

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

CONDITION NAME IN v2.1	Scleromyxedema
<p>PROPOSED APPROACH:</p> <p>To retain Scleromyxedema in <i>Exceptional circumstances</i> only with the changes as outlined.</p>	<p>SUMMARY OF RATIONALE:</p> <p>The recommended changes are supported by factors including that:</p> <ul style="list-style-type: none"> - These criteria have been developed in consultation with the Australasian College of Dermatologists which has confirmed an ongoing role for Ig therapy in the treatment of this rare and potentially fatal condition. - While generally refractory to immunomodulation therapy, multiple case series and reports' most commonly reported treatment success is with IVIg (Rongioletti 2013, Blum 2008 and Kulczycki 2003, Caudill 2014, Hummers 2014, Majeski 2005, Rey 2009, Moser 2012). Successful treatment has been reported of Ig therapy alone and in combination with thalidomide (Dolenc-Voljc 2013, Efthimiou 2008) or lenalidomide (Brunet-Possenti 2013). - In the three largest case series(Rongioletti 2013, Blum 2008 and Kulczycki 2003), CNS involvement occurred in 10-15% of patients and this complication is usually associated with poor outcome, however most of the successful treatments reported for this often fatal manifestation are with Ig therapy. - Ig usage has been reasonably stable for the last 5 years from 6,000-8,000 g annually treating between 7 and 14 patients nationally. This level of use is not expected to change as a result of the revised criteria. - While this condition is not listed in either the UK (UK Department of Health, 2011) or Canadian (Ontario Regional Blood Coordinating Network, 2016) guidelines, it is noted that very rare immune-mediated disorders with evidence of immunoglobulin efficacy are not necessarily listed in such guidelines but may still be approved for funded use in those countries.
<p>v2.1 CONDITION CATEGORY: Condition for which Ig use is in exceptional circumstances only (Chapter 7)</p> <p>v3.0 CONDITION CATEGORY: Condition for which Ig use is in exceptional circumstances only (Chapter 7)</p>	
<p>Role of Ig therapy: Scleromyxedema is a rare systemic potentially fatal disease of unknown etiology, presenting with progressive dermal mucin deposition causing skin thickening with or without a paraproteinaemia. Systemic manifestations by deposition into internal organs results in gastrointestinal, renal, pulmonary, cardiac, and neurologic complications, of which the latter two usually result in death.</p> <p>There is no standard treatment for Scleromyxedema as the rarity prevents the execution of controlled clinical trials. Melphalan used to be the main treatment, however, is likely to have contributed to deaths from inducement of hematologic malignancies (Brunet-Possenti, 2013). Similarly, long term treatment with steroids causes side effects and long term complications. Intravenous immunoglobulin therapy for Scleromyxedema is well documented, and while the mechanism of action is not clear, it has been used alone, with thalidomide or lenalidomide (Blum 2008, Dolenc-Voljc 2013, Brunet-Possenti, 2013).</p>	

Given the long term nature of treatment, and the lack of long term alternative therapies, immunoglobulin is recognized as playing an important role in treatment of this rare, unpleasant and potentially fatal condition.

ITEM	CRITERIA v2.1	PROPOSED REVISIONS TO THE CRITERIA	SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CLARIFICATIONS
Condition Name	Scleromyxedema	Scleromyxedema	Unchanged
Specialty	Immunology	Immunology	Unchanged
Category	<i>Exceptional circumstances only</i>	<i>Exceptional circumstances only</i>	Unchanged
Specific Conditions		Scleromyxedema – skin involvement only Scleromyxedema - skin and systemic disease	Specific conditions have been defined to support data analysis.
Level of Evidence	Insufficient data (Category 4a)	Insufficient data (Category 4a)	Unchanged, and is unlikely to change due to the rarity of this condition.
Justification for Evidence Category		Prognostic outcomes of therapy in this condition are poorly understood as the literature is limited to case reports or small series. A 2008 case series demonstrated full or partial remission in eight out of ten patients treated with IVIg, although maintenance therapy was required to maintain ongoing control of disease. Three of six patients treated with IVIg achieved full remission in a mainly retrospective multi-centre study of 30 patients in 2013, with three of the remaining patients achieving partial responses. In the European case series, IVIg was used in 13 out of 25 patients, all showing either complete or partial response. IVIg responders have included where patients were treated with Ig	This section has been developed after reference to more recent literature, and consultation with the Australasian College of Dermatologists.

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		as first line therapy or after failure to respond to steroids and other immunosuppressant agents.			
Indications		Scleromyxedema (skin involvement only) unresponsive to steroids and other immunosuppressant agents or where contra-indicated Scleromyxedema - systemic involvement as first line therapy			Two indications have been developed to support differing types of access to Ig therapy. Patients with skin involvement only, must be non-responsive to alternative medications while first-line treatment is allowed for patients with systemic disease.
Description and Diagnostic Criteria	Intravenous immunoglobulin (IVIg) may be indicated in select cases not responding to steroids, or when steroids and other alternative treatments (e.g. thalidomide) are contraindicated.	<p>Scleromyxedema is a chronic, idiopathic disorder characterized by excessive deposition of mucin in the skin in association with increased dermal collagen and absence of thyroid disease, and usually associated with a monoclonal gammopathy. Extracutaneous systemic manifestations also occur with neurologic, rheumatologic, pulmonary, renal, muscular and/or cardiac involvement.</p> <p>This is a rare condition with proven difficulty in establishing specific or definitive treatment. Successful treatment of skin disease has been reported with melphalan, dexamethasone, thalidomide, lenalidomide and IVIg. In the three largest case series, CNS was predominantly involved in 10-15% of cases associated with poor clinical outcome, often with global CNS dysfunction with encephalopathy, seizures and coma. The pathophysiology of this fatal complication of Scleromyxedema remains unknown. Evidence supporting effective treatment may suggest that targeting the paraprotein may be of benefit. Most of the reports of successful treatment of CNS manifestations are with IVIg.</p>			The description and diagnostic criteria section has been updated to reflect the findings of more recently published evidence regarding disease presentation, progression and management.
Diagnosis is		Yes	By which specialty	Dermatologist Clinical	Due to its rarity, diagnosis and treatment of this condition is recommended to be limited

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required				Immunologist	to Dermatologists or Clinical Immunologists.
Diagnosis must be verified		No	By which specialty		
Exclusion Criteria					
Qualifying Criteria		<p>Scleromyxedema (skin involvement only) unresponsive to steroids and other immunosuppressant agents or where contra-indicated</p> <ul style="list-style-type: none"> Moderate to severe scleromyxedema proven by skin biopsy and confirmed absence of thyroid disease <p>AND</p> <ul style="list-style-type: none"> Unresponsive to standard steroid therapy and at least one other immunosuppressant agent <p>OR</p> <ul style="list-style-type: none"> Immunosuppressant medication has resulted in unacceptable side effects or significant toxicity <p>OR</p> <ul style="list-style-type: none"> Corticosteroids and/or immunosuppressant agents are contraindicated 			For patients with disease limited to the skin, Ig therapy will be authorised once patients have demonstrated non-responsiveness to steroid therapy and treatment with at least one immunosuppressant medication, unless contraindicated or unacceptable side effects or significant levels of toxicity have been demonstrated.

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		<p>Scleromyxedema - systemic involvement as first line therapy</p> <ul style="list-style-type: none"> • Diagnosis of Scleromyxedema proven by skin biopsy <p>AND</p> <ul style="list-style-type: none"> • Systemic manifestations of disease are present 	The type(s) of systemic involvement will be captured for data analysis purposes.
Review Criteria		<p>Scleromyxedema (skin involvement only) unresponsive to steroids and other immunosuppressant agents or where contra-indicated</p> <p>Review is required every six months by a Dermatologist or Clinical Immunologist. Response must be demonstrated at the initial review at six months, and improvement must be demonstrated for continuation of supply.</p> <p>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.</p> <p>Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.</p> <p>On review of the initial authorisation period</p> <p>Clinical effectiveness of Ig therapy can be demonstrated by:</p> <ul style="list-style-type: none"> • A reduction in the number of lesions and severity of disease <p>On review of a continuing authorisation period</p> <p>For stable patients on maintenance treatment, review by a dermatologists or clinical immunologist is required six monthly.</p> <p>Clinical effectiveness of Ig therapy, or criteria for continued use can be demonstrated by:</p> <ul style="list-style-type: none"> • Improvement in or stabilisation of disease compared to the 	Review criteria have been developed in consultation with the Australasian College of Dermatologists.

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		<p>previous review assessment</p> <p>AND</p> <ul style="list-style-type: none"> • A trial-off Ig therapy is planned or the reason why a trial is not planned is provided <p>AND</p> <ul style="list-style-type: none"> • If continuing Ig therapy, a reduction in dose is planned or, the reason why a reduction is not planned is provided <p>Scleromyxedema - systemic involvement as first line therapy</p> <p>Review is required every six months by a Dermatologist or Clinical Immunologist. Response must be demonstrated at the initial review at six months and improvement must be demonstrated for continuation of supply.</p> <p>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.</p> <p>Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.</p> <p>On review of the initial authorisation period</p> <p>Clinical effectiveness of Ig therapy can be demonstrated by:</p> <ul style="list-style-type: none"> • A reduction in the number of lesions and severity of disease including systemic symptoms 	

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		<p>On review of a continuing authorisation period</p> <p>For stable patients on maintenance treatment, review by a dermatologists or clinical immunologist is required six monthly.</p> <p>Clinical effectiveness of Ig therapy, or criteria for continued use can be demonstrated by:</p> <ul style="list-style-type: none"> Improvement in or stabilisation of disease compared to the previous review assessment <p>AND</p> <ul style="list-style-type: none"> A trial-off Ig therapy is planned or the reason why a trial is not planned is provided. <p>AND</p> <ul style="list-style-type: none"> If continuing Ig therapy, a reduction in dose is planned or, the reason why a reduction is not planned is provided. 	
Dose	<p>Dosing above 1 g/kg per day is contraindicated for some IVIg products.</p> <p>Refer to the current product information sheet for further information.</p>	<p>Scleromyxedema (skin involvement only) unresponsive to steroids and other immunosuppressant agents or where contra-indicated</p> <p>Induction Dose – 2 g/kg over 5 days</p> <p>Maintenance Dose – 0.5 to 2 g/kg over 2 to 5 days, four to six weekly. A maximum dose of 2 g/Kg may be given in any 4 week period.</p> <p>The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.</p>	<p>While there are no clinical trials to indicate the effectiveness or appropriate dosage for Ig therapy, based on case reports, 2 g/kg per month initially has been shown to be very effective and is supported by the Australasian College of Dermatologists.</p> <p>A range of dosing is defined due to the need to support weaning patients from treatment</p>

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	The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.	<p>Refer to the current product information sheet for further information on dose, administration and contraindications.</p> <p>Scleromyxedema - systemic involvement as first line therapy</p> <p>Induction Dose: 2 g/kg over 5 days</p> <p>Maintenance Dose: 0.5 to 2 g/kg over 2 to 5 days, four to six weekly. A maximum dose of 2 g/Kg may be given in any 4 week period</p> <p>The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.</p> <p>Refer to the current product information sheet for further information on dose, administration and contraindications.</p>	and to determine the minimal effective dose based on clinical response.
<p style="text-align: center;">References</p> <p style="text-align: center;">(most recent update: August 2016)</p>			
<p>Blum M, Wigley FM and Hummers LK (2008) Scleromyxedema: a case series highlighting long-term outcomes of treatment with intravenous immunoglobulin (IVIG). <i>Medicine (Baltimore)</i>, 87 (1):10.</p> <p>https://www.ncbi.nlm.nih.gov/pubmed/18204366</p> <p>Brunet-Possenti F, Hermine O, Marinho E, et al (2013) Combination of intravenous immunoglobulins and lenalidomide in the treatment of scleromyxedema. <i>Journal of the American Academy of Dermatology</i>, 69:31.</p> <p>https://www.ncbi.nlm.nih.gov/pubmed/23866873</p> <p>Caudill L and Howel I (2014) Scleromyxedema: a case clinically and histologically responsive to intravenous Immunoglobulin. <i>Journal of Clinical Aesthetic Dermatology</i>, 7(5):45-7.</p> <p>https://www.ncbi.nlm.nih.gov/pubmed/24847409</p> <p>Dolenc-Voljc M, Jurcic V, Hocevar A, et al (2013) Scleromyxedema with subcutaneous nodules: successful treatment with thalidomide and intravenous immunoglobulin. <i>Case Rep Dermatology</i>, 5:309–315.</p>			

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		<p>https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3843934/</p> <p>Efthimiou P and Blanco M (2008) Intravenous gammaglobulin and thalidomide may be an effective therapeutic combination in refractory scleromyxedema: case report and discussion of the literature. <i>Semin Arthritis and Rheumatology</i>, 38:188–194.</p> <p>https://www.ncbi.nlm.nih.gov/pubmed/18221985</p> <p>Gabriel SE, Perry HO, Oleson GB, et al (1988) Scleromyxedema: a scleroderma-like disorder with systemic manifestations. <i>Medicine (Baltimore)</i>, 67:58– 65.</p> <p>https://www.ncbi.nlm.nih.gov/pubmed/3336281</p> <p>Hummers, L (2014) Scleromyxedema. <i>Current Opinion in Rheumatology</i>, 26(6):658–662.</p> <p>https://www.ncbi.nlm.nih.gov/pubmed/25215418</p> <p>Kulczycki A, Nelson M, Eisen A, et al (2003) Scleromyxedema: treatment of cutaneous and systemic manifestations with high-dose intravenous immunoglobulin. <i>British Journal of Dermatology</i>, 149(6):1276–81.</p> <p>https://www.ncbi.nlm.nih.gov/labs/articles/14674909/</p> <p>Majeski C, Taher M, Grewal P, et al (2005) Combination oral prednisone and intravenous immunoglobulin in the treatment of scleromyxedema. <i>Journal of Cutaneous Medicine and Surgery</i>, 9(3): 99–104.</p> <p>https://www.ncbi.nlm.nih.gov/pubmed/16392012</p> <p>Moser DW and Griffin TA, (2012) Treatment of scleromyxedema with IVIg. <i>Pediatric Rheumatolgy Online Journal</i>, 10(Suppl 1): PMC3403064</p> <p>https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3403064/</p> <p>Rey JB and Luria RB (2009) Treatment of scleromyxedema and the dermatoneuro syndrome with intravenous immunoglobulin. <i>Journal of American Academy of Dermatology</i>, 60:1037–1041.</p> <p>https://www.ncbi.nlm.nih.gov/pubmed/19249127</p> <p>Rongioletti F, Merlo G, Cinotti E, et al, (2013) Scleromyxedema: a multicenter study of characteristics, comorbidities, course, and therapy in 30 patients. <i>Journal of American Academy of Dermatology</i>, 69(1):66-72.</p> <p>https://www.ncbi.nlm.nih.gov/pubmed/23453242</p>	

POTENTIAL OPERATIONAL IMPACT	
There is not expected to be any significant operational impact as a result of the proposed changes, although there will be some data entry required compared to the previous Ig request process. The revised criteria are thought to reflect current clinical practice.	
POTENTIAL IMPACT ON PATIENTS, DEMAND AND EXPENDITURE	
Potential impact on patients:	<p>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 expected clinical management of patients with this rare condition and these criteria have been developed in consultation with the Australasian College of Dermatologists. The formal access criteria now proposed for this condition require that either a dermatologist or a clinical immunologist makes the diagnosis and manages the ongoing treatment. This is because this is a very rare condition and it is important to ensure its correct diagnosis and treatment. There are a number of treatments that are available for treating Scleromyxedema. When Scleromyxedema only affects the skin, Ig therapy is only used after patients have not responded to other treatments (unless they are unavailable or inappropriate), and it can be used in combination with other medications or used on its own. When organs other than the skin are involved, Ig therapy may be accessed immediately, once the diagnosis is proven.</p> <p>For existing patients on Ig therapy, six monthly reviews are required to confirm that Ig maintenance therapy is continuing to improve symptoms or to maintain stable disease. Patients will already be regularly reviewed by their dermatologist or clinical immunologist, so this requirement will not place an added burden on patients. If improvements are not achieved or disease worsens, Ig therapy will be stopped and a different treatment approach will be required. A trial of reducing dose and then stopping Ig therapy will be considered by doctors after at least twelve months treatment and when patients are stable. If patients relapse once Ig treatment has been stopped, a further request to restart ongoing Ig therapy can be made.</p> <p>New patients authorised to receive Ig therapy will require an initial check after the first six months of Ig treatment to confirm that Ig therapy is improving disease in the skin and/or the affected organ. This review can be performed as part of the specialist's usual monitoring process. If patients have not improved after the six months treatment, Ig therapy will be ceased and substituted with a different treatment approach. If improvement has been demonstrated, further checks every six months are required to confirm that Ig maintenance therapy is continuing to improve symptoms or maintain stable disease. The ongoing arrangements for maintenance therapy are as outlined above for existing patients.</p>
Impact on demand	Demand is not expected to alter from current levels for this rare condition as the revised criteria are anticipated to

		reflect current clinical practice and Ig use.				
	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	8	7	6	7	14	
Total Grams issued	7,843	5,769	5,897	6,426	7,861	
% Total Grams issued	0.24%	0.16%	0.15%	0.14%	0.16%	
Specialist Working Group knowledge development opportunities and recommendations						
None identified at this stage.						

END OF PUBLIC CONSULTATION DOCUMENT

Next review: Twelve to eighteen months from BloodSTAR v3.0 implementation