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

v2.1 CONDITION NAME: **Pure red cell aplasia (PRCA)**	
v3.0 CONDITION NAME: **Pure red cell aplasia (PRCA)**	
PROPOSED APPROACH: **To retain Pure red cell aplasia (PRCA) in *Exceptional circumstances only* with the changes outlined.**	**SUMMARY OF RATIONALE:** The recommended changes are supported by factors including that*:* - The level of evidence has been upgraded from 4b to 2a with definite clinical response being demonstrated in patients with Parvovirus B19 associated PRCA with defined immunosuppressed states. Several smaller case series suggest probable benefit in patients with refractory PRCA following immunosuppressive therapy. - PRCA associated with Parvovirus is listed as a 'blue' condition (medium priority in times of shortage, recommended for short term use), with non-Parvo PRCA is 'grey' (low priority in times of shortage) in the United Kingdom (UK Department of Health, 2011) and in Canada (Ontario Regional Blood Coordinating Network, 2016) for both Parvo virus B19 associated PRCA and refractory PRCA following immunosuppressant therapy. - While an increasing trend is observed for Ig use in this condition, it is related to the increasing incidence of leukaemia and the use of immunosuppressant therapy with an increase seen in PRCA as a result. The clinical benefit from Ig therapy in this context is recognised as being cost effective (Mouthon, 2015).
v2.1 CONDITION CATEGORY: Condition for which Ig is used in exceptional circumstances only (Chapter 7) **v3.0 CONDITION CATEGORY: Condition for which Ig is used in** exceptional circumstances only (Chapter 7)	

Role of Ig therapy: This is an uncommon life threatening clinical condition with severe anaemia, very low reticulocyte numbers and a selective deficiency of erythroid progenitors demonstrated on bone marrow biopsy. IVIg is considered first-line therapy for viral PRCA associated with parvovirus B19 in immunocompromised patients, and is also used in the treatment of patients with immunological PRCA who have failed other therapies (e.g. prednisone or cyclosporine). While all the evidence is from case studies rather than formal clinical trials, there are over 130 reported cases demonstrating a clinical response to dosing of at least 2 g/kg for up to three months in Parvo B19 associated PRCA. Several smaller case series suggest probable benefit in patients with refractory PRCA following immunosuppressive therapy.

Ig therapy is supported in both the UK (UK Department of Health, 2011) and Canadian guidelines recommended for government funded IVIg use (Ontario Regional Blood Coordinating Network, 2016), consistent with these recommendations.

ITEM	v.2.1	PROPOSED REVISIONS TO THE CRITERIA	SPECIALIST WORKING GROUP RATIONALE FOR PROPOSED CHANGE
Condition Name	Pure red cell aplasia (PRCA)	Pure red cell aplasia (PRCA)	
Specialty	Haematology	Haematology	
Category	*Exceptional circumstances only*	*Exceptional circumstances only*	
Specific Conditions	Pure red cell aplasia		
Level of Evidence	Nil (Category 4b)	Evidence of probable benefit – more research needed (Category 2a)	A search of the literature identified many published case series reporting probable benefit supporting a recommendation to revise the evidence level.
Justification for Evidence Category		Whilst there are no randomised controlled trials for this condition there are many published case studies demonstrating benefit of Ig in the therapy of Parvovirus B19 associated PRCA in over 130 patients with defined	This new section was drafted by the SWG to summarise the literature.

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		Immunosuppressed states (Crabol 2013, Geetha 2000, Kawano 2013, Koda 2013, Koduri 1999, Lejeune 2014, Mouthon 2005, Mouthon 2015, Nair 2016, Zhang 2015). These case series suggest doses of 2g/kg are most effective, with most response demonstrated with 1- 3 doses. Several small case series suggest potential benefit in patients receiving Ig therapy for refractory PRCA following immunosuppressive therapies (Koda 2013, Nair 2016, Zhang 2015).	
Indications		PRCA associated with Parvo B19 infection in immunocompromised patients or autoimmune mediated refractory to immunosuppressant medication.	A new indication, based on recent publications, was developed. .
Description and Diagnostic Criteria	PRCA is a rare syndrome of severe anaemia, reticulocytopenia and a selective deficiency of erythroid progenitors. Intravenous immunoglobulin (IVIg) should be considered as first-line therapy for viral PRCA associated with parvovirus B19 in immunocompromised patients. IVIg is a reasonable option for patients with immunological PRCA who have failed other therapies (e.g. prednisone or	PRCA is a rare syndrome of severe anaemia, reticulocytopenia and a selective deficiency of erythroid progenitors. IVIg should be considered as first-line therapy for viral PRCA associated with parvovirus B19 in immunocompromised patients. IVIg is a reasonable option for patients with immunological PRCA who have failed other therapies (e.g. prednisone or cyclosporine).	No change from v2.1

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	cyclosporine).				
Diagnosis is required		Yes	By which specialty	Haematologist	Specialist Working Group advised that this indication is diagnosed, treated and managed by haematologists.
Diagnosis must be verified		No	By which specialty		
Exclusion Criteria					
Qualifying Criteria		• Parvo B19 virus associated PRCA in immunosuppressed patient proven by bone marrow biopsy OR • Immune- mediated PRCA proven by bone marrow biopsy refractory to treatment with at least two Immunosuppressant therapies OR • Immune-mediated PRCA and immune-suppressant medications are contraindicated			New qualifying criteria have been defined based on Specialist Working Group consensus. For Immune-mediated PRCA, patients will have been demonstrated to have been non-responsive to immunosuppressant therapies such as cyclosporine, prednisolone or cyclophosphamide. Valid contraindication reasons will include reasons such as pregnancy, significant infection including sepsis, potential for life threatening infection or malignancy.
Review Criteria		Review is not mandated for this condition. Clinical effectiveness of Ig therapy may be demonstrated by: • Recovery of bone marrow • Reduced transfusion dependence			Review has not been mandated for this condition as ongoing therapy is not supported.

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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– 2 g/kg over 2 or 5 days** Up to 2 additional monthly doses are allowed when recovery is incomplete. Conditions for additional dose: After 4 and 8 weeks, further 2 doses allowed if inadequate response is demonstrated. A maximum of 3 doses is allowed. 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.**	The dose has been defined based on Specialist Working Group consensus and are consistent with the UK criteria supporting up to three doses, one month apart (UK Department of Health, 2011).

References

(most recent update: May 2016)

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Zhang M, Zhong X, Zhang W, Xu J, Zhang M, Shen Y, et al (2015) Human parvovirus B19 infection induced pure red cell aplasia in liver transplant recipients. *International Journal of Clinical Practice Supplementary*, 183:29-34.

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POTENTIAL OPERATIONAL IMPACT

Any potential operational impact of this change is considered to be minor as the proposed criteria are expected to be in line with existing clinical practice. However, the revised criteria will ensure that patients with immune PRCA following immunosuppressant therapy have been unresponsive to steroid and cyclophosphamide or cyclosporine therapy (unless contraindicated), prior to treatment with Ig therapy. The criteria will also define appropriate dosing levels and treatment period (up to three doses only) which are not currently stated.

POTENTIAL IMPACT ON PATIENTS, DEMAND AND EXPENDITURE

Description of impact on patients:	There is not anticipated that there will be any direct impact on patients as a result of these criteria given that the proposed changes are in line with current clinical practice in managing patients with this rare condition. The changes are also in line with international treatment guidelines. The formal access criteria proposed now require that a haematologist makes the diagnosis and manages the ongoing treatment. This is because it is important to ensure its correct diagnosis and treatment. When the very low red blood cell count is caused by an infection, Ig treatment can be given immediately, however, when it is immune mediated, Ig therapy is only used after patients have not responded to other treatments unless such therapies are considered inappropriate. In both instances, treatment is short lived to a maximum of three doses and transition planning will ensure that any patients in the midst of treatment will be not be impacted at the time of implementation. .
Impact on demand:	The increasing trend is usage is likely to be related to an increase in the number of patients being treated for haematological malignancy (due to the ageing of the population and increasing incidence of leukaemia) with the resultant unintended consequence of PRCA related to immunosuppressant therapy. This trend will be unchanged as a result of the proposed changes.

	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	**18**	**27**	**30**	**31**	**24**	
Total Grams issued	**5,867**	**7,034**	**8,398**	**8,091**	**8,422**	
% Total Grams issued	**0.18%**	**0.2%**	**0.21%**	**0.18%**	**0.17%**	

Specialist Working Group knowledge development opportunities and recommendations

None identified at this stage.
END OF PUBLIC CONSULTATION DOCUMENT **Next review: Twelve to eighteen months after BloodSTAR v3.0 implemented**