Specialist Working Group for Neurology

Proposed changes to the *Criteria for the clinical use of intravenous immunoglobulin in Australia, Second Edition*

ITEM	CRITERIA FOR THE CLINICAL USE OF INTRAVENOUS IMMUNOGLOBULIN IN AUSTRALIA, SECOND EDITION (CRITERIA)	PROPOSED CHANGES TO THE CRITERIA	RATIONALE FOR PROPOSED CHANGES
Condition Name	IgM paraproteinaemic neuropathy	IgM paraproteinaemic demyelinating neuropathy	Addition: "demyelinating" added to qualify paraproteinaemic neuropathies and distinguish from axonal types. (A)
Specialty	Neurology	Neurology	
Chapter	6	6	
Specific Conditions			
Level of Evidence	Conflicting evidence of benefit (Category 2c).	Conflicting evidence of benefit (Category 2c).	
Justification for Evidence Category	The Biotext (2004) review included three low quality studies (one RCT, one case-control and one case- series) with 20 patients. No benefit from treatment with IVIg was demonstrated in the case-control study (Biotext 2004). The Frommer and Madronio (2006) found a Cochrane systematic review of five medium-quality RCTs with 97 patients of any age with a diagnosis of MGUS. There was inadequate evidence of efficacy of IVIg in anti-myelin-associated glycoprotein paraprotein peripheral neuropathies.	Two randomized placebo-controlled crossover trials with IVIg have been performed (Dalakas 1996, Comi 2002), encompassing 33 patients with IgM paraproteinaemic demyelinating neuropathy. Neither provided 6 or 12 months assessments. The results of these trials are summarized in Cochrane reviews (2006, 2012), which concluded that the studies provide low-quality evidence for very short term improvement (2–4 weeks). Six other uncontrolled studies reported transient improvement in 22 of 50 participants with IVIg, whereas another did not report improvement. EFNS guidelines (Elovaara et al 2008) state that routine use of IVIg cannot be recommended in IgM paraproteinaemic neuropathy. A trial of IVIg may be	Justification for Evidence section has been revised and updated to include Cochrane reviews and EFNS guidelines indicating routine use cannot be recommended. A trial may be considered in patients with significant disability or rapid worsening, although efficacy is unproven. (A) The SWG recommends use to be limited to patients with significant and progressive disability. (B)

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		considered in patients with significant disability or rapid worsening, although its efficacy is not proven.			
Description and Diagnostic Criteria	IgM paraproteinaemic neuropathy is a slowly progressive, predominantly distal sensory neuropathy that may eventually produce disabling motor symptoms. The condition is associated with IgM paraprotein, which is a monoclonal antibody to myelin associated glycoprotein (MAG). IgM paraproteinaemic neuropathy is the most common subgroup of the monoclonal gammopathy of undetermined significance (MGUS) group. It is distinguishable from chronic inflammatory demyelinating polyneuropathy (CIDP) by: • 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. Nerve conduction studies usually show symmetrical conduction slowing with prolonged distal motor latencies and distal attenuation (distal index is prolonged) .Test for antibodies to neural antigens (MAG or other neural antigens) may be helpful.	IgM paraproteinaemic neuropathy is a slowly progressive, predominantly distal sensory neuropathy that may eventually produce disabling motor symptoms. The condition is associated with IgM paraprotein, which may demonstrate antibody reactivity to myelin-associated glycoprotein (MAG). IgM paraproteinaemic neuropathy is the most common subgroup of the monoclonal gammopathy of undetermined significance (MGUS) group. It is distinguishable from chronic inflammatory demyelinating polyneuropathy (CIDP) by: • the presence of tremor; • a greater severity of sensory loss, with ataxia and relatively mild or no weakness; • damage tends to be permanent and degree of improvement in IgM paraproteinaemic neuropathy is much smaller than the improvement observed in CIDP patients. Nerve conduction studies usually show symmetrical conduction slowing with markedly prolonged distal motor latencies and reduced or absent sensory responses . Testing for antibodies to neural antigens (MAG or other neural antigens) may be helpful. Due to the variable and often poor response to IVIg, a treatment trial is only indicated for significant progressive disability.			
Diagnosis is	Diagnosis by a neurologist of IgM paraproteinaemic	Yes	By which specialty	Neurologist	The system validates the requirement for

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required	neuropathy		diagnosis which is unchanged from requiring to be made by a neurologist
Diagnosis must be verified		No / By which specialty	
Exclusion Criteria			No exclusion criteria required.
Indications	**Patients with IgM paraproteinaemic neuropathy with functional impairment in whom other therapies have failed or are contraindicated or undesirable**	**IgM paraproteinaemic neuropathy with significant progressive disability where other therapies have failed or are contraindicated** **Relapse of patients with IgM paraproteinaemic Neuropathy within 6 months commencement of trial-off Ig therapy.**	Minor change to wording with replacement of 'funcitonal impairment' with 'signifcant and progressive disability'. (A) New indication for re-entry of patients where relapse with demonstrable deterioration occurs during first 6 months off Ig therapy. (A)
Qualifying Criteria	Diagnosis by a neurologist of IgM paraproteinaemic neuropathy with: Functional impairment of activities of daily living; AND Other therapies have failed or are contraindicated or undesirable	**IgM paraproteinaemic neuropathy with significant progressive disability where other therapies have failed or are contraindicated.** Significant progressive disability as defined by the Inflammatory Neuropathy Cause and Treatment (INCAT) Disability Score of greater than one point AND At least two alternative therapies have failed to deliver clinical improvement, unless alternative	The criteria for eligibility have been more clearly defined. The INCAT Score has been selected as the single, most easily measurable, accessible and simple assessment to determine disability in adults. Patients will qualify for initial treatment when the level of disability as defined by an INCAT disability score is greater than 1. The INCAT Score assesses both walking and significance of the disability, addressing all the criteria supporting the indication. A reference for INCAT (with link) will be available within the Ig system. (A)

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		therapies are contraindicated. **Relapse of patients with IgM paraproteinaemic neuropathy within six months commencement of trial-off Ig therapy.** Once a patient has relapsed when trialled off Ig treatment, a second-line immunomodulatory agent should be strongly considered as additional therapy. Previously stable adult with IgM paraproteinaemic neuropathy demonstrates a deterioration in disability as measured by the Adjusted INCAT Disability Score by an increase of at least one point compared to the patient's previous review score. AND Relapse occurs within six months of the last Ig dose.	This condition does not occur in children so no alternative assessment method is required. A formal requirement for at least 2 alternative therapies to have been used which will be documented, unless contraindicated. (A) Alternative therapies include: i) Steroids ii) Rituximab iii) Azathioprine iv) Methotrexate v) Mycophenolate vi) Cyclophosphamide vii) Plasmapheresis During the annual review, prescribers will consider trialling patients off IVIg therapy at the annual review. Given that some patients may relapse during a trial off therapy, a new indication is required to test eligibility for recommencement on Ig treatment. (A) The degree of deterioration will be formally assessed and reported. (A)
Review Criteria	IVIg should be used for three to six months (three to six courses) before determining whether the patient has responded. If there is no benefit after three to six courses, IVIg therapy should be abandoned.	**IgM paraproteinaemic neuropathy with significant progressive disability where other therapies have failed or are contraindicated.** IVIg should be used for a maximum of four months	Initial patient response is expected to be no longer that 4 months (1 month induction and 3 cycles of treatment). For patients on treatment of frequency greater than monthly, this means less than 4 cycles of treatment. (B)

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	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: Improvement in functional scores (activities of daily living — ADLs) OR quantitative muscle scores, OR Medical Research Council (MRC) muscle assessment OR neuropathy score; OR 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	(induction plus three maintenance cycles) before determining whether the patient has responded. If there is no benefit after four months, IVIg therapy should be abandoned. Clinical documentation of effectiveness is necessary for continuation of IVIg therapy. Consideration of a trial off IVIg should be considered annually in patients stable on maintenance therapy to identify patients who are in remission. Once a patient has relapsed in the first six months of a trial-off therapy, a further trial off IVIg might be considered after at least two years. **On review of the initial authorisation period** Adult demonstrating improvement in disability as measured by a decrease in the Adjusted INCAT Disability Score of at least one point. **On review of a continuing authorisation period** Adult demonstrating stabilised or continued improvement in disease as measured by the Adjusted INCAT Disability Score (unchanged or less than previous review score). AND A trial-off Ig therapy is planned or reason provided as to why a trial is not being planned. For stable patients on maintenance treatment	Cessation is to be considered at initial review (4 months) and once stable and potentially in remission, annually (Continuing Review). In this instance, a patient may then relapse and require re-commencement of treatment. If the relapse occurs within the first 6 months, patients should be able to re-commence therapy without full re-qualification, however, it was agreed that an assessment of deterioration in INCAT or MRC score is still required before recommencing Ig treatment. (A) **Review of initial authorisation period** Four months has been selected as it is a long enough period to determine response and should also allow time for city neurologists with rural patients to undertake the initial review. (A) The initial authorisation review criteria are re-defined as shown. Formal improvement in disability is sought with documentation of the level achieved after 4 cycles of treatment including induction. The Adjusted INCAT Score is required at review because variation in some upper limb flexors are not valid as contributing to the definition of response. Therefore the INCAT is 'adjusted' to exclude these for Review purposes.(A)

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	scores.	review by a neurologist is required at least annually. **Relapse of patients with IgM paraproteinaemic neuropathy within six months commencement of trial-off Ig therapy** IVIg should be used for a maximum of four months (induction plus three maintenance cycles) before determining whether the patient has responded. If there is no benefit after four months or (1 + 3 cycles), IVIg therapy should be abandoned. Once a patient has relapsed when trialled off Ig treatment, a second-line immunomodulatory agent should be strongly considered as additional therapy. Once in remission on maintenance, cessation should be considered annually at the continuing review. Once a patient has relapsed in the first six months of a trial-off therapy, a further trial might be considered after at least two years. Regular review by a neurologist is required; frequency as determined by the clinical status of the patient. Clinical documentation of efficacy is necessary for continuation of IVIg therapy. **On review of the initial authorisation** Adult demonstrating improvement in disability as measured by a decrease in the Adjusted INCAT Disability Score of at least one point compared to the qualifying score. Regular review by a neurologist is required within 4	Some tolerance is required in authorisation values for stability as prescribers are being encouraged to find the minimal effective dose for patients and they may deteriorate when an ineffective dose is eventually used. Patients will be eligible provided they have not continued to deteriorate while on treatment. (A) Patients will only be identified to be in long term remission if a trial off therapy is attempted. The continuing review criteria will have a question promting prescribers to consider a trial off therapy and including an option to comment when a trial was last attempted or the reason why a trial is not planned. (A) The review requirements for re-entry after relapsing during a trial off therapy were defined such that the initial review criteria would need to be met - eg after induction plus 3 cycles, improvement must be demonstrated. Once response achieved, the patient would move to an annual review. Once patients relapse and recommence Ig treatment, they should not be trialled off therapy again for at least 2 years. After that time, once stable, a further trial may be considered. Once a patient has relapsed, it is appropriate for them to return to Ig therapy but a second line immunomodulatory agent should be strongly considered as additional therapy. (A)

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		months. For stable patients on maintenance treatment, review by a neurologist is required at least annually **On review of a continuing authorisation period** Adult demonstrating stabilised or continued improvement in disease as measured by the Adjusted INCAT Disability Score compared to the previous review score. AND A trial-off Ig therapy is planned or reason is provided as to why a trial is not being planned.	
Dose	**Induction** - 2 g/kg in 2 to 5 divided doses. **Maintenance** - 0.4–1 g/kg, 2–6 weekly. The amount per dose should be titrated to the individual's response. Aim for minimum dose to maintain optimal functional status. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**	**IgM paraproteinaemic neuropathy with significant progressive disability where other therapies have failed or are contraindicated** **Induction** - 2 g/kg in 2 to 5 divided doses. **Maintenance**: 0.4–1 g/kg, 2 to 6 weekly. The amount per dose should be titrated to the individual's response. A maximum dose of 2 g/kg may be given in any four-week period. This might be by divided doses more frequently than fortnightly. Aim for minimum dose to maintain optimal functional status. **Refer to the current product information sheet for further information.** **Relapse of patients with IgM paraproteinaemic**	The dosing approach is the same for both indications. Induction dose is unchanged. The minimum dose was set to 0.01 to accommodate doses less than 0.4mg/Kg which could be efficacious. (A) The maximum dose interval was set to 8 weekly. A divided dose is supported for maintenance to allow the splitting of a 4 week total dose to be given up to weekly. (B)

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		neuropathy within six months commencement of trial-off Ig therapy. Once a patient has relapsed when trialled off Ig treatment, a second-line immunomodulatory agent should be strongly considered as additional therapy. **Induction:** 2 g/kg in 2 to 5 divided doses. **Maintenance:** 0.4–1 g/kg, 2 to 6 weekly. The amount per dose should be titrated to the individual's response. A maximum dose of 2 g/kg may be given in a four- week period. This might be by divided doses more frequently than fortnightly. The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient. Maintenance treatment only with clear objective improvement. **Refer to the current product information sheet for further information.**	

POTENTIAL OPERATIONAL IMPACT

The introduction of the INCAT scoring method for disability will require clinicians to follow the link in the system and enter the raw scores into a template that will be provided within the system. If they are unfamiliar with the scoring system – there will be a learning curve for the first few patients. Time will be required for the assessment.

No operational impact is expected due to shortening of the initial review period from 6 to 4 months.

Prescribers will be asked if they plan to trial the patient off therapy at each annual review. If the patient relapses within 6 months commencement of the trial, they can be considered for re-authorisation, but will require assessment by a neurologist.

It is important that patients will have given informed consent to Ig treatment, eg been provided with advice regarding the requirement for trialling off therapy once stable,

because patients will be required to undertake a trial off therapy to test whether long-term remission has been achieved.			
POTENTIAL IMPACT ON DEMAND			
Patient Numbers **2013-14** **Usage 2013-14**	**Total treated: 76** **<1%**	Some reduction in use likely due to: • Potential for reduction in new patients receiving Ig given that eligibility will be formally tested and limited to patients with significant and progressive disability. • The requirement to document the alternative therapies that have been trialled with no response may reduce the number of patients being treated, and/or delay the use of IVIg. • Initial treatment period reduced by up to 2 months for most patients with cessation of treatment where response is not achieved in new or relapsed patients. • Formalised requirement to trial long-term patients off therapy. Treatment can only recommence where documented relapse occurs within 6 months of trial commencement. If patients do not relapse, they'll remain off therapy.	Given that usage in this condition is less than 1% total Ig use - any reduction in total use will be marginal.
POTENTIAL IMPACT ON COST			
Current cost		**Anticipated reduction in cost, if any** **Marginal** = borderline or unchanged from current cost **Minor** = decrease by $500K - $1.99M from current cost **Major** = decrease $2M+ from current cost	**Marginal**
BIBLIOGRAPHY			
Biotext 2004, 'Summary data on conditions and papers', in *A systematic literature review and report on the efficacy of intravenous immunoglobulin therapy and its risks*, commissioned by the National Blood Authority on behalf of all Australian Governments, pp. 151–154. Available from: http://www.nba.gov.au/pubs/pdf/report-lit-rev.pdf. Comi, G, Roveri, L, Swan, A, et al 2002, A randomised controlled trial of intravenous immunoglobulin in IgM paraprotein associated demyelinating neuropathy, *Journal of*			

Neurology, 249, no. 10, pp. 1370–7.
Dalakas, MC, Quarles, RH, Farrer, RG, et al 1996, A controlled study of intravenous immunoglobulin in demyelinating neuropathy with IgM gammopathy, *Annals of Neurology*, vol. 40, no. 5, pp. 792–5.
Frommer, M & Madronio, C 2006, The use of intravenous immunoglobulin in Australia. *A report for the National Blood Authority*, Part B: systematic literature review, Sydney Health Projects Group, University of Sydney, Sydney, pp. 40–1.
Elovaara, I, Apostolski, S, Van Doorn, P et al 2008, 'EFNS guidelines for the use of intravenous immunoglobulin in treatment of neurological diseases', *European Journal of Neurology*, vol. 15, pp. 893–908.
European Federation of Neurological Societies, Peripheral Nerve Society, Hadden, RD, Nobile-Orazio, E, et al 2006, 'European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of paraproteinaemic demyelinating neuropathies: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society', *European Journal of Neurology,* vol. 13, no. 8, pp. 809–18.
Lunn, MPT & Nobile-Orazio, E 2006, 'Immunotherapy for IgM anti- Myelin-Associated Glycoprotein paraprotein-associated peripheral neuropathies (Cochrane Review)', in *The Cochrane Library*, Issue 2, John Wiley & Sons, Ltd, Chichester, UK.
Mariette, X, Chastang, C, Clavelou, P, et al 1997, 'A randomised clinical trial comparing interferon-alpha and intravenous immunoglobulin in polyneuropathy associated with monoclonal IgM. The IgM-associated Polyneuropathy Study Group', *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 63, no. 1, pp. 28–34.

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