 m	topical	9000 mg/kg/24h	peak: 10590 mg/l	70 h	silver sulfadiazine	Hyperosmolality Cardiorespiratory arrest (possibly related to PG)
<i>Glover, Reed, 1996</i> PG: the safe diluent that continues to cause harm	case report	healthy boy, 10kg BW	1	2 y	oral	approx. 200mg/kg	n.i.	single ingestion	styling hair gel	Central nervous system depression Severe metabolic acidosis Hyperosmolality
<i>Guillot et al., 2002</i> Home environment and acute PG intoxication in a two-year old.	case report	healthy boy, 12.25kg BW	1	2 y	oral	n.i.	peak: 50mg/l	1 night	disposable cleansing towels	CNS depression Dyspnoea Metabolic acidosis
<i>Huggon et al., 1990</i> Hyperosmolality related to PG in an infant treated with enoximone infusion	case report	3.4 kg boy after open heart surgery	1	infant	i.v.	2.7 mg/kg/min = 3888 mg/kg/day	Estimation based on osmolal gap: 10000mg/l	at least 4 days	enoximone, glyceryl trinitrate	Hyperosmolality
<i>Kelner, M.J., Bailey D.N., 1985</i> PG as a Cause of Lactic Acidosis	case series	3 infants: 1 intraventricular shunt/1 subdural hematoma/1 meningococcal meningitis	3	2/4/4 m	i.v.	267/771/512 mg/kg/day	peak: 711/173/304 mg/l	at least: 9 days/2.5 days/8.5 hours	Phenytoin, sulfamethoxazoltrimethoprim preparation, pentobarbital, diazepam	Lactic acidosis No hyperosmolality Anion gap

Study	Design	Patients	N (PG)	Age	via	PG Dose	PG Plasma Levels	Exposure Duration	PG excipient for	Relevant Outcomes
<i>Levy et al., 1995</i> PG toxicity following continuous etomidate infusion for the control of refractory cerebral edema	case report	boy with severe head injury, Glasgow Coma Scale score <7, 77.3 kg BW	1	14 y	i.v.	Estimated 89970 mg over 24h;	n.i.	24 hours	etomidate	Diminished renal function Hyperosmolality Metabolic acidosis
<i>Marshall et al., 1995</i> Diarrhea associated with enteral benzodiazepine solutions	case report	child with tracheobronchial malacia, bronchopulmonary dysplasia, pneumonitis, 11 kg BW	1	9 m	enteral	3400 mg/24h = 309 mg/kg/day	n.i.	At least 3 days	lorazepam oral solution	Diarrhoea
<i>Meshitsuka et al., 1999</i> Screening of urine by one-dimensional and pulsed-field gradient two-dimensional 1H NMR spectroscopy: intoxication by PG in an infant patient	case report	hydrocephalus, respiratory failure, convulsions	1	49 d	oral	2,1 ml/day	n.i.	n.i.	phenobarbital elixir	Liver dysfunction
<i>Van de Wiele et al., 1995</i> PG Toxicity Caused By Prolonged Infusion of Etomidate	case report	boy with large left hemispheric arteriovenous malformation, 34 kg BW	1	9 y	i.v.	approx. 400 mg/kg/h	2300 mg/l (4h post infusion)	12 hours	etomidate	Haemoglobinuria Hemolysis Metabolic acidosis Hyperosmolality
<i>Yorgin et al., 1997</i> PG-induced proximal renal tubular cell injury	case report	adolescent boy with peptic ulcer disease	1	16 y	i.v.	10800-90300 mg/day (mean: 39100 mg/day)	d13: 21 mg/l, d19: 41 mg/l	at least 19 days, possibly 3 weeks	phentobarbital, phenobarbital	Acute renal failure (proximal renal tubular cell swelling and vacuole formation)

3. Conclusion

Given the scarcity of the available non-clinical data that could be relevant to the low age group under discussion, and the existing human experience with propylene glycol, it is considered that any recommendations to set a minimum threshold for a warning in the labelling of the product for the age group in consideration should be based on a weight of evidence from data derived from studies in animals but also in humans as much as possible. Additional information from non-clinical juvenile studies assessing the toxicity and toxicokinetics of propylene glycol following repeated administration in the relevant species and age groups may be considered useful to assess the safety risks (particularly central nervous system toxicity) inherent to a formulation containing propylene glycol.

Clinically, the weak evidence and the reliance on predominantly non-comparative data and case reports, severely limit the robustness of any recommendation regarding safe propylene glycol exposure levels. A variety of relevant aspects are to be considered when considering a safe dose of propylene glycol. These include patient characteristics such as (developmental) age, weight, health status, concomitant medication, administration route, pattern and duration of use.

In pre-term infants where metabolism and secretion mechanisms are yet immature, accumulation of propylene glycol can occur more easily, thus leading to an increased potential toxicity. Propylene glycol is used as excipient for a variety of medicinal products frequently applied in an intensive care unit (ICU) setting, where the patient collective will arguably display a variety of severe health conditions that could accentuate but also mask any adverse effects due to propylene glycol. In this regard, studies considered for this review have been conducted in an ICU setting. Finally, the hardly quantifiable impact of co-medication and its excipients (e.g. mannitol) or sources of propylene glycol other than those investigated could potentially distort the clinical picture and the interpretation of data, accordingly.

The current regulatory recommendations concerning propylene glycol have been made for oral intake via food products (FAO/WHO) or focus on the alcohol effect of propylene glycol only (European Medicines Agency - EMA). It should be noted that the recommendations in the EU concerning propylene glycol may evolve based on the Guideline on the Excipients in the Label and Package Leaflet of Medicinal Products for Human Use (CPMP/463/00) which is currently under revision (EMA/CHMP/SWP/888239/2011).

Attempts to define a safety threshold for propylene glycol administration have not been utterly conclusive so far. For children, it was concluded that "a median PG exposure of 34mg/kg/24h seems well tolerated and does not affect normal postnatal maturational changes in renal, metabolic and hepatic function" (*Allegaert et al. 2010⁹, Kulo et al. 2012¹³*). Determining a safe upper limit of propylene glycol exposure of 34 mg/kg/day might be a possible, rather conservative, approach. Importantly however, study specifics limit the generalizability of the proposed threshold: mainly (pre-term) infants in an ICU setting, short-term exposure (48h), use of historical controls, and assessment of selected endpoints only.

In the publication by *De Cock et al. (2012)* two different approaches are described to provide a basis for maximum acceptable concentrations of propylene glycol in neonates:

- First, the exposure to propylene glycol (upon administration of propylene glycol with paracetamol or phenobarbital) was compared to levels observed in a previously published study in 69 preterm and term neonates in which tolerability of propylene glycol was evaluated. No toxic effects were reported (*Allegaert et al 2010⁹*). However, although

propylene glycol exposure did not affect postnatal renal, metabolic and hepatic adaptations, it remains unclear if all adverse events were monitored and reported systematically;

- Second, the maximum propylene glycol concentration may be defined on basis of the toxic effects related to the osmolar changes. The increase in osmolar gap can directly be linked to propylene glycol concentrations and is the first indicator of propylene glycol accumulation that may result in toxic effects. The authors estimated that the maximum allowed propylene glycol plasma concentration in neonates should remain below 608 mg/l, which corresponds to a maximum change in osmolar gap of 8 mOsm/l. Osmolarity was not reported in the study of *Allegaert (2010⁹)*.

As in the final analysis document provided by *K. Allegaert*, the population mean values for peak and trough propylene glycol concentrations varied between 300-1038 mg/l and 70-557 mg/l respectively, when simulating propylene glycol concentrations based on a limit of 200 mg/kg. The peak values exceed the 608 mg/l limit postulated above whereas simulations with the lower daily propylene glycol dose limit according to recommendations of the FAO/WHO, i.e. 25 mg/kg, resulted in peak and trough PG concentrations of 35-130 mg/l and 9-66 mg/l, respectively, depending on birth weight (630-3500 g) and postnatal age (1-28 days).

Based on all currently available data, no firm recommendation on a safe/acceptable propylene glycol dose for the paediatric population can be made. Definite correlations between propylene glycol exposure, patient characteristics and reported adverse events are not established. While there is a trend of increasing safety concerns with propylene glycol doses in excess of several hundred mg of PG/kg/day in infants, the data limitations do not allow for a more precise statement. Furthermore, there is a lack of data on long-term use.

When attempting to set safe limits for propylene glycol amount in paediatric formulations, it should be taken into account other component in the formulation, e.g. excipients that may affect the metabolism of propylene glycol, such as ethanol or other potentially toxic excipients.

In conclusion, propylene glycol may be avoidable in some paediatric formulations, but this may not be feasible, nor the alternatives more safe, in all cases. A sound justification for its use needs to be provided and weighed against the benefit-risk balance of the medicinal product in the disease to be treated.

Well-designed clinical trials investigating the safety of propylene glycol exposure, reflective of common clinical use in terms of duration and quantity are needed to allow a better understanding of propylene glycol safety in children. In view of the vulnerability of the paediatric population this needs to be carefully considered on a case by case basis. However, the evidence reviewed in this report suggests that studies on excipient safety in children are in principle possible. The following aspects should also be considered:

An alternative approach would be to identify existing neonatal/low birth weight/premature cohort(s) where e.g. long-term central nervous system outcome has been evaluated, and in this population estimate their propylene glycol exposure. This less costly, faster approach has the potential to include a larger range of propylene glycol exposure levels, and focus on the most concerning safety outcome from the perspective of propylene glycol exposure. However, recording of medicine administration in the detail required and quantitative data on excipient content might not generally be available.

Furthermore, while long term central nervous system (CNS) outcome is being investigated in some registry studies in the youngest cohorts, it is certainly challenging to assess CNS outcomes specifically related to excipient exposure as compared to the exposure to the medicinal product or outcomes primarily related to the underlying disease.

Desirably, a broad range of safety outcomes to be investigated, including laboratory as well as clinical parameters, should be predefined and observation and follow-up periods should be of sufficient duration (thus covering possible long-term effects of propylene glycol). Nonetheless, outcome may be confounded by other aspects of patient management, in particular the characteristics of the medicinal product/active substance used or the disease treated.

Ideally, different age groups and patients from non-ICU settings should be included to account for differences in maturation of metabolism and baseline health status, nevertheless the trial setting would be driven by the candidate medicinal product reflecting the actual use of the relevant medicinal products in terms of age, disease and comorbidities.

4. Overall conclusion

The CHMP considered the procedure under Article 5(3) of Regulation (EC) No 726/2004 on the excipient, propylene glycol in medicines for children as per questions posed.

Based on the limited overall quality, non-clinical and clinical data available, the Committee considered that

- no recommendation on a safe dose for propylene glycol can be made based on the current available data;
- correlations between PG exposure, patient characteristics and reported adverse events are not established;
- while there is a trend of increasing safety concerns with propylene glycol doses in excess of several hundred mg /kg/day in infants, the limitations of the available data do not allow for a definite conclusion;

The Committee therefore concluded that well designed clinical trials investigating the safety of propylene glycol exposure and reflective of common clinical use in terms of duration and quantity are needed to allow a better understanding of propylene glycol safety in children. Additional information from non-clinical juvenile studies assessing the toxicity and toxicokinetics of propylene glycol following repeated administration in the relevant species and age groups may be considered useful to assess the safety risks (particularly central nervous system toxicity) inherent to the formulation.