BACKGROUND INFORMATION ON THE PROCEDURE

1. Submission of the dossier

The applicant Abbott Laboratories submitted on 26 February 1996 an application for Marketing Authorisation to the European Agency for the Evaluation of Medicinal Products (EMEA) for Norvir oral solution 80 mg/ml and hard capsules 100 mg, through the centralised procedure. Norvir 100 mg soft capsules have further been developed to replace the hard capsules. ***Please refer to modules "STEPS AFTER ASSESSMENT" and "SCIENTIFIC DISCUSSION" (Section 2).*** After agreement by the CPMP on 18 September 1995, this medicinal product is referred to Part B in the Annex of the Council Regulation EEC No 2309/93 of 22 July 1993; indent 7 as it contains a new active substance.

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

Rapporteur: Dr. H. Van Bronswijk Co-Rapporteur: Pharm. J. Genoux-Hames

Licensing status:

Norvir has been given a Marketing Auorisation in several countries including in the USA on 1 March 1996.

2. Steps taken for the assessment of the product

- The procedure started on 13 March 1996.
- During the meeting in April, the CPMP agreed to perform a GMP inspection on the USA manufacturing facility for the finished medicinal product (Norvir capsules) by the U.K. Inspectorates.
- The company submitted additional information with regard to the correlation of the changes in viral and immunological parameters and the clinical outcomes in study M94-247 as requested by the Rapporteur. In addition subgroup analysis according to treatment regimens in study M94-247 was provided as requested. These supplementary analyses were distributed to all CPMP Members during the April CPMP meeting 15-18 April 1996.
- A preliminary Co-Rapporteur's pharmaceutical and preclinical assessment report was circulated to all CPMP Members on 25 April 1996. A preliminary Co-Rapporteur's clinical assessment report was circulated to all CPMP Members on 26 April 1996.
- The Rapporteur's assessment report was circulated to all CPMP Members on 26 April 1996. The Co-Rapporteur's assessment report, partially revised, was circulated to all CPMP Members on 30 April 1996.
- The company submitted to the Rapporteur and Co-Rapporteur additional information in response to their objections and points for clarifications raised on 13 May 1996.
- A break-out session on Norvir was organised on 20 May 1996, between Rapporteur and Co-Rapporteur assessment teams and experts in AIDS field, to prepare a draft opinion for Norvir and a list of questions which were circulated during the May CPMP meeting.
- A hearing was held on 21 May 1996 with the company during the CPMP meeting to address concerns related to quality aspects (stereoselective synthesis and control of stereoisomers, bulk drug impurity limits, finished product degradate limits, control of polyoxyl 35 castor oil) and clinical aspects (updated data on studies M94-247 and M94-245, information on ongoing clinical trials and studies planned to be conducted). The applicant provided additional information, which, for most of them were considered acceptable. The remaining points were included in the list of commitments the applicant, after agreement, would have to fulfil.

- The applicant submitted on 22 May 1996 their letter of commitments for providing information on clinical aspects (submission of the finalised reports of both phase III studies, submission of detailed study programme for an expanded investigation of antiretroviral combination therapy) as part of the re-assessment of the benefit/risk profile. The applicant also committed to provide additional data on specified quality, safety and efficacy aspects.
- The assessment report on the applicant's responses was jointly prepared by the Rapporteur and Co-Rapporteur on 23 May 1996 and was circulated to all CPMP members on 24 May 1996.
- The CPMP in the light of the overall data submitted and the scientific discussion within the Committee, issued on 23 May 1996 positive opinions for granting a marketing authorisation under exceptional circumstances for both presentations of Norvir.
- Following a rapid alert from France on the 14 June 1996, drawing attention to reports of spontaneous bleedings in haemophiliac patients involved in the *Autorisation Temporaire d'Utilisation (ATU)* program, the CPMP during their meeting of 16-17 July 1996 agreed to revise the opinions adopted on 23 May 1996. In the revised opinions warnings have been introduced into the Summary of Product Characteristics and in the Package Leaflet in the light of the information available. The wordings proposed by the CPMP have been discussed between the Chairman of the Committee and the companies involved in the marketing of protease inhibitors. An agreement on the warnings to be introduced has been reached on Monday, 22 July 1996.
- The CPMP revised opinions were forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decisions on 26 August 1996.