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DOCUMENT 1

Application for the inclusion of Polyvalent Human Immunoglobulins for subcutaneous administration

For inclusion in the WHO Model List of Essential Medicines for children

Submitted by the Primary Immune Deficiency Committee of IUIS

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Summary of the proposal

Polyvalent Human Immunoglobulins for intravenous and intramuscular administrationare now included in the WHO Essential Medicines List and are in the draft Essential Medicines List for Children. However intravenous administration is difficult in children and the advent of products suitable for subcutaneous administration has transformed treatment with these products. For children in particular, provision of freedom of movement of both arms as well as greater mobility and shorter infusion times have improved compliance with therapy hugely. Efficacious replacement doses of immunoglobulin can now be given safely without recourse to venepuncture.

Polyvalent Human Immunoglobulins are crucial in the life-long treatment of Primary Immune Deficiencies (PIDs), as there is no other treatment for most of these disorders. At present there are no autoimmune conditions for which the use of subcutaneous immunoglobulin [SCIg] is appropriate, so this application for SCIg is restricted to PIDs.

Human blood contains protective IgG antibodies against the whole range of infectious diseases. Polyvalent Human Immunoglobulins are prepared from pooled plasma from no fewer than 1,000 normal donors and contain a distribution of antibodies which reflects that in normal human blood. Adequate doses of these products restore protection against bacterial infections in those with immune deficiencies. Immunoglobulins are readily accessible from the blood, whether given subcutaneously or intravenously.

The major advantages of SCIg in relation to IVIg relate to the ease of administration, reduced incidence of side effects, better patient compliance and shorter infusion times.

The IVIg and SCIg products are identical in all respects other than in concentration. SCIgs are more concentrated in order to compensate for the restricted volume. Half-life is longer, due to gradual absorption from the subcutaneous tissues, though due to the limited volume given subcutaneously, these infusions need to be performed more frequently (usually every 10 days rather than 21 days).

Equitable access to and use of both types of Polyvalent Human Immunoglobulins, IVIg and SCIg, worldwide will guarantee the same level of health to children with PIDs, prevent avoidable deaths, reduce suffering and disease burden in these life-long conditions.

Clinical research data on the effectiveness and safety of SCIg in the treatment of PIDs are outlined in this application; much of the data is in press and as yet unpublished information is given where possible. The previous application for Polyvalent Human Immunoglobulins to be included on the EML in March is available online and that data will not be repeated here.

http://mednet3.who.int/EML/expcom/expcom15/reinstatement.htm

This application outlines the essential nature and importance of SCIg as a major worldwide public health tool in the treatment and management of children (and adults) with primary immune deficiencies.

1. Summary statement of the proposal for inclusion, change or deletion

Polyvalent Human Immunoglobulins for intravenous use are included in the World Health Organisation (WHO) Model List of Essential Medicines for life-long replacement therapy in individuals with primary & secondary immune deficiencies. This application is for Polyvalent Human Immunoglobulins for subcutaneous use to be included in the EML for Children.

2. Name of the focal point in WHO submitting or supporting the application

Dr Ann Gardulf, Associate Professor at the Karolinska University Hospital and Karolinska Institute in Stockholm, Sweden. Government Chief Nurse for Sweden and member of Swedish delegation to WHO.

3. Name of the organization(s) consulted and/or supporting the application

This submission should be taken in conjunction with those supporting the application to the 15th EML. Some of the main organizations supporting this application include:

3.1 International Union of Immunological Societies [IUIS] (formerly WHO) Primary Immune Deficiencies Committee

3.2 IUIS National Member Organisations

The National Immunological Societies – see http://www.iuisonline.org/pages/societ.htm

3.3 International Organisations supporting the application

- European Society for Immunodeficiencies (ESID)
- European Federation of Immunological Societies (EFIS)
- International Nursing Group for Immunodeficiencies (INGID) and their National Member Organisations (Names – see Website)
- The Plasma Protein Therapeutics Association (PPTA)
- The International Plasma Fractionation Association (IPFA)
- International Patient Organisation for Primary Immunodeficiencies

3.4 International Experts

In 2006, an international panel of leading experts in the field provided a consensus statement on the vital importance of both SCIg and IVIg therapeutic immunoglobulins to patients and of its cost-effectiveness (see *Document3*). This was submitted previously but has been approved by the PID-IUIS committee for use again, to support SCIg particularly. The original Expert Group was largely based in Europe and North America.

This application, for inclusion of immunoglobulins for subcutaneous use, is supported by an additional Expert group from the Asia Pacific region composed mainly of paediatricians. - attached *Document 2*.

4. International Nonproprietary Name (INN, generic name) of the medicine

Polyvalent Human Normal Immunoglobulin. *Immunoglobulinum humanum normale.*

- for subcutaneous use

5. Formulation proposed for inclusion; including adult and paediatric (if appropriate)

There is no single formulation due to patent law. There are standards as mentioned in the Pharmacopoeia monographs – see section 14. Children and adults may receive immunoglobulin therapy by the same routes of administration.

6. International availability – sources, if possible manufacturers

See *Document 4* for list of manufacturers.

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Listing is requested on the WHO Model List of Essential Medicines as a therapeutic group under:

- section 11.2 *Plasma Fractions for specific use*

Complementary list

To be added to existing products

11.2 Plasma fractions for specific use	
All plasma fractions should comply with the WHO Requirements for the Collection, Processing and Quality Control of Blood, Blood Components and Plasma Derivatives (Revised 1992). (WHO Technic al Report Series, No. 840, 1994, Annex 2).	
Complementary List	
human normal immunoglobulin	***Subcutaneous administration 15%, 16% protein solution*** *Intravenous administration: 5%, 10% protein solution. Intramuscular administration: 16% protein solution.*

A square box symbol is not required

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

8.1 Epidemiological information on disease burden

see EML submission – March 2007
http://mednet3.who.int/EML/expcom/expcom15/reinstatement.htm

8.1.2 Disease burden

see EML submission – March 2007
http://mednet3.who.int/EML/expcom/expcom15/reinstatement.htm

Without treatment with Polyvalent Human Immunoglobulins, the morbidity and mortality rates of patients affected by the conditions listed in section 8.3 are significantly higher and life expectancy is reduced from 50 years to 12 years.

8.2 Assessment of current use

The recognition of the safe and efficacious treatment of PIDs patients with immunoglobulins for subcutaneous, as well as intravenous use, is confirmed by recognized regulatory authorities worldwide. – *see attached document 4*

Clinical data have clearly demonstrated that subcutaneous treatment, as well as intravenous treatment, with Polyvalent Human Immunoglobulins for patients affected by these conditions can be life saving (reduced mortality and morbidity) as well as greatly improve their quality of life – *see attached document 5.*

8.3. Target Population

8.3.1. Primary Immunodeficiencies

People with primary immunodeficiencies have no protection against common pathogenic organisms and as a result suffer life-long life-threatening infections and increasing, permanent, damage to various body organs, especially the lungs and guts. This increasing damage with each infection renders the person more susceptible to more severe and frequent infections. Many of the conditions are genetic and there are no known reliable cures, resulting in a need for life long replacement immunoglobulin therapy. Regular replacement therapy with immunoglobulin is the only way to provide protection and enable those affected to enjoy the benefits of antibodies to fight infection. The provision of immunoglobulin is essential to prevent morbidity and mortality in this group of patients, in whom there was, prior to treatment, a considerably shorter lifespan and

significant mortality due to life threatening infections – *see EML submission – March 2007* http://mednet3.who.int/EML/expcom/expcom15/reinstatement.htm

9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostic or treatment facilities and skills)

The following dosage recommendations are given in the current European core SPC referred to above and attached document 8 – these are under continuous review:

Indication	**Dose**	**Frequency of injections**
Replacement therapy in primary immunodeficiency	Following IVIg loading, 0.4-0.6 g/Kg	SCIg every 1- 2 weeks to obtain IgG trough level of at least 6 g/I

10. Summary of comparative effectiveness in a variety of clinical settings (Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data) / Summary of available data (appraisal of quality, outcome measures, summary of results) / Summary of available estimates of comparative effectiveness)

The clinical evidence for the effectiveness of immunoglobulins in PIDs has been extensively reviewed in clinical studies and by regulators worldwide *and can be see EML submission – March 2007* http://mednet3.who.int/EML/expcom/expcom15/reinstatement.htm

and attached Document 5 (table for effectiveness).

Institution of immunoglobulin replacement therapy increases life expectancy, from 12 years to 50 years, (Chapel HM Data presented to European Union Conference on PIDs, Langen, June 2006), reduces the rate of bacterial infections, days of antibiotic usage, days of fever and hospital admissions.

Long term intravenous immunoglobulin (IVIG) infusion is an effective treatment for children with immunodeficiencies, but can be complicated by poor venous access, systemic adverse reactions, and the need for frequent hospital admission.

Subcutaneous IgG (SCIG) therapy, using small portable pumps for once-per-week self infusions is an effective, convenient, and well tolerated alternative to intravenous treatment. It is essential in children and adult patients with poor venous access.

Advantages of SCIG therapy

- Safe, with very few adverse effects
- Shorter infusions
- Can be used for patients with previous severe or anaphylactoid reactions to intravenous administration of IgG
- Leads to normal and constant serum IgG levels and good protection against infections.
- No significant differences in efficacy between immunoglobulin replacement therapy given subcutaneously or intravenously
- Facilitates home therapy, as the self-infusion technique is easy for children, adults and elderly patients to learn
- No requirement for venous access

- No long-term reactions at the site of administration.
- Leads to a significant improvement in the quality of life of patient and family, with flexibility, independence and empowerment by self-therapy.
- Reduces the costs of treatment; hospital and patient time and medical / nursing resources.

Disadvantages of SCIG Therapy

- Limitation in the volume that can be administered at any one time, necessitating more frequent dosing
- Requirement for adherence if a patient is to self or home infuse

11. Summary of comparative evidence on safety (Estimate of total patient exposure to date / Description of adverse effects/reactions / Identification of variation in safety due to health systems and patient factors / Summary of comparative safety against comparators)

The risks of treatment with immunoglobulins, whether given by the subcutaneous or intravenous route, are divided into two categories: those of an infusion related adverse event and the risks of transmissions of blood-borne viruses by the immunological product. *see EML submission – March 2007* http://mednet3.who.int/EML/expcom/expcom15/reinstatement.htm

Please see attached Document 6 (list of data demonstrating the safety of SCIg in PIDs).

Appendices A & B from an Open study due to be reported shortly: A total of 50 PIDs patients including 15 paediatric patients <12 years (mean age of 6.2 years (range 0.8-10.6)) and 7 teenagers 12-<20 years (mean age of 15.2 years (range 12.1-18.0)).

12. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group

Please see attached Document 7 (list of data demonstrating the cost-effectiveness of SCIg in PIDs).

Professor Ann Gardulf (Karolinska Hospital, Sweden) also gave a presentation at the European Parliament's Scientific and Technology Options Assessment (STOA) Panel on 'Primary Immune Deficiency Diseases – Quality of Life and Health Service Costs: Why Diagnosis and Optimal Treatment is Good for the Patient and Good for Healthcare Systems and Services' on 17 March 2004. The conclusion was that treatment with immunoglobulin was cost effective.

13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

SCIgs are registered with the pharmaceutical regulators in many regions of the world, including the USA, the European Union, Australasia, South America.

Please see attached *Document 8* - EMEA core SPC CPMP/BPWG/282/00

14. Availability of pharmacopoieal standards (British Pharmacopoeia, International Pharmacopoiea, United States Pharmacopoeia)

Many countries have their own pharmacopoeial standards but the European Pharmacopoeia contains a monograph for Human Normal Immunoglobulin (01/2005:0918).

15. Proposed (new/adapted) text for the WHO Model Formulary

Proposed text for the WHO Model Formulary for Children

Polyvalent Human Normal Immunoglobulin. *Immunoglobulinum humanum normale.*
For intravenous use: 5%, 10% or 12% solutions depending on the manufacturer [IVIg]
For subcutaneous use: 15% or 16% solutions depending on the manufacturer [SCIg]
For intramuscular use: 16% solutions depending on the manufacturer [IMIg]

Uses: Replacement therapies in primary immune deficiencies – SCIG and IVIg. Immuno-modulation in selected patients with specific autoimmune diseases – IVIg only. The appropriate use of immunoglobulin therapy is only for those patients for which no effective alternative treatment is available.

Contraindications: none

Precautions: Severe adverse reactions to blood or blood products in the past; vascular instability; hyperviscosity; pre-existing hypercoagulopathy; severe impairment of hepatic, pulmonary or renal function. Adverse reactions more likely in presence of pre-existing serious bacterial infection. Immunoglobulins may be contraindicated in patients with known, very high titre, class specific antibodies to Immunoglobulin IgA. Immunoglobulins may interfere with the immune response to live virus vaccines (with the exclusion of yellow fever vaccination); such vaccines should therefore only be given at least 3 weeks before, or 3 months after, an immunoglobulin infusion.

Interactions: none

Dosage:
For replacement therapy in primary immune deficiencies: Initial loading intravenously in divided doses until serum IgG level is > 6 g/l. Maintenance doses by intravenous, subcutaneous or intramuscular routes: normally 0.4 – 0.8 g/ Kg / month for children and adults. Dose to be titrated depending on inter-current infections or trough serum IgG level. Intravenous doses may be given at one, two, three or four week intervals. Subcutaneous doses may be given at one, two, three, four or seven day intervals.

For immuno-modulation in autoimmune conditions: Maximum recommended dose is 2g/Kg over at least 48 hours. Depending on specific autoimmune disease: 0.4 g/Kg/day for 5 days or 0.8- 1 g/Kg the first day and repeated once if indicated.

Administration: Infusion rates of < 8 g per hour are recommended. Immunoglobulin should be administered under the supervision of an immunologist or other experienced physician. In general, this should be in a hospital with adequate facilities for monitoring the infusion as well as the condition for which it is being administered, until the patient is stable, when treatment at home can be considered after formal training in an expert centre.

Adverse effects:
For IM, IV and SC administration, adverse effects are more common in relation to the first few infusions: nausea, vomiting, dizziness, dry mouth, headache, chills, sweating, hypothermia, fever, eczematous rash, urticaria, hypotension, wheeze. Rare cases of anaphylactoid reactions have been reported.
SC administration: local swelling, pruritus and redness are common for first few infusions but resolve in 6 –24 hours.
IV administration: delayed headache and nausea up to 24 hours after infusion. With immuno-modulatory doses: immune haemolysis, aseptic meningitis, increased plasma viscosity, hypercoaguability, renal acute tubular dysfunction.
Preventative measures against adverse reactions include premedication with mild anti-inflammatory agents (paracetamol, aspirin, non-steroidal anti-inflammatory agents, hydrocortisone)
All immunoglobulins comply with WHO requirements for blood and plasma products.

WHO requirements for blood and plasma products.