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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

CONCEPT PAPER ON REVISION OF:

- **Note for Guidance on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration (IVIg) (CPMP/BPWG/388/95 rev.1)**
- **Core SPC for Human Normal Immunoglobulin for Intravenous Administration (IVIg), (CPMP/BPWG/859/95 rev. 2)**

AGREED BY THE BLOOD PRODUCTS WORKING GROUP (BPWG)	22 February 2005
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	16 March 2005
END OF CONSULTATION (deadline for comments)	30 June 2005

Comments should be provided to Nicola.Martin@emea.eu.int Fax: (44-20) 74 18 85 45

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 45
E-mail: mail@emea.eu.int http://www.emea.eu.int

CONCEPT PAPER ON THE REVISION OF CHMP GUIDELINES ON:

NOTE FOR GUIDANCE ON THE CLINICAL INVESTIGATION OF HUMAN NORMAL IMMUNOGLOBULIN FOR INTRAVENOUS ADMINISTRATION (IVIg) (CPMP/BPWG/388/95 REV.1)

CORE SPC FOR HUMAN NORMAL IMMUNOGLOBULIN FOR INTRAVENOUS ADMINISTRATION (IVIg), (CPMP/BPWG/859/95 REV. 2)

1. Introduction

The current Note for Guidance (NfG) on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration (IVIg) (CPMP/BPWG/388/95 rev.1) and the Core SPC for Human Normal Immunoglobulin for Intravenous Administration (IVIg), (CPMP/BPWG/859/95 rev. 2) have been in operation since December 2000[i]. Medical knowledge and treatment regimens in the areas covered by the NfG and cSPC are in a state of continual development. Especially the past 5-10 years have seen many changes e.g. in the therapy of AIDS, in the use of new antibiotics, but also in a better understanding of autoimmune illnesses and therapy options.

2. Problem Statement

Due to medical developments, the question arises whether the currently recommended studies, "established indications" and their respective posologies require modification to more adequately reflect current clinical practice with IVIgs.
In addition, IVIgs used in other areas have proved beneficial and the possible inclusion of other indications may reflect current clinical practice. In the case of rare indications, there is the question of the extent of clinical data needed before the indication can be considered as "established" for IVIgs.
Since there is a need for IVIg treatment of children, more specific guidance relating to the clinical investigation of IVIg products in paediatric populations needs to be considered, taking into account the Regulation on Medicinal Products for Paediatric Use, which is in development.

3. Discussion on the Problem Statement and Recommendation

It is proposed to consider the following aspects:

A. Guideline:
A.I Reconsider the data necessary to support the safe and effective use of IVIg in the core indications.

A.II Primary immunodeficiency (PID) study requirements
The FDA recommendations (according to Golding [1]) for pharmacokinetic, efficacy and safety studies in PID patients, in order to see if there is scope for harmonisation of recommendations.

A.III Idiopathic (autoimmune) thrombocytopenic purpura (ITP)
Whether there is a need to distinguish between modified and non-modified IVIg products in the criteria for proof of efficacy and safety in ITP. (Products that are Fc-modified have shown to be of limited efficacy in ITP.)

A.IV Paediatric Use
The design of the clinical studies needed to support regulatory approval for treatment of children.

A.V The data needed to support an indication in rare disorders.

[i] The Core SPC was revised in 2004 (revision 2) with respect to thromboembolic events.

B. cSPC

B.I. Changes to currently established indications:

1. Chronic lymphocytic leukaemia (CLL)

   What is the current role of IVIg in CLL treatment in view of the wide spectrum of antibiotics that has been developed to combat infectious complications? It is argued in a recent retrospective study (Hensel[2]) that disease activity and pre-treatment are the major risks for infectious complications in CLL.

2. Allogeneic bone marrow transplantation (ABMT)

   What is the current role of IVIg in ABMT treatment? In recent studies[3 4 5] the use of prophylactic IVIg in ABMT has been questioned. In one study[3] there was no benefit over placebo.

3. Paediatric AIDS

   Whether the indication should be modified to define more precisely the current use of IVIg in paediatric AIDS.

B.II New Indications to be discussed include:

1. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
2. Neonatal sepsis

Second line therapy option

3. Severe myasthenia gravis
4. Dermatomyositis,
5. Progressive, symptomatic multifocal motor neuropathy

B.III. Posology issues:

1. Are the current dosage recommendations and targeted trough levels of IgG given in the cSPC still adequate for PID patients? Recent literature[6] suggests higher doses should be used, if patients develop more than 2 severe infections/year despite standard therapy.
2. Recent literature[7] recommends a single 2 g/kg dose for Kawasaki's syndrome rather than two or more doses over 2-5 days.
3. Recent literature[8] recommends 5-7 days treatment in Guillain Barré Syndrome rather 3-7 days stated in the cSPC.

B.IV General review of contraindications, precautions and warnings, and undesirable effects taking into account the revision of the SPC Guideline.

4. Timetable and resource requirements for preparation

The revision of these documents will be discussed during the meetings of the BPWP. In addition, a specific expert meeting may be held to discuss issues arising from the revision[ii]. It is anticipated that a draft revision of the documents will be available for a final discussion at the Blood Products Working Party in 2006.

5. **Involvement of external parties**

Interested parties with specific interest in this topic will be consulted during the revision of these guidelines, including IPFA, PPTA, EPPIC, ESID, EFIS, EFNS, ENMC and the Cochrane Neuromuscular Disease Review Group[iii].

[ii] It is anticipated that this will involve experts from other CHMP working parties and scientific advisory groups with an interest in the topics under discussion, including experts from the Efficacy Working Party, Scientific Advice Working Party, Paediatric Working Party and Pharmacovigilance Working Party. Representatives from external parties will also be invited to participate.

[iii] IPFA: International Plasma Fractionation Association
PPTA: Plasma Protein Therapeutics Association
EPPIC: European Patients Primary Immunodeficiency Collaboration
ESID: European Society for Immunodeficiencies
EFIS:European Federation of Immunological Societies
EFNS: European Federation of Neurological Societies
ENMC: European Neuromuscular Centre

6. Impact Assessment

The revised guidelines will better reflect current clinical practice and the regulatory assessments of IVIg products. A harmonised regulatory approach will encourage a more consistent assessment of products by regulators, and set clear standards and expectations for Industry. In addition, this will provide physicians and patients with reassurance about the safe and effective use of IVIg products.

The resource implications for revision of the guidelines are considered justified by the fact that application of updated guidance will make assessment easier and will result in less resources being needed during assessment.

Literature references

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