BACKGROUND INFORMATION ON THE PROCEDURE

1. Submission of the dossier

The company Biogen S.A., France, submitted on 2 May 1995 to the European Agency for the Evaluation of Medicinal Products (EMEA) an application to obtain marketing authorisation for the medicinal product AVONEX, in accordance with the centralised procedure falling within the scope of Part A of the Annex to Council Regulation No. (EC) 2309/93 of 22 July 1993.

The CPMP confirmed the status of the Rapporteur and Co-Rapporteur as follows:

Rapporteur:	Prof. Dr. Fernando de Andres-Trelles	Co-Rapporteur:	Dr. Hans van Bronswijk

Licensing status:

The product was not licensed in any country inside or outside the EEC at the time of submission of the application.

A new drug application was filed in the United States of America in May 1995 and was authorised on 17 May 1996.

2. Steps taken for the assessment of the product

- The CPMP in its meetings of 7-8 June 1995 discussed the issue of the proposed tradename AVONEX.
- The company submitted a proposal for a modified trade name on the 7 July 1995.
- The CPMP in its meeting of 11-13 July 1995 discussed the new proposal submitted by the company on the 7t July 1995, for a modified trade name. The new proposal was not accepted in principle because of its possible confusion with other existing medicinal products. It was also requested that the biotechnology issues be discussed at the Biotechnology Working Party (BWP) on 7 September 1995.
- The Rapporteur's initial assessment report was circulated to all members of the CPMP on24 July 1995.
- The Co-Rapporteur's initial assessment report was circulated to all members of the CPMP on 20 July 1995.
- The Biotechnology Working Party during its meeting on 8 September 1995, discussed the outstanding biotechnology issues and prepared a list of comments and a recommendation to the CPMP.
- The CPMP in its meeting of 12-13 September 1995 considered the major objections to the dossier and agreed on a consolidated list of substantial objections. During this pre-authorisation discussion it was decided that the inspection planned to take place in the non-EU manufacturing site should be postponed until the company had addressed the more fundamental issues.
- The CPMP consolidated List of Questions was sent to the company on 18 September 1995.
- During a meeting with the Rapporteur, Co-Rapporteur, the company and their individual expert teams on 18 October 1995, the list of objections was clarified, in particular in relation to the issue of bioequivalence of the two relevant substances in the clinical data and also to the lack of pharmacokinetic data.
- On 3 November 1995 the company was reminded by the EMEA about two issues related to the postponed inspection and to the suitability of the trade name, to be resolved before the CPMP opinion could be granted.

- On 5 February 1996, a meeting was held with the company experts, the Rapporteur, Co-Rapporteur and their respective assessor teams as well as additional BWP experts. During this meeting the company gave an overview of their intended responses. The purpose of this meeting was to advise the company on the preparation of their responses to the consolidated List of Questions.
- The CPMP in its meeting of 13-15 February 1996 agreed the conduction of the postponed pre-authorisation inspections of the manufacturing sites of the active substance and dosage form.
- On 1 March 1996, a meeting was held with the company during which advice on administrative and regulatory issues was sought.
- The company submitted their responses to the CPMP consolidated list of questions on 14 March 1996.
- On 15-16 April 1996, the Dutch Inspectorate and an expert of the Rapporteur's team inspected the manufacturing site of the dosage form, Ben Venue Laboratories in the United States of America. Three deficiencies were observed which were required to be resolved before a pre-authorisation approval.
- On 17-19 April 1996, a positive recommendation was made by the Dutch Inspectorate regarding the manufacturing site of the active ingredient, Biogen Inc., in the United States of America, despite some minor objections in relation to Ben Venue Laboratories.
- The Rapporteur's responses assessment report was circulated on 19 April 1996.
- The Co-Rapporteur's responses assessment report was circulated on 15 April 1996.
- The CPMP in its meeting of 16-18 April 1996, discussed the possibility of finalising an opinion in May following an in-depth discussion and an oral presentation by the company.
- The Biotechnology Working Party in its meeting of 7-8 May 1996, was presented with an oral explanation by the company on 8 May 1996. Following this hearing a BWP Report to the CPMP recommending a positive opinion with regard to the quality issues, including a proposal for the pharmaceutical follow-up measures was drafted.
- The CPMP during its meeting of 21-23 May 1996, was presented with an oral explanation by the company on 21 May 1996. The CPMP, having considered the BWP recommendation and the discussion following the oral explanation, concluded that further data was required to resolve the remaining issues, particularly on neutralising activity in patients treated with AVONEX. On 22 May 1996, the CPMP agreed on the conclusions drawn following the hearing (CPMP/456/96) and the clock was stopped.
- The CPMP conclusion on the remaining issues to be resolved (CPMP/456/96) was sent to the company on 24 May 1996.
- On 9 September 1996, a meeting was held with the company experts, the Rapporteur and the Co-Rapporteur. During this meeting the company presented an overview of the proposed responses to the remaining antigenicity issues raised at the CPMP meeting of 21-23 May 1996. The proposed responses were discussed and suggestions were put forward to aid in the preparation of the responses. On 4 October 1996, the company submitted their responses to the CPMP conclusion of May 1996, as well as four reports addressing pharmaceutical points identified as follow-up measures during the BWP meeting in May 1996.
- On 15 October 1996, the Dutch Inspectorate informed the manufacturer of the dosage form in the United States of America that there were no outstanding pre-authorisation issues arising from the inspection of Ben Venue Laboratories performed on 15-16 April 1996, following their five follow-up responses on the deficiencies.
- The Rapporteurs assessment report and recommendation to the CPMP on the company's responses to the CPMP conclusions following the oral hearing in May 1996 was circulated on 21 October 1996.
- The Rapporteur's assessment report on the additional pharmaceutical data was circulated on 22 October 1996.

- The CPMP, during its November meeting, considered and discussed the additional information provided by the Applicant. A favourable opinion was unanimously adopted recommending a marketing authorisation for AVONEX to be granted under exceptional circumstances.
- The tradename issue was considered to be resolved, provided that no changes intervened with the current pharmaceutical forms of AVONEX (powder and solvent for solution for injection) and of Daivonex (ointment).
- The specific obligations to be fulfilled by the Marketing Authorisation Holder were discussed and agreed and the information will be reviewed by the EMEA in the annual reassessment of the risk/benefit balance.