I BACKGROUND INFORMATION ON THE PROCEDURE

1. Submission of the dossier

The company Bristol-Myers Squibb Pharma EEIG submitted on 31 July 1995 an application for marketing authorisation to the EMEA for Zerit capsules 15 mg, 20 mg, 30 mg or 40 mg and powder for oral solution, 1 mg/ml, through the centralised procedure. After agreement by the CPMP on April 1995, this medicinal product was referred to List B in the Annex of the Council Regulation EEC No 2309/93, indent 7 as it contains a new active substance.

The Rapporteur and the Co-rapporteur appointed by the CPMP and the evaluation teams were as follows:

Rapporteur:	Dr. P. Sjöberg	Co-rapporteur:	Dr. J.L. Robert
Evaluators:	Dr. B. Jonsson	Evaluators:	Dr. S. Singh
	Dr. M. Ekblom		Prof. J. Lewis
	Dr. I. Anundi		Dr. H. Schroeder
	Dr. K. Bergman		Dr. P. Helboe
	Dr. S.E. Hillver		

Licensing status

Zerit capsules 15 mg, 20 mg, 30 mg and 40 mg have been registered in several countries including:

United States (24 June 1994)	Australia (15 January 1996)	Brazil (7 April 1995)
Canada (26 March 1996)	Peru (12 May 1995)	Switzerland (26 July 1996)
Argentina (20 June 1995)		

2. Steps taken for the assessment of the product

- During the CPMP September meeting 1995, it was agreed to perform an inspection on the USA manufacturing facility for the finished medicinal product by the Swedish and French Inspectorates.
- The Rapporteur's initial Assessment Report was circulated to all Members of the CPMP on 25 October 1995. The Co-Rapporteur's initial Assessment Report was circulated to all Members of the CPMP on 27 October 1995.
- During the November 1995 CPMP meeting, the Rapporteur and Co-Rapporteur presented their Assessment Reports. A consolidated list of questions was proposed to be adopted at the December 1995 CPMP meeting. The CPMP also agreed on accepting an expedited review process of this application.
- On 5 December 1995, the Rapporteur circulated an updated version of his overall conclusions on this medicinal product together with a draft consolidated list of objections and points for clarification prepared jointly with the Co-Rapporteur. These related to issues on quality (e.g. clarification of the hydrolytic degradation of stavudine, purity, enantiomeric purity), safety (e.g. carcinogenicity results, safety data obtained from more treated children), and efficacy (e.g. subgroup efficacy analysis, cross-resistance induction). Proposed amendments of the Summary of Product Characteristics (SPC), Package Leaflet (PL) and Labelling to reflect these points were also circulated.
- The CPMP in its meeting in December 1995 agreed on a consolidated list of questions as prepared by the Rapporteur and Co-Rapporteur. This list was sent to the Applicant on 20 December 1995. A hearing with the applicant was planned to be held on 16 January 1996 at the CPMP meeting in order to address any remaining concerns. The Rapporteur presented a preliminary report on the inspection of the USA manufacturing facility to all CPMP members.
- The applicant submitted the responses to the consolidated list of questions on 3 January 1996.
- The Rapporteur circulated the comments on the applicant's response to the consolidated list of questions to all CPMP Members on 9 January 1996.

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- A hearing was held on 16 January 1996, at the CPMP meeting, where the applicant provided answers to the outstanding issues related to quality issues (details on methods used to confirm the purity of the reference standard, enantiomeric purity of stavudine, thymine specifications in stavudine, specifications for the two preservatives used) and efficacy issues (*in vitro* phosphorylation interactions with stavudine, *Pneumocystis carinii* pneumonia events, incidence of pancreatitis in women, indication for paediatric patients, risk/benefit of 40 mg stavudine twice daily (bid) vs 20 mg, food effect). These answers were either considered as acceptable or resulted in modifications of the SPC and PL.
- The applicant submitted on 16 January 1996 a letter of commitment (CPMP/057/96; CPMP/058/96) for providing results on the ongoing rodent carcinogenicity studies and on the development of a chromatographic method for the identification of the flavour constituent in the powder for oral solution. An additional commitment (CPMP/091/96) on proposing strategies to evaluate the incidence of *Pneumocystis carinii* pneumonia (PCP) and potential interactions of stavudine with PCP prophylactic agents was agreed by the applicant on 18 January 1996. The applicant provided on 17 January a letter (CPMP/059/96) describing the ongoing stavudine clinical trials in combination therapy and in children.
- 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 to the different oral presentations and strengths of stavudine on 18 January 1996. The CPMP opinions were forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decisions on 8 May 1996.

3. Steps taken after granting the Marketing Authorisation

- On 8 October 1996, the Marketing Authorisation Holder (MAH) submitted in parallel three different applications for a Type I variation in accordance with Commission Regulation (EC) No. 542/95. The MAH applied for:

  1. the change of the manufacture site responsible for the production of the capsules, for the importation of the powder for oral solution and for the batch release in the EEA of both pharmaceutical forms. On 10 October 1996, the EMEA approved the variation. This variation required amendments to be incorporated in the relevant sections of the Commission Decision.
  2. the change of the manufacturing site for the labelling of the powder for oral solution. On 16 October 1996, the EMEA approved the variation. This variation did not require any amendments to the Commission Decision, as amended.
  3. the change of the batch size of the finished product for Zerit 15 mg capsules. On 7 November 1996, the EMEA approved the variation. This variation did not require any amendments to the Commission Decision, as amended.

- On 23 September 1996, the MAH submitted an application for a type II variation in accordance with Commission Regulation (EC) No. 542/95. The scope of the variation concerned the update of the statement into the SPC related to *Pneumocysitiis carinii* pneumonia (PCP) prophylaxis. On 17 October 1996, the CPMP agreed on the wording to be implemented into the SPC and adopted the opinion on the type II variation and the respective Commission Decision was issued on 3 February 1997.
- On 16 January 1997, the MAH submitted in parallel three applications for a type II variation, in accordance with Commission Regulation (EC) No. 542/95. The MAH applied for:

  1. the extension of the therapeutic indication of Zerit to include paediatric patients
  2. the update of the SPC with additional data for the prescribing physician for patients with end-stage renal disease
  3. the update of the SPC related to the carcinogenic potential of Zerit following the finalisation of the studies.

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The CPMP considered these variations acceptable and agreed on the wording to be introduced into the appropriate sections of the SPC and reflected into the PL. The CPMP adopted on 16 April 1997 an opinion on the three type II variations, and the respective Commission Decision was issued on 28 July 1997.

- On 17 July 1997, the MAH submitted an application for a type II variation, in accordance with Commission Regulation (EC) No. 542/95. The MAH applied for the update of the safety sections of the SPC with regard to the occurrence of cases of lactic acidosis and to the streamlining of some undesirable effects. The CPMP considered this variation acceptable and agreed on the wording to be introduced into the appropriate sections of the SPC. The CPMP adopted on 24 September 1997 an opinion on the type II variation, and the respective Commission Decision was issued on 12 December 1997.
- In accordance with Article 10(3) of Council Directive 92/27/EEC of 31 March 1992, the EMEA issued on 4 March 1998 a Notification for amendment of the addresses of the local representatives mentioned in the Package Leaflet, as applied by the MAH.
- On 14 April 1998, the MAH submitted an application for a type I variation in accordance with Commission Regulation (EC) 542/95 related to the change of the batch size of the finished product for Zerit capsules 20 mg. On 11 May 1998 the EMEA approved the variation which did not lead to any changes to Commission Decision.
- In accordance with Article 10(3) of Council Directive 92/27 EEC of 31 March 1992, the EMEA issued on 8 September 1998 a Notification for amendments of the addresses of the local representatives included in the package leaflet as applied by the MAH.

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II GENERAL CONDITIONS FOR THE MARKETING AUTHORISATION

1. Manufacturing Authorisation Holders and inspection status

(1) Manufacturers of the finished product

Capsules:

Bristol-Myers Squibb, Champ "Lachaud", La Goualle, 19250 Meymac, France.

(Authorisation issued by the French Medicines Agency on 19 February 1993). GMP certificate was issued by the French Authorities on 20 January 1996.

Powder for oral solution:

Bristol-Myers Squibb Pharmaceuticals Ltd, 2400 W. Lloyd Expressway, Evansville, Indiana 47721, United States of America

Following the discussion at the September CPMP 1995 meeting, an inspection of this manufacturing site was requested. This was carried out by the Swedish and French inspectorates on 7-10 November 1995. The findings of the inspection and subsequent correspondence with the manufacturer have confirmed that the facilities and operations for powder for oral solution are in compliance with Community GMP requirements.

The labelling of the powder for the oral solution takes place in the following manufacturing site: Bristol-Myers Squibb, Champ "Lachaud", La Goualle, 19250 Meymac, France.

Manufacturer responsible for import of the powder for oral solution and batch release for both pharmaceutical forms in the European Economic Area:

Bristol-Myers Squibb, Champ "Lachaud", La Goualle, 19250 Meymac, France.

2. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted non-renewable medical prescription.

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