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

| **v2.1 CONDITION NAME: Systemic capillary leak syndrome (SCLS)** |
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| **PROPOSED APPROACH:****To retain Systemic capillary leak syndrome in *Exceptional circumstances only* with the changes as outlined.**  | **SUMMARY OF RATIONALE:** The recommended changes are supported by factors including that*:* * SCLS is an extremely rare and life threatening condition of unknown aetiology.
* For prevention of recurrent episodes, Ig therapy is regarded as first line treatment internationally (Druey et al, 2010).
* Well documented studies have established that prophylactic Ig therapy can effectively reduce the number of acute episodes for extended periods (years) and therefore, be life-saving (Xie et al, 2015; Abueguen et al, 2010; Druey et al, 2010 and Gousseff et al, 2011).
* While not formally listed in the UK (UK Department of Health, 2011) or Canadian (Ontario Regional Blood Coordinating Network, 2016) guidelines that recommend access to funded Ig therapy, it is considered appropriate to continue to be available for exceptional use by the small group of patients in Australia affected by this rare and life threatening condition.
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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:** Treatment of the acute phase of SCLS is supportive,focusing on adequate fluid resuscitation. While many agents have been used to try to prevent recurrent attacks, immunoglobulin therapy is now regarded as first line in preventative therapy for this rare and life threatening condition.The aetiology of this condition is unknown, however it is associated with a monoclonal gammopathy. The mechanism of action for IVIg is also unknown.  |

| **ITEM** | **CRITERIA v2.1**  | **PROPOSED REVISIONS TO THE CRITERIA** | **SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CLARIFICATIONS** |
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| **Condition Name** | Systemic capillary leak syndrome (SCLS) | Systemic capillary leak syndrome | No change |
| **Specialty** | Immunology | Immunology | No change |
| **Category**  | *Exceptional circumstances only*  | *Exceptional circumstances only* | No change |
| **Specific Conditions** | Systemic capillary leak syndrome | Systemic capillary leak syndrome | No change |
| **Level of Evidence** | Insufficient data (Category 4a) |  Insufficient data (Category 4a) | No change |
| **Justification for Evidence Category** |   | Based on clearly documented studies, IVIg prophylaxis was associated with an 89% decrease in the number of SCLS flares (252 pre-treatment to 29 post-treatment) in 27 patients for periods of up to thirteen years (median duration of follow up 32 months). Fifteen out of 27 patients receiving IVIg experienced no SCLS episodes for periods of up to twelve years, and 24 out of 27 subjects had at least a 50% reduction in the number of flares. The optimal dose, schedule, and duration of IVIg therapy remain to be determined. While most patients (78%) received 2 g/kg/month, three patients have remained episode-free for greater than two years on 1-1.25 g/kg/month. Only a small number were controlled with 0.4 g/kg/month. | New text based on assessment of the literature.  |
| **Indications** |  | **Prevention of recurrent life-threatening episodes of hypotensive shock with hypoalbuminaemia in diagnosed SCLS** |  The Specialist Working Group indicated that only a single indication is required for both prevention and treatment. |
| **Description and Diagnostic Criteria** | SCLS is an extremely rare condition that is characterised by life-threatening attacks of reversible capillary hyperpermeability, accompanied by haemoconcentration and hypoalbuminaemia. Other therapies may be appropriate. | Systemic capillary leak syndrome (SCLS) is an extremely rare condition that is characterised by recurrent life-threatening attacks of reversible capillary hyperpermeability accompanied by haemoconcentration and hypoalbuminaemia. | No change |
| **Diagnosis is required** |  A diagnosis by a consultant physician, emergency specialist or intensive care unit specialist is required. | Yes | By which specialty | General PhysicianEmergency Medicine SpecialistIntensive Care SpecialistClinical Immunologist | Clinical Immunologist added as patients may present to, or be managed by clinical immunologists in additional to those listed in v2.1 |
| **Diagnosis must be verified** |  | By which specialty |  |
| **Exclusion Criteria** |   |  |  |
| **Qualifying Criteria** | Approval will be provided for an initial period of 12 months only. | **Prevention of recurrent life-threatening episodes of hypotensive shock with hypoalbuminaemia in diagnosed SCLS*** Recurrent episodes of unexplained hypotension and oedema

AND* Hemoconcentration, shock and hypoproteinaemia as a result of the loss of plasma into the extravascular space

AND* Other causes have been excluded
 | Some patients will have one-off attacks without further episodes, and therefore the criteria seek to both confirm the clinical diagnosis and establish that episodes have been recurrent. The symptoms of shock must be described to establish sufficient severity of a life threatening nature including that hospitalisation has been required on more than one occasion. The presence of a paraprotein will be ascertained as it is a negative finding indicating a likely need for longer term therapy. Other causes, such as sepsis must have been excluded.  |
| **Review Criteria** | Clinicians requesting ongoing intravenous immunoglobulin (IVIg) therapy after the initial 12-month period are required to confirm in writing that the patient experienced a reduced number of severe episodes requiring hospital admission when treated with IVIg. | **Prevention of recurrent life-threatening episodes of hypotensive shock with hypoalbuminaemia in diagnosed SCLS** Review by a General Physician or Clinical Immunologist is required within six months to assess the evidence of clinical benefit, and annually thereafter. The duration of requirement for ongoing IVIg is unknown. Although most subjects note rapid diminution of SCLS-related symptoms, few patients who have responded favourably have been reported to have discontinued treatment on long term follow-up.**On review of the initial authorisation period**Clinical effectiveness of Ig therapy may be demonstrated by: * Reduction in SCLS-related symptoms including oedema and hypotension post Ig treatment compared to the qualifying assessment

AND* A reduction in the number of severe episodes requiring hospital admission compared to pre-treatment levels

**On review of a continuing authorisation period*** Further improvement in or stabilisation of the number of episodes requiring hospital admission compared to the previous review period

AND* Once stable in remission, a reduction in dose and or a trial off Ig therapy is planned or if not planned, a reason is provided.
 |  No evidence supporting specific treatment timeframes and/or timing of cessation of therapy were identified in the literature. The Specialist Working Group recommends an initial review at six months and annual review periods thereafter. Where patients have been well controlled for a long period of time, a reduction in dose or trial off Ig therapy should be considered. The Specialist Working Group acknowledges that this is a clinical decision. Doctors are required to indicate the reason for not trialling off Ig. This information will help to inform improvements to *the* *Criteria* over time.  |
| **Dose** | Maximum dose of 1–2 g/kg per month.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. | **Induction Dose:** 1 – 2 g/kg in single or divided doses**Maintenance Dose**: 0.4 – 2 g/kg monthlyThe 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.**  | Where patients have been controlled for a long period of time a reduction in dose or trial off Ig therapy should be considered.  |

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| **References****(most recent update: May 2016)** |
| Abueguen P, Chennebault JM and Pichard E (2010) Immunoglobulins for the treatment of systemic capillary leak syndrome. *American Journal of Medicine*, 123:3–4.<https://www.ncbi.nlm.nih.gov/pubmed/25193271>Druey KM and Greipp PR (2010) Narrative review: the systemic capillary leak syndrome. *Annals of Internal Medicine*, 153:90–8.<https://www.ncbi.nlm.nih.gov/pubmed/20643990>Gousseff M, Arnaud L, Lambert M, Hot A, Hamidou M, Duhaut P, Pap T, et al (2011) The systemic capillary leak syndrome: a case series of 28 patients from a European registry. *Annals of Internal Medicine*, 154:464–71.<https://www.ncbi.nlm.nih.gov/pubmed/21464348>Govig BA and Javaheri S (2010) The systemic capillary leak syndrome (letter). *Annals of Internal Medicine*, 153: 764.<https://www.ncbi.nlm.nih.gov/pubmed/21135305>Lambert M, Launay D, Hachulla E, Morrell-Dubois S, Soland V, Queyrel V, et al (2008) High-dose intravenous immunoglobulins dramatically reverse systemic capillary leak syndrome. *Critical Care Medicine*, 36:2184–7.<https://www.ncbi.nlm.nih.gov/pubmed/18552679>Marra AM, Gigante A and Rosato E (2014) Intravenous immunoglobulin in systemic capillary leak syndrome: a case report and review of the literature. *Expert Review of Clinical Immunoogyl,* 10: 349-52.<https://www.ncbi.nlm.nih.gov/pubmed/24490827>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.pdfXie Z, Chan E, Long LM, Nelson C and Druey KM (2015) High dose intravenous immunoglobulin therapy of the Systemic Capillary Leak Syndrome (Clarkson disease). *American Journal of Medicine*, 128(1):91–95. <https://www.ncbi.nlm.nih.gov/pubmed/25193271>Zipponi M, Eugster R and Birrenbach T (2011) High-dose intravenous immunoglobulins: A promising therapeutic approach for idiopathic systemic capillary leak syndrome. *BMJ Case Reports*, May 3; 2011. <https://www.ncbi.nlm.nih.gov/pubmed/22696704> |

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| **POTENTIAL OPERATIONAL IMPACT** |
| The operational impact is anticipated to be minor, however, given that there have not previously been criteria for access, a communication strategy will be developed to inform prescribers regarding the changes.  |
| **POTENTIAL IMPACT ON PATIENTS, DEMAND AND EXPENDITURE** |
| **Description of impact on patients:** | There is not anticipated to be any significant impact on patients as a result of these criteria given that the proposed changes align with the current clinical management of patients with this very rare condition. Current levels of Ig use are consistent with the expected number of patients that should require ongoing Ig treatment. The formal access criteria proposed for this condition now include a clinical immunologist as being amongst the specialists that can make the diagnosis and manage the ongoing treatment. This is because while this is a very rare condition, patients may present to and be treated by clinical immunologists in addition to the other specialties already listed. Existing patients will need to be reviewed every year to confirm that Ig therapy continues to be effective in reducing or controlling the number of acute episodes that require admission to hospital. Patients will already be undergoing regular review by their treating specialist so this requirement will not place an added burden on patients. Where patients have been well controlled for a long period of time, a trial of reducing dose and then stopping Ig therapy will be considered by doctors. However, if patients relapse once Ig treatment has been stopped, a further request to restart ongoing Ig therapy can be made.New patients will require an initial check after six months Ig treatment to confirm that Ig therapy has been effective in reducing the number of severe acute episodes requiring hospital admission and the severity of symptoms. Patients will already be undergoing regular review by their treating specialist so this requirement will not place an added burden on patients. If patients have not improved after the six month treatment, Ig therapy will be ceased and substituted with a different treatment approach. If improvement has been demonstrated, annual checks on progress to assess the ongoing effectiveness of Ig maintenance therapy will be performed as part of the usual monitoring process by specialists. Arrangements for maintenance therapy will be the same as outlined above for existing patients.  |
| **Impact on Demand** | The number of patients undergoing treatment has increased in recent years and may be due to the greater recognition in recent years that Ig therapy should be part of first line treatment for recurrent disease (Marra et al, 2014). The prevalence is reported to be less than 1 in 1 million and 9 patients in Australia is consistent with this level. It is possible that patients have been commenced on Ig therapy without establishing that recurrent episodes requiring hospitalisation has occurred. If this was the case, there could potentially be a small reduction in use if patients are managed on a reduced dose and/or a trial off Ig therapy is successful. However, demand is not anticipated to change markedly given the small number of patients being treated currently and ongoing low incidence expected. |
|  | **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** | **0** | **<5** | **<5** | **9** | **9** |
| **Total Grams issued** | **0** | **<2,000** | **<3,000** | **8,238** | **8,407** |
| **% Total Grams issued** | **0.00%** | **<0.05%** | **<0.07%** | **0.18%** |  **0.17%** |
| **Specialist Working Group knowledge development opportunities and recommendations** |
| None identified at this time.  |
| **END OF PUBLIC CONSULTATION DOCUMENT****Next review: Eighteen months following implementation of BloodSTAR v3.0** |