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

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| **CONDITION NAMES IN v2.1**  | **Limbic encephalitis — non-paraneoplastic****Limbic encephalitis – paraneoplastic (Paraneoplastic neurological syndromes)** |
| **PROPOSED APPROACH:****To remove Limbic encephalitis — non-paraneoplastic and Limbic encephalitis – paraneoplastic as stand-alone conditions in *Exceptional circumstances only* and allow accessfor eligible patients under Autoimmune encephalitis mediated by antibodies targeting cell surface antigens (AMAE) in *Emerging therapeutic role***  | **SUMMARY OF RATIONALE:** Further revisions to these conditions were planned as part of the review of the category of *Exceptional circumstances only*, and a number of contributing factors support the recommended changes: * As can be seen from the BloodSTAR v2.1 qualifying criteria below, both forms of Limbic encephalitis are recognised to be associated with the development of autoantibodies to cell surface neural proteins such as NMDA and AMPA in the current criteria. The same autoantibodies are associated with encephalitis in other parts of the brain beyond the limbus (as described in AMAE).
* The restructuring of conditions for v3.0 is simplified by including all patients with Autoimmune encephalitis mediated by antibodies targeting cell surface neural antigens (AMAE) in the same condition and category. In this way, consistent qualifying and review criteria are applied, and provided patients meet the criteria, they will be eligible.
* This is supported by recent evidence (Graus et al, 2016) which describes the diagnostic criteria for a number of related conditions now included under qualification for Ig therapy in AMAE.
* International evidence (see below) confirms the role of Ig therapy as first line treatment in combination with IV corticosteroids with improved clinical outcomes being demonstrated in response to earlier treatment, and similar outcomes being achieved in sero-negative patients.
* Ig usage has been increasing over recent years, probably in part due to theincreasing recognition of the evidence supporting improved clinical outcomes with earlier immune therapy in limbic encephalitis. The revised criteria will ensure that prescribing practice is appropriate and in line with emerging international practice.
* Autoimmune encephalitis is listed as ‘grey’ under ‘Immune mediated disorders with limited evidence of efficacy’ in the NHS Clinical Guidelines for Ig use (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.N-methyl-D- aspartate (NMDA) encephalitis is listed in the national Canadian IVIg Management Guidelines (Ontario Regional Blood Coordinating Network, 2016).
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| **Role of Ig therapy:**  This condition primarily only responds to Immunotherapy, or where a tumour is responsible for generating the causative antibody, tumour resection. The tenets of the evidence emphasise the importance of instituting Ig treatment early (including prior to antibody confirmation) and that immune therapy is better than no immune therapy. Second line treatment improves outcome if first line treatment fails and no treatment increases the risk of relapse. Seronegative patients who have the clinical features of autoimmune encephalitis respond as well to immune therapy as seropositive patients - given the fact there are probably other autoantibodies not currently described (Hacohen et al, 2012). Patients with limbic encephalitis will need to demonstrate compliance with the international diagnostic criteria for ‘cell surface antibody positive limbic encephalitis or suspected or sero-negative limbic encephalitis’. If eligible, evidence supports treatment with IV corticosteroids in combination with IVIg or plasmapheresis as first line therapy with the addition of a second line immunosuppressant therapy if no clinical response is demonstrated, ideally within two weeks. (See AMAE - Attachment B for full detail).  |
| **References**  |
| Armangue T, Moris G, Cantarin-Extremera V et al (2015) Autoimmune post-herpes simplex encephalitis of adults and teenagers. *Neurology*, 85:1736-1743.<https://www.ncbi.nlm.nih.gov/pubmed/26491084>Graus F, Titlaer MJ, Balu R, Benseler S et al (2016) A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurology*, 15:391-404. <https://www.ncbi.nlm.nih.gov/pubmed/26906964>Hacohen Y, Wright S, Waters P et al (2013) Paediatric autoimmune encephalopathies: clinical features, laboratory investigations and outcomes in patients with or without antibodies to known central nervous system autoantigens. *J Neurol Neurosurg Psychiatry,* 84:748-755. <https://www.ncbi.nlm.nih.gov/pubmed/23175854>Maarten J. Titulaer Romana H€oftberger,et al (2014) Overlapping Demyelinating Syndromes and Anti–N-Methyl-D-Aspartate Receptor Encephalitis. *Annals of Neurology*, 75:411–428<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4016175/>Nosadini M, Mohammad SS, Ramanathan FB and Dale RC (2015) Immune therapy in autoimmune encephalitis: a systematic review. *Expert Review of Neurotherapeutics*, 15:1391-1419.<https://www.ncbi.nlm.nih.gov/pubmed/26559389> |
| **Access Information in BloodSTAR v2.1 as at August 2016** |
| **Condition Name** | **Limbic encephalitis - nonparaneoplastic** |
| **Condition Category**  | Condition for which Ig use is in Exceptional circumstances only (Chapter 7) |
| **Level of Evidence** | Insufficient data (Category 4a) |
| **Description**  | Blank |
| **Qualifying Criteria**  | There appears to be a role for intravenous immunoglobulin (IVIg) in nonparaneoplastic limbic encephalitis associated with neuronal antibodies to cell surface antigens. This includes VGKC antibodies, as well as NMDA receptor antibodies and AMPA receptor antibodies. |
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| **Condition Name** | **Paraneoplastic neurological syndromes: Limbic encephalitis - paraneoplastic** |
| **Condition Category**  | Condition for which Ig use is in Exceptional circumstances only (Chapter 7) |
| **Level of Evidence** | Insufficient data (Category 4a) |
| **Description**  | Blank |
| **Qualifying Criteria**  | IVIg may be indicated in select cases, in combination with tumour therapy (tumour resection and/or oncological treatment) where the latter has not led to an improvement in the neurologic syndrome; where other immunomodulatory therapies are contraindicated or have failed; or if the neurologic features warrant urgent intervention**.** |
| **References**  |
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| Bataller L, Galiano R, Garcia-Escrig M, Martinez B, Sevilla T, Blasco,R, et al (2010) Reversible paraneoplastic limbic encephalitis associated with antibodies to the AMPA receptor. Neurology, 74(3):265–7.<https://www.ncbi.nlm.nih.gov/pubmed/20083804>Henry C, Husson H, de Broucker T (2009) Autoimmune limbic encephalitis with anti-NMDA receptor antibodies and ovarian teratoma: a treatable form of paraneoplastic limbic encephalitis (in French), Revue neurologique (Société de neurologie de Paris), 165(1):70–5.http://europepmc.org/abstract/med/18809188 |

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| **POTENTIAL OPERATIONAL IMPACT** |
| The development of specific qualifying and review criteria will represent a change for this condition with the revised criteria providing significantly greater guidance for appropriate access to Ig therapy and patient management expectations. A neurologist will be required to diagnose and manage patient treatment, although it is recognised that this may be as part of a broader clinical team. 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 using a Modified Rankin Scale, however, the scale will be presented as ‘drop-down’ menu options within BloodSTAR v3.0 and will be simple to apply. It is likely that a greater awareness of the condition, diagnostic criteria will develop and as a result, requests for antibody testing will increase. There is limited testing currently available within Australia, however, availability is likely to improve over time. |
| **POTENTIAL IMPACT ON PATIENTS, DEMAND AND EXPENDITURE** |
| **Potential impact on patients:** | Under the proposed changes, patients with Limbic encephalitis will be eligible to receive Ig therapy under the criteria for the condition ‘Antibody mediated autoimmune encephalitis’ (AMAE). This is because it is recognised that these patients are likely to meet the criteria for access and the disease process that responds to Ig therapy, is consistent with the other conditions included under AMAE. The formal access criteria now proposed for these conditions require that a neurologist, who may be part of a clinical team, makes the diagnosis and manages the treatment. This is because the condition is uncommon, can be misdiagnosed and it is important that the correct, early treatment is given to patients. Ig therapy is given at the same time as other treatments.  While numerous patients have been treated with Ig therapy under this condition, the greater guidance for prescribers by applying appropriate diagnostic criteria and instituting second line treatment very early when patients do not respond to first line treatment, has been shown to result in improved patient outcomes. For existing patients on Ig maintenance therapy, six monthly reviews are required to assess the effectiveness of the treatment to improve or stabilise symptoms and the degree of disability. Given that patients will already require very regular review by their neurologist, this requirement will not place an added burden on patients. If an existing patient on ongoing treatment is not being managed by a neurologist, referral to a neurologist will be required. If Ig therapy has not been effective in stabilising symptoms, it will be ceased as a different treatment should be used. A trial of reducing dose and then stopping Ig therapy will be considered by doctors when patients are well and symptoms are stable. New patients authorised to receive Ig therapy will require an initial check after the first three months of treatment to confirm that Ig therapy has been effective in improving the severity of symptoms and that the level of disability has not worsened. If improvement has been demonstrated after four months treatment, Ig maintenance therapy will be continued. If a response has not been demonstrated, a second medication must have been started and a further six months Ig therapy will be given. Further six monthly reviews will assess how effective the combination therapy has been to improve or stabilise the symptoms and ensure that no further worsening has occurred in disability. If the combination therapy has not been effective, Ig therapy will be stopped and a different treatment approach will be required. The ongoing arrangements for maintenance therapy are as outlined above for existing patients. |
| **Impact on demand** | Limbic encephalitis (paraneoplastic or non-paraneoplastic) has become increasingly recognised as a diagnosis requiring Ig therapy as first line treatment as demonstrated in the increasing usage data over the last 4 years. This trend is likely to continue, however, the more specific access criteria defined in AMAE (which will now be applied to all patients with a diagnosis of Limbic encephalitis) may mean that fewer patients will be eligible for Ig therapy than would have received treatment as there are no criteria currently defined for access to Ig therapy. The requirement to meet formal diagnostic and review criteria and the introduction of trials of weaning, may contribute to a reduction in potential demand. However, given that this condition is being increasingly diagnosed and recognised, demand for AMAE overall is expected to continue to rise. |
| **Patient number** | **2011-12** | **2012-13** | **2013-14** | **2014-15** | **2015-16** | The Specialist Working Group estimated magnitude of effect:Marginal: <$500K reduction against projected demand |
| **LE-Non-para-neoplastic** | **0** | **61** | **122** | **147** | **188** |
| **LE – paraneoplastic** | **0** | **9** | **19** | **26** | **46** |
| **Total Grams issued**  |  |  |  |  |  |
| **LE-non-para-neoplastic** | **0** | **10,900** | **27,787** | **36,076** | **48,098** |
| **LE – paraneoplastic** | **0** | **1,672** | **7,280** | **6,080** | **8,114** |
| **% Total Grams issued** |  |  |  |  |  |
| **LE-Non-para-neoplastic** | **0.00%** | **0.3%** | **0.69%** | **0.81%** | **0.97%** |
| **LE – paraneoplastic** | **0.00%** | **0.05%** | **0.18%** | **0.14%** | **0.16%** |  |
| **Specialist Working Group knowledge development opportunities and recommendations relevant to transition to v3.0** |
| None identified at this stage. |

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| **END OF PUBLIC CONSULTATION DOCUMENT****Next review: This condition will be reviewed as a specific condition (Limbic encephalitis) within AMAE.**  |