EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on 'Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg) and Core SmPC'

Draft

Agreed by Blood Products Working Party	February 2014
Adopted by CHMP for release for consultation	24 July 2014
Start of public consultation	1 August 2014
End of consultation (deadline for comments)	31 October 2014

The proposed guidelines will replace Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg) (EMA/CHMP/BPWP/94033/2007 rev. 2) and core SmPC for Human Normal Immunoglobulin for Intravenous Administration (IVIg), (CHMP/BPWP/94038/2007 rev.4)

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Keywords	Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), Multifocal motor neuropathy (MMN), intravenous immunoglobulin

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1. Introduction

The current Note for Guidance (NfG) on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration (IVIg) (EMA/CHMP/BPWP/94033/2007 rev.2) and the coreSmPC for Human Normal Immunoglobulin for Intravenous Administration (IVIg), (CHMP/BPWP/94038/2007 rev.4) have been in operation since December 2000 and underwent a major revision process from 2006 (EMA Workshop) through 2010.

IVIg products are administered in replacement therapy for primary immunodeficiencies (PID), certain secondary immunodeficiencies (CLL, MM, AIDS in children, ABMT) and in the immunomodulatory setting for Kawasaki's Disease, immune thrombocytopenia (ITP) and Guillain-Barré Syndrome (GBS). Especially the indications in the immunomodulatory setting are in a state of continual development. The past 3-4 years have seen some additional studies in these areas.

2. Problem statement

Approximately 33% of all immunoglobulin use is off-label in over 50 different diseases. For certain indications there is a relatively broad consensus in the medical community that immunoglobulins are efficacious (chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN), dermatomyositis/polymyositis, myasthenia gravis (during exacerbations), Lambert Eaton myasthenic syndrome, stiff person syndrome, Birdshot retinopathy). The largest area of IVIg use in the field of neurology is for CIDP and MMN.

The question arises whether the Guidelines on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration (IVIg) and the coreSmPC for Human Normal Immunoglobulin for Intravenous Administration (IVIg), should be updated to include CIDP and MMN as being "established indications"

Additionally, some international experts recommend that dosing in replacement therapy and in immunomodulation should be re-evaluated, possibly with adjustment according to lean body weight.

3. Discussion (on the problem statement)

Certain IVIg products have recently obtained Marketing Authorisation (MA) within the EU for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and multifocal motor neuropathy (MMN). Due to these additional studies performed with different IVIgs, a body of evidence has accumulated for these immunomodulatory indications. Use of IVIg in these diseases is also a recommendation of the European Federation of Neurological Societies (EFNS: CIDP –IVIg Recommendation Level A). These recommendations are not product-based.

The general question thus arises of the extent of clinical data needed before an indication can be considered as "established" for IVIgs.

Linked to this is the question of the extent of clinical data needed in the paediatric population.

In a recent centralised procedure the PDCO recommended accepting the assumption of extrapolation of adult efficacy data to the paediatric population in CIDP. It was deemed necessary to obtain safety information for each immunoglobulin in the paediatric population. However, all marketed products to date have supplied safety data in children within the PID indication for their marketing authorisation.

The PDCO suggested that a possible way to obtain further information on the use of immunoglobulin use in CIDP in children could be via a post-authorisation safety study. In addition, the product information highlights that only limited experience is available of use of IVIg in children with CIDP.

Based on the discussion on the problem statement the existing guideline may need to be updated, taking into account the various considerations addressed:

- Possible new "established" indications to be discussed encompass:
    1. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
    2. Multifocal motor neuropathy (MMN)
- Is the available data adequate to provide evidence for a class effect of IVIgs and to allow inclusion in the Core SmPC of CIDP and MMN as established indications?
- Data extrapolation from adults to children, in relation to how these data should be incorporated into the Guideline on Clinical Investigation and the Core SmPC and generally if there is a specific need for dedicated studies.

During this revision, the opportunity will be taken to discuss the question of dose adjustment according to lean body weight in replacement therapy and in immunomodulation. In view of the worldwide increase in body weight and given the scarce resource of IVIG this is considered to be a relevant issue. It might also be a measure for reducing the risk of certain adverse reactions.

4. Recommendation

Depending on the discussion as outlined above changes in the Guideline and/or coreSmPC may result to the list of "established" indications, to dosing recommendations, to data extrapolation from adults to children and on the extent of clinical data needed before an indication can be considered as "established" for IVIgs.

5. Proposed timetable

Q4/2013 – 2/2014 Discussion of Concept Paper in BPWP

Q3/2014 Changes in NfG and coreSPC to be discussed at BPWP

Q3-4/2014 Presentation of proposed NfG and core SmPC to relevant WPs

Q1/2015 Release for public consultation for 6 months

6. Resource requirements for preparation

The revision of these documents will be discussed during the meetings of the BPWP. External parties will have the opportunity to comment during the public consultation phase.

7. Impact assessment (anticipated)

Studies are costly both for the pharmaceutical companies and for the health system which has to cover the resulting increased costs of the products. Studies should therefore not be performed in areas where sufficient knowledge on the benefit-risk has accumulated. By adding CIDP and MMN to the

established indications, studies could be performed in other areas where the benefit has not yet been so soundly established. In addition, health systems could choose from all available IVIg products to treat CIDP and MMN patients. By spreading the treatment more evenly between available products shortages are less likely to occur.

The revised guidelines will better reflect the current medical knowledge and clinical practice.

The resource implications for revision of the guidelines are considered minimal and do not exceed the normal costs for the BPWP.

8. Interested parties

Involvement of external parties:

Interested parties with specific interest in this topic will be consulted during the revision of these guidelines, including IPFA, PPTA, EFNS[1]

9. References to literature (from 2008), guidelines, etc.

CIDP

Hughes RA, Donofrio P, Bril V et al; ICE Study Group. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial. Lancet Neurol 2008;7:136–44.

Eftimov F, Winer JB, Vermeulen M, de Haan R, van Schaik IN. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy. Cochrane Database Syst Rev 2009;1: CD001797

Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating olyradiculoneuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. First Revision. J Peripher Nerv Syst 2010;15:1-9

Merkies ISJ, van Nez SI, Hanna K et al Confirming the efficacy of intravenous immunoglobulin in CIDP through minimum clinically important differences: shifting from statistical significance to clinical relevance . J Neurol Neurosurg Psychiatry 2010;81:1194-1199 doi:10.1136/jnnp.2009.194324

MMN

van der Pol WL, Elisabeth A. Cats EA, van den Berg LH. Intravenous Immunoglobulin Treatment in Multifocal Motor Neuropathy. J Clin Immunol (2010) 30 (Suppl 1):S79–S83

Vlam L, van den Berg LH, Cats EA, Piepers S, van der Pol WL. Immune pathogenesis and treatment of multifocal motor neuropathy. J Clin Immunol. 2013 Jan;33 Suppl 1:S38-42. doi: 10.1007/s10875-012-9779-8. Epub 2012 Sep 2.

[1] IPFA - International Plasma Fractionation Association ; PPTA - Plasma Protein Therapeutics Association; EFNS - European Federation of Neurological Societies

Marketing Authorisations in EU and national

CIDP

IgVena (AT, DE, EL, PL, PT)

Gamunex (AT, BE, CY, CZ, DK, EL, FI, HU, IE, LU, NL, PL, PT, SE, UK)

Privigen (EU)

Multigam (BE)

Tegeline (FR)

MMN

KIOVIG (EU)

Tegeline (FR, PT)

Gammagard (NL)

Multigam (BE)