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

| **v2.1 CONDITION NAME: Potassium channel antibody-associated encephalopathy, Limbic encephalitis- non-paraneoplastic, Limbic encephalitis paraneoplastic and Hashimotos encephalopathy****PREVIOUS PUBLIC CONSULTATION NAME: Autoimmune encephalitis mediated by antibodies targeting cell-surface antigens (AMAE)****v3.0 CONDITION NAME: Autoimmune encephalitis mediated by antibodies targeting cell-surface antigens (AMAE)** |
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| In 2015 **AMAE (previously named Potassium channel antibody-associated encephalopathy)** was endorsed by NIGAC and JBC as a condition for which Ig has an *Emerging therapeutic role*. At the time, the need for further significant review was acknowledged and scheduled to be undertaken as part of the formal review of conditions from the *Exceptional circumstances only* category.**PROPOSED APPROACH:****To retain AMAE in *Emerging therapeutic role* with the changes as outlined including addition of eligible patients with Limbic encephalitis and Hashimoto’s encephalopathy.** **As a result, along with Potassium channel antibody-associated encephalopathy, the following conditions will no longer be retained as standalone conditions in any category****• Limbic encephalitis - non- paraneoplastic****• Limbic encephalitis paraneoplastic and** **• Hashimoto’s encephalopathy** | **SUMMARY OF RATIONALE:** A number of contributing factors support the recommended changes: * Ig therapy is internationally recognised as being first line treatment of AMAE (including limbic encephalitis), in combination with corticosteroids, where clinical outcomes have been demonstrated to improve with earlier treatment and over 500 patient case reports/series are now published that have reported benefit of Ig therapy.
* Recent publications (Graus et al, 2016 and Nosadini et al, 2015) have contributed to the strength of evidence and provide formal diagnostic criteria for definite, probable and possible AMAE which have been applied to these revised qualifying criteria.
* Seronegative patients meeting the diagnostic and review criteria have been proven to derive benefit from Ig therapy (Hachoen et al, 2013).
* The review of all conditions in the category of *Exceptional circumstances only* has resulted in the restructuring of a number of conditions and supports the inclusion of patients with other relevant conditions under AMAE (including Limbic encephalitis and eligible patients with Hashimoto’s encephalitis).
* This review has contributed to the formal removal of other conditions (paraneoplastic syndromes) from the Criteria.
* Ig usage has been increasing over recent years, probably in part due to the increasing recognition of the evidence supporting improved clinical outcomes with earlier immune therapy. The revised criteria will ensure that prescribing practice is appropriate and in line with emerging international practice. It is recognised that this is an emerging area that will continue to undergo review as evidence becomes available, access to antibody testing increases and clinical practice is better established.
* Autoimmune encephalitis 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. It is also listed (as NMDA encephalitis) in the national Canadian IVIg Management Guidelines (Ontario Regional Blood Coordinating Network, 2016).
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| **v2.1 CONDITION CATEGROY:** AMAE was not included. **2015 Public Consultation CONDITION CATEGORY:** Condition for which Ig has anEmerging therapeutic role (Chapter 6)**v3.0 CONDITION CATEGORY:** Condition for which Ig has anEmerging therapeutic role (Chapter 6) |
| **Role of Ig therapy:** This condition primarily only responds to Immunotherapy, or tumour resection where a tumour is responsible for generating the causative antibody. 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 using 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 - likely due to the presence of unrecognized autoantibodies (Hacohen et al, 2013).First line immunotherapy typically includes intravenous methylprednisolone and IVIg or plasmapheresis. Due to the behavioural and/or autonomic manifestations of this disease, plasmapheresis, with large bore catheters may be clinically inappropriate. International best practice is to use IVIg as first line treatment, concurrently with IV steroids. Second line treatment includes rituximab and cyclophosphamide. The consensus opinion is that one would progress to the addition of second line treatment in a standard case if no clinical improvement is observed after approximately two weeks of first line therapy and no tumour is found. In these criteria, IVIg is proposed to be approved for one induction cycle (2g/kg over 2- 5 days) in conjunction with systemic steroids (unless contraindicated). Two subsequent monthly doses (each 0.4-1 g/kg) may be given at which stage the patient must be reviewed to determine whether there has been a clinical response prior to further Ig authorisation. The patient is closely monitored to confirm continuing response and no further deterioration in disability. Once symptoms are stable, weaning from Ig therapy is commenced. |

| **ITEM** | **2015 JBC APPROVED WORDING** | **REVISIONS TO 2015 JBC APPROVED WORDING** | **SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CLARIFICATIONS** |
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| **Condition Name** | Autoimmune encephalitis mediated by antibodies targeting cell-surface antigens | Autoimmune encephalitis mediated by antibodies targeting cell-surface antigens | No change |
| **Specialty** | Neurology | Neurology  | No change |
| **Category** | *Emerging therapeutic role*  | *Emerging therapeutic role*  | No change |
| **Specific Conditions** | Encephalitis associated with antibodies to NMDA Encephalitis associated with antibodies to VGKC Encephalitis associated with antibodies to LGI1 Encephalitis associated with antibodies to ASPR2 Encephalitis associated with antibodies to DPPX Encephalitis associated with antibodies to AMPA Encephalitis associated with antibodies to glycine. | Encephalitis associated with antibodies to NMDA receptorEncephalitis associated with antibodies to VGKCEncephalitis associated with antibodies to LGI1Encephalitis associated with antibodies to CASPR2Encephalitis associated with antibodies to DPPX Encephalitis associated with antibodies to AMPA receptor Encephalitis associated with antibodies to glycine receptorEncephalitis associated with antibodies to GABA (A or B) receptor.Suspected autoimmune encephalitis Sero-negative autoimmune encephalitisSuspected autoimmune limbic encephalitis | This section has been revised to include additional antibodies and values to support analysis by antibody type and to identify sero-negative patients and those with suspected diagnoses treated under this condition.  |
| **Level of Evidence** | Insufficient data (Category 4a). |  Evidence of probable benefit - more research needed (Category 2a) | The level of evidence has been upgraded in line with the large number of publications (including over 500 case reports/ series) that have reported benefit.  |
| **Justification for Evidence Category** | Owing to the recent recognition of this condition and its rarity, there are no RCTs examining the efficacy of IVIg in anti-NMDA receptor encephalitis. Most publications are of case reports or case series. Cohort studies as described below have been undertaken. In these studies, systemic steroids and IVIg are prescribed in tandem. None have prospectively compared the efficacy of IVIg vs plasmapheresis.Titulaer et al described a cohort study of 577 adult and paediatric patients (of whom 501 had follow-up of at least 4 months) with anti-NMDAR encephalitis. 197 (38%) had an underlying neoplasm which was resected in 189. First line immunotherapy was defined as the use of steroids, IVIg or plasma exchange alone or in combination. Amongst the 501 patients, 461 (92%) were treated with first line immunotherapy (of these, 202 patients received steroids and IVIg) and 134 (27%) progressed to second line immunotherapy. Of the patients who received first line treatment, 251 patients achieved treatment response (defined by a reduction in the modified Rankin score to < 4 within 4 weeks). Over the first 24 months, 241 of 251 reached a modified Rankin score of 0-2 (median 3 months). At 24 months 111 of 115 patients had a good outcome. Publications by the same group have suggested that earlier treatment with both first line and second line therapies is associated with a better outcome. Armangue et al reported similar findings in 20 patients aged less than 19 years with anti-NMDAR encephalitis. 19 patients received first line immunotherapy at the first episode of encephalitis. All patients received at least a short course of high dose steroids and 14 received IVIg (median 2 cycles, range 1-12 cycles). At median follow up of 17.5 months, 17 (85%) had substantial improvement, 2 had moderate or severe disability and 1 died. The median time from start of immunotherapy to first sign of improvement was 11.5 days.International best practice is to use IVIg as first line treatment, concurrently with IV steroids. Incrementation to second line therapies should be considered early by the treating physicians after familiarisation with the case literature. Treatment of other syndromes is less well defined and follows similar lines of immunotherapy plus the use of adjunctive therapies for symptom management. | Owing to the recent recognition of this condition and its rarity, there are no RCTs examining the efficacy of IVIg in anti-NMDA receptor encephalitis. Most publications are of case reports or case series. Cohort studies as described below have been undertaken. In these studies, systemic steroids and IVIg are prescribed in tandem. None have prospectively compared the efficacy of IVIg vs plasmapheresis.Titulaer et al (2014) described a cohort study of 577 adult and paediatric patients (of whom 501 had follow-up of at least 4 months) with anti-NMDAR encephalitis. 197 (38%) had an underlying neoplasm which was resected in 189. First line immunotherapy was defined as the use of steroids, IVIg or plasma exchange alone or in combination. Amongst the 501 patients, 461 (92%) were treated with first line immunotherapy (of these, 202 patients received steroids and IVIg) and 134 (27%) progressed to second line immunotherapy. Of the patients who received first line treatment, 251 patients achieved treatment response (defined by a reduction in the modified Rankin score to < 4 within 4 weeks). Over the first 24 months, 241 of 251 reached a modified Rankin score of 0-2 (median 3 months). At 24 months 111 of 115 patients had a good outcome. Publications by the same group have suggested that earlier treatment with both first line and second line therapies is associated with a better outcome. Armangue et al (2015) reported similar findings in 20 patients aged less than 19 years with anti-NMDAR encephalitis. 19 patients received first line immunotherapy at the first episode of encephalitis. All patients received at least a short course of high dose steroids and 14 received IVIg (median 2 cycles, range 1-12 cycles). At median follow up of 17.5 months, 17 (85%) had substantial improvement, 2 had moderate or severe disability and 1 died. The median time from start of immunotherapy to first sign of improvement was 11.5 days.International best practice is to use IVIg as first line treatment, concurrently with IV steroids. Escalation to second line therapies should be considered early by the treating physicians after familiarisation with the case literature. In the systematic review (retrospective case series) by Nosadini et al (2015), three tenets and common themes were reported: 1. Immune therapy is better than no immune therapy2. If a patient fails to respond to first line therapy, second line therapy improves outcomes. Steroids and IVIg are generally considered first line3. No treatment increases the risk of relapse. | The final paragraph has been replaced to present the key tenants from Nosadini et al (2015), a systematic review of retrospective case series of autoimmune encephalitis. |
| **Indications** | First line treatment for autoimmune encephalitis mediated by antibodies targeting neuronal cell surface antigens | **Cell surface antibody positive AMAE or limbic encephalitis** **Suspected AMAE – antibody results not available or sero-negative AMAE or seronegative limbic encephalitis** | Indications have been revised to better support different criteria for different patient groups which were not previously distinguished. |
| **Description and Diagnostic Criteria** | Anti-N-methyl-D-aspartate-receptor encephalitis is an antibody mediated neurological disease initially described in 2005. It is the most common and best described of the encephalitides associated with antibodies to neuronal cell surface antigens. Patients present with psychiatric symptoms (agitation, paranoia, hallucinations and aggression) which progresses to dyskinesias, seizures, autonomic instability, decreased consciousness, catatonia and central hypoventilation leading to a need for ventilator support in ICU. There are variations on the classical presentation including seizures first, milder forms and cases associated with CNS inflammatory lesions. There is compelling evidence suggesting the role for IgG1 and IgG2 antibodies in binding to the GluN1 subunit of the NMDA-receptor. A proportion of cases are associated with underlying teratomas and tumour removal may be curative.Treatment thus consists of immunotherapy and tumour resection. First line immunotherapy typically includes intravenous methylprednisolone and IVIg or plasmapheresis. Due to the behavioural and/or autonomic manifestations of the disease, plasmapheresis, with large bore catheters may be clinically inappropriate. Second line treatment includes rituximab and cyclophosphamide. The consensus opinion is that one would progress to the addition of second line treatment in a standard case if no clinical improvement is observed after approximately two weeks of first line therapy and no tumour is found.There are a variety of rarer neuroimmunological syndromes for which there is good evidence of antibodies binding physiologically relevant neuronal surface antigens with a case literature describing responses to immunotherapy often including IVIg. All these syndromes have both distinctive clinical syndromes described matching particular antibodies but also have some cases described where there is clinical overlap with those described with other antibodies or other CNS inflammatory disorders. In many of these syndromes associations with malignancies have been identified and clinicians treating such cases should be familiar with the literature and investigate accordingly. Some cases also have more than one antibody identified.Rare cases occur in which an infectious trigger is identified. In these cases it may be unclear if the antibody identified is associated with a clinically relevant undesirable response suggesting a need for immunotherapy, or a desirable immune response where immunotherapy may be undesirable. VGKC-Abs have been described in heterogeneous disorders such as Limbic encephalitis or Isaac and Morvan syndromes. The antibodies bind associated proteins such as Lgi1 (limbic encephalitis) and Caspr2 (neuromyotonia) rather than the VGKC itself in almost all cases. An associated tumor is observed rarely in patients with Lgi1 Ab and less than 30% patients with Caspr2 Ab. A different potassium channel associated protein DPPX has also been described. Limbic encephalitis and other clinical encephalitis syndromes can occur with other antibodies directed against cell surface synaptic antigens (AMPAr, GABAa, GABAb, glycine). At the time of writing testing is available in Australia for only some of these antibodies. For others samples will need to be sent for testing at international reference laboratories and this is not the role of NBA / ARCBS. Testing CSF in addition to serum has a higher yield than serum alone and should be performed ab initio on both serum and CSF unless there are strong reasons to avoid lumbar puncture. | Anti-N-methyl-D-aspartate-receptor (NMDAR) encephalitis is an antibody mediated neurological disease initially described in 2005. It is the most common and best described of the encephalitides associated with antibodies to neuronal cell surface antigens. There is compelling evidence suggesting the role for IgG1 and IgG2 antibodies in binding to the GluN1 subunit of the NMDA-receptor. A proportion of cases are associated with underlying teratomas and tumour removal may be curative.A probable diagnosis can be made (Graus et al, 2016) when all three of the following criteria have been met: 1. Rapid onset (less than three months) of at least four symptom groups including: • Abnormal (psychiatric) behaviour or cognitive dysfunction• Speech dysfunction (Pressured speech, verbal reduction, mutism)• Seizures• Movement disorder, dykinesias or rigidity/ abnormal postures• Decreased level of consciousness• Autonomic dysfunction or central hypoventilation2. At least one of the following laboratory study results: • Abnormal EEG (focal or diffuse slow or disorganised activity, epileptic activity or extreme delta brush) • CSF with pleocytosis or oligoclonal bands3. Reasonable exclusion of other disorders. Diagnosis can also be made in the presence of three of the above symptom groups accompanied by a systemic teratoma. A definite diagnosis can be made in the presence of one or more of the six major symptom groups and IgG anti-GluN1 antibodies after reasonable exclusion of other disorders. Treatment thus consists of immunotherapy and tumour resection. First line immunotherapy typically includes intravenous methylprednisolone and IVIg or plasmapheresis. Due to the behavioural and/or autonomic manifestations of the disease, plasmapheresis, with large bore catheters may be clinically inappropriate. Second line treatment includes rituximab and cyclophosphamide. The consensus opinion is that one would progress to the addition of second line treatment in a standard case if no clinical improvement is observed after approximately two weeks of first line therapy and no tumour is found.There are a variety of rarer neuroimmunological syndromes for which there is good evidence of antibodies binding physiologically relevant neuronal surface antigens with a case literature describing responses to immunotherapy often including IVIg. All these syndromes have both distinctive clinical features described matching particular antibodies but also have some cases described where there is clinical overlap with those associated with other antibodies or other CNS inflammatory disorders. In many of these syndromes associations with malignancies have been identified and clinicians treating such cases should be familiar with the literature and investigate accordingly. Some cases also have more than one antibody identified.Rare cases occur in which an infectious trigger is identified. Herpes simplex virus encephalitis induced anti-NMDAR encephalitis is an autoimmune process and immune responsive condition which has a 50% mortality in children and immune suppression and modulation (steroid, IVIg, rituximab) have a role (Armangue et al, 2015). VGKC-Abs have been described in heterogeneous disorders such as limbic encephalitis or Isaac and Morvan’s syndromes. The antibodies bind associated proteins such as Lgi1 (limbic encephalitis) and Caspr2 (neuromyotonia) rather than the VGKC itself in almost all cases. An associated tumour is observed rarely in patients with Lgi1 Ab and less than 30% patients with Caspr2 Ab. A different potassium channel associated protein DPPX has also been described. Limbic encephalitis and other clinical encephalitis syndromes can occur with alternate antibodies directed against cell surface synaptic antigens (AMPAr, GABAa, GABAb, glycine). At the time of writing (Jan 2017) testing is available in Australia for only some of these antibodies. For others samples will need to be sent for testing at international reference laboratories and this is not the role of NBA / ARCBS. Testing CSF in addition to serum has a higher yield than serum alone and should be performed ab initio on both serum and CSF unless there are strong reasons to avoid lumbar puncture. The term Hashimoto’s encephalopathy has been previously used to describe acquired acute or subacute encephalopathy in patients with autoimmune thyroid disease. This syndrome is immune responsive and also called steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT). It is generally agreed that the anti-thyroid antibodies do not cause the brain disease, but instead represent an ‘autoimmune predisposition’ in these individuals. It should also be noted that the presence of anti-thyroid antibodies alone is not diagnostic of autoimmune disease, as these antibodies are seen in well individuals with a family history of thyroid or related autoimmunity.It is now considered likely that patients with Hashimoto’s encephalopathy have other autoantibodies which are more likely to be the pathogenic mediators of disease, such as anti-NMDAR antibodies (in the context of encephalitis), or anti-MOG antibodies (in the context of demyelination). Therefore patients with suspected ‘Hashimoto’s encephalopathy’ may be better categorised under autoimmune encephalitis, either associated with known cell surface antibodies, or seronegative suspected autoimmune encephalitis (as described in this section). | The previous version of criteria had been written from a perspective of ‘antibody detection’, however some patients may never have antibodies identified, and there is strong evidence that they still demonstrate benefit(Hacohen et al, 2013). Delaying therapy until antibody test results are available would be inconsistent with best practice, supported by evidence, to start Ig treatment early. A new publication (Graus et al, 2016) has proposed a more clinical approach and defines diagnostic criteria – including ‘probable diagnoses’, which have been included to allow a more progressive approach supporting an accurate diagnostic perspective with access to early treatment and escalation to second line therapy where a clinical response is not demonstrated within a short period. Greater detail has been provided in this descriptive section in order to better support and educate prescribers regarding this emerging condition. Explanation has been provided regarding the pathogenesis of Hashimoto’s Encephalopathy (HE) and the role of autoantibodies (other than anti-thyroid) being more likely to be the pathogenic mediators of disease, such as anti-NMDAR antibodies (in the context of encephalitis), or anti-MOG antibodies (in the context of demyelination). Alternatively, HE may be seronegative AMAE. As such, patients with Hashimoto’s Encephalopathy may be eligible for treatment under this condition provided they meet the qualifying (diagnostic) criteria. Hashimoto’s encephalopathy is recommended to no longer exist as a standalone condition in *the Criteria*, and search words will refer prescribers to AMAE.  |
| **Diagnosis is required** |  Neurologist | Yes | By which specialty | Neurologist  | No change. It is acknowledged that while clinical immunologists with specific experience may be part of the clinical team treating these patients, neurologists must make the diagnosis and be involved in patient management and review. |
| **Diagnosis must be verified** | No | By which specialty |  |
| **Exclusion Criteria** |  Anti-GAD or thyroid antibody associated syndromes and the classical intracellular anti-neuronal antibodies are not considered under this condition.  |  | The previously excluded conditions may now be eligible under this condition, provided they meet the qualifying criteria, so the statement has been removed.  |
| **Qualifying Criteria** | Clinical features consistent with antibody mediated autoimmune encephalitis including seizures, cognitive impairment, psychiatric symptoms, dyskinesias, autonomic instability, encephalopathy, catatonia, central hypoventilation ANDA baseline assessment of function is measured by the Modified Rankin ScoreANDNeuronal antibodies to cell surface antigens have been demonstrated, unless tests results are unavailable. Note anti-GAD or thyroid antibody associated syndromes and the classical intracellular antineuronal antibodies are not considered under this condition. IVIg is approved for one induction cycle (2g/kg over 5 days) in conjunction with systemic steroids (unless contraindicated). Two subsequent monthly doses (each up to 0.4g/kg) may be given at which stage the patient must be reviewed to determine whether there has been a clinical response prior to further Ig authorisation. | **Cell surface antibody positive AMAE or Limbic encephalitis**• Rapid onset over less than three months of clinical features consistent with a diagnosis of Autoimmune antibody mediated encephalitis or Limbic encephalitisAND• Testing confirms presence of cell surface neural antibody in CSF (or serum with confirmatory tests e.g. live neurons or tissue immunohistochemistry)AND• Disability as measured by the Modified Rankin Score to a value of at least 2 points.**Suspected AMAE - antibody results not available or sero-negative AMAE or sero negative limbic encephalitis** [Group1] * Sero negative encephalitis or antibody results not yet available

**AND** [meets criteria in either 2a OR 2b OR 2c)[Group 2] [Group 2a]* Probable AMAE with a rapid onset over less than three months of at least four symptom groups from:

- abnormal (psychiatric) behaviour / cognitive dysfunction, - speech dysfunction, - seizures, - movement disorders; - a decreased level of consciousness - autonomic dysfunction / central hypoventilation - presence of a systemic teratomaAND* Abnormal EEG or MRI or CSF consistent with encephalitis

OR [Group 2b]* Probable limbic encephalitis with rapid onset over less than 3 months of working memory deficits (short term memory loss), altered mental status or psychiatric symptoms

AND* Bilateral brain abnormalities on MRI suggestive of encephalitis with CSF pleocytosis and/or EEG abnormalities

 OR [Group 2c]* Possible autoimmune encephalitis with rapid onset of less than three months of working memory deficits (short term memory loss), altered mental status or psychiatric symptoms

AND* At least one of new focal CNS findings or seizures

AND* At least one of abnormal CSF or MRI features suggestive of encephalitis

**AND** [meets all criteria in Group 3][Group 3]* Alternative causes have been reasonably excluded

AND* Disability as measured by the Modified Rankin Score to a value of at least 2 points.
 | Given that the symptoms vary with the antibody target, a description of the relevant symptoms for each patient will be captured together with a baseline assessment using the Modified Rankin Score as the standard method across all patients. The rating scale being applied is: 0 - No symptoms at all1 - No significant disability despite symptoms; able to carry out all usual duties and activities2 - Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance3 - Moderate disability; requiring some help, but able to walk without assistance4 - Moderately severe disability; unable to walk without assistance and unable to attend to own bodilyneeds without assistance5 - Severe disability; bedridden, incontinent and requiring constant nursing care and attention 6 DeadA drop down menu listing the appropriate antibodies will be available.The qualifying criteria relating to each indication for AMAE have been adapted from the diagnostic criteria cited in Graus et al (2016). In general, the key clinical symptoms and the outcome of the relevant investigation are used. Three paths with different diagnostic and therefore qualifying criteria for suspected AMAE are now supported when patients are sero-negative or results are not yet available: 1. Probable AMAE
2. Probable limbic encephalitis
3. Possible AMAE.

Evidence items support each criteria and will support the analysis of Ig use in this emerging condition. These include both specific clinical findings and abnormal investigations (CSF, MRI or EEG) and alternative diagnoses must have been excluded. By asking for a baseline description of symptoms and an assessment of disability using the Modified Rankin, the authoriser can compare the clinical response to Ig therapy at initial review to confirm that improvement has been demonstrated.  |
| **Review Criteria** | IVIg should be used for a maximum of three months (induction plus two maintenance cycles) before determining whether the patient has responded. However if a patient has not responded within the first month, the addition of second line treatment should be considered well before the end of that three-month period. Review by a Neurologist is required within three months of treatment to determine whether the patient has responded. Thereafter, six monthly reviews are required. Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.**On review of an initial authorisation period*** Patient demonstrates a clinically significant improvement in the severity of symptoms (including cessation of seizures, improved cognition or conscious state and/or improved psychosis) compared to the severity of symptoms at qualifying

 AND* There has been no further deterioration in function as assessed by the Modified Rankin Score compared to qualifying and Testing confirms the presence of antibodies against neural cell surface antigens (if not already known)

OR* Patient has failed to demonstrate a clinically significant improvement in symptoms compared to the severity of symptoms at qualifying and as measured by the Modified Rankin Score compared to qualifying value

 AND* Second line treatment with immune-suppressant agents has been commenced and testing confirms the presence of antibodies against neural cell surface antigens.

**On review of a continuing authorisation period** * Re-authorisation may only be approved where there is clinical improvement or stability in symptoms

AND* There has been no further deterioration as measured by a Modified Rankin Score that is greater than or equal to the previous review score

AND* 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.
 | **Cell surface antibody positive AMAE or Limbic encephalitis**IVIg should be used for a maximum of three months (induction plus two maintenance cycles) before determining whether the patient has responded. However if a patient has not responded within the first month, the addition of second line treatment should be considered well before the end of that three month period. Review by a neurologist is required within 3 months of initiation of treatment to determine whether the patient has responded, and six monthly thereafter. Documentation of clinical effectiveness is necessary for continuation of IVIg therapy. **On review of the initial authorisation period**Clinical effectiveness of Ig therapy, or criteria for continued use may include:* Clinically significant improvement in the severity of symptoms (including cessation of seizures, improved cognition or conscious state and/or improved psychosis) compared to qualifying.

AND* No further deterioration in function as assessed by the Modified Rankin Score compared to the qualifying assessment

OR* No significant improvement in symptoms (including psychiatric behaviour, cognitive dysfunction, seizures, movement disorders) or disability as measured by the Modified Rankin Score compared to the severity at the qualifying assessment

AND* Second line treatment with immune-suppressant agents has been commenced

**On review of a continuing authorisation period**  Clinical effectiveness of Ig therapy may be demonstrated by: * Definite clinical improvement or stability in symptoms (including psychiatric behaviour, cognitive dysfunction, seizures, movement disorders) compared to the previous review

AND* No further deterioration in disability as measured by a Modified Rankin Score that is greater than or equal to the previous review score

AND* A trial of weaning is planned or a valid reason provided as to why a trial is not being planned or is contraindicated at this time.

**Suspected AMAE - results not available or sero-negative AMAE or sero negative limbic encephalitis** IVIg should be used for a maximum of three months (induction plus two maintenance cycles) before determining whether the patient has responded. However if a patient has not responded within the first month, the addition of second line treatment should be considered well before the end of that three month period. Review by a Neurologist is required within 3 months of treatment to determine whether the patient has responded, and six monthly thereafter. Documentation of clinical effectiveness is necessary for continuation of IVIg therapy. **On review of the initial authorisation period**Clinical effectiveness of Ig therapy, or criteria for continued use may include:[Group 1]* Clinically significant improvement in the severity of symptoms (including working memory deficit/ short term memory loss, altered memory status or psychiatric symptoms) compared to the severity of symptoms at qualifying.

AND* No further deterioration in function as assessed by the Modified Rankin Score compared to the qualifying assessment

OR* No significant improvement in the severity of symptoms (including working memory deficit/ short term memory loss, altered memory status or psychiatric symptoms) or disability as measured by Modified Rankin Score compared to the qualifying assessment.

AND* Second line treatment with immuno-suppressant agents has been commenced

AND[Group 2]* Testing confirms the presence of antibodies against neural cell surface antigens

OR* Patient is seronegative to all antibody testing

**On review of a continuing authorisation period** Clinical effectiveness of Ig therapy may be demonstrated by: * Definite clinical improvement or stability in symptoms compared to the previous review

AND* No further deterioration in disability as measured by a Modified Rankin Score that is greater than or equal to the previous review score

AND* A trial of weaning is planned or a valid reason provided as to why a trial is not being planned or is contraindicated at this time.
 | If a significant improvement in symptoms has not been demonstrated after 3 months Ig therapy at the initial review, a second line immunosuppressant agent must have been added to the patient treatment. At the continuing review, stable or improvement in symptoms must have been demonstrated with no deterioration in disability. |
| **Dose** |  **Induction - 2 g/kg in 2 to 5 divided doses.****IVIg is approved for one induction cycle in conjunction with systemic steroids (unless contraindicated). Two subsequent monthly doses (each up to 0.4g/kg) may be given before initial review.** **Maintenance - 0.4–1 g/kg, 4 weekly.****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.** | **Cell surface antibody positive antibody mediated autoimmune encephalitis or Limbic encephalitis****Induction Dose –2g/kg over 2 - 5 divided days**. IVIg is approved for one induction cycle in conjunction with systemic steroids (unless contraindicated). Two subsequent monthly doses (each 0.4 – 1 g/kg) may be given before initial review.**Maintenance Dose- 0.4–1 g/kg, 4 weekly.****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 on dose, administration and contraindications.** **Suspected AMAE – antibody results not available or sero-negative AMAE or seronegative limbic encephalitis****Induction Dose –2g/kg over 2 - 5 divided days.** IVIg is approved for one induction cycle in conjunction with systemic steroids (unless contraindicated). Two subsequent monthly doses (each 0.4 – 1 g/kg) may be given before initial review. **Maintenance Dose- 0.4–1 g/kg, 4 weekly.****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 on dose, administration and contraindications.** | Dosing is unchanged  |

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| **References****(most recent update: April 2016)** |
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| **POTENTIAL OPERATIONAL IMPACT** |
| The revised criteria provide significantly greater guidance for access to Ig therapy and patient management and more data entry will be required during the Ig request process. 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. 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 and diagnostic criteria will develop and, as a result, requests for antibody testing may increase. There is limited testing currently available within Australia, however, availability is likely to improve over time. |
| **POTENTIAL IMPACT ON PATIENTS, DEMAND AND EXPENDITURE** |
| **Description of impact on patients:** | These criteria provide greater guidance for prescribers by applying specific diagnostic criteria and to ensure that second line treatment is started very early if patients do not respond to first line treatment. This approach has been shown to result in improved patient outcomes. Patients who do not respond to Ig therapy after three months treatment will be commenced on a second medication in addition to Ig therapy. The formal access criteria proposed for this condition require that a neurologist, who may be part of a wider clinical team including clinical immunologists, 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. 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 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:** | AMAE has become increasingly recognised as a diagnosis responding to Ig treatment as demonstrated in the increasing usage data over the last 4 years for Potassium channel antibody-associated encephalopathy and both forms of limbic encephalitis. More specific access criteria and a requirement for a trial of weaning will be applied to all patients previously treated under the four relevant conditions now covered under AMAE, and while fewer patients may be eligible for Ig therapy than are currently receiving treatment, it is expected that demand over all will continue to rise for this condition as it is increasingly being diagnosed and Ig therapy is provided as first line treatment. |
|  | **2011-12** | **2012-13** | **2013-14** | **2014-15** | **2015-16** | \*Data has been generated for this purpose by including patients with Potassium channel, Limbic encephalitis, and Hashimoto’s encephalopathy as an indicative baseline for this condition. The Specialist Working Group estimated magnitude of effect: See individual conditions for potential impact against projected demand  |
| **Patient number** | **75** | **123** | **182** | **210** | **269** |
| **Total Grams issued** | **20,068** | **27,588** | **46,363** | **55,082** | **69,901** |
| **% Total Grams issued** | **0.61%** | **0.77%** | **1.15%** | **1.24%** | **1.4%** |
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| **Specialist Working Group knowledge development opportunities and recommendations relevant to the transition to v3.0** |
| None identified at this stage.  |

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| **END OF PUBLIC CONSULTATION DOCUMENT****Next review: Twelve to eighteen months after BloodSTAR v3.0 implementation** |