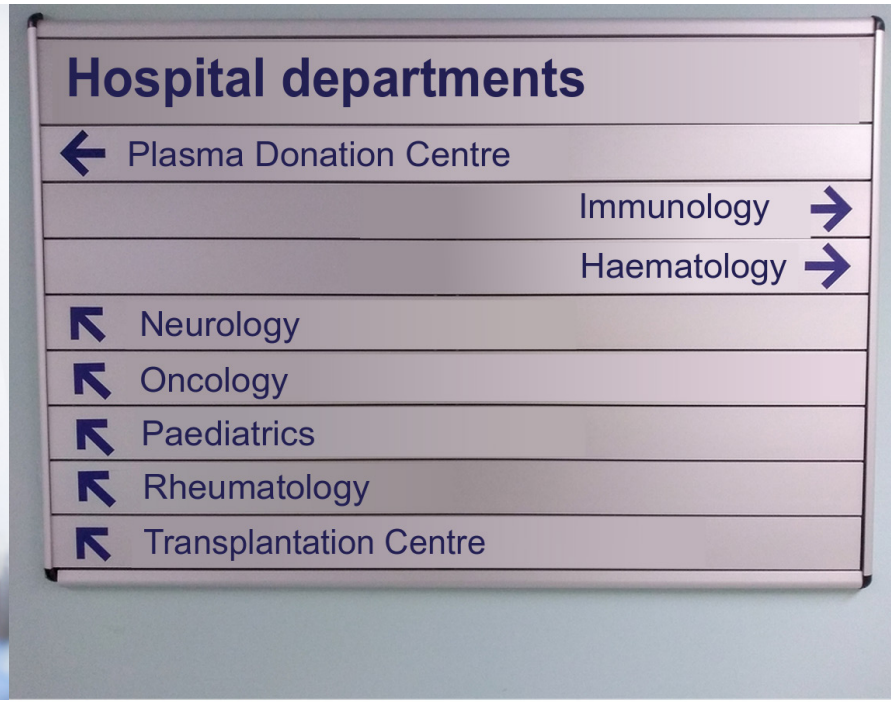
KCE REPORT 336S

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

POLYVALENT IMMUNOGLOBULINS – PART 2: USE IN BELGIUM – PART 2

SUPPLEMENT



KCE REPORT 336S
HEALTH TECHNOLOGY ASSESSMENT

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POLYVALENT IMMUNOGLOBULINS – PART 2: USE IN BELGIUM – PART 2

SUPPLEMENT

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COLOPHON

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Acknowledgements:	All 40 hospital pharmacists that responded to the online survey; Marina van den Bosch-Vos (Ministry of Health, Welfare and Sports, the Netherlands); Jo Cameron (National Blood Authority, Australia); Tjonglie Ching (Ministry of Health, Welfare and Sports, the Netherlands); Irina Cleemput (KCE); Carl Devos (KCE); Martine Dewitte (RIZIV/INAMI); Kris Doggen (Sciensano); Anaïs Fauche (FAGG-AFMPS); Gaelle Guyader (ANSM, France); Jillian Harrison (KCE); Celine Pouppez (KCE); Eva Priem (Octapharma); Sabine Stordeur (KCE); Paul Van Rijn (Sanquin, the Netherlands); Karen Vermis (UZ Gent); Irm Vinck (KCE); Lieven Zwaenepoel (APB).
Reported interests:	'All experts and stakeholders consulted within this report were selected because of their involvement in the topic of Immunoglobulins. Therefore, by definition, each of them might have a certain degree of conflict of interest to the main topic of this report' Membership of a stakeholder group on which the results of this report could have an impact: Els Devriese (working at CSL Behring), Eva Priem (working at Octapharma). Participation in scientific or experimental research as an initiator, principal investigator or researcher: Jan De Bleecker (CSL Behring sponsored study on IVIg use in CIDP) Consultancy or employment for a company, an association or an organisation that may gain or lose financially due to the results of this report: Jan De Bleecker (CSL Behring, advisory boards on myasthenia gravis an myositis and IVIg treatment)

	Payments to speak, training remuneration, subsidised travel or payment for participation at a conference: Isabelle Meyts (Seminar for paediatricians on PID – sponsored by CSL Behring), Presidency or accountable function within an institution, association, department or other entity on which the results of this report could have an impact: Jean-Marc Minon (Presidency); Kristel Claeys (Chair for neuromuscular and neurodegenerative diseases - CSL Behring)
Layout:	Ine Verhulst
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Publication date:	23 December 2020
Domain:	Health Technology Assessment (HTA)
MeSH:	Immunoglobulins, Intravenous, Infusions, Subcutaneous, Medicine/therapeutic use
NLM Classification:	QW 601
Language:	English
Format:	Adobe® PDF™ (A4)
Legal depot:	D/2020/10.273/39
ISSN:	2466-6459
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How to refer to this document?

De Meester C, Bourgeois J, Devriese S, San Miguel L. Polyvalent Immunoglobulins – Part 2: Use in Belgium – Part 2 – Supplement. Health Technology Assessment (HTA) Brussels: Belgian Health Care Knowledge Centre (KCE). 2020. KCE Reports 336S. D/2020/10.273/39.

This document is available on the website of the Belgian Health Care Knowledge Centre.

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1 SUPPLY PROBLEMS – MARKET

Table 1 – Overview of temporary unavailability since January 2018 till Sept 2020

Products		Firm	Supply problem date	Current status in sept 2020
Gamunex®	10% 100ml	Grifols	August 1, 2017 till July 2, 2018	Off the market
Gammanorm®	3,3g/ 20ml	Octapharma	Jun 11, 2019 till Jul 31, 2019	Available
Iqymune®	2g/20ml, 5g/50ml, 10g/100ml, 20g/200ml	CAF-DCF	Dec 21, 2018 till Oct 31, 2019 April 8, 2020 till 31 Oct 2020,	2g/20ml and 20g/200ml unavailable, 5g/50ml off the market
Pangyza®	10g/100ml	Octapharma	Apr 15, 2019 till Dec 31, 2019	Off the market

Based on communication with FAMHP and www.farmastatus.be/human

Table 2 – Market withdrawals since 2008

Product		Firm		Year withdrawn from market
Multigam ®	5%, 20ml	CAF-DCF	IVIg	2020
Iqymune®	5g/50ml	CAF-DCF	IVIg	2020
Panzyga®	100mg/ml	Octapharma	IVIg	2020
Multigam®	10 g / 200 ml, and all 10% formulations	CAF-DCF	IVIg	2018-2019
Gamunex®	10% 100ml	Grifols	IVIg	2018
Kiovig®	all formulations	Baxter AG	IVIg	2015
Gammagard®	all formulations	Baxter AG	IVIg	2013
Sandoglobulin®	1g/50ml; 3g/100ml	CSL Behring	IVIg	2014
Subcuvia®	all formulations	Baxter AG - Shire	SCIg	2013
Vivaglobin®	all formulations	CSL Behring	SCIg	2013

Based on communication with FAMHP and www.farmastatus.be/human

2 QUANTITY PER PRODUCT

Table 3 – Reimbursed quantity of immunoglobulins in kg by manufacturer and product for the period 2010-2018

Product (Administration way)	Manufacture	Quantity of Immunoglobulins (kg)									
		2010	2011	2012	2013	2014	2015	2016	2017	2018	2019 (12 months extrapolation)[a]
VIVAGLOBIN (SC)	CSL BEHRING	62.0	59.4	34.9	0.2	-	-	-	-	-	
HIZENTRA (SC)	CSL BEHRING	-	-	43.0	126.5	146.6	159.3	199.4	216.4	237.9	276.6
GAMMANORM (SC)	OCTAPHARM A BENELUX	-	1.0	3.1	9.1	13.6	15.2	17.7	17.0	20.9	20.4
SUBCUVIA (SC)	BAXTER	33.4	36.2	34.8	0.2	-	-	-	-	-	
SANDOGLOBULINE (IV)	CSL BEHRING	392.5	379.1	254.2	224.9	167.1	161.8	151.0	145.2	102.9	128.8
PRIVIGEN (IV)	CSL BEHRING	-	49.2	245.1	374.1	476.8	585.7	708.0	760.8	928.9	1219.0
MULTIGAM 5% (IV)	C.A.F.-D.C.F.	548.1	583.9	618.2	700.6	663.1	705.3	746.1	645.3	593.2	316.3
MULTIGAM 10% (IV)	C.A.F.-D.C.F.	-	-	-	-	-	-	0.8	55.3	64.2	3.0
NANOGAM (IV)	C.A.F.-D.C.F.	-	-	9.5	28.9	34.5	38.1	33.7	31.4	34.0	76.2
OCTAGAM 5% (IV)	OCTAPHARM A BENELUX	1.2	-	-	0.9	-	-	0.2	0.5	5.8	54.1
OCTAGAM 10% (IV)	OCTAPHARM A BENELUX	-	3.2	14.6	27.7	25.3	25.4	24.6	22.7	22.5	70.0
GAMMAGARD (IV)	BAXTER	80.8	56.1	27.7	1.3	-	-	-	-	-	
KIOVIG (IV)	BAXTER	7.9	87.6	124.4	36.9	3.5	-	-	-	-	
IQYMUNE (IV)	LFB BIOMED.	-	-	-	-	-	-	-	-	-	11.7
Total		1125.9	1255.7	1409.4	1531.4	1530.6	1690.8	1881.6	1894.6	2010.3	2164.3*

Source: INAMI-RIZIV; IV: intravenous, SC: subcutaneous; [e]for the year 2019, data were only available for the first six months. CAF-DCF is a part of the LFB group since 2016.

[a] Data for the year 2019 are only available for the six first months, based on an extrapolation, in order to compensate Ig delivered in 2019 but included in the count of the year 2020. Twelve-months data here presented are the result of a second extrapolation (by doubling the 6-month quantities).

3 IG EXPENDITURE

Table 4 – RIZIV expenses per product per year in million €

	2010	2011	2012	2013	2014	2015	2016	2017	2018
GAMMAGARD	3.65	2.54	1.25	0.06					
KIOVIG	0.35	3.95	5.60	1.66	0.16				
SUBCUVIA	1.73	1.88	1.81	0.01					
MULTIGAM 5%	24.76	26.36	27.51	30.59	28.81	30.63	32.41	28.02	25.76
MULTIGAM 10%							0.03	2.39	2.78
NANOGAM			0.38	1.14	1.35	1.49	1.33	1.23	1.33
HIZENTRA			2.10	6.24	7.24	7.86	9.82	10.55	11.61
PRIVIGEN		2.22	11.02	16.85	21.40	26.27	31.75	34.12	41.65
SANDOGLOBULINE	17.80	17.20	11.31	9.63	7.10	6.87	6.40	6.15	4.36
VIVAGLOBIN	2.95	2.83	1.64	0.01					
GAMMANORM		0.05	0.15	0.46	0.69	0.76	0.89	0.84	1.03
OCTAGAM 5%	0.05	0.00	0.00	0.04			0.01	0.02	0.25
OCTAGAM 10%		0.14	0.66	1.25	1.14	1.15	1.11	1.02	1.01
IQYMUNE									
TOTAL	51.3	57.2	63.4	67.9	67.9	75.0	83.7	84.3	89.8

Source: INAMI-RIZIV

Table 5 – RIZIV expenses per administration way and pharmacy per year in million €

	2010	2011	2012	2013	2014	2015	2016	2017	2018
IV – Hospital Pharmacy	46.62	52.40	57.74	61.22	59.95	66.40	73.04	72.95	77.15
SC – Hospital Pharmacy	1.02	0.96	1.13	0.62	0.58	0.50	0.61	0.56	0.58
SC – community Pharmacy	3.66	3.80	4.58	6.10	7.35	8.13	10.10	10.83	12.06
TOTAL	51.3	57.2	63.4	67.9	67.9	75.0	83.7	84.3	89.8

Source: INAMI-RIZIV, IV: Intravenous, SC: Subcutaneous

Table 6 – Table on changing market

Product	Firm	Dose (g)	Introduction Date	Last Modification	Public price (€)	Day-care price (€)	Inpatient price (€)	Ex-factory price (€)
SUBCUTANEOUS PRODUCTS								
Subcuvia	Baxter	0.8	1/09/2005	**	55.95	53.45		53.45
		1.6	1/09/2005	**	51.61	49.01		49.01
Vivaglobin	CSL Behring	1.6	1/09/2006	**	46.56	44.07		44.07
Gammanorm	Octapharma Benelux	0.99*	1/01/2017	1/08/2020	57.90	54.88	47.70	45.00
		1.65*	1/12/2010	1/08/2020	54.84	52.01	47.70	45.00
		3.3*	1/01/2017	1/08/2020	52.00	49.85	47.70	45.00
Hizentra	CSL Behring	1*	1/03/2012	1/01/2020	54.46	51.67	44.56	42.04
		2*	1/03/2012	1/01/2020	50.62	48.12	44.56	42.04
		4*	1/03/2012	1/01/2020	48.27	46.34	44.56	42.04
INTRAVENOUS PRODUCTS								
Gammagard	Baxter	2.5	1/09/1997	1/11/2012**		49.05		
		5	1/09/1997	1/07/2013**		45.98		
		10	1/09/1997	1/07/2013**		45.27		
Kiovig	Baxter	1	1/09/2010	1/07/2014**		51.67		
		2.5	1/09/2010	1/07/2014**		47.41		
		5	1/09/2010	1/07/2014**		45.98		
		10	1/09/2010	1/07/2014**		45.27		
		20	1/09/2010	1/07/2014**		44.92		
		30	1/11/2011	1/07/2014**		44.80		
Multigam 5%	CAF - DCF	1	1/02/2003	1/09/2019**		50.85	43.74	41.26
		2,5	1/02/2003	1/09/2019**		45.68	42.84	40.42
		5*	1/02/2003	1/09/2019		44.26	42.84	40.41
		10	1/02/2003	1/04/2013**		43.55	42.84	40.41

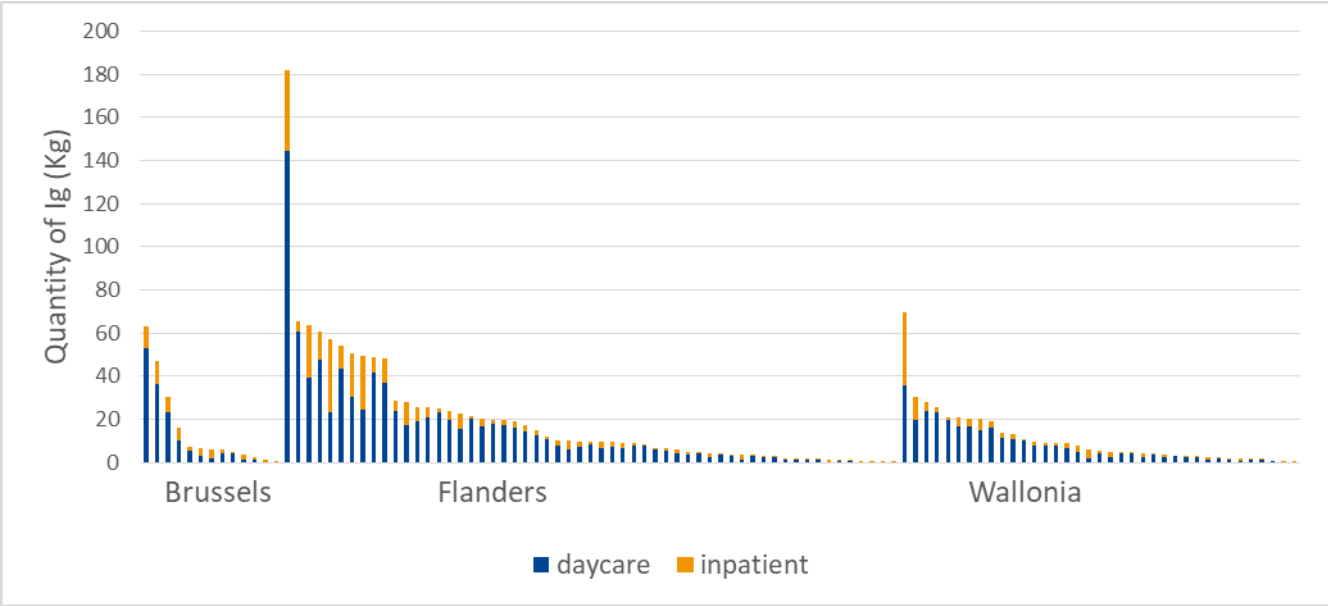
Product	Firm	Dose (g)	Introduction Date	Last Modification	Public price (€)	Day-care price (€)	Inpatient price (€)	Ex-factory price (€)
Multigam 10%	CAF - DCF	1	1/06/2016	1/06/2016**		51.67		
		5	1/06/2016	1/04/2019**		44.26	42.84	40.41
		10	1/06/2016	1/04/2019**		43.55	42.84	40.41
		20	1/06/2016	1/04/2019**		43.19	42.84	40.41
Nanogam	CAF - DCF	1*	1/06/2008	1/05/2020		66.87	59.76	56.38
		2,5*	1/06/2008	1/04/2013		50.98	48.14	45.41
		5*	1/06/2008	1/09/2019		41.58	40.15	37.88
		10*	1/06/2008	1/09/2019		38.89	38.18	36.02
		20*	1/06/2008	1/09/2019		38.54	38.18	36.02
Privigen 10%	CSL Behring	2,5*	1/05/2011	1/09/2019		47.27	44.43	41.91
		5*	1/05/2011	1/09/2019		45.85	44.42	41.91
		10*	1/05/2011	1/09/2019		45.14	44.43	41.91
		20*	1/05/2011	1/09/2019		44.78	44.42	41.91
Sandoglobuline	CSL Behring	1	1/11/1991	1/01/2014**			48.87	
		3	1/02/1988	1/01/2014**			44.14	
		6*	1/02/1988	1/04/2019		42.96	41.77	39.41
Octagam 5%	Octapharma Benelux	2,5*	1/07/1998	1/02/2020		50.48	47.64	44.94
		5*	1/07/1998	1/03/2020		49.06	47.63	44.94
		10*	1/07/1998	1/02/2020		48.34	47.63	44.93
Octagam 10%	Octapharma Benelux	2*	1/09/2010	1/05/2020		52.05	48.50	45.75
		5*	1/09/2010	1/05/2020		49.91	48.49	45.75
		10*	1/09/2010	1/05/2020		49.20	48.49	45.75
		20*	1/09/2010	1/05/2020		48.85	48.49	45.75
Panzyga 10%	Octapharma Benelux	1	1/09/2017	1/04/2019**		49.94	42.83	40.41
		2,5	1/09/2017	1/04/2019**		45.68	42.84	40.41

Product	Firm	Dose (g)	Introduction Date	Last Modification	Public price (€)	Day-care price (€)	Inpatient price (€)	Ex-factory price (€)
		5	1/09/2017	1/04/2019**		44.26	42.83	40.41
		6	1/09/2017	1/04/2019**		44.02	42.84	40.41
		10	1/09/2017	1/04/2019**		43.55	42.84	40.41
		20	1/09/2017	1/04/2019**		43.19	42.83	40.41
		30	1/09/2017	1/04/2019**		43.07	42.83	40.41
Iqymune	LFB Biomedicaments	2*	1/04/2018	1/09/2019		46.39	42.84	40.41
		5	1/04/2018	1/09/2019**		44.26	42.83	40.41
		10*	1/04/2018	1/09/2019		43.55	42.84	40.41
		20*	1/04/2018	1/09/2019		43.19	42.83	40.41

*Source: INAMI-RIZIV; *Ig products still on the Belgian market in September 2020. **Date of disappearance on the Belgian market;*

4 QUANTITY OF IG BY HOSPITAL IN 2018

Figure 1 – Quantity of immunoglobulin by hospital (in kg), and the type of stay (2018)



Source: TCT

5 PROXY INDICATIONS

Details of results on the number of patients per year per proxy-indication

Firstly each stay was linked to a proxy indication, and thereafter each patient was linked to one proxy indication.

After excluding hospital stays without any specific diagnostic codes, 139 377 stays (108 655 daycare and 30 722 inpatient) in the available period (2012-2018) remained for the analysis. Each of the 139 377 hospital stays with Ig is linked to a single proxy indication. When there were multiple possible proxy indications, a hierarchy/algorithm was used to only link a single indication to that stay (see methods section 2.2.1.4).

For 83 125 stays Ig proxy indication was determined by the principal diagnosis (which means that in the TCT database an Ig proxy indication was already determined as the principal diagnosis for the admission into the hospital as it was the primary reason for the hospital stay), and while for 25 646 stays Ig the secondary diagnosis was used (see section 2.2.1.4 for details on how we determined proxy indication), and 30 606 stays Ig had no proxy indication.

On the 25 646 stays Ig where the proxy indication was determined with the secondary diagnosis, 5 600 had two diagnosis, 462 had three diagnosis, 22 had four diagnosis and 1 had five diagnosis. Combinations with primary immunodeficiency (PID) is the most frequent (80.3%). PID is often combined with secondary Immunodeficiency (SID) (in 93.3% of all PID combinations). Consulted experts found this a strange observation for which there is no explanation except possible coding errors or demonstrating the diagnosing difficulty. Combinations with SID (without PID) is the second most frequent (16.8%), where the second diagnosis most frequently found is solid organ rejection (63.2%).

Table 23 shows the combinations of proxy indications for stays and patients with multiple secondary diagnosis (across the years 2012-2018).

Similarly, patients with multiple stays in the same year were attributed one proxy indication for that year to avoid double counting. In line with the methods described in 2.2.1.4 those patients with multiple identified proxy indications were categorised to the proxy indications highest in the algorithm/hierarchy.

Of the in total 19 084 patients with Ig use in the TCT database, for 16 028 (84.0%) patients a proxy indication could be linked. In 2 122 patients (13.2% of the patients with a linked proxy indication) more than one potential proxy indication was identified. Similarly to the analysis per stay, the combinations with primary immunodeficiency (PID) is the most frequent (84.3%). In most of the PID combinations the second diagnosis identified is secondary Immunodeficiency (SID) (90.8%). Experts found this combination a strange observation (see above). Combinations with SID (without PID) is the second most frequent (8.4%), where in one quarter the combinations second diagnose are toxic shock syndrome (35.2%) and solid organ rejection (30.7%).

Table 7 – Proxy indication determined by multiple secondary diagnosis for stays and patients

Combination with			Number of stays	%	Number of patients	%
PID	SID	-	4171	68.55%	1532	72.20%
		PIT	64	1.05%	12	0.57%
		Toxic Shock Syndrome	76	1.25%	44	2.07%
		Solid organ Rejection	232	3.81%	32	1.51%
		Other	13	0.21%	6	0.28%
	PIT	-	43	0.71%	43	2.03%
		Solid organ Rejection	1	0.02%	-	-
		Other	-	-	5	0.24%
	CIDP	-	13	0.21%	7	0.33%
		Toxic Shock Syndrome	1	0.02%	-	-
	Toxic Shock Syndrome	-	109	1.79%	45	2.12%
		Solid organ Rejection	5	0.08%	-	-
		FNAIT	20	0.33%	-	-
	Solid organ Rejection	-	64	1.05%	56	2.64%
	Myasthenia gravis	-	18	0.30%	-	-
	FMAIT/NAIT	-	36	0.59%	-	-
	Other	-	18	0.30%	8	0.38%
SID	PIT	-	111	1.82%	35	1.65%
		Guillain-Barré Syndrome	1	0.02%	-	-
		Toxic Shock Syndrome	5	0.08%	-	-
		Solid organ Rejection	11	0.18%	1	0.05%
		CIDP	-	-	1	0.05%
	CIDP	-	62	1.02%	12	0.57%
		Toxic Shock Syndrome	1	0.02%	-	-
		Other	-	-	3	0.14%
	Guillain-Barré Syndrome	-	12	0.20%	6	0.28%
		MMN	1	0.02%	-	-
		Toxic Shock Syndrome	2	0.03%	-	-

		Solid organ Rejection	1	0.02%	-	-
	Toxic Shock Syndrome	-	109	1.79%	60	2.83%
		Solid organ Rejection	45	0.74%	-	-
		antibody-mediated types of encephalitis	1	0.02%	-	-
		Other	-	-	3	0.14%
	Solid organ Rejection	-	646	10.62%	55	2.59%
	Other	-	14	0.23%	3	0.14%
PIT	Toxic Shock Syndrome	-	24	0.39%	4	0.19%
	Other	-	4	0.07%	7	0.33%
CIDP	Guillain-Barré Syndrome	-	26	0.43%	76	3.58%
		Toxic Shock Syndrome	1	0.02%	-	-
	Myasthenia gravis	-	53	0.87%	-	-
	MMN	-	1	0.02%	49	2.31%
		Other	-	-	2	0.09%
	Other	-	7	0.12%	9	0.42%
Guillain-Barré Syndrome	Toxic Shock Syndrome	-	16	0.26%	-	-
	Other	-	4	0.07%	3	0.14%
Kawasaki disease	Other	-	3	0.05%	-	-
Toxic Shock Syndrome	Hemolytic disease in newborns	FNAIT	2	0.03%	-	-
	Other	-	29	0.48%	3	0.14%
Hemolytic disease in newborns	Other	-	8	0.13%	-	-
Myasthenia gravis	Other	-	1	0.02%	-	-

Source: TCT; PID: primary immunodeficiency, SID: secondary immunodeficiency, PIT: Primary immune thrombocytopenic, GB: Guillain-Barré, CIDP: Chronic Inflammatory Demyelinating Polyneuritis, MMN: Multifocale Motor Neuropathy, FNAIT: Fetal and neonatal alloimmune thrombocytopenic; these patient numbers represent all unique patients during the data-analysis 2012-2018.

Table 8 – Ig diagnosis according to patient's stay

	2012		2013		2014		2016		2017		2018	
	DC	IP	DC	IP	DC	IP	DC	IP	DC	IP	DC	IP
OFFICIAL REIMBURSED INDICATIONS IN BELGIUM												
PID	6067	899	7793	840	6848	810	8923	965	8551	793	8896	813
SID - Multiple Myeloma	1176	203	1337	191	1117	175	1780	189	1673	201	2220	178
- Chronic Lymphatic leukemia	974	133	1084	126	773	124	1227	97	1222	103	1339	96
- Other	1334	382	1611	377	1253	380	1645	387	1821	431	2111	419
PIT	800	523	825	526	649	473	670	554	665	546	673	522
CIDP	843	1243	718	1332	714	1326	980	1570	866	1516	915	1451
GB Syndrome	27	276	<5	248		238	18	313	36	310	28	332
Kawasaki Disease		111		83	<5	82	<5	116		89		106
MMN	28	62	19	58	25	75			18	315	45	348
Streptococcus toxic shock syndrome		40		38		28		180	<5	126	<5	156
INDICATIONS COMMONLY REIMBURSED IN OTHER COUNTRIES												
Solid Organ transplant rejection	57	90	42	108	49	130	179	99	111	61	70	37
Hemolytic disease in newborns	<5	17		19		15		17		23		13
Myasthenia gravis	<5	14	23	18	13	21	25	13	16	11	13	9
FNAIT	<5	13		15		7		11		11	<5	8
Von Willebrand's disease		11		10		7	11	11	<5		<5	<5
Inflammatory myopathies	8	42	9	41	4	37	22	43	13	34		21
Stiff-person syndrome		<5		<5	<5	<5				<5	<5	<5
Erythroblastopenia	<5	<5						<5				<5
Pemphigus (vulgaris-foliculae)-nunobullous disease				<5						<5		<5
Posttransfusion purpura										<5		
Antibody-mediated types of encephalitis		10		7	<5	<5	8	6		9	<5	7
No Identidied indication	4333	905	3627	979	3695	823	4997	973	4403	734	4553	584
Total	15655	4978	17092	5018	15147	4756	20486	5545	19400	5320	20875	5105

Source: TCT, DC: Day Care, IP: Inpatient stay; small cells have been replaced by <5 and totals adapted; PID: primary immunodeficiency, SID: secondary immunodeficiency, PIT: Primary immune thrombocytopenic, GB: Guillain-Barré, CIDP: Chronic Inflammatory Demyelinating Polyneuritis, MMN: Multifocale Motor Neuropathy, FNAIT: Fetal and neonatal alloimmune thrombocytopenic

Table 9 – Proportion of inpatient and day care stays according to frequency of hospitalisation by patient and by proxy-indication during the 2012-2018 period

Indication	Number of hospitalisations											
	≤5		5-10		10-15		15-20		20-25		>25	
	Inpat.	DC	Inpat.	DC	Inpat.	DC	Inpat.	DC	Inpat.	DC	Inpat.	DC
OFFICIAL REIMBURSED INDICATIONS IN BELGIUM												
• **PID**	44,0%	56,0%	18.5%	81.5%	12.1%	87.9%	8.7%	91.3%	6.7%	93.3%	4.7%	95.3%
• **SID - Multiple Myeloma**	42.0%	58.0%	10.4%	89.6%	6.1%	93.9%	6.9%	93.1%	5.8%	94.2%	3.7%	96.3%
- Chronic Lymphatic leukaemia	38.8%	61.2%	12.0%	88.0%	5.1%	94.9%	7.5%	92.5%	5.3%	94.7%	3.6%	96.4%
- Other	52.4%	47.6%	20.5%	79.5%	14.1%	85.9%	10.5%	89.5%	6.9%	93.1%	15.7%	84.3%
• **PIT**	73.0%	27.0%	40.5%	59.5%	32.6%	67.4%	20.4%	79.6%	22.5%	77.5%	13.8%	86.2%
• **CIDP**	79.7%	20.3%	58.6%	41.4%	64.0%	36.0%	73.8%	26.2%	73.3%	26.7%	68.0%	32.0%
• **GB Syndrome**	99.4%	0.6%	36.4%	63.6%								
• **Kawasaki Disease**	99.5%	0.5%										
• **MMN**	77.3%	22.7%	20.5%	79.5%	97.1%	2.9%	100.0%	0.0%	81.7%	18.3%	65.5%	34.5%
• **Streptococcus toxic shock syndrome**	97.3%	2.7%	27.3%	72.7%	19.4%	80.6%					1.7%	98.3%
INDICATIONS COMMONLY REIMBURSED IN OTHER COUNTRIES												
• **Solid Organ transplant rejection**	91.9%	8.1%	30.7%	69.3%	8.2%	91.8%	5.8%	94.2%	6.8%	93.2%	2.9%	97.1%
• **Hemolytic disease in newborns**	99.1%	0.9%										
• **Myasthenia gravis**	95.5%	4.5%	100.0%	0.0%			5.6%	94.4%			0.0%	100.0%
• **FNAIT**	95.5%	4.5%										
• **Von Willebrand's disease**	77.8%	22.2%										
• **Inflammatory myopathies**	89.2%	10.8%	100.0%	0.0%	100.0%	0.0%	0.0%	100.0%			100.0%	0.0%
• **Stiff-person syndrome**	66.7%	33.3%	66.7%	33.3%								
• **Erythroblastopenia**	100.0%	0.0%										
• **Pemphigus (vulgaris-foliculae)-immunobullous disease**	100.0%	0.0%										
• **Posttransfusion purpura**	100.0%	0.0%	16.7%	83.3%								
• **Antibody-mediated types of encephalitis**	95.1%	4.9%	0.0%	100.0%								
No Identidied indication	66.0%	34.0%	15.6%	84.4%	11.5%	88.5%	8.0%	92.0%	4.9%	95.1%	11.2%	88.8%

Source: TCT, Inpat: inpatient, DC: day care; PID: primary immunodeficiency, SID: secondary immunodeficiency, PIT: Primary immune thrombocytopenic, GB: Guillain-Barré, CIDP: Chronic Inflammatory Demyelinating Polyneuritis, MMN: Multifocale Motor Neuropathy, FNAIT: Fetal and neonatal alloimmune thrombocytopenic

6 DOSAGE PER PATHOLOGY

Table 10 – Average number of stays per year per patient

Indication		Average number of stays per patient						
		2012	2013	2014	2016	2017	2018	% increase
OFFICIAL REIMBURSED INDICATIONS IN BELGIUM								
PID		5.7	6.0	5.5	6.0	6.0	6.5	13.3
SID	**- Multiple Myeloma**	4.6	4.7	4.4	5.2	4.8	5.0	7.3
	- Chronic Lymphatic leukaemia	4.5	4.9	3.8	4.8	4.5	5.2	15.6
	- Other	4.1	4.0	3.7	4	3.9	4.0	-0.8
PIT		2.2	2.2	2.1	2	2.1	2.1	-7.0
CIDP		4.5	4.8	4.7	5.3	5.2	5.1	13.2
GB Syndrome		1.1	1.1	1.1	1.1	1.1	1.0	-9.4
Kawasaki Disease		1	1.0	1.1	1.0	1.0	1.0	-1.7
MMN		6.1	4.9	6.7	7.3	4.8	4.6	-25.1
Streptococcus toxic shock syndrome		1.5	1.3	1.4	1.2	1.3	1.2	-23.2
INDICATIONS COMMONLY REIMBURSED IN OTHER COUNTRIES								
Solid Organ transplant rejection		1.7	2.5	2.3	3.1	2.2	2.2	26.9
Hemolytic disease in newborns		1.0	1.1	1.0	1.0	1.0	1.0	
Myasthenia gravis		1.1	2.5	2.1	2.8	2.3	2.6	
FNAIT		1.0	1.1	1.0	1.2	1.0	1.0	
Von Willebrand's disease		1.0	1.0	1.0			1.5	
Inflammatory myopathies		5.3	4.5	4	4.3	4.9	3.5	
Stiff-person syndrome		1.0	1.0	1.0		3.0	3	
Erythroblastopenia		1.0			1.0			
Pemphigus (vulgaris-foliculae)-immunobullous disease			1.0			1.0		
Posttransfusion purpura						3.5		
Antibody-mediated types of encephalitis		1.2	2.0	1.3	2.3	1.0	1.1	
No identified indication		1.7	2.5	2.3	3.1	2.2	2.2	26.9

Source: TCT; PID: primary immunodeficiency, SID: secondary immunodeficiency, PIT: Primary immune thrombocytopenic, GB: Guillain-Barré, CIDP: Chronic Inflammatory Demyelinating Polyneuritis, MMN: Multifocale Motor Neuropathy, FNAIT: Fetal and neonatal alloimmune thrombocytopenia

Table 11 – Recommended dosage according to pathology

Indication	Recommended dose used in our estimations	Sources for recommended doses
1. CHRONIC treatment: Average Ig quantity for treatment by stay		
PID	0,4-0,6g/kg every 3-4 weeks for IVIg and 0.1-0.15g/kg weekly or biweekly for SCIg (≈30-45gr for IV)	Australia: 0,4-0,6g/kg UK: 0,4-0,6g/kg KCE phase 1 report: 0,4Kg/kg
SID	0,4-0,6g/kg every 3-4 weeks for IV and weekly or biweekly for SCIg (≈30-45gr for IV)	Australia: 0,4-0,6g/kg UK: 0,4-0,6g/kg KCE phase 1 report: 0,4g/kg
CIDP	Maintenance: 0,4-1g/kg (≈30-75g) every 2-6 weeks	Australia: Initiation 2g/kg; maintenance 0,4-1g/kg UK: Initially 2g/kg; maintenance dependant on response KCE phase 1 report: Initiation 2g/kg; maintenance 0,4-1g/kg
MMN	2g/kg (≈150g) given over 2 to 5 days and repeated after 6 weeks	Australia: Initial: 1-2 g/kg in 2 to 5 divided doses; maintenance: 0.4–1 g/kg, 2–6 weekly UK: 2g/Kg over 2-5 days followed by 1g/Kg after 3 weeks and a further 1g/kg three weeks later KCE phase 1 report: 1-2g/Kg every 4-8 weeks
Inflammatory myopathies	Maintenance: 0,4-1g/kg (≈30-75g), every 4-6 weeks	Australia: Initially: 2 g/kg in 2-5 divided doses maintenance: 0,4-1g/kg, 4-6 weekly UK: 2g/Kg over 2-5 days KCE phase 1 report: 2g/Kg over 2 days
Stiff-person syndrome	Maintenance: 0,4–1g/kg, (≈75g) given over 2 to 5 days and repeated after 2- 6 weeks	Australia: Initially up to 2 g/kg in 2-5 divided doses; maintenance: 0,4–1g/kg, 2–6 weekly UK: 2g/Kg over 2-5 days KCE phase 1 report: 2g/Kg over 2-5 days
2. ACUTE treatment: Global Ig quantity for treatment duration < 6 months		
PIT	Adults: 1g/kg/single infusion (≈75g) Children: 0,8-1g/kg/single dose (mean dose highly dependent on age) A second infusion can be given after 24-48 hours if severe or life threatening bleeding or If a an adequate platelet count is not achieved	Australia: Initial: 0.8–2g/kg as a single or divided dose; maintenance (for recurrent): 0.4–2g/kg in a single or divided dose at 4 to 6 weekly. Children (<15): initial: 0.8 g/kg; recurrent: 0.4–2g/kg in a single or divided dose at 4 to 6 weekly.

Indication	Recommended dose used in our estimations	Sources for recommended doses
		UK: adults: 1g/kg/single infusion. A 2nd dose may be needed if serious risk of bleeding; children: 0,8-1g/Kg. A 2nd dose may be needed if serious risk of bleeding KCE phase 1 report: 0,2g/Kg over 5 days
Guillain-Barré Syndrome	2g/kg (≈150g) over 5 days. May be repeated at 14 days	Australia: 2g/kg in2-5 doses UK: 2g/kg over 5 days KCE phase 1 report: 2g/kg
Kawasaki Disease	2g/kg in a single dosis. Because it are mostly children this leads to a dosage of ≈50g. Exceptionally a second dose is needed	Australia: 2g/kg UK: Currently under review KCE phase 1 report: 2g/kg
Toxic shock syndrome	2g/kg in a single dose (≈150g)	Australia: 2g/kg UK: Currently under review KCE phase 1 report: No data on dosing
Solid Organ transplant rejection	Up to 2 g/kg to a maximum of 140 g as a single dose.	Australia: Up to 2 g/kg to a maximum of 140 g as a single dose; recurrent doses: 0.1 to 0.5 g/kg up to a max of 2g/Kg/8 week UK: Currently under review KCE phase 1 report: No data on dosing
Myasthenia gravis	1-2g/Kg over 2-5 days (≈75-150g)	Australia: crisis: 1-2g/kg ; maintenance: 0,4-1g/kg UK: crisis: 1g/Kg and a further 1g/Kg if deterioration; maintenance: minimal dose optimisation KCE phase 1 report: 1-2g/kg (no difference in outcomes)
FMAIT or NAIT	Maternal: 0,5-1g/kg weekly through pregnancy. Neonatal: 1g/kg in a single dose. A 2nd dose may be given (≈3,2g)	Australia: Maternal: 1-2g/kg Australia: Neonatal: 1g/Kg UK: Maternal: 0,5-1g/kg weekly during pregnancy UK: Neonatal: 1g/kg in a single dose KCE phase 1 report: Maternal: 1g/kg weekly during pregnancy KCE phase 1 report Neonatal: No dose mentioned
Hemolytic disease in newborns	0,5g/Kg over 4 hours (≈1,6g)	Australia: 1g/Kg UK: 0,5g/Kg over 4 hours KCE phase 1 report: No dose mentioned

Indication	Recommended dose used in our estimations	Sources for recommended doses
Von Willebrand's disease	2g/kg (≈150g) (0.4g/kg for 5 days or 1g/Kg for 2 days)	Australia: No data on dosing UK: 0.4g/kg for 5 days or 1g/Kg for 2 days KCE phase 1 report: No data on dosing
Both Erythroblastopenia & Parvovirus	1-2g/Kg in divided doses over 2-5 days (≈75-150g)	Australia: 2g/kg in divided doses over 2-5 days UK: 1-1,2g/Kg in divided doses KCE phase 1 report: 2g/kg usually divided over 5 days
Pemphigus (vulgaris-foliculae)-immunobullous disease	Max 2g/kg per month (≈150g)	Australia: up to 2 g/kg per month UK: No data on dosing
Post-transfusion purpura	1 - 2g/kg in divided doses over two to five days (≈75-150g)	Australia: 1 g/kg as a single dose, repeated if necessary UK: 1 - 2g/kg in divided doses over two to five days KCE phase 1 report: No data on dosing
Antibody-mediated types of encephalitis	2g/kg given over 2-5 days(≈150g)	Australia: 2g/Kg over 2-5 days UK: 2g/kg given over 2-5 days and repeated monthly for three months for initial trial

Source: Australia: https://www.criteria.blood.gov.au/*;*
UK : http://igd.mdsas.com/wpcontent/uploads/NHSE_Commissioning_Criteria_for_the_use_of_Ig_V1.4_November_2019.pdf
KCE Phase 1 report: https://kce.fgov.be/sites/default/files/atoms/files/KCE_327_Polyvalent_Immunoglobulines_Report.pdf
PID: primary immunodeficiency, SID: secondary immunodeficiency, ITP: Idiopathic thrombocytopenic purpura, CIDP: Chronic Inflammatory Demyelinating Polyneuritis, MMN: Multifocale Motor Neuropathy, FMAIT: Fetomaternal alloimmune thrombocytopenia, NAIT: Neonatal alloimmune thrombocytopenia; The calculations in dosage per administration are based on the average weight of an adult person: 75 kg; the exceptions are Kawasaki for which the average weight of 25kg was taken as it almost always concerns children, and Hemolytic disease of the newborn and FNAIT where 3,2 kg was used.

7 ONGOING CLINICAL TRIALS

Trial-ID	Indication	Title	Sample size	Intervention	Comparator	Anticipated end date	status
Controlled studies							
NCT01757418	Sickle Cell	IV Gammaglobulin for Sickle Cell Pain Crises	94	IVIG	Normal saline	July 2023	Recruiting
NCT01621204	ITP	A Trial of Eltrombopag or IV Immune Globulin Before Surgery for Immune Thrombocytopenia Patients	74	Eltrombopag	IVIG	aug/19	completed
NCT02308982	Encephalitis	Investigating the Role of Early Intravenous Immunoglobulin Treatment for Children With Encephalitis	308	IVIg: Privigen®	Placebo	February 2020	unknown
NCT03194815 2016-000118-31	Acute psychosis associated with anti-neuronal membranes/Autoimmune Encephalitis	A Randomised Phase II Double-blinded Placebo-controlled Trial of IV Ig and Rituximab in Patients With Antibody-associated Psychosis (SINAPPS2)	80	IVIg + Rituximab	Placebo	dec/21	Recruiting
NCT02176863 2013-004503-39	Post-polio Syndrome	Study of the Efficacy and Safety IVIg (Human) Flebogamma® 5% DIF in Patients With Post-polio Syndrome (FORCE)	210	IVIg: Flebogamma 5% DIF ®	Placebo	dec/22	Recruiting
NCT02728752 2016-002902-37	Dermatomyositis	Study Evaluating Efficacy and Safety of Octagam 10% in Patients With Dermatomyositis (Idiopathic Inflammatory Myopathy) (IIM) ProDERM study	94	IVIg: Octagam 10% ®	Placebo	October 2019	completed but no results yet
NCT03401073	Small Fiber Neuropathy	A Double-Blind, Placebo Controlled Trial of IV Immunoglobulin Therapy in Patient With Small Fiber Neuropathy Associated With Autoantibodies to TS-HDS and FGFR3	20	IVIg	Placebo: NaCl 0.9%	June 2021	Recruiting
2015-002624-31 NCT02637700	Small Fiber Neuropathy	IVIg therapy for small fiber neuropathy: a randomised, double-blind, placebo-controlled study on efficacy and safety.	60	IVIg: Gamunex®	Placebo	mrt/19	completed but no results yet
NCT03700138	Sjögren's Syndrome Associated Painful Sensory Neuropathies	IVIg for the Treatment of Primary Sjögren's Syndrome Associated Painful Sensory Neuropathies (TINISS)	24	IVIg: Privigen ®	Placebo: NaCl 0,9%	July 2021	Recruiting
NCT01785056	Systemic Sclerosis	IVIg Treatment in Systemic Sclerosis	14	IVIg: Privigen®	Placebo: Albuminar®-5	January 2019	unknown

Trial-ID	Indication	Title	Sample size	Intervention	Comparator		Anticipated end date	status
NCT03342638	Multiple Sclerosis, Relapsing-Remitting	Maximizing Outcome of Multiple Sclerosis Transplantation (MOST)	200	IVIg +treatment regimen (methylprednisolon, cyclophoshamide, mesna, rATG, G-CSF, autologous stem cells)	treatment regimen (methylprednisolon, cyclophoshamide, mesna, rATG, G-CSF, autologous stem cells)		January 1, 2024	terminated (sabatical of principal investigator)
NCT02915263	Diabetes	The Efficacy Of IV Immunoglobulin Therapy In Treatment Induced Neuropathy Of Diabetes	20	IVIg-C	Placebo: NaCl 0.9%		sep/21	recruting
NCT03684018	CIDP	Single vs. Multiple PrIVIgen Dose Regimens in Pediatric CIDP	30	IVIg: IgPro10 (single dose)	IVIg: IgPro10 (multiple dose)		January 2023	not recruting in belgium
NCT02638207 2015-005443-14	CIDP	Prospective, double-blind, randomized, multicenter phase III study evaluating efficacy and safety of three different dosages of NewGam in patients with chronic inflammatory demyelinating poly(radiculo)neuropathy (ProCID)	142	IVIg: Newgam® 0,5g/kg	IVIg:Newgam® 1g/kg	IVIg: Newgam® 2g/kg	sep/19	completed with results but quality not assured
2012-005150-34	CIDP	Dose response trial of IV immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy (DRIP-study)	17	IVIg: Kiovig® high frequency low dosage (as maintenance)	IVIg: Kiovig® low frequency high dosage (as maintenance)		not specified	no info
NCT03919773	Postural tachycardia syndrome patients with evidence of autoimmunity.	IVIg (Gamunex-C) Study of Treatment for Autoimmune Neuropathic Dysautonomia/Postural Tachycardia (POTS)	20	IVIg: Gamunex®-C	Placebo: albumin		dec/21	Enrolling by invitation
NCT04033276	Kidney Transplant antibody-mediated rejection (AMR)	IVIg/Rituximab vs Rituximab in Kidney Transplant With de Novo Donor-specific Antibodies	50	high-dose IVIg + Rituximab	Rituximab		January 2021	Recruiting

Trial-ID	Indication	Title	Sample size	Intervention	Comparator	Anticipated end date	status
NCT03380936	Kidney Transplant antibody-mediated rejection (AMR)	Pilot Study of Treatment for Subclinical AMR (Antibody-mediated Rejection) in Kidney Transplant Recipients	50	Tacrolimus	PE + IVIg + rituximab	nov/21	Terminated (Slower than expected recruitment rate)
NCT02659891	Kidney Transplant	IVIg to Treat BK Viremia in Kidney Transplant Recipients	60	IVIg: Privigen®	Placebo	feb/21	Active, not recruiting
NCT02690038	COPD	Feasibility and Safety of Immunoglobulin (Ig) Prophylactic Treatment in COPD Patients With Frequent Exacerbations: A Pilot Study	48	IVIg	Placebo: Normal Saline	June 2020	completed but no results yet
NCT03018652	COPD	Feasibility and Safety of Immunoglobulin (Ig) Treatment in COPD Outpatients With Frequent Exacerbations: Pilot Study 1	22	IVIg	Placebo: normal saline	June 2020	completed but no results yet
NCT03584802 2018-002632-24	Severe Acute exacerbation for Idiopathic pulmonary fibrosis (IPF)	Therapeutic Plasma Exchange, Rituximab and IV Ig for Severe Acute Exacerbation of Idiopathic Pulmonary Fibrosis Admitted in ICU: an Open, Randomized, Controlled Trial	40	Plasma exchange + IVIg + Rituximab	Standard of Care (mostly corticosteroids)	mrt/21	recruiting
NCT03286556	Idiopathic Pulmonary Fibrosis	Study of Therapeutic Plasma Exchange, Rituximab and IV Immunoglobulin for Acute Exacerbations of Idiopathic Pulmonary Fibrosis (STRIVE-IPF)	51	Plasma exchange + IVIg + rituximab	Standard of Care (Antibiotics and steroids)	sep/22	Recruiting
NCT02184741	Recurrent Miscarriage	A Randomized, Placebo-controlled, Double-blinded Study With GB-0998 for Unexplained Primary Recurrent Miscarriage	80	IVIg: GB-0998 (Venoglobulin ®I 2.5g/50ml)	Placebo	jun/21	Recruiting
2014-005419-18	Pregnancy loss	Clinical trial, phase III, randomised double blind placebo controlled with IV immunoglobulin human for the treatment of repeat abortion with immune etiology	66	IVIg	Placebo	2 years	
NCT03289403	Infertility-Autoimmune Thyroiditis	The Role of Immunomodulatory Treatment in Success of ICSI in Patients With Autoimmune Thyroiditis	100	thyroxine + immunomodulatory drugs (Prednisolone + hydrochloroquine)	thyroxine (and no immunomodulatory drugs)	sep/19	completed but no results yet

Trial-ID	Indication	Title	Sample size	Intervention	Comparator		Anticipated end date	status
				In case no response to immunomodulatory drugs ==> Ig				
NCT04041765	Neonatal Sepsis	Efficacy of Prophylactic IgM-Enriched Immunoglobulin for the Management of Early-Onset Neonatal Sepsis in Very Low Birth Weight Preterm Neonates; A Randomized Controlled Trial	70	IgM-enriched IVIg given with dose of 0.25g/kg/ 3 days + Antibiotics	Antibiotics		aug/20	Not yet recruiting
NCT02899702	Toxic Shock Syndromes in Children	Effectiveness of IV Ig (IVIg) in Toxic Shock Syndromes in Children (IGHN2)	156	IVIg: Privigen®	Placebo: Albumin		sep/24	Not yet recruiting
NCT03560011 2017-000826-36	Nephrotic syndrome	Efficacy and safety of immunoglobulin associated with rituximab versus rituximab alone in Childhood-Onset steroid-dependent nephrotic syndrome	90	IVIg: Privigen® + rituximab	Rituximab		apr/23	Recruiting
2016-001788-34 NCT03334006	Sepsis / Septic shock (peritonitis)	Prospective, randomized study concerning personalized medicine with Pentaglobin® after interventional infectious source control in peritonitis patients	200	IgM-enriched IVIg (Pentaglobin®) + Standard of Care	Standard of Care		dec/21	Suspended (Due to safety-relevant aspects with regard to internal processes of the sponsor (Austria Germany)
NCT03065244	Kawasaki disease	KIDCARE (Kawasaki Disease Comparative Effectiveness Trial) (KIDCARE)	250	IVIg (crossover)	Infliximab		sep/20	Recruiting
NCT02540720	Henoch-Schoenlein Purpura (vasculitis affecting small vessels)	The Research of Standard Diagnosis and Treatment for Severe HSP in Children	30	Dexamethasone	Dexamethason + gammaglobulin	Dexamethason + Hemoperfusion	07/20	recruiting
NCT03647852	Henoch-Schönlein Purpura (IgA vasculitis)	Clinical Study on Strategy for Refractory Henoch-Schönlein Purpura	150	IVIg (+ blood purification)	Methylprednisolon		October 30, 2021	recruiting

Trial-ID	Indication	Title	Sample size	Intervention	Comparator		Anticipated end date	status
					(+blood purification)			
NCT03939533	PIDD	Study to Monitor SC Human Ig Administered at Modified Dosing Regimens in Patients With Primary Immunodeficiency Diseases	65	SCIg: Cutaquig® weekly and increase volumes every 4 week	SCIg: Cutaquig® weekly and increase infusion rate every 4 weeks	SCIg: Cutaquig® every 2 weeks increased dose (twice their body beight)	March 2021	Recruiting
NCT04044690	Dermatomyositis	A Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of IgPro20 in Adults With Dermatomyositis (DM) -The RECLAIIM Study	126	SCIg: IgPro20 (Hizentra®)	Placebo		feb/24	Recruiting
NCT02549170 2014-005496-87	CIPD	A Phase III Study to Evaluate the Efficacy, Safety, and Tolerability of Immune Globulin Infusion 10% (Human) With Recombinant Human Hyaluronidase (HYQVIA/HyQvia) and Immune Globulin Infusion (Human), 10% (GAMMAGARD LIQUID/KIOVIG) for the Treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)	232	SCIg: Hyqvia®as maintenance therapy	0.25% Albumin placebo solution with rHuPH20		December, 2021	recruiting
2018-003592-34	CIPD	Randomized, parallel study of SC versus IV immunoglobulin in treatment-naïve patients with chronic inflammatory demyelinating polyneuropathy	60	SCIg: Hizentra®	IVIg: Privigen®		6 year	not recruting in belgium
NCT03737617	Bronchiectasis	Ig Replacement Therapy for Immunoglobulin G Subclass 2 Deficient Patients With Bronchiectasis	20	SCIg: Cuvitru® 20 %	Standard of care		dec/24	Suspended
NCT04450654	HMG-CoA Reductase Auto-Antibody Positive Necrotizing Myopathy	Monotherapy IVIG Gamunex-C for HMG-CoA Reductase Auto-Antibody Positive Necrotizing Myopathy Treatment (The MIGHT Trial)	10	Gamunex-C®	Albumin		jul/22	recruiting
CTRI/2020/08/027019	Neonatal sepsis	Role of intravenous immunoglobulin in the management of neonatal sepsis : A randomized controlled trial.	60	IVIg 5% (Gobucel®)	5% dextrose			Not yet recruiting
NCT04550611	Guillain barre	Mini-pool Intravenous Immunoglobulin (MP-IVIG) in Guillain-Barré Syndrome	50	IVIg from minipools (20 donors)	Plasma exchange		dec/22	Not yet recruiting
NCT04153422	small fiber neuropahty	IVIG in the Treatment of Autoimmune Small Fiber Neuropathy With TS-HDS or FGFR-3 Antibodies	20	IVIg:Gammagard®	Placebo		sep/24	Not yet recruiting

Trial-ID	Indication	Title	Sample size	Intervention	Comparator	Anticipated end date	status
NCT04137224	systemic sclerosis	Evaluate the Safety and Pharmacokinetics of IgPro20 (Subcutaneous Immunoglobulin, Hizentra®) and IgPro10 (Intravenous Immunoglobulin, Privigen®) in Adults With Systemic Sclerosis (SSc)	26	IVIg: Privigen®	SCIg: Hizentra®	aug/21	recruiting
NCT04438382	Steroid-Refractory Pneumonitis	Infliximab and Intravenous Immunoglobulin Therapy in Treating Patients With Steroid-Refractory Pneumonitis	36	IVIg + cortico	Infliximab + corticosteroid	mei/24	recruiting
NCT04302805	kidney transplantation (antibody-mediated rejection)	rATG Versus rATG Combined With Intravenous Immunoglobulin (IVIG) Induction Immunosuppression in HLA Incompatible Transplantation (INHIBIT)	138	IVIg (Privigen®)+Plasma exchange + Thymoglobuline®	Plasma exchange + Thymoglobuline®	apr/23	Not yet recruiting
NCT04566692	PIDD	A Study to Evaluate IGSC 20% Biweekly Dosing in Treatment-Experienced Participants and Loading/Maintenance Dosing in Treatment-Naïve Participants With Primary Immunodeficiency	31	SCIg 20% weekly	SCIg 20% biweekly	aug/22	Not yet recruiting
NCT04400994	pemphigus	The Use of IVIG in Combination With Rituximab VS Rituximab as the First Line Treatment of Pemphigus	20	IVIg (Privigen®)+ rituximab	Rituximab	dec/24	recruiting
NCT04138485	Diffuse Cutaneous Systemic Sclerosis	Efficacy and Safety of IgPro10 in Adults With Systemic Sclerosis (SSc)	144	IVIg: IgPro10	Placebo: Albumin	nov/23	withdrawn*
Sinlge-arm Studies							
NCT03866798	Chronic immune thrombocytopenia	Post-Marketing Study to Evaluate the Efficacy and Safety of PANZYGA in Pediatric Patients With Chronic Immune Thrombocytopenia (ITP)	20	IVIg: Panzyga®		mrt/22	recruiting
NCT03829826	Stiff-persons syndrome	Efficacy and Mechanism of Action of SCIg in Patients With Stiff Person Syndrome (SPS)	22	IVIg: Hyqvia®		mei/20	Not yet recruiting
NL888	Autoimmune epilepsy	Autoimmune epilepsy Modulated by IVIg – effects on Cortical Excitability, the AMICE study (single arm)	55	IVIg		1/09/2023	recruiting
2016-004766-26	idiopathic inflammatory myopaties	Intravenous immunoglobulins as early treatment in newly diagnosed idiopathic inflammatory myopathies (IMMEDIATE): a pilot study. (single arm - phase 2)	20	IVIg (Privigen®)			completed

Trial-ID	Indication	Title	Sample size	Intervention	Comparator	Anticipated end date	status
NCT04535518	Kawasaki	Efficacy of Immunoglobulin Plus Infliximab for the Early Regression of Coronary Artery Lesion in Kawasaki Disease	220	Aspirin+Infliximab+IVIg		sep/22	Not yet recruiting
NCT03348618	Pediatric Acute-onset Neuropsychiatric Syndrome (PANS)	Multi-site, Open-Label, Pilot Study to Evaluate the Benefit of Octagam 5%® in Subjects With Pediatric Acute-onset Neuropsychiatric Syndrome (PANS)	21	IVIg: Octagam 5%		mrt/20	active, not recruiting
2017-002024-24	CIPD	Randomized, cohort study of standardized reduction of SCIg treatment in patients with chronic inflammatory demyelinating polyneuropathy	60	dose reductions: Gammanorm®, Hizentra®, Subcuvia®		1 year	completed
NCT02374736	Kidney Transplant antibody-mediated rejection (AMR)	Pilot Study on the Effect of Privigen Against Graft Loss:	15	IVIg: Privigen®		dec/20	Active, not recruiting
Specific Covid-19 trials in 2020							
EUCTR2020-001890-56-ES	COVID-19	Clinical trial to evaluate the efficacy and safety of the use of intravenous gammaglobulins in the treatment of patients with COVID-19	100	IVIg: Flebogamma®	Placebo	1 year	ongoing
NCT04350580	COVID-19	Value of Early Treatment With Polyvalent Immunoglobulin in the Management of Acute Respiratory Distress Syndrome Associated With SARS-CoV-2 Infections	138	IVIg: Claryg®	Placebo	jun/21	recruiting
IRCT20200501047259N1	COVID-19	Pilot study: Intravenous immunoglubolin (IVIG) effect on improvement of severe pulmonary damage in COVID 19 disease	40	IVIg: Flebogamma® 5%	Placebo	jun/20	recruiting complete
NCT04400058	COVID-19	Octagam 10% Therapy in COVID-19 Patients With Severe Disease Progression	208	IVIg (Octagam® 10%)	Placebo	dec/20	recruiting
NCT04432324 EUCTR2020-001696-32-ES	COVID-19	Study to Evaluate the Safety and Efficacy of High Dose IVIG in Patients with Mild/Moderate COVID19	100	IVIg: Flebogamma® 5%-10% + SMT	SMT	dec/20	recruiting
NCT04261426	COVID-19	Evaluate the Efficacy of Intravenous Immunoglobulin Therapy in Patients With Severe 2019-nCoV Pneumonia	80	IVIg + SMT	SMT	jun/20	not yet recruiting

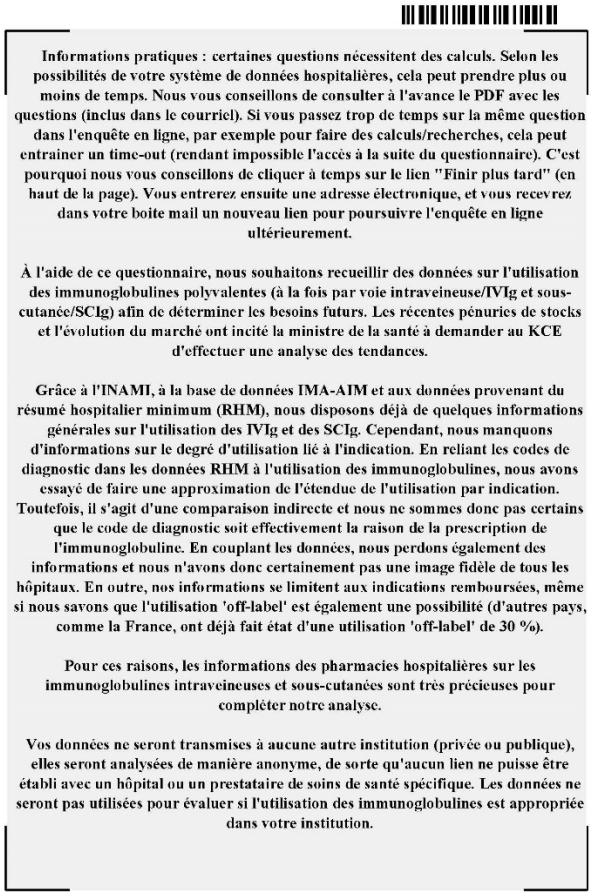
Trial-ID	Indication	Title	Sample size	Intervention	Comparator	Anticipated end date	status
NCT04500067	COVID-19	Intravenous Immunoglobulin (IVIG, Bioven) Efficacy Assess for COVID-19 / SARS-CoV-2 Severe Pneumonia Complex Treatment	76	IVIg: Bioven® 10% + SMT	SMT	sep/20	completed
NCT04548557	COVID-19	Intravenous Immunoglobulins for the Treatment of Covid-19 Patients: a Clinical Trial	60	IVIg + SMT	SMT	nov/20	not yet recruiting
NCT04480424	COVID-19	Evaluate Safety and Efficacy of High Dose Intravenous Immune Globulin (IVIG) Plus Standard Medical Treatment (SMT) Versus SMT Alone in Subjects With COVID-19 Requiring Admission to the Intensive Care Unit	100	IVIg (Gamunex® - C (10%)) + SMT	SMT	feb/21	recruiting
NCT04411667	COVID-19	Standard of Care Plus Intravenous Immunoglobulin (IVIG) Compared to Standard of Care Alone in the Treatment of COVID-19 Infection	40	IVIg (Octagam® 10%)+ SMT	SMT	nov/20	non peer reviewed results
NCT04403269	COVID-19	Study of the efficiency of IVIg in patients aged 75 years and over COVID 19 with severe acute respiratory failure (Geronima 19 study)	35	IVIg		mei/21	recruiting
NCT04381858	COVID-19	Convalescent Plasma vs Human Immunoglobulin to Treat COVID-19 Pneumonia	500	Convalescent plasma	Human immunoglobulin	sep/20	recruiting
NCT04264858	COVID-19	Exploratory Clinical Study on the Treatment of Acute Severe 2019-nCoV Pneumonia With Immunoglobulin From Cured 2019-nCoV Pneumonia Patients	10	Immunoglobulin of cured patients	Gammaglobulin	mei/20	Not yet recruiting

*SMT: Standard medical treatment; * this study was planned to recruit in Belgian sites, however this study was withdrawn since 17 November, due to business reasons, not safety issues*

8 SURVEY TO THE HOSPTIAL PHARMACISTS

8.1 The questions

French version



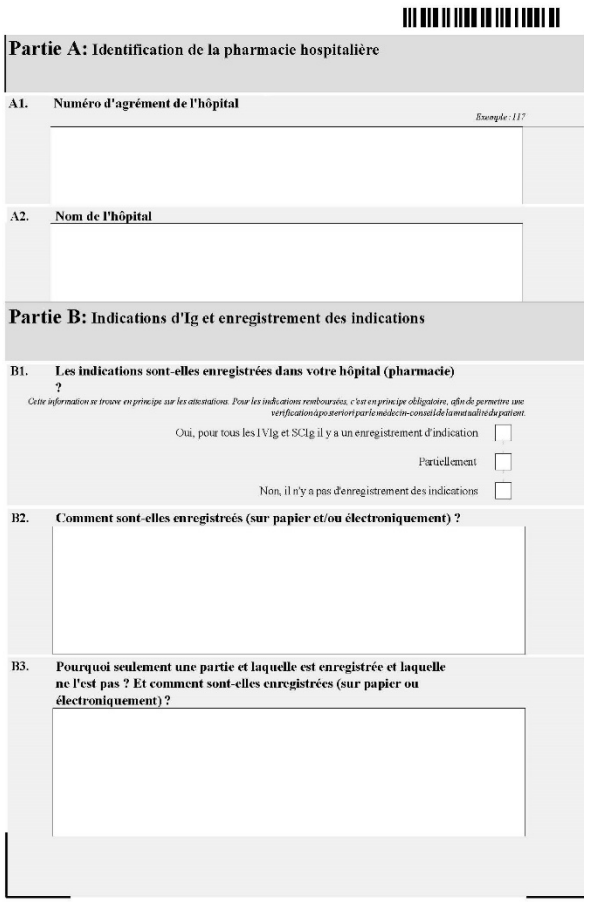
Informations pratiques : certaines questions nécessitent des calculs. Selon les possibilités de votre système de données hospitalières, cela peut prendre plus ou moins de temps. Nous vous conseillons de consulter à l'avance le PDF avec les questions (inclus dans le courriel). Si vous passez trop de temps sur la même question dans l'enquête en ligne, par exemple pour faire des calculs/recherches, cela peut entrainer un time-out (rendant impossible l'accès à la suite du questionnaire). C'est pourquoi nous vous conseillons de cliquer à temps sur le lien "Finir plus tard" (en haut de la page). Vous entrerez ensuite une adresse électronique, et vous recevrez dans votre boite mail un nouveau lien pour poursuivre l'enquête en ligne ultérieurement.

À l'aide de ce questionnaire, nous souhaitons recueillir des données sur l'utilisation des immunoglobulines polyvalentes (à la fois par voie intraveineuse/IVIg et sous-cutanée/SCIg) afin de déterminer les besoins futurs. Les récentes pénuries de stocks et l'évolution du marché ont incité la ministre de la santé à demander au KCE d'effectuer une analyse des tendances.

Grâce à l'INAMI, à la base de données IMA-AIM et aux données provenant du résumé hospitalier minimum (RHM), nous disposons déjà de quelques informations générales sur l'utilisation des IVIg et des SCIg. Cependant, nous manquons d'informations sur le degré d'utilisation lié à l'indication. En reliant les codes de diagnostic dans les données RHM à l'utilisation des immunoglobulines, nous avons essayé de faire une approximation de l'étendue de l'utilisation par indication. Toutefois, il s'agit d'une comparaison indirecte et nous ne sommes donc pas certains que le code de diagnostic soit effectivement la raison de la prescription de l'immunoglobuline. En couplant les données, nous perdons également des informations et nous n'avons donc certainement pas une image fidèle de tous les hôpitaux. En outre, nos informations se limitent aux indications remboursées, même si nous savons que l'utilisation 'off-label' est également une possibilité (d'autres pays, comme la France, ont déjà fait état d'une utilisation 'off-label' de 30 %).

Pour ces raisons, les informations des pharmacies hospitalières sur les immunoglobulines intraveineuses et sous-cutanées sont très précieuses pour compléter notre analyse.

Vos données ne seront transmises à aucune autre institution (privée ou publique), elles seront analysées de manière anonyme, de sorte qu'aucun lien ne puisse être établi avec un hôpital ou un prestataire de soins de santé spécifique. Les données ne seront pas utilisées pour évaluer si l'utilisation des immunoglobulines est appropriée dans votre institution.



Partie A: Identification de la pharmacie hospitalière

A1. **Numéro d'agrément de l'hôpital**

Exemple : 117

A2. **Nom de l'hôpital**

Partie B: Indications d'Ig et enregistrement des indications

B1. **Les indications sont-elles enregistrées dans votre hôpital (pharmacie) ?**

Cette information se trouve en principe sur les attestations. Pour les indications remboursées, c'est en principe obligatoire, afin de permettre une vérification a posteriori par le médecin-conseil de la mutualité du patient.

Oui, pour tous les IVIg et SCIg il y a un enregistrement d'indication ☐

Partiellement ☐

Non, il n'y a pas d'enregistrement des indications ☐

B2. **Comment sont-elles enregistrées (sur papier et/ou électroniquement) ?**

B3. **Pourquoi seulement une partie et laquelle est enregistrée et laquelle ne l'est pas ? Et comment sont-elles enregistrées (sur papier ou électroniquement) ?**

B4. Pourquoi n'y a-t-il pas d'enregistrement des indications ?

B5. S'il y a effectivement un enregistrement de l'indication, comment cet enregistrement est-il détaillé ? Par indication ou par paragraphe de remboursement ?

Par exemple, le paragraphe 6790100 prévoit six indications telles que l'immunodéficience primaire, les malignités des cellules B, la maladie de Kawasaki, la thrombocytopénie idiopathique/immune, le syndrome de Guillain-Barré, les patients présentant une hypogammaglobulinémie après une transplantation de cellules souches.

B6. Si le logiciel de votre hôpital vous permettait d'extraire facilement des données sur les indications d'utilisation des IVIg et SCIg (pas seulement le paragraphe sur le remboursement), seriez-vous prêt à transférer ces données au KCE comme une sorte de validation de notre méthode actuelle ?

Si cela vous convient, nous vous demanderons dans une deuxième phase (août/septembre) des données agrégées sur les IVIg et les SCIg par indication : le volume total par produit et par indication et le nombre de patients par produit et par indication dans votre hôpital. Ces données sont anonymes, ne contiennent pas d'informations personnelles car nous ne demandons pas de données au niveau du patient individuel. Nous traitons ces données de manière confidentielle et ne divulguons pas les hôpitaux qui y ont participé. Ces données seront utilisées pour valider notre analyse actuelle, qui est basée sur une indication de substitution (un proxy : la raison de l'admission d'un patient dans un hôpital).

Oui ☐

Non ☐

B7. Quel est l'état d'avancement du déploiement des CIVAR (Chapter IV Agreement Request System) dans votre hôpital ?

Partie C: Utilisation non remboursée et off-label

Les immunoglobulines sont autorisées pour un nombre limité d'indications (6 à 10 indications dans la plupart des pays). Certains pays font état d'une utilisation 'off-label' de 30 %. Nous supposons donc qu'il pourrait y avoir un besoin d'utilisation 'off-label' en Belgique. En Belgique, la règle veut que les médicaments non autorisés pour une indication donnée ne soient pas remboursés par l'assurance maladie obligatoire. C'est également le cas pour les immunoglobulines. En outre, toutes les indications autorisées ne sont pas couvertes en tant que telles par l'assurance maladie obligatoire ; il existe des critères spécifiques pour chaque indication. Dans les questions suivantes, nous évaluons l'utilisation non remboursée des Ig dans votre hôpital, notamment pour avoir une idée de sa prévalence.

C1. Des IVIg et/ou SCIg ont-elles été délivrées à votre hôpital pour des indications non remboursées par l'INAMI (ne répondant pas aux critères ou des indications 'off-label') au cours des 3 dernières années ?

Des calculs sont nécessaires pour cette question.

Non, en 2017, 2018 ou 2019, aucun IVIg ou SCIg n'a été délivrée pour lequel il n'y a pas eu de remboursement de la part de l'INAMI ☐

Oui, au cours des années 2017, 2018 ou 2019, des IVIg ou SCIg ont été délivrées pour lesquelles il n'y avait pas de remboursement de la part de l'INAMI ☐

Il n'est pas possible de répondre à cette question ☐

C3. Plus précisément pour l'année 2017, y a-t-il eu des délivrances d'IVIg et/ou de SCIg sans être remboursées par l'INAMI ?

Non, pas d'Ig livrée en 2017 qui n'a pas été remboursée par l'INAMI. ☐

Oui, en 2017, des Ig ont été délivrées pour des indications qui n'étaient pas remboursées par l'INAMI. ☐

Il n'est pas possible de répondre à cette question ☐

Veuillez communiquer vos chiffres. Nous sommes principalement intéressés par le volume utilisé (en g), mais si possible, merci d'adjoindre le nombre de patients correspondant.

Exemple de réponse : en 2017, 540 g d'IVIg et de SCIg ont été livrés à notre hôpital pour une indication non remboursable, sur une livraison annuelle totale de 10 kg → 8,4 % volume d'utilisation non remboursable. Si possible, veuillez préciser à combien de patients ce volume correspond : cela correspond à 4 patients qui ont une indication non remboursée ou 'off-label' sur un total de 100 patients traités par an.

C5. **Plus précisément pour l'année 2018, y a-t-il eu des délivrances d'IVIg et/ou de SCIg sans être remboursées par l'INAMI ?**

Non, pas d'Ig livrée en 2018 qui n'a pas été remboursée par l'INAMI. ☐

Oui, en 2018, des Ig ont été délivrées pour des indications qui n'étaient pas remboursées par l'INAMI. ☐

Il n'est pas possible de répondre à cette question ☐

totale d'immunoglobulines cela représente-t-il dans votre hôpital ?

Veuillez communiquer vos chiffres. Nous sommes principalement intéressés par le volume utilisé (en g), mais si possible, merci d'adjoindre le nombre de patients correspondant.

Exemple de réponse : en 2018, 840 g d'IVIg et de SCIg ont été livrés à notre hôpital pour une indication non remboursable, sur une livraison annuelle totale de 10 kg → 8,4% volume d'utilisation non remboursable. Si possible, veuillez préciser à combien de patients ce volume correspond : cela correspond à 4 patients qui ont une indication non remboursée ou 'off-label' sur un total de 100 patients traités par an.

C7. **Plus précisément pour l'année 2019, y a-t-il eu des délivrances d'IVIg et/ou de SCIg sans être remboursées par l'INAMI ?**

Non, pas d'Ig livrée en 2019 qui n'a pas été remboursée par l'INAMI. ☐

Oui, en 2019, des Ig ont été délivrées pour des indications qui n'étaient pas remboursées par l'INAMI. ☐

Il n'est pas possible de répondre à cette question ☐

d'adjoindre le nombre de patients correspondant.

Exemple de réponse : en 2019, 840 g d'IVIg et de SCIg ont été livrés à notre hôpital pour une indication non remboursable, sur une livraison annuelle totale de 10 kg → 8,4% volume d'utilisation non remboursable. Si possible, veuillez préciser à combien de patients ce volume correspond : cela correspond à 4 patients qui ont une indication non remboursée ou 'off-label' sur un total de 100 patients traités par an.

C9. **Quelle est la tendance de l'utilisation des Ig pour les indications non remboursables ou 'off-label' dans votre hôpital au cours des 5 dernières années ?**

Est-elle stable ? Est-ce qu'elle augmente ? Y a-t-il des fluctuations ? Veuillez préciser les raisons ou observations éventuelles.

C10. **Pourriez-vous communiquer les indications les plus courantes pour cette utilisation non remboursable ou'off-label' ?**

Par exemple : cette indication est notée sur une attestation ou est-elle capturée dans le logiciel ? Cela est-il discuté avec le prescripteur ? etc.

Non ☐

Oui ☐

Veuillez préciser quelles sont les indications les plus courantes (en termes de nombre de patients).

C13. **Y a-t-il eu des essais cliniques, des urgences médicales ou des programmes d'usage compassionnel pour les IVIg/SCIg dans votre hôpital au cours des deux dernières années ? Si oui, veuillez préciser dans les questions suivantes pour quelles indications et combien de patients ont été traités cette année-là.**

Nous ne demandons pas de détails sur les protocoles d'étude, nous voulons pouvoir donner un aperçu de ce qui se passe dans notre rapport. Un exemple : en 2018, il y a eu 3 essais cliniques dans des hôpitaux belges représentant environ 300 patients recevant des IVIg ou des SCIg. Les indications de ces essais cliniques étaient...

Oui ☐

Non ☐

Il n'est pas possible de répondre à cette question ☐

C14. **Veuillez expliquer pourquoi cela n'est pas possible.**

C15. **Plus précisément pour l'année 2018, y avait-il des études/programmes dans votre hôpital avec l'IVIg/SCIg ?**

Non, pas d'études ni de programmes ☐

Oui ☐

traités en 2018.

C17. **Plus précisément pour l'année 2019, y avait-il des études/programmes dans votre hôpital avec l'IVIg/SCIg ?**

Non, pas d'études ni de programmes ☐

Oui ☐

C19. **Des essais cliniques, des urgences médicales ou des programmes d'usage compassionnel des Ig (IVIg ou SCIg) ont-ils commencé dans votre hôpital en 2020 ?**

Non, pas d'études ni de programmes ☐

Oui ☐

Il n'est pas possible de répondre à cette question ☐

C20. **Pour quelles indications et combien de patients prévus en 2020 ?**

C21. **Y a-t-il eu des patients traités avec des IVIg ou des SCIg dans votre hôpital au cours des 2 dernières années dont le patient paie les Ig (de sa propre poche) ?**

Oui ☐

Non ☐

Il n'est pas possible de répondre à cette question ☐

C23. **Plus précisément pour l'année 2018, y a-t-il eu des patients dans votre hôpital qui ont payé de leur poche l'IVIg/SCIg ?**

Non ☐

Oui ☐

C25. **Plus précisément pour l'année 2019, y a-t-il eu des patients dans votre hôpital qui ont payé de leur poche l'IVIg/SCIg ?**

Non ☐

Oui ☐

C26. **Pour quelles indications et combien de patients dans votre hôpital ?**

C27. **Y a-t-il d'autres mécanismes possibles au sein de votre hôpital que ceux mentionnés ci-dessus (autres que l'usage compassionnel, les études cliniques, le fonds spécial de solidarité) pour les patients dont les indications n'ont pas été remboursées par l'INAMI ?**

C28. **L'Ig est-elle utilisée pendant cette crise coronarienne, pour les patients atteints de covid-19 ?**

S'il n'est pas possible de répondre à cette question, pouvez-vous vérifier si l'utilisation a augmenté depuis mars 2020 et faire un commentaire à ce sujet ?

Oui ☐

Non ☐

Pensez-vous que les Ig seront utilisées à l'avenir pour les patients atteints de covid-19 ou pour les conséquences cliniques du covid-19 ? (dans le cadre d'essais cliniques, d'un usage compassionnel ou d'autres programmes ?)

Partie D: Procédure de livraison et d'appel d'offres

En 2018 et 2019, il y a eu quelques problèmes de livraison, principalement en raison de l'évolution du marché après le début de la procédure d'appel d'offres (depuis novembre 2018, au moins 50 % des Ig intraveineuses pour les indications remboursées dans les hôpitaux doivent être Privigen® ou Sandoglobulin®).

D1. **Votre hôpital a-t-il rencontré des difficultés d'approvisionnement depuis septembre 2019 ?**

Oui ☐

Non ☐

D3 **Avez-vous des commentaires concernant la fourniture de produits Ig à votre hôpital ?**

D4 **Selon vous, quels sont les facteurs déterminants des pénuries et des problèmes d'approvisionnement ?**

Partie E: Considérations et perspectives

E1. **Y a-t-il des commentaires, des facteurs concernant l'utilisation des Ig que nous devrions prendre en compte dans notre analyse ?**

E2. **Seriez-vous (ou un collègue) disposé à participer à une réunion d'experts à l'automne 2020 pour discuter des résultats de notre analyse et aider à l'interprétation des résultats ? En principe, nous planifions cela dans le bâtiment du KCE à Bruxelles si les circonstances le permettent.**

Si nous avons la chance d'avoir de nombreux candidats potentiels, nous devrons faire une sélection en fonction de la faisabilité.

Oui ☐

Non ☐

E3. **Veuillez transmettre les coordonnées de contact (adresse électronique).**

Nous vous remercions sincèrement pour votre collaboration.

Dutch version

Praktische info: voor bepaalde vragen zijn berekeningen nodig. Al naargelang de mogelijkheden van uw ziekenhuisdatasysteem kan dit vlot of minder vlot gaan. Wij raden u aan op voorhand de PDF met vragen (bijgestuurd in de mail) te bekijken. Indien U in de online survey te lang op een zelfde vraag blijft stilstaan, bijvoorbeeld om berekeningen/opzoekingen te doen, kan dit leiden tot een time-out (waardoor het onmogelijk is om de rest van de vragenlijst te bekijken). Daarom raden we aan om tijdig op de knop "hervat later" (bovenaan op de pagina) te klikken. Daaropvolgend geeft u een emailadres in, en ontvangt u een nieuwe link om de online survey op een later moment verder in te vullen.

Met deze vragenlijst willen we data verzamelen omtrent het gebruik van de polyvalente immunoglobulines (zowel intraveneus/IVIg als subcutaan gebruik/SCIg) met als objectief de toekomstige nood te bepalen. Recente stockbreuken en een veranderende markt hebben de Minister van Volksgezondheid ertoe aangezet om het KCE te vragen om een trendanalyse uit te voeren.

Gebaseerd op RIZIV, de IMA databank en de Minimale ziekenhuisgegevens (MZG) hebben we reeds wat algemene informatie omtrent het gebruik van IVIg en SCIg. Maar we missen informatie over hoe groot het gebruik is gelinkt aan de indicatie. Door het koppelen van diagnostische codes in de Minimale ziekenhuisgegevens aan het immunoglobuline gebruik hebben we getracht een benadering te maken van de grootte van gebruik per indicatie. Maar dit is een indirecte vergelijking en we zijn dus niet zeker of de diagnostische code wel degelijk de reden is voor het immunoglobuline voorschrijven. Door het koppelen van de data verliezen we ook informatie en we hebben dus zeker niet het beeld van alle ziekenhuizen. Daarbij is onze informatie gelimiteerd tot terugbetaalde indicaties en dat terwijl we weten dat off-label gebruik ook een mogelijkheid is (ander landen zoals Frankrijk, rapporteerden reeds 30% off-label gebruik).

Om deze redenen, is informatie vanuit de ziekenhuisapotheken over enerzijds intraveneuze immunoglobulines als subcutane heel waardevol om onze analyse aan te vullen.

Uw data zal niet doorgegeven worden aan een andere instelling (privé of overheidsinstanties), ze zal geanalyseerd worden in een geanonimiseerde wijze, zodat er geen link mogelijk is naar een specifiek ziekenhuis of met een specifieke zorgverlener. De data zal niet gebruikt worden om te beoordelen of het immunoglobulinegebruik gepast is in uw instelling.

Sectie A: Identificatie ziekenhuisapotheek

A1. Erkenningsnummer ziekenhuis

Voorbeeld: 117

A2. Naam ziekenhuis

Sectie B: Indicaties van Ig en de registratie van indicaties

B1. Worden in uw ziekenhuis(apotheek) de indicaties geregistreerd?

U kan deze info normaal via de attest-aanvragen terugvinden. Voor terugbetaalde indicaties is dit in principe verplicht, om zo mogelijke a posteriori verificatie door de adviserend geneesheer van de mutualiteit mogelijk te maken.

- Ja voor alle IVIg en SCIg is er een registratie van indicatie ☐
- Gedeeltelijk ☐
- Nee, geen registratie van indicaties ☐

B2. Hoe worden ze geregistreerd (op papier en/of elektronisch)?

B3. Waarom enkel gedeeltelijk en welk deel dan wel en niet? En hoe worden ze geregistreerd (op papier, of elektronisch)?

B4. **Waarom is er geen registratie van indicaties?**

B5. **Indien er inderdaad een registratie van de indicatie gebeurt, hoe is deze registratie gedetailleerd? Per indicatie of per terugbetalingsparagraaf?**

Bijvoorbeeld onder paragraaf 670100 zitten er zes indicaties zoal sprimaire immunodeficiëntie, B-cel maligniteiten, ziekte van Kawasaki, Idiopatische/Immuun trompocytopenia, Guillain-Barré syndroom, patiënten met hypogammaglobulinemia na een stamceltransplantatie.

B6. **Indien de software van uw ziekenhuis het zou toelaten om gemakkelijk data te extraheren omtrent de indicaties voor IVIg en SCIg gebruik, (niet enkel de terugbetalingsparagraaf) zou u bereid zijn om deze data te transfereren aan het KCE als een soort validatie van onze huidige methode?**

Indien u dit mogelijk acht zullen we in een tweede fase (augustus/september) vragen naar geaggregeerde data van IVIg en SCIg per indicatie: totaal volume per product per indicatie en het aantal patiënten per product en per indicatie in uw ziekenhuis. Deze data zijn anonieme data, bevatten geen persoonlijke info bevatten aangezien we geen data op individueel patientniveau vragen. We behandelen deze data met confidentialiteit en zullen niet bekend maken welke ziekenhuizen hebben deelgenomen. Deze data zal gebruikt worden om onze huidige analyse, die gebaseerd is op een proxy indicatie (nl. de reden van opname van een patiënt in een ziekenhuis), te valideren.

Ja ☐

Nee ☐

B7. **Met betekking tot het capteren van indicaties via bestaande software, wat is de status van de rollout van CIVARs (Chapter IV Agreement Request System) in uw ziekenhuis?**

Sectie C: Niet terugbetaald en off-label gebruik

Immunoglobulines hebben een vergunning/licentie voor een gelimiteerd aantal indicaties (in de meeste landen zijn dat 6 tot 10 indicaties). Sommige landen rapporteren 30% off-label gebruik. Daarom gaan we er vanuit dat er in België ook nood kan zijn aan off-label gebruik.

In België is het de regel dat medicatie die geen licentie heeft voor een indicatie, niet terugbetaald wordt door de nationale ziekteverzekering. Zo is dit ook voor immunoglobulines.

Daarenboven worden niet alle vergunde indicaties als dusdanig door de nationale ziekteverzekering gedekt; er zijn specifieke criteria bij elke indicatie.

In de volgende vragen peilen we naar het niet-terugbetaald gebruik van Ig in uw ziekenhuis, in het bijzonder om een idee te krijgen hoe prevalent dit is.

C1. **Werd er in uw ziekenhuis IVIg en/of SCIg afgeleverd voor indicaties niet terugbetaald door het RIZIV (niet voldoen aan criteria of off-label indicaties) in de laatste 3 jaar?**

Voor deze vraag zijn berekeningen nodig.

Neen, in 2017, 2018 of 2019 werd er geen IVIg of SCIg afgeleverd waarvoor er geen terugbetaling was van het RIZIV ☐

Ja, in de voorbijgaande jaren 2017, 2018, 2019, is er IVIg of SCIg afgeleverd waarvoor er geen terugbetaling was van het RIZIV ☐

Niet mogelijk om deze vraag te beantwoorden ☐

C2. **Wat is de reden waarom dit niet mogelijk is?**

C3. **Specifiek voor het jaar 2017, werd er IVIg en/of SCIg afgeleverd die niet-terugbetaald is door het RIZIV?**

Nee, in 2017 geen Ig afgeleverd die niet werden terugbetaald door het RIZIV ☐

Ja, in 2017 zijn er Ig afgeleverd voor indicaties die niet werden terugbetaald door het RIZIV ☐

Niet mogelijk om te antwoorden ☐

C4. **Wat is het volume (hoeveel g) en welke proportie van het totaal immunoglobuline gebruik stelt dit voor in uw ziekenhuis?**

Gelieve uw cijfers te melden. Focus ligt op het volume (in g) gebruik maar indien mogelijk mag u ook het corresponderende aantal patiënten meedelen.

Voorbeeld van antwoord: in 2017 werd er in ons ziekenhuis 840 g IVIg en SCIg afgeleverd voor een niet-terugbetaalde indicatie, op een totaal jaarlijkse aflevering van 10 kg → 8.4% volume niet terugbetaald gebruik.

Indien mogelijk, verduidelijk graag met hoeveel patiënten dit volume correspondeert: Dit correspondeert met 4 patiënten die een niet terugbetaalde indicatie of off-label indicatie hebben op een totaal van 100 behandelde patiënten per jaar.

C5. **Specifiek voor het jaar 2018, werd er IVIg en/of SCIg afgeleverd die niet-terugbetaald is door het RIZIV?**

Nee, in 2018 geen Ig afgeleverd die niet werden terugbetaald door het RIZIV ☐

Ja, in 2018 zijn er Ig afgeleverd voor indicaties die niet werden terugbetaald door het RIZIV ☐

Niet mogelijk om te antwoorden ☐

Immunoglobuline gebruik stelt dit voor in uw ziekenhuis?

Gelieve uw cijfers te melden. Focus ligt op het volume (in g) gebruik maar indien mogelijk mag u ook het corresponderende aantal patiënten meedelen.

Voorbeeld van antwoord: in 2018 werd er in ons ziekenhuis 840 g IVIg en SCIg afgeleverd voor een niet-terugbetaalde indicatie, op een totaal jaarlijkse aflevering van 10 kg → 8.4% volume niet terugbetaald gebruik.

Indien mogelijk, verduidelijk graag met hoeveel patiënten dit volume correspondeert: Dit correspondeert met 4 patiënten die een niet terugbetaalde indicatie of off-label indicatie hebben op een totaal van 100 behandelde patiënten per jaar.

C7. **Specifiek voor het jaar 2019, werd er IVIg en/of SCIg afgeleverd die niet-terugbetaald is door het RIZIV?**

Nee, in 2019 geen Ig afgeleverd die niet werden terugbetaald door het RIZIV ☐

Ja, in 2019 zijn er Ig afgeleverd voor indicaties die niet werden terugbetaald door het RIZIV ☐

Niet mogelijk om te antwoorden ☐

C8. **Wat is het volume (hoeveel g) en welke proportie van het totaal immunoglobuline gebruik stelt dit voor in uw ziekenhuis?**

Gelieve uw cijfers te melden. Focus ligt op het volume (in g) gebruik maar indien mogelijk mag u ook het corresponderende aantal patiënten meedelen.

Voorbeeld van antwoord: in 2019 werd er in ons ziekenhuis 840 g IVIg en SCIg afgeleverd voor een niet-terugbetaalde indicatie, op een totaal jaarlijkse aflevering van 10 kg → 8.4% volume niet terugbetaald gebruik.

Indien mogelijk, verduidelijk graag met hoeveel patiënten dit volume correspondeert: Dit correspondeert met 4 patiënten die een niet terugbetaalde indicatie of off-label indicatie hebben op een totaal van 100 behandelde patiënten per jaar.

C9. **Wat is de trend van het Ig gebruik voor niet terugbetaalde of off-label indicaties in uw ziekenhuis de laatste 5 jaar?**

Is het stabiel? Stijgt het? Fluctuaties? Verduidelijk de mogelijke redenen of observaties.

C10. **Is het mogelijk om te weten wat de meest voorkomende indicaties zijn voor dit niet-terugbetaald of off-label gebruik?**

Bijvoorbeeld: deze indicatie staat genoteerd op een attest, of wordt het reeds gecapteerd in de software? Wordt het besproken met voorschrijver? enz.

Nee ☐

Ja ☐

C12. **Gelieve te verduidelijken wat de meest voorkomende indicaties zijn (qua patiënten aantallen).**

C13. **Zijn er klinische studies, medische nood of compassionate use programmas voor IVIg/SCIg in uw ziekenhuis de laatste 2 jaar? Indien ja, verduidelijk in de volgende vragen voor welke indicaties en hoeveel patiënten er behandeld werden dat jaar.**

We vragen niet naar details van studieprotocollen, we willen in het rapport een overzicht kunnen geven van wat er allemaal lopende is.

Een voorbeeld: in 2018 waren er in de Belgische ziekenhuizen 5 klinische studies die ongeveer 300 patiënten vertegenwoordigen die IVIg of SCIg krijgen. De indicaties in deze klinische studies waren...

Ja ☐

Nee ☐

Niet mogelijk om deze vraag te beantwoorden ☐

C15. **Specifiek voor het jaar 2018, waren er studies/programma's in uw ziekenhuis met IVIg/SCIg?**

Nee, geen studies of programma's ☐

Ja ☐

C17. **Specifiek voor het jaar 2019, waren er studies/programma's in uw ziekenhuis met IVIg/SCIg?**

Nee, geen studies of programma's ☐

Ja ☐

behandeld in 2019.

C19. **Zijn er klinische studies, medische nood of compassionate use programmas voor Ig (IVIg of SCIg) opgestart in 2020 in uw ziekenhuis?**

Nee, geen studies of programma's ☐

Ja ☐

Niet mogelijk om deze vraag te beantwoorden ☐

C21. **Werden er de afgelopen 2 jaar patiënten behandeld met IVIg of SCIg in uw ziekenhuis, waarvan de patiënt de Ig betaalt (out-of-pocket)?**

Ja ☐

Nee ☐

Niet mogelijk om deze vraag te beantwoorden ☐

C23. **Specifiek voor het jaar 2018, waren er in uw ziekenhuis patiënten die IVIg/SCIg out-of-pocket betaalden?**

Nee ☐

Ja ☐

C25. **Specifiek voor het jaar 2019, waren er in uw ziekenhuis patiënten die IVIg/SCIg out-of-pocket betaalden?**

Nee ☐

Ja ☐

Zijn er binnen uw ziekenhuis andere mogelijke mechanismen buiten diegene hierboven vermeld (andere dan compassionate use, klinische studies, bijzonder solidariteitsfonds) voor patiënten met indicaties die niet terugbetaald zijn via het RIZIV?

C28. **Wordt Ig gebruikt tijdens deze corona-crisis, voor patiënten met covid-19?**

Wanneer het niet mogelijk is om deze vraag te beantwoorden, kunt u nagaan of het gebruik gestegen is sinds maart 2020 en becommentaar er dit in een opmerking?

Ja ☐

Nee ☐

C29. **Denkt u dat Ig gebruikt zal worden voor covid-19 patiënten of voor de klinische gevolgen van covid-19 in de toekomst? (ofwel in klinische studies, compassionate use of andere programma's?)**

Sectie D: Leverings- en aanbestedingsprocedure

In 2018 en 2019 waren er wat leveringsproblemen, voornamelijk door de veranderende markt na de start van de tenderprocedure (sinds november 2018 moet tenminste 50% van het intraveneus Ig voor terugbetaalde indicaties in de ziekenhuizen Privigen® of Sandoglobuline® zijn).

D1. **Heeft uw ziekenhuis moeilijkheden gehad voor de bevoorrading sinds september 2019?**

Ja ☐

D2. **Voor welke producten?**

D3. **Heeft uw opmerkingen omtrent de bevoorrading van Ig producten naar uw ziekenhuis?**

D4. **Wat zijn volgens u de drijvende factoren van tekorten en problemen met de levering?**

Sectie E: Bedenkingen en toekomst

E1. **Zijn er opmerkingen, factoren betreffende Ig gebruik waar we moeten mee rekening houden in onze analyse?**

E2. **Zou u (of een collega) bereid zijn om deel te nemen in een expertvergadering in de herfst van 2020 om de resultaten van onze analyse te bespreken en te helpen met de interpretatie van de resultaten? Normaliter plannen we dit in het KCE gebouw in Brussel als de omstandigheden het toelaten.**

Indien we gezegend zijn met vele potentiele kandidaten, moeten we voor de haalbaarheid een selectie doen.

Ja ☐

Nee ☐

Gelieve de contactgegevens (email adres) toe te voegen.

Hartelijk dank voor uw medewerking.

8.2 The results

These results have been incorporated in different parts of the main body of the report.

The hospital pharmacy is the place where most Ig are acquired and dispensed. In order to get an impression of the workfield, a survey amongst Belgian hospital pharmacists was performed. This survey aimed at capturing the most recent data (2017, 2018, 2019) on **non-reimbursed use**, as well as info on how indications are **registered** in the hospital pharmacy and recent problems with **supply**. This consisted of a semi-qualitative questionnaire with open questions (see list of questions in appendix). An important limitation is that the information captured from hospital pharmacists is limited to the use in hospitals. Gathering information on non-reimbursed Ig use or supply problems in the ambulatory sector, distributed via the community pharmacy, was deemed not feasible within the given timeframe. However on supply issues, the General Pharmaceutical association (APB) did not detect any specific problems other than the officially unavailable product list (in the ambulatory sector only SCIg product Gammanorm® in 2019).

Method

In May-June 2020 the questionnaire was drafted in collaboration with the Belgian Society for Hospital pharmacists (BVZA-ABPH). The platform 'Lime survey' was used to distribute the survey online and to gather data. The questionnaire was tested by two hospital pharmacists in June 2020 and their comments considered before launching a final version of the survey.

In order to increase the response rate, the BVZA-ABPH sent out the invitation to participate to this survey to all hospital pharmacists in Belgium on July 2nd 2020, with the request to complete one survey per hospital pharmacy by 1 September 2020. The survey was closed the 10th of September.

Results

The response rate of the survey was 38%. Of the 107 hospitals which had Ig use in 2018 (last available year in the data-analysis) 40 hospitals responded to the survey[b].

Characteristics of participating hospital pharmacies:

The response rate differed in the three Regions. The highest response rate was obtained in the Flemish region, 50% (28/56), followed by the Walloon region

25% (9/36) and Brussels 23% (3/13)). Next to the 39 general hospitals, one revalidation centre replied.

In terms of hospital categories, out of the 7 university hospitals only three participated, and of the 17 hospitals with an academic character, 8 responded.

The hospitals were categorised in big users (≥50kg annually in 2018), medium users (10-50 kg) and small users (<10kg). Among the 9 big users, four hospitals responded (response rate of 44%), among the 33 medium users, 16 responded (48%), and among the 63 hospitals with less than 10kg use per year there were 20 hospitals responding (32%). Details can be found in Table A.

[b] In 2018 there were 107 hospitals with Ig use, but due to mergers this corresponds to 105 hospitals in 2020.

Table A: Response rate depending on the quantity of Ig use in the Belgian hospitals (2018)

Volume Ig (kg)	Number of hospitals	Hospital with a response	% response rate.
[0-5[	40	9	22,5%
[5-10[	23	11	47,8%
[10-20[	12	4	33,3%
[20-30[	15	8	53,3%
[30-40[	2	0	0,0%
[40-50[	4	4	100,0%
≥50	9	4	44,4%

Registration

For the question of whether or not there was any registration of the indications of Ig use, all hospital pharmacies responded that indications are captured via the **mandatory application** form for reimbursed Ig (attestation). But the extent to which the capture of such information is **digitalised largely differs between hospitals**. In 14 out of 40 centres (35%), only paper versions of the application forms for reimbursement are consultable at the hospital pharmacy. Nevertheless, for the majority of responders (26/40), these documents are registered in the hospital pharmacy software (either via extra input by the hospital pharmacist based on the paper version, or either directly via electronic prescribing in the hospital software) In the vast majority of cases, **only the reimbursement paragraph** is indicated, so details on the indication are generally lacking. Only in three hospital pharmacies the indication is systematically registered in the pharmacy software.

For non-reimbursed Ig, there is no registration of indications. Responders indicate that the indication can be found in the medical file of the patient.

Next to the questions on current data registration, there was also the question to the hospital pharmacist on how the specific eHealth application CIVARS (Chapter IV Information Consultation System) is rolled out and accessible in their hospital. CIVARS launched in 2017 as application for the electronic exchange of administrative data, more specifically the agreements for medications with conditional reimbursement (i.e. chapter IV and chapter VIII medications). It is accessible via a browser but it is the intention that this tool is integrated in the software of the hospitals and health care practitioners. Physicians can request a reimbursement and send an application to the insurance (advising physicians), who, in turn, can then forward the admission or refusal. The pharmacist at the moment has a **consulting role**, he can consult and check whether or not there is a positive advice for reimbursement. At the moment, the roll-out of CIVARs differs between hospitals. The answers in the survey showed that some hospitals have to work via a stand-alone web application, and in other hospitals the service is already integrated in their hospital software (most of the time linked to the electronic patient record, and sometimes also to the hospital pharmacy

software). Most hospital pharmacies replied that the online stand-alone tool works and that they are using it for the medication groups for which it is compulsory. At a later stage of the CIVARS rollout, the pharmacist will be able to register the prescription online with the health insurance company.

Non-reimbursed use

Twenty one of the 40 responders, reported no non-reimbursed Ig use in the years 2017, 2018, 2019. In 19 hospitals there was some non-reimbursed use during that timeframe.

The 19 hospitals with non-reimbursed use and the 21 hospitals without, differ in characteristics. The hospitals with non-reimbursed use are bigger hospitals and had a larger volume of reimbursed Ig use. (Respectively mean bed size of 778,16, 95%CI 551,98-1004,34, and 394,8 95%CI 305-485). The mean volume of reimbursed Ig use was respectively 38,01kg (95%CI 19,79 - 56,23) and 9,53kg (95%CI 6,03 - 13,02).

The volume of non-reimbursed Ig use in those 19 hospitals was 6831 gr in 2017, 9823 gr in 2018, and 10912 gr in 2019 (increase of 43% in 2018 and 11% in 2019). Therefore, although **most hospitals reported stable non-reimbursed use**, representing **less than 1%** of their total Ig volume dispensed, overall, there is an **increase** in non-reimbursed use during those three years. Given that there is also a rise in Ig volume for reimbursed

indications in the hospitals (5% increase in 2018), there is the perception of a stable proportion non-reimbursed use.

Given the proportion of reimbursed Ig use represented by the responders to our survey in 2018 (52.3% respectively), a crude extrapolation of that number could imply that the non-reimbursed Ig use in all the hospitals could equal 18782gr, around 19kg per year. When we compare this with an annual reimbursed Ig use of 1764kg in the hospitals (RIZIV-INAMI), the non-reimbursed use represents 1.0% in the hospitals. A limitation in this approach is that the extrapolation is based on the proportion of reimbursed use assuming that the distribution of reimbursed and non-reimbursed use in the Belgian hospitals is similar. It is possible that the nonresponding hospitals have a higher or lower non-reimbursed Ig use.

In most hospitals the non-reimbursed use corresponds to a limited amount of patients (less than 10 patients in the timeframe 2017-2019 in 15 hospitals, and only in 4 hospitals this was more than 10).

Most hospital pharmacies indicated that often **the patient pays** the cost for non-reimbursed Ig out-of-pocket. Although they mentioned that this could also be submitted to private additional insurance. Two hospitals also specified that there are foreign patients that do not have a Belgian national insurance and therefore pay the Ig out-of-pocket.

Four hospitals indicated that use of Ig in non-reimbursed indications as part of **clinical studies or medical need programs** is also a possibility and that there were some the last years (e.g. myasthenia gravis crisis and acquired von Willebrand disease[c]) Also the **Special Solidarity Fund** bore the cost for some patients. Three hospitals also referred to the possibility for the prescribing physician to request **'free samples'** from the firms. A prescriber can receive a maximum number of eight samples per medicinal product, per calendar year.[d] The FAMPH is responsible to evaluate this practice and compile every two years statistics.

Supply

Following the supply problems in 2018, mostly due to a **changing Belgian market (the national tender** procedure), some government initiatives were taken in September 2019. RIZIV-INAMI harmonised the reimbursable indications for all the IVIg products (except Octagam 10% which is not reimbursed for streptococcal toxic shock, MMN and CIDP). FAMHP installed a monitoring of IVIg sales figures (only sales figures to the hospitals). Notwithstanding these initiatives, 11 of the 40 responding hospitals indicated that there are still problems in 2020. These shortages appear to have affected most frequently Iqymune® and Multigam® (both from the firm CAF-DCF), although not exclusively. In the national database on unavailability of medicines, Iqymune® appeared several times in 2019/2020. As for Mutigam®, only one package size is left on the market, and the other is taken off the market in 2020. This could indicate that the firm plans to not actively commercialise Multigam®. The other products for which supply problems were noticed by the hospital pharmacies, did not have an official registration of (temporary) unavailability (such as Privigen®, Sandoglobulin®) in the FAMPH database[e].

As a consequence of the national tender, hospital pharmacists indicated that it also takes extra time to monitor the two tender dossiers (both national and commercial) and complicates accounting, e.g. when it are two different firms, or when there is only one firm supplying both the national and commercial part, this means that there could be two different purchasing prices.

The hospital pharmacists gave the following **reasons** for supply problems:

[c] Privigen® for a medical need program - https://www.fagg-afmps.be/nl/MENSELIJK_gebruik/geneesmiddelen/geneesmiddelen/onderzoek_ontwikkeling/gebruik_in_schrijnende_63

[d] BS-MB 11 January 1993 - Royal decree laying down the conditions under which medicines for human use may be handed over in the form of samples.

[e] https://farmastatus.be/human

The fluctuation and **unpredictable** usage in some hospitals. The use can rise as a consequence of better diagnosis and expansion of indications. The firms apply **strict quota** both for the national tender where it is based on RIZIV-INAMI reimbursement numbers of previous years, and for the commercial tender, based on sales data of the previous years. For those hospitals with supply problems, often the forecasted amount of Ig is not adapted to current needs. On the other hand there were also hospital pharmacies that had a surplus, because Ig use decreased (e.g. when a prescribing physician left the hospital). There is the suggestion that there must be the ability to sell to other hospitals and not stock.

On a more **international** level, hospital pharmacies indicate that firms will sell the product in a **market** where the price is higher or where the market is bigger, and these conditions do not apply to the Belgian market.

In Belgium, but also worldwide there is a **limited supply of raw material (blood plasma)** with a slow and lengthy production process which prevents quick corrections, leaving also the firms with tight stocks.

Hospital pharmacists explained that supply problems had important **consequences**:

Supply problems impact the **quality of patient care**, as patients had to switch products, or had to postpone the administration. The Ig products are not always interchangeable, giving sometimes adverse events. In addition, there is also the **administrative burden** (checking stocks, whether the reimbursement criteria are met, contacting firms, and extra communication on product switching to physicians).

Revenues/profits in hospital pharmacies are often a pillar in the general hospital financing[f]. The hospital pharmacy profits depend on the discounts they get from the firms and how this compares to the reimbursement of the NIHDI. For Ig products, most of the time the ex-factory price per gram is the same regardless the package size and place of delivery. An economic margin of 7,11 euro per package is foreseen for the hospital pharmacist when they dispense to patients in day-care and polyclinic use. Both the national tender and the commercial tender of Ig products contribute to a significant proportion of hospital pharmacy profits. For the national tender products, the sales price is 38,05 euro per gram (including VAT), while the reimbursement of RIZIV-INAMI is between 41,77 euro (Sandoglobulin®) and 47,27 euro (Privigen®) per gram, depending on the package size, and depending on whether it is dispensed for ambulatory patients or inpatients. Consequently the revenue for the hospital pharmacy ranges between 3,72 and 9,22 euro per gram. The profits made on products reimbursed via the commercial tender remain confidential as the sales price depends on whether or not discounts were possible. In the event that one firm does not supply the product at the agreed commercial tender price, other firms have to step in, but often without giving a discount, which could **impact the planned pharmacy revenue.**

As a result of the supply problems, some hospitals may **stock products**.

[f] MAHA-report:https://www.belfius.be/about-us/dam/corporate/press-room/press-articles/downloads/nl/2019/Persbericht-StudieMAHA-09102019.pdf