Date: 16 February 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Heparin Sintetica, solution for infusion

International non-proprietary name: heparin sodium
Pharmaceutical form: solution for infusion
Dosage strength: 20,000 IU/48 ml
Route(s) of administration: i.v.
Marketing Authorisation Holder: Sintetica SA
Marketing Authorisation No.: 67780
Decision and Decision date: approved on 20 December 2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance heparin sodium of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

Treatment of thromboembolic disease of all causes and at any site, and relay treatment following thrombolytic therapy; in the event of myocardial infarction; inhibition of coagulation in the event of extracorporeal circulation and haemodialysis.
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2.2.2 Approved Indication

Treatment of thromboembolic disease of all causes and at any site, and relay treatment following thrombolytic therapy; in the event of myocardial infarction; inhibition of coagulation in the event of extracorporeal circulation and haemodialysis.

2.2.3 Requested Dosage

As required based on the results of coagulation tests or schematically depending on the indication.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	25 November 2019
Formal control completed	30 June 2020
List of Questions (LoQ)	27 October 2020
Answers to LoQ	23 April 2021
Predecision	22 July 2021
Answers to Predecision	21 September 2021
Final Decision	20 December 2021
Decision	approval

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3 Medical Context

Unfractionated heparins (UFH) are a natural combination of polysaccharides of varying chain lengths and are generally administered intravenously for anticoagulation.

The medical need for the proposed product is justified with the dosage strength of 416 IU/ml administered at an infusion rate of 1 ml/h, resulting in a standard daily dose of 10,000 IU/24h.

4 Quality Aspects

4.1 Drug Substance

INN: Heparin sodium
Molecular mass: between 3,000 and 40,000 g/mol
Molecular structure: Polymers of alternating derivatives of α-D-glucosamine (N-sulfated, O-sulfated or N-acetylated) and uronic acid (α-L-iduronic acid or β-D-glucuronic acid) joined by glycosidic linkages, sodium salt.
Physico-chemical properties: Heparin sodium occurs as a white or almost white hygroscopic powder, freely soluble in water.

Manufacture: Heparin sodium is prepared from the intestinal mucosae of pigs. As required by Ph. Eur. monograph 0333, the intestines are collected from healthy animals suitable for human consumption, and all stages of production and sourcing are subject to a quality management system that ensures full traceability. The manufacturing process is well described, and the process controls have been justified. Process validation batches representative of the commercial process showed consistent results for the process parameters, in-process controls and product quality. The process was validated with material from each supplier of the intermediate.

Specification: The specification includes all the tests described in the current Ph. Eur. monograph 0333 as well as additional tests. All non-compendial analytical procedures have been validated in accordance with ICH guidelines.

Stability: Based on the stability data submitted, the proposed storage conditions and shelf life of the drug substance are considered satisfactory.

4.2 Drug Product

Description and composition: The drug product is an injectable solution containing 20,000 IU/48 ml (417 IU/ml) of heparin sodium, which delays clotting of the blood by catalysing the inhibition of thrombin (factor IIa) and factor Xa by antithrombin. Sodium chloride is included as an iso-osmotic agent.

The dosage strength has been developed for intravenous administration using a syringe pump, avoiding any dilution steps.

Manufacture: The manufacturing process is comprised of compounding, filtration, terminal sterilisation, inspection, labelling and secondary packaging. Process validation studies were executed at commercial scale using three validation batches.

Specification: The specifications include validated analytical procedures that demonstrate the quality, identity, strength, purity and safety of the product. All non-compendial analytical procedures have been validated in accordance with ICH guidelines.

Container-closure system: The 50 ml glass vial and the bromobutyl rubber stopper comply with the requirements of the respective Ph. Eur. chapter.

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Stability: Real-time and accelerated stability support the shelf life of 18 months for the drug product stored at 15-25°C, protected from light.

4.3 Quality Conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated. Safety aspects with regard to viral and non-viral contaminants were satisfactorily addressed. The risk for adventitious agents is minimised.

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5 Nonclinical Aspects

A nonclinical programme to support the marketing authorisation application for Heparin Sintetica (heparin sodium) has not been carried out.

Since heparin as a drug substance is present in several medicinal products, has already been approved worldwide, and there is lengthy clinical experience, pharmacodynamic, pharmacokinetic and toxicology studies have not been performed and are not considered to be warranted. Swissmedic accepted this approach since it is in line with the legal framework, current guidelines and the 3R principles.

The efficacy and safety of Heparin Sintetica are based solely on quality comparability data and clinical safety data.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Efficacy and Safety

The efficacy and safety profile of unfractionated heparins (UFH) can be considered to be known. The review of the primarily literature-based documentation gave no indication that the efficacy and safety profile of the proposed product would be different than already established.

Laboratory analyses, particularly those to prove the standards to be met for heparin according to the EU pharmacopoeia, support this assumption of comparability.

6.2 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

The anticoagulative efficacy of Heparin Sintetica can be considered to be justified. Further investigations did not give any indication of a safety profile for Heparin Sintetica that differs from UFHs currently available on the Swiss market. The benefit-risk profile is rated positive.

6.3 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Heparin Sintetica, solution for infusion, was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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HEPARIN SINTETICA

Composition

Active substances
Heparin sodium (extracted from pig intestinal mucosa).

Excipients

Sodium chloride.
Water for injections.
1 mL of solution for infusion contains 3.8 mg sodium.

Pharmaceutical form and active substance quantity per unit

Solution for intravenous infusion.
1 vial of 48 mL solution for infusion contains 20,000 IU heparin sodium.
1 mL contains 417 IU heparin sodium.

Indications/Uses

Treatment of thromboembolic disease of all causes and at any site, and relay treatment following thrombolytic therapy; in the event of myocardial infarction; inhibition of coagulation in the event of extracorporeal circulation and haemodialysis.

Dosage/Administration

Usual dosage

The dosage of Heparin Sintetica must be adjusted to the specificities of each case (disease type and progression, patient body weight and age, adverse reactions, etc.).

Close observation is required to ensure the dosage is adequate, because insufficient doses allow the thrombotic process to continue progressing with the continued risk of a fatal embolism.

The dosage should be selected based on coagulation test results (thrombin time, partial thromboplastin time, activated partial thromboplastin time); in the event of repeated IV injections, these results also allow subsequent doses to be scheduled. Clinical experience has demonstrated that the heparin dosage varies greatly depending on the indication. When administering low heparin doses for thromboprophylaxis, coagulation tests are generally not necessary.

Special dosage instructions

In patients with hepatic or renal impairment or coagulation disorders, treatment with Heparin Sintetica must be based on coagulation test results.

1. Treatment of thromboembolic diseases

Close monitoring of treatment with determination of coagulation parameters is absolutely necessary in all cases. Treatment monitoring and dose adjustments are generally based on the activated partial thromboplastin time (APTT) which should be 1.5-2.5 ULN. Follow-up APTT tests are recommended 1-2 hours, 6 hours, 12 hours and 24 hours after initiation of heparin treatment as a continuous intravenous infusion.

Dosage in adults

Infusion (first-line method of administration): An initial dose of 5,000-10,000 IU is to be injected, followed

by an infusion of 10,000-30,000 IU daily using a syringe pump.

The heparin solution for infusion provided is ready for use.

These dosage instructions are a guideline only. Daily doses must be increased on the first day of treatment for pulmonary embolism associated with shock, guided by laboratory test results (e.g., infusion of 40,000-60,000 IU).

Treatment monitoring (four to six hours following an IV injection) with laboratory tests (thrombin time, partial thromboplastin time, activated partial thromboplastin time) allows the dosage to be adjusted to individual needs. The total duration of treatment is based on clinical response. As a general rule, heparin treatment is maintained until the thromboembolic process has stabilised or regressed; anticoagulant therapy is then continued via the oral route (e.g., phenprocoumon) for several weeks to months in addition to heparin for the first few days.

2. Extracorporeal circulation

Heparin is administered to the patient at a dosage of 150-300 IU Heparin Sintetica per kg body weight, guided by the exact coagulation test results. Heparin is added to stored blood at a dosage of 1,500-2000 IU Heparin Sintetica per 500 mL.

3. Artificial kidney

The heparin dosage is based on coagulation tests, as blood coagulation is often impaired in these patients.

Contraindications

Heparin Sintetica is contraindicated in the event of hypersensitivity to the active substance or to any of the excipients listed under "Composition", in the event of current or past thrombocytopenia induced by heparin (heparin-induced thrombocytopenia), in the event of diseases associated with a predisposition to haemorrhage (e.g., haemorrhagic diathesis, coagulation factor deficits [except for consumption coagulopathy in the hypercoagulable phase], severe liver, kidney or pancreas diseases, severe thrombocytopenia), in the event of diseases associated with suspected vascular lesions (e.g., gastrointestinal tumours and ulcers, hypertension [> 105 mmHg diastolic], brain haemorrhage, CNS trauma or surgery, eye surgery, retinopathy, vitreous haemorrhage, aneurysm of a cerebral artery, subacute bacterial endocarditis), in the event of imminent abortion, spinal anaesthesia, epidural anaesthesia or lumbar puncture.

Warnings and precautions

Suspected malignant tumour with a tendency to haemorrhaging, kidney stones, ureteral stones, chronic alcoholism. IM injections should be avoided during heparin treatment due to the risk of haematoma.

Close monitoring and coagulation parameter testing is required in infants, children and patients with renal/hepatic impairment; this applies also to thromboprophylaxis (low-dose treatment).

In patients who develop (or who have developed) clinically relevant thrombocytopenia during heparin use which may be accompanied by a paradoxical additional risk of developing arterial thrombosis, convention low-molecular-weight heparins may be administered only once a negative *in vitro* platelet aggregation test is available.

Heparin Sintetica is contraindicated if this test result is positive.

Heparin-induced thrombocytopenia (HIT) is observed more frequently with unfractionated heparin than with low-molecular-weight heparin. Alternative anticoagulants in affected patients are

danaparoid (a heparinoid) and lepirudin (a direct thrombin inhibitor).

In patients with a medical history indicative of heparin-induced thrombocytopenia, an alternative to unfractionated heparin must be considered, even if the platelet aggregation test is negative.

A platelet count is required:

- before administering heparin,
- one day after initiating heparin treatment, and
- regularly thereafter, every 3 to 4 days during the first three weeks of treatment. Particularly careful medical monitoring is required:
- during pregnancy, particularly with prolonged use (see "Pregnancy, lactation");
- in elderly patients, particularly female patients;
- in the event of co-administration with fibrinolytics or oral anticoagulants, platelet aggregation inhibitors and/or glycoprotein IIb/IIIa receptor antagonists;
- in the event of co-administration with medicinal products that increase serum potassium. Blood potassium must be monitored in at-risk patients (e.g., patients with diabetes, renal impairment, or those taking medicinal products that increase potassium levels).

This medicinal product contains 183.3 mg sodium per vial, equivalent to 9.2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Interactions

Substances that affect platelet aggregation or blood coagulation are likely to increase the risk of haemorrhage (e.g., acetylsalicylic acid, ticlopidine, clopidogrel, glycoprotein IIb/IIIa receptor antagonists, dipyridamole, coumarin derivatives, fibrinolytics, dextran, high-dose penicillins).

The effect of Heparin Sintetica may be potentiated in the event of co-administration with non-steroidal anti-inflammatory drugs.

Co-administration of basic medicinal products such as tricyclic psychotropics, antihistamines and quinine with heparin may result in salt formation with a mutual loss of effect of the administered drugs.

Intravenous nitroglycerin infusions may reduce the effect of heparin. Consequently, discontinuation of nitroglycerin may lead to a sudden increase in TPT. In the event of concomitant nitroglycerin infusions, close monitoring of TPT and heparin dose adjustments are vital.

Heparin increases the free fractions of lidocaine, propranolol and diazepam due to an effect on protein binding. The clinical relevance of this finding is not known. Heparin may potentiate the effect of digitoxin by displacing it from its protein binding sites.

Co-administration of heparin and dihydroergotamine may lead to a potentiation of the effect of heparin. The combination of heparin and corticoids increases the risk of gastrointestinal haemorrhage.

Pregnancy, lactation

Pregnancy

There are no clinical data on the use of Heparin Sintetica in pregnant women or preclinical data from animal studies. As heparin does not cross the placenta, no direct teratogenic effects on human foetuses are expected. In clinical studies on heparin, no malformations were described, but an increased risk of premature parturition and stillbirth was observed when anticoagulants were administered during pregnancy. However, if the indication is strictly necessary during pregnancy, heparin remains the first-line anticoagulant (see "Warnings and precautions"). Caution is required in the event of use during

pregnancy.
Lactation

As heparin is not excreted in breast milk, Heparin Sintetica is also unlikely to be excreted in breast milk. As a result, there is no evidence to suggest an increased risk during breast-feeding.
Fertility

There are no clinical or preclinical data on the effect of Heparin Sintetica on fertility.

Effects on ability to drive and use machines

No corresponding studies have been performed.

Undesirable effects

Haemorrhage is uncommonly observed during heparin treatment, e.g., manifesting as haematuria or subcutaneous haematoma at pressure points or injection sites. Depending on their size, lesions may persist in some cases. Before each injection of Heparin Sintetica, a careful investigation is required both for any signs of bleeding around the operation site, renal capsule and injection site, and for any bruising at pressure points (buttocks, back).

To avoid haemorrhage, IM injections should be avoided during anticoagulant therapy; however, there are no problems with injecting medicinal products via the SC or especially IV routes. Inconsequential bleeding, particularly minor haematomas, does not warrant discontinuation of heparin treatment. A dose reduction can be considered based on the individual case. In the event of major haemorrhage, discontinuation of heparin treatment is recommended while the effect of the drug abates. In the event of dangerous bleeding, heparin treatment must be interrupted and any circulating heparin must be neutralised using a protamine hydrochloride injection (see "*Overdose*").

The frequency of the adverse reactions listed below was defined using the following convention: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000 <1/100), rare (≥1/10,000 <1/1,000), very rare (<1/10,000).

The most common adverse reactions are those pertaining to the coagulation system. Depending on the heparin dose, the onset of bleeding must often be taken into account.

Blood and lymphatic system disorders
Common: administration site haemorrhage, cutaneous and subcutaneous haemorrhage (at pressure points) as well as mucosal haemorrhage, gastrointestinal haemorrhage, urogenital haemorrhage such as haematuria or bleeding around the renal capsule.

Common: thrombocytopenia (further details below).

Immune system disorders
Rare: allergic reactions (urticaria, erythema, nausea/vomiting, pruritus, dyspnoea, bronchospasm and decreased blood pressure).
Very rare: anaphylactic shock, Stevens-Johnson syndrome, epidermal necrolysis.

Metabolism and nutrition disorders
Very rare: hyperkalaemia and metabolic acidosis, particularly in patients with renal impairment or diabetes.

Hepatobiliary disorders
Common: increased serum transaminases (ASAT, ALAT) (generally reversible and with no clinical relevance).
Very rare: increased gamma-GT, LDH and lipase (generally reversible and with no clinical relevance).

Skin and subcutaneous tissue disorders
Uncommon: local tissue reactions (induration, redness).
Rare: skin necrosis.
Very rare: alopecia (reversible).

Musculoskeletal and connective tissue disorders
Common: osteoporosis in the event of prolonged high-dose treatment.

Reproductive system and breast disorders
Very rare: priapism.

Note on the onset of thrombocytopenia

There are two distinct clinical forms of thrombocytopenia: mild, transient thrombocytopenia (type I) is observed more frequently at initiation of heparin treatment, with platelet counts 100,000-150,000/mcL. Such cases do not generally lead to complications. As a result, treatment may be continued.

In up to 3% of patients, severe thrombocytopenia mediated by antibodies (type II) occurs, with platelet counts <100,000/mcL or with a rapid decrease to a count <50% baseline. In unsensitised patients, the decrease in platelet count generally begins 6-14 days after treatment initiation; in sensitised patients, it may set in within a few hours. The following complications can occur: arterial and venous thrombosis/thromboembolism, consumption coagulopathy with possible skin necrosis at the injection site, petechiae, purpura and melena. The anticoagulant effect of heparin may be reduced as a result (heparin resistance).

Heparin Sintetica must be immediately discontinued in such cases. The patient must also be advised that they may have no further treatment with heparin-based products in the future.
Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Heparin overdose leads to increased hypocoagulation with an increased risk of haemorrhage. As stated above, dose reduction and suspension of heparin administration are appropriate countermeasures. In serious cases, protamine hydrochloride may be administered to rapidly neutralise the heparin (for the dosage and method of administration, see the corresponding product information or package leaflet).

Properties/Effects

ATC code

B01AB01

Mechanism of action

Heparin is a high-sulfate, mucopolysaccharide glycosaminoglycan polymer. Its many sulfate and carboxyl groups make it acidic in aqueous media.
Heparin has anticoagulant effects. Heparin acts as a catalyst, significantly increasing the speed at which antithrombin (a heparin cofactor) neutralises thrombin and activated coagulation factor X (Xa). Antithrombin (AT) generally neutralises these coagulation factors by slowly forming irreversible complexes with them via stoichiometry.

Pharmacodynamics

Heparin inhibits coagulation in the presence of antithrombin. The heparin-antithrombin complex (*in vivo* and *in vitro*) inactivates the activated coagulation factors IX, X, XI and XII, thereby inhibiting thrombin formation. At high concentrations, heparin also inhibits platelet aggregation.

Low doses of heparin accelerate antithrombin III activity, particularly its anti-Xa and anti-IIa activity. This is why low-molecular-weight heparin is used for low-dose heparin treatment.

Heparin also has an anti-inflammatory effect. It is involved in lipid metabolism by releasing lipoprotein lipase.

Due to its marked polarity and high molecular weight, heparin very poorly crosses membrane barriers, particularly in the gastrointestinal mucosa. It must therefore be administered parenterally for its anticoagulant activity to take effect.

The bleeding time is generally not affected by heparin. Different times (activated coagulation time, activated partial thromboplastin time, prothrombin time, total blood coagulation time) are prolonged by full therapeutic doses of heparin; in most cases, they are not affected in a detectable manner by low heparin doses.

Clinical efficacy

No data available.

Pharmacokinetics

Absorption

Heparin can be administered intravenously as either an injection or an infusion. In the event of administration via injection or infusion, it is 100% bioavailable.
Due to its relatively high molecular weight and negative surface charge, heparin is not absorbed from the gastrointestinal tract. However, absorption via inhalation is possible.
The effect of heparin is immediate following intravenous injection.
The interindividual half-life of heparin is 90-120 minutes. It depends on the administered dose, renal and hepatic function and the type of disease.

Distribution

Heparin is highly bound to plasma proteins. Effective therapeutic plasma concentrations are 0.6±0.3 IU/mL, and effective prophylactic plasma concentrations are 0.05-0.2 IU. The volume of distribution in adults is approx. 0.07 L/kg.

Metabolism

Following parenteral administration, heparin is eliminated from the blood via absorption into the reticuloendothelial system before undergoing cleavage in the liver (heparinase).

Elimination

Inactive and depolymerised heparin is eliminated primarily via the urine. Heparin is eliminated equally by both glomerular filtration and tubular secretion. The interindividual elimination half-life varies from 30-120 minutes.

Kinetics in specific patient groups
Severe hepatic or renal impairment may lead to heparin accumulation.

Preclinical data

No conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity or reproductive toxicity have been performed with Heparin Sintetica.

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack. For microbiological reasons, the ready-to-use preparation should be used immediately after opening.

Special precautions for storage

Store in the original packaging in order to protect the contents from light. Store at room temperature (15-25°C).
Keep out of the reach of children.

Instructions for handling

After opening, use immediately. Any remaining solution must be discarded.

Authorisation number

67780

Packs

Vials containing 48 mL (B)

Marketing authorisation holder

Sintetica SA, CH-6850 Mendrisio (Switzerland).

Date of revision of the text

July 2021