

Public Assessment Report
Decentralised Procedure

**Heparin Sodium 5,000 IU/ml,
solution for injection**

(Heparin Sodium)

UK/H/6565/0001/DC
UK Licence No: PL 44124/0008

PANPHARMA

LAY SUMMARY

Heparin Sodium 5,000 IU/ml, solution for injection (heparin sodium)

This is a summary of the Public Assessment Report (PAR) for Heparin sodium 5,000 IU/ml, solution for injection (PL 44124/0008; UK/H/6565/0001/DC). It explains how Heparin sodium 5,000 IU/ml, solution for injection was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Heparin sodium 5,000 IU/ml, solution for injection.

The product will be referred to as Heparin throughout the remainder of this public assessment report (PAR).

For practical information about using Heparin, patients should read the package leaflet (PIL) or contact their doctor or pharmacist.

What is Heparin?

Heparin contains the active substance heparin sodium and belongs to a group of medicines called anticoagulants.

How does Heparin work?

Heparin is a naturally occurring anticoagulant and prevents the formations of clots.

How is Heparin used?

Heparin is used to treat and prevent: blood clots in leg veins; blood clots in the lung as well as the treatment of chest pains resulting from disease of the heart arteries; the treatment of severe blockages affecting arteries in the legs; the prevention of blood clots in the heart following a heart attack. Heparin is also used during heart and lung operations and during kidney dialysis.

What benefits of Heparin have been shown in studies?

The therapeutic benefit of Heparin in the specified indications has been well-established over the many years it has been used as an anticoagulant.

What are the possible side effects of Heparin?

The most common complication that may result from Heparin therapy is haemorrhage. An overly prolonged clotting time or minor bleeding during therapy can usually be controlled by withdrawing the drug.

Why was Heparin approved?

The MHRA decided that the benefits of Heparin outweigh the risks and recommended its approval.

What measures are being taken to ensure the safe and effective use of Heparin?

Suitable safety information has been included in the summary of product characteristics and the package leaflet for Heparin, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Heparin

The marketing authorisation for Heparin was granted on 21st July 2017. This medicine is subject to restricted medical prescription. For more information about treatment with Heparin, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in September 2017.

The full PAR for Heparin follows this summary.

TABLE OF CONTENTS

I	Introduction	P5
II	Quality assessment	P5
III	Non-clinical assessment	P7
IV	Clinical assessment	P8
V	User consultation	P9
VI	Overall conclusions and risk benefit assessment	P9
	Annex 1 – Table of content of the PAR update for MRP and DCP	P11

I INTRODUCTION

Based on the review of data on safety and efficacy the UK granted a Marketing Authorisation to Panpharma for the medicinal product Heparin (PL 44124/0008) on 21st July 2017. This product is a restricted prescription only medicine and is used to treat and prevent: blood clots in leg veins; blood clots in the lung as well as the treatment of chest pains resulting from disease of the heart arteries; the treatment of severe blockages affecting arteries in the legs; the prevention of blood clots in the heart following a heart attack.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference member State (RMS) and Malta as Concerned Member State (CMS), as a line extension to a previous DCP procedure UK/H/6565/1/DC for Heparin 5,000 IU/mL solution for injection (5mL vial) which was positively concluded 17th May 2016. This application was submitted under Article 10(a) of Directive 2001/83/EC, as amended, as a well-established use application. A clinical development programme was not undertaken and scientific clinical advice was not sought.

Heparin is a highly sulfated glycosaminoglycan polymer of varying chain size that is widely used as an injectable anticoagulant. Pharmaceutical-grade heparin is extracted from the mucosa of pig intestines or cattle lungs.

Heparin binds to the enzyme inhibitor antithrombin III causing a conformational change that results in its activation that then inactivates thrombin and other proteases involved in blood clotting, most notably factor Xa. The rate of inactivation of these proteases by antithrombin III can increase by up to 1000-fold following binding of heparin.

No new non-clinical or clinical data were submitted, which is acceptable given that this is a well-established use product that has been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and release of the product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letter' or 'exchange of information' issued by the inspection services of the competent authorities (of those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the application could be approved at the end of the procedure on 17th April 2017. After a subsequent national phase, a licence was granted in the UK on 21st July 2017.

II QUALITY ASPECTS

II.1 Introduction

Heparin sodium is a white or almost white powder, hygroscopic, freely soluble in water.

Heparin is a highly sulfated glycosaminoglycan polymer of varying chain size (molecular weight from 3 to 30 kDa) that is widely used as an injectable anticoagulant (though its physiological role in the body remains unknown). Pharmaceutical-grade heparin is extracted from the mucosa of pig intestines.

Heparin binds to the enzyme inhibitor antithrombin III causing a conformational change that results in its activation that then inactivates thrombin and other proteases involved in blood clotting, most notably factor Xa. The rate of inactivation of these proteases by antithrombin III can increase by up to 1000-fold following binding of heparin.

The finished product is packed into type I glass ampules in pack sizes of 10 ampules of 1ml of solution for injection.

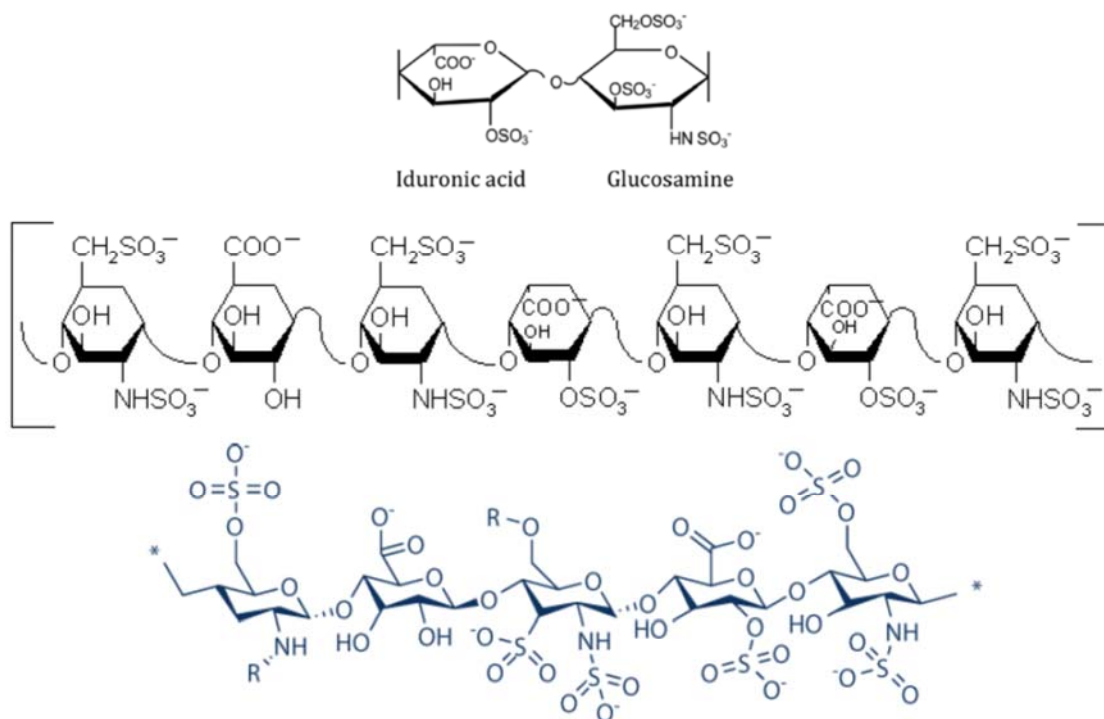
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug substance

INN: Heparin sodium

Chemical name: Heparin sodium

Structural formula: Heparin is a biopolymer belonging to the class of mucopolysaccharides. More than 70% of the structure of conventional heparins can be accounted for by repeating disaccharide units consisting of 1, 4-linked L-iduronic acid and D-glucosamine, the iduronic acid residues are O-sulphated at position 2, and the glucosamine residues are N-sulphated and O-sulphated at position 6.



Molecular formula: $C_{26}H_{41}NO_{34}S_4$

Molecular mass: The average molecular weight of heparin sodium is 12,000 Daltons

Appearance: A white, or almost white powder.

Solubility: Freely soluble in water, insoluble in ethanol, acetone, or other organic solvents.

Synthesis of the active substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specification tests are in place for all starting materials and reagents. The purification processes used are sufficient to inactivate any potential viral contamination of the

drug substance. All heparin sodium produced complies with the requirements of the current monograph for Heparin Sodium Ph. Eur. (01/2015:0333).

II.3 Medicinal Product

Pharmaceutical Development

The initial heparin sodium formulation was authorised in France in 1977 and presented in a 5mL vial. This initial formulation was administered with an electric syringe and therefore a preservative was added (initially methylparaben then changed to benzyl alcohol). The next presentation to be developed was 1mL ampoules of heparin sodium 5,000 IU/mL using benzyl alcohol as a preservative. As the current presentation of heparin sodium 5, 000 IU/mL in 1 mL ampoules is for single use only, the preservative, benzyl alcohol, has been removed. Heparin sodium 5,000 IU/mL is administered by continuous intravenous infusion in 5% glucose or 0.9% sodium chloride or by intravenous injection, or by subcutaneous injection. The excipients are sodium chloride, sodium hydroxide, hydrochloric acid and water for injections.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients. The specifications of excipients are as per the requirements of the European Pharmacopoeia Monographs.

None of the excipients used contain material of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing processes have been validated at commercial scale batch size and have shown satisfactory results.

Finished Product Specification

The finished product specification is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided which comply with the release specification. Certificates of Analysis have been provided for several batches.

Stability of the product

Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of five years with the storage conditions 'do not freeze'. In addition, a shelf-life after reconstitution in glucose 5% and in 0.9% sodium chloride solution has been demonstrated for 48 hours at 18-22°C.

II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of this application from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of Heparin are well-established, no new non-clinical studies are required and none have been provided.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)

As Heparin is intended for generic substitution, it is not expected to lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS**IV.1 Introduction**

The clinical pharmacology of Heparin is well-known. No new pharmacodynamics or pharmacokinetic data are provided or required for this application.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of Heparin.

IV.2 Pharmacokinetics

No new pharmacokinetic data were submitted and none were required for an application of this type.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy

No new clinical efficacy data were submitted and none were required for an application of this type.

IV.5 Clinical safety

No new clinical safety data were submitted and none were required for an application of this type.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), 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 Heparin.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Summary table of safety concerns:

Summary of safety concerns	
Important identified risks	• Hypersensitivity • Bleeding disorders • Heparin induced thrombocytopenia and thromboembolic complications • Toxic or anaphylactoid reaction to benzyl alcohol content. • Abortion or premature births in case of use during pregnancy • Osteoporosis or exacerbation of osteoporosis especially in predisposed patients and in case of use during pregnancy or breastfeeding • Hyperkalemia
Important potential risks	• Skin necrosis
Missing information	• None

Routine pharmacovigilance and routine risk minimisation are proposed. No additional pharmacovigilance or additional risk minimisation measures are proposed. Follow up forms are proposed in order to gather follow up information on any cases of pregnancy. This is considered a routine pharmacovigilance activity.

IV.7 Discussion on the clinical aspects

There are no objections to the approval of this application from a clinical viewpoint.

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 PIL was English.

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

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with Heparin is considered to have demonstrated the therapeutic value of the compound. The product is bioequivalent to the marketed reference product and the benefit-risk balance is considered similar and positive.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The following labelling is the approved label mock-ups for this medicine.

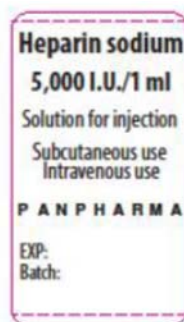
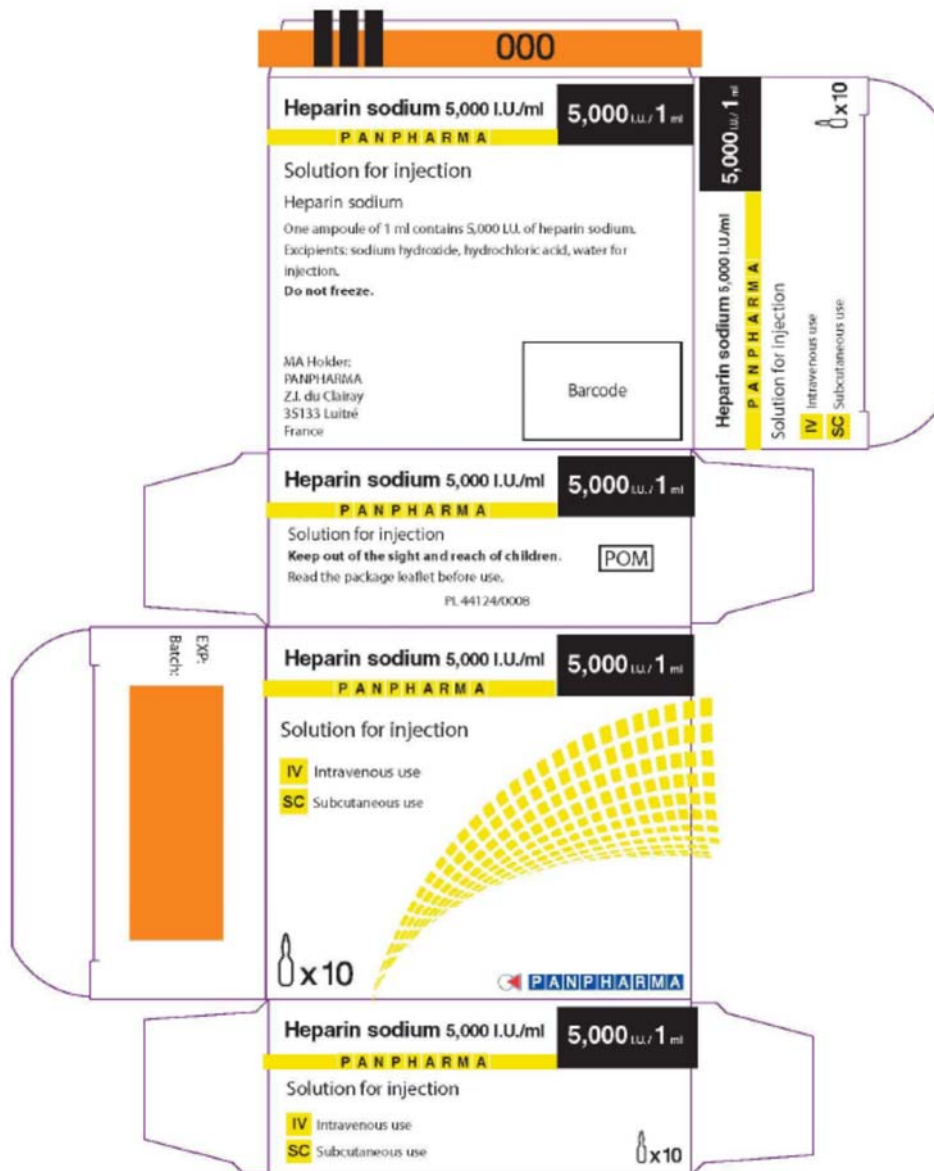


Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment
Report (Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)