AUSTRALIAN PRODUCT INFORMATION – GLYCOPHOS® (SODIUM GLYCEROPHOSPHATE)

1. NAME OF THE MEDICINE

Sodium glycerophosphate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sodium glycerophosphate 4.32 g/20 mL ampoule.

Each 1 mL of Glycophos® contains 306.1 mg of sodium glycerophosphate hydrate, equivalent to 216 mg of sodium glycerophosphate.

Each 1 mL of Glycophos® corresponds to 1 mmol of phosphate and 2 mmol of sodium.

For the full list of excipients, see Section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

Glycophos® Concentrated injection solution for infusion is a sterile, clear, colourless solution essentially free from visible particles.
Osmolality: 2760 mOsm/kg water
pH: 7.4

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Dose and method of administration

Method of administration

For intravenous infusion only. Glycophos® must not be given undiluted. The infusion duration depends on the admixture; the infusion must be administered over a period of at least 8 hours.

Dosage (dose and interval)

ADULTS
The recommended dosage should be individualized 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 PN 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 individualized 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.

Instructions for use

Glycophos® must not be given undiluted.
For single use in one patient only. Any excess infusion solution in an opened package must be discarded and must not be kept for later use.

Compatibility

Additions should be made aseptically.

Glycophos® is used as an additive to TPN admixtures in compounded bags where compatibility data are available. Compatibility of Glycophos® has been demonstrated for use with the named branded products SMOFlipid, Aminoven 10%, Addaven, Soluvit N and Vitalipid N in defined amounts and standard IV solutions of glucose and electrolytes in defined concentrations. Glycophos® can also be added to the SmofKabiven and Kabiven range of products.

In addition,

- up to 10 mL of Glycophos® and 10 mmol of calcium (as calcium chloride) can be added to 1000 mL of Glucose 50 mg/mL.
- up to 20 mL of Glycophos® and 20 mmol of calcium (as calcium chloride) can be added to 1000 mL of Glucose 200 mg/mL.
- up to 60 mL of Glycophos® and 24 mmol of calcium (as calcium chloride) can be added to 1000 mL of Glucose 500 mg/mL.

Infusion time

The infusion duration depends on the admixture; the infusion must be administered over a period of at least 8 hours.

Stability

When additions are made to an infusion solution, the infusion should be completed within 24 hours at 20-25°C from the time of preparation to avoid microbiological contamination.

4.3 Contraindications

Glycophos® should not be given to patients in a state of dehydration or with hypernatraemia, hyperphosphataemia, severe renal insufficiency or shock.

4.4 Special warnings and precautions for use

Identified precautions

Glycophos® should be used with caution in patients with impaired renal function. The serum phosphate levels of all patients should be monitored regularly.

Glycophos® must not be given undiluted.

Use in the elderly

No data is available.

Paediatric use

Glycophos® is recommended for use is paediatric patients.

Effects on laboratory tests

No data is available.

Long term parenteral nutrition

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.

4.5 Interaction with other medicines and other forms of interactions

No interactions with other drugs have been observed, but a moderate fall in serum phosphate can be seen during carbohydrate infusions.

4.6 Fertility, pregnancy and lactation

Effects on fertility

The potential effects of Glycophos® on fertility and general reproductive performance have not been determined in animal studies.

Use in pregnancy

Animal reproduction studies or clinical investigations during pregnancy have not been carried out with Glycophos®. However, the requirements of phosphate in a pregnant woman are slightly increased compared to non-pregnant women.

No adverse events are to be expected when Glycophos® is administered during pregnancy.

Use in lactation

It is not known whether Glycophos® can enter maternal milk. Glycophos® should be used during lactation only if clearly needed.

4.7 Effects on ability to drive and use machines

No effects on the ability to drive and use machines are to be expected.

4.8 Adverse effects (undesirable effects)

Glycophos® is generally safe and very well-tolerated in recommended doses.

In two (2) phase I studies, Glyc-001-C P1 and KABI-0003-C P1, conducted in healthy individuals, TEAEs were coded using MeDRA. The incidence of TEAEs reported in these studies is provided in Table 1 below.

Table 1: Number and Percentage of Subjects Who Experienced Treatment-Emergent Adverse Events in Studies Glyc-001-C P1 and KABI 003-C P1 (Healthy Adult Volunteers)

	Study Glyc-001-C P1		**Study KABI-003-C P1**	
MedDRA System Organ Class Preferred Term	**I-Phosphate n (%) N = 25**	**Glycophos® n (%) N = 25**	**Kabiven Peripheral n (%) N = 10**	**Glycophos® n (%) N = 10**
Any Adverse Event	11 (44.0)	9 (36.0)	0	3 (30.0)
Gastrointestinal Disorders				
Dry mouth	0	1 (4.0)	0	0
Nausea	1 (4.0)	0	0	0
Constipation	0	0	0	1 (10.0)
General Disorders and Administration Site Conditions				
Infusion site haematoma	0	0	0	1 (10.0)
Infections and Infestations				
Nasopharyngitis	1 (4.0)	0	0	0
Oral herpes	1 (4.0)	1 (4.0)	0	0
Investigations				
Haemoglobin decreased	1 (4.0)	0	0	0
Neutrophil count decreased	1 (4.0)	1 (4.0)	0	0
Metabolic and Nutrition Disorders				
Hypocalcaemia	5 (20.0)	4 (16.0)	0	0
Musculoskeletal and Connective Tissue Disorders				
Back pain	0	1 (4.0)	0	0
Nervous System Disorders				
Headache	0	2 (8.0)	0	1 (10.0)
Reproductive System and Breast Disorders				
Dysmenorrhoea	1 (4.0)	0	0	0

MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients
Study Glyc-001-C P1 used a crossover design; therefore, the subjects are identical in both treatment groups.

In two (2), two-way cross-over healthy adult trials, the observed drug-related Treatment- Emergent Adverse Events (TEAEs) with investigator implied causality in both Glycophos® and comparator pooled groups are presented in the Table 2 below.

Table 2: Summary of Drug-related TEAEs

Drug-related TEAEs, n (%) of subjects	**Glycophos® (n=35)**	**Comparator (n=35)**
Metabolism and nutrition disorders Hypocalcaemia	4 (11%)	5 (14%)
Nervous system disorders Headache	1 (3%)	-

No other adverse reactions have been reported with glycerophosphate.

Post marketing

From 1993 until June 2017, 98 adverse drug reactions (ADRs) were reported in 46 patients. These included 4 serious listed ADRs in 2 patients (central line infection, blood pressure decreased, tremor, and rash), all from spontaneous or regulatory authority reports, and 28 serious unlisted ADRs in 13 patients; 5 serious unlisted ADRs in 2 patients were from clinical studies (body temperature increase, sweating, sepsis, chills, malaise), and 23 serious unlisted ADRs in 11 patients were from spontaneous or regulatory authority reports (cardiac arrest, tachycardia, lip oedema, vomiting, administration site reaction, fever [2 cases], hyperpyrexia, chills, allergic reaction, Pantoea agglomerans infection [3 cases], salmonella infection, oxygen saturation decreased, hypernatremia, hypoglycaemia, tremor, unresponsive to stimuli, respiratory symptoms (includes dyspnoea) [2 cases], rash, petechial).

Reporting of suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

4.9 Overdose

No adverse effects of an overdose have been reported. Most patients in need of intravenous nutrition have an increased capacity to handle glycerophosphate. See also Section 4.3 Contraindications.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia) or 0800 764 766 (New Zealand).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Glycerophosphate is a metabolic intermediate in fat metabolism.

Clinical trials

The efficacy and safety of Glycophos® as a supplement to parenteral nutrition to meet the daily requirements of phosphorus has been examined in one randomised, prospective, double-blind, parallel-group study in neonates. In the study 41 neonates aged < 1 month were administered 1 mmol/kg/day phosphate from either Glycophos® (19 patients) or inorganic phosphate

(22 patients), administered as part of each patient's parenteral nutrition regimen over 24 hours/day for up to 7 days.

Premature discontinuation of the study, due to the unforeseen difficulties in the timely recruitment of patients resulted in 18 on inorganic phosphate and 17 on glycerophosphate completing the study.

In the study the primary efficacy variables were AUC for serum phosphate and serum calcium with secondary variables accumulated urinary phosphate and urinary calcium. The ratio of AUCs for serum phosphate and serum calcium for patients who received Glycophos® to those who received inorganic phosphate were 2.15 for serum phosphate and 1.21 for serum calcium. Statistical significance for the difference could not be shown between the two groups for the primary efficacy variables (AUCs for serum calcium and serum phosphate)®. For the secondary efficacy variables, accumulated urinary phosphate (A_eP) and urinary calcium (A_eCa) ratios for patients who received Glycophos® to those who received inorganic phosphate were 1.10 for serum phosphate and 0.61 for serum calcium. There were no differences in adverse events between the two treatment groups, and no adverse events were considered to be related to treatment.

A study comparing bioavailability of phosphate from a parenteral all-in-one solution (Kabiven Peripheral) with that from Glycophos® was a double blind, randomised two sequence, two treatment crossover study in 10 healthy adults. Subjects received Glycophos® and Kabiven Peripheral providing equimolar amounts of phosphate (0.101 mmol/kg). The primary PK variables were $AUC_{0\text{-}36h}$, C_{max}, and C_{ss}, and secondary variables included t_{max}, λ_z, $t_{1/2}$, and A_e. Additionally, the areas under the serum concentration-time curves during the infusion (from Hour 0 to Hour 8; $AUC_{0\text{-}8h}$), the 8 hours immediately following the infusion (from Hour 8 to Hour 16; $AUC_{8\text{-}16h}$), and the last hours of the observation period (from Hour 16 through Hour 36; $AUC_{16\text{-}36h}$) were also calculated. The 90% CI of the ratio for Kabiven Peripheral/Glycophos® for all primary parameters ($AUC_{0\text{-}36h}$, C_{max}, and C_{ss}) were within the range of 0.8 to 1.25; thus, bioequivalence for inorganic phosphate concentration in serum of both treatments was accepted. The A_e of inorganic phosphate was greater with administration of Glycophos® compared to Kabiven Peripheral (the lower limit of the 90% CI (0.6266) was below 0.8, rejecting bioequivalence between both investigational products). Also, statistical significance for the difference was not shown ($p = 0.0694$).

There is limited clinical trial data available on the use of Glycophos® but there is considerable postmarketing experience on the use of glycerophosphate.

5.2 Pharmacokinetic properties

To become bio-available, it is necessary for the phosphate group to be hydrolysed from the glycerophosphate molecule. The hydrolysis occurs maximally at a plasma concentration of >0.7 mmol/L. The release of phosphate into the incubation medium over a 2-hour period corresponded to a hydrolysis rate of 0.12 mmol/L/h for glycerophosphate. Subsequent studies on 3 other samples using lower glycerophosphate concentrations gave a mean hydrolysis rate of approximately 0.09 mmol/L/h. Assuming that all hydrolysis of glycerophosphate takes place in plasma, about 12-15 mmol of sodium glycerophosphate will be hydrolysed each day in individuals with normal serum alkaline phosphatase. The accuracy of these kinetic rates of hydrolysis *in vitro* in relation to the rates *in vivo* has not been established.

No pharmacokinetic data is available for infants.

5.3 Preclinical safety data

No data is available.

Genotoxicity

No data is available.

Carcinogenicity

No data is available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Hydrochloric acid (pH adjuster)
- Water for injections

6.2 Incompatibilities

Glycophos® may only be added to or mixed with other medicinal products for which compatibility has been documented. For compatibility information, please refer to section 4.2 Dose and method of administration.

6.3 Shelf life

Shelf Life before mixing
3 years. The expiry date can be found on the packaging.

Shelf Life after mixing
Chemical and physical in-use stability of the mixed product has been demonstrated for 24 hours at 20-25°C.
To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2°-8°C for not more than 24 hours or 6 hours at room temperature.

6.4 Special precautions for storage

Store below 25°C.
Do not use after the expiry date stated on the label.
Product is for single use in one patient only. Discard any residue.

6.5 Nature and contents of container

The product is contained in a 20 mL polypropylene ampoule.

Pack size

Box of 20 x 20 mL ampoules, AUST R 312021

6.6 Special precautions for disposal

For single use in one patient only. Any excess infusion solution in an opened package must be discarded and must not be kept for later use.

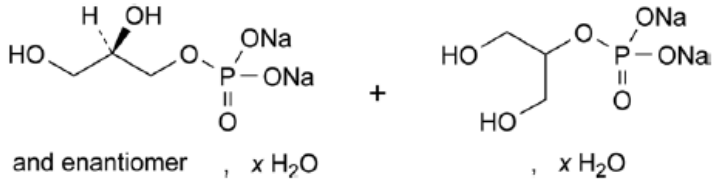
Disposal

In Australia, any unused medicinal product or waste material should be disposed in accordance with local requirement.

6.7 Physicochemical properties

Chemical structure

Sodium glycerophosphate hydrate



Empirical formula: $C_3H_7Na_2O_6P$, x H_2O where the degree of hydration (x) = 4 to 6
Molecular weight: 234.05 g/mol (hydrated); 216.05 g/mol (anhydrous)

CAS number

55074-41-1 (hydrated)
1334-74-3 (anhydrous)

7. MEDICINE SCHEDULE (POISONS STANDARD)

Australia: Not Scheduled.
New Zealand: General Sale Medicine

8. SPONSOR

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Level 2, 2 Woodland Way
Mount Kuring-gai, NSW 2080
Australia.

Fresenius Kabi New Zealand Limited
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Mangere, Auckland 2022
New Zealand.

9. DATE OF FIRST APPROVAL

14 November 2019

10. DATE OF REVISION

Not applicable

Summary table of changes:

Section changed	Summary of new information
N/A	New Australian Product Information