Intravenous immunoglobulin (IVIg) Clinical Practice Guideline template

November 2015: Prepared by Blood Matters www2.health.vic.gov.au/bloodmatters
Updated November 2016, February 2017, November 2018, October 2019

Purpose: To administer IVIg safely and according to the manufacturers' instructions (product information sheets). This information is a guide only. Health service procedures based on the information contained in this document should be implemented and monitored for compliance with best practice, safety guidelines and all other requirements specific to the products available. All health service policies/procedures should be developed in accordance with local procedure development policies and should be approved/endorsed by the appropriate committee/s.

Indications:
Refer to the Criteria for the clinical use of intravenous immunoglobulin in Australia 3rd Edition October 2018

Contraindications: Refer to Appendix A

Precautions: Refer to Appendix A
Please refer to the product insert for the prescribed IVIg product and preparation for further information.

Presentation:
Please refer to appendix A for specific information regarding product presentations.

Please note: Administration rates and protocols will vary between products and presentations. Products/presentations are not interchangeable.

Storage Conditions: Refer to Appendix A
- Some Immunoglobulins can be stored at room temperature, while others require refrigeration (please refer to product insert for storage information)
- If refrigerated, once the product has reached room temperature it must not be re-refrigerated
- Do not freeze

Compatibilities:
- IVIg should be administered separately from other intravenous fluids or medications
- IVIg can interfere with the response to live, attenuated vaccines. Please see appendix A for further information

Inspection:
- Immunoglobulin is a sterile, clear or slightly opalescent, colourless or pale yellow solution for intravenous injection
- Do not use if the solution appears cloudy or contains deposits

Infusion Equipment:
- IVIg may be administered through any standard IV infusion giving set

Priming and Flushing:
- Lines may be primed with 0.9% normal saline

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Preparation for the infusion:

- the patient has consented to receive IVIg
- IVIg has been prescribed
- baseline observations have been taken and recorded
- any pre-infusion symptom which may be confused with an adverse reaction has been noted

Pre-infusion infusion check:

- patient identity following usual hospital protocol
- the right product as prescribed for this patient
- the right dose for this patient
- the right date/time the infusion is due
- the right rate of infusion – the correct corresponding infusion protocol, different IVIg products are given according to different infusion schedules
- Please refer to appendices B-E for infusion rates.

Observations

Perform and document the patient's temperature, pulse, respiration rate and blood pressure at the following points **as a minimum:**

- prior to commencing
- each rate increase and hourly once maximum rate achieved
- on completion
- observe patient for 20 minutes post completion

Please be aware that local policies may require more frequent observations. Similarly, if a patient experiences an adverse reaction to IVIg infusion, more frequent observations may be required.

Adverse effects tend to be rate related.

Consideration should be given to patients who receive IVIg:

- for the first time
- when there has been a long interval since the previous infusion (8 weeks).
- When there is a change in product

The types of reactions that may occur include:

Acute symptoms & signs	Management	Delayed reactions
- malaise - abdominal pain - headache - chest-tightness - facial flushing or pallor - erythema - hot sensations - dyspnoea or respiratory difficulty - non-urticarial skin rash - cutaneous vasculitis - pompholyx on hands/palms - itching - tissue swelling - change in blood pressure - nausea or vomiting	- the infusion should be stopped temporarily - assess patient - notify medical staff - following medical review, and once the patient improves clinically, cautiously recommence at a slower rate	- nausea - vomiting - chest pain - rigor - aching legs These reactions may occur post infusion, normally within 24 hours. Please ensure medical staff are notified.

References

Flebogamma 5% DIF, product information. Grifols Australia Pty Ltd. 2011

Flebogamma 10% DIF, product information. Grifols Australia Pty Ltd. 2013

Intragam® 10, product information. CSL Behring (Australia) Pty Ltd. 2015

Privigen, Product information. CSL Behring (Australia) Pty Ltd. 2014

Gamunex® 10%, product information. Grifols Australia Pty Ltd. 2019

Acknowledgements

Blood Matters would like to acknowledge the Victorian Transfusion Nurse Team of the Australian Red Cross Blood Service for their contributions to this document.

Further information

Further information can be found on the National Blood Authority and Australian Red Cross Blood Service websites:

http://www.blood.gov.au/Ig-governance

http://www.transfusion.com.au/blood_products/fractionated_plasma/IVIg

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Appendix A

	Intragam® 10 (CSL Behring)	**Privigen (CSL Behring)**	**Flebogamma (Grifols)**	**Gamunex® (Grifols)**
Presentation	10% solution Vial size: 2.5g in 25mL, 5g in 50mL, 10g in 100mL, 20g in 200mL	10% solution Vial size: 5g in 50mL, 10g in 100mL, 20g in 200mL, 40g in 400mL	5% and 10% solution Vial size: 5% solution: 0.5g, 2.5g, 5g, 10g and 20g 10% solution: 5g, 10g and 20g	10% solution Vial size: 5g in 50mL, 10g in 100mL, 20g in 200mL
Stabiliser	Glycine	L-proline	Sorbitol	Glycine
Storage	Store at 2°C to 8°C. Once removed from refrigeration, store below 25°C and use within 3 months.	Store at room temperature (<25°C) for up to 3 years	Store at room temperature (<30°C) for up to 2 years.	Store at 2-8˚C for up to 36 months. Once removed from refrigeration, store below 30°C and use within 6 months.
	Do not freeze Protect from light			Do not freeze
Indications	Criteria for the clinical use of Intravenous immunoglobulins in Australia, version 3. All requests for IVIg must be made through BloodSTAR.			
Contraindications	Intragam® 10 is contraindicated in patients who have had a true anaphylactic reaction to human immunoglobulins (especially in patients with antibodies against IgA) or to the excipient glycine.	Privigen® is contraindicated in patients: - who exhibit hypersensitivity to the active substance or to the excipient - with hyperprolinaemia	Flebogamma 5% & 10% is contraindicated in patients - who exhibit hypersensitivity to the active substance or to any of the excipients - with hereditary fructose intolerance. - in babies and young children as hereditary fructose intolerance may not yet be diagnosed and may be fatal	Gamunex® is contraindicated in individuals with known anaphylactic or severe systemic response to human immunoglobulin or any of the excipients of the product. This applies in particular to individuals with severe, selective IgA deficiencies (serum IgA <0.05 g/L) who have known antibodies against IgA (anti-IgA antibody), due to the risk of severe immediate hypersensitivity reactions including anaphylaxis.
Precautions - general	Aseptic Meningitis Syndrome (AMS)			
	Aseptic meningitis syndrome has been reported to occur in association with IVIg treatment. Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae.			
	Hypersensitivity			
	True hypersensitivity reactions are rare. They can occur in the very seldom cases of IgA deficiency with anti-IgA antibodies. Rarely, IVIg can induce a fall in blood pressure with anaphylactic reaction, even in patients who have tolerated previous treatment with human normal immunoglobulin.			
	Thromboembolism			
	There is clinical evidence of an association between IVIg administration and thromboembolic events such as myocardial infarction, stroke, pulmonary embolism and deep vein thromboses. Caution should be exercised in prescribing and infusing IVIg in obese patients and in patients with pre-existing risk factors for thrombotic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited			

	thrombophilic disorders, patients with prolonged periods of immobilisation, severely hypovolemic patients, and patients with diseases which increase blood viscosity).			
	Acute renal failure			
	There have been occasional reports of renal dysfunction and acute renal failure in patients receiving IVIG products. Patients at increased risk are those with pre-existing renal insufficiency, diabetes mellitus, age greater than 65 years, volume depletion, sepsis and paraproteinaemia, and those taking concomitant nephrotoxic drugs.			
	Haemolytic Anaemia			
	IVIg products can contain blood group antibodies which may act as haemolysins and induce in vivo coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction (direct Coomb's test) and, rarely, haemolysis. Haemolytic anaemia can develop subsequent to IVIg therapy due to enhanced red blood cell (RBC) destruction or sequestration. IVIg recipients should be monitored for clinical signs and symptoms of haemolysis.			
	Infusion rate			
	Certain reactions to IVIg tend to be related to higher rates of infusion rate and are most likely to occur during the first hour. It is recommended that the patient's vital signs and general status are monitored regularly throughout the infusion.			
Precautions - specific	See product insert			
Pathogen safety -	See product insert			
Drug interactions - specific	The interaction of IVIg preparations with other medicines has not been established in appropriate studies. Immunoglobulin infusion may interfere with the response to live attenuated vaccines. Therefore administration of such vaccines e.g. poliomyelitis or measles should be deferred until approximately three months after intravenous immunoglobulin administration. See product insert for further information.			
Effects on Fertility	No fertility studies conducted			
Use in pregnancy – general	Clinical experience with immunoglobulins suggests that no harmful effects on the course of the pregnancy or the foetus/neonate are to be expected.			
Use in lactation	Refer to product information			
Paediatric use	The use of Intragam® 10 in the paediatric population has not been established in clinical studies.	Although limited data is available, it is expected that the same warnings precautions and risk factors apply to the paediatric population.	Flebogamma 5% Special precautions should be taken with babies and young children because this fructose intolerance may not yet be diagnosed and may be fatal. Flebogamma 10% DIF is contraindicated in babies and young children as hereditary fructose intolerance may not yet be diagnosed and may be fatal.	Proceed with caution, No data available.
Use in the elderly	Refer to product insert for further information			
Genotoxicity	Refer to product insert for further information			
Carcinogenicity	No carcinogenicity studies have been conducted			

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<table>
<tr><td>Adverse Effects- general</td><td colspan="4">After infusion of immunoglobulin the transitory rise of various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing.
Passive transmission of antibodies to erythrocyte antigens e.g. A, B, D may interfere with some serological tests for red cell antibodies for example the antiglobulin test.</td></tr>
<tr><td></td><td colspan="4">The following adverse reactions may occur during or after IVIg treatment:
- chills
- headache
- fever
- vomiting
- allergic reactions
- nausea
- arthralgia
- low blood pressure
- moderate low back pain

Should any of these reactions develop during infusion, the infusion should be temporarily stopped, the patient assessed, a medical officer notified. Following medical review, and if patient improves clinically, then it may be considered to cautiously recommence the infusion at a slower rate.

IVIg therapy has been associated with an increase in serum creatinine level and/or acute renal failure.

The following patients may experience a higher frequency of adverse events, including those of a minor nature when receiving IVIG:
- those receiving IVIg for the first time
- when there has been a long interval since the previous infusion or
- in rare cases, when the human normal immunoglobulin product is switched</td></tr>
<tr><td>Adverse Effects - specific</td><td colspan="2">See product insert</td><td>For patients experiencing adverse reactions with Flebogamma® 10% DIF, it is advisable to reduce the infusion rate in subsequent infusions and limit the maximum rate to 0.04ml/kg/min or administer 5% concentration.</td><td>See product insert</td></tr>
<tr><td>Monitoring</td><td colspan="4">Monitor as above</td></tr>
<tr><td>Compatible fluids/ dilution</td><td colspan="4">IVIg should be administered separately from other IV fluids or medications the patient might be receiving</td></tr>
<tr><td></td><td>0.9% saline
Intragam® 10 can be used undiluted but may also be infused diluted with up to 2 parts 0.9% saline</td><td>5% dextrose (5% glucose noted in PI)
Privigen® can be diluted with 5% dextrose (5% glucose noted in PI) solution, using aseptic technique.</td><td>None listed
Dilution not mentioned in PI</td><td>If dilution is required, Gamunex® may be diluted with 5% dextrose in water (D5/W). Do not dilute with saline. Gamunex® infusion line can be flushed with 5% dextrose in water (D5/W) or 0.9% sodium chloride for injection.</td></tr>
</table>

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				AVOID: simultaneous administration with Heparin through a single lumen delivery system device due to Gamunex®, Heparin **incompatibilities.**
Administration				
Appearance	All products should be clear or slightly opalescent liquids ranging from colourless to pale yellow, If the product appears turbid or to contain any sediment it must not be used.			
Infection control	Intragam® 10 contains no antimicrobial preservative. It must therefore, be used immediately after opening the bottle. Use in one patient on one occasion only. Any unused portion should be discarded appropriately.	Privigen® contains no antimicrobial preservative. It must, therefore, be used immediately after opening the bottle. Use in one patient on one occasion only. Any unused portion should be discarded appropriately.	Flebogamma® 5%/10% DIF contains no antimicrobial preservative. It must therefore, be used immediately after opening the bottle. Use in one patient on one occasion only. Any unused portion should be discarded appropriately.	Gamunex® 10% contains no antimicrobial preservative. It must therefore, be used immediately after opening the bottle. Use in one patient on one occasion only. Any unused portion should be discarded appropriately.
Traceability	The name and batch number of every IVIg bottle administered to a patient must be recorded for traceability purposes.			
Equipment/Giving set	Administered via any standard IV infusion giving set. Venting is required.			
Rate of Infusion	Intragam®10 The infusion should be commenced at a rate of 1 mL/minute. After 15 minutes the rate may be gradually increased to a maximum of 3–4 mL/minute over a further 15 minutes. **Maximum rate = 4mL/ minute (240mL/hr)** **Paediatrics:** Consideration should be given to running IVIg at slower rates for paediatric/neonatal patients. Suggest discussing rate of infusion with a Consultant Paediatrician or Blood Service Haematologist to determine the best rate for each child/infant/neonate.	Privigen® The initial infusion rate is 0.3 mL/kg//hr. If well tolerated, the rate of administration may gradually be increased to 4.8 mL/kg body weight/hr. **Maximum infusion rate = 4.8 mL/kg/hr**. **Maximum infusion rate for patients with ITP is 2.4mL/kg/hr as per product information.**	**Flebogamma 5% DIF** should be infused intravenously at an initial rate of 0.01 - 0.02 ml/kg/min for the first thirty minutes. If well tolerated, the rate of administration may gradually be increased to a maximum of 0.1ml/kg/min. **Maximum rate = 6mL/kg/hr** **Flebogamma 10% DIF** Initial rate of 0.01ml/kg/min for the first thirty minutes. If tolerated advance to 0.02 ml/kg/min for the second thirty minutes If tolerated advance to 0.04 ml/kg/min for the third thirty minutes If tolerated advance to 0.06 ml/kg/min for the fourth thirty minutes If tolerated advance to a maximum rate of 0.08 ml/kg/min for the fifth thirty minutes **Maximum rate = 4.8mL/kg/hr**	Gamunex should initially be infused at a rate of 0.01 mL/kg/min for the first 30 min. If well-tolerated, the rate may be increased gradually to a maximum of 0.08 mL/kg/min (8mg/kg/min). **Maximum rate = 4.8mL/kg/hr** If side effects occur, the rate may be reduced, or the infusion interrupted until symptoms subside. The infusion may be resumed at the rate which is comfortable for the patient.

	Infusion rates for acutely ill, febrile, and or elderly patients, and those with known cardiac or renal insufficiencies should be raised cautiously and frequently will not reach the maximum rate. The patient's predisposition to circulatory overload should always be considered when selecting infusion rates.
Considerations	Consideration should be given to reducing the rate of infusion in paediatric/neonatal patients, elderly patients and in patients with pre-existing renal disease. In patients at risk for acute renal failure or thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable.

Appendix B – Intragam® 10 (10%) infusion rate guide

Adult Patients

- The infusion should be commenced at the rate of 1 mL per minute (60mL/hr).
- After 15 minutes the rate may be gradually increased to a maximum of 3 to 4 mL per minute (180-240mL/hr) over a further 15 minutes
- Maximum rate 240mL/hr

Paediatric Patients

- Commence 1mL/kg/hr
- If tolerated, increase by 0.5-1mL/kg/hr every 30 minutes as tolerated
- Maximum rate 240mL/hr

Paediatrics: Consideration should be given to running IVIg at slower rates for paediatric/neonatal patients. Suggest discussing rate of infusion with a Consultant Paediatrician or Blood Service Haematologist to determine the best rate for each child/infant/neonate.

Appendix C – Flebogamma® 5% DIF infusion rate guide

Maximum Rate: 0.1 ml/kg/min

Infusion rate		Patient weight (kg)											
mL/kg/min	mL/kg/hr	10	20	30	40	50	60	70	80	90	100	110	120
0.01	0.6	6	12	18	24	30	36	42	48	54	60	66	72
0.02	1.2	12	24	36	48	60	72	84	96	108	120	132	144
0.03	1.8	18	36	54	72	90	108	126	144	162	180	198	216
0.04	2.4	24	48	72	96	120	144	168	192	216	240	264	288
0.05	3.0	30	60	90	120	150	180	210	240	270	300	330	360
0.06	3.6	36	72	108	144	180	216	252	288	324	360	396	432
0.07	4.2	42	84	126	168	210	252	294	336	378	420	462	504
0.08	4.8	48	96	144	192	240	288	336	384	432	480	528	576
0.09	5.4	54	108	162	216	270	324	378	432	486	540	594	648
0.10	6.0	60	120	180	240	300	360	420	480	540	600	660	720

- Increase the rate by 0.01 mL/kg/min (0.6 mL/kg/hr) every 30 minutes to a maximum of 0.10mL/kg/min (6mL/kg/hr) as tolerated by the patient
- This table was developed using the FLEBOGAMMA® 5% DIF product information, always refer to the product information and your local Clinical Practice Guidelines for more information

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Appendix D – Flebogamma® 10% DIF infusion rate guide

Maximum rate: 0.08 ml/kg/min

Infusion Rate		Patient's Weight (kg)											
mL/kg/min	mL/kg/hr	10	20	30	40	50	60	70	80	90	100	110	120
0.01	0.6	6	12	18	24	30	36	42	48	54	60	66	72
0.02	1.2	12	24	36	48	60	72	84	96	108	120	132	144
0.03	1.8	18	36	54	72	90	108	126	144	162	180	198	216
0.04	2.4	24	48	72	96	120	144	168	192	216	240	264	288
0.05	3.0	30	60	90	120	150	180	210	240	270	300	330	360
0.06	3.6	36	72	108	144	180	216	252	288	324	360	396	432
0.07	4.2	42	84	126	168	210	252	294	336	378	420	462	504
0.08	4.8	48	96	144	192	240	288	336	384	432	480	528	576

- Increase the rate by 0.01 mL/kg/min (0.6 mL/kg/hr) every 30 minutes to a maximum of 0.08 mL/kg/min as tolerated by the patient.
- Consider using a slower maximum rate of infusion for the elderly and patients with renal insufficiency to reduce the risk or fluid overload and hyper-viscosity.
- Patients should be well hydrated and observed closely during infusion to reduce the risk of adverse events.
- This table was developed using the FLEBOGAMMA 10% DIF Product Information Leaflet, always refer to the Product Information Leaflet (supplied with the product) and your local Clinical Practice Guidelines for more Information.

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Appendix E – Privigen® 10% infusion rate guide

Maximum rate: 4.8 mL/kg/hr

Biotherapies for Life™ CSL Behring

Privigen®: Normal Immunoglobulin (Human) 10% (100 g/L), intravenous injection
Infusion Rate (mL/hr) Calculator†1–5

† The infusion calculator below is provided as a guide only. The infusion rate needs to be individualised to the patient's risk factors, comorbidities and tolerability.

Infusion Rate (mL/kg/hr)	Pump rate	Patient's body weight (kg)																		
		10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100
0.3	mL/hr	3	4.5	6	7.5	9	10.5	12	13.5	15	16.5	18	19.5	21	22.5	24	25.5	27	28.5	30
0.6	mL/hr	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60
1.2	mL/hr	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96	102	108	114	120
2.4*	mL/hr	24	36	48	60	72	84	96	108	120	132	144	156	168	180	192	204	216	228	240
3.6*	mL/hr	36	54	72	90	108	126	144	162	180	198	216	234	252	270	288	306	324	342	360
4.8*	mL/hr	48	72	96	120	144	168	192	216	240	264	288	312	336	360	384	408	432	456	480

*Step rate rises between 2.4 mL/kg/hr and 4.8 mL/kg/hr are at the discretion of the healthcare professional and as tolerated by the patient

Initiation rate[1–4]
0.3 mL/kg/hr

→

If well tolerated, the rate can be gradually increased at 30 minute intervals, to a recommended maximum rate[1–4]

→

Maximum infusion rate:
PID & CIDP - 4.8 mL/kg/hr (with exception of the first three infusions, where the maximum rate is 2.4 mL/kg/hr)[3,5]
ITP - 2.4 mL/kg/hr[2] *

As with all intravenous immunoglobulins (IVIgs) the patient needs to be adequately hydrated prior to being infused and should be closely monitored and carefully observed for any symptoms both during and after the infusion.[1] In patients at risk for acute renal failure, or thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable.[1] In the case of an adverse reaction, the rate of administration must be reduced or the infusion stopped.[1]

PID=Primary Immune Deficiency; CIDP=Chronic Inflammatory Demyelinating Polyneuropath; ITP=Idiopathic Thrombocytopenic Purpura; IVIg = Intravenous Immunoglobulins

privigen®
Normal immunoglobulin (Human) 10% (100 g/L), intravenous injection

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Appendix F – Gamunex® 10% infusion rate guide

Maximum rate: 0.08 ml/kg/min

Infusion Rate		Patient's Weight (kg)											
mL/kg/min	mL/kg/hr	10	20	30	40	50	60	70	80	90	100	110	120
0.01	0.60	6	12	18	24	30	36	42	48	54	60	66	72
0.02	1.20	12	24	36	48	60	72	84	96	108	120	132	144
0.03	1.80	18	36	54	72	90	108	126	144	162	180	198	216
0.04	2.40	24	48	72	96	120	144	168	192	216	240	264	288
0.05	3.00	30	60	90	120	150	180	210	240	270	300	330	360
0.06	3.60	36	72	108	144	180	216	252	288	324	360	396	432
0.07	4.20	42	84	126	168	210	252	294	336	378	420	462	504
0.08	4.80	48	96	144	192	240	288	336	384	432	480	528	576

- Commence at a rate of 0.01 mL/kg/min for the first 30 minutes
- If well tolerated, the rate may be gradually increased to a maximum of 0.08mL/kg/min
- If side effects should occur, the rate may be reduced, or the infusion interrupted until symptoms subside

This table was developed using the Gamunex® 10% product information, always refer to the product information and for more information