

2017 (v3.0) Proposed changes to v2.1 of the Criteria for the clinical use of intravenous immunoglobulin in Australia

v3.0 CONDITION NAME: Neuromyelitis Optica Spectrum Disorders (NMOSD)	
v2.1 CONDITION NAME: Devic Disease (neuromyelitis optica)	
PROPOSED APPROACH: To retain Neuromyelitis Optica Spectrum Disorders (NMOSD) (previously named Devic disease) in <i>Exceptional circumstances only</i> with changes as outlined.	SUMMARY OF RATIONALE: The recommended changes are supported by factors including that: <ul style="list-style-type: none">• NMOSD is a relatively rare and devastating condition characterised by recurrent bouts of optic neuritis and myelitis, which is recognised as being an entity distinct from multiple sclerosis requiring different treatment.• International consensus diagnostic criteria were revised in 2015 to include a broader group of patients and these criteria have been applied to the qualifying criteria (Wingerchuk et al, 2015).• International expert opinion has also informed the recommendation of the treatment approach to anti-MOG positive and sero-negative patients.• Ig usage in Australia has been increasing over the last 2 years presumably as a result of increased recognition of the disease and more appropriate treatment. More cost effective Ig use will be assured by the revised criteria which confirm compliance with the international diagnostic criteria and better control access to Ig therapy.• While this condition is not listed in either the UK (UK Department of Health, 2011) or Canadian (Ontario Regional Blood Coordinating Network, 2016) guidelines, it is noted that very rare immune-mediated disorders with evidence of immunoglobulin efficacy are not necessarily listed in guidelines but may still be approved for funded use in those countries.
v2.1 CONDITION CATEGORY: Condition for which Ig use is in Exceptional circumstances only (Chapter 7)	
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Role of Ig therapy: First line treatment is with intravenous corticosteroids and plasma exchange in acute attacks of NMOSD. IVIg is only used when there is significant disability and there is no response to first line therapy or when first line treatments are contra-indicated (or plasmapheresis is unavailable). Importantly, IVIg does not generally have a role in chronic immune modulation of AQP4 antibody positive NMOSD. Chronic immune suppression is required for most of these patients, and immune suppressant agents such as azathioprine, mycophenolate mofetil, methotrexate, rituximab and cyclophosphamide reduce annualized relapse rates in uncontrolled retrospective and prospective studies. A newer antigenic target, myelin oligodendrocyte glycoprotein (MOG) has been identified which corresponds to 20% of previously sero-negative patients and antibodies to MOG are more commonly detected in paediatric populations. The disease course is slightly different and literature is still emerging, however, a relapsing course with steroid dependence will require more than a single course of Ig and/or immunosuppressant therapy.

ITEM	CRITERIA v2.1	PROPOSED REVISIONS TO THE CRITERIA	SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CLARIFICATIONS
Condition Name	Devic disease (neuromyelitis optica)	Neuromyelitis optica spectrum disorders	The revised name more accurately reflects the condition for which Ig therapy is warranted.
Specialty	Neurology	Neurology	
Category	<i>Exceptional circumstances only</i>	<i>Exceptional circumstances only</i>	
Specific Conditions	Devic disease (neuromyelitis optica)	NMOSD –AQP4 ab positive NMO NMOSD-MOG ab positive NMOSD - seronegative LETMS	The specific conditions have been more clearly articulated and reflect diagnoses within the spectrum and differing serology results.
Level of Evidence	Insufficient data (Category 4a)	Insufficient data (Category 4a)	No change
Justification		There is significant anecdotal evidence to support the use of IVIg in	No change

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for Evidence Category		the treatment of acute attacks of NMOSD if plasma exchange and/or intravenous corticosteroids are contra-indicated or have failed. There is no evidence for the use of IVIg as long-term therapy or prophylaxis. Two very small studies (Viswanathan et al, 2015 and Elson et al, 2014), show that IVIg may be effective in reducing relapse risk although both are of limited significance.	
Indications		<p>Acute relapse of NMOSD with significant disability and corticosteroids and/or plasmapheresis have failed, are contraindicated or unavailable</p> <p>Further significant relapse post Ig therapy with significant disability and resistant to corticosteroids and other immunosuppressant agents</p>	Two indications have been defined to both manage initial treatment and support treating relapse, which is likely to occur in MOG ab positive patients who are steroid resistant.
Description and Diagnostic Criteria	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	<p>NMOSD is an idiopathic, antibody mediated astrocytopathy 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, have shown variable benefit in this otherwise devastating disorder.</p> <p>Diagnostic criteria have been published in 2015 by the International panel for NMO diagnosis (Winderchuk et al, 2015). There are only small retrospective case series of IVIg for this condition, with no RCTs. Recent work has clearly defined that plasma exchange and intravenous corticosteroids are the treatment of choice for acute attacks (Kleiter et al, 2016). Chronic immune suppression is required</p>	Two paragraphs were added to incorporate more recent publications relating to diagnostic criteria and new information about myelin oligodendrocyte glycoprotein. Background is provided explaining that steroid dependent MOG antibody positive patients may be treated with additional Ig therapy, not necessarily in combination with immunosuppression (unlike AQP4 positive disease).

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	<p>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 intravenous immunoglobulin (IVIg) therapy. Single case reports of various therapies, including IVIg, have shown variable benefit in this otherwise devastating disorder.</p>	<p>for most patients with AQP4 ab NMOSD, and immune suppressant agents such as azathioprine, mycophenolatemofetil, methotrexate, rituximab and cyclophosphamide reduce annualized relapse rates in uncontrolled retrospective and prospective studies. IVIg does not generally have a role in chronic immune modulation of AQP4 ab NMOSD.</p> <p>A newer antigenic target, myelin oligodendrocyte glycoprotein (MOG) has been identified which accounts for 20% of previously sero-negative patients and is more commonly detected in paediatric populations. The disease course is slightly different and literature is still emerging, however, a relapsing course with steroid dependence will require more than a single course of Ig, and/or immunosuppressant therapy.</p>			
Diagnosis is required		Yes	By which specialty	Neurology	<p>This condition must now be diagnosed by a neurologist for access to Ig. The tests required to demonstrate disease severity are commonly used within this discipline.</p>
Diagnosis must be verified		No	By which specialty		
Exclusion Criteria					
Qualifying Criteria		Acute relapse of NMOSD with significant disability and corticosteroids and/or plasmapheresis have failed, are			<p>Evidence items supporting the criteria include confirming compliance with the diagnostic</p>

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		<p>contraindicated or unavailable</p> <ul style="list-style-type: none"> • Diagnosis of NMOSD consistent with criteria of the International panel for NMO diagnosis and significant disability as measured by Expanded Disability Status Scale score of at least 2 points. <p>AND</p> <ul style="list-style-type: none"> • Presence of AQP4-IgG or MOG IgG antibodies <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • Diagnosis of sero-negative NMOSD or testing unavailable. (Note: Multiple Sclerosis has been excluded or is considered unlikely) <p>AND</p> <ul style="list-style-type: none"> • No clinical response has been achieved following standard steroid therapy. <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • Steroid therapy is contraindicated <p>AND</p> <ul style="list-style-type: none"> • Plasmapheresis therapy is ineffective or contra-indicated <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • Plasmapheresis treatment is unavailable <p>Further significant relapse post Ig therapy with significant disability and resistant to corticosteroids and other immunosuppressant agents</p> <ul style="list-style-type: none"> • Diagnosis is consistent with criteria of the International panel for NMO diagnosis and further relapse with significant disability as measured by Expanded Disability Status Scale 	<p>criteria as determined by international consensus in 2015 (Wingerchuk et al, 2015) and a text description of the key symptoms. Standardisation of the assessment method for the level of disability has been defined and will be accessible within BloodSTAR.</p> <p>Consistency with the required diagnostic criteria is confirmed.</p>

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		<p>score of at least 2 points.</p> <p>AND</p> <ul style="list-style-type: none"> • Improvement was demonstrated in the severity of symptoms and degree of disability following Ig treatment as measured by EDSS compared to the pre-treatment qualifying assessment <p>AND</p> <ul style="list-style-type: none"> • No clinical response has been achieved following standard steroid therapy. <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • Steroid therapy is contraindicated <p>AND</p> <ul style="list-style-type: none"> • No clinical response following treatment with prolonged plasma exchange and/or at least 2 Immunosuppressant agents <p>Ig therapy for steroid resistant NMOSD is recommended to be used as combination therapy</p>	<p>Confirmation that the patient did respond to previous Ig therapy.</p> <p>Script advising that Ig therapy should be used in combination with immunosuppressant medications.</p>
Review Criteria		<p>Acute relapse of NMOSD with significant disability and corticosteroids and/or plasmapheresis have failed, are contraindicated or unavailable</p> <p>Review is not mandated for this condition.</p> <p>Clinical effectiveness of Ig therapy can be demonstrated by:</p> <ul style="list-style-type: none"> • Post Ig treatment improvement in the severity of symptoms and degree of disability as assessed by EDSS compared to 	<p>Review is not required for the first indication as one-off treatment is given. Outcome measures have been defined.</p> <p>Once a patient has qualified for Ig therapy to</p>

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		<p>the qualifying assessment</p> <p>Further significant relapse post Ig therapy with significant disability and resistant to corticosteroids and other immunosuppressant agents</p> <p>Review by a Neurologist is required within 6 months of treatment and six monthly thereafter. Documentation of clinical effectiveness is necessary for continuation of Ig therapy.</p> <p>On review of the initial authorisation period</p> <p>Clinical effectiveness of Ig therapy can be demonstrated by:</p> <ul style="list-style-type: none"> • Post Ig treatment improvement in the severity of symptoms and degree of disability as assessed by EDSS compared to qualifying <p>On review of a continuing authorisation period</p> <p>Clinical effectiveness of Ig therapy can be demonstrated by:</p> <ul style="list-style-type: none"> • Improvement in the severity of symptoms and degree of disability as assessed by EDSS compared to the previous review <p>AND</p> <ul style="list-style-type: none"> • A trial of Ig weaning is planned for clinically stable patients to identify those in remission, or a valid reason provided as to why a trial is not planned or is contraindicated at this time <p>A trial of Ig weaning should be considered annually in stable</p>	<p>treat relapse, initial review at six months will confirm that a clinical response has been demonstrated by improvement in symptoms compared to the qualifying assessment and as assessed by an increase in EDSS Score of at least one full point.</p> <p>Further improvement needs to be demonstrated at the continuing review, six months later.</p> <p>A trial of weaning has been defined for stable patients to identify patients in remission.</p>

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		<p>patients on maintenance therapy to identify patients who are in remission.</p>	
Dose		<p>Acute relapse of NMOSD with significant disability and corticosteroids and/or plasmapheresis have failed, are contraindicated or unavailable</p> <p>Induction dose– 2 g/kg in divided doses over 2 to 5 days</p> <p>The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.</p> <p>Refer to the current product information sheet for further information on dose, administration and contraindications.</p> <p>Further significant relapse post Ig therapy with significant disability and resistant to corticosteroids and other immunosuppressant agents</p> <p>Induction dose– 2 g/kg in divided doses over 2 to 5 days</p> <p>Maintenance dose – 1 g/kg in single or divided doses over 2 to 5 days, four to six weekly. Ig therapy is intended to be used in combination with an immunosuppressant agent</p> <p>The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.</p> <p>Refer to the current product information sheet for further information on dose, administration and contraindications.</p>	<p>Dosing has been developed after consultation of the literature and agreed by expert consensus.</p> <p>Acute relapse is supported by a single one-off dose while maintenance is also defined for managing relapse, with control limits extending below 1 g/kg to support weaning. Access to an additional induction dose is supported in case a further relapse should occur while on maintenance therapy.</p>

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(most recent update: February 2016)

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POTENTIAL OPERATIONAL IMPACT

The revised criteria provide significantly greater guidance for access to Ig therapy and patient management and a neurologist is required to diagnose and manage patients with the condition. There will be increased data entry required (e.g. compliance with the international consensus diagnostic criteria) compared to the previous Ig request process. Patients will be required to be assessed at qualifying (and review for relapse) using an Expanded Disability Status Scale, which is routinely used by Neurologists in the assessment of multiple sclerosis and more information will be available from within the BloodSTAR v3.0 system. Where access to ongoing Ig therapy is approved, patients will be reviewed six monthly and weaning from Ig must be considered after 12 months' treatment to identify those patients in remission. If a patient relapses, a further request may be made.

POTENTIAL IMPACT ON PATIENTS, DEMAND AND EXPENDITURE

Description of impact on patients:

There is not anticipated to be any significant impact on patients as a result of these criteria given that the proposed changes align with the expected clinical management of patients with this rare condition. The formal access criteria proposed require that a neurologist makes the diagnosis and manages the treatment. This is because it is a very rare condition that can be misdiagnosed as Multiple sclerosis and it is important that the correct treatment is being given to patients. Ig therapy is only indicated after patients have not responded to other treatments or they are unavailable or inappropriate. Most patients will respond to the initial treatment with Ig therapy, and, if symptoms return after treatment, a further request for ongoing Ig therapy can be made. In the setting of ongoing therapy, Ig is recommended to be given in combination with a second medication.

For existing patients on Ig maintenance therapy, six monthly reviews are required to assess the effectiveness of the treatment to improve the severity of symptoms and degree of disability. Given that patients will already require regular review by their neurologist, this requirement will not place an added burden on patients. If patients relapse while they are on maintenance therapy, an extra Ig dose can be requested. A trial of reducing dose and then stopping Ig therapy will be considered by doctors after at least twelve months treatment and when patients are well and stable to test whether the disease is in remission. If, patients relapse after Ig treatment has been stopped, a further request to restart ongoing Ig therapy can be made.

New patients authorised to receive ongoing Ig therapy will require an initial check after the first six months of Ig treatment to confirm that Ig therapy is improving the severity of symptoms and degree of disability. If improvement has been demonstrated after six months ongoing treatment, Ig therapy will be continued; otherwise a different treatment would be required. The ongoing arrangements for maintenance therapy are as outlined above for existing patients.

Impact on demand:		In line with the recognition of the broader diagnostic criteria for NMOSD, there has been an increase in demand for Ig therapy since 2013-14. Given that the current <i>Criteria</i> do not provide any guidance regarding appropriate access or treatment periods, the revised criteria are likely to improve the cost effectiveness of Ig use and may reduce demand, relative to what it might have been prescribed. However, despite being increasingly recognised, given the relatively low prevalence, there is unlikely to be any measurable impact on overall demand.				
	2011-12	2012-13	2013-14	2014-15	2015-16	The Specialist Working Group estimated magnitude of effect: No impact against projected demand
Patient number	16	19	24	29	42	
Total Grams issued	3,541	5,385	7,151	8,821	12,477	
% Total Grams issued	0.11%	0.15%	0.18%	0.2%	0.25%	
Specialist Working Group knowledge development opportunities and recommendations relevant to the transition to v3.0						
None identified at this time.						

END OF PUBLIC CONSULTATION DOCUMENT

Next review: Twelve to eighteen months from BloodSTAR v3.0 implementation