COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Nitroglycerine-hameln 1 mg/ml, solution for infusion

(glyceryl trinitrate)

NL Licence RVG 119982

Date: 21 April 2020

This module reflects the scientific discussion for the approval of Nitroglycerine-hameln. The marketing authorisation was granted on 2 November 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
GTN	Glyceryl Trinitrate
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
NTG	Nitroglycerin
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Nitroglycerine-hameln 1 mg/ml, solution for infusion from Hameln Pharma Plus GmbH.

The product is indicated for:

- Unresponsive congestive heart failure, including that secondary to acute myocardial infarction; acute left-sided heart failure and acute myocardial infarction
- Refractory unstable angina pectoris and coronary insufficiency, including Prinzmetal's angina
- Control of hypertensive episodes and/or myocardial ischaemia during cardiac surgery.

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

This national procedure concerns a hybrid application. Reference is made to the product Nitro "Pohl" Infus voor perfusorpompsystemen 1 mg/ml, solution for infusion (NL Licence RVG 10393), which has been registered in the Netherlands by G. Pohl-Boskamp on 19 September 1984 (MRP NL/H/0613/001). The product at issue differs from the reference product with regard to the therapeutic indications. The following additional surgical indications were applied for:

- Control of hypertensive episodes and/or myocardial ischaemia during and after cardiac surgery.
- Induction of controlled hypotension for surgery.

Non-clinical and clinical studies were not performed with Nitroglycerine-hameln 1 mg/ml itself, but literature data are submitted to 'bridge' to Nitro "Pohl" indications and provide support for the additional indications. On the basis of the assessment of this literature data, the MEB proposed a revised indication. The assessment of the additional surgical indications is discussed in section IV.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Nitroglycerine-hameln 1 mg/ml is a clear, colourless solution with pH 3-4 and osmolality of 270 – 310 mOsm/kg. Each ml of solution contains 1 mg of glyceryl trinitrate.

The product is presented in the volumes of 5 mL, 10 mL, 25 mL, and 50 mL. The composition of the four presentations is identical. The 5 mL, 10 mL, and 25 mL presentations are packed in glass ampoules. The 50 mL presentation is packed in glass vials with bromobutyl rubber stoppers.

The excipients are: water for injections, glucose monohydrate, hydrochloric acid.

II.2 Drug Substance

The active substance is glyceryl trinitrate, an established active substance. It is a clear colourless to light yellowish oily liquid. As it is not stable in pure form, a 1.96% (w/w) mixture with glucose monohydrate is used in the manufacture of the drug product. The active substance in pure form or the mixture with glucose are not described in the European Pharmacopoeia. A monograph is available for glyceryl trinitrate solution (in ethanol). The active substance is insoluble in water. The active substance has no asymmetric carbon atom and isomerism is therefore not relevant. As the active substance is dissolved in the drug product, polymorphism is not relevant either.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Data on the mixture with glucose are included in the dossier. This is acceptable as glyceryl trinitrate is not stable in pure form. The mixture with glucose is manufactured by the ASMF holder as well.

Manufacturing process

The manufacturing process of glyceryl trinitrate consists of a one step synthesis with the starting materials glycerol and mixed acid. The latter is a mixture of concentrated sulphuric- and nitric acid containing free sulfur trioxide. Both starting materials are acceptable as they are commodities in non-pharmaceutical markets. Water is the only solvent used. No metal catalysts are used.
Mixing with glucose occurs in a manufacturing formulation bunker using remote control. The active substance was adequately characterized and acceptable specifications were adopted for the starting materials, the solvent water, and reagents. The glucose monohydrate used to stabilize the drug substance complies with the Ph.Eur.

Quality control of drug substance

The drug substance specification of the MAH for pure glyceryl trinitrate is identical to that of the ASMF holder and contains tests for assay, appearance, identity, water, free acid or free

alkali, nitrite, nitrate, Abel test value and related substances. The specification for the mixture with glucose contains tests for assay, appearance, identity, water, acidic or alkaline impurities, nitrite, nitrate and related substances. Both specifications are acceptable.
Batch analysis data of the drug product manufacturer are provided on three batches of 1.96% (w/w) glyceryl trinitrate (GTN) on glucose, demonstrating compliance with the drug substance specification in place at the time of analysis.

Stability of drug substance
Due to the explosive nature of the active substance, no regular stability studies were carried out. Pure glyceryl trinitrate is maximally stored for four weeks after manufacture.
Stability data were provided on three production scale batches of 2.25% (w/w) GTN on glucose-monohydrate. At 25°C/60%RH the product remains stable for 36 months and no trends or changes are observed in any of the tested parameters. At 30°C/65%RH the analytical values of the decomposition product show an increase. The provided results justify a retest period of 12 months when stored at 15 – 30°C.

II.3 Medicinal Product

Pharmaceutical development
Marginal information has been provided on formulation and manufacturing process development. The main objective was to develop a “physiological solution”. The osmolality of the product is indeed in the physiological range. The pH is acidic due to the stability of the drug substance. The lack of development data has been justified with the fact that more than 100 batches of the drug product filled in ampoules or vials have been successfully manufactured since 2005, in accordance with specifications registered in another EU country (UK).
The provided compatibility data with other solutions and materials support the information on the diluted product as stated in sections 4.2, 6.3 and 6.6 of the SmPC.

Manufacturing process
The manufacturing process consists of the preparation of the bulk solution, sterile filtration, filling, and terminal sterilisation under Ph. Eur. conditions. Cooling down of the bulk solution, filtration and filling are carried out under nitrogen. The manufacturing process is regarded as standard process.
The manufacturing process was successfully validated on three pilot-scale batches of the 5 mL, 10 mL and 25 mL presentations, two pilot-scale batches of 50 mL presentation and three commercial-scale batches of the 10 mL and 50 mL presentations.

Control of excipients
Glucose monohydrate, water for injections, and nitrogen comply with the Ph. Eur. The components used to produce dilute hydrochloric acid are of compendial quality as well. The specifications for the excipients are acceptable.

Quality control of drug product

The product specification includes tests for appearance, extractable volume, identity of glyceryl trinitrate and glucose, pH, related substances, assay of glyceryl trinitrate and glucose, sterility, bacterial endotoxins and particulate matter. The release and shelf life specifications differ with regard to the acceptance criteria for assay of glyceryl trinitrate and specified and unknown impurities. The specification is acceptable.

Batch analysis data were provided on three pilot-scale batches of each presentation as well as on three commercial-scale batches of the 10 mL ampoule and 50 mL vial presentations, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided on three pilot-scale batches of each presentation as well as of three larger batches of the 10 mL presentation and four larger batches of the 50 mL presentation. A bracketing design was applied for the pilot-scale batches (stored at 25°C/60% RH for 36 months and at 40°C/75% RH for six months) and a matrixing design for the larger batches (stored at 30°C/75% RH for 36 months). The conditions for the pilot-scale batches were according to the ICH stability guideline. The conditions for the larger batches are according to the conditions for climate zone IV. The 5 mL, 10 mL and 25 mL presentations were stored in glass ampoules and the 50 mL presentation in glass vials with a bromobutyl rubber stopper. No significant changes were observed for the three ampoule presentations. Significant changes in assay were seen in the 50 mL glass vials at all storage conditions

The provided stability data support a shelf-life of three years for the ampoules without any special temperature storage conditions. The shelf-life of the vials cannot exceed 24 months when stored below 25°C. Both the ampoules and the vials need to be stored in the original package in order to protect from light.

Based on the results of in-use stability studies, the diluted drug product is stable for 24 hours at a temperature up to 25°C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Nitroglycerine-hameln 1 mg/ml, solution for infusion has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Nitroglycerine-hameln is intended for hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Nitro "Pohl" which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

No new clinical studies were provided in support of this hybrid application. The MAH provided a clinical overview referencing 124 articles dated between January 1975 and October 2015. This overview adequately describes the accepted cardiac indications for glyceryl trinitrate:

- Unresponsive congestive heart failure, including that secondary to acute myocardial infarction; acute left-sided heart failure and acute myocardial infarction.
- Refractory unstable angina pectoris and coronary insufficiency, including Prinzmetal's angina.

In addition to the above motioned indications the MAH requested two additional surgical indications:

- Control of hypertensive episodes and/or myocardial ischaemia during and after cardiac surgery,
- Induction of controlled hypotension for surgery.

The MAH provided an updated clinical overview of extra literature data on studies that evaluated the efficacy and safety of NTG use in the perioperative setting.

IV.2 Pharmacokinetics

Nitroglycerine-hameln 1 mg/ml, solution for infusion is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Nitroglycerine-hameln 1 mg/ml is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

IV.3 Clinical efficacy

In the updated clinical overview the MAH provided extra literature data on studies that evaluated nitroglycerin (NTG) use in the perioperative setting. The submitted data demonstrate that NTG can effectively reduce the arterial blood pressure in the perioperative setting, in particular during cardiac surgery. However, it is not known whether this provides any long-term benefit. Also, NTG can control myocardial ischemia during cardiac surgery and its prevention is an accepted indication for Nitroglycerine-hameln. Hypertension can occur in conjunction with myocardial ischaemia and the efficacy of NTG during cardiac surgery is sufficiently demonstrated. There are insufficient data to assess the Benefit/Risk in the postoperative setting.

Therefore, the MAH is requested to amend the indications as follows:

- *Control of hypertensive episodes and/or myocardial ischaemia during ~~and after~~ cardiac surgery,*
- ~~*Induction of controlled hypotension for surgery.*~~

Considering the above adjustment, the approved indication for Nitroglycerine-hameln is:

- Unresponsive congestive heart failure, including that secondary to acute myocardial infarction; acute left-sided heart failure and acute myocardial infarction
- Refractory unstable angina pectoris and coronary insufficiency, including Prinzmetal's angina
- Control of hypertensive episodes and/or myocardial ischaemia during cardiac surgery.

IV.4 Clinical safety

The MAH provided an updated clinical overview regarding the requested surgical indications. In the updated clinical overview no new safety concerns were raised. Reflex tachycardia was found as the main side effect of NTG, which is a well-known side effect of NTG.

The extensive use of and experience with NTG does not lead to cause for concern about safety when used for control of hypertensive episodes and/or myocardial ischaemia during cardiac surgery.

IV.5 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 Nitroglycerine-hameln 1 mg/ml.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	- Methaemoglobinaemia
Important potential risks	None
Missing information	- Use in pregnant/lactating women - Use in the paediatric population

The MEB agrees that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.6 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Nitro "Pohl" Infus voor perfusorpompsystemen 1 mg/ml, solution for infusion. No new clinical studies were conducted. The MAH demonstrated through a clinical overview that the efficacy and safety can be considered established for the use of the product in unresponsive congestive heart failure, refractory unstable angina pectoris and coronary insufficiency and control of hypertensive episodes and/or myocardial ischaemia during cardiac surgery. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 test consisted of: a pilot test with 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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

Nitroglycerine-hameln 1 mg/ml, solution for infusion has a proven chemical-pharmaceutical quality and is a hybrid form of Nitro “Pohl” Infus voor perfusorpompsystemen 1 mg/ml, solution for infusion. Nitro “Pohl” Infus voor perfusorpompsystemen is a well-known medicinal product with an established favourable efficacy and safety profile.

Two additional indications were applied for: ‘control of hypertensive episodes and/or myocardial ischaemia during and after cardiac surgery’ and ‘induction of controlled hypotension for surgery’. In the Board meetings of 2 March 2017 and 19 October 2017, the application was discussed. The board came to a positive conclusion for the adjusted indication: ‘control of hypertensive episodes and/or myocardial ischaemia during cardiac surgery’. This indication was considered justified based on the provided clinical overview.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Nitroglycerine-hameln with the reference product, and has therefore granted a marketing authorisation. Nitroglycerine-hameln was authorised in the Netherlands on 2 November 2018.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Product Information affected	Date of end of the procedure	Approval/ non approval	Summary/ Justification for refuse