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	**Chronic inflammatory demyelinating polyneuropathy (CIDP), (including IgG and IgA paraproteinaemic neuropathies)**	**Chronic inflammatory demyelinating polyneuropathy (CIDP), (including IgG and IgA paraproteinaemic demyelinating neuropathies)**	Addition: "demyelinating" added to qualify paraproteinaemic neuropathies and distinguish from axonal types.
Specialty	Neurology	Neurology	
Chapter	5	5	
Specific Conditions	Chronic inflammatory demyelinating polyneuropathy (CIDP) IgA paraproteinaemic neuropathy IgG paraproteinaemic neuropathy	Chronic inflammatory demyelinating polyneuropathy (CIDP) IgA paraproteinaemic demyelinating neuropathy IgG paraproteinaemic demyelinating neuropathy	Addition: demyelinating" added to qualify paraproteinaemic neuropathies to distinguish from axonal types.
Level of Evidence	Clear evidence of benefit (Category 1).	Clear evidence of benefit (Category 1).	
Justification for Evidence Category	The Biotext (2004) review found one Cochrane review of six RCTs with a total sample size of 170. The quality of the studies was low–moderate, found IVIg improved disability in the short-term, and had comparable results to treatment with plasma exchange or prednisolone. The Frommer and Madronino (2006)	The Biotext (2004) review found one Cochrane review of six RCTs with a total sample size of 170. The quality of the studies was low–moderate, found IVIg improved disability in the short-term, and had comparable results to treatment with plasma exchange or prednisolone. 2013 Cochrane review of eight RCTs including 323 participants. A significantly higher proportion of patients had short term improvement in disability after IVIg	The justification of evidence category has been updated and now refers to Cochrane review 2013. Paragraph 2 was deleted – immunoadsorption is no longer used.

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	review found one low-quality RCT with a total sample size of 20, which demonstrated that more patients responded to immunoadsorption than IVIg, although the baseline disease duration was higher in the IVIg group. Differences were not significant.			compared with placebo RR2.4, NNT3 (high quality evidence). 1 study confirmed long term improvement over 24 and 48 weeks. IVIg had similar efficacy to Plasma Exchange, oral prednisolone and IV methyl prednisolone in the short term.			
Description and Diagnostic Criteria	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. 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.			CIDP is an acquired sensorimotor polyneuropathy characterised by a progressive or relapsing/ remitting course developing over at least 2 months with evidence of demyelination on electrophysiological or pathological studies and response to immunomodulating therapies. 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.			Addition: developing over at least 2 months – to qualify the progression of disease required for the diagnosis
Diagnosis is required	Yes	By which specialty	General physician or Neurologist	Yes	By which specialty	Neurologist	The system validates the requirement for diagnosis. Diagnosis is recommended to be limited to neurologists, if Ig is to be used. In order to support ongoing local rural patient care in some jurisdictions, once stable, patient referral to general physicians for review & ongoing management

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							of stable patients is required. This will involve formal handover between treating medical specialists within the Ig system. (See Review section)
Diagnosis must be verified	Yes	By which specialty	Neurologist (if neurologist did not make original diagnosis)	No	By which specialty		
Exclusion Criteria							No exclusion criteria required.
Indications	**First-line treatment for CIDP with treatment initiated when progression is rapid, or walking is compromised, or there is significant functional impairment.**			**Treatment of CIDP for patients in whom walking is compromised or there is significant disability** **Relapse of CIDP Patients within 6 months of commencement of trial off Ig therapy**			The indication has been modified to better describe eligible patients. Clinical assessments for efficacy now distinguish impairment and disability, with disability considered to be the most valid endpoint. A new indication was created to support re-entry of patients that relapse within 6 months of trial off ig treatment.
Qualifying Criteria	**First-line treatment for CIDP with treatment initiated when progression is rapid, or walking is compromised, or there is significant functional impairment.** Diagnosis of CIDP verified by a			**Treatment of CIDP for patients in whom walking is compromised or there is significant disability** • Adult or child (10 years or older) demonstrating significant disability or compromised walking as objectively			The criteria for eligibility have been more clearly defined. The INCAT-ONLS 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-ONLS disability score

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	neurologist; AND Significant functional impairment of activities of daily living (ADL).	measured by Inflammatory Neuropathy Cause and Treatment – Overall Neuropathy Limitations Scale (INCAT-ONLS) score of greater than 1 point. OR • Child (less than 10 years) demonstrating significant disability or compromised walking. (A baseline Modified Rankin ADL and Six minute walk test should be performed in order to assess the patient's response at initial review). **Relapse of CIDP Patients within 6 months commencement of trial off Ig therapy** • Previously stable adult or child (10 years or older) demonstrating a deterioration in disability as measured by a increase of greater than or equal to one point in the Adjusted INCAT-ONLS Score compared to the previous review score OR • Previously stable adult or child (10 years or older) demonstrating a deterioration in disability as measured by a reduction of greater than or equal to three points in the MRC Sum (12) Score compared to the previous review score. OR	is greater than 1. The INCAT-ONLS Score assesses both walking and significance of the disability, addressing all the criteria supporting the indication. Post public consultation, the assessment method was revised to a slightly more recent and sensitive version of the INCAT scoring system. A reference for INCAT-ONLS (with link) is be added to the system. It was noted that prescriptive qualification criteria are required to control access to Ig treatment, however, some patients may not always meet these criteria but would gain demonstrable benefit from Ig treatment. Consideration is recommended to be given to a national appeals process, potentially using peer review, to approve trials of Ig therapy to be used in association with other medication in such patients. The disability assessment systems for adults are not always appropriate for children with CIDP. A further option(s) was added for young children with review criteria defined. Due to the wide variability in young children, a written description regarding functional impairment will be assessed at qualifying (excessive falling over; lack of ability to get up from floor or out of a chair; impaired walking / running compared to before; unsteadiness on feet) and baseline assessments made by Modified Rankin ADL and Six minute walk test at qualifying and used to assess response at initial review. During the annual review, prescribers will consider

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		• Previously stable child (less than 10 years old demonstrating a deterioration in disability as measured by a reduction in the Six Minute Walk Test compared to the previous review score and an increase of at least one point in the Modified Rankin ADL Score AND **[Group 2]** • Relapse occurs within 6 months of the last Ig dose	trialling patients off therapy at the annual review, given that 50% of stable CIDP patients may achieve long term remission and would not require ongoing therapy. Given that some patients may relapse during a trial off therapy, a new indication is required to test eligibility for recommencement on Ig treatment.
Review Criteria	IVIg should be used for three to six months (three to six courses) before determining whether the patient has responded. Most individuals will respond within three months unless there is significant axonal degeneration whereby a six-month course will be necessary. If there is no benefit after three to six courses, IVIg therapy should be abandoned. Review Regular review by a neurologist is required: frequency as determined by clinical status of patient. For stable patients on maintenance treatment, review by a neurologist is	**Treatment of CIDP for patients in whom walking is compromised or there is significant disability** 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 this treatment, IVIg therapy should be abandoned. Review by a Neurologist is required within four months and annually thereafter (Neurologist or General Physician). Documentation of clinical efficacy is necessary for continuation of IVIg therapy. **On review of an initial authorisation period** • Adult or child (10 years or older)	The initial authorisation period is based on time, because 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 more than 4 months of treatment. General Physician was added to the "Who must undertake the review" field to allow local management for continuing review (only) for those rural patients requiring it. The initial review MUST be performed by a neurologist. Cessation is to be considered at initial review (4 months) and annually (Continuing Review). In this instance, a patient may then relapse and require recommencement of treatment. If the relapse occurs within 6 months, patients should be able to re-commence therapy without full re-qualification, however, it was agreed that

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	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 (activities of daily living — 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.	demonstrating improvement in disability as measured by a decrease of at least one point in the Adjusted INCAT-ONLS score compared to the qualifying score. OR • Adult or child (10 years or older) demonstrating improvement in impairment as measured by an increase in MRC sum score (12) of greater than three points compared to the qualifying score. OR • Child (less than 10 years) demonstrating improvement in disability as measured by the Six minute walk test compared to the qualifying score and a reduction of at least 1 point in the Modified Rankin ADL Score compared to qualifying. **On review of a continuing authorisation period** • Adult or child (10 years or older) demonstrating stabilisation or continued improvement in disease after previous evidence of deterioration in one or more of the Adjusted INCAT-ONLS Score and MRC Sum (12) Score compared to the previous review scores. OR • Child (less than 10 years) demonstrating stabilisation or continued improvement in	some assessment of deterioration in INCAT-ONLS or MRC score was still required before recommencing Ig treatment. 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. The initial authorisation review criteria were 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-ONLS 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-ONLS is adjusted for Review purposes. A second evaluation option for adults has been included in the review criteria. The MRC sum score is to be included for evaluation of disability at review in adults because a response in some patients could be present but not accurately measured by the INCAT-ONLS Score. It is not required at qualifying because Sensory CIDP & other variants would not be reflected in MRC sum score but are adequately assessed by INCAT-ONLS for qualification purposes.

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		disease after previous evidence of deterioration in the Six minute walk test and the Modified Rankin compared to the previous review scores. AND • A trial off therapy is planned or a valid reason provided as to why a trial is not being planned or is contra-indicated at this time. A trial off Ig therapy should be considered annually in stable patients on maintenance therapy to identify patients who are in remission. **Relapse of CIDP Patients within 6 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 this treatment, IVIg therapy should be abandoned. Review by a neurologist is required within four months and annually thereafter (Neurologist or General Physician). Documentation of clinical efficacy is necessary for continuation of IVIg therapy. Once a patient has relapsed when trialled off Ig treatment, a second line immunomodulatory agent should be strongly considered as additional therapy.	Some tolerance is required in authorisation values for stability as prescribers are being encouraged to find the minimal effective dose for patients. Patients would only be identified to be in long term remission if a trial off therapy is attempted. The continuing review screen 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. 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 three cycles, improvement must be demonstrated. Once response is achieved, the patient would move to an annual review. Once patients have relapsed and restarted 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 at some stage. The option should be offered. 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

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		On review of an initial authorisation period • Adult or child (10 years or older) demonstrating Improvement in disability as measured by a decrease in the Adjusted INCAT-ONLS score of at least one point and /or as measured by an increase in MRC sum (12) score of at least three points or both compared to the qualifying scores. OR • Child (less than 10 years) demonstrating improvement in disability as measured by an improvement in the Six minute Walk Test and a reduction of at least one point in the Modified Rankin ADL Score compared to the qualifying scores. **On review of a continuing authorisation period** • Adult or child (10 years or older) demonstrating stabilisation or continued improvement in disease after previous evidence of deterioration in one or both of INCAT-ONLS and MRC Sum (12) Scores compared to the previous review score. OR • Child (less than 10 years) demonstrating stabilisation or continued improvement in disease after previous evidence of deterioration as measured by the Six minute Walk Test and the Modified Rankin compared to the previous review scores.	as additional therapy . Text was added to the Review Preamble "Once a patient has relapsed when trialled off Ig treatment, a second line immunomodulatory agent should be strongly considered as additional therapy."

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		AND • A trial off therapy is planned or reason provided as to why a trial is not being planned or is contra-indicated at this time. Once a patient has relapsed in the first 6 months of a trial off therapy, a further trial might be considered after at least 2 years.	
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.**	**Induction** - 2 g/kg in 2 to 5 divided doses. **Maintenance** - Up to 0.4–1 g/kg, 2–6 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 4 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. Dosing above 1g/kg per day is contraindicated for some IVIg products. **Refer to the current product information sheet for further information.**	The dosing approach is the same for both indications. Induction dose is unchanged. Discussion regarding maintenance dosing indicated that changes are to be proposed in the next phase of work to consider published protocols (E.g. Mayo Clinic) where weekly dosing had proven to be efficacious. The limit on frequency under the current policy is 2 weekly. It was agreed that provided the total dose allowable in any month was not exceeded, dosing of patients on a weekly basis was acceptable under the policy. A statement to that effect was added to the maintenance dosing advice. The minimum dose was set to 0.01 to accommodate doses less than 0.4mg/Kg which could be efficacious. The maxiumum dose interval was set to 8 weekly. A divided dose is supported for maintenance to allow the aplitting of a 4 week total dose to be given up to weekly.

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