Acquired hypogammaglobulinaemia secondary to haematological malignancies chronic lymphocytic leukaemia (CLL), multiple myeloma (MM), non-Hodgkin lymphoma (NHL) and other relevant malignancies, and post-haemopoietic stem cell transplantation (HSCT)

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Condition for which IVIg has an established therapeutic role.

Specific Conditions	• Chronic lymphocytic leukaemia • Multiple myeloma • Non-Hodgkin lymphoma • Other relevant haematological malignancies • Post-haemopoietic stem cell transplantation
Indication for IVIg Use	• Prevention of recurrent bacterial infections due to hypogammaglobulinaemia associated with haematological malignancies. • Prevention of recurrent bacterial infections due to acquired hypogammaglobulinaemia secondary to stem cell transplantation for haematological malignancies.
Level of Evidence	Evidence of probable benefit – more research needed (Category 2a)
Description and Diagnostic Criteria	The manifestations of haematological malignancies can include a wide range of symptoms and physical and laboratory abnormalities in an individual patient. For diagnostic criteria, refer to the current World Health Organization classification criteria.
Justification for Evidence Category	One small crossover study of 12 patients with chronic lymphocytic leukaemia (CLL) or non-Hodgkin lymphoma (NHL) reported that the number of serious bacterial infections was significantly decreased ($p = 0.001$) in the months in which patients received immunoglobulin G (IgG) every three weeks for one year. Serious bacterial infections showed a trend to be associated with an IgG level <6.4 g/L. Three randomised controlled trials (RCTs) and one crossover trial of low–moderate quality reported a reduction in infection rates in CLL patients with hypogammaglobulinaemia after three- to four-weekly administration of intravenous immunoglobulin (IVIg) for one year. One placebo-controlled RCT of monthly IVIg given to 82 multiple myeloma (MM) patients for one year (with 22 withdrawing due to reaction) concluded that IVIg protects against life-threatening infections and significantly reduces risk of recurrent infections. The greatest benefit was seen in individuals who had a poor response to pneumococcal vaccine. A small prospective RCT with 30 MM patients reported a possible decrease in symptoms of chronic bronchitis. A recent systematic review and meta-analysis of patients undergoing haemopoietic stem cell transplantation (HSCT) (60 trials, >4000 patients) reported an increased risk of veno-occlusive disease with no survival benefit, particularly in studies conducted since 2000. The authors concluded that routine prophylaxis with IVIg is not supported, but suggest that its use may be considered in lymphoproliferative disorder patients with hypogammaglobulinaemia and recurrent infections, for reduction of clinically documented infections.

Qualifying Criteria for IVIg Therapy	Prevention of recurrent bacterial infections due to hypogammaglobulinaemia associated with haematological malignancies. • Recurrent or severe bacterial infection(s). AND • Evidence of hypogammaglobulinaemia (excluding paraprotein). OR • Hypogammaglobulinaemia with IgG <4 g/L (excluding paraprotein). Antibiotic therapy may be indicated in addition to immunoglobulin therapy. Prevention of recurrent bacterial infections due to acquired hypogammaglobulinaemia secondary to stem cell transplantation for haematological malignancies. • Recurrent or severe bacterial infection(s). AND • Evidence of hypogammaglobulinaemia (excluding paraprotein). OR • Hypogammaglobulinaemia with IgG <4 g/L (excluding paraprotein). Antibiotic therapy may be indicated in addition to immunoglobulin therapy.
Exclusion Criteria	HIV in children. - see HIV in children Transplantation-related immunomodulation (kidney transplantation). - see Kidney transplantation Transplantation-related immunomodulation (solid organ transplantation other than kidney). - see Solid organ transplantation (other than kidney) Thymoma-associated hypogammaglobulinaemia (Good's syndrome). - see Secondary hypogammaglobulinaemia (including iatrogenic immunodeficiency) Secondary hypogammaglobulinaemia (including iatrogenic immunodeficiency). - see Secondary hypogammaglobulinaemia (including iatrogenic immunodeficiency)

Review Criteria for Assessing the Effectiveness of IVIg Use	Prevention of recurrent bacterial infections due to hypogammaglobulinaemia associated with haematological malignancies. Initial review is required at six months with ongoing reviews at least annually to assess clinical benefit. Documentation of clinical effectiveness is necessary for continuation of immunoglobulin therapy. Cessation of immunoglobulin therapy should be considered at least after each 12 months of therapy. Treatment can be extended as required to enable cessation of therapy in September/October, with repeat clinical and/or immunological evaluation before re-commencement of therapy. **On review of an authorsation period** Clinical effectiveness of Ig therapy may be demonstrated by: • Monitoring of trough or random serum immunoglobulin level (IgG), with review of any bacterial infections during the authorisation period. AND • A trial cessation of Ig for the purposes of immunological evaluation will be undertaken. OR • A trial period of cessation of Ig for the purpose of immunological evaluation is medically contraindicated on safety grounds (such as neutropenia, immunosuppressant medication, active bronchiectasis and/or suppurative lung disease, or severe hypogammaglobulinaemia persists where no significant improvement has occurred in the underlying condition). In principle, Ig therapy should only be continued or renewed if there is a demonstrated clinical benefit. Antibiotic therapy may be indicated in addition to immunoglobulin therapy.

Prevention of recurrent bacterial infections due to acquired hypogammaglobulinaemia secondary to stem cell transplantation for haematological malignancies.

Initial review is required at six months with ongoing reviews at least annually to assess clinical benefit. Documentation of clinical effectiveness is necessary for continuation of Ig therapy.

Cessation of immunoglobulin therapy should be considered at least after each 12 months of therapy. Treatment can be extended as required to enable cessation of therapy in September/October, with repeat clinical and/or immunological evaluation before re-commencement of therapy.

On review of an authorisation period
Clinical effectiveness of Ig therapy may be demonstrated by:

- Monitoring of trough or serum immunoglobulin levels (IgG) and review of any bacterial infections during the authorisation period.

AND

- A trial period of cessation of Ig for the purposes of immunological evaluation will be undertaken.

  OR

- A trial period of cessation of therapy for the purpose of immunological evaluation is medically contraindicated on safety grounds (such as neutropenia, immunosuppressant medication, active bronchiectasis and/or suppurative lung disease, or severe hypogammaglobulinaemia persists where no significant improvement has occurred in the underlying condition).

In principle, Ig should only be continued or renewed if there is a demonstrated clinical benefit.

Antibiotic therapy may be indicated in addition to Immunoglobulin therapy.

Dose	Prevention of recurrent bacterial infections due to hypogammaglobulinaemia associated with haematological malignancies. • **Loading Dose** - one additional dose of 0.4 g/kg in the first month of therapy is permitted if the serum IgG level is <4 g/L. • **Maintenance Dose** - 0.4 g/kg every four weeks, modified to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range. Subcutaneous administration of immunoglobulin can be considered as an alternative to IVIg. A suggested dose is 0.1 g/kg lean body mass every week, modified to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range. **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.** **Refer to the current product information sheet for further information.** Prevention of recurrent bacterial infections due to acquired hypogammaglobulinaemia secondary to stem cell transplantation for haematological malignancies. • **Loading Dose** - one additional dose of 0.4 g/kg in the first month of therapy is permitted if the serum IgG level is <4 g/L. • **Maintenance Dose** - 0.4 g/kg every four weeks, modified to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range. Subcutaneous administration of immunoglobulin can be considered as an alternative to IVIg. A suggested dose is 0.1 g/kg lean body mass every week, modified to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range. **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.** **Refer to the current product information sheet for further information.**

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