

Polyvalent Human Immunoglobulins

Application for reinstatement to the WHO Model List

From: Plasma Protein Therapeutics Association (PPTA)

1. Summary statement of the proposal for inclusion, change or deletion
Polyvalent Human Immunoglobulins have been proved to be efficacious in the treatment of a number of serious medical conditions. Without this treatment many patients suffering from these conditions will suffer serious ill health or will die. Although some of these individual conditions may be relatively rare, the combined population benefiting from immunoglobulin treatment is significant.

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

Dr. Neelam Dhingra, Acting Co-ordinator, Blood Transfusion Safety, WHO

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

- European Patients Primary Immunodeficiency Collaboration (EPPIC)
- International Patient Organisation for Patients with Primary Immunodeficiencies (IPOPI)
- Primary Immunodeficiency Association (PiA)
- The Guillain-Barré Syndrome Support Group of the United Kingdom
- The Guillain-Barré Syndrome Foundation International
- The ITP (Idiopathic Thrombocytopenic Purpura) Support Association, UK
- The International Society of Blood Transfusion (ISBT)

4. International Non-proprietary Name (INN, generic name) of the medicine Polyvalent Human Immunoglobulins [immunoglobulin, human normal injection (intramuscular) and immunoglobulin, human normal injection (intravenous)]

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

Therapeutic group

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

Indications

The European Medicines Agency (EMA) lists the therapeutic indications for the intravenous preparation of Polyvalent Human Immunoglobulins in its document

CPMP/BPWG/859/95 'Core SPC for Human Normal Immunoglobulin for Intravenous Administration (IVIg)':

Replacement therapy in:

- *Primary immunodeficiency syndromes such as:*
- *Congenital agammaglobulinaemia and hypogammaglobulinaemia*
- *Common variable immunodeficiency*
- *Severe combined immunodeficiency*
- *Wiskott Aldrich syndrome*
- *Myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections*
- *Children with congenital AIDS and recurrent infections*
- *Immunomodulation*
- *Idiopathic Thrombocytopenic Purpura (ITP), in children or adults at high risk of bleeding or prior to surgery to correct the platelet count*
- *Guillain-Barré Syndrome*
- *Kawasaki disease*
- *Allogeneic bone marrow transplantation*

[Other product specific indications]

In the USA the FDA licenses the different Polyvalent Human Immunoglobulins on the market for a similar range of indications.

Prevalence

Exact prevalence figures for the above conditions vary according to author and to diagnosis rates in different countries, but the following data are representative of the international literature:

Condition **Prevalence rates per million population :**

Primary Immune Deficiencies

- | | |
|------------------------------------|--------|
| • X linked agammaglobulinaemia | 2.2 |
| • Hyper IgM syndrome | 1.9 |
| • Common variable immunodeficiency | 50.0 |
| • IgA deficiency | 1666.7 |
| • IgG subclass deficiency | 1666.7 |
| • Ataxia-telangiectasia | 2.5 |
| • SCID | 1.0 |
| • Multiple Myeloma | 53.7 |

• Chronic Lymphocytic Leukaemia	27.5
• Children with congenital AIDS and recurrent infections	Varies considerably according to location
• Chronic ITP - Children	46.0
• Guillain-Barré Syndrome	10.0
• CIDP	22.0
• Kawasaki	95.0
• Allogeneic BMT	12.8
• Total	3658

Non-Regulatory Approved Indications

In addition, Polyvalent Human Immunoglobulins are used for a number of conditions not included in the regulatory approvals but for which substantial clinical evidence exists for their safety and efficacy.

For example:

the *Comité d'Evaluation et de Diffusion des Innovations Technologiques*, CEDIT, (Committee for the Evaluation and the Promotion of Technological Innovations) of the Paris public hospitals (APHP) lists the following recognised indications' in addition to those in the European core SPC:

- Corticoresistant dermatomyositis
- Auto immune erythroblastopenia
- Acute myasthenia
- Multifocal motor neuropathies with permanent conduction block
- Chronic idiopathic polyradiculoneuritis
- Birdshot retinochoroiditis
- Autoantibody induced acquired anti-coagulation syndrome
- Stiffman syndrome
- Lewis and Sumner syndrome

In the USA, Medicare regions may cover use of Polyvalent Human Immunoglobulins in the following additional indications:

- Mucocutaneous blistering diseases eg Pemphigus Vulgaris
- Systemic Lupus Erythematosus
- Autoimmune Hemolytic Anemia
- Multifocal Motor Neuropathy
- Dermatomyositis, Polymyositis
- Polyvalent Human Immunoglobulins may also be used in:
- Post transfusion purpura
- Multiple sclerosis – relapsing remitting type
- Fetal alloimmune thrombocytopenia

Definition of Rare Disease

In the USA the Rare Disease Act of 2002 (HR 4013) and the US Orphan Drug Act define a rare disease or condition as one that

"(A) affects less than 200,000 persons in the United States,
or
(B) affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug."

Statistically speaking, with a population of 287,400,000, this represents approximately 700 per million of the US population.

The European Commission defines a rare disease as one affecting fewer than one in 2,000 population (500 per million).

Conclusion

It can therefore be seen that a number of the conditions potentially treatable with Polyvalent Human Immunoglobulins are, of themselves, not rare according to either of these definitions, either because of the prevalence rates or because a treatment is available.

Furthermore, the total prevalence of all the regulatory-approved conditions combined is five- to seven times higher than the definition threshold.

Polyvalent Human Immunoglobulins should not therefore be excluded from the WHO Model List on the grounds of the rarity of its use.

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

The dose and dosage regimens are dependent on the indication.

The following dosage guidelines are given in the European core SPC referred to above:

Indication

Dose & Frequency of injections

Replacement therapy in primary immunodeficiency
starting dose: 0.4 - 0.8 g/kg
thereafter: 0.2 - 0.8 g/kg

every 2 - 4 weeks to obtain IgG trough level of at least 4 - 6 g/l

Replacement therapy in secondary immunodeficiency

0.2 - 0.4 g/kg every 3 - 4 weeks to obtain IgG trough level of at least 4 - 6 g/l

Children with AIDS 0.2 - 0.4 g/kg every 3 - 4 weeks

Immunomodulation:

Idiopathic Thrombocytopenic Purpura

0.8 -1 g/kg or 0.4 g/kg/day on day 1, possibly repeated once within 3 days for 2 - 5 days

Guillain-Barré syndrome

0.4 g /kg/day for 3 -7 days

Kawasaki disease

1.6 - 2 g/kg or 2 g/kg in several doses for 2 - 5 days in association with acetylsalicylic acid in one dose

Allogeneic bone marrow transplantation:

- treatment of infections and prophylaxis of graft versus host disease
- persistent lack of antibody production

0.5 g/kg every week from day -7 up to 3 months after transplantation.
every month until antibody levels return to normal

8. 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 IVIG in the conditions listed in section 6 has been extensively reviewed by the European regulators and professional bodies mentioned.
- For a recent review see Sacher RA. Intravenous immunoglobulin consensus statement. *Journal of Allergy and Clinical Immunology*, October 2001, part 2 Vol 108 No 4, 139-146.
- The use of immunoglobulins in the immunomodulatory indications has recently been reviewed in: Nelson RP Jr., Ballow M. Immunomodulation and immunotherapy: drugs, cytokines, cytokine receptors, and antibodies. *Journal of Allergy and Clinical Immunology* 2003;111:S720-S743.

9. 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
- Immunoglobulins have been used for many years in many thousands of patients. Their safety profile is well established and each product placed on the market has to demonstrate product-specific safety to the relevant regulators.
- In many cases immunoglobulins are the only treatment available (for example primary immunodeficiency), and in others the alternative treatment has significantly more side effects (e.g. high dose steroids for ITP).
- A description of the general safety considerations is set out in the EMEA's core Summary of Product Characteristics referred to above.

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

- Range of costs of the proposed medicine Increased competition among manufacturers has led to a decrease in the price of immunoglobulins over recent years.
- According to calculations based on the figures contained in the Marketing Research Bureau's Eurodata 2001 report, the 2001 price per gram of IVIG ranged from \$18 to \$45 across the different European countries surveyed.
- Comparative cost-effectiveness presented as range of cost per routine outcome (e.g. cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented, or, if possible and relevant, cost per quality-adjusted life year gained)
- Few economic outcomes data have been published for the use of IVIG. The European Parliament's Scientific and Technical Options Assessment (STOA) panel held a workshop on 17 March 2004 at which Professor Ann Gardulf (Karolinska Hospital, Sweden) gave a presentation 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'. The conclusion was that treatment with immunoglobulin was cost effective.

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

- Polyvalent Human Immunoglobulins are registered with the pharmaceutical regulators in most countries of the world, including the USA, the European Union, Japan and others.

12. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia)

The European Pharmacopoeia contains a monograph for Human Normal Immunoglobulin for Intravenous Administration (01/2005:0918).

13. Proposed (new/adapted) text for the WHO Model Formulary Complementary List

- Human normal immunoglobulin
- Lyophilised or liquid preparations