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

v2.1 CONDITION NAME:	**Graves ophthalmopathy**
PROPOSED APPROACH: **To retain Graves ophthalmopathy in *Exceptional circumstances only* with changes as outlined**	**SUMMARY OF RATIONALE:** The recommended changes are supported by factors including that*:* - Access to Ig therapy will be limited to patients with severe and persistent Graves ophthalmopathy which may result in blindness - Alternative therapies are available and these changes limit access to Ig therapy as third line treatment after failure to respond to both high dose corticosteroids and rituximab and two other alternative treatments (unless contraindicated or unavailable). - For such patients where previous treatments have not been successful, Ig therapy may be a sight saving treatment. - This approach is consistent with published European guidelines (Bartelena, 2016) and has been developed in consultation with both the Endocrine Society of Australia and the Royal Australian and New Zealand College of Ophthalmologists. It is anticipated that they reflect current clinical practice. - Graves ophthalmopathy is not recommended for funded access in the UK (UK Department of Health, 2011) and is not mentioned in the Canadian IVIg Management Guidelines (Ontario Regional Blood Coordinating Network, 2016). - Five or fewer patients have been treated each year in the last 5 years and demand is not expected to increase as a result of these changes.
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: While IVIg has been shown to be as effective as corticosteroids, due to cost and risks, IVIg is considered to be third line therapy after high dose glucocorticoids followed by a second course of intravenous glucocorticoids combined with orbital radiotherapy or cyclosporine or rituximab. If active Graves ophthalmopathy persists after this treatment, Ig therapy can effectively improve clinical outcome and is preferably given in the setting of multi-disciplinary care with co-ordination between Ophthalmology, Immunology and Endocrinology. Rituximab should be considered ahead of IVIg, unless the risk of dysthyroid optic neuropathy is high, as rituximab can precipitate this complication and would be contra-indicated. These criteria for access have been developed in consultation with both the Endocrine Society of Australia (ESA) and the Royal Australian and New Zealand College of Ophthalmologists (RANZCO).	

ITEM	CRITERIA v2.1	PROPOSED REVISIONS TO THE CRITERIA	SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CLARIFICATIONS
Condition Name	Graves ophthalmopathy	Graves ophthalmopathy	No change
Specialty	Immunology	Immunology	No change
Category	*Exceptional circumstances only*	*Exceptional circumstances only*	No change
Specific Conditions	Graves ophthalmopathy	Graves ophthalmopathy	No change
Level of Evidence	Evidence of probable benefit – more research needed (Category 2a)	Evidence of probable benefit – more research needed (Category 2a)	No change
Justification for Evidence Category		A randomised trial (Kahaly G et al, 1996) studied nineteen patients with active GO, treated with a twenty week course of oral prednisolone starting at 100 mg daily for one week, and tapering by 5 mg/week, and twenty-one patients with 1g IVIg/kg body weight for two consecutive days every three weeks, repeated six times. The proportion of responders was similar in both groups: 12/19, 63% in the prednisolone arm and 13/21, 62% in the IVIg arm. In that study, responders to treatment in both groups showed similar moderate improvements in proptosis, and reductions of exophthalmos and soft tissue involvement. The authors' discussion of their results, mirrored in the EUGOGO guidelines, refers to the high cost and potential risks	This section has been drafted to summarise the literature.

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		as limiting factors for the use of IVIg.	
Indications	Intravenous immunoglobulin (IVIg) may be indicated in select cases. Tagami et al (1996) have shown that IVIg is effective in this condition. Other studies have shown IVIg to be as effective as corticosteroids, with fewer side effects. May be indicated where steroids have failed or are contraindicated.	**Severe disease where immunosuppressant treatments have failed or are contraindicated**	The revised indication is based on the available evidence.
Description and Diagnostic Criteria		Graves ophthalmopathy is an inflammatory disorder of eye occurring in association with Auto-Immune thyroid disease which can result in adverse visual outcome in few severe cases. The most severe complications include corneal ulcerations, Globe subluxation and dystrophic optic neuropathy. Evidence-based guidelines of the European Group on Graves Ophthalmopathy (EUGOGO) by Bartalena et al (2016) advocate high dose glucocorticoids, preferably intravenous as first line therapy for moderate- to-severe and active Graves ophthalmopathy. For second line therapy, the guidelines recommend shared decision making with a second course of intravenous glucocorticoids, oral glucocorticoids combined with orbital radiotherapy or cyclosporine, or rituximab. Orbital decompression surgery, or squint or eyelid surgery are recommended	Section added to reflect the literature. It has been reviewed by the College of Ophthalmologists.

ITEM	CRITERIA v2.1	PROPOSED REVISIONS TO THE CRITERIA			SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CLARIFICATIONS
		for patients when Graves ophthalmopathy has been managed conservatively and inactivated by immunosuppressive treatment. IVIg is considered third line therapy if active Graves ophthalmopathy persists after treatment with glucocorticoid and other therapies, preferably in the setting of multi-disciplinary care with co-ordination between Ophthalmology, Immunology and Endocrinology. Rituximab should be considered ahead of IVIg, unless the risk of dysthyroid optic neuropathy is high, as rituximab can precipitate this complication.			
Diagnosis is required		Yes	By which specialty	Ophthalmologist Clinical immunologist	Diagnosis must now be made by an Ophthalmologist or Clinical immunologist as these specialities are most likely to manage patients with this rare condition.
Diagnosis must be verified		No	By which specialty		
Exclusion Criteria					
Qualifying Criteria		**Severe disease where immunosuppressant treatments have failed or are contraindicated** Rituximab has been shown to be effective in the treatment of Graves Ophthalmopathy. A course of Rituximab should be considered for this patient if not already trialled, unless contraindicated. • Persistent and severe ophthalmic disease AND			The Specialist Working Group developed these new criteria in consultation with the ESA and RANZCO. The Bartelena clinical activity score (Bartelena et al, 2016) has been adapted in the development of evidence items to ensure that qualifying patients have an appropriate level of disease severity. These assessments will be used as a baseline against which to compare progress at initial and continuing review to assess clinical

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		• Unresponsive to intravenous steroid treatment OR • Steroid treatment is contraindicated AND • A trial of rituximab has failed to demonstrate a response, three months following the last dose. OR • Rituximab is contraindicated or unavailable AND • A trial of at least two alternative treatments has been undertaken	improvement. The Specialist Working Group noted that while Rituximab is the treatment of choice for this devastating condition, it is not always available or may be contra-indicated, and as such, there continues to be limited circumstances where Ig therapy is warranted. Alternative treatments include Cyclosporine, Methotrexate, Orbital radiotherapy and orbital decompression surgery.
Review Criteria		Review by an Ophthalmologist is required within 3 months of treatment to determine whether the patient has responded, and six monthly thereafter. If no response has been demonstrated by three months, IVIg therapy should be abandoned. 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: • Improvement in the severity and level of activity of eye disease compared to the qualifying assessment AND • A reduction in dose is planned or if not planned, a valid reason is provided.	The initial treatment period has been defined and review criteria to demonstrate a clinical response, supported by evidence items, have been developed. An assessment of each of the Bartelena Activity Score measures of severity will be captured as 'improved/ worsened/stable' for monitoring and to inform future measurement of clinical response. Patients will be authorised for continuing therapy if some improvement has been demonstrated. Prescribers are encouraged to determine the minimal effective dose for patients.

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		On review of a continuing authorisation period For stable patients on maintenance treatment, review by an Ophthalmologist is required every six months. Clinical effectiveness of Ig therapy can be demonstrated by: • Further improvement in severity or stabilisation of eye disease AND • A reduction in dose is planned or if not planned, a valid reason is provided. **Rituximab has been shown to be effective in the treatment of Graves Ophthalmopathy. A course of Rituximab should be reconsidered for this patient if not already trialled, unless contraindicated.**	A script has been added to raise awareness of the effectiveness of Rituximab in existing patients that will transition to maintenance therapy in BloodSTAR v3.1 and may not have already been trialled on Rituximab.
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.	**Induction Dose –** Up to 2 g/kg over 2 days **Maintenance Dose –** 0.4 to 2 g/kg in single or divided doses monthly. A maximum dose of 2 g/Kg may be given in any 4 week period. This might be by divided doses more frequently than monthly. 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 controls have been defined and are consistent with international guidelines and have been endorsed by the ESA and RANZCO.
References			

(most recent update: April 2016)

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POTENTIAL OPERATIONAL IMPACT	
These criteria are thought to reflect current clinical practice and minimal operational impact is anticipated. If existing patients receiving Ig therapy have not already been treated with Rituximab (and Rituximab treatment is not contraindicated), a trial with Rituximab should be considered, as it has been proven to achieve excellent clinical outcomes in patients and is more cost effective than Ig therapy. While there will be some data entry required at review, the assessments will be presented as drop down menus so as not to be burdensome. Prescribers will be expected to consider a reduction in dose at each review in order to establish the minimal effective dose for each patient.	
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. In addition, they have been developed in consultation with both the Endocrine Society of Australia and the Royal Australian and New Zealand College of Ophthalmologists. The formal access criteria proposed require that an ophthalmologist or a clinical immunologist makes the diagnosis and manages the ongoing treatment given that these specialties are most likely to manage patients, in association with endocrinologists. Alternative therapies are available to treat this condition and international treatment guidelines recommend that Ig therapy would only be used after patients fail to respond to a number of alternative treatments (unless contraindicated or unavailable). If existing patients receiving Ig therapy have not already been treated with Rituximab (and Rituximab treatment is not contraindicated), a trial with Rituximab may be undertaken, as it has been proven to achieve excellent clinical outcomes in patients and is more cost effective than Ig therapy. Existing patients known to be unresponsive to Rituximab (or where unavailable or inappropriate) will require regular reviews at least every six months by their ophthalmologist to confirm that the Ig treatment continues to be effective in reducing the severity and level of activity of eye disease. This may be undertaken as part of their specialist's usual monitoring process so will not place an added burden on patients. Doctors will start to reduce the dose of Ig therapy as the eye disease improves. New patients authorised to receive Ig therapy will require an initial check after three months treatment to confirm that the Ig has been effective in improving the eye disease. If patients do not respond after this time, Ig therapy will be stopped and a different treatment approach used. These checks again can be performed as part of the usual regular reviews undertaken by Ophthalmologists to monitor the eye disease. Patients will qualify for maintenance Ig therapy provided improvement in eye disease had been confirmed after the initial three months Ig therapy, and the arrangements for maintenance therapy will be the same as outlined above for existing patients on Ig therapy.

Impact on demand		Given the low level of usage over the last 5 years and development of the criteria in collaboration with the ESA and RANZCO, there is not anticipated to be any impact on use as they 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	**<500**	**<1000**	**<2000**	**<2,500**	**2,810**	
% Total Grams issued	**<0.02%**	**<0.02%**	**<0.05%**	**<0.07%**	**0.06%**	
Specialist Working Group knowledge development opportunities and recommendations						
The assessment of Graves ophthalmopathy severity using the measures of the Bartelena Score at review will enable a review of clinical outcome and the best future method to assess and understand the benefit of Ig therapy. This message will require promulgation via a communication strategy.						

END OF PUBLIC CONSULTATION DOCUMENT

Next review: Eighteen months after implementation of BloodSTAR v3.0