I. BACKGROUND INFORMATION ON THE PROCEDURE

1. Submission of the dossier

The applicant Shire Pharmaceutical Contracts Limited submitted on 26 March 2002 an application for Marketing Authorisation to the European Agency for the Evaluation of Medicinal Products (EMEA) through the centralised procedure for Xagrid, which was designated as an orphan medicinal product EU/3/00/010 on 29 December 2000.

The Rapporteur and Co-Rapporteur appointed by the CPMP were:

Rapporteur: Dr E. Abadie Co-Rapporteur: Dr P. Neels

Orphan Drugs:

Anagrelide hydrochloride was designated as an orphan medicinal product in the following indication: treatment of essential thrombocythaemia.

Scientific Advice:

The applicant received Scientific Advice from the CPMP on 15 November 2001. The Scientific Advice pertained to part IV of the dossier.

Licensing status:

Xagrid has been given a Marketing Authorisation in Switzerland (December 1999) and Latvia (October 2003). Agrylin (tradename used outside of the EEA) has been given a Marketing Authorisation in the United States (March 1997), Canada (November 1997), Israel (July 1998), Korea (October 1999), Australia (November 1999), South Africa (October 2000), Brazil (August 2002), Taiwan (May 2003), Hong Kong (December 2003) and Singapore (March 2004).

2. Steps taken for the assessment of the product

- The procedure started on 22 April 2002.
- The Rapporteur's first Assessment Report was circulated to all CPMP members on 28 June 2002. The Co-Rapporteur's first Assessment Report was circulated to all CPMP members on 28 June 2002.
- During the meeting on 23 – 25 July 2002 the CPMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 26 July 2002.
- The company submitted the responses to the CPMP consolidated List of Questions on 10 December 2002.
- The summary report of the inspection carried out at the manufacturing site Mallinckrodt Inc between 3-4 October 2002 of the MCA was issued on 20 November 2002.
- The final integrated report of the inspections carried out for study 700-014, at two clinical sites in the USA, between 15-17 October 2002 and 21-24 October 2002, was issued on 17 December 2002.
- The Rapporteur circulated the response Assessment Report on the company's responses to the List of Questions to all CPMP members on 28 January 2003.
- During the CPMP meeting on 18 – 20 February 2003 the CPMP adopted a List of Outstanding Issues to be addressed by the applicant in writing and if necessary during an oral explanation. The List of Outstanding Issues was sent to the applicant on 21 February 2003.
- The company submitted the responses to the CPMP List of Outstanding Issues on 25 April 2003.

- The Rapporteur circulated the Rapporteurs' Joint Review on the company's responses to the List of Outstanding Issues to all CPMP members on 12 May 2003.
- During the CPMP meeting on 20 – 22 May 2003 the CPMP adopted a List of Outstanding Issues to be addressed by the applicant in writing and if necessary during an oral explanation. The List of Outstanding Issues was sent to the applicant on 23 May 2003.
- The company submitted the responses to the CPMP List of Outstanding Issues on 4 June 2003.
- The Rapporteur circulated the Rapporteurs' Joint Review on the company's responses to the List of Outstanding Issues to all CPMP members on 16 June 2003.
- During the CPMP meeting on 24 – 26 June 2003, outstanding issues were addressed by the applicant during a hearing before the CPMP on 24 June 2003.
- During the meeting on 22 – 24 July 2003 the CPMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation under exceptional circumstances to Xagrid on 24 July 2003.
- The post-marketing commitments agreed as part of the CPMP Opinion on 24 July 2003 had included a specific obligation to provide efficacy and safety data from an ongoing UK Medical Research Counciltrial in patients with essential thrombocythaemia. In September 2003, Shire informed the CPMP that the anagrelide plus aspirin arm of the MRC trial had been discontinued. The issue was discussed by the CPMP during its meeting on 23-25 September 2003.
- The European Commission, at the request of the EMEA, put the Standing Committee phase on hold pending the outcome of the CPMP discussion regarding thediscontinuation of the anagrelide plus aspirin arm of the study.
- During the CPMP meeting on 23-25 September, oral explanations were given by the applicant on 23 September 2003.
- During the CPMP meeting on 23-25 September the CPMP adopted a List of Questions to be addressed by the applicant in writing. The List of Questions was sent to the applicant on 25 September 2003.
- The company submitted the responses to the CPMP List of Questions on 5 December 2003.
- The Rapporteur circulated the response Assessment Report on the company's responses to the List of Questions to all CPMP members on 2 February 2004.
- During the meeting on 24– 26 February 2004 the CPMP adopted a List of Outstanding Issues to be addressed by the applicant in writing and if necessary during an oral explanation. The List of Outstanding Issues was sent to the applicant on 27 February 2004.
- The company submitted the responses to the CPMP List of Outstanding Issues on 12 March 2004.
- The Rapporteur circulated the Rapporteurs' Joint Review on the company's responses to the CPMP List of Outstanding Issues to all CPMP members on 9 April 2004.
- During the meeting on 20 – 22 April 2004 the CPMP adopted a revised List of Outstanding Issues to be addressed by the applicant in writing and if necessary during an oral explanation. The List of Outstanding Issues was sent to the applicant on 23 April 2004.
- The company submitted the responses to the revised CPMP List of Outstanding Issues on 12 May 2004.
- The Rapporteur circulated the Rapporteurs' Joint Review on the company's responses to the revised List of Outstanding Issues to all CHMP members on 8 June 2004.
- In the margin of the CHMP meeting on 22 – 23 June 2004, an *ad hoc* expert meeting took place on 21 June 2004. During the CHMP meeting on 22 – 23 June 2004, it was decided that in the

light of the outcome of the *ad hoc* expert meeting there was no longer any need for the applicant to address outstanding issues during an oral hearing before the CHMP.

- During the meeting on 27 -29 July 2004, the CHMP adopted a report from the *ad hoc* expert meeting of 21 June 2004.
- The company submitted revised documents for consideration by CHMP on 7 July 2004.
- The Rapporteur circulated the Rapporteurs' Joint Review on the revised documents on 16 July 2004.
- During the meeting on 27 – 29 July 2004 the CHMP, in the light of the overall revised data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation under exceptional circumstances to Xagrid on 29 July 2004.
- The CHMP opinions were forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decisions on 16 November 2004.

2. GENERAL CONDITIONS FOR THE MARKETING AUTHORISATION

1. Manufacturing authorisation holder

Manufacturers of the active substance

- Cambridge Major Laboratories Inc., North 115 West 19392 Edison Drive, Germantown, WI 53022, United States
- Powdersize Inc., 20 Pacific Drive, Quakertown, PA 18951, United States

Manufacturers of the finished product

- Mallinckrodt Inc., Main Plant and Office, Building 1, 58 Pearl Street, P.O. Box P, Hobart, NY 13788, United States

An inspection of this manufacturing site was carried out by the MCA on 3-4 October 2002. The findings of the inspection are in compliance with the Community Good Manufacturing Practice requirements.

- Wasdell Packaging Limited, Upper Mills Estate, Bristol Road, Stonehouse, Gloucestershire, GL10 2BJ, United Kingdom

Manufacturer responsible for import and batch release in the European Economic Area

- Wasdell Packaging Limited, Upper Mills Estate, Bristol Road, Stonehouse, Gloucestershire, GL10 2BJ, United Kingdom

Manufacturing authorisation issued on 11 January 1999 by the MCA.

2. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, 4.2).

Other conditions

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

3. Specific obligations and/or follow-up measures of the Marketing Authorisation Holder

Pursuant to article 13 (2) of Council Regulation (EEC) No 2309/93 and Part 4 G of the Annex I to Directive 2001/83/EC, the applicant agreed to provide, as requested by the CHMP, additional clinical data which will form the basis of a re-assessment of the benefit/risk ratio of Xagrid. In addition, the applicant will submit PSURs at 6-, 12-, 18-, 24-months, 3 years, 4 years and as part of the renewal application, as of the granting of the Commission Decision for Xagrid.

In addition, the applicant agreed to submit to the EMEA, within a defined timeframe, further information requested by the CHMP on quality and pre-clinical aspects.