



Australian Health
Ministers' Conference

Criteria for the
clinical use of
**intravenous
immunoglobulin**
in Australia

quick
REFERENCE
guide

December 2007

Disclaimer: Important information about this document

This document is not a substitute for medical advice obtained from an attending clinician in relation to a particular patient's condition. The relevance and appropriateness of the information and recommendations in this document depend, amongst other things, on a correct diagnosis being made, the severity of the relevant condition being properly ascertained, and other relevant circumstances of the particular patient.

This document is designed to provide information to assist clinical decision making. The information and recommendations represent informed opinion based, where possible, upon systematic review of the evidence which was finalised by mid 2006. In the absence of published evidence, recommendations are based on clinical advice provided to the parties involved in developing this document (i.e. the Jurisdictional Blood Committee IVlg Working Party and its clinical advisers and consultants, the Jurisdictional Blood Committee, and the Commonwealth of Australia) up to June 2007.

This document deals only with the use of intravenous immunoglobulin and does not include any advice on other forms of treatment relevant to the conditions described.

Each of the parties involved in developing this document and each of their relevant employees expressly disclaims and accepts no responsibility for any consequences arising from relying upon the information or recommendations contained herein.

This document was prepared under the auspices of the Jurisdictional Blood Committee for and on behalf of the Australian Health Ministers' Conference. It is intended that this document will be updated periodically. This document and its subsequent updates will be available on the National Blood Authority website at www.nba.gov.au.

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Introduction

This quick reference guide is an abbreviated version of the *Criteria for the Clinical Use of Intravenous Immunoglobulin in Australia*, approved by all Australian Health Ministers in December 2007. The complete document should be referred to in the first instance. Both documents have been produced to assist clinicians and transfusion medicine professionals to identify the conditions and circumstances for which the use of intravenous immunoglobulin (IVIg) is appropriate. IVIg is a precious biological product. Its use should be consistent with the evidence-base and for the treatment of patients who are likely to benefit from IVIg therapy and for whom there are no alternative safe and effective treatments.

The growth in demand for IVIg has prompted action by Australian governments to ensure it is reserved for use in those with the greatest need. Where safe, effective and affordable alternative therapies exist, these are considered preferable to IVIg. When IVIg is used, the lowest dose for the shortest duration required to achieve the desired outcome should be chosen. For ongoing therapy, the achievement of measurable clinical outcomes is a requirement and IVIg should not be continued in patients with no demonstrable clinical benefit.

The conditions listed in the *Criteria for the Clinical Use of Intravenous Immunoglobulin in Australia* are categorised according to the evidence identified through systematic reviews of the literature and the advice of clinical experts (see 'Level of evidence categories' table on page 3). In conjunction with government policy, this publication may be used to identify those conditions and circumstances for which IVIg products can be accessed under the National Blood Agreement. Governments have agreed to provide funded IVIg for the conditions and uses described in the *Criteria for the Clinical Use of Intravenous Immunoglobulin in Australia* in Chapters 5, 6 and 7 (conditions for which there is reasonable evidence and/or clinical support for the use of IVIg therapy).

IVIg funded under the National Blood Agreement is not available for use to treat conditions identified in Chapter 8, which are considered non-indications for IVIg therapy at this time.

For conditions **not** described in Chapters 5, 6 or 7, Approved Recipients may obtain IVIg via the Jurisdictional Direct Order component of the IVIg Standing Offer arrangements.

In the first instance, users should refer to the complete criteria and the current product information sheets for IVIg products for further information.

Governments recognise the need for the conditions identified and the criteria for the clinical use of IVIg to be regularly reviewed to take account of the evolving processes of disease diagnosis, treatment and outcome evaluation.

This document was prepared under the auspices of the Jurisdictional Blood Committee for and on behalf of the Australian Health Ministers' Conference.

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Principal clinical advisers to the IVIg Working Party were Associate Professor John Gibson, Associate Professor Andrew Kornberg and Dr Sean Riminton. The Australian Red Cross Blood Service Transfusion Medicine Team contributed substantially to this review. Many other clinical experts gave generously of their time and expertise and are listed in Appendix F of the full criteria document. All contributions are gratefully acknowledged.

It is intended that this document will be updated periodically.

This quick reference guide along with the full Criteria document and their subsequent updates will be available on the National Blood Authority website at www.nba.gov.au.

Level of evidence categories

CATEGORY	STUDIES	EVIDENCE
1	High-quality RCTs	Clear evidence of benefit
2a	Some RCTs and/or case studies	Evidence of probable benefit – more research needed
2b	Some RCTs and/or case studies	Evidence of no probable benefit – more research needed
2c	High-quality RCTs with conflicting results	Conflicting evidence of benefit
3	High-quality RCTs	Clear evidence of no benefit
4a	Small case studies only	Insufficient data
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Conditions for which IVIg use is Not indicated - not funded under the National Blood Arrangements

Conditions for which IVIg use is NOT INDICATED – not funded under the National Blood Arrangements	
Acute optic neuritis	Diamond Blackfan syndrome
Acute rheumatic fever	Female infertility
Adrenoleukodystrophy	Glomerulonephritis – IgA nephritis
Amegakaryocytic thrombocytopenia	Haemolytic uraemic syndrome
Antiphospholipid syndrome (non-obstetric)	Henoch-Schonlein purpura
Aplastic anaemia/pancytopenia	HIV/AIDS – adult
Asthma	Idiopathic dilated cardiomyopathy
Atopic dermatitis/eczema	Linear IgA disease
Autism – young adults	Lupus nephritis
Autologous haemopoietic stem cell transplantation	Motor neuron disease/ amyotrophic lateral sclerosis
Cardiac surgery with bypass – prophylaxis	Myalgic encephalomyelitis
Congestive cardiac failure	Narcolepsy/cataplexy
Crohn's disease	Nephrotic syndrome

Conditions for which IVIg use is **NOT INDICATED** – not funded under the National Blood Arrangements

Obsessive compulsive disorders	Sensory neuropathy associated with anti-Hu antibodies
Paraneoplastic cerebellar degeneration (Yo antibodies)	Sepsis (other than neonatal sepsis)
Polyneuropathy of critical illness	Sickle cell disease
Recurrent foetal loss (with or without antiphospholipid syndrome)	Systemic lupus erythematosus
Rheumatoid arthritis	Ulcerative colitis

A vertical decorative strip on the left side of the page, featuring a repeating pattern of stylized botanical motifs in a light purple color. The motifs include clusters of small, oval-shaped elements resembling seeds or berries, and larger, more complex structures that look like stylized leaves or flower parts. The strip is set against a white background and is bordered by a dark purple color on the left and bottom.

Conditions

Medical condition	ACQUIRED HYPOGAMMAGLOBULINAEMIA SECONDARY TO HAEMATOLOGICAL MALIGNANCIES (Condition for which IVIg has an <i>established</i> therapeutic role)
Indication for IVIg use	<ul style="list-style-type: none"> • Prevention of recurrent bacterial infections due to antibody failure associated with haematological malignancies. • Prevention of recurrent bacterial infections in patients undergoing HSCT for haematological malignancies.
Level of evidence	Category 2a – Some RCTs and/or case studies – Evidence of probable benefit – more research needed.
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 WHO classification criteria.
Qualifying criteria	Diagnosis of NHL, CLL, MM or other relevant B-cell tumour with: <ol style="list-style-type: none"> 1. Recurrent or severe bacterial infection(s) and evidence of hypogammaglobulinaemia (excluding paraprotein); <p>OR</p> <ol style="list-style-type: none"> 2. Hypogammaglobulinaemia with IgG <4g/L (excluding paraprotein) with a lack of functional IgG response to vaccine challenge. <p>Note: For data tracking purposes, the type of malignancy being treated should be recorded with each request for IVIg.</p>

Medical condition	ACQUIRED HYPOGAMMAGLOBULINAEMIA SECONDARY TO HAEMATOLOGICAL MALIGNANCIES (Condition for which IVIg has an <i>established</i> therapeutic role)
Review criteria	<ul style="list-style-type: none"> • Six-month review assessing evidence of clinical benefit. • Depending on the clinical circumstance, cessation of IVIg should be considered after 12 months of therapy with repeat clinical and/or immunological evaluation prior to re-commencement of therapy.
Dose	<p><i>Maintenance dose:</i> 0.4g/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.</p> <p><i>Loading dose:</i> One additional dose of 0.4g/kg in the first month of therapy is permitted if the serum IgG level is <4g/L.</p> <p><i>Subcutaneous administration</i> of immunoglobulin can be considered as an alternative to IVIg. A suggested dose is 0.1g/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.</p> <p>Refer to the current product information sheet for further information.</p>

Medical condition	ACUTE DISSEMINATED ENCEPHALOMYELITIS (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Indication for IVIg use	<ol style="list-style-type: none"> 1. ADEM unresponsive to steroid therapy or where steroids are contraindicated (e.g. suspicion of CNS infection). 2. Recurrent or multiphasic ADEM unresponsive to steroid therapy or where steroid therapy has become intolerable or is contraindicated.
Level of evidence	Category 2a – Some RCTs and/or case studies – Evidence of probable benefit – more research needed.
Description and diagnostic criteria	<p>Acute disseminated encephalomyelitis (ADEM) is a monophasic inflammatory condition of the central nervous system that usually presents in children and young adults. It typically occurs following a viral prodrome with multifocal neurological disturbance and altered conscious state. ADEM usually follows a monophasic course but patients may experience recurrence of the initial symptom complex (recurrent ADEM) or a second episode of ADEM (multiphasic ADEM). The majority make a full recovery.</p> <p>ADEM is thought to have an autoimmune basis. Pathologic similarities to experimental allergic encephalomyelitis (EAE), an animal model of inflammatory demyelination, support this theory. It is postulated that a common antigen shared by an infectious agent and a myelin epitope results in an autoimmune response.</p>

Medical condition	ACUTE DISSEMINATED ENCEPHALOMYELITIS (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Description and diagnostic criteria <i>(continued)</i>	<p>Patients show multiple demyelinating lesions on MRI in the deep and subcortical white matter. The differential diagnosis includes other inflammatory demyelinating disorders such as multiple sclerosis, optic neuritis, and transverse myelitis.</p> <p>High-dose corticosteroids are first-line treatment of ADEM. IVIg has been used for patients who fail to respond to steroid therapy or in patients where steroids are contraindicated. Most patients with ADEM recover completely over a period of 6 weeks from onset.</p> <p>There is no biological marker for ADEM. Diagnosis is by clinical recognition of the multifocal neurological disturbance and altered conscious state, with the typical MRI findings of demyelination.</p>
Qualifying criteria	<ol style="list-style-type: none"> 1. ADEM unresponsive to steroid therapy or where steroids are contraindicated (e.g. suspicion of CNS infection). Note: Assessment by a neurologist is recommended, but not mandatory. <p>OR</p> <ol style="list-style-type: none"> 2. Recurrent or multiphasic ADEM unresponsive to steroid therapy, or where steroid therapy has become intolerable or is contraindicated, with assessment by a neurologist mandatory.
Review criteria	<ul style="list-style-type: none"> • Objective evidence of improvement in relapse rate in comparison to pre-treatment levels. • Six monthly review by a neurologist is required for recurrent or multiphasic ADEM.

Medical
condition

ACUTE DISSEMINATED ENCEPHALOMYELITIS
(Condition for which IVIg has an *emerging*
therapeutic role)

Dose

Induction: 2g/kg in 2 to 5 divided doses.

Maintenance dose: For recurrent or multiphasic ADEM only: 0.4–2g/kg 4–6 weekly.

Aim for *minimum dose* to maintain optimal functional status and prevent relapses.

In recurrent or multiphasic ADEM, assessment by a neurologist is *mandatory*.

Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.

Medical condition	ACUTE LEUKAEMIA IN CHILDREN (Condition for which IVIg use is in <i>exceptional</i> circumstances only)
Indication for IVIg use	<p>[Includes acute lymphoblastic or lymphoid leukaemia (ALL) and acute myeloblastic leukaemia (AML)].</p> <p>IVIg may be considered in cases of ALL or AML with neutropenic sepsis in patients aged ≤ 15 years in whom conventional antimicrobial therapy has been ineffective and who have life-threatening infection.</p> <p>Refer to the current product information sheet for further information.</p>
Level of evidence	<p>Category 2a – Some RCTs and/or case studies – Evidence of probable benefit – more research needed</p>

Medical condition	ANCA-POSITIVE NECROTISING VASCULITIS (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Indication for IVIg use	Control of vasculitic activity in rare cases of ANCA-positive systemic necrotising vasculitis failing to respond to corticosteroids and cytotoxic immunosuppression.
Level of evidence	Category 2a - Some RCTs and/or case studies - Evidence of probable benefit – more research needed.
Description and diagnostic criteria	<p>Anti-neutrophil cytoplasmic antibody (ANCA) associated systemic necrotising vasculitides are life-threatening immune-mediated inflammatory diseases comprising one of four clinical syndromes:</p> <ol style="list-style-type: none"> 1. Wegener's granulomatosis 2. Microscopic polyangiitis 3. Churg-Strauss Syndrome 4. ANCA (PR3 or MPO)-positive idiopathic rapidly progressive glomerulonephritis. <p>In these cases the ANCA specificity is directed against the neutrophil cytoplasmic antigens proteinase 3 (PR3) and myeloperoxidase (MPO). ANCA that lack MPO or PR3 specificity tend to be non-specific. Biopsy of affected tissue is required to establish the diagnosis.</p> <p>Standard combinations of corticosteroids and cytotoxic immunosuppression are generally effective at controlling disease, but relapses are common. IVIg has a limited role as one of several therapeutic options in relapsing disease.</p>

Medical condition	ANCA-POSITIVE NECROTISING VASCULITIS (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Qualifying criteria	<p>MPO or PR3 ANCA positive systemic necrotising vasculitis with both of the following:</p> <ol style="list-style-type: none"> 1. Current (or within the previous 6 months) standard cytotoxic immunosuppressive ANCA-vasculitis regimens; <p>AND</p> <ol style="list-style-type: none"> 2. Persistent active disease.
Exclusion criteria	Initial therapy.
Review criteria	<ul style="list-style-type: none"> • Six-month review assessing evidence of clinical benefit. • Reduction in the Birmingham vasculitis activity score (BVAS) of more than 50% after 3 months. • Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) concentration. • ANCA titre.
Dose	<p>2g/kg in single or divided doses.</p> <p>Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.</p>

Medical condition	AUTOIMMUNE CONGENITAL HEART BLOCK (Condition for which IVIg use is in <i>exceptional</i> circumstances only)
Indication for IVIg use	IVIg therapy may be indicated during pregnancy when there is a history of autoimmune congenital heart block in at least one previous pregnancy and maternal SS-A and/or SS-B antibodies are present. Refer to the current product information sheet for further information.
Level of evidence	Category 4a – Small case studies only – insufficient data.

Medical condition	AUTOIMMUNE DIABETIC NEUROPATHY (Condition for which IVIg use is in <i>exceptional</i> circumstances only)
Indication for IVIg use	<p>A RCT of IVIg vs. corticosteroids vs. placebo is understood to be in progress but results are not yet available. However, use of steroids in this patient group can be very difficult. IVIg may be indicated in specific circumstances when steroids are not tolerated or not effective in managing the neuropathy.</p> <p>Refer to the current product information sheet for further information.</p>
Level of evidence	Category 4a – Small case studies only – insufficient data.

Medical condition	AUTOIMMUNE HAEMOLYTIC ANAEMIA (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Indication for IVIg use	To reduce haemolysis in patients not responding to corticosteroid therapy.
Level of evidence	Category 4a – Small case studies only – insufficient data.
Description and diagnostic criteria	<p>Autoimmune haemolytic anaemia (AIHA) is a rare but serious autoimmune disease in which an individual's antibodies recognise antigens on their own red blood cells (RBCs). It presents as an acute or chronic anaemia characterised by the occurrence of biochemical parameters of red cell destruction associated with a positive direct antiglobulin test indicating the presence of antibodies and/ or complement on the red cell surface. It may be secondary to a number of underlying disorders or drugs.</p> <p><i>Investigations:</i></p> <p>A full blood count will confirm the presence of anaemia. A peripheral blood smear may reveal evidence of spherocytes along with polychromasia due to reticulocytosis. A direct antiglobulin test is usually positive, the serum LDH is raised, and there is a reduction in serum haptoglobin.</p> <p><i>Prognosis:</i></p> <p>The prognosis of AIHA is good in most cases although severe refractory AIHA can cause cardio-respiratory problems because of severe anaemia especially in adults.</p>

Medical condition	AUTOIMMUNE HAEMOLYTIC ANAEMIA (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Description and diagnostic criteria <i>(continued)</i>	<p><i>Standard therapy:</i> Corticosteroid administration is the cornerstone of therapy. For those with relapsing disease, splenectomy and immunosuppression are second line treatments while anti-CD20 antibodies have shown promise in individual cases of refractory disease.</p>
Qualifying criteria	<ol style="list-style-type: none"> 1. Symptomatic or severe AIHA (Hb <60g/L, except patients with co-morbidities) refractory to conventional therapy with corticosteroids; <p>OR</p> <ol style="list-style-type: none"> 2. As a temporising measure prior to splenectomy; <p>OR</p> <ol style="list-style-type: none"> 3. As initial and maintenance therapy in AIHA in patients unsuitable for splenectomy or immunosuppression.
Exclusion criteria	<p>Patients in whom a trial of corticosteroids has not been undertaken.</p>
Review criteria	<ul style="list-style-type: none"> • Resolution of haemolytic anaemia (rising haemoglobin concentrations, falling bilirubin and LDH). • Clinical improvement in symptoms and signs.
Dose	<p>Up to 2g/kg as a single or divided dose.</p> <p>Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.</p>

Medical condition	AUTOIMMUNE NEUTROPENIA (Condition for which IVIg use is in <i>exceptional</i> circumstances only)
Indication for IVIg use	<p>Autoimmune neutropenia is a rare disorder caused by peripheral destruction of antibody-sensitised neutrophils by cells of the reticuloendothelial system. IVIg may be considered among treatment options in rare circumstances when the standard treatment of G-CSF fails.</p> <p>Refer to the current product information sheet for further information.</p>
Level of evidence	Category 4a – Small case studies only – insufficient data.

Medical condition	AUTOIMMUNE UVEITIS (Condition for which IVIg use is in <i>exceptional</i> circumstances only)
Indication for IVIg use	<p>Uveitis refers to inflammation of the uvea of the eye and can be caused by infection, exposure to toxins or autoimmune disorders. Symptoms may include redness of the eye, blurred vision, unusual sensitivity to light, dark floating spots in the vision and eye pain. Ocular inflammation of this kind may threaten sight and be resistant to standard immunosuppression.</p> <p>IVIg therapy may be considered for immune-mediated, sight-threatening uveitis with persistent activity despite both oral corticosteroid and systemic immunosuppressive therapy. Uveitis of non-immune origin is not indicated.</p> <p>Recommended dose is 1.5g/kg/month for 3 months, with further maintenance dependant upon evidence of significant improvement in visual acuity and ocular inflammation.</p> <p>Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.</p>
Level of evidence	Category 4a – Small case studies only – insufficient data.

Medical condition	BULLOUS PEMPHIGOID (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Indication for IVIg use	Bullous pemphigoid resistant to topical and systemic glucocorticoids and immunosuppressive therapy.
Level of evidence	Category 4a – Small case studies only – insufficient data.
Description and diagnostic criteria	<p>BP is a rare disease of elderly people characterised by tense blisters and vesicles with a prominent inflammatory component. The cause is unknown. Lesions result from a failure of basal keratinocytes to adhere to the epidermal basement membrane.</p> <p>The course of BP is characterised by exacerbations and remissions. Pruritis is a common feature and an increase in pruritis may herald an exacerbation.</p> <p>In most patients, BP is not a life-threatening disease. The side effects of systemic immunosuppressive therapy need to be managed. In most patients, the disease spontaneously clears within 6 years and all medication can be stopped. In a small group the disease recurs after treatment is stopped. Skin infection is the most common complication.</p> <p>A submission by the Australasian College of Dermatologists (ACD) recommends IVIg use in BP only in severe cases where improvement with conventional therapy is not readily achieved.</p>

Medical condition	BULLOUS PEMPHIGOID (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Qualifying criteria	<p>Moderate to severe disease diagnosed by a dermatologist; AND</p> <ol style="list-style-type: none"> 1. Corticosteroids or immunosuppressive agents are contraindicated; <p>OR</p> <ol style="list-style-type: none"> 2. Condition is unresponsive to corticosteroids and immunosuppressive agents; <p>OR</p> <ol style="list-style-type: none"> 3. Presenting with severe side effects of therapy.
Review criteria	<ul style="list-style-type: none"> • Response demonstrated at review at 6 months. Improvement to be demonstrated for continuation of supply. • Reduction in recurrence of disease or relapse. • Ability to reduce dose or discontinue other therapies. • Improved quality of life. • Resolution of blisters and healing of affected skin. • Resolution of pruritis.
Dose	<p>Efficacy demonstrated with doses of at least 2g/kg per monthly treatment cycle.</p> <p>Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.</p>

Medical condition	CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME (Condition for which IVIg use is in <i>exceptional</i> circumstances only)
Indication for IVIg use	IVIg is appropriate therapy for the well-defined situation of catastrophic antiphospholipid syndrome. It is not indicated for the treatment of antiphospholipid syndrome in most other cases. Refer to the current product information sheet for further information.
Level of evidence	Category 4a – Small case studies only – insufficient data.

Medical condition	CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (Condition for which IVIg has an <i>established</i> therapeutic role)
Indication for IVIg use	First-line treatment for CIDP with treatment initiated when progression is rapid, or walking is compromised, or there is significant functional impairment.
Level of evidence	Category 1 – High-quality RCTs – Clear evidence of benefit.
Description and diagnostic criteria	<p>Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired sensorimotor polyneuropathy characterised by a progressive or relapsing/ remitting course with evidence of demyelination on electrophysiological or pathological studies and response to immunomodulating therapies.</p> <p>There is no specific diagnostic test but characteristic clinical and laboratory findings help distinguish this disorder from other immune mediated neuropathic syndromes. Serum protein electrophoresis with immunofixation may be indicated to search for monoclonal gammopathy and associated conditions.</p>
Qualifying criteria	<ol style="list-style-type: none"> 1. Diagnosis of CIDP verified by a neurologist; <p>AND</p> <ol style="list-style-type: none"> 2. Significant functional impairment of activities of daily living.

Medical
condition

**CHRONIC INFLAMMATORY DEMYELINATING
POLYNEUROPATHY**

(Condition for which IVIg has an *established*
therapeutic role)

Review
criteria

IVIg should be used for 3–6 months (3–6 courses) before determining whether the patient has responded. Most individuals will respond within 3 months unless there is significant axonal degeneration whereby a 6-month course will be necessary.

If there is no benefit after 3–6 courses, IVIg therapy should be abandoned.

Review

Regular review by neurologist is required: frequency as determined by clinical status of patient.

For stable patients on maintenance treatment review by a neurologist is required at least annually.

Effectiveness

Clinical documentation of effectiveness is necessary for continuation of IVIg therapy.

Effectiveness can be demonstrated by objective findings of either:

1. Improvement in functional scores (ADLs) or quantitative muscle scores or Medical Research Council (MRC) muscle assessment or neuropathy score;

OR

2. Stabilisation of disease as defined by stable functional scores (ADLs) or quantitative muscle scores or MRC muscle assessment or neuropathy score after previous evidence of deterioration in one of these scores.

Medical condition	CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (Condition for which IVIg has an <i>established</i> therapeutic role)
Dose	<i>Induction:</i> 2g/kg in 2 to 5 divided doses. <i>Maintenance:</i> 0.4–1g/kg 2–6 weekly. The amount per dose should be titrated to the individual’s response. Aim for <i>minimum dose</i> to maintain optimal functional status. Refer to the current product information sheet for further information.

Medical condition	CICATRICIAL PEMPHIGOID (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Indication for IVIg use	Cicatricial pemphigoid resistant to glucocorticoid and immunosuppressive therapy.
Level of evidence	Category 2a – Some RCTs and/or case studies – Evidence of probable benefit – more research needed.
Description and diagnostic criteria	<p>Cicatricial pemphigoid (CP) or mucous membrane pemphigoid (MMP) is a rare, acquired sub-epithelial blistering disease characterised by erosive lesions of mucous membranes and skin. Serious complications may occur due to erosions and scarring.</p> <p>Hoarseness, pain, tissue loss and even upper airway destruction can occur with nasopharyngeal or laryngeal involvement, and oesophageal and urogenital lesions may lead to stenosis or strictures. CP is usually a chronic, progressive disorder.</p> <p>The aim of long-term treatment is cessation of the self-destructive autoimmune process. Failure to do so results in invariable progression of the disease, culminating in progressive scarring. Permanent remission is usually possible if the disease is diagnosed early and treated sufficiently for 1–5 years.</p> <p>For the 70% of patients who have eye involvement the disease progresses to conjunctival scarring and shrinkage, but may take 10–20 years to reach the end stage of bilateral blindness.</p>

Medical condition	CICATRICAL PEMPFIGOID (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Qualifying criteria	<p>Moderate to severe disease diagnosed by a dermatologist; AND</p> <ol style="list-style-type: none"> 1. Corticosteroids or immunosuppressive agents are contraindicated; <p>OR</p> <ol style="list-style-type: none"> 2. Condition is unresponsive to corticosteroids and immunosuppressive agents; <p>OR</p> <ol style="list-style-type: none"> 3. Presenting with severe side effects of therapy.
Review criteria	<ul style="list-style-type: none"> • Response demonstrated at review at 6 months. Improvement to be demonstrated for continuation of supply. • Disease recurrence or relapse and duration of clinical remission. • Ability to reduce dose or discontinue other therapies. • Resolution of conjunctival inflammation. • Reduction of drug-related side effects.
Dose	<p>Efficacy demonstrated with doses of at least 2g/kg per monthly treatment cycle.</p> <p>Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.</p>

Medical condition

COAGULATION FACTOR INHIBITORS
(Condition for which IVIg use is in *exceptional* circumstances only)

Indication for IVIg use

Management of these rare and severe bleeding disorders should be undertaken only by or in consultation with haemophilia treatment centres. When indicated, IVIg only forms part of the management of these complex patients, with additional haemostatic support required.

IVIg may be considered in the following circumstances:

1. Inhibitors to factor VIII (FVIII) in haemophilia A and inhibitors to factor IX (FIX) in haemophilia B, especially in cases where there has been failure of immune tolerisation and poor response to recombinant factor VIIa or Factor Eight Inhibitor Bypassing Activity (FEIBA) – only as part of Malmö protocol for immune tolerance induction.
2. Autoimmune acquired von Willebrand syndrome (AVWS) – correction of FVIII and von Willebrand factor (VWF) levels for the management of bleeding and prior to invasive procedures, except cases associated with IgM paraprotein where response is unlikely. Use is indicated in failure to respond to chemotherapy/immunosuppressants or where there is insufficient time for chemotherapy/immunosuppressants to be given. Initial therapy either 0.4g/kg for 5 days or 1g/kg for 2 days. Continued therapy 1g/kg once every 3 to 4 weeks.
3. Acquired haemophilia A for:
 - a. support of correction of FVIII level for the management of bleeding and prior to invasive procedures in individuals in whom steroid or immunosuppressive therapy is contraindicated or has failed to eradicate the inhibitor (2g/kg over 2 to 5 days); or

Medical condition	COAGULATION FACTOR INHIBITORS (Condition for which IVIg use is in <i>exceptional</i> circumstances only)
Indication for IVIg use <i>(continued)</i>	<p>b. support of correction of FVIII level following failure of first line therapies (steroids and immunosuppressants) and poor response to recombinant factor VIIa or FEIBA when used as part of the Bonn–Malmö protocol.</p> <p>4. Other acquired (autoimmune) coagulation inhibitors, e.g. acquired Factor V inhibitors – to correct factor level for the management of bleeding and prior to invasive procedures in cases where other therapeutic approaches have failed or are contraindicated (2g/kg over 2 to 5 days).</p> <p>Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.</p>
Level of evidence	Category 2a – Some RCTs and/or case studies – Evidence of probable benefit – more research needed.

Medical condition	DEVIC DISEASE (neuromyelitis optica) (Condition for which IVIg use is in <i>exceptional</i> circumstances only)
Indication for IVIg use	<p>Devic disease is an idiopathic inflammatory demyelinating disorder of the central nervous system characterised by recurrent bouts of optic neuritis and myelitis. It is distinct from multiple sclerosis and evidence of B-cell autoimmunity has been found. A circulatory antibody to aquaporin-4 is found in many patients providing further evidence of B-cell autoimmunity in its pathogenesis and suggestive of a role for IVIg therapy. Single case reports of various therapies, including IVIg has shown variable benefit in this otherwise devastating disorder.</p> <p>Refer to the current product information sheet for further information.</p>
Level of evidence	Category 4a – Small case studies only – insufficient data.

Medical condition	EPIDERMOLYSIS BULLOSA ACQUISITA (Condition for which IVIg use is in <i>exceptional</i> circumstances only)
Indication for IVIg use	IVIg should be considered for severe cases refractory to conventional immunosuppressive therapy. Refer to the current product information sheet for further information.
Level of evidence	Category 4a – Small case studies only – insufficient data.

Medical condition	EPILEPSY (Condition for which IVIg use is in <i>exceptional</i> circumstances only)
Indication for IVIg use	<ul style="list-style-type: none"> • Rasmussen syndrome. • Landau-Kleffner syndrome. • Lennox-Gastaut syndrome. <p>IVIg should be considered only in rare childhood cases.</p> <p>Refer to the current product information sheet for further information.</p>
Level of evidence	<p>Category 2a – Some RCTs and/or case studies</p> <p>– Evidence of probable benefit – more research needed.</p>

Medical condition	EVANS SYNDROME (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Indication for IVIg use	To reduce platelet destruction and improve haemolysis in patients not responding to corticosteroid therapy.
Level of evidence	Category 4a – Small case studies only – insufficient data.
Description and diagnostic criteria	<p>Evans syndrome is a rare but serious autoimmune disease defined by the simultaneous or sequential occurrence of autoimmune haemolytic anaemia (AIHA) and immune thrombocytopenia (ITP) without underlying aetiology. As such, it is a diagnosis of exclusion and other disorders such as collagen vascular diseases, especially systemic lupus erythematosus (SLE) and scleroderma should be ruled out.</p> <p>The 2005 review by Norton and Roberts provides perspective on diagnosis, clinical features and management.</p>
Qualifying criteria	<p>Evans syndrome:</p> <ol style="list-style-type: none"> 1. Refractory to conventional therapy with corticosteroids; <p>OR</p> <ol style="list-style-type: none"> 2. Where corticosteroids are contraindicated; <p>OR</p> <ol style="list-style-type: none"> 3. As a temporising measure prior to splenectomy.
Exclusion criteria	Patients in whom a trial of corticosteroids has not been undertaken (providing corticosteroids are not contra-indicated and can be tolerated at the required doses).

Medical condition	EVANS SYNDROME (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Review criteria	<ul style="list-style-type: none"> • Maintenance therapy rarely required. • Resolution of haemolytic anaemia. • Improvement in platelet count. • Clinical improvement in symptoms and signs.
Dose	<p>Up to 2g/kg in divided dose.</p> <p>Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.</p>

Medical condition	FOETO-MATERNAL/NEONATAL ALLOIMMUNE THROMBOCYTOPENIA (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Indication for IVIg use	Prevention or treatment of foetal or neonatal thrombocytopenia or haemorrhage.
Level of evidence	Category 4a – Small case studies only – insufficient data.
Description and diagnostic criteria	<p>FMAIT develops because of maternal sensitisation to foetal platelets that possess a paternally inherited antigen. In Caucasians, the antigen is HPA-1a in 80% of cases and HPA-5b in 15%, but other antigens are also implicated. The mother's antibodies cross the placenta and coat the baby's platelets, with accelerated platelet clearance leading to thrombocytopenia. This may result in serious and potentially life threatening bleeding in the foetus or neonate. Pathogenesis is analogous to that of haemolytic disease of the newborn due to red cell antigen-antibody incompatibility.</p> <p>The aim of management of the thrombocytopenic foetus or neonate is to increase the platelet count.</p> <p>If foetal blood sampling reveals thrombocytopenia, IVIg may be administered weekly to the mother, with or without steroids, until delivery. Recent studies using IVIg weekly from around 20 weeks' gestation, without foetal blood sampling, have shown reduced foetal and neonatal morbidity. This approach may be used for current pregnancies where the condition in a previous pregnancy was not associated with a foetal death or severe haemorrhage. Testing on maternal blood for foetal DNA or early genetic testing of the foetus (for platelet genotype) may predict the need to use IVIg.</p>

Medical condition**FOETO-MATERNAL/NEONATAL ALLOIMMUNE THROMBOCYTOPENIA**

(Condition for which IVIg has an *emerging* therapeutic role)

Description and diagnostic criteria

(continued)

Management of this condition is a specialised area and may include administration of HPA-compatible intrauterine and/or neonatal platelet transfusions. Further information regarding specialised platelet support is available from the Australian Red Cross Blood Service. Random (non-HPA-matched) platelets may be of benefit in the neonatal setting when matched platelets are not available (Kiefel, 2006).

Qualifying criteria

Clinical suspicion of FMAIT in antenatal or neonatal setting based on clinical and laboratory features, including:

1. Thrombocytopenia or spontaneous haemorrhage in the foetus;

OR

2. Thrombocytopenia with or without haemorrhage in the neonate;

OR

3. Unexplained foetal death in a previous pregnancy and the presence of maternal platelet-specific alloantibodies that are known or suspected to cause this condition (most commonly HPA-1a or HPA-5b).

Medical condition	FOETO-MATERNAL/NEONATAL ALLOIMMUNE THROMBOCYTOPENIA (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Review criteria	<ul style="list-style-type: none"> • Foetal or neonatal morbidity and mortality in the context of maternal alloantibodies. • Occurrence and severity of thrombocytopenia in the neonate. • Maternal HPA-1a antibody level (if assay is available). Note that the strength/titre of maternal antibody level, even if available, is not proven clinically relevant and not able to be compared readily between laboratories at this time.
Dose	<p><i>Maternal dose:</i> 1g/kg weekly throughout pregnancy, with starting time tailored to individual risk profile and history if relevant. Other doses and schedules have been used and some studies have used IVIg in conjunction with steroids.</p> <p><i>Treatment of the neonate:</i> 1g/kg. Occasionally more than one dose is required if thrombocytopenia persists.</p> <p>Refer to the current product information sheet for further information.</p>

Medical condition	GRAVES OPHTHALMOPATHY (Condition for which IVIg use is in <i>exceptional circumstances only</i>)
Indication for IVIg use	<p>IVIg may be indicated in select cases. Tagami <i>et al</i> have shown that IVIg is effective in this condition. Other studies have shown IVIg to be as effective as corticosteroids with fewer side effects. May be indicated where steroids have failed or are contraindicated.</p> <p>Refer to the current product information sheet for further information.</p>
Level of evidence	<p>Category 2a – Some RCTs and/or case studies</p> <p>– Evidence of probable benefit – more research needed.</p>

Medical condition	GUILLAIN-BARRÉ SYNDROME (Condition for which IVIg has an <i>established</i> therapeutic role)
Indication for IVIg use	GBS and its variants with significant disability and progression.
Level of evidence	Category 1 – High-quality RCTs – Clear evidence of benefit.
Description and diagnostic criteria	<p>GBS is the commonest cause of acute flaccid paralysis in the West. The syndrome typically presents with rapidly progressive, relatively symmetrical ascending limb weakness consistent with a polyradiculoneuropathy and often with associated cranial nerve involvement.</p> <p>Motor signs and symptoms usually predominate over sensory signs and symptoms. Loss of tendon reflexes occurs in most cases. Major complications include respiratory failure and autonomic dysfunction.</p> <p>The disease is monophasic, reaching its nadir usually within 2 weeks, although arbitrary definition accepts a limit of 4 weeks. A plateau phase of variable duration follows the nadir before gradual recovery. Although recovery is generally good or complete in the majority of patients, persistent disability has been reported to occur in about 20% and death in 4 to 15% of patients.</p> <p>IVIg has been shown to have the same efficacy as plasma exchange. The choice is based on availability, practicality, convenience, cost and ease or safety of administration (Asia-Pacific IVIg Advisory Group).</p> <p><i>Investigations</i></p> <p>There is no biological marker for GBS. It is diagnosed by clinical recognition of rapidly evolving paralysis with areflexia. Investigations include:</p>

Medical condition	GUILLAIN-BARRÉ SYNDROME (Condition for which IVIg has an <i>established</i> therapeutic role)
Description and diagnostic criteria <i>(continued)</i>	<ul style="list-style-type: none"> • CSF protein elevation, although the level may be normal in the first 2 weeks of illness. The CSF white cell count may rise transiently, but a sustained pleocytosis suggests an alternative diagnosis or association with an underlying illness e.g. HIV. • Electrophysiological studies may show changes after the first or second week of the illness, including conduction block, conduction slowing or abnormalities in F waves.
Qualifying criteria	<p>Patients with GBS (or variant) with significant disability and disease progression.</p> <p><i>Note:</i> Assessment by a neurologist is recommended, but not mandatory.</p>
Review criteria	<p><i>Primary outcome measures</i></p> <p>Improvement in disability grade 4 weeks after treatment:</p> <ul style="list-style-type: none"> (0) healthy (1) minor symptoms or signs of neuropathy but capable of manual work (2) able to walk without support of a stick but incapable of manual work (3) able to walk with a stick, appliance or support (4) confined to bed or chair bound (5) requiring assisted ventilation (6) dead

Medical condition	GUILLAIN-BARRÉ SYNDROME (Condition for which IVIg has an <i>established</i> therapeutic role)
Review criteria <i>(continued)</i>	<p><i>Secondary outcome measures:</i></p> <ol style="list-style-type: none"> (1) time until recovery of unaided walking (2) time until recovery of walking with aid (3) time until discontinuation of ventilation (for those ventilated) (4) death or disability (inability to walk without aid after 12 months) (5) treatment-related fluctuation
Dose	<p>2g/kg in 2 to 5 divided doses.</p> <p>Approximately 10% of patients relapse, which may require a second treatment with IVIg. A second dose of IVIg must only be on the advice of and after assessment by a neurologist.</p> <p>Refer to the current product information sheet for further information.</p>

Medical condition	HAEMOLYTIC DISEASE OF THE NEWBORN (Condition for which IVIg use is in <i>exceptional</i> circumstances only)
Indication for IVIg use	<p>Haemolytic disease of the newborn (HDN) arises from foetomaternal antigen incompatibility and can result in clinically significant foetal/neonatal haemolysis, severe anaemia and hyperbilirubinaemia.</p> <p>Although prophylaxis programs have reduced the frequency of Rhesus (Rh) D HDN, antibodies to RhD remain the most common cause in Australia. Antibodies to other antigens in the Rh system (e.g. Rhc, E), ABO and other antigens (e.g. K) may also cause disease ranging from mild to life threatening.</p> <p>IVIg may be used in selected cases in consultation with experts in foetomaternal medicine and transfusion medicine. Hammerman <i>et al</i> (1996) identified some factors that may predict response to IVIg.</p> <p>Refer to the current product information sheet for further information.</p>
Level of evidence	Category 4a – Small case studies only – insufficient data.

Medical condition	HAEMOLYTIC TRANSFUSION REACTION (Condition for which IVIg use is in <i>exceptional</i> circumstances only)
Indication for IVIg use	IVIg may be considered in the management or prevention of severe haemolytic transfusion reaction not responding to other interventions (e.g. corticosteroids). Refer to the current product information sheet for further information.
Level of evidence	Category 4a – Small case studies only – insufficient data.

Medical condition	HAEMOPHAGOCYTIC SYNDROME (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Indication for IVIg use	Management of severe haemophagocytic syndrome not responding to other treatments.
Level of evidence	Category 4a – Small case studies only – insufficient data.
Description and diagnostic criteria	Haemophagocytic syndrome is characterised by fever, splenomegaly, jaundice, rash and the pathologic finding of haemophagocytosis (phagocytosis by macrophages of erythrocytes, leukocytes, platelets and their precursors) in bone marrow and other tissues with peripheral blood cytopenias. Haemophagocytic syndrome has been associated with a wide range of infectious, autoimmune, malignant and other disorders (modified from Fisman, 2000). Mortality is high.
Qualifying criteria	<p>Bone marrow diagnosis or other biopsy evidence of haemophagocytosis in the characteristic clinical setting.</p> <p><i>Note:</i> Since other therapies (cytotoxic agents) have major potential side effects optimal therapy is not yet defined.</p>
Review criteria	<ul style="list-style-type: none"> • Amelioration of cytopenia(s), hepato/splenomegaly and lymphadenopathy if present. • Survival or death.
Dose	<p>2g/kg is the most widely published dose.</p> <p>Emmenegger <i>et al</i> reported that better outcomes were associated with early administration of IVIg in their small series (10 patients).</p> <p>Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.</p>

Medical condition	HIGH-RISK ALLOGENEIC HAEMOPOIETIC STEM CELL TRANSPLANTATION (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Indication for IVIg use	Prevention of graft-versus-host disease in high-risk allogeneic haemopoietic stem cell transplantation (mismatched family or unrelated donor).
Level of evidence	Category 2c – Conflicting evidence of benefit.
Description and diagnostic criteria	<p>HSCT involves eliminating an individual's haemopoietic and immune system by chemotherapy and/or radiotherapy and replacing it with stem cells. The transplanted stem cells may be from another individual (allogeneic) or they may have been previously harvested from the patient (autologous). HSCT encompasses bone marrow transplantation (where stem cells are collected from the bone marrow) or peripheral blood stem cell transplantation (where stem cells are collected from peripheral blood).</p> <p>Human leukocyte antigen (HLA) compatibility between donor and recipient is an essential prerequisite to allogeneic transplants. Apart from graft failure, a complication of allogeneic transplants is graft-versus-host disease (GvHD).</p> <p>The incidence of GvHD varies among clinical units. Several factors influence its occurrence, including: the degree of major histocompatibility complex mismatch; age; and sex-matched donors and recipients versus sex-mismatched donors and recipients.</p>

Medical condition	HIGH-RISK ALLOGENEIC HAEMOPOIETIC STEM CELL TRANSPLANTATION (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Description and diagnostic criteria <i>(continued)</i>	Acute GvHD is a primary or contributory cause of death in 15–40% of patients who develop GvHD. The risk of death is directly related to severity. Chronic GvHD occurs in 15–50% of patients who survive 3 months after transplantation. Chronic GvHD most commonly occurs as a transition from acute GvHD, but it can occur <i>de novo</i> in 20–30% of patients. Bronchiolitis obliterans contributes to mortality; sepsis remains the most common cause in patients who die with chronic GvHD.
Qualifying criteria	High-risk allogeneic transplants from unrelated donors, mismatched family donors or multiple cord blood donations.
Exclusion criteria	<ol style="list-style-type: none"> 1. Autologous transplants (except where the patient has established humoral deficiency). 2. Uncomplicated matched sibling transplantation.
Review criteria	<ul style="list-style-type: none"> • Review no later than 3 months post transplant. • Occurrence of GvHD. • Grade and severity of GvHD.
Dose	<p>0.4 g/kg weekly, starting one day before transplantation and continuing to day 100 post-transplant.</p> <p>Refer to the current product information sheet for further information.</p>

Medical condition	HIV IN CHILDREN (Condition for which IVIg use is in <i>exceptional</i> circumstances only)
Indication for IVIg use	<p>The need for IVIg in paediatric HIV has been substantially reduced with the advent of highly active antiretroviral therapy (HAART). A trial of therapy may however be considered in children with significant recurrent bacterial infections despite HAART.</p> <p>Refer to the current product information sheet for further information.</p>
Level of evidence	<p>Category 2a – Some RCTs and/or case studies – Evidence of probable benefit – more research needed.</p>

Medical condition	IgM PARAPROTEINAEMIC NEUROPATHY (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Indication for IVIg use	Patients with IgM paraproteinaemic neuropathy with functional impairment in whom other therapies have failed or are contraindicated or undesirable.
Level of evidence	Category 2c – Conflicting evidence of benefit.
Description and diagnostic criteria	<p>IgM paraproteinaemic neuropathy is a slowly progressive, predominantly sensory neuropathy that may eventually produce disabling motor symptoms. The condition is associated with IgM_k paraprotein, which is a monoclonal antibody to myelin associated glycoprotein (MAG).</p> <p>IgM paraproteinaemic neuropathy is the most common subgroup of the Monoclonal Gammopathy of Undetermined Significance (MGUS) group. It is distinguishable from CIDP by:</p> <ul style="list-style-type: none"> • the presence of tremor; • a greater severity of sensory loss, with ataxia and relatively mild or no weakness; • damage tends to be permanent and the degree of improvement in IgM paraproteinaemic neuropathy is much smaller than the improvement observed in CIDP patients. <p>Nerve conduction studies usually show uniform symmetrical conduction slowing with prolonged distal latencies and distal attenuation (distal index is prolonged).</p> <p>Test for antibodies to neural antigens (MAG or other neural antigens) may be helpful.</p>

Medical condition	IgM PARAPROTEINAEMIC NEUROPATHY (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Qualifying criteria	<p>Diagnosis by a neurologist of IgM paraproteinaemic neuropathy with:</p> <ol style="list-style-type: none"> 1. Functional impairment of activities of daily living; <p>AND</p> <ol style="list-style-type: none"> 2. Other therapies have failed or are contraindicated or undesirable.
Review criteria	<p>IVIg should be used for 3–6 months (3–6 courses) before determining whether the patient has responded. If there is no benefit after 3–6 courses, IVIg therapy should be abandoned.</p> <p><i>Review</i></p> <p>Regular review by neurologist is required: Frequency as determined by clinical status of patient.</p> <p>For stable patients on maintenance treatment review by a neurologist is required at least annually.</p> <p><i>Effectiveness</i></p> <p>Clinical documentation of effectiveness is necessary for continuation of IVIg therapy.</p> <p>Effectiveness can be demonstrated by objective findings of either:</p> <ol style="list-style-type: none"> 1. Improvement in functional scores (ADLs) or quantitative muscle scores or MRC muscle assessment or neuropathy score; or 2. Stabilisation of disease as defined by stable functional scores (ADLs) or quantitative muscle scores or MRC muscle assessment or neuropathy score after previous evidence of deterioration in one of these scores.

Medical
condition

IgM PARAPROTEINAEMIC NEUROPATHY
(Condition for which IVIg has an *emerging*
therapeutic role)

Dose

Induction: 2g/kg in 2-5 divided doses.

Maintenance: 0.4-1g/kg 2 to 6 weekly.

Maintenance treatment only with clear, objective improvement.

Aim for *minimum* dose to maintain optimal functional status.

Refer to the current product information sheet for further information.

Medical condition	INFLAMMATORY MYOPATHIES (Condition for which IVIg has an <i>established</i> therapeutic role)
Indication for IVIg use	<ol style="list-style-type: none"> 1. Patients with PM or DM with significant muscle weakness unresponsive to corticosteroids and other immunosuppressive agents. 2. Patients with IBM who have dysphagia affecting function. 3. Patients with rapidly progressive IBM.
Level of evidence	Category 2a – Some RCTs and/or case studies – Evidence of probable benefit – more research needed.
Description and diagnostic criteria	<p>The inflammatory myopathies are a group of three discrete disorders of skeletal muscle – dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (IBM).</p> <p>These disorders are acquired and have in common the occurrence of significant muscle weakness and the presence of an inflammatory response within the muscle.</p> <p>The diagnosis of DM, PM or IBM is usually made by neurologists or rheumatologists and relies on the combination of careful clinical evaluation, an elevated creatine kinase level, electromyography, and muscle biopsy.</p>
Qualifying criteria	<p>Diagnosis made by a neurologist, rheumatologist, or immunologist of:</p> <ol style="list-style-type: none"> 1. Patients with PM or DM who have significant muscle weakness or dysphagia and have not responded to corticosteroids and other immunosuppressive agents;

Medical condition	INFLAMMATORY MYOPATHIES (Condition for which IVIg has an <i>established</i> therapeutic role)
Qualifying criteria <i>(continued)</i>	<p>OR</p> <p>2. Patients with IBM who have dysphagia affecting nutrition;</p> <p>OR</p> <p>3. Patients with rapidly progressive IBM.</p>
Exclusion criteria	Expert consensus does not recommend IVIg to treat the limb weakness of IBM.
Review criteria	<p>IVIg should be used for 3–6 months (3–6 courses) before determining whether the patient has responded. If there is no benefit after 3–6 courses, IVIg therapy should be abandoned.</p> <p><i>Review</i></p> <p>Regular review by a neurologist is required: frequency as determined by clinical status of patient.</p> <p>For stable patients on maintenance treatment review by a neurologist is required at least annually.</p> <p><i>Effectiveness</i></p> <p>Clinical documentation of effectiveness is necessary for continuation of IVIg therapy.</p> <p>Effectiveness can be demonstrated by objective findings of either:</p> <ol style="list-style-type: none"> 1. Improvement in functional scores (ADLs) or quantitative muscle scores or Medical Research Council (MRC) muscle assessment; OR 2. Stabilisation of disease as defined by stable functional scores (ADLs) or quantitative muscle scores or MRC muscle assessment after previous evidence of deterioration in one of these scores.

Medical
condition

INFLAMMATORY MYOPATHIES
(Condition for which IVIg has an *established*
therapeutic role)

Dose

Induction: 2g/kg in 2 to 5 divided doses.

Maintenance: 0.4–1g/kg 4–6 weekly.

Aim for the *minimum* dose to maintain optimal functional status.

Refer to the current product information sheet for further information.

Medical condition	ITP IN ADULTS (including thrombocytopenia arising as a result of HIV infection) (Condition for which IVIg has an <i>established</i> therapeutic role)
Indication for IVIg use	<ol style="list-style-type: none"> 1. Refractory ITP: Patients with severe thrombocytopenia (platelets $<30 \times 10^9/L$) who have not responded to corticosteroid therapy. 2. ITP with life-threatening haemorrhage: Patients with severe thrombocytopenia ($<30 \times 10^9/L$) with clinical evidence of a haemostatic defect (e.g. mucous membrane haemorrhage) or active bleeding. 3. ITP in pregnancy: <ol style="list-style-type: none"> a. Platelets $<30 \times 10^9/L$. b. Impending delivery. 4. Specific circumstances: <ol style="list-style-type: none"> a. Planned surgery. b. Severe ITP (platelets $<30 \times 10^9/L$) where corticosteroids and immunosuppression are contraindicated. c. Chronic refractory ITP. 5. HIV – associated ITP: Patients with severe ITP associated with HIV infection.
Level of evidence	Category 2a – Some RCTs and/or case studies – Evidence of probable benefit – more research needed.
Description and diagnostic criteria	Idiopathic (autoimmune) thrombocytopenic purpura is a reduction in platelet count (thrombocytopenia) resulting from shortened platelet survival due to anti-platelet antibodies. When counts are very low ($<30 \times 10^9/L$) bleeding into the skin (purpura) and mucous membranes can occur. Bone

Medical condition	ITP IN ADULTS (including thrombocytopenia arising as a result of HIV infection) (Condition for which IVIg has an <i>established</i> therapeutic role)
<p>Description and diagnostic criteria <i>(continued)</i></p>	<p>marrow platelet production (megakaryopoiesis) is morphologically normal. In some cases, there is additional impairment of platelet function related to antibody binding to glycoproteins on the platelet surface. ITP is divided into chronic and acute forms. It is a common finding in patients with HIV and while it may be found at any stage of the infection its prevalence increases as HIV disease advances.</p> <p>Around 80% of adults with ITP have the chronic form of disease. The highest incidence of chronic ITP is in women aged 15–50 years, although some reports suggest increasing incidence with age.</p> <p>Chronic ITP may relapse and remit spontaneously and the course may be difficult to predict. If the platelet count can be maintained at a level that prevents spontaneous bleeding or bruising the outlook is good.</p>
<p>Qualifying criteria</p>	<p>1. Refractory ITP:</p> <ol style="list-style-type: none"> a. Patients qualify for initial IVIg therapy when conventional doses of corticosteroids have failed. The objective of therapy is to induce a prompt increase in the platelet count ($>30 \times 10^9/L$) while other therapies are introduced. b. Patients qualify for continuing doses when splenectomy has failed or is contraindicated AND where therapy with at least one immunosuppressive agent and dapsone has been unsuccessful in maintaining a platelet count $>30 \times 10^9/L$.

Medical condition

ITP IN ADULTS (including thrombocytopenia arising as a result of HIV infection)
(Condition for which IVIg has an *established* therapeutic role)

Qualifying criteria
(continued)

With ongoing therapy, IVIg may be administered to achieve a platelet count $>30 \times 10^9/L$. Further doses may be administered in responsive patients for up to six months (thereafter see 'chronic refractory ITP'). The frequency and dose should be titrated to maintain a platelet count of at least $30 \times 10^9/L$. The objective of therapy is to maintain a safe platelet count while other therapeutic options are explored.

2. ITP with life-threatening haemorrhage:

IVIg therapy may be given when conventional doses of corticosteroids have failed. The objective of therapy is to induce a prompt increase in the platelet count ($>30 \times 10^9/L$) while other therapies are introduced.

3. ITP in pregnancy:

- a. Platelets $<30 \times 10^9/L$: IVIg therapy may be used to avoid corticosteroids, immunosuppressive agents and splenectomy. Further doses titrated to maintain a platelet count $>30 \times 10^9/L$ may be administered every three to four weeks throughout the pregnancy.
- b. Impending delivery: IVIg therapy may be used to achieve a platelet count considered safe for delivery ($80-100 \times 10^9/L$).

4. Specific circumstances:

- a. Planned surgery: IVIg may be used to achieve a platelet count considered safe for surgery. The safe threshold will vary with the nature of the surgery ($50-100 \times 10^9/L$).

Medical condition	ITP IN ADULTS (including thrombocytopenia arising as a result of HIV infection) (Condition for which IVIg has an <i>established</i> therapeutic role)
Qualifying criteria <i>(continued)</i>	<p>b. Severe ITP: IVIg may be used where corticosteroids and immunosuppression are contraindicated.</p> <p>c. Chronic refractory ITP unresponsive to all other available therapies: these patients may be considered for long-term maintenance therapy with IVIg subject to regular review by a haematologist.</p> <p>5. HIV associated ITP:</p> <p>a. Failure of antiretroviral therapy with platelet count $<30 \times 10^9/L$;</p> <p>OR</p> <p>b. Life-threatening haemorrhage secondary to thrombocytopenia.</p>
Review criteria	<ul style="list-style-type: none"> • In chronic refractory ITP, 6-month review assessing evidence of clinical benefit. • Resolution of bleeding. • Increment in platelet count.
Dose	<p><i>Initial therapy:</i> 1–2g/kg as a single or divided dose.</p> <p><i>Ongoing therapy:</i> When indicated, 1–2g/kg in single or divided dose at 4 to 6 weekly intervals titrated to symptoms and platelet count.</p> <p>Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.</p>

Medical condition	ITP IN CHILDREN (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Indication for IVIg use	ITP with platelet count $<30 \times 10^9/L$ with significant bleeding.
Level of evidence	Category 1 – High-quality RCTs – Clear evidence of benefit.
Description and diagnostic criteria	<p>Idiopathic (autoimmune) thrombocytopenic purpura is a reduction in platelet count (thrombocytopenia) resulting from shortened platelet survival due to anti-platelet antibodies. When counts are very low ($<30 \times 10^9/L$) bleeding into the skin (purpura) and mucous membranes can occur. Bone marrow morphology is normal. In some cases, there is additional impairment of platelet function related to antibody binding to glycoproteins on the platelet surface. ITP is divided into chronic and acute forms. In children the acute form is the most common. The disease tends to present abruptly with dramatic evidence of bleeding into the skin (petechiae and purpura) and mucous membranes (gum bleeding, nose bleeds, blood blisters).</p> <p><i>Occurrence</i></p> <p>Girls and boys are affected equally. In 75% of patients, the episode follows vaccination or a viral infection such as varicella or infectious mononucleosis.</p> <p><i>Prognosis</i></p> <p>At least 80–90% of children will have spontaneous remission of their disease within 6–12 months. In 5–10% of cases, the disease may become chronic (lasting > 6 months). Morbidity and mortality from acute ITP is very low.</p>

Medical condition	ITP IN CHILDREN (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Qualifying criteria	<p><i>Note:</i> While the effectiveness of IVIg is not disputed, clinical experts advise that most children with ITP do not require IVIg therapy; indeed, no treatment at all is required for many children. Corticosteroids are the alternative therapy to IVIg.</p> <p><i>Acute ITP</i></p> <ol style="list-style-type: none"> 1. Life threatening bleeding due to thrombocytopenia; <p>OR</p> <ol style="list-style-type: none"> 2. Thrombocytopenia with platelet count $<30 \times 10^9/L$ and moderate to severe mucosal and/or cutaneous bleeding. <p><i>Chronic ITP</i></p> <ol style="list-style-type: none"> 1. Life threatening bleeding due to thrombocytopenia; <p>OR</p> <ol style="list-style-type: none"> 2. In responsive patients for treatment of thrombocytopenia ($<30 \times 10^9/L$) with moderate to severe bleeding symptoms where other therapeutic options have failed or are contraindicated; <p>OR</p> <ol style="list-style-type: none"> 3. In responsive patients given prior to surgery to elevate the platelet count to haemostatically safe levels.
Exclusion criteria	<ol style="list-style-type: none"> 1. Platelet count $>30 \times 10^9/L$. 2. Absence of significant bleeding.
Review criteria	<ul style="list-style-type: none"> • Platelet count at 48 hours. • Control or resolution of bleeding. • Duration of effect. • Progression to chronic ITP.

Medical
condition

ITP IN CHILDREN
(Condition for which IVIg has an *emerging*
therapeutic role)

Dose

Acute ITP:

Life threatening bleeding: up to 2g/kg total dose, generally given as 2 doses of 1g/kg.

Other indications: 0.5g/kg given as a single dose, repeated at 24–48 hr if the response is inadequate. 5–10% of cases may require a higher total dose of 2g/kg.

Duration of response to initial dose is typically 2–4 weeks. A repeat dose may be considered if recurrent symptomatic thrombocytopenia occurs.

Chronic ITP:

Life threatening bleeding: up to 2g/kg total dose, generally given as 2 doses of 1g/kg.

Other indications: 0.5 to 1g/kg at intervals generally >3 weekly.

Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.

Medical condition	KAWASAKI DISEASE (Condition for which IVIg has an <i>established</i> therapeutic role)
Indication for IVIg use	Early in Kawasaki disease to prevent coronary artery pathology.
Level of evidence	Category 1 – High-quality RCTs – Clear evidence of benefit.
Description and diagnostic criteria	<p>Kawasaki disease is an acute, febrile, multi-system disease of children and young infants often involving the coronary arteries. Coronary artery aneurysms may occur from the second week of illness during the convalescent stage.</p> <p>The cause of the condition is unknown but there is evidence that the characteristic vasculitis results from an immune reaction characterised by T-cell and macrophage activation to an unknown antigen, secretion of cytokines, polyclonal B-cell hyperactivity, and the formation of autoantibodies to endothelial cells and smooth muscle cells. It is likely that in genetically susceptible individuals one or more uncharacterised common infectious agents, possibly with super-antigen activity may trigger the disease.</p> <p><i>Diagnosis</i></p> <p>A diagnosis of Kawasaki disease is generally made if fever of four or more days' duration is associated with at least four of the following changes, which often appear sequentially:</p> <ul style="list-style-type: none"> • bilateral (non purulent) conjunctival infection; • changes of the mucous membranes of the upper respiratory tract and oropharynx, including diffuse redness of pharyngeal mucosa, dry fissured lips, red fissured lips, and/or 'strawberry tongue';

Medical condition**KAWASAKI DISEASE**
(Condition for which IVIg has an *established* therapeutic role)**Description and diagnostic criteria**
(continued)

- changes of the extremities, including peripheral erythema, peripheral oedema, and subsequent periungual or more generalised desquamation;
- polymorphous rash;
- cervical lymphadenopathy.

A diagnosis of Kawasaki disease may be made if fever and fewer than four of the changes listed above is present where there is strong clinical suspicion of Kawasaki disease (refer to Newburger, 2004). Between 10–20% of cases, particularly in younger infants, present with fever and less than four of the listed criteria. Expert advice should be sought.

Data support the use of IVIg while there is ongoing inflammation (usually taken as ongoing fever or raised acute inflammatory markers). Prognosis is worse if IVIg is used after 10 days post-onset, but should be used at any time if there is evidence of inflammation. Up to 15% of patients do not respond to initial IVIg therapy. Consensus is for re-treatment with 2g/kg of IVIg before considering steroids.

Qualifying criteria

Clinical diagnosis of Kawasaki disease by a paediatrician or immunologist.

Dose

2g/kg in a single dose over 10–12 hours unless cardiac function necessitates the administration of a prolonged or divided treatment dose, usually once only.

Re-treatment with 2g/kg in a single dose may be given when there is ongoing inflammation.

Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.

Medical condition	KIDNEY TRANSPLANTATION (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Indication for IVIg use	<p><i>Pre-transplantation:</i> Patients in whom an antibody or antibodies prevent transplantation (donor specific anti-HLA antibody/ies or anti-blood group antibody).</p> <p><i>Post-transplantation:</i></p> <ol style="list-style-type: none"> To treat steroid-resistant acute rejection which may be cellular or antibody mediated. For prevention and/or treatment of rejection where other therapies are contraindicated or pose a threat to the graft or patient.
Level of evidence	Category 1 – High-quality RCTs – Clear evidence of benefit.
Description and diagnostic criteria	<p>Transplant rejection occurs when a recipient's immune system attacks a transplanted organ or tissue. Despite the use of immunosuppressants, one or more episodes of rejection can occur after transplantation. Both cellular and humoral (antibody-mediated) effector mechanisms can play a role.</p> <p>The presence and pattern of rejection need to be established by biopsy. Laboratory tests to assess the presence and strength of antibodies to the donor antigens can provide additional useful information. Clinical assessment, blood tests, ultrasound and nuclear imaging are used primarily to exclude other causes of organ dysfunction.</p> <p>Acute cellular rejection occurs in between 15 and 30% of renal transplants and is responsive to steroids in over 90% of cases. When rejection is steroid resistant, IVIg is a safer therapy than anti-T cell antibody therapy with equal efficacy.</p>

Medical condition

KIDNEY TRANSPLANTATION
(Condition for which IVIg has an *emerging* therapeutic role)

Description and diagnostic criteria
(continued)

Antibody mediated rejection (AbMR) occurs in 5 to 10% of renal transplants that have been performed with a compatible cross match. Prior to the use of IVIg and plasma exchange, AbMR failed to respond adequately to therapy in the majority of cases. Additionally, complications from therapy were severe and sometimes fatal. AbMR responds to IVIg with or without plasma exchange in over 85% of patients.

Qualifying criteria

Pre-transplantation:

Patients in whom an antibody or antibodies prevent transplantation (donor specific anti-HLA antibody/ies or anti-blood group antibody);

Post-transplantation:

1. Biopsy proven cellular rejection unresponsive to steroids with clinical evidence of graft dysfunction;

OR

2. Acute antibody mediated rejection with clinical evidence of graft dysfunction;

OR

3. As treatment or prophylaxis for rejection where conventional immunosuppressive therapy is contraindicated, for example:

- in a patient with life threatening infection in whom conventional immunosuppression will place the patient at even greater risk;
- when the transplant is at risk, e.g. due to BK virus infection.

Medical condition	KIDNEY TRANSPLANTATION (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Review criteria	<ul style="list-style-type: none"> • Allograft organ function tests. • Biopsy response. • Laboratory monitoring of anti-HLA antibody and/or anti-blood group antibody responses. • Duration of graft and patient survival. • Reversal of clinical graft dysfunction.
Dose	<p><i>IVIg with plasma exchange:</i> 0.1 to 0.5g/kg post exchange.</p> <p><i>IVIg alone:</i> 2g/kg to a maximum of 140g as a single dose or 2 to 3.5 g/kg in divided dose.</p> <p>When IVIg is used alone, further doses may be warranted 2 to 4 weeks after initial therapy depending on clinical response and/or biopsy findings.</p> <p>Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.</p>

Medical condition	LAMBERT-EATON MYASTHENIC SYNDROME (Condition for which IVIg has an <i>established</i> therapeutic role)
Indication for IVIg use	Short-term therapy for severely affected non-paraneoplastic LEMS patients.
Level of evidence	Category 2a – Some RCTs and/or case studies – Evidence of probable benefit – more research needed.
Description and diagnostic criteria	<p>Lambert-Eaton myasthenic syndrome (LEMS) is a disorder of neuromuscular transmission first recognised clinically in association with lung cancer and subsequently in cases in which no neoplasm was detected.</p> <p>Patients with LEMS have a presynaptic neuromuscular junction defect. The clinical picture is characterised by proximal muscle weakness with augmentation of strength after exercise, mild oculomotor signs, depressed deep tendon reflexes and autonomic dysfunction (dry mouth, constipation, erectile failure).</p>
Qualifying criteria	<p>Mandatory assessment by a neurologist;</p> <p>AND</p> <p>Severely affected non-paraneoplastic LEMS patients in whom other therapy (e.g. with 3,4-diaminopyridine) has failed.</p>
Review criteria	<p>IVIg should be used for 3–6 months (3–6 courses) before determining whether the patient has responded. If there is no benefit after 3–6 courses, IVIg therapy should be abandoned.</p> <p><i>Review</i></p> <p>Regular review by neurologist is required: frequency as determined by clinical status of patient. Initial review 3 to 6 monthly.</p>

Medical condition	LAMBERT-EATON MYASTHENIC SYNDROME (Condition for which IVIg has an <i>established</i> therapeutic role)
Review criteria <i>(continued)</i>	<p>For stable patients on maintenance treatment review by a neurologist is required at least annually.</p> <p><i>Effectiveness</i></p> <p>Clinical documentation of effectiveness is necessary for continuation of IVIg therapy.</p> <p>Effectiveness can be demonstrated by objective findings of either:</p> <ol style="list-style-type: none"> 1. Improvement in functional scores (ADLs) or quantitative muscle scores or Medical Research Council (MRC) muscle assessment; OR 2. Stabilisation of disease as defined by stable functional scores (ADLs) or quantitative muscle scores or MRC muscle assessment after previous evidence of deterioration in one of these scores.
Dose	<p><i>Induction:</i> 2g/kg in 2 to 5 divided doses.</p> <p><i>Maintenance:</i> 0.4–1 g/kg 2–6 weekly.</p> <p>Aim for <i>minimum dose</i> to maintain optimal functional status.</p> <p>Refer to the current product information sheet for further information.</p>

Medical condition	MULTIFOCAL MOTOR NEUROPATHY (Condition for which IVIg has an <i>established</i> therapeutic role)
Indication for IVIg use	First-line therapy for MMN with persistent conduction block.
Level of evidence	Category 1 – High-quality RCTs – Clear evidence of benefit
Description and diagnostic criteria	<p>Multifocal motor neuropathy (MMN) is a relatively rare disorder characterised by slowly progressive, asymmetric, predominately distal limb weakness without sensory impairment. Weakness often begins in the arms and the combination of weakness, wasting, cramps and fasciculations may suggest a diagnosis of motor neuron disease. However, clinical examination may demonstrate that the pattern of weakness follows the distribution of individual nerves rather than a spinal segmental pattern.</p> <p>Investigations will typically show conduction block on nerve conduction studies. IgM anti-GM-1 antibodies have been reported in a large number of patients with MMN and provide confirmatory evidence but are not essential for the diagnosis.</p>
Exclusion criteria	Presence of upper motor neuron signs.
Qualifying criteria	Patients who have a multifocal motor neuropathy with persistent conduction block as diagnosed by a neurologist.
Review criteria	IVIg should be used for 3–6 months (3–6 courses) before determining whether the patient has responded. Most individuals will respond within 3 months unless there is significant axonal degeneration whereby a 6-month course will be necessary. If there is no benefit after 3–6 courses, IVIg therapy should be abandoned.

Medical condition	MULTIFOCAL MOTOR NEUROPATHY (Condition for which IVIg has an <i>established</i> therapeutic role)
Review criteria <i>(continued)</i>	<p><i>Review</i></p> <p>Regular review by neurologist is required: frequency as determined by clinical status of patient.</p> <p>For stable patients on maintenance treatment review by a neurologist is required at least annually.</p> <p><i>Effectiveness</i></p> <p>Clinical documentation of effectiveness is necessary for continuation of IVIg therapy.</p> <p>Effectiveness can be demonstrated by objective findings of either:</p> <ol style="list-style-type: none"> 1. Improvement in functional scores (ADLs) or quantitative muscle scores or Medical Research Council (MRC) muscle assessment or neuropathy score; <p>OR</p> <ol style="list-style-type: none"> 2. Stabilisation of disease as defined by stable functional scores (ADLs) or quantitative muscle scores or MRC muscle assessment or neuropathy score after previous evidence of deterioration in one of these scores.
Dose	<p><i>Induction:</i> 2g/kg in 2 to 5 divided doses.</p> <p><i>Maintenance:</i> 0.4–2g/kg 2–6 weekly. The amount per dose should be titrated to the individual's response.</p> <p>Aim for <i>minimum dose</i> to maintain optimal functional status.</p> <p>Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.</p>

Medical condition	MULTIPLE SCLEROSIS (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Indication for IVIg use	<p>Short term therapy in patients with clinically definite relapsing remitting MS in the following circumstances:</p> <ol style="list-style-type: none"> 1. Pregnancy and the immediate post partum period when other immunomodulation is contraindicated; 2. Young patients with severe relapsing remitting disease in whom other therapies have failed; 3. Severe relapse with no response to high dose methylprednisolone.
Level of evidence	<p>Category 2a – Some RCTs and/or case studies – Evidence of probable benefit – more research needed.</p>

Medical condition	MULTIPLE SCLEROSIS (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Description and diagnostic criteria	<p>MS is a chronic disorder of the central nervous system characterised by a triad of inflammation, demyelination and gliosis. Lesions of MS, known as plaques, are typically disseminated in time and location throughout the brain and spinal cord.</p> <p>Four clinical types of MS have been described: relapsing/remitting MS (RRMS), primary progressive MS (PPMS), secondary progressive MS (SPMS), and progressive/relapsing MS (PRMS).</p> <p>Diagnosis requires two or more episodes of symptoms and two or more signs that reflect pathology in anatomically non-contiguous white matter tracts of the CNS. Symptoms must last >24 hours and occur as separate episodes at least one month apart. At least one of the two signs must be present on neurological examination, while the other may be detected by paraclinical tests such as intrathecal IgG (oligoclonal bands and visual evoked potentials).</p>

Medical condition**MULTIPLE SCLEROSIS**
(Condition for which IVIg has an *emerging* therapeutic role)**Qualifying criteria**

Clinically definite RRMS as defined by McDonald criteria and *confirmed by a neurologist* with one of the following indications:

1. Pregnancy and immediate post partum period when other immunomodulation is contraindicated;
OR
2. Young patients with severe relapsing remitting disease in whom other therapies have failed;
OR
3. Severe relapse with no response to high dose methylprednisolone.

Application for IVIg use for these indications will be considered on a case-by-case basis and may be reviewed by an expert neurologist in MS in each state.

Note: There are numerous immunomodulatory therapies available for multiple sclerosis. IVIg is not available for routine ongoing treatment for patients with MS.

Exclusion criteria

1. Primary progressive MS.
2. Progressive phase of MS without relapses.

Review criteria

- Six monthly review by a neurologist is required.
- Objective evidence of improvement in relapse rate in comparison to pre-treatment levels.
- Other measures that may be useful include:
 - Expanded Disability Status Scale (EDSS)
 - MS Functional Scores
 - Other functional measures.

Medical condition	MULTIPLE SCLEROSIS (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Dose	<i>Induction:</i> 1–2g/kg in 2 to 5 divided doses. <i>Maintenance dose for indications 1 and 2 above:</i> 0.4–1g/kg 4 to 6 weekly. Aim for <i>minimum dose</i> to maintain optimal functional status. Refer to the current product information sheet for further information.

Medical condition	MYASTHENIA GRAVIS (Condition for which IVIg has an <i>established</i> therapeutic role)
Indication for IVIg use	<ol style="list-style-type: none"> 1. As an alternative treatment to plasma exchange in acute exacerbation (myasthenic crisis) or prior to surgery and/or thymectomy. 2. As maintenance therapy for moderate to severe MG when other treatments have been ineffective or caused intolerable side effects.
Level of evidence	Category 1 – High-quality RCTs – Clear evidence of benefit
Description and diagnostic criteria	<p>Myasthenia gravis (MG) is an autoimmune disease associated with the presence of antibodies to acetylcholine receptors (AChR) or to muscle-specific tyrosine kinase (MuSK) at the neuromuscular junction. Some patients with myasthenia gravis are antibody negative.</p> <p>Clinical features are characterised by fluctuating weakness and fatigability of voluntary muscles, namely levator palpebrae, extraocular, bulbar, limb and respiratory muscles. Patients usually present with unilateral or bilateral drooping of eyelid (ptosis), double vision (diplopia), difficulty in swallowing (dysphagia) and proximal muscle weakness. Weakness of respiratory muscles can result in respiratory failure in severe cases or in acute severe exacerbations (myasthenic crisis).</p> <p>Diagnosis is suspected based on the clinical picture described above, without loss of reflexes or impairment of sensation. Repetitive nerve stimulation typically shows a decreasing response at 2–3Hz, which repairs after brief exercise (exercise facilitation). Edrophonium can be used for confirmation. Other useful investigations include</p>

Medical condition	MYASTHENIA GRAVIS (Condition for which IVIg has an <i>established</i> therapeutic role)
Description and diagnostic criteria <i>(continued)</i>	serum anti-AChR or MuSK antibody titre, or SFEMG (single-fibre electromyography).
Qualifying criteria	Mandatory diagnosis and assessment by a neurologist; AND 1. As an alternative treatment to plasma exchange in acute exacerbation (myasthenic crisis) or prior to surgery and/or thymectomy; OR 2. As maintenance therapy for moderate to severe MG when other treatments have been ineffective or caused intolerable side effects.
Review criteria	IVIg should be used for 3–6 months (3–6 courses) before determining whether the patient has responded. If there is no benefit after 3–6 courses, IVIg therapy should be abandoned. <i>Review</i> Regular review by neurologist is required: frequency as determined by clinical status of patient. Initial review 3 to 6 monthly. For stable patients on maintenance treatment review by a neurologist is required at least annually. <i>Effectiveness</i> Clinical documentation of effectiveness is necessary for continuation of IVIg therapy. Effectiveness can be demonstrated by improvement in fatigability and weakness.

Medical condition	MYASTHENIA GRAVIS (Condition for which IVIg has an <i>established</i> therapeutic role)
Review criteria <i>(continued)</i>	Various scores can be used, including: <ul style="list-style-type: none"> • Forward arm abduction time (up to a full 5 minutes). • Quantitative Myasthenia Gravis Score (Duke). • Respiratory function, e.g. forced vital capacity. • Quantitative dynamometry of proximal limb muscles. • Variation of a myasthenic muscular score (MSS).
Dose	<p><i>Maintenance:</i> 0.4–1g/kg 4–6 weekly.</p> <p><i>Prior to surgery or during myasthenic crisis:</i> 1–2g/kg in 2 to 5 divided doses.</p> <p>Aim for <i>minimum dose</i> to maintain optimal functional status.</p> <p><i>Note:</i> smaller dosage may be of greater efficacy.</p> <p>Refer to the current product information sheet for further information.</p>

Medical condition	MYOCARDITIS IN CHILDREN (Condition for which IVIg use is in <i>exceptional</i> circumstances only)
Indication for IVIg use	<p>There is some evidence that IVIg improves cardiac function in children with proven or likely myocarditis. Confirmatory cardiac biopsy or positive viral isolation/PCR at presentation is required.</p> <p>Refer to the current product information sheet for further information.</p>
Level of evidence	Category 4a – Small case studies only – insufficient data.

Medical condition	NEONATAL HAEMOCHROMATOSIS (Condition for which IVIg has an <i>established</i> therapeutic role)
Indication for IVIg use	Pregnant women who have had a previous pregnancy affected by neonatal haemochromatosis.
Level of evidence	Category 2a – Some RCTs and/or case studies – Evidence of probable benefit – more research needed.
Description and diagnostic criteria	<p>NH manifests in the foetus and newborn and is characterised by abnormal accumulation of iron in the liver and extra-hepatic tissues. Affected neonates present with fulminant liver failure, usually in the context of a history of prematurity, intrauterine growth retardation and oligohydramnios. NH differs from most other causes of neonatal liver disease, other than congenital infections, in that the condition begins in utero and fulminant liver disease is manifested in the first few days of life. The aetiology and pathogenesis remains uncertain. The NH phenotype may be the outcome of numerous disease processes. There is also evidence, however, that NH is an alloimmune disorder. First, there is an approximate 80% likelihood of NH once a woman has an affected baby. Second, mothers can have affected babies with different fathers. It has not been described that fathers can have affected half-siblings with different mothers.</p> <p><i>Symptoms and signs</i> Affected neonates present with signs of liver failure including extreme cholestasis, hypoalbuminaemia, coagulopathy, ascites, and hypoglycaemia.</p> <p>Diagnosis of neonatal haemochromatosis is made after other causes of neonatal liver failure have been ruled out.</p>

Medical condition	NEONATAL HAEMOCHROMATOSIS (Condition for which IVIg has an <i>established</i> therapeutic role)
Description and diagnostic criteria <i>(continued)</i>	<p>In addition to extensive iron deposition (siderosis), liver biopsy would show cirrhosis with diffuse fibrosis, bile duct proliferation, and giant cells. Siderosis is also present in other tissues and viscera (e.g. epithelial tissues and the heart) but not in reticuloendothelial cells.</p> <p><i>Occurrence</i></p> <p>NH is a rare disease but the rate of recurrence after the index case in a sibship is up to 80%.</p> <p><i>Prognosis</i></p> <p>About 20% survival with medical treatment.</p>
Qualifying criteria	<p>Women who are pregnant or attempting to conceive and their most recent pregnancy ended in delivery of a foetus shown to have had NH.</p>
Review criteria	<ul style="list-style-type: none"> • Occurrence of NH, or evidence of liver disease (serum ferritin and α-fetoprotein levels, coagulopathy) in the offspring of women who have previously given birth to an NH-affected neonate. • Requirement for liver transplantation in these neonates. • Survival and development of infants following maternal IVIg therapy during pregnancy.
Dose	<p>1g/kg body weight weekly from the 18th week until the end of gestation.</p> <p>Refer to the current product information sheet for further information.</p>

Medical condition	OPSOCLONUS MYOCLONUS ATAXIA (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Indication for IVIg use	Long-term maintenance therapy of OMA in association with other tumour therapies.
Level of evidence	Category 4a – Small case studies only – insufficient data.
Description and diagnostic criteria	<p>OMA is an immune-mediated monophasic or multiphasic disorder consisting of opsoclonus (conjugate chaotic eye movements), cerebellar ataxia, and arrhythmic myoclonus affecting the trunk, the head and the extremities.</p> <p>OMA may be either paraneoplastic or idiopathic, presumably para-infectious (e.g. post-viral). In children, OMA complicates about 2–3% of neuroblastomas. In adults, it may occur in association with several cancers, most commonly small-cell lung cancer and breast cancer.</p>
Qualifying criteria	<p>Diagnosis of OMA by a neurologist:</p> <ol style="list-style-type: none"> In children; <p>OR</p> <ol style="list-style-type: none"> As second-line treatment following the use of ACTH or corticosteroids. <p><i>Note:</i> Given the rarity of OMA and its devastating effects, IVIg should be used where it is considered appropriate by a neurologist.</p>
Exclusion criteria	Adult paraneoplastic OMA.

Medical condition	OPSOCLONUS MYOCLONUS ATAXIA (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Review criteria	<p><i>Review</i></p> <p>Regular review by neurologist is required: frequency as determined by clinical status of patient.</p> <p>For stable patients on maintenance treatment review by a neurologist is required at least annually.</p> <p><i>Effectiveness</i></p> <p>Objective indicators of relief of symptoms of OMA and improvement or stabilisation of scores of ADLs.</p>
Dose	<p><i>Induction:</i> 1–2g/kg in 2 to 5 divided doses.</p> <p><i>Maintenance:</i> 0.4–1g/kg 4 to 6 weekly.</p> <p>Aim for <i>minimum dose</i> to maintain optimal functional status.</p> <p>Refer to the current product information sheet for further information.</p>

Medical condition	PANDAS (Condition for which IVIg use is in <i>exceptional</i> circumstances only)
Indication for IVIg use	<p>Paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) was first described in the early 1990s. PANDAS is characterised by rapid-onset tics associated with obsessive-compulsive disorder (OCD) in the context of recovery from streptococcal infection. Molecular mimicry between streptococcal antigens and the CNS is thought to underlie the cause. Symptomatic therapy is used with variable response.</p> <p>A single randomised placebo controlled trial using IVIg for PANDAS showed very prolonged and significant improvement in obsessive-compulsive symptoms, anxiety, depression, emotional lability and overall function compared with placebo. Improvements in symptoms were still evident at 1-year follow-up.</p> <p>Refer to the current product information sheet for further information.</p>
Level of evidence	Category 2a – Some RCTs and/or case studies – Evidence of probable benefit – more research needed.

Medical condition	PARANEOPLASTIC SYNDROMES (Condition for which IVIg use is in <i>exceptional</i> circumstances only)
Indication for IVIg use	<p>IVIg may be indicated in selected cases where treatment of the underlying disease has not led to an improvement in the neurologic syndrome, where other therapies are contraindicated or have failed, or if the neurologic features warrant urgent intervention.</p> <p>Refer to the current product information sheet for further information.</p>
Level of evidence	Category 4a – Small case studies only – insufficient data.

Medical condition	PEMPHIGUS FOLIACEUS (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Indication for IVIg use	Pemphigus foliaceus resistant to corticosteroids and immunosuppressive therapy or when these agents are contra-indicated.
Level of evidence	Category 4a – Small case studies only – insufficient data.
Description and diagnostic criteria	<p>PF is a rare autoimmune blistering skin disease characterised by loss of cohesion of cells (acantholysis) in the superficial (sub corneal) layers of the epidermis. The lesions are generally well demarcated and do not coalesce to form large eroded areas (as seen in PV). It is mediated by an autoantibody that targets desmoglein 1, a cell-to-cell protein molecule that binds the desmosomes of neighbouring keratinocytes in the epidermis.</p> <p>The disease has a long-term course with patients maintaining satisfactory health. Spontaneous remissions occasionally occur.</p>
Qualifying criteria	<p>Severe widespread PF, defined as disease involving 30% or more of body surface area, diagnosed by a dermatologist; AND</p> <ol style="list-style-type: none"> 1. Corticosteroids or immunosuppressive agents are contraindicated; <p>OR</p> <ol style="list-style-type: none"> 2. Condition is unresponsive to corticosteroids and immunosuppressive agents; <p>OR</p> <ol style="list-style-type: none"> 3. Presenting with severe side effects of therapy.

Medical condition	PEMPHIGUS FOLIACEUS (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Review criteria	<ul style="list-style-type: none"> • Response demonstrated at review at 6 months. Improvement to be demonstrated for continuation of supply. • Clinical progression: Treatment is stopped when patients are clinically free of disease and have a negative finding on direct immunofluorescence. • Autoantibody titres reflect the response to systemic therapy.
Dose	<p>Efficacy demonstrated with doses of at least 2g/kg per monthly treatment cycle.</p> <p>Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.</p>

Medical condition	PEMPHIGUS VULGARIS (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Indication for IVIg use	Moderate to severe PV as an adjuvant to prolonged corticosteroid treatment.
Level of evidence	Category 2a – Some RCTs and/or case studies – Evidence of probable benefit – more research needed.
Description and diagnostic criteria	<p>PV is a rare but potentially fatal condition accounting for approximately 70% of pemphigus cases. While the cause is unknown, an immuno-genetic predisposition is well established. PV may also be drug-induced. Drugs reported to be most significantly associated with PV include penicillamine, captopril and other thiol-containing compounds. Rifampicin and emotional stress have recently been reported as triggers for PV.</p> <p>The oral cavity is almost always affected and erosions can be scattered and extensive, with subsequent dysphagia. Blistering and erosions secondary to the rupture of blisters may be painful and limit the patient's daily activities.</p> <p>Pemphigus may occur in patients with other autoimmune diseases, particularly myasthenia gravis and thymoma.</p> <p><i>Prognosis</i></p> <p>The severity and natural history of PV are variable. Before the advent of steroids, most patients with PV died. Treatment with systemic steroids has reduced the mortality rate to 5–15%. Most deaths occur during the first few years of disease and if the patient survives 5 years the prognosis is good. Early disease is easier to control than widespread disease and mortality may be higher if therapy is delayed.</p>

Medical condition	PEMPHIGUS VULGARIS (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Description and diagnostic criteria <i>(continued)</i>	Morbidity and mortality are related to the extent of disease, the maximum dose of corticosteroid required to induce remission, and the presence of other diseases.
Qualifying criteria	<p>Moderate to severe disease diagnosed by a dermatologist; AND</p> <ol style="list-style-type: none"> 1. Corticosteroids or immunosuppressive agents are contraindicated; <p>OR</p> <ol style="list-style-type: none"> 2. Condition is unresponsive to corticosteroids and immunosuppressive agents; <p>OR</p> <ol style="list-style-type: none"> 3. Presenting with severe side effects of therapy.
Review criteria	<ul style="list-style-type: none"> • Response demonstrated at review at 6 months. Improvement to be demonstrated for continuation of supply. • Titres of serum antibodies against keratinocytes. • Whether systemic corticosteroids can be gradually discontinued. • Total dose and duration of corticosteroid therapy, and number of relapses before and after the initiation of IVIg therapy.
Dose	<p>Efficacy demonstrated with doses of at least 2g/kg per monthly treatment cycle.</p> <p>Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.</p>

Medical condition	POST-TRANSFUSION PURPURA (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Indication for IVIg use	Treatment of profound thrombocytopenia associated with bleeding.
Level of evidence	Category 4a – Small case studies only – insufficient data.
Description and diagnostic criteria	<p>PTP is caused by antibodies to platelet-specific antigens, usually anti-HPA1a. PTP may result in profound thrombocytopenia with associated life-threatening bleeding. While the platelet count typically recovers spontaneously, this can take several weeks or more.</p> <p>Specialised investigations (antibody screening, patient/donor genotyping) and antigen-matched platelet and/or red cell transfusion support may be required – contact the ARCBS for more information.</p>
Qualifying criteria	<p>Clinical diagnosis/suspicion of PTP with thrombocytopenia associated with life-threatening bleeding.</p> <p><i>Note:</i> Laboratory confirmation is desirable where possible in the time frame (usually an urgent, life-threatening clinical situation).</p>
Review criteria	<ul style="list-style-type: none"> • Platelet counts in the days and weeks following IVIg. • Resolution of bleeding.
Dose	<p>1g/kg as a total dose, repeated if necessary.</p> <p>Refer to the current product information sheet for further information.</p>

Medical condition	POTASSIUM CHANNEL ANTIBODY-ASSOCIATED ENCEPHALOPATHY (Condition for which IVIg use is in <i>exceptional</i> circumstances only)
Indication for IVIg use	<p>Case reports of benefit from various therapies, including IVIg are reviewed by Vincent A <i>et al</i>: Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. <i>Brain</i>. 2004;127(Pt 3):701-12.</p> <p>Refer to the current product information sheet for further information.</p>
Level of evidence	<p>Category 4a – Small case studies only – insufficient data.</p>

Medical condition	PRIMARY IMMUNODEFICIENCY DISEASES (Condition for which IVIg has an <i>established</i> therapeutic role)
Indication for IVIg use	Management of infection related to antibody deficiency.
Level of evidence	Category 2a – Some RCTs and/or case studies – Evidence of probable benefit – more research needed.
Description and diagnostic criteria	<p>Primary immunodeficiency diseases (PID) comprise a group of more than 120 separate conditions. Many of these are manifest by failure of protective antibody production. Key diagnoses include common variable immunodeficiency (CVID), severe combined immunodeficiencies (SCID), transient hypogammaglobulinaemia of infancy, Wiskott Aldrich syndrome and X-linked agammaglobulinaemia (XLA). In certain conditions such as Wiskott Aldrich syndrome antibody failure may not be manifest as hypogammaglobulinaemia but functional antibody responses will be impaired.</p> <p>Some PID do not involve antibody failure, such as chronic granulomatous disease and deficiencies of complement components. In these cases, antibody replacement therapy is not justified.</p>
Qualifying criteria	In each case, a specific PID diagnosis must be established under the supervision of a specialist clinical immunologist and the diagnosis must be advised for IVIg to be approved.
Exclusion criteria	<p>The following conditions should not be approved under this indication:</p> <ol style="list-style-type: none"> 1. Miscellaneous hypogammaglobulinaemia; 2. Specific antibody deficiency; 3. IgG subclass deficiency.

Medical condition	PRIMARY IMMUNODEFICIENCY DISEASES (Condition for which IVIg has an <i>established</i> therapeutic role)
Review criteria	<p>Review criteria for primary immunodeficiency diseases with antibody deficiency are not mandated.</p> <p>Nevertheless, the following may be of value to the clinician:</p> <ul style="list-style-type: none"> • Frequency of clinical episodes of infection. • Trough levels. • Renal function.
Dose	<p><i>Maintenance dose:</i> 0.4g/kg every four weeks, modified to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range.</p> <p><i>Loading dose:</i> One additional dose of 0.4g/kg in the first month of therapy is permitted if the serum IgG level is markedly reduced.</p> <p><i>Chronic suppurative lung disease:</i> Dosing to achieve IgG trough level of up to 9g/L is permitted if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range.</p> <p><i>Subcutaneous administration</i> of immunoglobulins (SCIG) is a suitable alternative to IVIg in this disease.</p> <p>Refer to the current product information sheet for further information.</p>

Medical condition	PURE RED CELL APLASIA (Condition for which IVIg use is in <i>exceptional</i> circumstances only)
Indication for IVIg use	<p>Pure red cell aplasia (PRCA) is a rare syndrome of severe anaemia, reticulocytopenia and a selective deficiency of erythroid progenitors. IVIg should be considered as first line therapy for viral PRCA associated with parvovirus B19 in immunocompromised patients. IVIg is a reasonable option for patients with immunological PRCA who have failed other therapies (e.g. prednisone or cyclosporine).</p> <p>Refer to the current product information sheet for further information.</p>
Level of evidence	Category 4b – no studies included.

Medical condition	PURE WHITE CELL APLASIA (Condition for which IVIg use is in <i>exceptional</i> circumstances only)
Indication for IVIg use	<p>Pure white cell aplasia (PWCA) is a rare syndrome of severe neutropenia and a selective deficiency of granulocyte progenitors. IVIg is a reasonable option for patients with immunological PWCA who have failed other therapies (e.g. prednisone or cyclosporine).</p> <p>Refer to the current product information sheet for further information.</p>
Level of evidence	<p>Category 4b – no studies included.</p>

Medical condition	SCLEROMYXEDEMA (Condition for which IVIg use is in <i>exceptional</i> circumstances only)
Indication for IVIg use	IVIg may be indicated in select cases not responding to steroids, or when steroids and other alternative treatments (e.g. thalidomide) are contraindicated. Refer to the current product information sheet for further information.
Level of evidence	Category 4a – Small case studies only – insufficient data.

Medical condition	SECONDARY HYPOGAMMAGLOBULINAEMIA (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Indication for IVIg use	<p>Replacement therapy for life-threatening infection due to hypogammaglobulinaemia related to other diseases or medical therapy, including haemopoietic stem cell transplantation.</p> <p><i>Note:</i> The following secondary causes of hypogammaglobulinaemia are considered elsewhere:</p> <ol style="list-style-type: none"> 1. Acquired hypogammaglobulinaemia secondary to haematological malignancies; 2. Paediatric HIV infection; 3. Solid organ transplantation.
Level of evidence	Category 4b – no studies included.
Description and diagnostic criteria	<p>Recurrent and/or severe bacterial infections may arise from hypogammaglobulinaemia of diverse causes.</p> <p>Hypogammaglobulinaemia may arise from protein losing states, malnutrition and medical immunosuppression. In most cases, successful management of the underlying condition will reverse the immunodeficiency, restoring immunocompetence. In some cases, recurrent or severe infection may arise from secondary immunodeficiency where the underlying cause cannot be reversed, or where there are unwanted effects of removing or reducing immunosuppressive therapy. New immunosuppressive regimens such as monoclonal B-cell depletion with Rituximab or equivalent agents do not generally induce hypogammaglobulinaemia at standard doses.</p>

Medical condition**SECONDARY HYPOGAMMAGLOBULINAEMIA
(Condition for which IVIg has an *emerging* therapeutic role)****Description and diagnostic criteria**
(continued)

However, repeated cycles of B-cell depletion in combination with other agents used to treat life-threatening immune-mediated diseases may increase rates of infection related to hypogammaglobulinaemia.

Qualifying criteria

Hypogammaglobulinaemia secondary to underlying disease or medical therapy (including HSCT) with *all* of the following:

1. Serum IgG less than the lower limit of the reference range on two separate occasions;

AND

2. Underlying cause of hypogammaglobulinaemia cannot be reversed or reversal is contraindicated;

AND

3. At least one of the following:
 - a. One invasive or life threatening bacterial infection (e.g. pneumonia, meningitis, sepsis) in the previous year; or
 - b. Clinically active bronchiectasis confirmed by radiology.

Exclusion criteria

Reversible underlying cause of hypogammaglobulinaemia.

The following conditions should not be approved under this indication:

1. Acquired hypogammaglobulinaemia secondary to haematological malignancies;
2. Paediatric HIV infection;
3. Transplantation related immunomodulation (HSCT and solid organ transplantation).

Medical condition	SECONDARY HYPOGAMMAGLOBULINAEMIA (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Review criteria	IVIg therapy for a maximum of one year with repeat immunological evaluation required prior to recommencement of IVIg.
Dose	<p><i>Maintenance dose:</i> 0.4g/kg every four weeks, modified to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range.</p> <p><i>Loading dose:</i> One additional dose of 0.4g/kg in the first month of therapy is permitted if the serum IgG level is markedly reduced.</p> <p><i>Chronic suppurative lung disease:</i> Dosing to achieve IgG trough level of up to 9g/L is permitted if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range.</p> <p><i>Subcutaneous administration</i> of immunoglobulins (SCIG) is a suitable alternative to IVIg in this disease.</p> <p>Refer to the current product information sheet for further information.</p>

Medical condition	SEPSIS – NEONATAL (Condition for which IVIg use is in <i>exceptional</i> circumstances only)
Indication for IVIg use	<p>A meta-analysis of trials found a 6-fold decrease in mortality when IVIg was added to conventional therapies in the treatment of neonatal sepsis. This benefit was far greater than that derived from the prophylactic use of IVIg in preventing neonatal sepsis.</p> <p>Refer to the current product information sheet for further information.</p>
Level of evidence	<p>Category 2a – Some RCTs and/or case studies – Evidence of probable benefit – more research needed.</p>

Medical condition	SJOGREN'S SYNDROME (Condition for which IVIg use is in <i>exceptional</i> circumstances only)
Indication for IVIg use	IVIg may be indicated in certain highly selected cases where other treatments have not been effective. Refer to the current product information sheet for further information.
Level of evidence	Category 4a – Small case studies only – insufficient data.

Medical condition	SOLID ORGAN TRANSPLANTATION (other than kidney) (Condition for which IVIg use is in <i>exceptional</i> circumstances only)
Indication for IVIg use	<p>IVIg may be indicated in</p> <ul style="list-style-type: none"> (i) highly sensitised patients awaiting transplantation; (ii) transplant recipients with acute antibody mediated rejection with clinical evidence of graft dysfunction; and (iii) transplant recipients as treatment or prophylaxis for rejection where conventional immunosuppressive therapy is contraindicated, for example, in a patient with life threatening infection in whom conventional immunosuppression will place the patient at greater risk, or when the transplant is at risk, e.g. due to infection, e.g. BK virus. <p>Refer to the current product information sheet for further information.</p>
Level of evidence	<p>Category 4a – Small case studies only – insufficient data.</p>

Medical condition	SPECIFIC ANTIBODY DEFICIENCY (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Indication for IVIg use	Prevention of infections in individuals with frequent infections who have demonstrated failure to mount protective antibody responses on vaccine antigen challenge despite normal total serum IgG levels.
Level of evidence	Category 4a – Small case studies only – insufficient data.
Description and diagnostic criteria	<p>The use of IVIg replacement for functional antibody deficiency has been considered in two international consensus statements (Orange <i>et al.</i> J Allergy Clin Immunol, 2006;117:S525-53, Bonilla <i>et al.</i> Ann Allergy Asthma Immunol, 2005;94:S1-63). The terms specific or selective antibody deficiency are synonymous with functional antibody deficiency although tend to be used in the more restrictive sense of applying to polysaccharide antibody responses only.</p> <p>“Patients who have normal total IgG levels but impaired production of specific antibodies, including those with isolated deficient responses to numerous polysaccharide antigens after vaccination can present a diagnostic challenge. IgG replacement therapy should be provided when there is well-documented severe polysaccharide non-responsiveness and evidence of recurrent infections with a documented requirement for antibiotic therapy” (Orange <i>et al.</i> J Allergy Clin Immunol, 2006;117:S525-53).</p> <p>It is now generally agreed that IgG subclass level estimation in serum is relatively poorly predictive of infectious risk and is of limited value in the definition of those patients most likely to benefit from IVIg</p>

Medical condition	SPECIFIC ANTIBODY DEFICIENCY (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Description and diagnostic criteria <i>(continued)</i>	therapy. Many patients with previously diagnosed IgG subclass deficiency and recurrent infection on IVIg may have functional antibody deficits. Enumeration of peripheral blood CD27+IgM memory B-cells may prove to have value in the assessment of host defence to encapsulated bacteria.
Qualifying criteria	<ol style="list-style-type: none"> 1. Approval by a clinical immunologist; <p>AND</p> <ol style="list-style-type: none"> 2. Frequent bacterial infections despite continuous oral antibiotic therapy for three months; <p>AND</p> <ol style="list-style-type: none"> 3. Documented failure of serum antibody response to unconjugated pneumococcal or protein vaccine challenge.
Exclusion criteria	<ol style="list-style-type: none"> 1. Isolated IgG subclass deficiency in the absence of evidence of functional antibody deficiency. 2. Low total IgG. This should be considered under primary or secondary immunodeficiency.
Review criteria	<ul style="list-style-type: none"> • IVIg therapy for a maximum of one year with repeat immunological evaluation required prior to recommencement of IVIg. Consideration should be given to an immunoglobulin washout period of 4 to 6 months prior to repeat immunological evaluation. • Patients previously receiving IVIg therapy for IgG subclass deficiencies should be reviewed under these criteria if they are no longer experiencing serious infections. • IgG trough levels are of no value in this setting.

Medical condition	SPECIFIC ANTIBODY DEFICIENCY (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Dose	<i>Maintenance dose:</i> 0.4g/kg every four weeks. <i>Loading dose:</i> Not approved. <i>Subcutaneous administration</i> of immunoglobulins (SCIG) is a suitable alternative to IVIg in this setting. Refer to the current product information sheet for further information.

Medical condition	STIFF PERSON SYNDROME (Condition for which IVIg has an <i>established</i> therapeutic role)
Indication for IVIg use	Treatment of significant functional impairment in patients who have a verified diagnosis of stiff person syndrome.
Level of evidence	Category 2a - Some RCTs and/or case studies - Evidence of probable benefit – more research needed.
Description and diagnostic criteria	<p>Patients with stiff person syndrome present with symptoms related to muscular rigidity and superimposed episodic spasms. The rigidity insidiously spreads involving axial muscles, primarily abdominal and thoracolumbar, as well as proximal limb muscles. Typically, co-contraction of truncal agonist and antagonistic muscles leads to a board-like appearance with hyperlordosis. Less frequently, respiratory muscle involvement leads to breathing difficulty and facial muscle involvement to a mask-like face.</p> <p>Investigations that may be useful for diagnosis include auto-antibodies to GAD-65 or GAD-67, EMG recordings from stiff muscles that may show continuous discharges of motor unit, and CSF oligoclonal bands.</p>
Qualifying criteria	Significant functional impairment in patients who have a verified diagnosis of stiff person syndrome made by a neurologist.

Medical condition	STIFF PERSON SYNDROME (Condition for which IVIg has an <i>established</i> therapeutic role)
Review criteria	<p><i>Review</i></p> <p>Regular review by neurologist is required: frequency as determined by clinical status of patient.</p> <p>For stable patients on maintenance treatment review by a neurologist is required at least annually.</p> <p><i>Effectiveness</i></p> <p>Objective indicators of relief of symptoms of stiffness, including:</p> <ul style="list-style-type: none"> • improvement or stabilisation of scores of ADLs • other specialised scoring systems such as Distribution-of-stiffness index and Heightened sensitivity scale.
Dose	<p><i>Induction:</i> 2g/kg in 2 to 5 divided doses.</p> <p><i>Maintenance:</i> 1–2g/kg 4–6 weekly.</p> <p>Aim for <i>minimum dose</i> to maintain optimal functional status.</p> <p>Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.</p>

Medical condition	SUSAC SYNDROME (Condition for which IVIg use is in <i>exceptional</i> circumstances only)
Indication for IVIg use	<p>Susac syndrome is a rare, micro-angiopathic disorder characterised by encephalopathy, hearing loss and retinal artery branch occlusions. Case reports show benefit of IVIg therapy in combination with corticosteroids, with or without other immunosuppressive agents. Dose: 1–2g/kg/month for one year providing documented clinical improvement.</p> <p><i>Note:</i> Effectiveness of IVIg therapy may be difficult to determine due to the fluctuating course of disease.</p> <p>Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.</p>
Level of evidence	Category 4a – Small case studies only – insufficient data.

Medical condition	TOXIC EPIDERMAL NECROLYSIS/STEVEN JOHNSON SYNDROME (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Indication for IVIg use	To limit progression of TEN or SJS/TEN when administered in early stages.
Level of evidence	Category 4a – Small case studies only – insufficient data.
Description and diagnostic criteria	<p>Toxic epidermal necrolysis (TEN) is a rare, life-threatening hypersensitivity reaction to certain medications, such as sulphonamides, antibiotics, non-steroidal anti-inflammatory drugs and anti-convulsants. Drug-induced epidermal apoptosis has been proposed as possible pathogenesis. SJS is a less extensive manifestation of the same phenomenon.</p> <p>TEN and SJS are characterised by severe bullous reaction with extensive destruction of the epidermis, and morphologically by ongoing apoptotic keratinocyte cell death that results in the separation of the epidermis from the dermis.</p> <p>The term SJS is now used to describe patients with blistering and skin detachment involving a total body surface area of <10%. SJS/TEN describes patients with 10–30% detachment and TEN describes patients with >30% skin detachment.</p>

Medical
condition

**TOXIC EPIDERMAL NECROLYSIS/STEVEN
JOHNSON SYNDROME**
(Condition for which IVIg has an *emerging*
therapeutic role)

Qualifying
criteria

TEN or SJS/TEN overlap with ALL of the following:

1. Diagnosis by a dermatologist;

AND

2. Body surface area (erythema and/or erosions) of
10% or more;

AND

3. Evidence of rapid evolution.

Notes:

- IVIg should be initiated as early as possible, preferably within 24 hours of diagnosis.
- Urgent skin biopsy should be performed for confirmation but should not delay IVIg therapy if indicated.
- ADRAC should be notified of the inciting medication.

Exclusion
criteria

SJS alone.

Dose

2g/kg, preferably as a single dose, or divided over
3 consecutive days.

**Dosing above 1g/kg per day is contraindicated for
some IVIg products. Refer to the current product
information sheet for further information.**

Medical condition	TOXIC SHOCK SYNDROME (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Indication for IVIg use	<p>1. <i>Streptococcal TSS</i>: In view of the high mortality risk IVIg is indicated for early use in both adults and children.</p> <p>2. <i>Staphylococcal TSS</i>: IVIg is indicated where rapid improvement is not obtained with fluid resuscitation and inotropes.</p> <p>In both conditions IVIg is used in addition to surgical intervention, antibiotic therapy and supportive measures.</p>
Level of evidence	Category 4a – Small case studies only – insufficient data.
Description and diagnostic criteria	<p>Toxic shock is a life-threatening illness characterised by hypotension and multi-organ failure. It may be caused by <i>Staphylococcus aureus</i> (rarely isolated) or <i>Streptococcus pyogenes</i> that produce and release superantigenic exotoxins. The exotoxins activate T-cells on a large scale resulting in a massive release of inflammatory cytokines.</p> <p><i>Streptococcal TSS</i> is defined by:</p> <ul style="list-style-type: none"> I Group A Streptococci (<i>Strep. pyogenes</i>) isolated from: <ul style="list-style-type: none"> (IA) a normally sterile site (e.g. blood, CSF, pleural or peritoneal fluid, tissue biopsy, surgical wound); or (IB) a non-sterile site (e.g. throat, sputum, vagina, superficial skin lesion). IIA. Hypotension: systolic blood pressure ≤ 90 mmHg in adults or in the 5th percentile for age in children; and IIB. Two or more of the following:

Medical condition

TOXIC SHOCK SYNDROME
(Condition for which IVIg has an *emerging* therapeutic role)

Description and diagnostic criteria
(continued)

1. Renal impairment: serum creatinine for adults at least twice the upper limit of normal for age; in patients with existing renal disease, elevation over baseline by a factor of at least 2;
2. Coagulopathy: platelet count of $\leq 100 \times 10^9/L$ or disseminated intravascular coagulation, defined by prolonged clotting times, low fibrinogen level, and the presence of fibrin degradation products;
3. Liver involvement: alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin level at least twice the upper limit of normal for age; in patients with existing liver disease, elevation over baseline by a factor of 2;
4. Adult respiratory distress syndrome, defined by acute onset of diffuse pulmonary infiltrates and hypoxaemia in the absence of cardiac failure; or evidence of diffuse capillary leak manifested by acute onset or generalised oedema; or pleural or peritoneal effusions with hypoalbuminaemia;
5. Generalised erythematous macular rash that may desquamate;
6. Soft tissue necrosis, including necrotising fasciitis or myositis; or gangrene.

A *definite case* is an illness fulfilling criteria IA and II(A and B).

A *probable case* is an illness fulfilling criteria IB and II(A and B) where no other aetiology is identified.

(Working Group on Severe Streptococcal Infections, 1993).

Medical
condition

TOXIC SHOCK SYNDROME
(Condition for which IVIg has an *emerging*
therapeutic role)

Description
and
diagnostic
criteria

Staphylococcal TSS is defined by:

1. Fever: temperature $\geq 38.9^{\circ}\text{C}$;
2. Hypotension: systolic blood pressure ≤ 90 mmHg in adults or in the 5th percentile for age in children;
3. Diffuse macular rash with subsequent desquamation 1–2 weeks after onset (including palms and soles);
4. Multisystem involvement (three or more of the following):
 - a. Hepatic: bilirubin or aminotransferase ≥ 2 times normal;
 - b. Haematologic: platelet count $\leq 100 \times 10^9/\text{L}$;
 - c. Renal: blood urea nitrogen or serum creatinine level ≥ 2 times normal;
 - d. Mucous membranes: vaginal, oropharyngeal or conjunctival hyperaemia;
 - e. Gastrointestinal: vomiting or diarrhoea at onset of illness;
 - f. Muscular: severe myalgia or serum creatine phosphokinase level ≥ 2 times upper limit;
 - g. Central nervous system: disorientation or alteration in consciousness without focal neurological signs and in the absence of fever or hypotension.

A *confirmed* case is a case with all of the manifestations described above. However, in severe cases death may occur before desquamation develops.

Medical condition	TOXIC SHOCK SYNDROME (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Description and diagnostic criteria <i>(continued)</i>	<p>A <i>probable case</i> is an illness with all but any one of the manifestations described above (Wharton <i>et al</i>, 1990).</p> <p><i>Prognosis</i></p> <p>Streptococcal TSS has a mortality rate of 30–80% in adults and 5–10% in children, with most deaths secondary to shock and respiratory failure.</p> <p>Staphylococcal TSS can also be fatal but mostly has a better prognosis.</p>
Qualifying criteria	<ol style="list-style-type: none"> 1. Diagnosis of streptococcal or staphylococcal TSS in accordance with criteria listed above, preferably with isolation of organism; <p>AND</p> <ol style="list-style-type: none"> 2. Failure to achieve rapid improvement with fluid resuscitation, inotropes, surgery, antibiotic therapy and other supportive measures.
Dose	<p>2g/kg as a single dose.</p> <p><i>Schrage et al</i> (2006) reported differences between various preparations of IVIg and their ability to neutralise streptococcal superantigens. They commented that 'the variations between IVIg preparations from different manufacturers are most likely caused by the different geographical regions from which the plasma samples were collected and might reflect differences in ... group A streptococcal ... exposure.' The clinical significance of these findings is not yet known.</p>

Medical condition	TOXIC SHOCK SYNDROME (Condition for which IVIg has an <i>emerging</i> therapeutic role)
Dose (continued)	<p>Darenberg <i>et al</i> (2004) suggested that higher doses of IVIg might be required for staphylococcal TSS than streptococcal TSS, based on in vitro neutralisation of superantigens.</p> <p>Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.</p>

