### Specialist Working Group for Immunology

#### Proposed changes to the *Criteria for the clinical use of intravenous immunoglobulin in Australia, Second Edition*

| **ITEM** | **CRITERIA FOR THE CLINICAL USE OF INTRAVENOUS IMMUNOGLOBULIN IN AUSTRALIA, SECOND EDITION (CRITERIA)** | **PROPOSED REVISIONS TO THE CRITERIA**  | **SWG RATIONALE FOR PROPOSED CHANGE****(A) Administrative)****(B) Progressive** **(C) Programmed** |
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| **Condition Name** | **Cicatricial pemphigoid (CP) or mucous membrane pemphigoid (MMP)** | **Cicatricial pemphigoid (CP) or mucous membrane pemphigoid (MMP)** |  |
| **Specialty** | Dermatology | Dermatology, Ophthalmology | Ophthalmology added to support treatment of conjunctival disease (A) |
| **Chapter** | 6 | 6 |  |
| **Specific Conditions**  |  | Cicatricial pemphigoid (CP) Mucous Membrane Pemphigoid (MMP)  | Specific conditions will be tracked in the Ig system (A) |
| **Level of Evidence**  | Evidence of probable benefit ([Category 2a](http://www.blood.gov.au/pubs/ivig/development-and-maintenance-of-the-criteria.html#el-2a)). | Evidence of probable benefit ([Category 2a](http://www.blood.gov.au/pubs/ivig/development-and-maintenance-of-the-criteria.html#el-2a)). |  |
| **Description and Diagnostic Criteria**  | CP or MMP is a rare, acquired subepithelial blistering disease characterised by erosive lesions of mucous membranes and skin. Serious complications may occur due to erosions and scarring. Hoarseness, pain, tissue loss and even upper airway destruction can occur with nasopharyngeal or laryngeal involvement, and oesophageal and urogenital lesions may lead to stenosis or strictures. CP is usually a chronic, progressive disorder.The aim of long-term treatment is cessation of the self-destructive autoimmune process. Failure to do so results in invariable progression of the disease, culminating in progressive scarring. Permanent remission is usually possible if the disease is diagnosed early and treated sufficiently for one to five years.For the 70% of patients who have eye involvement, the disease progresses to conjunctival scarring and shrinkage, but may take 10–20 years to reach the end stage of bilateral blindness. | CP or MMP is a rare, acquired subepithelial blistering disease characterised by erosive lesions of mucous membranes and skin. It is associated with autoantibodies to antigenic proteins in the epidermal basement membrane. Serious complications may occur due to erosions and scarring of affected tissues. Nasopharyngeal or laryngeal involvement may cause hoarseness, pain, tissue loss and even upper airway destruction, and oesophageal and urogenital lesions may lead to stenosis or strictures. CP/MMP is usually a chronic, progressive disorder.The aim of long-term treatment is cessation of the autoimmune process. Failure to do so results in invariable progression of the disease, culminating in progressive scarring. Permanent remission is usually possible if the disease is diagnosed early and treated sufficiently for one to five years.For the 70% of patients who have eye involvement, the disease progresses to conjunctival scarring and shrinkage, but may take 10–20 years to reach the end stage of bilateral blindness. | Diagnostic criteria have been revised. (A) |
| **Justification for Evidence Category**  | Prolonged clinical remission and reduction in side effects was demonstrated in one small case series (15 cases) of patients with CP/MMP unresponsive to systemic corticosteroids and immuno-suppressive agents or presenting with multiple side effects of therapy (Biotext 2004).A small non-randomised, non-blinded trial (16 patients) showed significant improvement in the mean time for clinical control, recurrence, disease progression and drug-related side effects among patients receiving IVIg compared to conventional immunosuppressive therapy (Frommer and Madronio 2006).The (2003) consensus statement from the Harvard Medical School Department of Dermatology identified a study of 10 MMP patients who had progressive ocular involvement and did not respond to corticosteroids or immunosuppressants. IVIg administration as monotherapy arrested the progression and vision was maintained after IVIg was discontinued. The authors cited two other studies of oral pemphigoid in 15 and 7 patients respectively who could not be treated with dapsone; IVIg was compared to immunosuppressants. IVIg led to early and long-term remission and no disease progression. | A review of case reports and reports on small series of patients published in 2012 identified 72 patients who had received IVIg therapy for CP/MMP (Czernik A et al, 2012). The majority of patients experienced an improvement of disease manifestations and a decline in serum levels of autoantibodies to epidermal basement membrane antigens, where examined. Disease remissions for at least 12 months were common. Doses of IVIg given were usually higher than used for other autoimmune diseases, at 2-3g/kg over 3-5 days every 2 weeks, because CP/MMP that is unresponsive to steroids and immunosuppressant therapy may cause considerable disability, particularly blindness from conjunctival ulceration and oesophageal strictures from oesophageal ulceration. Preliminary data suggest that a combination of IVIg and therapeutic B cell depletion through the use of Rituximab arrests disease progression and prevents blindness in patients with conjunctival involvement that is unresponsive to corticosteroid and immunosuppressant therapy (Foster CS et al, 2010). | Justification for Evidence has been reviewed and rewritten to include more convincing evidence and combination therapy with rituximab, in particular in the treatment of ocular disease to prevent blindness. (A)  |
| **Diagnosis is required** | Moderate to severe disease diagnosed by a dermatologist; | Yes | Which Speciality | Dermatologist or Ophthalmologist or Clinical Immunologist | Addition of Ophthalmologist for treatment of conjunctival disease. Post public consultation, addition of Clinical Immunologist. (A) |
| **Diagnosis must be verified** |   | No  | Which Specialty |  |  |
| **Exclusion Criteria**  |  |  |  |
| **Indication for use** | CP resistant to glucocorticoid and immunosuppressive therapy. | CP/MMP resistant to corticosteroid and immunosuppressant therapy, or when corticosteroid and immunosuppressant therapy is contra-indicated. | Addition of eligibility when cortico-steroid or immunosuppressant therapy is contra-indicated. (A) |
| **Qualifying Criteria** | Moderate to severe disease diagnosed by a dermatologist;AND1. Corticosteroids or immunosuppressive agents are contraindicated;

OR1. Condition is unresponsive to corticosteroids and immunosuppressive agents;

OR1. Presenting with severe side effects of therapy.
 | * Moderate to severe CP/MMP disease with involvement of multiple sites, oesophageal involvement alone or conjunctiva alone, proven by autoantibody testing and/or biopsy.

AND* Persistent disease despite standard corticosteroid and treatment with at least two immunosuppressant agents or B cell depletion therapy (Rituximab)

OR* Severe side effects prohibit the continuation of corticosteroids and immunosuppressive agents unless corticosteroids or immunosuppressant agents are contraindicated.
 | Qualifying criteria have been expanded to require diagnostic confirmation and appropriate disease sites required for ‘moderate to severe disease’. It is recognised that not all patients have demonstrable autoantibodies, however all patients will have a biopsy. (A)Criteria are consistent with original version with details defined. (A)E.g. immunosuppressant therapeutics that need to have been tried include: * Corticosteroids
* Azathioprine
* Cyclophosphamide
* Methotrexate
* Mycophenolate
* Rituximab

Severe side effects of immunosuppressant therapy include: * Significant infection including sepsis
* Malignancy
* Marrow suppression and cytopenia
* Unstable Diabetes
* Severe osteoporosis
* History of avascular necrosis
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| **Review Criteria** | * Response demonstrated at review at six months. Improvement to be demonstrated for continuation of supply.
* Disease recurrence or relapse and duration of clinical remission.
* Ability to reduce dose or discontinue other therapies.
* Resolution of conjunctival inflammation.
* Reduction of drug-related side effects.
 | Review is required every six months by a Dermatologist or Opthalmologist or Clincial Immunologist.Response must be demonstrated at the initial review at six months and improvement must be demonstrated for continuation of supply.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.**On review of an initial authorisation period*** Response has been demonstrated by a reduction in the number and severity of lesions compared to qualifying.

**On review of a Continuing authorisation period*** Response has been demonstrated by a reduction in the number and severity of lesions compared to the previous review or disease has stabilised.

AND* A trial off Ig therapy is planned or a reason provided as to why a trial is not planned or is contra-indicated

AND* If continuing therapy, a reduction in dose is planned or if not planned, a reason is provided.
 | Initial review to confirm response is unchanged, however, ongoing six monthly review has been added with specific criteria defined for ongoing treatment. (A)Consideration is now given to trial off therapy once disease is stable and/or reduce Ig dose. |
| **Dose** | Efficacy demonstrated with doses of at least 2 g/kg per monthly treatment cycle.**Dosing above 1 g/kg per day is contraindicated for some IVIg products.****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.** | **Maintenance -** Efficacy demonstrated with doses of at least 2g/kg per month, up to 3g/kg in any four week period. Two weekly dosing is supported where eye sight is threatened.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.Dosing above 1 g/kg per day is contraindicated for some IVIg products.**Refer to the current product information sheet for further information.** | Upper and lower dose limits have been defined including supporting 2 weekly dosing when eye sight is threatened**.** Dosing script added to indicate two weekly dosing is supported when eyesight is threatened. **(A)** |

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| **BIBLIOGRAPHY** |
| Ahmed, AR & Dahl, MV, for the Consensus Development Group 2003, ‘Consensus statement on the use of intravenous immunoglobulin therapy in the treatment of autoimmune mucocutaneous blistering diseases’, Archives of Dermatology, vol. 139, pp. 1051–9.Daoud, YJ & Amin, KG 2006, ‘Comparison of cost of immune globulin intravenous therapy to conventional immunosuppressive therapy in treating patients with autoimmune mucocutaneous blistering diseases’, International Immunopharmacology, vol. 6, no. 4, pp. 600–6.Letko, E, Miserocchi, E, Daoud, YJ, et al 2004, ‚A nonrandomized comparison of the clinical outcome of ocular involvement in patients with mucous membrane (cicatricial) pemphigoid between conventional immunosuppressive and intravenous immunoglobulin therapies’, Clinical Immunology, vol. 111, no. 3, pp. 303–10.Orange, JS, et al 2006, 'Use of intravenous immunoglobulin in human disease: A review of primary evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology’, Journal of Allergy and Clinical Immunology, vol. 117, no. 4, pp. S525–53. |
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**catricial pemphigoid (CP) or mucous membrane pemphigoid (MMP)**