London, 20 January 2005
Product name: **ENBREL**
Procedure No. **EMEA/H/C/262/X/47**

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Page

1. INTRODUCTION

Enbrel (etanercept) is a sterile, preservative-free, lyophilised powder for subcutaneous injection after reconstitution with 1-mL sterile water for injections. Etanercept is a fully human protein produced by recombinant DNA technology in a Chinese hamster ovary (CHO) cell mammalian expression system and is comprised of the extracellular domains of two human tumour necrosis factor receptors (TNFR2/p75) attached to the Fc domain of human IgG1. Etanercept contains 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons.

The original approved product was Enbrel 25 mg: each vial contains 25 mg of etanercept. The recommended dosing schedule for Enbrel 25 mg in adults with rheumatoid arthritis is 25 mg twice-weekly. The administration of 50 mg once weekly, using two 25 mg injections given on the same day has been approved by Type II variation on 23 July 2004. For plaque psoriasis, the recommended dose of Enbrel is 25 mg administered twice weekly. Alternatively, 50 mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 25 mg twice weekly.

This application was an extension application for a new 50 mg strength of Enbrel for use in adults with rheumatoid arthritis or plaque psoriasis according to the recommended dosing schedules.

The formulation for the 50 mg vial is identical to the approved 25 mg vial except that the amount of etanercept has been doubled. A once-weekly dosing regimen using the 50 mg vial would substantially improve the convenience of use for patients who self-administer Enbrel and thus improve compliance.

2. QUALITY ASPECTS

There are no changes to the active substance. Enbrel 50 mg/vial drug product differs from Enbrel 25 mg/vial drug product only in the amount of etanercept protein that is filled into the vial. There are no modifications in the identity, quality or quantities of excipients of the medicinal product.

The main pharmaceutical development issues were those associated with optimisation of a revised freeze-drying (lyophilisation) cycle for the product, which is effectively 25 mg heavier due to the additional quantity of active substance.

Appropriate pharmaceutical development studies have been performed for the new lyophilisation cycle and the critical lyophilisation parameters for 50 mg/vial Enbrel drug product have been defined.

Three lots of 50 mg/mL process intermediate batches were prepared at pilot scale under GMP conditions at Amgen's Cell Culture Facility in Bothell, Washington, USA. The starting material was 25 mg/mL GMP pilot drug substance manufactured at the Bothell Cell Culture Facility. The GMP pilot 50 mg/mL process intermediate batches were stored in stainless steel containers and placed on stability at -20°C, plus accelerated testing at 2°C to 8°C and 25°C. These met all specifications when stored in stainless steel containers for 6 months at -20°C or for 3 months at 2°C to 8°C. Developmental studies show that 50 mg/mL process intermediate can undergo freezing and thawing under fast and slow conditions for up to ten cycles without impacting protein quality.

Satisfactory validation of the process parameters, including the sterilising filters has been performed.

Four drug product GMP conformance lots (307283, 307305, 307306, 307307) were manufactured in the production freeze dryers. These lots have been placed on stability at 2°C to 8°C plus accelerated stability at 25°C and 40°C. During the manufacture of the conformance lots, additional sampling was

performed to examine vial-to-vial and shelf-to-shelf variability. These samples were analysed for reconstitution time and percentage of residual moisture and found to be consistent and acceptable.

The batch analysis data for bioequivalence and four conformance lots demonstrate compliance with release specifications.

The recommended drug product storage is 2°C to 8°C for 24 months (to be confirmed by ongoing stability studies). GMP pilot lots are stable for 3 months at 25°C. During the procedure, the applicant took the opportunity to provide additional data to justify the shelf life of 3 years, which is the same as that for the currently authorised 25mg product.

The data provided from pilot lots indicated that the stability profile for 50 mg/vial drug product is comparable to that of the current 25 mg/vial drug product. Data from the commercial lots of 50 mg/vial drug product are consistent with historical data for the current 25 mg/vial drug product. The commercial scale stability study is designed to confirm 36 months expiry at the recommended storage condition of 2°C to 8°C. The applicant requests to establish the expiry dating at 36 months on the basis of the 18-month pilot scale data and the 6-month commercial scale data.

The applicant commits to report any out of specification results from the on-going commercial scale stability studies for Enbrel 50 mg with an assessment of the results and proposed corrective action.

The results provided support an extension of the expiry date of the 50 mg/vial product from 24 to 36 months when stored at 2°C to 8°C.

There are no major quality issues associated with the development of the new lyophilised product containing 50 mg of etanercept intended for once weekly administration in adults with rheumatoid arthritis.

In the List of Questions, one area of potential deficiency was identified, regarding the analysis of aggregate formation in the new 50 mg product. The applicant has subsequently confirmed using suitably sensitive methodology (size exclusion HPLC and SDS-PAGE) that processing etanercept 50 mg/ml does not result in a significant increase in aggregate formation. The applicant also provided further justification regarding the scale and expiry dates of batches used for pharmacokinetic studies.

3. CLINICAL ASPECTS

Two clinical studies have been submitted by the applicant to support this extension application:

Study 16.0036: Investigating the efficacy and safety of etanercept 25 mg twice weekly and 50 mg once weekly (2 stimultaneous 25-mg injections) compared with placebo in adults with rheumatoid arthritis. (Previously provided with Variation EMEA/H/C/262/II/37).

Study 20021643: A comparative bioavailability study of the pharmacokinetics of one 50 mg injection and 2 simultaneous 25 mg injections of etanercept.

The first study (16.0036) was the basis for the variation EMEA/H/C/262/II/37, that was approved on 23 July 2004. The second study (20021643) is a bioavailability study comparing the pharmacokinetic profile of two simultaneous injections of Enbrel 25 mg to one injection of Enbrel 50 mg.

Bioavailability/ bioequivalence

Study 20021643 was a single centre, open-label, randomised, crossover study with a wash-out period of at least 28 days in 30 healthy volunteers of whom 28 completed the study. Study power calculation was based on 26 subject providing an 80% power to determine comparability if the intra-subject coefficient of variation (RSD) lower than 25%.

Serum concentrations of etanercept were measured by ELISA with a LLOQ of 0.625 ng/ml.

The results of pharmacokinetic parameters for etanercept (arithmetic mean (SD) and LS geometric mean, except for t_{max}, median and range) were as follows:

	Test	Reference	Point Estimate	90 % C.I.
$AUC_{(0-\infty)}$ (mg.h/l)	502 (126)	487 (178)	102.3	92.5 - 113.1
$AUC_{(0-t)}$ (mg.h/l)	460 (179)	443 (169)	103.9	93.8 - 115.1
C_{max} (mg/l)	3.44 (1.92)	3.03 (1.22)	109.3	95.9 - 124.6
$AUC_{(0-Tmax)}$ (mg.h/l)	85.9 (35.6)	93.7 (49.3)		
t_{max} (h), median (range)	42 (4 - 96)	48 (24 - 96)		
CL/F (l/h)	0.118 (0.052)	0.126 (0.077)		
$t_{1/2}$ (h), mean (SD)	78.0 (17.4)	85.6 (19.7)		

Results indicate that the bioequivalence criteria ($AUC_{(0-\infty)}$ point estimate of 99.5 with a 90% confidence interval from 90.0 to 110.1; $AUC_{(0-t)}$ point estimate of 101.1 with a 90% confidence interval from 91.3 to 112.0 and C_{max} point estimate of 106.4 with a 90% confidence interval from 93.3 to 121.2) were met.

Plasma levels at pre-dose samples were above the LLOQ in 26 out of 28 subjects, because an insufficient wash-out period was allowed, indicating the presence of a carry-over effect. When these levels of AUC are compared with Cmax of the second period, they appear to be higher than 1% of the pre-dose levels, the latter stipulated as expected in the protocol.

Statistical analysis showed a significant period effect for AUC_{0-t} and $AUC_{0-\infty}$.

There were no serious adverse events. As expected, the most commonly reported adverse events were injection site reactions (12 subjects) with no difference between the two formulations.

The results of the bioequivalence study confirm similar average bioavailability between the two formulations.

There are no new safety concerns.

4. CONCLUSION

Benefit/risk assessment

The CHMP concluded that the benefit/risk balance for the proposed new dosage strength of 50 mg for Enbrel was considered to be positive.

Overall conclusions

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the benefit/risk balance for Enbrel 50 mg for the treatment of active rheumatoid arthritis and plaque psoriasis, was favourable and therefore recommended the granting of the marketing authorisation.