EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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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 subcutaneous and intramuscular use (CPMP/BPWG/283/00)

Core SPC for human normal immunoglobulin for subcutaneous and intramuscular use (CPMP/BPWG/282/00)

Agreed by Blood Products Working Party	November 2010
Adoption by CHMP for release for consultation	16 December 2010
End of consultation (deadline for comments)	31 March 2011

The proposed guidelines will replace Note for Guidance CPMP/BPWG/283/00 and core SmPC CPMP/BPWG/282/00.

Comments should be provided using this template. The completed comments form should be sent to ludmila.svobodova@ema.europa.eu

Keywords	*SC/IMIg, human normal immunoglobulin, primary immunodeficiency syndromes, hypogammaglobulinaemia, hepatitis A prophylaxis, multifocal motor neuropathy (MMN), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), myasthenia gravis exacerbations*

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1. Introduction

Subcutaneous and intramuscular immunoglobulin (SCIg/IMIg) products are prepared from pooled human plasma from not fewer than 1000 donations and contain mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents that is representative of the immunoglobulin range of the normal population. They have a distribution of immunoglobulin G subclasses closely proportional to that in native human plasma. Adequate doses of this medicinal product may restore abnormally low immunoglobulin G levels to the normal range

In 1952, Bruton identified the first case of X-linked agammaglobulinemia in an 8-year old boy. Subsequently immunoglobulin therapy was introduced as replacement treatment for primary immunodeficiencies (PID) initially given as subcutaneous injections (s.c), which were later replaced by intramuscular injections (i.m). However, the use of intramuscular immunoglobulin (IMIg) was limited by volume and pain. In the 1970's IMIgs were modified to be rendered virtually free of aggregates; other changes were made leading to the production of intravenous immunoglobulins (IVIg). The difference in production requirements between SC/IMIgs and IVIgs are captured in two different EU Monographs (01/2002:0338 and 01/2002:0918, respectively).

Over the ensuing decades since Bruton's discovery and with the use of portable syringe drivers, the administration of SCIgs has become widespread and the guidelines for clinical trials and treatment modalities are laid down in the NfG and Core SmPC for human normal immunoglobulin for subcutaneous (SCIg) and intramuscular use (IMIg) (CPMP/BPWG/283/00 and core SmPC CPMP/BPWG/282/00 respectively) which became effective in January 2003.

The current core SmPC indications are:

1. Replacement therapy in adults <and children> in primary immunodeficiency syndromes (PID) such as:

- congenital agammaglobulinaemia and hypogammaglobulinaemia
- common variable immunodeficiency
- severe combined immunodeficiency
- IgG subclass deficiencies with recurrent infections

2. Replacement therapy in myeloma or chronic lymphatic leukaemia with severe secondary hypogammaglobulinemia and recurrent infections

3. If the SC/IMIg has a minimum antibody content for HAV of 100 IU/ml it is also used for:

- Short term hepatitis A prophylaxis in travellers who present less than 2 weeks before possible exposure
- Hepatitis A prophylaxis in persons exposed less than 2 weeks previously.

2. Problem statement

Established indications

In the replacement therapy setting SCIgs are used for the same indications (see above Point 1 and 2) as IVIgs. In recent years the use of SCIg has become more widespread for home treatment of PID patients due to the greater convenience this route offers, the stable serum IgG concentration between

infusions, the high safety profile with very few systemic adverse reactions and to date no transmission of viral agents. According to the literature this translates to increases in patient and family treatment satisfaction and health-related quality of life. It also was found to be suitable for patients with previous adverse reactions to IVIg and to give clinicians and patients the opportunity to use the replacement therapy without any need for premedication with corticosteroids or antihistamines; it is easy for children, adults and elderly patients to learn and handle; and can reduce the costs for healthcare systems and families.

As the IVIg Guideline and core SmPC have recently been updated[1] to account for the latest developments in the field of replacement therapy, an update for SCIgs is in order to maintain consistency and transparency for clinical trials and treatment.

Off-label indications

In recent times SCIg use has been expanding to areas of immunomodulation similar to those described for IVIgs.

This issue was addressed in the revision of the IVIg guideline and certain indications were discussed in detail (chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), myasthenia gravis exacerbation, and multifocal motor neuropathy (MMN)) where modulation via immunoglobulins was considered to be advantageous by the scientific community. This approach is reflected in a number of neurological guidelines. To obtain these indications for a given IVIg product the IVIg guideline requests confirmatory data in addition to providing efficacy data in PID and primary immune thrombocytopenia (ITP).

For SCIgs some of the chronic neurological disorders have now become the focus of attention as home treatment would provide similar advantages to those mentioned above for PID.

Here again an update is deemed necessary to provide consistency between two classes of similar products (SCIg and IVIg), their clinical indications and possible future applications.

3. Discussion (on the problem statement)

Both SCIg/IMIg and IVIg products are produced from the same source material (human plasma) by very similar procedures and are administered to patients for the same indications in replacement therapy and recently in some of the off-label indications as well. Considering that the IVIg guideline and core SmPC have undergone a complete revision (effective in 2011) it is deemed necessary to update the SCIg/IMIg guideline and core SmPC accordingly in order to better reflect a coherent approach both in clinical trials and in clinical practice.

In addition, since the initial release of the SCIg guideline and core SmPC there has been increased experience in various EU states with the home and hospital administration of different SCIgs, which may necessitate some changes to the documents.

4. Recommendation

The Blood Products Working Party (BPWP) recommends revising the Note for Guidance (CPMP/BPWG/283/00) and Core SmPC for human normal immunoglobulin for subcutaneous and intramuscular use (CPMP/BPWG/282/00) in order to be consistent with the newly revised IVIg Guideline and core SmPC wherever possible.

[1] Guideline on the clinical investigation of human normal immunoglobulin for intravenous use (IVIg) (EMA/CHMP/BPWP/94033/2007 rev 2) and Core SmPC for human normal immunoglobulin for intravenous use (IVIg) (EMA/CHMP/BPWP/94038/2007 rev 3) becoming effective in Feb 2011 and May 2011, respectively.

Focus will be on the clinical trial requirements in PID patients (representative for replacement therapy) and the requirements necessary for immunomodulatory indications

The core SmPC will be applicable to new products and products already in the market.

5. Proposed timetable

This guideline will be discussed during the meetings of the BPWP in 2011 and 2012. It is anticipated that a draft CHMP document will be released for external consultation during 2012. The period for external comments for the draft text of the guideline will be 6 months.

6. Resource requirements for preparation

There will be one Rapporteur involved in the preparation of the guideline. The draft will be discussed during the meetings of the BPWP.

7. Impact assessment (anticipated)

The revised guidelines will better reflect current clinical practice and the regulatory assessments of SCIg 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, patients and patient associations with reassurance about the safe and effective use of SCIg 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.

8. Interested parties

Interested parties with specific interest in this topic will be consulted during the revision of these guidelines, including IPFA, PPTA, EPPIC, IPOPI, ESID, EFIS, EFNS, ENMC and the Cochrane Neuromuscular Disease Review Group and WHO. Within the European Medicines Agency, there will be consultation of Paediatric Committee, Biologics Working Party, and Pharmacovigilance Working Party.

9. References to literature, guidelines, etc.

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