Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Sodium glycerophosphate (as hydrate)

Proprietary Product Name: Glycophos

Sponsor: Fresenius Kabi Australia Pty Ltd

February 2020

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AUC	Area under the concentration time curve
AusPAR	Australian Public Assessment Report
ARTG	Australian Register of Therapeutic Goods
C_{max}	Maximum plasma concentration
LBS	Literature-based submission
PI	Product Information
PSUR	Periodic safety update report
SAE	Serious adverse event
SOS	Speed of sound
TEAE	Treatment emergent adverse event
UK	United Kingdom

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	13 November 2019
Date of entry onto ARTG:	14 November 2019
ARTG number:	312021
▼ *Black Triangle Scheme*	No
Active ingredient:	Sodium glycerophosphate (as hydrate)
Product name:	Glycophos
Sponsor's name and address:	Fresenius Kabi Australia Pty Ltd Level 2, 2 Woodland Way, Mount Kuring-gai, NSW 2080
Dose form:	Concentrated solution for injection
Strength:	4.32 g/20 mL
Container:	Ampoule
Pack size:	20 x 20 mL
Approved therapeutic use:	*Glycophos is indicated in adult and paediatric patients as a supplement to parenteral nutrition to meet the daily requirements of phosphate.*
Route of administration:	Intravenous infusion
Dosage:	*Adults* The recommended dosage should be individualised to each patient's phosphorus status and needs. Approximately 15 mmol of phosphate is provided by a litre of lipid emulsions or amino acid solutions. This should be considered when supplementing phosphate from Glycophos. The normal requirements during parenteral nutrition can be met by using 10 to 20 mL of Glycophos added to the infusion solution or admixture for which compatibility has been proven. *Paediatric population* The recommended dosage should be individualised to each patient's phosphorous status and needs. The recommended dose for children, infants and neonates is 1.0 to 1.5 mmol/kg body weight per day. For further information refer to the Product Information.

Product background

This AusPAR describes the application by Fresenius Kabi Australia Pty Ltd (the sponsor) to register Glycophos (sodium glycerophosphate (as hydrate)) concentrated solution for injection for the following proposed indication:

> *Glycophos is indicated in adult and paediatric patients as a supplement to parenteral nutrition to meet the daily requirements of phosphate.*

Phosphorous plays a role in the maintenance of the bony skeleton and is a component of phospholipids in cell membranes. The high-energy phosphate bonds that phosphorus contains are also relevant for energy metabolism. Phosphorous also controls the activity of many enzymes, is part of most metabolic pathways, controls oxygen delivery to the tissues, and is involved in buffering of the body.

Inorganic phosphate salts, usually as sodium or potassium salts, have been widely used as a parenteral phosphorous supplement. Although this is an effective form for the delivery of phosphorous to the patient, it can lead to pharmacological compatibility problems within the parenteral nutrition regimen especially when calcium or magnesium is present. The inorganic phosphate ions tend to form insoluble salt complexes with calcium and magnesium, which may lead to fatal consequences.

Glycophos is an intravenously administered supplement to parenteral nutrition containing sodium glycerophosphate (as hydrate), an organic form of phosphate, as the active ingredient. The sodium glycerophosphate in Glycophos is an alternative phosphorous supplement that overcomes precipitation issues, as it is much more soluble in water than inorganic phosphates.

This submission is a hybrid literature-based submission (LBS) based on a systematic review of the clinical literature and company sponsored clinical studies, as agreed with the TGA.

Regulatory status

Glycophos (sodium glycerophosphate (as hydrate) is a new chemical entity for Australian regulatory purposes.

There are currently multiple registered sources of parenteral phosphorus but they are for different salts and for different indications compared to those proposed for Glycophos in the submission discussed in this AusPAR. There are currently no intravenously-administered medicines registered on the Australian Register of Therapeutic Goods (ARTG) that contain sodium glycerophosphate as the only active ingredient, however, it is present as a source of phosphorus in the registered parenteral nutrition complex solutions Kabiven G 19% and Kabiven G 11% (Fresenius Kabi Australia Pty Ltd, ARTG R 97889 and 97895, respectively).

The product has been marketed overseas for more than 20 years. It has been approved in Europe (registered in Belgium in 1998 and the United Kingdom (UK) in 2003), New Zealand (2007), Singapore (2002) and Switzerland (1995).

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

Table 1 captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 1: Timeline for Submission PM-2018-04249-1-1

Description	Date
Submission dossier accepted and first round evaluation commenced	2 January 2019
First round evaluation completed	20 June 2019
Sponsor provides responses on questions raised in first round evaluation	16 July 2019
Second round evaluation completed	31 July 2019
Delegate's Overall benefit-risk assessment	20 October 2019
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	13 November 2019
Completion of administrative activities and registration on ARTG	14 November 2019
Number of working days from submission dossier acceptance to registration decision*	199

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

From the quality evaluation:

- Glycophos is to be supplied as a sterile, aqueous concentrated injection solution containing 306.1 mg of sodium glycerophosphate hydrate (in the pentahydrate form), which is equivalent to 216 mg sodium glycerophosphate. One millilitre (1 mL) of Glycophos containing sodium glycerophosphate equates to 1 mmol of phosphate and 2 mmol of sodium.
- The drug product is contained within a 20 mL polypropylene ampoule fitted with an integrated Luer lock. Thus, a 20 mL presentation of Glycophos contains 4.32 g of sodium glycerophosphate which in turn equates to 20 mmol of phosphate and 40 mmol of sodium.

- A pack size of twenty (20) ampoules is proposed for registration and is to be packed within a cardboard carton.

Approval is recommended for registration of the proposed drug products from a pharmaceutical chemistry and quality aspect.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical dossier consisted of the following studies:

- Clinical pharmacology studies:
  - Study Glyc-001-C P1: a Phase I, double blind, randomised, active controlled, 2 sequence, 2 way crossover, single dose, single centre study (Glycophos versus I-Phosphate, 25 healthy subjects). Conducted from 20 August to 2 October 2010.
  - Study Kabi-003-C P1: a Phase I, double blind, randomised, 2 sequence, 2 way crossover, single dose, single centre study (Kabiven Peripheral versus Glycophos, 10 healthy subjects). Conducted from 19 August to 7 September 2010.
- Efficacy/safety studies:
  - Study 91-114: a Phase III, multicentre, prospective, randomised, double blind, parallel group, active controlled study (Glycophos versus monopotassium phosphate, 41 paediatric patients). Conducted from 26 February 1994 to 27 February 1996. Appears previously submitted as Monforte, Study KP0734.
  - Study 90-024-00: a Phase III, open label, non-comparative study (sodium glycerophosphate, 20 adult patients). Conducted from 10 October 1990 to 2 June 1991. Appears previously submitted as Hermansson and Nilsson, an open study with sodium glycerophosphate, to document safety and metabolism of sodium glycerophosphate in postoperative patients requiring total parenteral nutrition. Report 91 96 531 (1992).
- Literature references for parenteral nutrition (organic phosphate):
  - Mazouri, A., et al. Does adding intravenous phosphorus (Glycophos) to parenteral nutrition has (sic) any effects on calcium and phosphorus metabolism and bone mineral content in preterm neonates? *Acta Medica Iranica*, 2017; 55: 395-398.
  - (As glucose-1-phosphate); Bonsante, F., et al. Initial amino acid intake influences phosphorus and calcium homeostasis in preterm infants - it is time to change the composition of the early parenteral nutrition? *PLoS ONE*. 2013; 8: e72880.
- Literature references for parenteral nutrition (organic versus inorganic phosphate):
  - Pereira-da-Silva, L., et al. Early high calcium and phosphorus (Glycophos) intake by parenteral nutrition prevents short-term bone strength decline in preterm infants. *J Pediatr Gastroenterol Nutr*. 2011; 52: 203-209.
  - Hanning, R, et al. Efficacy of calcium glycerophosphate versus conventional mineral salts for total parenteral nutrition in low-birth-weight infants: a randomized clinical trial. *Am J Clin Nutr*. 1991; 54:903-908. (study previously submitted and evaluated).
  - Devlieger, H., et al. Calcium and phosphorus retention in the preterm infant during total parenteral nutrition. A comparative randomised study between organic

(glucose-1-phosphate) and inorganic phosphate as a source of phosphorus. *Clin Nutr*. 1993; 12: 277-281.

- Tormo, C., et al. Organic (glucose-1-phosphate) versus inorganic phosphate administration in total parenteral nutrition: the source matters. *Clinical Nutrition*. 1994; 13: 56.

- Literature references for phosphate as therapy (both previously submitted and evaluated):
  - Costello, I., et al. Sodium glycerophosphate in the treatment of neonatal hypophosphataemia. *Arch Dis Child Fetal Neonatal Ed*. 1995; 73: F44-45.
  - (As glucose-1-phosphate); Bollaert, P., et al. Hemodynamic and metabolic effects of rapid correction of hypophosphatemia in patients with septic shock. *Chest*. 1995; 107: 1698-1701.
- Periodic safety update reports (PSURs): April 2010 to June 2017.

Pharmacology

Pharmacokinetics

In the submitted studies, sodium glycerophosphate produced a similar area under the concentration time curve (AUC) and maximum plasma concentration (C_{max}) profile to that of inorganic phosphate, but not of urinary excretion. In Study 90-024-00 the ratio between excreted inorganic phosphate and total phosphorus in the urine varied but indicated that almost all phosphate excreted in the urine was inorganic phosphate and that glycerophosphate was not excreted to any significant extent.

Pharmacodynamics

The proposed use of Glycophos is in adult and paediatric patients as a supplement to parenteral nutrition to meet the daily requirements of phosphate. Applicability of Study Glyc 001-C P1 of a single dose in the absence of parenteral nutrition even though limited, was acceptable for this submission. Mazouri et al.;[1] and Pereira-da-Silva et al.;[2] showed improvement in preterm infants on bone density, the former compared to no supplemental phosphate, the latter only with the use of 'high dose'. Schildt et al.;[3] is a case series which showed large positive balances of phosphate and calcium over Days 1 to 5 of treatment.

Dose selection

In Study 90-024-00 in adults 'the daily dose of 20 mmol glycerophosphate was to be given to all patients during the treatment period of five days. The dose chosen corresponds to the daily requirement of phosphorus'.[4] In Study 91-114 'all patients were to receive 1 mmol of phosphorus/kg body weight/day (given as glycerophosphate or inorganic phosphate) which is a normal dose used in newborn children.' 'Depending on the daily intake of Intralipid 20%, the daily intake of glycerophosphate was expected to vary from 0.75 to 1 mmol/kg body weight.'[5]

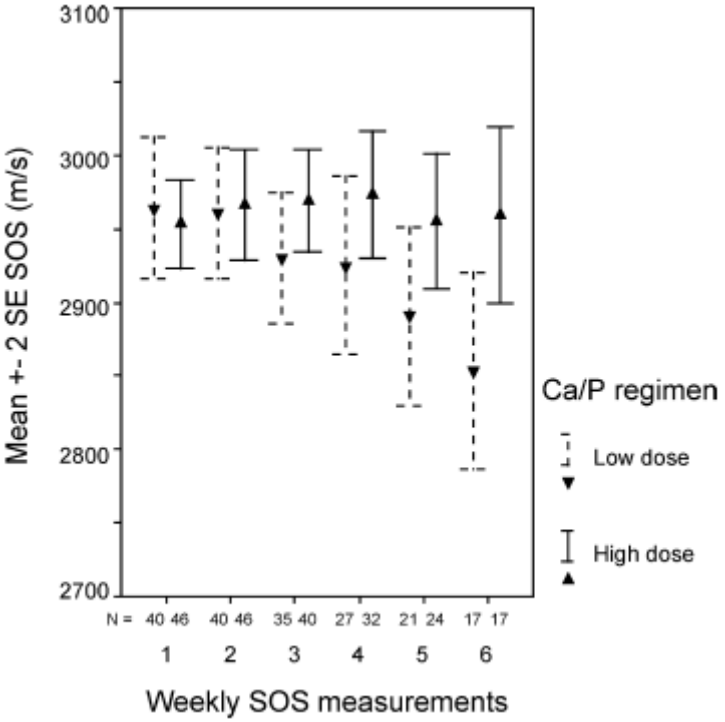
[1] Mazouri, A. et al. Does adding intravenous phosphorus (Glycophos) to parenteral nutrition has any effects on calcium and phosphorus metabolism and bone mineral content in preterm neonates? *Acta Medica Iranica*, 2017; 55: 395-398.
[2] Pereira-da-Silva, L. et al. Early high calcium and phosphorus (Glycophos) intake by parenteral nutrition prevents short-term bone strength decline in preterm infants. *J Pediatr Gastroenterol Nutr*. 2011; 52:203-209.
[3] Schildt et al, Addex electrolyte in total parenteral nutrition. Report L366 G3, 1982.
[4] As per the clinical study report for Study 90-024-00.
[5] As per the clinical study report for Study 91-114.

Efficacy

Study 90-024-00 looked at 20 patients for 5 days and had no comparator; Study 91-114 looked at only 17 patients for a maximum of 7 days and failed to show significant difference between treatments. While this may be a common duration for routine parenteral nutrition (post-surgical and neonatal pre-enteral feeding), it does not necessarily reflect the needs of long-term total parenteral nutrition, as highlighted by clinical evaluator.

In the literature report Mazouri et al.;[1] 25 neonates received a mean duration of parenteral nutrition of 9.8 ± 3.0 days and at the end of the fourth week, those who received Glycophos experienced more increase in bone mineral density than those in the control group (0.13 ± 0.01 versus 0.10 ± 0.02, $p < 0.001$). Likewise in Pereira-da-Silva et al.;[2] mean duration of parenteral nutrition in 86 (40 given low dose, 46 given high dose) neonates was 2 weeks at which time there was really no difference in speed of sound (SOS; see Figure 1).
By 6 weeks in 34 (17 low dose, 17 high dose) neonates, the mean speed of sound in the low dose group from birth to the sixth week of life fell significantly ($p = 0.027$), while no significant difference from base line in the high dose group could be shown. Comparison between the 2 results was not made.

Figure 1: Mean (2 standard error) of speed of sound measurements (m/s) from Baseline (measurement 1) to the sixth week of life (measurement 6) in preterm infants receiving 2 different parenteral mineral regimens



Overall, the numbers exposed and completers were small, and the duration of exposure was approximately 2 weeks.

Safety

The number and duration of exposure in clinical trials, including the literature was considered low by clinical evaluator. The clinical evaluator also highlighted the need to restrict the duration of exposure and wording on warning in the proposed PI. This is being adequately addressed by the sponsor in the final version of the PI Section 4.4:

> 'The use of Glycophos for long-term parenteral nutrition has limited clinical experience and precautions need to be taken while using Glycophos for an extended duration. Glycophos may be used for a longer duration depending on the clinical judgement of the healthcare professional.'

In addition, there is a considerable (approximately 6.4 million patients have been treated with Glycophos) post marketing history of exposure. The sponsor reported none of the treatment emergent adverse events (TEAE), serious adverse events (SAE) or deaths reported in the studies was assessed as being related to study treatment.

Risk management plan

There was no requirement for a risk management plan evaluation for a submission of this type.[6]

Risk-benefit analysis

Delegate's considerations

Glycophos is a supplemental source of phosphorous for patients receiving parenteral nutrition and currently ARTG registered as a component of Kabiven. A greater solubility compared to other phosphate sources has been highlighted as a relevant importance to the patient requiring parental nutrition.

Efficacy from clinical studies seems marginal, and in the literature Glycophos has showed improvement in preterm infants on bone density compared to no supplemental phosphate, only with the use of 'high dose' as opposed to 'low dose'.

Even though the number and duration of exposure in clinical trials, including the literature is low, there has been considerable post marketing exposure. In addition, the sponsor reported none of the TEAEs, SAEs or deaths reported in the studies was assessed as being related to study treatment.

The PI was adequately amended to address the concerns of the Delegate and clinical evaluator.

As the recommended dosage are individualised to each patient's phosphorus status and needs, overall the Delegate thinks that benefit-risk balance of Glycophos is positive given the considerable (approximately 6.4 million patients have been treated with Glycophos) post marketing history of exposure and need for supplemental source of phosphorous for patients receiving parenteral nutrition.

Proposed action

Overall, the Delegate considers that sufficient data and justification have been provided to support the registration of Glycophos on quality, safety and efficacy grounds for the adult and paediatric patients as a supplement to parenteral nutrition to meet the daily requirements of phosphate.

[6] The sponsor must still comply with routine product vigilance and risk minimisation requirements.

Advisory Committee Considerations[7]

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Glycophos (sodium glycerophosphate (as hydrate) concentrated solution for injection, indicated for:

> *Glycophos is indicated in adult and paediatric patients as a supplement to parenteral nutrition to meet the daily requirements of phosphate.*

Specific conditions of registration applying to these goods

For all injectable products the Product Information must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Glycophos approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

[7] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

Therapeutic Goods Administration

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