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

v2.1 CONDITION NAME: **Autoimmune congenital heart block (neonatal lupus)**	
v3.0 CONDITION NAME: **Autoimmune congenital heart block**	
PROPOSED APPROACH: **To retain Autoimmune congenital heart block in *Exceptional circumstances only* with the changes as outlined.**	**SUMMARY OF RATIONALE:** The recommended changes are supported by factors including that: - These criteria have been developed in consultation with the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG). This expert group has confirmed a limited role for Ig therapy. - While there are no randomised controlled clinical trials due to the rarity of this condition, there are case series and reports demonstrating benefit in affected fetuses, particularly with the complication of evidence of cardiomyopathy (Saxena et al, 2014; Trucco et al, 2011 and Jaeggi et al, 2016). - Given the possible need for cardiac transplantation during childhood, even a small reduction in the incidence or severity of cardiomyopathy would be significant. - While alternative therapies are available, in situations where alternative therapies are very likely to result in long term adverse outcome, such as when a previous pregnancy has resulted in cardiomyopathy despite alternative therapy, Ig therapy should remain available. - While there has been minimal Ig therapy under the national blood arrangements, it is understood that it has occasionally been secured by Direct Order in some jurisdictions. It is also possible, that treatment has been accessed under Myocarditis in children. - 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 guidelines but may still be approved for funded use in those countries.
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: This condition is caused by placentally transferred maternal Ro/La antibodies that may damage the cardiac conduction tissues during fetal development leading to the blocking of signals from the atrio-ventricular node of the fetal heart. This results in a global mortality rate of 20% and pacemaker rates of at least 64% in the first year of life (Brito-Zeron, 2015). While there is little evidence suggesting that the administration of steroids or Ig therapy can reverse third-degree block in the fetus, these therapies have been demonstrated to be helpful in early first-and second-degree heard block and in reducing associated myocardial dysfunction. A combination of steroids, plasmapheresis and Ig therapy has been shown to be effective in such cases. This treatment has also been demonstrated to reverse the severity of heart block detected in the infants of women without previously affected pregnancies when used until delivery followed by IVIg in the infant until disappearance of maternal antibodies.

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Condition Name	Autoimmune congenital heart block (neonatal lupus)	Autoimmune congenital heart block	Condition name qualifier has been removed as there can be other manifestations of neonatal lupus, apart from congenital heart block.
Specialty	Immunology	Immunology	Unchanged
Category	*Exceptional circumstances only*	*Exceptional circumstances only*	Unchanged
Specific Conditions	Autoimmune congenital heart block	Prevention of recurrent autoimmune congenital heart block Maternal therapy for treatment of congenital heart block Post–natal treatment of congenital heart block	Three specific conditions aligning to periods of use have been defined to support data analysis.
Level of Evidence	Insufficient data (Category 4a).	Insufficient data (Category 4a)	Unchanged
Justification for Evidence Category		Multiple positive case reports and case series preceded and followed the report of a multicentre open-label study (Friedman et al, 2010). Enrolment criteria included: maternal	This section has been drafted following consultation of the literature and consensus of the Specialist Working Group.

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		anti-SS-A/Ro antibody, a previous child with CHB/rash, </= 20 mg prednisone, < 12 weeks pregnant. IVIG (400mg/kg) was given every 3 weeks from 12 to 24 weeks of gestation. Study prematurely ceased after 20 patients because stopping rule of 3 affected cases reached. However, majority of successful reports used higher doses +/- frequency of IVIG (1-2g/kg 2 to 4 weekly) which are more likely to be immunomodulatory, often throughout the pregnancy and sometimes, when evidence of early disease, extending to the newborn until disappearance of maternal antibodies. A combination treatment of steroids, plasmapheresis and IVIg until delivery followed by IVIg in the infant until disappearance of maternal antibodies resulted in reversal of the severity of heart block detected in the infants of 2 women without previous affected infants. The general conclusion is that it is well-tolerated and although replacement dose IVIg does not prevent CHB, high dose IVIg is effective in some patients.	
Indications		**Prevention of recurrent autoimmune congenital heart block where maternal SS-B (La) and/or SS-A (Ro) antibodies are present.** **Maternal therapy for treatment of congenital heart block where maternal SS-B (La) and/or SS-A (Ro) antibodies are identified.** **Post-natal treatment of congenital heart block where SSB-La and /or SSA – La are present.**	Three indications have been developed to support the differing qualifying criteria and treatment periods required.
Description		Congenital heart block (CHB), the most serious manifestation of neonatal lupus erythematosus, is an autoantibody	Background information has been developed

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and Diagnostic Criteria		mediated disorder potentially caused by placental transmission of maternal autoantibodies to 52-kd and 60-kd SSA/Ro +/-48-kd SSB/La ribonucleo- proteins. These antibodies can cause permanent and often life- threatening damage to the fetal heart. The incidence of CHB in the offspring of mothers with pathologic autoantibodies is 1-2% but the recurrence rate in subsequent pregnancies following the birth of a child with neonatal lupus is 18%.			by Specialist Working Group consensus.
Diagnosis is required		Yes	By which specialty	Obstetrician Immunologist	These diagnosing specialists have been included as they are those most likely to manage this condition.
Diagnosis must be verified			By which specialty		
Exclusion Criteria					
Qualifying Criteria		**Prevention of recurrent autoimmune congenital heart block where maternal SS-B (La) and/or SS-A (Ro) antibodies are present.** • Current pregnancy with a history of autoimmune congenital heart block in at least one previous pregnancy AND • Maternal SS-B (La)-and/or SS-A (Ro)-antibodies are present **Maternal therapy for treatment of Congenital heart block**			Qualifying criteria have been developed for each indication. Except where previous pregnancies have been affected, heart block and maternal anti-Ro and/or anti-La antibodies must be present to qualify for Ig therapy.

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		where maternal SS-B (La) and/or SS-A (Ro) antibodies are identified. • Current pregnancy and evidence of congenital heart block AND • Maternal SS-A (Ro) and/or SS-B (La) antibodies are identified AND • Steroid therapy with or without plasmapheresis being given concurrently OR • Steroid treatment is contraindicated **Post-natal treatment of congenital heart block where SSB-La and /or SSA – La are present.** • Neonate with congenital heart block AND • SS-B (La) and/or SS-A (Ro) antibodies are present	
Review Criteria		**Prevention of recurrent autoimmune congenital heart block where maternal SS-B (La) and/or SS-A (La) antibodies are present.** Review is not mandated for this indication. **Clinical effectiveness of Ig therapy may be demonstrated by:** • Absence of symptoms of CHB in fetus • Live birth of healthy neonate	For the first indication, treatment in instances where previous infants have been affected is given for a three month period from 12 to 24 weeks of pregnancy. If heart block is present at 24 weeks, re-qualification under the second indication is required.

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		AND • Reduction in the level or absence of maternal SS-A and/or SS-B antibodies **Maternal therapy for treatment of congenital heart block where maternal SS-B (La) and/or SS-A (Ro) antibodies are identified.** Review is not mandated for this indication **Clinical effectiveness of Ig therapy may be demonstrated by:** • Congenital heart block has improved in response to Ig therapy AND • Reduction in the level or absence of maternal SS-B (La) and/or SS-A (Ro) antibodies **Post-natal treatment of congenital heart block where SSB-La and /or SSA – La are present.** Review is not mandated for this indication **Clinical effectiveness of Ig therapy may be demonstrated by:** • Congenital heart block has improved in response to Ig therapy AND • Reduction in the level or absence of maternal SS-A and/or SS-B antibodies	For the second indication, treatment is given for up to 6 months - until delivery of the infant. For the third indication, where the infant does have Congenital heart block - the infant may require ongoing treatment. The evidence of benefit is strongest when preventative therapy was started. Once the infant is born, the literature suggests about 4 month's treatment or until maternal Ab have disappeared.
Dose		**Prevention of recurrent autoimmune congenital heart block**	

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		where maternal SS-B (La) and/or SS-A (La) antibodies are present. **Induction Dose –** Up to 2 g/kg in a single or divided dose. This may be given as two doses of 1 g/kg at fortnightly intervals **Maintenance Dose -**1-2 g/kg monthly in single or divided doses. A maximum dose of 2 g/kg may be given in any four week period. This might be by divided doses more frequently than monthly. **Refer to the current product information sheet for further information on dose, administration and contraindications.** **Maternal therapy for treatment of congenital heart block where maternal SS-B (La) and/or SS-A (Ro) antibodies are identified.** **Induction Dose–** Up to 2 g/kg in single or divided dose. This may be given as two doses of 1 g/kg at fortnightly intervals **Maintenance Dose -** 1- 2g/kg monthly in single or divided doses. A maximum dose of 2 g/kg may be given in any four week period. This might be by divided doses more frequently than monthly. **Refer to the current product information sheet for further information on dose, administration and contraindications.** **Post-natal treatment of congenital heart block where SSB-La and /or SSA – La are present.** **Induction Dose –** Up to 2 g/kg in single or divided dose. This	

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		may be given as two doses of 1 g/kg at fortnightly intervals **Maintenance Dose -** 1-2 g/kg monthly in single or divided doses. A maximum dose of 2 g/kg may be given in any four week period. This might be by divided doses more frequently than monthly. **Refer to the current product information sheet for further information on dose, administration and contraindications**	

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(most recent update: October 2016)

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POTENTIAL OPERATIONAL IMPACT

There is not anticipated to be any operational impact as a result of these changes, given that usage is very low and maintenance treatment continues to be supported. Formal qualifying criteria are now in place, however, Ig therapy is not routinely used for Autoimmune congenital heart block.

POTENTIAL IMPACT ON PATIENTS, DEMAND AND EXPENDITURE

Description of impact on patients:	These criteria are anticipated to align with current clinical practice and will support the ongoing treatment of any existing patients on treatment at the time of implementation should that be required, so there is not expected to be any impact on patients as a result of these changes. The criteria have been developed in consultation with the Royal Australian and New Zealand College of Obstetricians and Gynaecologists who have advised that there is a limited role for Ig therapy. The very low level of use indicates that current clinical practice is in line with this advice. The formal access criteria proposed for this condition require that either an obstetrician or a clinical immunologist makes the diagnosis and manages the ongoing treatment. This is because Autoimmune congenital heart block (ACHB) is a rare condition, and is often treated by these specialists during pregnancy or in the new born. There are a number of options that are available in the treatment of ACHB, and while Ig therapy is not used routinely, it has been shown to be effective when used in combination with other treatments in certain clinical circumstances which are provided for by these criteria.
Impact on Demand:	Given that demand is so low, no impact on demand is anticipated.

	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**	**0**	**0**	**0**	**<5**	
Total Grams issued	**0**	**0**	**0**	**0**	<500	
% Total Grams issued	**0**	**0**	**0**	**0**	<0.01%	

Specialist Working Group knowledge development opportunities and recommendations

None identified at this stage

END OF PUBLIC CONSULTATION DOCUMENT

Next review: Eighteen months to two years after BloodSTAR v3.0 implementation