

PROCEDURAL STEPS TAKEN AFTER GRANTING THE MARKETING AUTHORISATION

For procedures finalised after 1 February 2004 please refer to module 8B.

- The MAH submitted an Urgent Safety Restriction on 14 November 2001 to introduce changes in the instructions for use and handling in the SPC and in the instructions for use detailed in the pictogram on the inner lid of the folding box, following a number of reports suggesting that the instructions for use of the product may not have been followed appropriately. In addition, the MAH informed treating physicians by means of a Dear Health Care Professional letter and the EMEA published a Public Statement. The EPAR was updated shortly afterwards as a consequence of the changes to the MA. These changes are reflected in the SPC and labelling.

Subsequent post Marketing Authorisation applications agreed upon are summarised in the table below:

Scope	Application number	Type of modification ³	Notification/Opinion issued on ⁴	Commission Decision Issued/amended on
To produce the sterilised water for injections also at Boehringer Ingelheim Pharma KG, Biberach (Germany) using a 10 ml syringe made of cycloolefine-copolymer (TopPac syringe by Schott Polymer GmbH).	II/03	II	30.05.02	18.09.02
To revise section 4.8 of the SPC to reflect fatal cases of haemorrhage, particularly intracranial haemorrhage. In addition, section 4.8 has been revised taking into account the assessment of the 3 rd PSUR.	II/04	II	17.10.02	23.01.03
Minor changes in the local representatives section of the package leaflet, such as: change in the name of the Spanish local representative, new telephone number in Germany, change in the name of the company in France, change in the address for Luxembourg and change in the Swedish address.	II/05	I	14.10.02	27.11.02
A minor change of the purification process in the manufacturing process of the active substance to include a 180KD Viresolve filtration step into reprocessing i. e. the repetition of the viral removal step restricted to the failure of the filter membrane integrity test (MIT) or equipment malfunction.	II/06	I	22.05.03	N/A
A replacement of the approved Bioset transfer system by an alternative product kit where reconstitution can be performed either by a vial adapter or a needle, which are included in the pack. The section 6.5 Nature and Content of the container and 6.6. Instructions for Use in the SPC and the pictogram contained in the labelling will be changed accordingly. In addition changes to the details of the local representative of Finland were introduced in the Package Leaflet.	II/07	II	25.04.03	23.07.03
A change in the name of the manufacturer of the active substance and the medicinal product in charge of the batch release in the EEA from Boehringer Ingelheim Pharma KG to Boehringer Ingelheim Pharma GmbH & Co. KG.	II/08	I	21.05.03	25.06.03

¹ In accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended: **I** refers to a minor variation (Type I variation); **II** refers to a major variation (Type II variation); **I/II** refers to a minor variation following the procedure set out in Article 6, 7 and 8 of the Regulation; **X** refers to an Annex II application.

T refers to a transfer of a Marketing Authorisation in accordance with Commission Regulation (EC) No 2141/96 of 7 November 1996.

N refers to a notification in accordance with Article 10(3) of Council Directive 92/27/EEC of 31 March 1992.

² For Notifications and Type I variations, the date of entry into force of the change is the EMEA Notification date. The Commission Decision will be amended accordingly.

³ In accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended: **I** refers to a minor variation (Type I variation); **II** refers to a major variation (Type II variation); **I/II** refers to a minor variation following the procedure set out in Article 6, 7 and 8 of the Regulation; **X** refers to an Annex II application.

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⁴ For Notifications and Type I variations, the date of entry into force of the change is the EMEA Notification date. The Commission Decision will be amended accordingly.

The deletion of a contraindication in diabetic patients and its replacement by the appropriate warning following the publication of a CPMP position statement concerning the use of iv fibrinolytics in diabetic patients. In addition, the MAH has updated section 4.8 of the Summary of Product Characteristics in line with the Guideline on Summary of Product Characteristics..	II/09	II	25.09.03	27.01.04
To tighten specifications for the target protein to 7% and the limit for yield at harvest to NLT 70%.	II/10	I	02.07.03	N/A
A reduction of shelf-life of the lyophilised powder from 36 to 24 months at up to 30°C and change for the shelf-life of the reconstituted solution from 24 hours at 30°C to 24 hours at 2-8°C and 8 hours at 30°C. As a consequence the SPC and PL are revised accordingly.	II/11	II	25.09.03	27.01.04