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

| **v2.1 CONDITION NAME: Epidermolysis bullosa acquisita** |
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| **PROPOSED APPROACH:****To retain Epidermolysis bullosa acquisita in *Exceptional circumstances only* with the changes as outlined.**  | **SUMMARY OF RATIONALE:** The recommended changes are supported by factors including that*:* * Although not commonly prescribed, Ig therapy should remain as an option for use for patients with persistent severe disease given the life threatening potential and few available effective therapeutic modalities.
* The Australasian College of Dermatologists (ACD) has confirmed there is a role of Ig in the treatment of Epidermolysis bullosa acquisita and the criteria have been developed in consultation with this expert group.
* Ig usage is stable and very low with <5 patients annually over the last 5 years.
* Given that long term therapy is often required, concurrent use of immunosuppressant therapy will be confirmed along with a trial off therapy to confirm the requirement after three months Ig treatment for all patients.
* This condition is eligible under “Immunobullous disease” in the Clinical guidelines for Ig use of the United Kingdom (UK Department of Health, 2011) as a medium priority for long term use. It is not listed in the Canadian guidelines (Ontario Regional Blood Coordinating Network, 2016)..
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| **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: Epidermolysis bullosa acquisita** (EBA) is a potentially severe life threatening autoimmune disease which has no cure. Although the majority of patients may have mild disease with blistering over trauma prone areas, there have been cases of severe widespread disease that remains refractory to conventional therapies.  The end stage results of severe disease include ocular disease with conjunctival scarring and blindness, mucosal disease with oesophageal strictures and scarring fibrosis of the skin with alopecia, nail loss and mitten like deformities of the hands.  The ACD has confirmed that Ig therapy should remain as a fifth line treatment for refractory patients with severe disease that have not responded to treatment with colchicine, dapsone and at least two other immunosuppressant agents, unless immunosuppressant medication has resulted in unacceptable side effects or significant toxicity or is contraindicated. Rituximab is noted to be an effective medication but may not be accessible to all patients. |

| **ITEM** | **v2.1**  | **PROPOSED REVISIONS TO THE CRITERIA** | **SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CLARIFICATIONS** |
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| **Condition Name** | Epidermolysis bullosa acquisita | Epidermolysis bullosa acquisita | Unchanged |
| **Specialty** | Immunology | Immunology |  |
| **Category** | *Exceptional circumstances only*  | *Exceptional circumstances only*  | Unchanged |
| **Specific Conditions** | Epidermolysis bullosa acquisita | Epidermolysis bullosa acquisita |  Unchanged |
| **Level of Evidence** | Insufficient data ([Category 4a](http://www.blood.gov.au/pubs/ivig/development-and-maintenance-of-the-criteria.html#el-4a)). |  Insufficient data (Category 4a) |  The level of evidence is unchanged and is unlikely to change due to the rarity of this condition. |
| **Justification for Evidence Category** |   | Intravenous immunoglobulin (IVIg) may be an option in severe disease. Multiple case reports suggest that the periodic administration of IVIg alone or in combination with other agents is also effective for improving the clinical manifestations of EBA. In a 2011 review of published reports, 14 of 15 patients, mostly with severe widespread refractory disease, given IVIg as monotherapy or in conjunction with other therapies achieved clinical improvement (Gurcan, 2011). Multiple cycles of IVIg were typically given; each cycle usually consisted of a total of 1.5 to 2 g/kg of IVIg given over the course of three to five days. Thirteen of 15 patients remained on IVIg for maintenance treatment.A more recent retrospective case series demonstrated similar clinical response rates, but suggested IVIg may induce a more sustained remission (Ahmed, 2012). Ten patients, all nonresponsive to conventional treatments, were started on 2 g/kg/cycle of IVIg for a mean of 23 cycles over 39 months. All 10 demonstrated clinical response and were able to completely withdraw their previous therapy; no recurrence was observed during a mean follow-up period of 54 months after cessation of treatment.  | This section has been developed following assessment of the literature and consultation with the Australasian College of Dermatologists. |
| **Indications** | Intravenous immunoglobulin (IVIg) should be considered for severe cases refractory to conventional immunosuppressive therapy. | **Persistent severe EBA refractory to conventional immunosuppressive therapy.****Worsening of EBA disease in responding patients with ongoing flare after ceasing Ig therapy**  |  Two indications have been developed, the first to provide three months of initial Ig therapy in eligible severe refractory patients. All patients will then have a trial off Ig therapy and if worsening of EBA disease should occur, patients may be eligible for maintenance therapy provided a response to initial therapy can be demonstrated. |
| **Description and Diagnostic Criteria** |   | Epidermolysis bullosa acquisita is a rare, potentially severe life-threatening disease which has no cure. This sub-epidermal blistering disorder of the skin and mucous membranes primarily affects adults but has been described in a few children. Although the majority of patients may have mild disease with blistering over trauma prone areas, there have been cases of severe widespread disease that remains refractory to conventional therapies. The end stage results of severe disease include ocular disease with conjunctival scarring and blindness, mucosal disease with oesophageal strictures and scarring fibrosis of the skin with alopecia, nail loss and mitten like deformities of the hands.   EBA is an autoimmune disease characterized by the production of antibodies against type VII collagen resulting in immune-mediated disruption of the anchoring fibrils that connect the basement membrane to dermal structures and the clinical development of blistering. Diagnosis of EBA is based on history, full skin examination, and skin biopsies. There is limited data on treatment options for EBA and optimal approach to treatment has not been established. Suggested initial treatment is with colchicine or dapsone (Grade 2C). If treatment is not effective, these agents may be used simultaneously. EBA that is refractory to above requires more aggressive therapy. Agents that may have efficacy for refractory EBA include immunosuppressants, intravenous immunoglobulin, and rituximab. | This section has been developed following assessment of the literature and consultation with the Australasian College of Dermatologists. |
| **Diagnosis is required** |   | Yes | By which specialty | DermatologistClinical Immunologist | Treatment of will be limited to dermatologists and clinical immunologists as it is a rare condition, usually treated by these specialists. |
| **Diagnosis must be verified** | No | By which specialty |  |
| **Exclusion Criteria** |   |  |  |
| **Qualifying Criteria** |  | **Persistent severe EBA refractory to conventional immunosuppressive therapy*** Persistent severe EBA disease confirmed by biopsy and Immunofluorescence including ophthalmological and/or mucosal sites

AND* Persistent disease despite standard treatment with colchicine and dapsone and at least two other immunosuppressant agents

OR* Immunosuppressant medication has resulted in unacceptable side effects or significant toxicity

OR* Corticosteroids and/or immunosuppressant agents are contraindicated

**Three months treatment is authorised initially after which time a clinical response should have been demonstrated. If, in responding patients, disease worsens following cessation of Ig therapy, a request for low dose maintenance therapy can be made. Documentation of clinical effectiveness of initial Ig therapy will be required for further requests.** **Worsening of EBA disease in responding patients with ongoing flare after ceasing Ig therapy** * Ongoing flare of mucosal or ophthalmic EBA disease in previously responding patients

AND* Reduction in severity and/or the number of lesions was demonstrated in response to initial Ig therapy

AND* At least one Immunosuppressant medication is to be given concurrently
 |  The definition of persistent and severe disease for eligibility for Ig therapy has been limited to those patients with ophthalmological and /or mucosal disease. The use of Ig therapy is as a fifth line agent after failure to respond to alternative therapies unless contraindicated or an unacceptable level of side effects or toxicity has developed. Statement informing prescribers of the requirement to have demonstrated clinical response to previous Ig therapy and then relapsed prior to commencing maintenance treatment. The criteria confirm the worsening of mucosal and /or ophthalmological disease once Ig therapy is withdrawn in responding patients. A description of current symptoms is used for comparison to demonstrate response to Ig therapy at initial review. Maintenance Ig therapy must be given in combination with at least one immunosuppressant medication to all patients.  |
| **Review Criteria** |   | **Persistent severe EBA refractory to conventional immunosuppressive therapy** Review is not mandated for this condition. Clinical effectiveness of Ig therapy may be demonstrated by: * Reduction in number of blisters/ erosions and improved healing compared to the level at the qualifying assessment

**Worsening of EBA disease in responding patients with ongoing flare after ceasing Ig therapy**IVIg should be used for four months (induction and three maintenance cycles) before determining whether the patient has responded. If the patient has not responded after this time, Ig therapy should be abandoned. Review is required by a Dermatologist or Clinical Immunologist after the first four months treatment to confirm response, 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 can be demonstrated by: * Reduction in severity and number of erosions or blisters and improved healing compared to the level at the qualifying assessment

AND* At least one Immunosuppressant medication is given concurrently

**On review of a continuing authorisation period**Clinical effectiveness of Ig therapy may be demonstrated and conditions for continuing treatment include: * Reduction in the number of erosions or blisters and improved healing compared to the previous review

AND* There is remaining activity or stable disease requiring further treatment

AND* Immunosuppressant medication is given concurrently

AND* A trial-off Ig therapy is planned or, if not planned, a reason is provided.

**Consideration should be given to a trial-off immunoglobulin (Ig) therapy once the patient has achieved stabilised disease or clinical remission.**  | All patients will receive an initial trial of three months Ig therapy. Outcome measures are defined to indicate to prescribers of the expected clinical response. If a patient does not demonstrate a response after three months, IVIg treatment should be permanently abandoned. If a patient does demonstrate a response and then deteriorates with ongoing flares following the cessation of Ig therapy, a further request for maintenance therapy may be authorised under the second indication. An advisory statement has been included to inform prescribers that a trial off Ig therapy should be considered once patients have achieved stabilised disease or remission. |
| **Dose** | Refer to the current product information sheet for further information.The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient. | **Persistent severe EBA refractory to conventional immunosuppressive therapy****Dose -** 1.5 – 2 g/kg over 3 to 5 days, monthly for three months**Three months treatment is authorised initially after which time a clinical response should have been demonstrated. If the patient has not responded, Ig therapy should be abandoned. If disease worsens following cessation in responding patients, a request for low dose maintenance therapy can be made.** 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.****Worsening of EBA disease in responding patients with ongoing flare after ceasing Ig therapy** **Induction Dose -** 1.5 – 2 g/kg over 3 to 5 days**Maintenance Dose -**0.4 g/kg four to six weekly**Consideration should be given to a trial-off immunoglobulin (Ig) therapy once the patient has achieved stabilised disease or clinical remission. The minimal effective dose should be prescribed.**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 has been defined in consultation with the Australasian College of Dermatologists. |

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| **References****(most recent update: August 2016)** |
| Ahmed AR and Gürcan HM (2012) Treatment of epidermolysis bullosa acquisita with intravenous immunoglobulin in patients non-responsive to conventional therapy: clinical outcome and post-treatment long-term follow-up. *Journal of the European Academy of Dermatology and Venerology*, 26:1074-83.<https://www.ncbi.nlm.nih.gov/pubmed/21819451>Caldwell JB, Yancey KB, Engler RJ and James WD (1994) Epidermolysis bullosa acquisita: efficacy of high-dose intravenous immunoglobulins. *Journal of the American Academy of Dermatology*, 31:827-8.<https://www.ncbi.nlm.nih.gov/pubmed/7929940>Gürcan HM and Ahmed AR (2011) Current concepts in the treatment of epidermolysis bullosa acquisita. *Expert Opinion on Pharmacotherapy*, 12:1259-68. <https://www.ncbi.nlm.nih.gov/pubmed/21254861>Iranzo P, Herrero-González JE, Mascaró-Galy JM, Suárez-Fernández R and España A (2014) Epidermolysis bullosa acquisita: a retrospective analysis of 12 patients evaluated in four tertiary hospitals in Spain. British Journal of Dermatology, 171(5):1022-30. <https://www.ncbi.nlm.nih.gov/pubmed/24890437>Kirtschig G, Murrell D, Wojnarowska F and Khumalo N (2003) Interventions for mucous membrane pemphigoid and epidermolysis bullosa acquisita. *Cochrane Database of Systematic Reviews.* 2003(1). <https://www.ncbi.nlm.nih.gov/pubmed/12535507>Kofler H, Wambacher-Gasser B, Topar G, Weinlich G, Schuler G, Hintner H, et al (1997) Intravenous immunoglobulin treatment in therapy-resistant epidermolysis bullosa acquisita. *Journal of the American Academy of Dermatology*, 36:331.<https://www.ncbi.nlm.nih.gov/pubmed/9039213>Gourgiotou K, Exadaktylou D, Aroni K, et al (2002) Epidermolysis bullosa acquisita: treatment with intravenous immunoglobulins. *Journal of the European Academy of Dermatology and Venerology* ,16(1):77-80. <https://www.ncbi.nlm.nih.gov/pubmed/11952298>Meier F, Sönnichsen K, Schaumburg-Lever G, Dopfer R and Rassner G (1993) Epidermolysis bullosa acquisita: efficacy of high-dose intravenous immunoglobulins. *Journal of the American Academy of Dermatology*, 29:334-7.<https://www.ncbi.nlm.nih.gov/pubmed/8340508>Mohr C, Sunderkötter C, Hildebrand A, Biel K, Rütter A and Rütter GH (1995) Successful treatment of epidermolysis bullosa acquisita using intravenous immunoglobulins. *British Journal of Dermatology*, 132:824-6.<https://www.ncbi.nlm.nih.gov/pubmed/7772494>Oktem A, Akay BN, Boyvat A, et al (2016) Long-term results of rituximab-intravenous immunoglobulin combination therapy in patients with epidermolysis bullosa acquisita resistant to conventional therapy. *Journal of Dermatological Treatment*, 10:1-5.<https://www.ncbi.nlm.nih.gov/pubmed/27161164>Ontario Regional Blood Coordinating Network (2016). Ontario Intravenous Immune Globulin (IVIG) Utilization Management Guidelines, Version 3.0. [online]. Available at: http://transfusionontario.org/en/download/ontario-intravenous-immune-globulin-IVIg-utilization-management-guidelines-2/. UK Department of Health (2011) Clinical Guidelines for Immunoglobulin Use: Second Edition Update. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment\_data/file/216671/dh\_131107.pdfUK Department of Health (2011) Clinical Guidelines for Immunoglobulin Use: Second Edition Update: Summary Poster. Available at: https://www.igd.nhs.uk/wp-content/uploads/2016/04/DemandManagementPoster\_v4\_February2016.pdf |

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| **POTENTIAL OPERATIONAL IMPACT** |
| These criteria are largely thought to reflect current clinical practice for existing patients and minimal operational impact is anticipated. While there will be some data entry required at initial Ig request and review, the clinical assessments are largely presented as drop down menus and short descriptions so as not to be burdensome. A trial off Ig therapy for all patients after three months’ treatment may be a new requirement for new patients in the future. The need to consider a trial off Ig therapy once stabilised disease or clinical remission is demonstrated is expected to be supported given that relapsing (responding) patients are likely to be eligible to recommence treatment in due course. |
| **POTENTIAL IMPACT ON PATIENTS, DEMAND AND EXPENDITURE** |
| **Description of impact on patients:** | There is not expected to be any significant impact on patients as a result of the proposed changes because they are anticipated to align with the current clinical management of patients with this very rare condition. These criteria have been developed in consultation with the Australasian College of Dermatologists who have advised that Ig therapy should only be used in those patients with severe disease who have not responded to a series of other treatment options. The very low level of Ig use over the last five years indicates that current clinical practice aligns with this requirement.  The formal access criteria proposed for this condition require that either a dermatologist or a clinical immunologist makes the diagnosis and manages the ongoing treatment. This is because EBA is a rare condition, and is usually treated by these specialists. There are a number of options that are available in the treatment of EBA and while the majority of patients have mild disease, some experience severe widespread disease that can be unresponsive to conventional treatments. For existing patients on Ig therapy, a review of dose may be required and commencement of an additional medication to be used in combination with Ig if this is not already in place. This is because Ig therapy in combination with another agent has been shown to be more effective in achieving improvement in resistant EBA disease. Patients will require six monthly progress checks to assess that the ongoing Ig combination treatment is effectiveness in improving healing and these can be performed as part of the specialist’s usual monitoring process so as not to add any burden on patients. A trial of reducing dose and then stopping Ig therapy will be considered by doctors after at least twelve months treatment and when patients have stable disease or are in remission. If patients relapse once Ig treatment has been stopped, a further request to restart ongoing Ig therapy can be made.For new patients receiving Ig therapy, three months treatment is initially authorised after which time a clinical response should have been demonstrated.Patients will already be regularly reviewed by their dermatologist or clinical immunologist, and so the checks required to confirm that Ig therapy has been effective in improving skin lesions will not add any burden to patients. If patients do not respond after the first three months of Ig therapy, a different approach to treatment would be used. If patients do respond after three months Ig therapy, but then worsen after Ig therapy is stopped, a further request for low dose maintenance Ig therapy can be made, which is given in combination with another medication. After a further four months treatment, a further check is needed to confirm that improvement in skin lesions has been demonstrated in response to the combination treatment. If patients have not improved after this time, Ig therapy will be ceased and substituted with a different treatment approach. If patients have improved, the low dose maintenance combination therapy will continue in line with the arrangements described above for existing patients.  |
| **Impact on demand**  | Given the very low level of usage over the last 5 years and development of the criteria in collaboration with the ACD, there is not anticipated to be any impact on Ig demand as the criteria appear to be consistent with current clinical practice.  |
|  | **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** | **<5** | **<5** | **<5** | **<5** | **<5** |
| **Total Grams issued** | **<1500** | **<2000** | **<1500** | **<2500** | **<5000** |
| **% Total Grams issued** | **<0.05%** | **<0.05%** | **<0.04%** | **<0.06%** | **<0.11%** |
| **Specialist Working Group knowledge development opportunities and recommendations** |
| Once v3.1 has been implemented, consideration may be given to the development of treatment guidelines for this rare condition. |

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| **END OF PUBLIC CONSULTATION DOCUMENT****Next review: Eighteen months after Implementation of BloodSTAR v3.0** |