17 February 2011
EMA/CHMP/63302/2011
Committee for Medicinal Products for Human Use (CHMP)

Simulect

basiliximab

EMEA/H/C/000207/II/57

CHMP assessment report for paediatric use studies submitted according to Article 45 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Invented name/name:	Simulect
International non-proprietary name/common name:	basiliximab

Indication summary (as last approved):	Prophylaxis of acute organ rejection in *de novo* allogeneic renal transplantation in adult and paediatric patients (1-17 years)
Marketing authorisation holder:	Novartis Europharm Ltd.

1. Scope of the variation and changes to the dossier

Scope of the variation:	Update of section 5.1 of the SmPC with results from a clinical study in paediatric renal transplant recipients (DE01) as requested by the CHMP further to the assessment of FU2 033.1. In addition the PI is brought in line with latest QRD template and the list of the local representatives in the PL is amended.
Product presentations affected:	See Annex A to the Opinion
Dossier modules/sections affected:	Modules 1 and 2
Product Information affected:	Annex I and IIIB

2. Steps taken for the assessment

Step	Step date
Submission date:	02 December 2010
Start of procedure:	19 December 2010
Rapporteur's preliminary assessment report circulated on:	21 January 2011
Rapporteur's updated assessment report circulated on:	11 February 2011
CHMP opinion:	17 February 2011

3. Scientific discussion

3.1. Introduction

Simulect is a specific immunosuppressant consisting of a murine/human chimeric monoclonal antibody (IgG1κ) that is directed against the interleukin-2 receptor α-chain (CD25 antigen), which is expressed on the surface of T-lymphocytes in response to antigenic challenge. Simulect specifically binds to the

CD25 antigen on activated T-lymphocytes expressing the high activity interleukin-2 receptor and thereby prevents binding of inteleukin-2, the major signal for T-cell proliferation. Complete and consistent blocking of the interleukin-2 receptor is maintained as long as serum basiliximab levels exceed 0.2 µg/ml.

Simulect is indicated for the prophylaxis of acute organ rejection in *de novo* allogeneic renal transplantation in adult and paediatric patients. It is to be used concomitantly with cyclosporine for microemulsion- and corticosteroid-based immunosuppression, in patients with panel reactive antibodies less than 80%, or in a triple maintenance immunosuppressive regimen containing cyclosporine for microemulsion, corticosteroids and either azathioprine or mycophenolate mofetil.

In this variation, the MAH proposes to make changes to section 5.1 of the summary of product characteristics of Simulect to include the results of the paediatric study DE01 as requested by the CHMP further to the assessment of FU2 033.1 (CHMP conclusions adopted on 06 September 2010).

3.2. Clinical aspects

The paediatric indication for Simulect was approved on 1 December 2000. The key trial supporting the submission was study CHIB 152 (B152). This study included 41 paediatric de novo renal transplant patients from centres in Europe, the US and Canada. The main objective of the study was to define the pharmacokinetic and pharmacodynamic characteristics of basiliximab in the paediatric renal population and these results provided the support to the currently approved regimen.

On 23 June 2009, the MAH submitted (FUM 033) two completed paediatric studies for Simulect in accordance with Article 45 of Regulation (EC) No. 1901/2006 as amended. In addition to the previously mentioned study B152, results from the study CCHI621ADE01 (DE01) were submitted. Study DE01 was a 12-month, randomized, placebo-controlled, double-blind, multi-centre trial investigating Simulect in combination with CsA-ME, MMF and prednisone in the prevention of acute rejection in paediatric renal allograft recipients. It was a phase IV study designed by the principal investigators and the MAH's affiliate in Germany, which conducted and analysed the study.

The objective of the study was to demonstrate superiority of the treatment regime of cyclosporine microemulsion, MMF and prednisone in combination with basiliximab as compared to cyclosporine microemulsion, MMF and prednisone in the prevention of acute rejection during the first 6 months post-transplantation in paediatric renal allograft recipients.

There were 202 patients randomized into the study, 104 randomized to Simulect and 98 to the placebo group.

The primary efficacy analysis was performed as a survival analysis of the time to the first biopsy proven acute rejection (BPAR) or treatment failure (which was defined as graft loss, death or presumptive rejection) within the first 6 months post-transplant. The results of the study have been published in two peer-reviewed articles (Hoecker 2008, Offner 2008).

The primary efficacy endpoint, time to first biopsy-proven acute rejection (BPAR) episode or treatment failure defined as graft loss, death or presumptive rejection within the first 6 months post transplantation, occurred in 16.7% of basiliximab-treated patients and 21.7% of placebo-treated patients (HR: 0.72, 90% CI: [0.42; 1.26]),. With regard to the incidence of the combined criteria "graft loss, death and/or clinical (biopsy-proven or presumptive) rejection" within 6 months after transplantation (primary efficacy variable) there was no statistically significant difference between the

two treatment groups (incidence rates [Kaplan-Meier estimates]: 26.0% [basiliximab] versus 23.9% [placebo], HR: 1.04, 90% CI: [0.64; 1.68], ITT population) when borderline rejections were included.

When biopsies with the histological diagnosis "borderline" were not considered as rejections (additional analysis), the incidence rate of biopsy-proven acute rejections was lower under basiliximab compared to placebo (incidence rates [Kaplan-Meier estimates]: 9.4% [basiliximab] versus 17.4% [placebo], HR: 0.50, 90% CI: [0.25; 0.99]). When borderline rejections were included, the rates for the separate analyses of the single events "biopsy-proven rejection" (incidence rates [Kaplan-Meier estimates] were: 20.8% [basiliximab] versus 19.6% [placebo], HR: 1.01, 90% CI: [0.59; 1.72]).

Changes to the product information

The MAH agreed to implement the following changes to section 5.1 of the SmPC for Simulect (new text in **bold and underlined**):

Section 5.1 Pharmacodynamic properties

Paediatric ***population***
The efficacy and safety of basiliximab were evaluated in two paediatric studies.

Basiliximab was used concomitantly with ciclosporin for microemulsion and steroids in an uncontrolled study in 41 paediatric *de novo* renal transplant recipients. Acute rejection occurred in 14.6% of patients by 6 months post-transplantation, and in 24.3% by 12 months. Overall the adverse event profile was consistent with general clinical experience in the paediatric renal transplantation population and with the profile in the controlled adult transplantation studies.

A 12-month, randomised, placebo-controlled, double-blind, multicentre study investigated basiliximab in combination with ciclosporin for microemulsion, mycophenolate mofetil and steroids in paediatric renal allograft recipients. The primary objective of the study was to demonstrate superiority of this combination versus treatment with ciclosporin for microemulsion, mycophenolate mofetil and steroids in the prevention of acute rejections. Of the 202 patients, 104 were randomised to basiliximab and 98 to placebo. The primary efficacy endpoint, time to first biopsy-proven acute rejection (BPAR) episode or treatment failure defined as graft loss, death or presumptive rejection within the first 6 months post transplantation, occurred in 16.7% of basiliximab-treated patients and 21.7% of placebo-treated patients. When borderline rejections were included in the primary efficacy endpoint, the rates were 26.0% and 23.9% respectively, with no statistically significant difference between the basiliximab- and placebo-treated groups (HR: 1.04, 90% CI: [0,64; 1.68]). The rates of BPAR were 9.4% in the basiliximab group and 17.4% in the placebo group (HR: 0.50, 90% CI: [0.25; 0.99]). When borderline rejections were included, the rates were 20.8% and 19.6% respectively (HR: 1.01, 90% CI: [0.59; 1.72]). The overall safety profiles were similar in both groups. The incidence rates of adverse events and the pattern of adverse events were comparable between the two treatment groups and to be expected for the treatment regimens and the underlying diseases.

The MAH has also updated the product information in accordance with the latest QRD templates which was agreed by the CHMP.

Discussion

Further to the assessment of FUM 33 in September 2009, the CHMP requested the MAH to provide a response document including supplementary tables, figures and listings for study report DE01 and to

comprehensively discuss the benefit and risk of basiliximab in paediatric kidney transplantation. Following this recommendation the MAH reanalysed the data from the paediatric study DE01. Further to the assessment of the data provided (FU2 33.1) the CHMP concluded that the MAH provided a comprehensive discussion on the benefit and risk of basiliximab in paediatric kidney transplantation. Apart from deficiencies in the clinical trial conduct and analysis one major problem is the lack of understanding of the relevance of "borderline" changes in the biopsies. Exclusion of borderline cases from the definition of acute rejection leads to clearer benefit of basiliximab therapy, inclusion of borderline cases decreases the differences between both treatment arms. Of note, inclusion of borderline cases and analysing the Kaplan-Meier curves for the primary composite endpoint (survival, graft survival, acute rejection) show merely a delay of events and an aligning of the curves at a later time point.

The safety is difficult to evaluate as multiple confounding factors are present in this patient population. The imbalance in the cases of death between both treatment arms is of concern, as a contribution of basiliximab on the causes of death cannot be excluded. Because of its mechanism of action it is expected that basiliximab contributes to the overall immunosuppression and might therefore have contributed to the infections that were observed in the fatal cases. However, it is unknown how long this immunosuppressive effect persists, whether any longer lasting changes are impacted on the immune system and therefore it is unknown if the late occurring deaths have any connection with basiliximab therapy at a considerably earlier time. Even less is known for the impact on a potentially immature immune system and the impact of basiliximab on naturally occurring T regulatory cells, which also carry CD25.

Both randomised trials of Simulect in the paediatric population failed to meet their primary endpoint, the one discussed in this FUM with an approved combination of immunosuppressives, a second one with tacrolimus as part of another commonly used regimen. The MAH makes the point that these trials were underpowered and this is agreed to by the CHMP.

The CHMP agrees that the data in summary indicate that basiliximab may reduce the rate of acute biopsy proven rejection but a proof is lacking. It also remains unclear whether the assumed reduction of biopsy proven rejection translates into a longer lasting benefit for the patient. This is similar to the situation in adults but the prevention of acute rejections has been accepted as a treatment goal in itself since it is associated with a better long term outcome.

Taken together the benefit risk balance appears to be similar in children and adults.

As requested by the CHMP, the results from the DE01 trial (both analyses (with and without borderline cases)) have been incorporated in a short version in the SmPC. The changes to section 5.1 of the SmPC are considered acceptable.

4. Conclusion

On 17 February 2011 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the in the Summary of Product Characteristics and Package Leaflet.