European Medicines Agency

London, 24 January 2007
Doc. Ref. CHMP/EWP/263148/2006

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

CONCEPT PAPER ON THE DEVELOPMENT OF A CHMP GUIDELINE ON CLINICAL INVESTIGATION OF IMMUNOSUPPRESSANTS FOR SOLID ORGAN TRANSPLANTATION

AGREED BY THE EFFICACY WORKING PARTY	October 2006 – January 2007
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	24 January 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 April 2007

Comments should be provided to Line.Jensen@emea.europa.eu
Fax: +44 20 7418 86 13

KEYWORDS	Solid organ transplantation, concept paper

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 86 13
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

1. INTRODUCTION

Solid organ transplantation is one of the most efficient therapies for the end stage organ failures. After introduction of more selective immunosuppressants (e.g., ciclosporin A, anti CD25 Mab, MMF) relatively safe use of immunosuppressants prompted increase in magnitudes of solid organ transplantation in EU and investigation/development of new/other immunosuppressants (e.g., ISA(TX)247, new mTOR inhibitors, mizoribine, leflunomide, FK778, FTY720, HuOKT3γ, HuM291, alemtuzumab, rituximab, LEA29Y, intravenous immunoglobulins, MEDI-507) or new pharmacological regimens (steroid withdrawal and avoidance, drug minimisation) in the field of transplantation.

2. PROBLEM STATEMENT

Solid allograft rejection's prophylaxis and treatment modalities are specifically influenced by several intrinsic (both donor and recipient related) and external risk factors. Risk factors for higher rejection rate have been intensively investigated during last 20 years and reported in scientific literature and although not universally accepted ignorance of characterisation of these risk factors leads to diversified baseline and treatment arms characteristics of patient populations. Numerous prognostically important risk factors evolves before/during/after transplantation take place and they have to be considered as influencing physiological features of both host and transplanted allograft. These physiological changes might change PK/PD profile of medicinal products from pre- to post-transplantation and during early to late post-transplantation periods. If these variations are investigated non-properly, use of immunosuppressant might have consequences for clinical safety and/or efficacy.

Different types of solid organ transplantation (renal, liver, heart transplantation etc.,) have certain pathophysiological specificities in course of peri-transplantation period. These relate to specific risk and/or time factors and have to be considered during development of an immunosuppressant regimen.

There are number of risk and time dependent factors to be considered for renal transplantation. Differences are seen in peri-transplantation period in host and allograft interaction. These differences lead to certain risk/time dependent variation in pharmacodynamic and dose-response profile of immunosuppressant and prompts different prophylaxis regimens to be investigated properly e.g., for renal transplantation, acute rejection prophylaxis is to be investigated for specific type of prophylaxis –for induction, initial and/or maintenance prophylaxis separately. Also, different pathophysiological features in acute and chronic rejection types urges investigate chronic rejection separately and specifically. Data gathered after more tailored investigational programme will rationalise a use of immunosuppressant for chronic rejection excluding non-immunological cases of chronic allograft nephropathy.

Liver transplantation bears additional risk for both PK/PD profile and safety due to host sensitivity to several ADRs (e.g., nephrotoxicity in case of hepatorenal syndrome or neurotoxicity in fulminant hepatitis). Heart and/or lung transplantations bear also certain specific risk factors that are still debatable for their clinical relevance (e.g., relevance of immunological risk stratification). Majority of other solid organ transplantations (e.g., thymus, larynges, pancreatic islet and others) are less intensively investigated therefore more guidance is needed.

Certain other specific to immunosuppression regimen safety and efficacy issues should be considered also during product development/regulatory evaluation process (e.g., co-infection with HCV, EBV, and HIV).

Known specific safety issues relevant to immunosuppression in transplantation (e.g., consequences of chronic immunosuppression for developing infectious or malignant complications, developments of chronic allograft pathologies, features of different age and specific patient groups) to certain extend should be evaluated prospectively during pre (post) approval development and accordingly be properly considered in a risk minimisation programme.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

- What are the best methods to provide evidence that medicinal product is effective and safe for seeking marketing authorisation as immunosuppressant for particular settings in transplantation:
    - In the prophylaxis of allograft rejection (inductive, initial, maintenance, tolerance induction, if applicable);
    - In the treatment of allograft rejection (acute, chronic, resistant, if applicable).
- Describe different aspects of immunosuppressant agent to be considered for distinctive type of allograft during clinical efficacy and safety investigation in (pre-approval) clinical development programme, e.g.:
    - Define essential patient baseline and (concurrent) treatment characteristics;
    - Define most suitable place for mono-, dual-, triple- or quadruple therapy;
    - Define specificities in pharmacokinetic and pharmacodynamic variations and interactions.
- Describe specific donor risk factors as per type of allograft.
- Describe different approaches to be taken to fit within proper pathophysiological type of allograft rejection (cellular, humoral type of rejection, tolerance induction, if applicable).
- Describe integrative (surgical and therapeutic) approaches to be considered during proper product development/investigation and/or regulatory evaluation procedures.
- Describe whether additional constrains are necessary (e.g., valgancilovir or sulphamethoxazole/trimethoprim as prophylaxis against CMV or PCP).
- Specific long-term safety issues (such as malignancies and infections) to be considered during development process.

4. RECOMMENDATION

The CHMP Efficacy Working Party recommends drafting a guidance document detailing what data are required to be included in dossier of an immunosuppressant for solid organ transplantation and what kind of post-marketing information may be needed. Recommendation will also be given regarding presentation and interpretation of results.

5. PROPOSED TIMETABLE

It is anticipated that a draft CHMP Guideline may be available 12 months after adoption of the Concept paper to be later released for 3 to 6 months for external consultation and finalisation within 6 months.

6. RESOURCE REQUIREMENTS FOR PREPARATION

The preparation of this Guideline will involve only the CHMP Efficacy Working Party.

7. IMPACT ASSESSMENT (ANTICIPATED)

The development of this Guideline will result in a dossier regarding immunosuppressants of adequate quality and quantity and sufficient level of detail, thus, facilitating the assessment of these submissions and decrease uncertainties related to development of immunosuppressants for transplantation.

8. INTERESTED PARTIES

International scientific societies in transplantation (relevant to renal, liver, pancreas, heart and pulmonary diseases).

9. REFERENCES TO LITERATURE, GUIDELINES ETC

Bertoux F on behalf of the EBPG Expert Group on Renal Transplantation. European Best Practice Guidelines on Renal Transplantation. Part 1. *Nephrology Dialysis Transplantation.* 15(Suppl 7):3-85 **(2000)**.

Bertoux F on behalf of the EBPG Expert Group on Renal Transplantation. European Best Practice Guidelines on Renal Transplantation. Part 2. *Nephrology Dialysis Transplantation.* 17(Suppl 4):1-67 **(2002)**.

Knoop C et al., "Immunosuppressive therapy after human lung transplantation". *Eur Resp J.* 23:159-171 **(2004)**.

Lindenfeld J et al., "Drug therapy in the Heart Transplant Recipient. Part I: Cardiac Rejection and Immunosuppressive Drugs". *Circulation.* 110:3734-3740 **(2004)**.

Primer on Transplantation (Ed. By Norman DJ and Turka LA), 2nd edition, NJ, American Society of Transplantation, 732 pp. **(2001).**

Transplantation of the Liver (Ed. by Busuttil W and Klintmalm GB), 2nd edition, Philadelphia, Sounders 1485 pp. **(2005)**.