

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 REVISIONS TO THE CRITERIA	SWG RATIONALE FOR PROPOSED CHANGE (A) Administrative (B) Progressive (C) Programmed
Condition Name	Lambert–Eaton myasthenic syndrome	Lambert–Eaton myasthenic syndrome (LEMS)	
Specialty	Neurology	Neurology	
Chapter	5	5	
Specific Conditions			
Level of Evidence	Evidence of probable benefit (Category 2a).	Evidence of probable benefit (Category 2a).	
Description and Diagnostic Criteria	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. Patients with LEMS have a presynaptic neuromuscular junction defect. The clinical picture	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. Patients with LEMS have a presynaptic neuromuscular junction defect. The clinical	Diagnostic criteria have been updated to include specific requirements for confirming the diagnosis.

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	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).	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). Diagnosis should be confirmed by the presence of antibodies to Voltage gated calcium channels, electrophysiology consistent with LEMS, or both.	
Justification for Evidence Category	In the Biotext (2004) review, one systematic review (containing one RCT with 9 patients) and one case series of 7 patients with a crossover design were included. IVIg appeared to provide some benefit to patients with LEMS. However, both studies only included a small number of patients. Expert consensus states that IVIg produces temporary improvement in patients with LEMS. It therefore has a role as second line therapy (Asia-Pacific IVIg Advisory Board 2004). One submission to the National Blood Authority reported on a randomised controlled trial that showed significant improvement in strength associated with a decline in the level of pathogenic antibodies (NSW IVIg User Group).	In the Biotext (2004) review, one systematic review (containing one RCT with 9 patients) and one case series of 7 patients with a crossover design were included. IVIg appeared to provide some benefit to patients with LEMS. However, both studies only included a small number of patients. Expert consensus states that IVIg produces temporary improvement in patients with LEMS. It therefore has a role as second line therapy (Asia-Pacific IVIg Advisory Board 2004). Treatment of LEMS with 3,4DAP and pyridostigmine has been shown to be efficacious in an RCT (Wirtz Clinical pharmacology & Therapeutics; VOLUME 86 NUMBER 1, JULY 2009) and should be regarded as combined firstline therapy. 3,4DAP is not a licensed medication in Australia but can be	Section has been revised including evidence for Ig treatment of paraneoplastic LEMS. <u>Post public consultation, modified to clarify that immunosuppression not used in paraneoplastic LEMS.</u>

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		sourced as an import and used under the SASB scheme. One submission to the National Blood Authority reported on a randomised controlled trial that showed significant improvement in strength associated with a decline in the level of pathogenic antibodies (NSW IVIg User Group). IVIG may provide additional benefit. Immunosuppression with prednisone, azathioprine or cyclosporine has been reported in cases to be beneficial in non-paraneoplastic LEMS however has not been subject to an RCT. Treatment of paraneoplastic LEMS including with 3,4DAP, pyridostigmine or with IVIG will not treat the underlying neoplasia but may be necessary for symptomatic reasons. Treatment of the underlying neoplasia often helps the LEMS. (Newsom-Davis Semin Neurol 2003). Patients with paraneoplastic LEMS due to small cell lung cancer has been associated with a significantly longer mean survival than patients with small cell lung cancer suggesting an immune vs tumour effect. Accordingly immunosuppression (<u>as opposed to IVIg</u>) has not generally been applied in paraneoplastic LEMS.	

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Diagnosis is required	Mandatory assessment by a neurologist.	Yes	By which specialty	Neurologist	Given that LEMS is very rare, diagnosis is already likely to be made by neurologists.
Diagnosis must be verified		No	By which specialty		
Exclusion Criteria	Adult paraneoplastic OMA.				The SWG could not find any evidence as to why this exclusion existed. The incidence was very rare, and was treated in the same way as Idiopathic OMA in adults, that is, with Ig as second line treatment after steroids.
Indications	Short-term therapy for severely affected nonparaneoplastic LEMS patients.	Additional therapy for LEMs patients with disability where symptomatic therapy is insufficient.			Revised Indication replacing “short term therapy” to additional therapy once alternative therapy has been tried. The limitation to non-paraneoplastic patients was rejected by the SWG (see update to justification for evidence section). The condition is very rare and can be very debilitating. SWG confirmed that Ig treatment is necessary in practice while patients have chemo & Radiotherapy. The 9 person

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			double blind cross over RCT by JNDs group was non paraneoplastic but case reports in paraneoplastic LEMS have confirmed benefit in that group as well. As noted above the other options are not desirable in paraneoplastic LEMS.
Qualifying Criteria	Mandatory assessment by a neurologist; AND Severely affected nonparaneoplastic LEMS patients in whom other therapy (e.g. with 3,4-diaminopyridine) has failed.	[Group 1] - Severe LEMS with impairment as demonstrated by MRC Sum (12) Score OR - Severe LEMS with significant autonomic involvement AND [Group 2] - Alternative therapies have failed or an insufficient response has been achieved.	The SWG confirmed MRC Sum (12) Score to be the appropriate evidence item to assess disability in LEMS with motor involvement. SWG noted that there is no standard of measure in LEMS but MRC Sum Score will adequately assess disability for those without autonomic symptoms. The MRC Sum Score qualifying value will be used to measure as a baseline for response at review. The SWG noted that while Plasma exchange can be used as an alternative to IVIg, is reported in reviews to be less effective than Plasma Exchange (PLEX) in Myasthenia Gravis. SWG noted that

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			autonomic involvement which occurs in 80% of LEMS often leads to significant cardiovascular instability during PLEX treatment. The types of alternative therapy that must be trialled are Cholinesterase inhibitors such as Peritostigmine or Amidopyrines (3,4 Diaminopyridine) It is noted that 3,4DAP is not a licensed medication in Australia but can be sourced as an import and used under the SASB scheme. As prescribers may not be able to access for patients, cholinesterase inhibitors may be the only alternative medication available.
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. Review Regular review by neurologist is required: frequency as determined by clinical status of	Additional therapy for LEMs patients with disability where symptomatic therapy is insufficient IVIg should be used for four months (induction plus three maintenance cycles) before determining whether the patient has responded. If there is no benefit after this treatment, IVIg	SWG confirmed that 3 months treatment, with induction is sufficient to know if it is beneficial. The timeframe for induction with 3 months treatment is 4 months. Patients can be reviewed earlier than this if response has occurred. It was noted that rural patients are problematic to review under 4

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	patient. Initial review three to six monthly. 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 (ADL) or quantitative muscle scores or Medical Research Council (MRC) muscle assessment; OR 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.	therapy should be abandoned. Review by a Neurologist is required within four months of treatment and annually thereafter. DClinical documentation of <u>clinical</u> effectiveness is necessary for continuation of IVIg therapy. On review of an initial authorisation period Re-authorisation may only be approved where a an improvement reduction in impairment is demonstrated, <u>as measured</u> by: - Clinically significant improvement in muscle weakness as measured by an increase in the MRC Sum (12) Score compared to the qualifying score. OR - A clinically significant improvement in the severity of autonomic symptoms compared to the severity of symptoms at qualifying. On review of a continuing authorisation period [Group 1]	months. A link to MRC Scoring system will be available within the system: <i>Kleyweg RP, van der Meche FGA, Schmitz PIM. Muscle Nerve 1991;14:1103-1109</i>

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		Re-authorisation may only be approved where there is stabilised disease as demonstrated by: • MRC Sum (12) Score that is greater than or equal to the previous review score and greater than the qualifying score. OR • Stability in autonomic symptoms compared to previous review and sustained improvement compared to symptoms at qualifying. AND [Group 2] • A trial off Ig therapy is planned or a valid reason provided as to why a trial is not being planned or is contraindicated at this time.	SWG confirmed the need for clinically significant improvement in muscle weakness or autonomic symptoms is required for a response to Ig treatment. This would be measured by MRC Score for motor weakness and described in text for autonomic disability. SWG confirmed that a trial off therapy is appropriate. Given that LEMS is very rare, and the number of patients very small, re-authorisation could be managed by re-qualifying with a new authorisation request as

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			the criteria for eligibility will be the same.
Dose	Induction: 2 g/kg in 2 to 5 divided doses. Maintenance: 0.4–1 g/kg, 2–6 weekly. 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 - 0.4–1 g/kg, 2–6 weekly. 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. The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient. Refer to the current product information sheet for further information.	Dosing is unchanged, however, the capacity to treat more frequently than fortnightly should be provided. A reduced or same dose can be given with superior clinical benefit in some patients. The total dose allowable under the current Criteria will not be exceeded. This provides consistency with CIDP and other conditions.
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