

19 December 2022

Dear colleagues, and friends,

In this 3rd letter on the alteplase and tenecteplase shortage the European Stroke Organisation (ESO) Executive Committee (EC) will inform you about

1. the results from the latest **meeting** with Boehringer Ingelheim (**BI**) and
2. correspondence with the European Medicines Agency (**EMA**)
3. the upcoming expedited ESO **recommendations** for the use of **tenecteplase** in acute ischemic stroke are currently under review in European Stroke Journal

During the latest telephone conference, BI informed us about the following points:

Ongoing and short-term measures:

- On 3.8.2022 the German Federal Institute for Drugs and Medical Devices (BfArM) approved a variation for an optimized drug substance manufacturing process which will lead to a higher yield of alteplase.

Several measures on alteplase allocation have been installed in cooperation with EMA and National Health Authorities (HA). As of November 2022, Actilyse allocation definition for 2023 foresees a worldwide increase vs 2022.

Planned medium and longer-term measures:

- Registration and implementation of an additional production facility of alteplase, which is expected for submission of variation application **Q2 2024** (A scientific advice meeting with BfArM took place on 28.09.2022 to discuss about opportunities to accelerate the process)
- BI is discussion with EMA the registration of a new indication of tenecteplase for patients with acute ischemic stroke.

For **other measures taken so far** please refer to our 1st and 2nd letter to ESO members on **28.07.2022** and **28.09.2022** respectively.

On 25.10.2022, the ESO Executive Committee sent a **letter to** the European Medicines Agency (**EMA**) suggesting for an emergency approval for ACTIVASE in the EU. Activase is an alteplase product registered in the USA and Canada, but not in the EU, indicated for Acute Ischemic Stroke (AIS) within 3 hours of symptom onset.

- ESO received back an **answer** from EMA on 29.11.2022. EMA informed us about the following points:
 - EMA is **aware** of this critical shortage and is in a continuous **exchange** with National Competent Authorities (NCAs) in the EU/EEA and BI.
 - This shortage has been given the **highest priority**.

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- EMA had newly created an Executive Steering Group on Safety and Shortages of medicines (**MSSG**) where BI was invited to explain the causes of the shortage and plans for mitigation.
- EMA has explored options of dealing with the shortage which include importing medicinal products from other countries outside EU/EEA.
 - There is no additional product (Activase) available from USA/Canada markets. Furthermore, EMA explained, should Activase become available, NCAs can import the product without the need for an emergency approval with necessary support from EMA.
 - There are no products from other regions in the world.
 - Bio-Copies might be in use, but EMA was not able to evaluate these products as respective dossiers are not made available to EMA.
- EMA also tries to mitigate the shortage by measures such as
 - regular supply and demand monitoring and overseeing the distribution process in cooperation with NCAs and BI.
 - supporting the increase of the production needs by expediting the regulatory review and approval of critical manufacturing changes which could increase production

Recommendations ESO (as in our last letter no 2):

- **Localize storage/s** in your institution / hospital: Keep track of the locations where alteplase is stocked and check if stock is appropriate. Ensure that everyone involved is aware of the stock locations.
- Set an **inventory target** of alteplase: To do this, you should use the average alteplase consumption of your clinic (e.g., cumulative amount in mg per month) and assess the needs without creating unnecessary overstocking.
- **Establish communication** with the **pharmacy**: establish a fixed communication structure with the hospital pharmacy and regularly (at least once a month) be informed about the status of stocks.
- Information to **neighbouring disciplines**: Inform other specialist departments site about the shortage, because the need for alteplase can also arise here (e.g., therapy of pulmonary artery embolism). Moreover, use of alteplase for the clearance of occluded catheters should be reserved to particular situations.
- Follow the information regarding extension of the **shelf life of thrombolytic agents** and be prepared to use the **10 and 20 mg vials** instead of the 50 mg vials, when available/introduced in your country, so to avoid waste through leftovers.
- Ensure the **right dosages** are present in each stroke bag: ideally, 1 pack 50 mg Actilyse, 2 packs 20 mg, 1 pack 10 mg or alternatively 50/20/10/10 (where available). Replenish only with replacement of the used strengths.
- **Local networking**: Inform the local emergency services about the current situation, exchange with neighbouring SUs in a structured way and document it. There may be existing structures you might want to use like neurovascular networks, tele-stroke networks, stroke registries. The aim is to improve regional availability of thrombolytic therapy by supporting each other. We are aware that the situation in metropolitan areas is different than in rural regions. Thus, this may need to be adapted to the regional needs.

- Definition of **emergency measures**: Discuss with the emergency services and the neighbouring SUs possible measures in case of critical stock reduction of alteplase. Again, local conditions need to be taken into account.
- It is of utmost importance to **keep close contact with BI** to maximize the reliability of the demand which is key.

In case you have questions, feedback, or suggestions please contact esoinfo@eso-stroke.org

ESO is in constant exchange with the company.

Best wishes,

Thrombolysis taskforce of the ESO Executive Committee

European Stroke Organisation (ESO)



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