Unit: Technical Assessment Unit

Public assessment report for biological products

Metalyse

Administrative information:

Trade name of the medicinal product:	Metalyse
INN (or common name) of the active substance(s):	TENECTEPLASE 25 mg
Manufacturer of the finished product	Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer Strasse 65, Biberach an der Riss 88397, GERMANY.
Marketing Authorization holder	Boehringer Ingelheim International GmbH, Binger Strasse 173, 55216 Ingelheim am Rhein - GERMANY;
Applied Indication(s):	Thrombolytic treatment of acute ischaemic stroke (AIS) within 4.5 hours from last known well and after exclusion of intracranial haemorrhage
Pharmaceutical form(s) and strength(s):	- Powder for Solution for IV Injection -5000 U (25 mg)
Route of administration	I.V
Approved Pack	10 mL clear glass vial with a coated (B2-44) grey rubber stopper and a crimp cap filled with powder for solution for injection each vial contains 25 mg Tenecteplase
Registration track	Reliance Level 2
Type of registration (EMA/FDA – Local)	EMA approved

List of abbreviations:

AcT	Alteplase Compared to Tenecteplase in Ischemic Stroke Trial
AIS	Acute Ischaemic Stroke
cGMP	Current Good Manufacturing Practice
DP	Drug product
DS	Drug substance
I.V	Intravenous
mg	Milligram
MoA	Mode of Action
mg	Milligram
PAI-1	Plasminogen Activator Inhibitor 1
PD	Pharmacodynamics
PK	Pharmacokinetics
STEMI	ST-Elevation Myocardial Infarction
TNK	Tenecteplase
TNK-tPA	Trivial name and BI code for Tenecteplase
U	Unit

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Dossier initial submission and evaluation process:

-The file evaluated according to EDA regulation based on reliance pathway (Reliance level 2), the company submitted Complete CTD file.

1. Introduction

-Tenecteplase (TNK-tPA) is a multidomain serine protease, which proteolytically converts plasminogen to plasmin, primarily in the presence of fibrin. Tenecteplase is produced by recombinant DNA technology.

-Tenecteplase is a genetically engineered variant of alteplase (human tissue plasminogen activator) and exhibits, in comparison to alteplase, increased resistance to the plasminogen, activator inhibitor PAI-1, increased relative fibrin specificity, and a slower plasma clearance rate.

-Metalyse 25 mg/vial is a white to pale yellow lyophilisate. Prior to administration, the lyophilisate is reconstituted with 5 mL of water for injections, yielding an isotonic, preservative-free solution for injection.

1. **Quality aspects:**

- **Manufacturer(s):**

- **Drug Substance**

- The Active substance is manufactured at.Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer Strasse 65, Biberach an der Riss 88397, GERMANY.

- **Drug product**

- The Finished product is manufactured at Boehringer Ingelheim Pharma, Birkendorfer Strasse 65, Biberach an der Riss 88397, GERMANY.

-Manufacturing of both DS and DP are performed in accordance with cGMP regulations.

- **Stability**

Drug substance:

-Approved shelf life for the Active substance: 24 months

- Approved Storage Conditions of the Active substance: Store at (-20±5°C)

Drug product:

-Approved shelf life for the Finished product: 24 months

-Approved Storage Conditions of the Finished product:
Finished product:
- Do not store above (30 °C).
-Keep the container in the outer carton in order to protect from light.

Reconstituted solution:
-From a microbiological point of view, the reconstituted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 -8°C.

2. **Non –Clinical aspect & Clinical aspect:**

- All nonclinical studies presented are considered to support the registration of tenecteplase for thrombolytic treatment of AIS, recognizing that this is a potent thrombolytic agent with potential adverse PD effects.

- Considering all nonclinical and broad clinical data, tenecteplase at therapeutic doses can be considered a safe drug if used according to the patient information in the package leaflet of Metalyse.

-Clinical Pharmacology (PK & PD) conclusion.
Only limited data on the pharmacokinetics of TNK in AIS is available, however, the PK characteristics of TNK in AIS is not expected to relevantly differ from those established in patients with STEMI. The information proposed for section 5.2 of the SmPC (Pharmacokinetic properties) of the AIS TNK presentation is in line with the respective information given in the SmPC for the STEMI presentations. This is agreed, as it is clearly indicated that the information on TNK in patients is derived from the STEMI indication.
NK has a well-known MoA as thrombolytic agent and a well-established efficacy and safety profile in the treatment of acute myocardial infarction.
Tenecteplase and alteplase are closely related molecules that share the same mechanism of action. They are both well-established standard options for the thrombolysis of acute myocardial infarction, where Tenecteplase is at least as effective as alteplase

Clinical Efficacy conclusion
-The TNK posology proposed for AIS is fully in line with the regimen used in **the pivotal AcT trial**, i**.e. 0.25 mg/kg given in 5 dose tiers** and is endorsed.

Clinical Safety conclusion
-No unexpected safety concerns with regard to safety of the intended 0.25 mg/kg TNK dose for thrombolysis in AIS within 4.5 h, can be derived from the 12 investigator-initiated trials or from the meta-analyses of published studies referenced by the Applicant.

-The safety data in patients with AIS treated with tenecteplase 0.25 mg/kg within 4.5 h from last known well is in accordance with the established safety profile of Tenecteplase

Clinical Immunogenicity conclusion:
-No clinically relevant antibody formation was detected as part of PD assessment.

-In conclusion the overall benefit/risk of Metalyse 25 mg (5 000 U) powder for solution of injection (*tenecteplase 0.25 mg/kg) is favorable in the treatment of adult patients with AIS within 4.5 h from last known well*.

General Conclusion and Recommendations if any:
Based on the review of CTD modules and other supplementary documents, the product is approved.

For more information, please visit EMA published assessment report link:

https://www.ema.europa.eu/en/documents/product-information/metalyse-epar-product-information_en.pdf