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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

DEFITELIO

International non-proprietary name: defibrotide

Pharmaceutical form: concentrate for solution for infusion

Dosage strength: 80 mg/ml

Route(s) of administration: intravenous use

Marketing Authorisation Holder: Clinipace AG

Marketing Authorisation No.: 67667

Decision and Decision date: approved on 21 September 2020

Note:

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

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
HSCT	Haematopoietic stem-cell transplantation
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
SOS	Sinusoidal obstruction syndrome
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)
VOD	Veno-occlusive disease

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 defibrotide of the medicinal product mentioned above.

Orphan drug status

The applicant requested Orphan Drug Status in accordance with Article 4^{decies} no. 2 of the TPA. The Orphan Status was granted on 26 August 2014.

2.2 Indication and Dosage

2.2.1 Requested Indication

Defitelio is indicated for the treatment of severe hepatic veno-occlusive disease (VOD) also known as sinusoidal obstruction syndrome (SOS) in haematopoietic stem-cell transplantation (HSCT).

2.2.2 Approved Indication

Defitelio is indicated for the treatment of severe hepatic veno-occlusive disease (VOD) also known as sinusoidal obstruction syndrome (SOS) in haematopoietic stem-cell transplantation (HSCT) therapy in adults and in adolescents, children and infants of 1 month of age and above (*see Clinical efficacy section*).

2.2.3 Requested Dosage

The recommended dose is 6.25 mg/kg body weight every 6 hours (25 mg/kg/day).

There is limited efficacy and safety data on doses above this level and consequently it is not recommended to increase the dose above 25 mg/kg/day.

The treatment should be administered for a minimum of 21 days and continued until the symptoms and signs of severe VOD resolve.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	2 August 2019
Formal control completed	28 August 2019
List of Questions (LoQ)	16 December 2019
Answers to LoQ	12 March 2020
Predecision	10 June 2020
Answers to Predecision	8 July 2020
Final Decision	21 September 2020
Decision	approval

3 Medical Context

Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), is a life-threatening complication of conditioning procedures prior to haematopoietic stem cell transplantation (HSCT) and chemotherapy alone. VOD/SOS occurs in approx. 10-15% of adult patients who receive myeloablative conditioning followed by allogeneic HSCT. In patients receiving autologous HSCT or reduced-intensity conditioning, lower rates of VOD/SOS were observed (approx. 5%). A higher risk exists in the paediatric population.

VOD/SOS is characterised by multiple organ failure and a mortality of 20-30% in patients receiving HSCT and supportive treatment.

4 Quality Aspects

4.1 Drug Substance

Defibrotide is the sodium salt of a complex, polydisperse mixture of predominantly single-stranded polydeoxyribonucleotides obtained from porcine DNA. The mean oligonucleotide length is approximately 50 bases with a mean molecular weight of 13 - 20 kDa. This is due to defibrotide being produced by random, chemical cleavage (depolymerisation) of the DNA.

The requirements for the starting material, pooled porcine intestinal mucosae, as well as the organ and tissue collection are described. The intestines from healthy animals suitable for human consumption are supplied by three slaughterhouses. All stages of production and sourcing are subjected to a quality management system that ensures full traceability. The manufacturing process is well described, and the process controls have been justified. Three consecutive process validation batches representative of the commercial process showed consistent results for the process parameters, in-process controls, and product quality.

Owing to the very large number of individual components of different length and sequence, it is not possible to determine the sequence of the collective polydeoxyribonucleotides. The polydispersity of the components was studied using various chromatography and electrophoresis techniques. Various spectrometry methods were used to demonstrate the DNA nature of defibrotide. Nevertheless, apart from a consistent length and base composition, and a low percentage of double-stranded character, no defined structure of defibrotide can be established.

The biological activity of defibrotide was studied in two biochemical assays that showed dose-dependent enhancement of the fibrinolytic activity of plasmin.

Product-related and process-related impurities were adequately addressed.

The specifications include a panel of tests to assure identity, content, potency (two biochemical assays for fibrinolytic activity), purity, and safety of the drug substance. The analytical procedures have been validated in accordance with ICH guidelines.

Batch analysis data for toxicology batches, clinical batches, process validation batches, and commercial batches were presented, and are comparable.

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

4.2 Drug Product

Defitelio is a sterile concentrate for solution for infusion containing 80 mg of defibrotide per mL in clear glass type I vials sealed with a rubber stopper and blue aluminium flip-off seal.

The excipients of the finished product solution are water for injection as solvent, sodium citrate, sodium hydroxide, and hydrochloric acid. All excipients comply with Ph. Eur. requirements.

The finished product is supplied in single-use glass vials of 2.5 mL.

The drug product manufacturing process consists of compounding, sterile filtration, aseptic filling/stoppering/crimping, inspection, and packaging/labelling. Process validation studies were executed with three consecutive batches at commercial scale.

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.

Batch analysis data for toxicology batches, clinical batches, process validation batches, and commercial batches were presented, and are comparable.

The components of the container closure coming into contact with the finished product comply with Ph. Eur. requirements.

The proposed shelf life of 36 months for the finished product stored at 15-30°C is justified based on stability studies performed in accordance with ICH guidelines.

Compatibility studies have demonstrated that the finished product is stable when diluted with 0.9% sodium chloride solution for infusion or 5% glucose solution for infusion in infusion bags for up to 72 hours at 15-25°C. However, from a microbiological viewpoint the product should be used immediately.

4.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product have been demonstrated.

The manufacturing process for drug substance and drug product include adequate control measures to prevent contamination and maintain control with regard to adventitious agents safety.

5 Nonclinical Aspects

Regarding the marketing authorization application for Defitelio (active ingredient defibrotide) Swissmedic conducted an abridged evaluation, which was based on the assessment reports of Health Canada, FDA and EMA provided by the applicant, and the detailed Pharmacology Review of FDA (publicly accessible).

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Defitelio in the proposed indication. Although the pharmacological function has been studied intensively, the mechanism of action has not been fully elucidated. Defibrotide acts on endothelial cell functionality and plasmin activity. There were no particular safety issues identified in the nonclinical studies that would be of concern for the proposed short-term administration in humans. All nonclinical data that are relevant for safety are mentioned adequately in the information for healthcare professionals.

6 Clinical and Clinical Pharmacology Aspects

The evaluation of the clinical and clinical pharmacology data of this application has been carried out in reliance on previous regulatory decisions by EMA and FDA. The available assessment reports and corresponding product information from these authorities were used as a basis for the clinical and clinical pharmacology evaluation.

For further details concerning clinical pharmacology, dosing recommendations, efficacy and safety, see Chapter 8.1 of this report.

6.1 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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.

8 Appendix**8.1 Approved Information for Healthcare Professionals**

Please be aware that the following version of the information for healthcare professionals relating to Defitelio 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.

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Defitelio

Defitelio® 80 mg/mL concentrate for solution for infusion

Composition

Active substances

Defibrotide sodium*, produced from porcine intestinal mucosa.

Excipients

Sodium citrate*; Hydrochloric acid (for pH adjustment), Sodium hydroxide* (for pH adjustment), Water for injections.

**The maximum amount of sodium per vial is 20.4 mg (0.89 mmol).*

Pharmaceutical form and active substance quantity per unit

Concentrate for solution for infusion.

One mL of concentrate for solution for infusion contains defibrotide 80 mg. 1 vial of 2.5 mL contains 200 mg defibrotide. After dilution the concentration of the solution contains defibrotide in the range of 4 mg/mL to 20 mg/mL.

The solution is clear light yellow to brown, free from particulate matter or turbidity.

Indications/Uses

Defitelio is indicated for the treatment of severe hepatic veno-occlusive disease (VOD) also known as sinusoidal obstruction syndrome (SOS) in haematopoietic stem-cell transplantation (HSCT) therapy in adults and in adolescents, children and infants of 1 month of age and above (*see section clinical efficacy*).

Dosage/Administration

Defitelio must be prescribed and administered to patients by specialised physicians experienced in the diagnosis and treatment of complications of HSCT.

To ensure traceability of biological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Dosage

The recommended dose is 6.25 mg/kg body weight every 6 hours (25 mg/kg/day).

There is limited efficacy and safety data on doses above this level and consequently it is not recommended to increase the dose above 25 mg/kg/day.

Duration of treatment

The treatment should be administered for a minimum of 21 days and continued until the symptoms and signs of severe VOD resolve (see section “Clinical efficacy”).

Special dosage instructions

Patients with impaired hepatic function

No formal pharmacokinetic studies have been performed in patients with hepatic impairment; however, the medicinal product has been used in clinical trials of patients developing hepatic impairment without dose adjustment with no safety issues identified. No dose adjustment is therefore recommended but careful monitoring of patients should be undertaken (see section “Pharmacokinetics”).

Patients with impaired renal function

Dose adjustment is not required for patients with renal impairment or who are on intermittent haemodialysis (see section “Pharmacokinetics”).

Elderly patients

Clinical studies of Defitelio did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger patients.

Children and adolescents

The recommended dose for children aged 1 month and above to 18 years is the same mg/kg dose as for adults i.e. 6.25 mg/kg body weight every 6 hours.

The safety and efficacy of defibrotide in children aged less than 1 month has not yet been established. No data are available. The use of Defitelio in children aged less than one month is not recommended.

Mode of administration

Defitelio is for intravenous use. It is administered by intravenous infusion, over two hours.

Defitelio should always be diluted prior to use. It can be diluted with 5% glucose solution for infusion or 0.9% sodium chloride solution for infusion (see section “Instructions for handling” for concentration range and stability of the diluted solution), to a suitable concentration to permit infusion over 2 hours.

The total volume of infusion should be determined based on the individual patient's weight. The final concentration of Defitelio should be in the range of 4 mg/mL to 20 mg/mL.

Vials are intended for a single use and unused solution from a single dose must be discarded. For instructions on dilution of the medicinal product before administration, see section "Other Information": Instructions for handling.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed under "Composition".
- Concomitant use of thrombolytic therapy (e.g. t-PA) (see section "Interactions").

Warnings and precautions

Haemorrhage

Use of medicinal products that increase the risk of haemorrhage within 24 hours of Defitelio administration (within 12 hours in the case of unfractionated heparin) is not recommended.

Concomitant systemic anticoagulant therapy (e.g. heparin, warfarin, direct thrombin inhibitors and direct factor Xa inhibitors) (see section "Interactions"), except for routine maintenance or reopening of central venous line, requires careful monitoring. Consideration should be given to discontinuation of Defitelio during use of such therapy.

Medicinal products that affect platelet aggregation (e.g. non-steroidal anti-inflammatory agents) should be administered with care, under close medical supervision, during Defitelio administration.

In patients who have or develop clinically significant acute bleeding requiring blood transfusion, Defitelio is not recommended or should be discontinued. Temporary discontinuation of Defitelio is recommended in patients who undergo surgery or invasive procedures at significant risk of major bleeding.

Hypersensitivity Reactions

Hypersensitivity reactions have occurred in less than 2% of patients treated with Defitelio. These reactions include rash, urticaria and angioedema. One case of an anaphylactic reaction was reported in a patient who had previously received Defitelio. Monitor patients for hypersensitivity reactions, especially if there is a history of previous exposure. If a severe hypersensitivity reaction occurs, discontinue Defitelio, treat according to the standard of care, and monitor until symptoms resolve.

Haemodynamic Instability

Administration of defibrotide to patients who have haemodynamic instability, defined as inability to maintain mean arterial pressure with single pressor support, is not recommended.

Bolus administration

A bolus administration of Defitelio may cause flushing or a sensation of “generalised heat”. Bolus administration of Defitelio is not recommended.

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially “sodium-free”.

Interactions

Potential interactions with recombinant t-PA

In a mouse model of thromboembolism, recombinant t-PA potentiated the antithrombotic effect of defibrotide when given intravenously and thus co-administration may present an increased risk of haemorrhage and is contraindicated (see section “Contraindications”).

Potential interactions with antithrombotic fibrinolytic agents

Defibrotide has a profibrinolytic effect (see section “Properties/Effects”: Mechanism of action) and this may potentially enhance the activity of antithrombotic/fibrinolytic medicinal products.

There is currently no reported experience in patients on the concomitant treatment with Low Molecular Weight Heparins (LMWHs), warfarin or the concomitant treatment with direct thrombin inhibitors (e.g., dabigatran) or direct Factor Xa inhibitors (e.g., rivaroxaban and apixaban). Therefore, the use of defibrotide with antithrombotic/fibrinolytic medicinal products is not recommended. However, if used, in exceptional cases, caution should be exercised by closely monitoring the coagulation parameters (see section “Warnings and precautions”).

Potential interactions with other medicinal products

Pharmacokinetic drug-drug interactions are unlikely at therapeutic dose. Data from *in vitro* studies using human biomaterial demonstrate that defibrotide does not induce (CYP1A2, CYP2B6, CYP3A4, UGT1A1) or inhibit (CYP1A2, CYP2B6, CYP3A4, CYP2C8, CYP2C9, CYP2C19, CYP2D6, UGT1A1, UGT2B7) the major drug metabolizing enzymes and is not a substrate or inhibitor of the major drug uptake transporters (OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3) or efflux transporters (P-gp and BCRP).

Pregnancy, lactation

Pregnancy

A reliable contraceptive method should be used during treatment and for up to 1 week thereafter.

No clinical data available on use in pregnant patients.

Embryo-foetal developmental toxicology studies in pregnant rats and rabbits of defibrotide doses close to the recommended therapeutic human dose, revealed a high rate of haemorrhagic abortion (see section "Preclinical data").

The medicine should not be administered during pregnancy unless the clinical condition of the woman requires the treatment with Defitelio.

Lactation

It is not known whether defibrotide is excreted in human milk. Do not breastfeed during Defitelio treatment since the risks to the breastfed children cannot be excluded.

Fertility

There are no studies investigating the effects of defibrotide on human fertility.

Effects on ability to drive and use machines

Defitelio has no or negligible influence on the ability to drive and use machines.

However, patients would not be expected to drive or operate machinery due to the nature of the underlying disease.

Undesirable effects

In the Phase 3 pivotal treatment study (2005-01 Study), the overall incidence of adverse events was similar in the defibrotide treatment group and in the control group (historical). The safety data from the pivotal study are supported and confirmed with data from other studies from the clinical trial program and post-marketing data. For adverse reactions reported in all studies, the highest frequency was used in the table below.

The most frequent adverse reactions observed during the treatment of hepatic VOD are haemorrhage (including but not limited to gastrointestinal haemorrhage, pulmonary haemorrhage and epistaxis) and hypotension.

In addition, although in the defibrotide studies in VOD there have been no reports of hypersensitivity, cases of hypersensitivity including anaphylaxis were reported with defibrotide use, consequently hypersensitivity is included as an ADR.

Adverse reactions observed are listed below, by system organ class and frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1,000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1,000$), very rare ($< 1/10,000$).

Blood and lymphatic disorder

Common: Coagulopathy

Immune system disorders

Uncommon: Hypersensitivity, Anaphylactic reaction

Nervous system disorders

Common: Cerebral haemorrhage

Uncommon: Cerebral haematoma

Eye disorders

Uncommon: Conjunctival haemorrhage

Vascular disorders

Very common: Hypotension (11.7%)

Common: Haemorrhage

Respiratory, thoracic and mediastinal disorders

Common: Pulmonary haemorrhage, Epistaxis

Uncommon: Haemothorax

Gastrointestinal disorders

Common: Gastrointestinal haemorrhage, Vomiting, Diarrhoea, Nausea, Haematemesis, Mouth haemorrhage

Uncommon: Melaena

Skin and subcutaneous tissue disorders

Common: Rash, Pruritus, Petechiae

Uncommon: Ecchymosis

Renal and urinary disorders

Common: Haematuria

General disorders and administration site conditions

Common: Catheter site haemorrhage, Pyrexia

Uncommon: Injection site haemorrhage

Safety and efficacy in paediatric patients

In clinical trials performed in the treatment of VOD, over 50% of patients were under the age of 18 years. Safety and efficacy in children aged less than 1 month have not yet been established. In doses above the recommended dose of 25 mg/kg/day there was a higher proportion of patients with bleeding events in the high dose group. In the paediatric prevention study at 25 mg/kg/day there was an increased incidence of any bleeding events in the defibrotide group compared with the treatment group. However, there was no difference in incidence of serious bleeding or bleeding events with fatal outcome. The frequency nature and severity of adverse reactions in children are otherwise the same as in adults.

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 EIVIS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Treatment

There is no specific antidote for overdose and treatment should be symptomatic. Defibrotide is not removed by dialysis (see section "Pharmacokinetics").

Properties/Effects

ATC code

B01AX01

Mechanism of action

Defibrotide is an oligonucleotide mixture with demonstrated antithrombotic, fibrinolytic, anti-adhesive and anti-inflammatory actions. The mechanism of action is multifactorial. It primarily acts through reducing excessive endothelial cell (EC) activation (endothelial dysfunction), modulating endothelial homeostasis as well as restoring thrombo-fibrinolytic balance. However, the exact mechanism of action of defibrotide is not fully elucidated.

Defibrotide has demonstrated antithrombotic and fibrinolytic effects *in vitro* and *in vivo* by: increasing systemic tissue factor pathway inhibitor (TFPI), tissue plasminogen activator (t-PA) and

thrombomodulin (TM) expression; decreasing von Willebrand factor (vWF) and plasminogen activator inhibitor-1 (PAI-1) expression; and enhancing the enzymatic activity of plasmin to hydrolyse fibrin clots.

In vitro and *in vivo* studies have demonstrated that defibrotide inhibits leukocyte and platelet adhesion to endothelium by: suppressing P-selectin and vascular cell adhesion molecule-1 (VCAM)-1; interfering with lymphocyte function-associated antigen 1-intercell adhesion molecule (LFA-1-ICAM) mediated leukocyte transmigration; and increasing nitric oxide (NO), Prostaglandin I₂ (PGI₂) and Prostaglandin E₂ (PGE₂).

In vitro defibrotide demonstrates anti-inflammatory effects that attenuate the release and production of reactive oxygen species and inflammatory mediators such as interleukin 6, thromboxane A₂, leukotriene B₄ and tumour necrosis factor- α (TNF- α).

Defibrotide protects ECs from damage and promotes tissue homeostasis by decreasing fludarabine-mediated apoptosis of EC while maintaining its anti-leukemic effect and by inhibiting the expression of heparanase, shown in *in vitro* and *in vivo* studies respectively.

Pharmacodynamics

Cardiac Electrophysiology

At a dose 2.4 times the maximum recommended dose, Defitelio does not prolong the QTc interval to any clinically relevant extent.

PAI-1 Inhibition (Plasminogen Activator Inhibitor – 1)

Plasma concentration of PAI-1 were assessed on an exploratory basis as a potential pharmacodynamic marker for efficacy in 99-118. PAI-1 is an inhibitor of t-PA and therefore of fibrinolysis. Mean PAI-1 levels on Days 7 and 14 were lower than those at baseline in patients with complete response (CR) and in those who were alive at Day+100, but this trend did not reach statistical significance. There were no statistically significant differences in mean PAI-1 levels by treatment or outcome.

Clinical efficacy

The efficacy and safety of defibrotide in the treatment of severe VOD were studied in a pivotal Phase 3 historical controlled study (2005-01). Study 1 enrolled 102 adult and pediatric patients in the Defitelio treatment group with a diagnosis of VOD according to the following criteria (bilirubin of at least 2 mg/dL and at least two of the following findings: hepatomegaly, ascites, and weight gain

greater than 5% by Day+21 post-HSCT) with an associated diagnosis of multi-organ dysfunction (pulmonary, renal, or both) by Day+28 post-HSCT. Forty-four children and 58 adult patients with severe VOD post-HSCT, were treated with Defitelio 25 mg/kg/day intravenous by infusion, and compared with 32 historical control patients. Median length of therapy in those treated with Defitelio was 22 days (range 1-60).

Day+100 survival rate was improved in the Defitelio group with 38.2% (39/102) of the patients surviving versus 25.0% (8/32) in the historical control group. In addition, a higher proportion of patients in the Defitelio group achieved a complete response defined as total bilirubin less than 2 mg/dL and resolution of MOF (multiple organ failure); Day+100 complete response was 25.5% (26/102) with Defitelio versus 12.5% (4/32) in the historical control.

The efficacy data from this pivotal study are supported by data from a dose-finding study (25 mg/kg arm) and the Open Label Treatment-IND study, showing Day+100 survival rate at 44.0% and 49.5% respectively.

Pharmacokinetics

Absorption

After intravenous administration, peak plasma concentrations of defibrotide occur approximately at the end of each infusion.

Distribution

Defibrotide is highly bound to human plasma proteins (average 93%) and has a volume of distribution of 8.1 to 9.1L.

Metabolism

Though the precise pathway of defibrotide degradation in plasma *in vivo* is largely unknown, it has been suggested that nucleases, nucleotidases, nucleosidases, deaminases, and phosphorylases metabolize polynucleotides progressively to oligonucleotides, nucleotides, nucleosides, and then to the free 2'-deoxyribose sugar, purine and pyrimidine bases. The biotransformation of defibrotide was investigated *in vitro* by incubation with human hepatocytes from donors of different ages and showed that defibrotide does not undergo appreciable metabolism by human hepatocyte cell.

Elimination

After administration of the therapeutic dose (6.25 mg/kg) to healthy subjects, an average of 9.48% of the total dose administered is excreted in urine as unchanged defibrotide in 24 hours, with the majority excreted during the first collection interval of 0-4 hours (approximately 98%).

Metabolism followed by urinary excretion is likely the main route of elimination. The estimated total clearance was 3.4 to 6.1 L/h. The elimination half-life of defibrotide is less than 2 hours. Similar plasma concentration profiles were observed in VOD patients after initial and multiple-dose administration of 6.25 mg/kg every 6 hours for 5 days. Therefore, no accumulation is expected following multiple dose administration.

Kinetics in specific patient groups

Hepatic impairment

No formal pharmacokinetic studies have been performed in hepatic impaired patients. Defitelio has been used in clinical trials in patients with hepatic impairment without dose adjustment with no major safety issues identified (see section “Dosage/Administration”).

Renal impairment

Six patients with an estimated glomerular filtration rate <30 mL/min/1.73m² (calculated using the Modification of Diet in Renal Disease equation) and not currently on dialysis were compared to 6 healthy subjects with similar baseline demographics. Defitelio 6.25 mg/kg was administered intravenously over 2 hours to subjects every 6 hours. Compared to healthy controls, subjects with renal impairment demonstrated 1.6– and 1.4-fold increases in AUC and C_{max}, respectively and a half-life of about twice that of healthy subjects.

The amount of defibrotide excreted in urine over 24 hrs was about 5% of the total dose administered in those with renal impairment versus about 12% in healthy subjects.

Almost all renal excretion occurs within the first 4 hours. Accumulation of defibrotide over 4 doses was not found. Difference in exposure is not considered clinically relevant and so dose adjustment is not advised for patients with renal impairment (see section “Dosage/Administration”).

In a sub-study it was shown that haemodialysis did not remove defibrotide (see section “Dosage/Administration”).

Preclinical data

Non clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

In both species, the main findings were accumulation of vacuolated macrophages in liver of dogs and in liver, kidneys and lymph nodes of rats.

Carcinogenicity

No carcinogenicity studies have been conducted with intravenous administration of defibrotide.

Reproductive toxicity

Studies of fertility were not conducted with defibrotide administered by the intravenous route. In repeat dose general toxicology studies, when defibrotide was administered intravenously to rats and dogs for up to 13 weeks, there were no effects on male or female reproductive organs.

In the Segment II reproductive studies in rats and rabbits, defibrotide has shown maternal toxicity by inducing a high rate of haemorrhagic abortion when infused intravenously over two hours at all dose levels tested including doses close to the human dose. Due to this maternal toxicity, no conclusion can be drawn regarding the effects of defibrotide on embryo-foetal development. PAI-2 is known to be uniquely up-regulated in the placenta.

Juvenile toxicity

Repeated intravenous administration of defibrotide, at doses below and close to the human therapeutic dose, to juvenile rats resulted in a delay in the mean age of preputial separation, suggesting a delay in the onset of male puberty in rats. However, the clinical relevance of these findings is unknown.

Other information

Incompatibilities

This medicinal product may be mixed only with those medicinal products listed under Instructions for handling.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Shelf life after opening

The diluted/reconstituted preparation for infusion is not preserved. Chemical and physical in-use stability has been demonstrated for 72 hours at 15-25°C for a concentration range of 4 mg/mL to 20 mg/mL in 0.9% sodium chloride solution for infusion or 5% glucose solution for infusion. For microbiological reasons, the ready-to-use preparation should be used immediately after dilution.

If this is not possible, in-use storage times and conditions are the responsibility of the user and should normally be no longer than 24 hr at 2-8°C.

Special precautions for storage

Store at 15-30°C.

Do not freeze.

For storage conditions after dilution of the medicinal product, see section "Shelf life after opening".

Keep out of the reach of children.

Instructions for handling

The concentrated solution for infusion must be diluted using aseptic technique.

Preparation of Defitelio (use aseptic technique):

1. The total dose and thereby, the total volume of infusion and the total number of vials to be diluted is based on the individual patient's weight. The final concentration of Defitelio should be in the concentration range of 4 mg/mL – 20 mg/mL.
2. Before dilution, each vial should be inspected for particles. If particles are observed and/or the liquid in the vial is not clear, the vial must not be used.
3. The required volume from the Defitelio vials should be withdrawn and combined.
4. A volume of the 0.9% sodium chloride solution for infusion or glucose 5% solution for infusion from the infusion bag, equal to the total volume of Defitelio concentrated solution to be added, should be withdrawn and discarded.
5. The combined volumes of Defitelio should be added to the 0.9% sodium chloride solution for infusion or glucose 5% solution for infusion.
6. The solution for infusion should be mixed gently.
7. Prior to use the solution should be visually inspected for particulate matter. Only clear solutions without visible particles should be used. Depending on the type and amount of diluent the colour of the diluted solution may vary from colourless to light yellow. It is recommended that the diluted Defitelio solution be administered to patients using an infusion set equipped with a 0.2 µm in-line filter.
8. After the infusion is complete, the intravenous line should be flushed with 0.9% sodium chloride solution for infusion or glucose 5% solution for infusion.

9. Administer Defitelio as described above. Do not co-administer other drugs through the same intravenous line.

Authorisation number

67667

Packs

Defitelio 200 mg/2.5 mL concentrate for solution for infusion, 2.5 mL vials: Pack size of 10 vials (A)

Marketing authorisation holder

Clinipace AG, Volketswil

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