Dear colleagues and friends,

The European Stroke Organisation (ESO) Executive Committee (EC) and Boehringer Ingelheim (BI) had a discussion on the current shortage of alteplase and tenecteplase on 11.07.2022 and is on a constant exchange with the company since then. Today, we would like to give an update on the current situation and provide some recommendations to you:

Feedback from BI:

- There is a shortage of alteplase and tenecteplase which is currently expected to last up to 2 years.
- This shortage is mainly created by 4 related **causes**
  - a world-wide increasing thrombolysis rate
  - An increasing ageing of the population, translating into increased incidence of ischemic stroke
  - increasing use of current guidelines that recommend use of thrombolysis beyond approved indications[1, 2]
  - maximum production capacity reached in the only production site in Germany which is supplying the global use of Actilyse® (alteplase) and Metalyse® (tenecteplase)
- Calculation of the **scope of the problem**
  - Based on the consumption of 2020, BI calculated the gap between the need for alteplase and the amount of drug that can be produced with - 8.5%
  - Several short term mitigation measure applied by BI revealed a lower gap of - 2.3%
- **Measures** taken by **BI**
  - Immediate measures
    - Supply prioritization of Actilyse 10mg, 20mg and 50mg, with an expectation to be able to supply more than 90% of the Actilyse volumes needed in 2022 and 2023. Metalyse supply will remain limited for the next two years.
    - Prioritization of Actilyse production vs Metalyse, given the fact that Actilyse has 3 indications (AIS, STEMI, PE), and Metalyse only one (STEMI), and also that Actilyse is more widely approved than Metalyse
    - **Temporary discontinuation** of the **2 mg** strength of alteplase (Cathflo®), indicated in the "Thrombolytic treatment of occluded central venous access devices including those used for haemodialysis" to prioritize indications with the highest benefits for patients.
    - Substantial **communication** with health authorities, medical associations, and health care professionalson national levels
    - Establishment of an **allocation process** world-wide and on national levels based on the assessment of consumption and including the consultation of an independent Ethics Board to do this in an equitable and fair manner.
    - Establishment of a **global Task Force** with communication into **regional / national contacts** to minimize patient impact, ensure fair and equitable

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allocation of available drug product and resolve local situations as quick as possible.
    - BI has agreed with EU health authorities on a **shelf-life extension** of alteplase / tenecteplase on specific batches
      They remind that, after reconstitution alteplase has an in use stability of **up to 24 hours** given **adequate refrigeration**. The approved text in section 6.3 of the prescribing information reads as follows: “Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 24 hours at 2-8°C and 8 hours at 25°C. From a microbiological point of view, the product should be used immediately.” [3]

- Medium-term measures
    - **Steps to reduce wasted alteplase:** decision to produce more 20 mg vials and fewer 50 mg vials, with a total production quantity that remains constant. This should improve the fitting accuracy of the dosing and reduce material waste in those countries where lower strengths are available.
- Long-term measures
    - Development of an **additional 25mg vial** of tenecteplase for acute ischemic stroke, however not available before 2025.
    - Diversification of production into **new production sites by 2026**

Feedback from the ESO:

- The impression is that shortage may not be the same in all European countries: presumably countries with a very recent increase in the use may face more shortage since supply was calculated based on previous consumption. Further differences may be linked to distribution process differences among countries (e.g. wholesalers channels, direct sales to hospitals, etc…)
- BI was asked to **check again** with their regional / national contacts for current **consumption** and planned drug **allocation**.
- ESO is establishing a **working group**. Goals are
    - to receive updates from ESO countries on practical impact of supply issues on clinical care
    - to examine to what extent concrete “rescue options” can be derived.
    - to provide all ESO members and stroke physicians with current accurate information.
    - A **continuous exchange** of information was agreed with BI by regular meetings with members of ESO-EC / working group.

Recommendations by ESO:

- Measures to be taken in your own institution:
    - **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: We recommend a period of 3 to 4 weeks for a regularly dosed thrombolytic therapy as a stock target. To do this, you should use the average alteplase consumption of your clinic (e.g. cumulative amount in mg per month).
    - Regular **inventory check**: Instruct your stroke unit (SU) team to check the local stock to be recorded closely, if necessary daily. We recommend documentation of an inventory. You may want to consider a reporting concept from the SU established with traffic light colors:
        - Green: stock of Alteplase sufficient for > 4 weeks.
        - Yellow: stock of Alteplase sufficient for 2 - 4 weeks.
        - Red: stock of Alteplase < 2 weeks sufficient.

- Ensure **adequate medication ordering**: In case of falling below the targeted inventory you should inform the management of the department and immediately start the medication ordering process.
- If necessary, create an SOP: If desired, you can ask for an SOP example using the contact below.
- **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 stockouts.
- Information to **neighboring 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 strongly avoided
- 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 vial, when available/introduced in your county.
- Ensure the right dosages are present in each Stroke bag: ideally, 1 pack 50 mg Actilyse, 2 packs 20 mg, 1 pack 10 mg (where available). Replenish only with replacement of the used strengths.
- Local networking: Inform the local emergency services about the current situation, exchange with neighboring 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 neighboring SUs possible measures in case of critical stock reduction of alteplase. Again, local conditions need to be taken into account.
- In case you have questions, feedback, or suggestions please contact: esoinfo@eso-stroke.org

Best wishes
ESO Executive Committee

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