The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

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EMEA PUBLIC STATEMENT ON RAPILYSIN (reteplase) – INCOMPATIBILITY WITH HEPARIN AND PRECIPITATION FOLLOWING THE RECONSTITUTION – IMPORTANT NEW INSTRUCTIONS FOR USE

The European Commission granted a marketing authorisation for the European Union on 29 August 1996 for the medicinal product Rapilysin, which contains the active substance reteplase. The Marketing Authorisation Holder is Roche Registration Limited, UK. Rapilysin is marketed in all Member States.

Rapilysin is indicated for thrombolytic therapy of acute myocardial infarction (AMI) (within 12 hours after the onset of AMI symptoms). The European Medicines Evaluation Agency's (EMEA) scientific committee, the Committee for Proprietary Medicinal Products (CPMP) has been evaluating new safety information as it emerges.

The marketing authorisation holder recently informed the EMEA of 4 reports concerning a precipitation of Rapilysin suspected to be due to an incompatibility with heparin that occurred during the concomitant administration of Rapilysin and heparin in the same intravenous line. In addition, a report concerning the occurrence of a precipitate following the reconstitution of the solution of Rapilysin was provided. No adverse reaction has been reported. Following a review of this new information, the EMEA wishes to draw attention to the correct administration of the product:

As precipitation of the reconstituted solution may occur:

- **Visual inspection of the solution is necessary after reconstitution.**
- **Only clear, colourless solutions should be injected. If the solution is not clear and colourless it should be discarded.**
- **The reconstituted solution must be used immediately.**
- **Heparin and Rapilysin are incompatible when combined in solution. Other incompatibilities may also exist. No other medication should be added to the injection solution.**
- **Rapilysin should be injected preferably through an intravenous line whose sole purpose is the injection of Rapilysin.**
- **No other medication should be injected through the line reserved for Rapilysin, neither at the same time, nor prior to, nor following Rapilysin injection. This applies to all products including heparin, and acetylsalicylic acid, which should be administered before and following the administration of reteplase to reduce the risk of re-thrombosis.**

<u>In those patients where the same line has to be used</u>, this line (including Y-line) must be flushed thoroughly with a 0.9% sodium chloride or 5% dextrose solution prior to and following the Rapilysin injection.

As an urgent measure, the prescribing and patient information has been modified through a rapid procedure at the request of the Marketing Authorisation Holder. The EMEA considers it necessary to provide this new information to the public.

Relevant changes to the product information are indicated below. For the revised product information please consult the European Public Assessment Report, also available on the EMEA website.

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PROVISIONAL CHANGES INTRODUCED
TO PRESCRIBING AND PATIENT INFORMATION

INFORMATION TO PATIENTS:

Recommended dose and method of administration

The reconstituted solution must be used immediately. Visual inspection of the solution is necessary after reconstitution. Only clear, colourless solutions should be injected. If the solution is not clear and colourless it should be discarded.

Heparin and Rapilysin are incompatible when combined in solution. Other incompatibilities may also exist. No other medication should be added to the injection solution (see below and 6.2 Incompatibilities). Rapilysin should be injected preferably through an intravenous line whose sole purpose is the injection of Rapilysin. No other medication should be injected through the line reserved for Rapilysin, neither at the same time, nor prior to, nor following Rapilysin injection. This applies to all products including heparin, and acetylsalicylic acid, which should be administered before and following the administration of reteplase to reduce the risk of re-thrombosis.

In those patients where the same line has to be used, this line (including Y-line) must be flushed thoroughly with a 0.9% sodium chloride or 5% dextrose solution prior to and following the Rapilysin injection.

Instructions for use/handling

6. The reconstituted preparation results in a clear, colourless solution. If the solution is not clear and colourless, it should be discarded.

7. Heparin and Rapilysin are incompatible when combined in solution. Other incompatibilities may also exist. No other medication should be added to the injection solution.

INFORMATION FOR PRESCRIBERS:

4.2 Posology and method of administration

Reteplase is supplied as a freeze-dried substance in vials. The lyophilisate is reconstituted with the contents of the accompanying syringe (see chapter 6.6 Instructions for use and handling).

The reconstituted solution must be used immediately. Visual inspection of the solution is necessary after reconstitution. Only clear, colourless solutions should be injected. If the solution is not clear and colourless it should be discarded.

Heparin and Rapilysin are incompatible when combined in solution. Other incompatibilities may also exist. No other medication should be added to the injection solution (see below and 6.2 Incompatibilities). Rapilysin should be injected preferably through an intravenous line whose sole purpose is the injection of Rapilysin. No other medication should be injected through the line reserved for Rapilysin, neither at the same time, nor prior to, nor following Rapilysin injection. This applies to all products including heparin, and acetylsalicylic acid, which should be administered before and following the administration of reteplase to reduce the risk of re-thrombosis.

In those patients where the same line has to be used, this line (including Y-line) must be flushed thoroughly with a 0.9% sodium chloride or 5% dextrose solution prior to and following the Rapilysin injection.

6.2 Incompatibilities

Heparin and Rapilysin are incompatible when combined in solution. Other incompatibilities may also exist. No other medication should be added to the injection solution.

No other medication should be injected through the line reserved for Rapilysin, neither at the same time, nor prior to, nor following Rapilysin injection. This applies to all products including heparin, and acetylsalicylic acid, which should be administered before and following the administration of reteplase to reduce the risk of re-thrombosis.

In those patients where the same line has to be used, this line (including Y-line) must be flushed thoroughly with a 0.9% sodium chloride or 5% dextrose solution prior to and following the Rapilysin injection (see 4.2 Posology and method of administration).

6.3 Shelf-life

When reconstituted as directed, the solution must be used immediately.

6.6 Instructions for use, handling and disposal (if appropriate)

6. The reconstituted preparation results in a clear, colourless solution. If the solution is not clear and colourless, it should be discarded.

7. Heparin and Rapilysin are incompatible when combined in solution. Other incompatibilities may also exist. No other medication should be added to the injection solution.