Application for the inclusion of Polyvalent Human Immunoglobulins in the WHO Model List of Essential Medicines

Submitted by
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Summary of the proposal

The scope and relevance of Polyvalent Human Immunoglobulins in the life-long treatment of several Primary Immunodeficiencies (PIDs) is crucial as there is no other treatment in these genetic disorders. In addition, Polyvalent Human Immunoglobulins are equally important in the treatment of a number of acute and often life-threatening conditions such as Kawasaki Disease (KD), Guillain-Barré Syndrome (GBS) and Idiopathic Thrombocytopenic Purpura (ITP). In severe forms of these diseases treatment with Polyvalent Human Immunoglobulins has to be provided on an urgent basis – often within a few hours. The use of Polyvalent Human Immunoglobulins in the aforementioned acute conditions is particularly relevant to developing countries where Polyvalent Human Immunoglobulins are at present not readily available and, even when available, are priced prohibitively. This is simply not acceptable because access to these essential, life-saving medicines should be optimal as well as guaranteed. Polyvalent Human Immunoglobulins are relevant in several other diseases as a second line therapy if the disease is refractory to other therapies (e.g. rheumatological disorders like dermatomyositis and systemic lupus erythematosus) or where such therapies cannot be used on a long-term basis. Other situations where Polyvalent Human Immunoglobulins are being used in clinical practice also include: treatment of severe sepsis in low birth weight babies, prophylaxis against infection in premature babies, toxic shock syndrome and septic shock in older children.

Human blood contains IgG antibodies of both a protective and immunomodulatory nature. 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 this medicinal product restore protection against bacterial infections in those with immune deficiencies and provide immune modulation for patients with some diseases caused by auto-antibodies. Immunoglobulins are readily accessible and have a half-life of approximately 21-28 days, providing efficacy of treatment for at least this time.

Equitable access to and use of Polyvalent Human Immunoglobulins worldwide will guarantee the same level of health to patients, prevent avoidable deaths, reduce suffering and disease burden. Although Polyvalent Human Immunoglobulins are widely used, it must be stressed that, the access to these therapies is poorer in developing countries. This results in a significant disease burden in terms of infections, structural damage to lungs and malabsorption as well as deaths.

The mode of action of Polyvalent Human Immunoglobulins in PIDs is the replacement of protective antibodies, which protect against infectious pathogens throughout the world. Under-diagnosis of these conditions is relatively common problem and varies from 50–98% around the world. Mortality rates are subsequently very high for undiagnosed and therefore untreated patients, with a life expectancy of only 12 years of age. Morbidity rates are equally high. At present, majority of the children with PIDs in developing countries are dying in infancy and early childhood because of lack of access to immunoglobulin therapy.

Polyvalent Human Immunoglobulins are also used for immunomodulation in autoimmune diseases in children and adults, such as (KD, GBS, ITP) for which there is no other effective therapy; in these conditions, a single high-dose of immunoglobulins (1-2 g/kg) is usually sufficient but the treatment has to be given expeditiously. Polyvalent Human Immunoglobulins are additionally used in the emergency management of life-threatening conditions like acute myasthenia gravis crisis.

Clinical research data on the effectiveness in the treatment of the conditions referred to above are considerable as outlined in this application.

This application outlines the essential nature and importance of Polyvalent Human
Immunoglobulins as a major worldwide public health tool in the treatment and management of a number of conditions be they chronic or acute. Access to Polyvalent Human Immunoglobulins should be ensured to all patients regardless of their country of origin to avoid deaths and disease burden, and enable these patients to lead normal lives and contribute to society.
1. Summary statement of the proposal for inclusion, change or deletion
Polyvalent Human Immunoglobulins are proposed for the inclusion in the World Health Organisation (WHO) Model List of Essential Medicines for life-long replacement therapy in individuals with primary & secondary immune deficiencies and for immune modulation in those patients with responsive autoimmune conditions who have failed immunosuppressive treatments or in whom long term immune-suppression is not appropriate.

2. Name of the focal point in WHO submitting or supporting the application
Dr. Ana Padilla, WHO Medicines Policy and Standards Department (PSM)

3. Name of the organization(s) consulted and/or supporting the application
A comprehensive list of the organizations consulted and supporting this submission can be found in attached Annex 1. 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 IPOPI’s National Member Organisations
The International Patient Organisation for Primary Immunodeficiencies’ National Member Organisations including South Africa, Iran, Morocco, Argentina and India.

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)
- Kawasaki Disease Foundation
- The Guillain-Barré Syndrome (GBS)/Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) Foundation International
- The WHO’s Global Collaboration for Blood Safety
- The Plasma Protein Therapeutics Association (PPTA)
- The International Plasma Fractionation Association (IPFA)

3.4 International Experts
In 2006, an international panel of leading experts in the field provided a consensus statement on the vital importance of therapeutic immunoglobulin to patients and of its cost-effectiveness (see Annex 2)

4. International Nonproprietary Name (INN, generic name) of the medicine
Polyvalent Human Normal Immunoglobulin. Immunoglobulinum humanum normale.
- for intravenous use
- for subcutaneous use
- for intramuscular 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 Annex 3 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 19.2 Sera and Immunologicals:

<table>
<thead>
<tr>
<th>Polyvalent Human Immunoglobulin</th>
<th>Replacement therapy in primary immunodeficiency: 0.4 - 0.8 g/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Replacement therapy in secondary immunodeficiency: 0.2 - 0.4 g/kg</td>
</tr>
</tbody>
</table>

- section 11.2 Plasma Fractions for specific use

<table>
<thead>
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<th>Polyvalent Human Immunoglobulin</th>
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</tr>
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<tbody>
<tr>
<td></td>
<td>Replacement therapy in secondary immunodeficiency: 0.2 - 0.4 g/kg</td>
</tr>
</tbody>
</table>

- section 8.1 Immunosuppressive therapies and new subsection 8.1.1 Medicines used in immunomodulation:

<table>
<thead>
<tr>
<th>Polyvalent Human Immunoglobulin</th>
<th>Kawasaki Disease: 1.6 -2.0 g/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Idiopathic Thrombocytopenic Purpura (in bleeding / therapy resistant disease): 0.4 g/kg/d for 2-5 days</td>
</tr>
<tr>
<td></td>
<td>Guillain-Barré syndrome (severe): 0.4 g /kg/d for 3-7 days</td>
</tr>
</tbody>
</table>

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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

8.1.1 Prevalence
The exact prevalence figures for the below conditions vary according to diagnosis rates in different countries, but the following data are representative of the international literature. However these rates are unknown in most of the developing world. Under diagnosis, rates are believed to vary from 50-98%.
### Conditions

#### Primary Immune Deficiencies, including:
- X-linked agammaglobulinaemia
- Hyper IgM syndrome
- Common variable immunodeficiency
- IgA deficiency with infections
- IgG subclass deficiencies
- Wiscott-Aldrich syndrome
- Ataxia-telangiectasia

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Prevalence rates per million population</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Immune Deficiencies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.1.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Secondary Immune Deficiencies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.1.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Prevalence rates per million population**

- **Primary Immune Deficiencies, including:**
  - 500 - 2000
- **Secondary Immune Deficiencies**
  - 20
- **Kawasaki disease**
  - 120 to 150
- **Guillain-Barré Syndrome**
  - 20
- **CIDP**
  - 10
- **Chronic ITP – Children & adults**
  - 100
- **Total prevalence**
  - 2300

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

In conclusion, it can therefore be seen that a number of the conditions listed in the table under 8.1.1 and treatable with Polyvalent Human Immunoglobulins are, of themselves, not rare according to either of these definitions, or because of the prevalence rates. In addition, the total prevalence of the listed conditions combined is three to five 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 their use.

**8.1.2 Disease burden**

Primary immune deficiencies [PIDs]:

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. Clinical data have clearly demonstrated that appropriate treatment with Polyvalent Human Immunoglobulins of
patients affected by these conditions can be life saving as well as greatly improve their quality of life.

In the case of PIDs, “although diverse, [they] share the common feature of susceptibility to infection and result in substantial morbidity and shortened life spans. Most importantly, prompt diagnosis and treatment can now lead to life-saving treatment and result in marked improvements in the quality and length of life for persons with PI diseases” (Centers for Disease Control and Prevention, Morbidity and Mortality Weekly Reports. Applying Public Health Strategies to Primary Immunodeficiency Diseases, January 16, 2004 / 53(RR01);1-29). In addition, “early recognition of primary immunodeficiency is essential to reduce morbidity and mortality, and yet failure to recognize these conditions is still a major problem for clinicians around the world” (Sewell, W. A. C, et al., Early indicators of immunodeficiency in adults and children: protocols for screening for primary immunological defects, 2006 Clinical and Experimental Immunology 145:201–203). One major problem is that general practitioners, physicians and paediatricians lack familiarity with immunodeficiencies and lack guidance regarding the appropriate use of immunological investigations and treatment. This is particularly applicable in developing countries. The use of the WHO List of Essential Medicines and formulary would help in tackling this problem and helping raise the awareness of these treatable conditions.

The largest data collection comes from the UK Medical Research Council study, 1955–1966. The study’s main aims were to collect information on the natural history of hypogammaglobulinaemia and to capture nearly all the cases occurring in the UK; 184 untreated patients were admitted to the study (ascertainment has risen > x100 since that time). Ten-year survival rates were 36%. This has been followed by a study of treated patients followed by Cunningham-Rundles and Bodian, diagnosed by the Immunodeficiency Clinic at the Mount Sinai Medical Centre from 1973 to 1998. This comprised 248 patients. Ten-year survival rates had risen to 78% but still lagged behind US general figures of 98%; with higher doses this has now improved further to 92%. Recent data from Iran has confirmed the hugely increased serious infection burden in those patients without immunoglobulin treatment compared with those receiving Polyvalent Human Immunoglobulins (Aghamohammadi A. et al. Efficacy of IVIg on the prevalence of pneumonia in patients with agammaglobulinaemia. 2004 FEMS Immunology & Med. Microbiology 40: 113-118).

Kawasaki disease:


Autoimmune diseases: Neuromuscular.

Outcomes of controlled trials indicate that IVIG at a total dose of 2 g/kg is effective as first-line therapy in Guillain-Barré Syndrome [GBS], Chronic Inflammatory Demyelinating Polyneuropathy [CIDP], and Multifocal Motor Neuropathy [MMN]. In severe GBS patients may need artificial ventilation and in severe neuropathies patients are not only bed-bound but lose autonomic functions (swallowing etc); in these conditions, for which there may be no safe/accessible alternative, IVIg is used for those patients in whom alternative therapies fail though the appropriate dose for long-term maintenance therapy is not fully established. In other conditions such as the stiff-person syndrome,
dermatomyositis, myasthenia gravis, and Lambert-Eaton myasthenic syndrome IVIg is reserved for those with severe disease who have failed previous therapies (Dalakas MC, Intravenous immunoglobulin in autoimmune neuromuscular diseases; systematic review. JAMA. 2004 May 19;291(19):2367-75).

Autoimmune diseases: Immune Thrombocytopenic Purpura
Although this condition is self-limiting in children and some adults, the most serious complication of severe bleeding is life-threatening though rare (351 episodes in 61 patient years (El Alfy MS, Khalifa AS. Prospective evaluation of high-cost management of severe chronic ITP in children and adolescents<16 years in Egypt. Pediatr Blood Cancer. 2006 47:731-3). IVIg is used to raise the platelet count immediately to prevent a fatal outcome and to prevent major bleeding in urgent surgery.

8.2 Assessment of current use
The recognition of the safe and efficacious treatment of patients with the conditions listed under 8.3 with immunoglobulins is confirmed by recognized regulatory authorities worldwide.

8.2.1. Approved Regulatory Indications in the USA:
In the USA the FDA licenses the different Polyvalent Human Immunoglobulins on the market for a similar range of indications.

FDA-approved indications for immunoglobulins (Source: Orange et al., Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology, Journal of Allergy and Clinical Immunology, April 2006):

<table>
<thead>
<tr>
<th>No of FDA-licensed products</th>
<th>Disease state</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Primary Immunodeficiency disease or primary humoral immunodeficiency</td>
<td>Indicated for the treatment of primary immunodeficiency states or for the increase of circulating antibody levels in primary immunodeficiency diseases or for replacement therapy of primary immunodeficiency states in which severe impairment of anti-body forming capacity has been shown</td>
</tr>
<tr>
<td>5</td>
<td>Idiopathic Thrombocytopenic Purpura</td>
<td>Indicated when a rapid increase in platelet count is needed to prevent bleeding, control bleeding, or both in Idiopathic Thrombocytopenic Purpura or to allow a patient with Idiopathic Thrombocytopenic Purpura to undergo surgery</td>
</tr>
<tr>
<td>3</td>
<td>Kawasaki disease (syndrome)</td>
<td>Indicated for the prevention of coronary artery aneurysms associated with Kawasaki disease</td>
</tr>
<tr>
<td>2</td>
<td>B-cell chronic lymphocytic leukaemia</td>
<td>Indicated for the prevention of bacterial infections in patients with hypogammaglobulinemia, recurrent bacterial infections, or both associated with B-cell chronic lymphocytic leukaemia</td>
</tr>
</tbody>
</table>
### 8.2.2. Approved Regulatory Indications in Europe

The European Medicines Agency (EMA) lists the therapeutic indications for the intravenous preparation of Polyvalent Human Immunoglobulins in its document CPMP/BPG/859/95 rev2 (29 July 2004) ‘Core SPC for Human Normal Immunoglobulin for Intravenous Administration (IVIg). [Probable modifications due in 2007 are included].

**Replacement therapy in:**

**Primary immunodeficiency syndromes, such as:**
- Congenital agammaglobulinaemia and hypogammaglobulinaemia
- Common variable immunodeficiency
- Severe combined immunodeficiency
- Wiskott Aldrich syndrome

**Secondary immunodeficiency syndromes such as:**
- Myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections
- Children with congenital AIDS and recurrent infections
- Infection prevention after allogeneic bone marrow transplantation

**Immunomodulation:**
- Kawasaki disease
- Guillain-Barré Syndrome (GBS) [Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) – currently under discussion by the EMEA] and Multifocal Motor Neuropathy (MMN):
  - Idiopathic Thrombocytopenic Purpura (ITP), in children or adults at high risk of bleeding or prior to surgery to correct the platelet count

[Other product specific indications]
8.2.3. Approved Regulatory Indications in Australia
The Australian regulatory authorities list the following conditions as category 1 indications for immunoglobulins (Source: Australian Health Ministers’ Advisory Council, Blood and Blood Products Committee report: Review of the Use and Supply of Intravenous Immunoglobulins in Australia, June 2000):
Primary immunodeficiency syndromes, idiopathic thrombocytopenic purpura, post transfusion purpura, allogenic bone marrow transplantation, chronic lymphocytic leukaemia, myeloma, Kawasaki disease, chronic inflammatory demyelinating polyneuropathy, Guillain-Barré syndrome, multifocal motor neuropathy, other inflammatory myopathies, antibodies to coagulation factor VIII, miscellaneous haematology disorders

8.2.4 Approved Regulatory Indications in the Developing World
Polyvalent Human Immunoglobulins are regulated throughout the developing world. From Argentina to Iran, India to Thailand, regulatory authorities control product importation, licensure and approval, product release and post-marketing surveillance. Through the use of tender businesses/contracts and WHO batch release procedures and certificate, countries with limited resources are able and do in fact keep control and assurance of plasma-derived medicinal products, and Polyvalent Human Immunoglobulins in particular.

8.2.5. The Use of Polyvalent Human Immunoglobulins in the Developing World
Polyvalent Human Immunoglobulins are used in developing world countries to treat patients affected by life-threatening or life impairing conditions such as those listed under Priority of access to treatment with Polyvalent Human Immunoglobulin is usually given to acute conditions such as Kawasaki and severe GBS as short treatment with immunoglobulin will prevent death and enable patients to live normal lives again. However, in the case of primary immunodeficiencies and secondary immunodeficiencies, treating the cause of the patient condition through appropriate life-long replacement therapy with immunoglobulin rather than the symptoms will not only save lives but will also avoid important unnecessary costs to healthcare systems by significantly reducing the use of antibiotics and the days of extensive hospitalisation. This point is particularly relevant in the developing world countries, where healthcare budgets are more restricted. Extensive treatment of acute symptoms in intensive care units imposes an unnecessary costly burden on healthcare systems. In 2004, based on the distribution data from the Marketing Research Bureau, 11 tons of immunoglobulin were distributed in the developing world.

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 is a shorter lifespan and significant mortality due to life threatening infections.
8.3.2. Secondary Immunodeficiencies:
People with secondary immunodeficiencies may develop acute life-threatening or life-impairing conditions. The administration of immunoglobulin has proven to be an effective therapy for patients with secondary immunodeficiencies associated with lymphoid malignancies, or after receiving haemopoetic stem cell transplantation1.

8.3.3. Kawasaki Disease
This is a severe systemic cardiovascular disease of children. Untreated there is an 80% mortality and severe cardiac disability in the survivors. These patients do not respond sufficiently to antibiotics. Therapy with acetylsalicylic acid is important to reduce fever and inflammation. High-dose immunoglobulin treatment is essential to inhibit the systemic inflammation, to eliminate the causative pathogens, neutralise the compounding super-antigens and to prevent development of coronary artery abnormalities, which are an additional cause of death or long-term disability in 25% of children.

8.3.4. Guillain-Barré Syndrome (GBS), Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) and Multifocal Motor Neuropathy (MMN):
GBS, CIDP and MMN are demyelinating polyneuropathies and characterized by paralysis and weakness. Acute episodes can be life-threatening but IVIg therapy can induce clinical improvement efficiently within a few days or weeks. 25% of acute GBS patients are admitted to intensive care because of respiratory failure, often for several weeks/months. The mortality of severe GBS is 5-10%. Their length of paralysis is reduced by half if IVIg treatment is given within 14 days of onset. In severely affected patients with chronic diseases such as CIDP or MMN, IVIg is able to prevent further progression and permanent neurological and functional deficits.

8.3.5. Idiopathic Thrombocytopenic Purpura (ITP)
For patients with acute episodes of ITP, IVIg treatment is an essential treatment option to stop life threatening bleeding episodes. Administration of immunoglobulins to ITP patients is essential as an emergency measure or in preparation for a splenectomy or other operations in ITP patients with an enhanced bleeding risk. However recent trials do show that high dose steroids or anti-D are equally effective, though each therapy has specific serious risks.

9. 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 regimen are dependent on the indication and the severity of the disease.

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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Frequency of injections</th>
</tr>
</thead>
</table>
| 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 |

1 EMEA are looking at this
<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Frequency of injections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replacement therapy in secondary immunodeficiency</td>
<td>0.2 - 0.4 g/kg</td>
<td>every 3 - 4 weeks to obtain IgG trough level of at least 4 - 6 g/l</td>
</tr>
<tr>
<td>Immunomodulation:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic Thrombocytopenic Purpura</td>
<td>0.8 - 1.0 g/kg</td>
<td>on day 1, possibly repeated once within 3 days or for 2 - 5 days</td>
</tr>
<tr>
<td></td>
<td>or 0.4 g/kg/d</td>
<td></td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>0.4 g/kg/d</td>
<td>for 3 - 7 days</td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td>1.6 - 2 g/kg</td>
<td>in several doses for 2-5 days in association with acetylsalicylic acid in one dose in assoc. with ASA</td>
</tr>
<tr>
<td>or 2 g/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allogeneic bone marrow transplantation:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>persistent lack of antibody deficiency</td>
<td>0.5 g/kg</td>
<td>every month until antibody levels return to normal</td>
</tr>
</tbody>
</table>

An example of how Polyvalent Human Immunoglobulin is currently used in India is provided in Chandigarh Hospital’s protocol:

“We give 0.4-0.5 gm/kg IVIG every 3-4 weeks. Most of our patients take their injections at a hospital or local nursing home. Home based administration has only been done occasionally. We have never experienced any serious allergic or anaphylactic reactions” (Dr Surjit Singh, Chandigarh Hospital, India).

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 the conditions listed in section 8 has been extensively reviewed in clinical studies and by regulators worldwide.

Institution of immunoglobulin replacement therapy increases life expectancy, from 12 years to 50 years, (Chapel HM Data presented to European Society for Immune Deficiencies 2006), reduces the rate of bacterial infections, days of antibiotic usage, days of fever and hospital admissions. In early studies, in which diagnostic delay was common, pre-existing morbidity obscured some of the benefits of immunoglobulin therapy. However, once higher doses were used and diagnostic more stable, this benefit was statistically significant. (Aghamohammadi, A. et al., Efficacy of IVIg on the prevention of pneumonia in patients with agammaglobulinaemia,
The review conducted by Orange et al provides good evidence of the effectiveness of Polyvalent Human immunoglobulin and describes it as having “a number of important uses in the treatment of disease. Some of these are in disease for which acceptable treatment alternatives do not exist. In this review we have evaluated the evidence underlying a wide variety of IVIG uses and make specific recommendations on the basis of these data” (Orange et al. Use of human Ig in human disease: A review of evidence by members of the primary Immunodeficiency committe of the Am. Acad.Allergy and Immunology. J-Allergy Clin.Immunol. 2006; 117, S525-53). These recommendations are described in the tables from the review provided below:

**TABLE III. Uses of IGIV in primary and secondary immune deficiencies**

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Disease</th>
<th>Evidence category</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely beneficial</td>
<td>Primary immune defects with absent B cells</td>
<td>Ib</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Primary immune defects with hypogammaglobulinemia and impaired specific antibody production</td>
<td>Ib</td>
<td>B</td>
</tr>
<tr>
<td>Probably beneficial</td>
<td>Chronic lymphocytic leukaemia with reduced IgG and history of infections</td>
<td>Ib</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Prevention of bacterial infection in HIV-infected children</td>
<td>Ib</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Primary immune defects with hypogammaglobulinemia and impaired specific antibody production</td>
<td>III</td>
<td>C</td>
</tr>
<tr>
<td>Might provide benefit</td>
<td>Prevention of neonatal sepsis</td>
<td>Ib</td>
<td>A</td>
</tr>
<tr>
<td>Unlikely to be beneficial</td>
<td>Isolated IgA deficiency</td>
<td>IV</td>
<td>D</td>
</tr>
<tr>
<td></td>
<td>Isolated IgG4 Deficiency</td>
<td>IV</td>
<td>D</td>
</tr>
</tbody>
</table>

**TABLE IV. Uses of IGIV in autoimmune diseases**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Evidence category</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely beneficial</td>
<td>Graves ophthalmopaty</td>
<td>Ib</td>
</tr>
<tr>
<td></td>
<td>Idiopathic thrombocytopenic purpura</td>
<td>IIa</td>
</tr>
<tr>
<td>Probably beneficial</td>
<td>Dermatomyositis and polymyositis</td>
<td>IIa</td>
</tr>
<tr>
<td></td>
<td>Autoimmune nephritis</td>
<td>IIa</td>
</tr>
<tr>
<td>Might provide benefit</td>
<td>Severe rheumatoid arthritis</td>
<td>IIb</td>
</tr>
<tr>
<td></td>
<td>Autoimmune diabetes mellitus</td>
<td>IIb</td>
</tr>
<tr>
<td></td>
<td>Posttransfusion purpura</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>Vasculitides and antineutrophil antibody syndromes</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>Autoimmune neutropenia</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>Autoimmune hemolytic anemia</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>Autoimmune hemophilia</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>SLE</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>Familial autoimmune thrombocytopenia</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>Neonatal isoimmune hemolytic jaundice</td>
<td>III</td>
</tr>
<tr>
<td>Unlikely to be beneficial</td>
<td>Inclusion body nephritis</td>
<td>IIb</td>
</tr>
<tr>
<td></td>
<td>APS in pregnancy</td>
<td>III</td>
</tr>
</tbody>
</table>
The systematic review conducted by Hyde aims to "assess the effectiveness and cost-effectiveness of IgRT [Immunoglobulin Replacement Therapy] for patients with primary
immunoglobulin deficiency (PID) and immunoglobulin deficiency secondary to chronic lymphatic leukaemia (CLL)". Hyde also provides good evidence of the effectiveness of Polyvalent Human Immunoglobulin as shown in the tables below (Hyde C, Albon E and Liu Zulian, The effectiveness and cost effectiveness of immunoglobulin replacement therapy for primary immunodeficiency and chronic lymphocytic leukaemia: a systematic review and economic evaluation, Department of Public Health and Epidemiology West Midlands Health Technology Assessment Group, University of Birmingham, DPHE 2006, Report Number 54):

Table – cumulative from the systematic review: Secondary outcomes of the trials for PID:

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary Outcome</th>
<th>Secondary Outcome</th>
<th>Patient preference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chisari, 1995</td>
<td>Days in hospital</td>
<td>Days on antibiotic</td>
<td>All patients felt better.</td>
</tr>
<tr>
<td>Jayes, 1992</td>
<td>Days in hospital</td>
<td>Days on antibiotic</td>
<td>Days reduced to bed at home.</td>
</tr>
<tr>
<td>Watson, 2003</td>
<td>Days in hospital</td>
<td>Days on antibiotic</td>
<td>Almost identical in mean weekly numerical health status.</td>
</tr>
<tr>
<td>Watson, 2003</td>
<td>Days in hospital</td>
<td>Days on antibiotic</td>
<td>27% preferred intervention.</td>
</tr>
</tbody>
</table>

Note: All patients felt better except three who died from unrelated causes.

Data for both groups were similar.
<table>
<thead>
<tr>
<th>Trial of type</th>
<th>Fever events due to infection</th>
<th>Use of antibiotics</th>
<th>Hospital admission</th>
<th>Absence from school or work</th>
<th>Quality of life or feeling of well-being</th>
<th>Serum IgG level (g/L)</th>
<th>Optimal therapy vs less optimal</th>
<th>Patient preferences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salata, 1997</td>
<td>Improved product study</td>
<td>Patients 26 vs 5 Days: 5 vs 17</td>
<td>Patients 26 vs 5 Days: 5 vs 17</td>
<td>Patients 26 vs 5 Days: 5 vs 17</td>
<td>Patients 26 vs 5 Days: 5 vs 17</td>
<td>None patient showed any difference between the two periods on the two preparations in visual analog scale.</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Salata, 1995</td>
<td>Improved product study</td>
<td>Mean (SD) proportion of days with fever 26/0.1±0.33 days vs 24/0±0.52 days p&lt;0.05</td>
<td>Mean (SD) proportion of days with fever 26/0.1±0.33 days vs 24/0±0.52 days p&lt;0.05</td>
<td>Mean (SD) proportion of days with fever 26/0.1±0.33 days vs 24/0±0.52 days p&lt;0.05</td>
<td>Mean (SD) proportion of days with fever 26/0.1±0.33 days vs 24/0±0.52 days p&lt;0.05</td>
<td>Excerpt 4 patient no significant difference in the serum IgG levels between the preparations.</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Wolf, 1992</td>
<td>Improved product study</td>
<td>NR</td>
<td>Patients given antibiotics: 15 vs 8</td>
<td>1 vs 7</td>
<td>Days: 12.6±1.3</td>
<td>Patients: 7 vs 6, p&lt;0.05 Mean (SD) values for fever: 0.45 (0.3-1.3) vs 0.6 (0.3-1.3) p=0.30</td>
<td>Measurement of efficacy of fever: 7 vs 2 Patients felt 'very poor': 1 vs 0 (following the 4-patient 6% difference respectively)</td>
<td>NR</td>
</tr>
<tr>
<td>Pachon, 1987</td>
<td>Acute minor infections: Total: 12 vs 21 Upper respiratory tract infections: 10 vs 21 Colds: 1 vs 4 Uti: 0 vs 1 Skin infections: 3 vs 1</td>
<td>NR</td>
<td>Acute minor infections: Upper respiratory tract infections: 3 vs 0 Colds: 11 vs 10 Uti: 12 vs 11 Skin infections: 11 vs 10</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
Table – cumulative from the systematic review: Secondary outcomes of RCT trials of IVIg vs placebo for Secondary Antibody Deficiencies:

<table>
<thead>
<tr>
<th>Trial</th>
<th>N patients with infections</th>
<th>N patients infection, days</th>
<th>Infection severity</th>
<th>Duration of infections</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVIg vs No treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modica, 1998</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuncali, 1996</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eder, 1992</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goldstone, 1992</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cao et al., 1994</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please see:

- Annex 4 for a comprehensive table containing references of publications demonstrating the effectiveness of immunoglobulins in Primary Immunodeficiencies.
- Annex 5 for a comprehensive table containing references of publications demonstrating the effectiveness of immunoglobulins in Secondary Immunodeficiencies.
- Annex 6 for a comprehensive table containing references of publications demonstrating the effectiveness of immunoglobulins in Guillain-Barré Syndrome and Chronic Inflammatory Demyelinating Polyneuropathy
- Annex 7 for a comprehensive table containing references of publications demonstrating the effectiveness of immunoglobulins in Idiopathic Thrombocytopenic Purpura

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 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. The former have been reduced considerably in the last several years, due to improved manufacturing processes, as demonstrated in several trials (Ochs, 1980, Steele, 1987, Zuhrie, 1995, Schiff, 1997, Ballow, 2003, Wolf, 2003) in which the rate of infusion related reactions has gradually decreased. (Chapel 2001, Rasvi 2001, Quinti 2002). High level regulatory vigilance has since then prevented further outbreaks. There has not been any viral transmission of hepatitis C since 1994.

Immunoglobulins have been used for many years in tens of 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 long term 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.

Many studies have been conducted that provide convincing evidence on the safety of Ig as a life saving therapeutic product.

Please see Annex 8 for a comprehensive table of data demonstrating the safety of immunoglobulins.

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

- Range of costs of the proposed medicine

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 (contemporary data in preparation).

In developing countries such as India, the average cost in 2006 of IVIG is estimated to be $8 per gram. (Source: Chandigarh Hospital, India)

- 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)

The systematic review conducted by Hyde provides evidence quantifying the effect of immunoglobulin replacement therapy (IgRT) for PID on survival. Amongst its conclusions, the review points out that IgRT, particularly intravenous and subcutaneous immunoglobulin, is effective in terms of reduction of infection and appears to be cost effective as well in PID on the basis of evidence on effects on survival and utility that are not derived from RCTs. (Hyde C, Albon E and Liu Zulian, The effectiveness and cost effectiveness of immunoglobulin replacement therapy for primary immunodeficiency and chronic lymphocytic leukaemia: a systematic review and economic evaluation, Department of Public Health and Epidemiology, West Midlands Health Technology Assessment Group, University of Birmingham, DPHE 2006, Report Number 54)

At the recent EU Primary Immunodeficiencies Consensus Conference sponsored by the European Commission, more than 100 experts in clinical immunology, PID care, public health, genetics, EU/national ministries of health and agencies, academic centres, public health laboratories, industry, professional organisations and patient groups were brought together to identify and develop public health strategies for PIDs. The cost-effectiveness of Polyvalent Human Immunoglobulins in the treatment of PID was widely discussed. Amongst the conclusions of the Consensus Conference, the multi-discipline experts stated that “effective therapies for PIDs exist and early treatment saves lives, prevents morbidity and improves quality of life. There is also evidence that early treatment is cost-effective” (European Primary Immunodeficiencies Consensus Statement, see Annex 9)

The International Patient Organisation for Primary Immunodeficiencies (IPOPI) recently conducted a survey with 6 hospitals from different countries representing a good geographical diversity (South Africa, Iran, India, Hong Kong, Spain and Scotland) on the value and importance of early diagnosis of Immune Deficiencies (IDs) and proper treatment with Polyvalent Human Immunoglobulins. The outcomes of the questionnaire pointed to interesting results underlying good evidence of the advantages of early diagnosis of IDs and subsequent appropriate treatment with Polyvalent Human Immunoglobulins as well as to its cost-effectiveness (see Annex 10). The results of the questionnaire showed that 50 % of patients who are not properly treated with Polyvalent Human Immunoglobulins develop between 5 and 10 infections per year, 33.3% between 2 to 5
infections per year and 16.6% over 10 infections per year. These infections result in unnecessary costs incurred mostly by frequent use of antibiotics and hospital stays. 66.6% of patients not properly treated with Polyvalent Human Immunoglobulins are hospitalized between 2 to 5 times per year and need ambulatory care (outpatient visits) between 2 to more than 10 times per year. The questionnaire also showed that 100% of the surveyed hospitals believed that the impact of treatment with Polyvalent Human Immunoglobulins was very significant on the quality of life of patients with an Immune Deficiency. 84.4% of the surveyed hospitals believed that treatment of IDs with Polyvalent Human Immunoglobulins is cost effective as unnecessary costs such as use of antibiotics, increased hospitalization and ambulatory care are avoided. The remaining 16.6% believed treatment of IDs with Polyvalent Human Immunoglobulins is cost-effective due to a broader range of socio-economic benefits that are not just limited to healthcare costs (e.g. social insurance/security payments etc).

A survey conducted by the Jeffrey Modell Foundation highlighted similar results. The survey was conducted with experts from 76 Jeffrey Modell Diagnostic and referral centers and compared undiagnosed and diagnosed patients with PIDs. The survey indicated a much higher rate of infections and a much higher use of antibiotics, days in hospitals and school/work days missed with undiagnosed patients not receiving proper replacement therapy with Polyvalent Human Immunoglobulins as shown in the charts below:
Similar results can also be found in the 1996 survey conducted by the US Immune Deficiency Foundation (IDF) among patients from the first national patient survey who had been treated with IVIG (see Annex 11). Amongst its conclusions, the survey highlighted that “the cost of late diagnosis is a heavy burden of disease on the patient. The majority of patients suffered two or more hospitalizations before diagnosis. The majority experienced repeated ear infections, bronchitis, and pneumonias before diagnosis, which may cause permanent limitations. In addition, some suffered serious infections and potentially life-threatening infections before diagnosis, including sepsis, meningitis and hepatitis. Treatment significantly reduces the burden of disease among persons with primary immune deficiency diseases. The prevalence of pneumonia, bronchitis, diarrhea and repeated ear infections drops significantly after diagnosis. Nearly half of persons with primary immune deficiency diseases have had no hospitalizations since diagnosis. Two thirds of persons with primary immune deficiency diseases describe their current health as good, very good or excellent. Most say their health causes no limitations or only slight limitations on work, play and other activities. Three quarters have had no hospitalizations in the past year”.

The European Parliament’s Scientific and Technical Options Assessment (STOA) panel held a workshop on 17 March 2004 at which Professor Janne Björkander (Sahlgrenska University Hospital Göteborg, Sweden) provided a presentation (see Annex 12) on ‘the consequences of late diagnosis of primary immunodeficiency diseases’ which concluded that

- Late diagnosis of immune deficiencies and infections lead to disability and irreversible organ damage (irrespective of smoking history)
- About 70% of patients with antibody deficiencies (IgGsd) respond well to treatment with antibody replacement therapy (immunoglobulins) with decreased number of infections and increased wellbeing (p<0.0001)
- Undiagnosed and untreated patients need greater use of hospital services

Professor Ann Gardulf (Karolinska Hospital, Sweden) also gave a presentation (see Annex 13) at the EP 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’. The conclusion was that treatment with immunoglobulin was cost effective.

It can therefore be concluded that without proper immunoglobulin treatment patients suffering from PIDs will spent unnecessary time in hospital and will be treated with
inefficacious alternative treatment thereby requiring much higher unnecessary medical expenses.

13. 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 regions of the world, including Australasia, the European Union, India, Iran, Japan, South Africa, South America, the USA and others.


Many countries have their own pharmacopoeial standards but the European Pharmacopoeia contains a monograph for Human Normal Immunoglobulin (see Annex 14) which is regarded as being the pharmacopoeial gold standard.

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

**Polyvalent Human Normal Immunoglobulin.** *Immunoglobulinum humanum normale.*

*For intravenous use:* 5%, 10% or 12% solutions depending on the manufacturer

*For subcutaneous use:* 15% or 16% solutions depending on the manufacturer

*For intramuscular use:* 16% solutions depending on the manufacturer

**Uses:** Replacement therapies in primary immune deficiencies; immunomodulation in selected patients with specific autoimmune diseases

**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.

**Interactions:** none

**Dosage:**

*For replacement therapy:* Starting dose depends on pre-treatment serum IgG level. Initial loading intravenously in divided doses until serum IgG level is > 6 g/l. Maintenance doses by intravenous, subcutaneous or intramuscular routes: 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 Immunomodulation:* 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. Maximum recommended dose is 2 g/Kg over at least 48 hours

**Administration:** Infusion rates of < 8 g per hour are recommended

**Adverse effects:**

For both 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 resolves in 6 –24 hours.
IV administration: delayed headache and nausea up to 24 hours after infusion. With immunomodulatory doses: immune haemolysis, aseptic meningism, increased plasma viscosity, hypercoaguability, acute tubular renal 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.