

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

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| v2.1 CONDITION NAME: Epilepsy v3.0 CONDITION NAME: Childhood epileptic encephalopathy | |
| PROPOSED APPROACH: To change the condition name from Epilepsy to Childhood epileptic encephalopathy and retain in <i>Exceptional circumstances only</i> with the changes as outlined. | SUMMARY OF RATIONALE: The recommended changes are supported by factors including that: <ul style="list-style-type: none"> - While the literature on IVIg in Epileptic encephalopathy syndromes (including West syndrome, Landau Kleffner, Lennox Gaustaut) is limited to case reports and small case series, the Specialist Working Group concluded that a proportion of patients with these epileptic syndromes may benefit from IVIg, particularly those patients with demonstrable immune abnormalities in blood, CSF or neuroimaging. - Consultation with a number of paediatric specialist epileptologists nationally has confirmed that Ig therapy is being used as third line treatment and that the condition should be retained in the Criteria to treat those refractory children and help control their intractable epilepsy to ensure that neurodevelopmental and neurocognitive function improves as much as possible. - Usage data over five years confirms that demand is declining for this condition, with only small numbers of patients currently being treated, in line with expected prevalence. - Qualifying criteria have been defined to identify appropriate patients and limit access to those who respond clinically within three months. - This condition (intractable childhood epilepsy), is listed as a 'grey' indication in the UK NHS immunoglobulin guidelines (UK Department of Health, 2011). Indications are categorised as 'grey' if evidence is weak. The UK guidelines acknowledge that in many cases, this is because the disease is rare. Local approval is required to access IVIg for 'grey' indications. |
| v2.1 CONDITION CATEGORY: Condition for which Ig use is in Exceptional circumstances only (Chapter 7) v3.0 CONDITION CATEGORY: Condition for which Ig use is in Exceptional circumstances only (Chapter 7) | |

Role of Ig therapy: IVIg is a third line therapy after high dose corticosteroids and multiple anticonvulsant medications and access is required to remain for those patients who are either refractory to steroids (or are responsive but dependant or where steroids are an *absolute* contraindication) and remain unresponsive to multiple anticonvulsant medications. The disease invariably eventually goes into remission and once patients are stable, a trial of weaning is planned to be considered annually to identify those who may be in remission. If patients relapse once Ig therapy is ceased, they may requalify, provided a previous clinical response has been documented.

Ig use in this condition is reasonably stable over the last three years. The incidence of Lennox-Gestaut for example, is about one new case per year per tertiary paediatric centre nationally. Treatment of Lennox-Gestaut at induction is now very much more aggressive than previously and as a result, fewer patients progress to these chronic syndromes than was the case a decade ago. A number of children are now recognised to have genetic encephalopathy rather than an immune mediated condition and would not qualify for treatment.

| ITEM | CRITERIA v.2.1 | PROPOSED REVISIONS TO THE CRITERIA | SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CLARIFICATIONS |
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| Condition Name | Epilepsy | Childhood epileptic encephalopathy | The condition name better indicates that an inflammatory condition is being treated. |
| Specialty | Neurology | Neurology | |
| Category | <i>Exceptional circumstances only</i> | <i>Exceptional circumstances only</i> | |
| Specific Conditions | Epilepsy (rare childhood cases) | Landau Kleffner syndrome Lennox-Gastaut syndrome Atypical rolandic epilepsy West syndrome | One of the specific conditions must be selected. |
| Level of Evidence | Evidence of probable benefit – more research needed (Category 2a) | Evidence of probable benefit – more research needed (Category 2a) | Unchanged |
| Justification for Evidence | | The literature on IVIg in epileptic encephalopathy syndromes such as West syndrome, Landau Kleffner, Lennox Gaustaut is limited to case | Added a description of the justification for evidence category after consulting the |

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| Category | | reports and small case series and the quality of this literature is poor. It can be concluded that a proportion of patients with these epileptic syndromes may benefit from IVIg, particularly those patients with demonstrable immune abnormalities in blood, CSF or neuroimaging. | literature. |
| Indications | | <p>Children with Epileptic encephalopathy resistant to anti-epileptic medications and steroid therapy or steroid responsive but dependant</p> <p>Relapse of Epileptic encephalopathy following a trial of weaning from Ig therapy in a patient previously demonstrating response</p> | Two indications were developed to allow specific dosing and review criteria to be developed in these different scenarios. Weaning from Ig therapy is being encouraged to determine those patients that may be in remission, and therefore, relapsed patients will require to recommence treatment but should not need full requalification. |
| Description and Diagnostic | <ul style="list-style-type: none"> Landau–Kleffner syndrome | Epilepsy is a clinical syndrome of recurrent epileptic seizures and has multiple causes. Immune mediated mechanisms can result in epilepsy. Patients with epilepsy due to clear cut inflammatory | Greater detail is provided about the circumstances in which Ig therapy is able to be |

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| Criteria | <ul style="list-style-type: none"> Lennox–Gastaut syndrome <p>Intravenous immunoglobulin (IVIg) should be considered in childhood cases only after failure of all conventional therapies and full assessment by a Paediatric Neurologist.</p> | <p>syndromes such as autoimmune encephalitis, Rasmussen encephalitis or post encephalitic epilepsy are considered elsewhere.</p> <p>It is possible that immune mechanisms have a role in some cases of epilepsy, however defining these mechanisms is challenging. A few epileptic encephalopathy syndromes in infants and young children are responsive to steroids, and for this reason, an immune mechanism is possible. IVIg has been trialled in these patients with mixed success. A subgroup of patients with West syndrome, Landau Kleffner syndrome and Lennox Gaustaut syndrome have been observed to respond to steroids or IVIg and there is uncontrolled case report data that supports a possible improvement of symptoms with IVIg.</p> | | | accessed under this condition. |
| Diagnosis is required | | Yes | By which specialty | Neurology | Diagnosis is now required by a Neurologist to ensure accurate diagnosis and subsequent appropriate access to Ig therapy for this condition. |
| Diagnosis must be verified | | No | By which specialty | | |
| Exclusion Criteria | | <p>Rasmussen encephalitis - refer separate condition</p> <p>Post encephalitic epilepsy - see Autoimmune encephalitis mediated by extracellular antibodies</p> | | | Direction has been provided regarding access to Ig for other similar conditions. |
| Qualifying Criteria | | Children with Epileptic encephalopathy resistant to anti-epileptic medications and steroid therapy or steroid responsive but dependant | | | Explicit qualifying criteria have been developed. It was noted that while it may be desirable to look for evidence of inflammation |

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| | | <p>[Group 1]</p> <ul style="list-style-type: none"> • Diagnosis of Landau Kleffner syndrome, Lennox-Gastaut syndrome, West syndrome or Atypical rolandic epilepsy confirmed by EEG <p style="text-align: center;">AND</p> <ul style="list-style-type: none"> • Refractory epilepsy with ongoing seizures of at least weekly frequency <p style="text-align: center;">AND</p> <ul style="list-style-type: none"> • Associated neurodevelopmental or neurocognitive issues <p>AND</p> <p>[Group 2]</p> <ul style="list-style-type: none"> • Failure of steroid therapy to control seizures <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • Steroid responsive but patient is steroid dependant for seizure control <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • Steroid therapy is an <i>absolute</i> contraindication <p>AND</p> <p>[Group 3]</p> <ul style="list-style-type: none"> • Persistent seizures despite treatment with multiple anti-convulsant medications <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • Persistent seizures despite surgical intervention to control epilepsy <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • Surgical intervention is inappropriate | <p>in these children, routine CSF studies will not be helpful and there is no literature supporting the relevance of evidence of inflammation in these conditions. A clinical diagnostic approach has been recommended with assessment and reporting of the frequency of seizures, which must be at least weekly to qualify. Neurodevelopmental delays and /or neurocognitive issues must also be documented.</p> |

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| | | <p>Relapse of Epileptic encephalopathy following a trial of weaning from Ig therapy in a patient previously demonstrating response</p> <ul style="list-style-type: none"> • Documented deterioration in symptoms of Epileptic encephalopathy within 3 months of ceasing Ig therapy <p>AND</p> <ul style="list-style-type: none"> • Increased frequency of seizures compared to the previous review assessment when receiving Ig therapy | |
| <p>Review Criteria</p> | | <p>Children with Epileptic encephalopathy resistant to anti-epileptic medications and steroid therapy or steroid responsive but dependant</p> <p>IVIg should be used for up to three months before determining whether the patient has responded. If there is no benefit after this treatment, IVIg therapy should be abandoned.</p> <p>Review by a Neurologist is required within 3 months of treatment to determine whether the patient has responded, and annually thereafter. Documentation of clinical effectiveness (such as maintaining a seizure diary) is necessary for continuation of IVIg therapy.</p> <p>Once patients are stable, a trial of weaning from Ig therapy may be considered every year to identify those in remission.</p> | <p>Detailed review criteria have been developed in consultation with paediatric epileptologists and Specialist Working Group consensus.</p> |

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| | | <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"> • Documented improvement in the severity of symptoms (including improved cognition or behaviour or ambulation) compared to at qualifying. <p>AND</p> <ul style="list-style-type: none"> • Reduction in the severity and/or frequency of seizures compared to the qualifying assessment <p>On review of a continuing authorisation period</p> <p>For patients on maintenance therapy, review by a Neurologist is required at least annually. Once patients are stable, a trial of weaning from Ig therapy should be considered every year to identify those in remission.</p> <p>Clinical effectiveness of Ig therapy can be demonstrated by:</p> <ul style="list-style-type: none"> • Further documented improvement in or stabilisation of symptoms (cognition or behaviour or ambulation) compared to the previous review assessment. <p>AND</p> <ul style="list-style-type: none"> • Further documented improvement in or stabilisation of seizures compared to the previous review <p>AND</p> <ul style="list-style-type: none"> • A trial of weaning from Ig therapy is considered annually for | <p>An assessment of clinical response is confirmed at initial review for re-authorisation of Ig therapy.</p> |

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| | | <p>patients who are clinically stable to identify those in remission or a valid reason provided as to why a trial is not being planned or is contra-indicated at this time.</p> <p>Relapse of Epileptic encephalopathy following a trial off Ig therapy</p> <p>IVIg should be used for up to three months before determining whether the patient has responded. If there is no improvement after this treatment, IVIg therapy should be abandoned.</p> <p>Review by a Neurologist is required within 3 months of treatment to determine whether the patient has responded, and annually thereafter. Documentation of clinical effectiveness (such as maintaining a seizure diary) is necessary for continuation of IVIg therapy.</p> <p>Once patients are stable, a trial of weaning from Ig therapy should be considered every year to identify those in remission.</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"> • Documented improvement in the severity of symptoms (improved cognition or behaviour or ambulation) compared to the severity of symptoms of relapse. <p>AND</p> <ul style="list-style-type: none"> • Reduction in the severity and/or frequency of seizures compared to the qualifying assessment | |

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| | | <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"> • Further documented improvement in or stabilisation of symptoms (improved cognition or behaviour or ambulation) compared to the previous review assessment. <p>AND</p> <ul style="list-style-type: none"> • Further documented improvement in or stabilisation of seizures compared to the previous review <p>AND</p> <ul style="list-style-type: none"> • A trial of weaning from Ig therapy is considered annually for patients who are clinically stable to identify those in remission or a valid reason provided as to why a trial is not being planned or is contra-indicated at this time. | |
| <p>Dose</p> | <p>Refer to the current product information sheet for further information.</p> <p>The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.</p> | <p>Children with Epileptic encephalopathy resistant to anti-epileptic medications and steroid therapy or steroid responsive but dependant</p> <p>Induction Dose – 2 g/kg as divided dose over 2 to 5 days</p> <p>Maintenance Dose – 1 g/kg as divided dose over 2 to 5 days monthly</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</p> | <p>Dosing was defined by the Specialist Working Group to allow higher initial dosing with lower maintenance dosing should ongoing therapy be required.</p> |

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| | | <p>information on dose, administration and contraindications.</p> <p>Relapse of Epileptic encephalopathy following a trial of weaning from Ig therapy in a patient previously demonstrating response</p> <p>Induction Dose – 2 g/kg as divided dose over 2 to 5 days</p> <p>Maintenance Dose – 1 g/kg as divided dose over 2 to 5 days monthly</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>References (most recent update: March 2016)</p> | | | |
| <p>Geng J, Dong J, et al (2011) Intravenous immunoglobulin for epilepsy, <i>Cochrane database of systematic reviews</i> (online) 1(1):CD008557 January 2011 DOI:10.1002/14651858.CD008557.pub2</p> <p>Geva-Dayan K, Shorer Z et al (2012) Immunoglobulin treatment for severe childhood epilepsy. <i>Pediatric Neurology</i>, 46(6):375-81.</p> <p>Mikati MA, Kurdi r et al (2010) Intravenous immunoglobulin therapy in intractable childhood epilepsy: open-label study and review of literature. <i>Epilepsy & Behaviour</i>, 17(1):90-94.</p> | | | |

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| POTENTIAL OPERATIONAL IMPACT | |
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| <p>There is expected to be minimal operational impact as a result of these changes as they are anticipated to align with existing clinical practice. There will be slightly increased data entry required (e.g. compliance with diagnostic and other criteria) compared to the previous Ig request and review processes. Review frequency is expected to align with the usual follow-up for patients. Patients will be required to be assessed at qualifying and review for both the frequency of seizures and an assessment of any changes in neurodevelopmental or neurocognitive function. A trial of weaning should be considered after at least twelve months, and once the patient's symptoms are stabilised. If patients relapse after Ig treatment has been ceased, a further request can be made.</p> | |
| POTENTIAL IMPACT ON PATIENTS, DEMAND AND EXPENDITURE | |
| <p>Description of impact on patients:</p> | <p>There is not anticipated to be any significant impact on patients as a result of these criteria given that the proposed changes are based on how neurologists already diagnose and manage patients with these very rare conditions. The formal access criteria proposed for this group of conditions require that a neurologist makes the diagnosis and manages the treatment. This is to ensure that the correct diagnosis has been made and appropriate treatment given. Unlike some other types of epilepsy, an immune process is believed to be causing the seizures in this group of conditions. Ig therapy will be used only for patients where other treatments have been unsuccessful in controlling seizures.</p> <p>For existing patients on Ig maintenance therapy, annual reviews are required to assess the effectiveness of the treatment to improve or stabilise the severity of symptoms and severity and/or frequency of seizures. Given that patients will already require regular review by their specialist, this requirement will not place an added burden on patients. The use of a seizure diary to record any change in how often patients are having seizures while receiving Ig therapy is encouraged but is not essential. A trial of reducing dose and then stopping Ig therapy will be considered by doctors after at least twelve months treatment and after patients are well and stable. This is because the conditions will eventually go into remission and Ig treatment will not be required. If patients relapse and seizures start again after Ig therapy has been stopped, a further request for ongoing Ig therapy can be made.</p> <p>New patients or relapsed patients authorised to receive Ig therapy will require an initial check after the first three months of Ig treatment to confirm that Ig therapy is improving the severity of symptoms and severity and/or frequency of seizures. If improvement has been demonstrated after three months 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.</p> |
| <p>Impact on demand</p> | <p>The Specialist Working Group notes that around 25 patients have required treatment annually over the last four years,</p> |

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| | | | | | | <p>with a number of these patients having been treated for over twelve months. The use is reasonably stable and appropriate for the expected prevalence of the condition as these patients are likely to be under the care of paediatric neurologists specialising in the treatment of epilepsy. The revised criteria will ensure that use is controlled and appropriate with evidence of a clinical response requiring to be demonstrated after three months' treatment. Symptoms must continue to improve or stabilise to remain on Ig therapy.</p> <p>There is not expected to be any material impact on overall demand as a result of these changes.</p> |
| | 2011-12 | 2012-13 | 2013-14 | 2014-15 | 2015-16 | <p>The Specialist Working Group estimated magnitude of effect:</p> <p>No impact against projected demand</p> |
| Patient number | 40 | 27 | 23 | 24 | 20 | |
| Total Grams issued | 11,750 | 8,281 | 7,641 | 5,507 | 5,685 | |
| % Total Grams issued | 0.36% | 0.23% | 0.19% | 0.12% | 0.11% | |
| <p>Specialist Working Group knowledge development opportunities and recommendations relevant to transition to v3.0</p> | | | | | | |
| <p>None identified at this stage.</p> | | | | | | |

END OF PUBLIC CONSULTATION DOCUMENT

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