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Public Assessment Report

Scientific discussion

Sodium glycerophosphate Fresenius
Sodium glycerophosphate

2021/01851-REG

Date: April 2025

This module reflects the scientific discussion for the approval of Sodium glycerophosphate Fresenius. The marketing authorisation was issued on 14 August 2024. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the State Institute for Drug Control has granted a marketing authorisation for **Sodium glycerophosphate Fresenius.** 216 mg/mL, concentrate for solution for infusion from Fresenius Kabi s.r.o., Czech Republic.

The product is indicated in adults, adolescents and children as a supplement to parenteral nutrition to meet the requirements of phosphate.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC, which corresponds to Article 49 (1) b) of Law on medicinal products and medical devices No. 362/2011.

II. QUALITY ASPECTS

II.1 Introduction

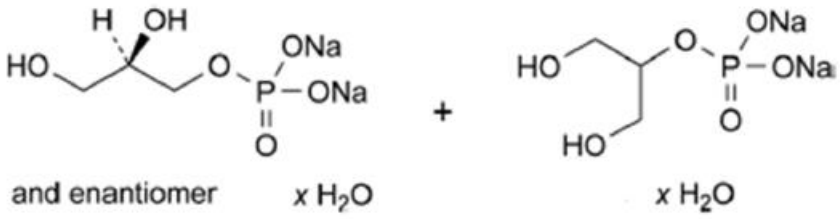
The finished product is presented as a concentrate for solution for infusion containing 216 mg/mL of sodium glycerophosphate as an active substance. Concentrate for solution for infusion is packed in polypropylene ampoule (20 ml) and available as packs of 20 ampoules. It is a clear and colourless solution with pH 7.4. Osmolality of the solution is 2760 mosm/kg water.

The other ingredients are:
hydrochloric acid (for pH adjustment)
water for injections

II.2 Drug Substance

Sodium glycerophosphate, hydrated

Active substance structure:



Empirical formula: $C_3H_7Na_2O_6P \times H_2O$

Degree of hydration x = 4 to 6, corresponding water content 25.0 - 35.0%

Chemical name: sodium glycerophosphate, hydrated

Appearance: White or almost white, crystalline powder or crystals.

Solubility: Freely soluble in water, practically insoluble in acetone and in ethanol (96 per cent).

Manufacturing: Active substance master file (ASMF) procedure was followed and approved for this drug substance. The manufacturing process, its control, validation and materials used were described in sufficient details.

Specifications: The active pharmaceutical ingredient (API) specification follows the Ph. Eur. monograph on sodium glycerophosphate, hydrated No. 1995 with the addition of the microbiological tests and test for residual solvent ethanol.

Stability: Stability results of five batches cover 60 months at long term storage conditions (25°C / 60% RH). Stability study of three batches at intermediate (30°C / 65% RH) and accelerated (40°C / 75% RH) storage conditions cover 12 months and 6 months.
Retest period of 36 months when kept in well-closed containers, in a dry place and at room temperature was accepted.

II.3 Medicinal Product

Pharmaceutical development

The proposed manufacturing process using the Blow-Fill-Seal (BFS) technique was developed in 1995-1997. The drug product consists of API dissolved in water for injections. Hydrochloric acid is used to adjust the pH. The solution is filled in polypropylene ampoules and terminally sterilised by validated steam sterilization cycle ($121°C \geq F_o = 12$).
The pharmaceutical development was satisfactorily presented.
Two studies of drug product compatibility with other Fresenius Kabi products performed in 1989 and 1992 were enclosed. The composition of the Fresenius Kabi products used in admixtures was included in the reports and conclusions were presented.

Manufacturing of the product

The drug product is manufactured as a concentrate for solution for infusion by following steps:
1. Preparation of the solution
2. Preparation of the ampoule by BFS system
3. Filling
4. Sterilisation
5. Packaging
6. Final physical inspection

A manufacturing flow chart with highlighted in-process control (IPC) and CPs, narrative description of manufacturing process and list of manufacturing equipment have been provided.

Product specification

The finished product release and shelf-life specifications include appropriate tests and limits for appearance: colour and clarity (Ph.Eur.), assay: sodium, phophorus, free phosphorus (in-house), pH (Ph.Eur.), extractable volume (in-house), sub-visible particles (Ph.Eur.), bacterial endotoxins (Ph.Eur.), and sterility (Ph.Eur.). The proposed specification for the finished product is in line with ICH Q6A.

Stability

The long-term stability studies (25°C/40% RH, 30°C/35% RH, 30°C/75% RH) were supplemented by results covering 24 months. All results were well within the acceptance criteria showing only little variation.
Based on provided stability data covering 24 months shelf-life of 36 months with no special storage conditions was accepted.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance, and finished product was presented in a suitable manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The quality of the product is considered acceptable when used in accordance with the conditions defined in the SmPC.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of sodium glycerophosphate are well known. As sodium glycerophosphate is a widely used, well-known active substance, the applicant has not provided additional studies, and further studies were not required. An overview based on the literature review was, thus, appropriate.

The Non-Clinical Overview on the pre-clinical pharmacology, pharmacokinetics and toxicology was adequate.

III.2 Pharmacology

Primary pharmacodynamics

Special studies on the mode of action and/or effects of glycerophosphate in relation to its desired therapeutic target (primary pharmacodynamics) have not been performed. The primary pharmacodynamic effect of sodium glycerophosphate as a phosphate supplement is to compensate phosphate deficiency in hypophosphatemia states or to avoid hypophosphatemia.

Secondary pharmacodynamics

Special studies on the mode of action and/or effects of a substance not related to its desired therapeutic target (secondary pharmacology) have not been performed. Secondary pharmacodynamic effects should not occur at the doses employed (e.g. substitution therapy with physiological doses). Furthermore, no effects on blood pressure, heart rate or respiratory rate due to glycerophosphate have been reported in clinical trials.

The applicant has provided a summary on the secondary pharmacology of glycerol and justification of not performing any studies with glycerophosphate, which was considered acceptable.

III.3 Pharmacokinetics

The pharmacokinetics of DL-glycerol-3-phosphate (alpha-glycerophosphate) after single injection or continuous infusion has been studied in rats (Bässler and Hassinger 1976). L-glycerol-3-phosphate was rapidly eliminated from the blood following a single injection (0.5 mmol/kg BW of the racemate in 30 sec) with an elimination half-life of 11 min. About 40% of the L-enantiomer administered was excreted in the urine, which indicates that metabolism only accounts for a part of the overall elimination. The enzymatic method used for blood and urine analyses only measured the L-form and thus nothing can be said about the elimination of the D-enantiomer. During intravenous infusion of the racemate for 6 hours, at a dose roughly equivalent to 0.2 g/kg bw (approximately 1 mmol/kg bw), the urinary excretion only amounted to 10% of the administered dose (or 20% of the administered L-form). Increased blood levels of inorganic phosphate, glycerol, and total phosphate as well as

increased urinary excretion of these substances suggested intravascular hydrolysis. The fact that the urinary excretion of esterified phosphate was exactly twice that of the L-form indicates that the two enantiomers are hydrolysed in the blood to the same extent, which was also confirmed by *in vitro* experiments.

The *in vitro* hydrolysis in plasma of sodium glycerophosphate was found to be complete and in general the rate of breakdown correlated well with the alkaline phosphatase catalytic activity concentration.

III.4 Toxicology

Single dose administration of glycerophosphate administered *i.v.* bolus to rats resulted in LD_{50} values of 3,800 and 3,400 mg/kg bw, respectively, for α- and ß-glycerophosphate.

The applicant has presented a tabular summary of the available repeat dose toxicity studies performed either with glycerophosphate or glycerol in rodents and non-rodents. Toxicity, when observed was only seen at dose levels much higher than anticipated trough treatment with this medicinal product.

Based on *in vivo* as well as *in vitro* tests as presented by the applicant, there was no evidence about any mutagenic potential for glycerophosphate or glycerol.

There have been no studies on the carcinogenicity of glycerophosphate. It can be agreed that no carcinogenicity is expected since glycerophosphate is an endogenous substance.

No specific reproduction studies have been performed with glycerophosphate. This is acceptable provided that glycerophosphate is endogenous substance.

III.5 Ecotoxicity/environmental risk assessment (ERA)

According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMA, Doc. Ref. EMEA/CHMP/SWP/4447/00, June 2006), vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempted from performing ERA because they are unlikely to result in significant risk to the environment.
As the active pharmaceutical ingredient of Sodium glycerophosphate Fresenius is sodium glycerophosphate, hydrated, ATC-group: electrolyte solutions (B05XA14), ERA was not required.

III.6 Discussion on the non-clinical aspects

No new non-clinical studies were performed by the applicant. An overview based on literature review was appropriate for a chosen legal basis, i.e. bibliographic application. This was also considered acceptable in view and the nature of the active substance, sodium glycerophosphate and decades of experience with the clinical use of this active substance. Sodium glycerophosphate Fresenius is intended to maintain/re-establish physiological levels of phosphate, thus when administered under proper monitoring and appropriate dose adjustment, no relevant toxic effects are expected.
The active substance of Sodium glycerophosphate Fresenius is a natural substance. Therefore, it is not expected to represent a risk for the environment and an environmental risk assessment was not deemed necessary.

The toxicological properties of glycerophosphate have been reviewed adequately in the applicant's non-clinical overview. Data include information regarding the acute and chronic toxicity of glycerophosphate from numerous animal models (rodents and non-rodents). No mutagenic or carcinogenic potential was described and is expected according to the submitted data. Reproductive and developmental toxicity data was comprehensively reviewed and confirms no teratogenic, embryotoxic and fetotoxic effect of glycerophosphate in different animal species.

This information about summary of non-clinical data is adequately presented in section 5.3 of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

Sodium glycerophosphate is indicated in adult patients and in paediatric population as a supplement in intravenous nutrition to meet the requirements of phosphate. Phosphorus as phosphate is an essential element for key enzymatic processes such as glycolysis, ammonia genesis, oxidative phosphorylation, buffering, and it influences the oxygen-carrying capacity of haemoglobin. Subjects requiring prolonged or long-term total parenteral nutrition may experience significant and clinically relevant symptoms of hypophosphatemia.

This marketing authorisation application was submitted based on scientific bibliographical evidence supporting the risk-benefit profile for sodium glycerophosphate and provides adequate justification for the marketing approval of the product. A literature review was undertaken to identify and retrieve relevant research articles describing the clinical pharmacology, efficacy and the safety profile of sodium glycerophosphate.

IV.2 Pharmacokinetics

Pharmacokinetic profile of glycerophosphate was evaluated in three studies, two studies in healthy volunteers (Study Glyc-001-C P1 and Study KABI-003-C P1) and one (Study 90-024-00) in postoperative patients.

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. Study KABI-003-C P1 proved similar pharmacokinetic profile of glycerophosphate for pharmacokinetic variables $AUC_{0\text{-}36h}$, C_{max}, and C_{ss}. Although the study Glyc-001-C P1 did not demonstrate bioequivalence for the primary pharmacokinetic parameter (Ae), secondary parameters (AUC and C_{max}) of inorganic phosphate were, however, similar.

Overall, according to the submitted studies, sodium glycerophosphate showed 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.

IV.3 Pharmacodynamics

The proposed use of Sodium glycerophosphate Fresenius is in adult and paediatric patients as a supplement to parenteral nutrition to meet the requirements of phosphate.
Pharmacodynamic effects of Sodium glycerophosphate Fresenius were evaluated in clinical study; Study Glyc 001-C P1 conducted by the applicant. Expected pharmacodynamic effect was shown for parathormone levels, which increased after administration of Sodium glycerophosphate Fresenius or I-Phosphate. No significant difference was detected between the two treatments. Furthermore, for calcium, sodium and potassium in serum and urine, similar changes were observed for Sodium glycerophosphate Fresenius and I-Phosphate.

Pharmacodynamic effects were further documented by 5 other published studies, 4 of which were conducted in paediatric (low birth weight neonates/preterm neonates) and 1 in adult patients. The studies presented by the applicant demonstrate the claimed pharmacodynamic effect of glycerophosphate in the management of daily requirements of phosphate as part of the parenteral nutrition.

IV.4 Clinical efficacy

To support the clinical efficacy the applicant provided 4 clinical studies which were conducted directly with Sodium glycerophosphate Fresenius and a review of published literature. Three studies (Study Glyc-001-C P1, Study KABI-003-C P1 and Study 91-114) were conducted as randomised double-blind and active controlled studies. Sodium glycerophosphate Fresenius was compared to either inorganic phosphate (monopotassium phosphate) or other glycerophosphate containing medicinal product.

Study 90-024-00 was designed as an open study with sodium glycerophosphate, to document safety and metabolism of sodium glycerophosphate in postoperative patients requiring total parenteral nutrition. This study had no comparator. The daily dose of 20 mmol of glycerophosphate was administered and corresponded to the daily requirements of phosphorus in adults.

The efficacy of Sodium glycerophosphate Fresenius was evaluated based on AUC for phosphate and calcium, cumulative excretion of phosphorus and calcium and phosphate balance, sodium, potassium and parathormone levels. Response to changes in systemic phosphate levels were evaluated. In addition to this, the efficacy was demonstrated by measuring bone mineral density and mean bone strength in preterm neonates as presented in supportive published studies.

The applicant also presented a review of 5 published studies which evaluated parenteral administration of organic phosphate to neonates. Glycerophosphate was administered to neonates in 2 of the discussed studies (Costello, 1995 and Pereira-da-Silva, 2011), and one of them refers directly to Glycophos (Pereira-da-Silva, 2011). Other studies where products containing different organic phosphates (calcium glycerophosphate, disodium glucose-1-phosphate) were administered to the patients considered as supportive only.

IV.5 Clinical safety

The safety data of Sodium glycerophosphate Fresenius based on two Phase 3 and two Phase 1 studies were reviewed.
There were no treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) or deaths reported as related to glycerophosphate in these studies, except of hypocalcaemia and headache in the healthy volunteer's study group (Phase 1 studies Glyc-001-C P1 and KABI-003-C P1). Both hypocalcaemia and headache are listed as adverse effects in SmPC.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Sodium glycerophosphate Fresenius.

- Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

IV.7 Discussion on the clinical aspects

No new clinical studies were performed by the applicant. An overview based on literature review was appropriate for a chosen legal basis, i.e. bibliographic application. Scientific bibliographical evidence supported the risk-benefit profile for sodium glycerophosphate and provided adequate justification for

the marketing approval of the product. Information about summary of clinical data is adequately presented in sections 4 and 5 of the SmPC.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was Czech.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

This was a marketing authorisation application (MAA) of medicinal product for human and use as it is defined in Article 10(a) (bibliographic application) of the European Directive 2001/83/EC as amended corresponding to Article 49 (1) b) of Law on medicinal products and medical devices No. 362/2011 as amended. MAA was submitted via national procedure according to Article 52 of Law on medicinal products and medical devices as amended.

From a (non-)clinical point of view, the application contained adequate (non-)clinical data that supported chosen legal basis – bibliographic application.

Quality aspects of the dossier were adequately described; specifications of the active pharmaceutical ingredient (API) follow the Ph. Eur. monograph on sodium glycerophosphate, hydrated No. 1995 and that of finished medicinal product are in line with ICH Q6A.

Based on submitted data referring to published scientific literature applicant adequately addressed the requirements for a bibliographical application and sufficiently demonstrated the quality of a medicinal product in the scope of this MAA. Therefore, the State Institute for Drug Control granted the marketing authorisation on 14 August 2024.

Literature references (mentioned in PAR)

Bassler KH, Hassinger W. [The suitability of DL-glycerol-3-phosphate for parenteral substitution of inorganic phosphate]. Transfus Med Hemother. 1976;3(3):138-42.

Costello I, Powell C, Williams AF. Sodium glycerophosphate in the treatment of neonatal hypophosphataemia. Arch Dis Child Fetal Neonatal Ed. 1995;73(1):F44-5.

Pereira-da-Silva L, Costa A, Pereira L, Filipe A, Virella D, Leal E, Moreira A, Rosa M, Mendes L, Serelha M. Early high calcium and phosphorus intake by parenteral nutrition prevents short-term bone strength decline in preterm infants. J Pediatr Gastroenterol Nutr. 2011;52(2):203-9.