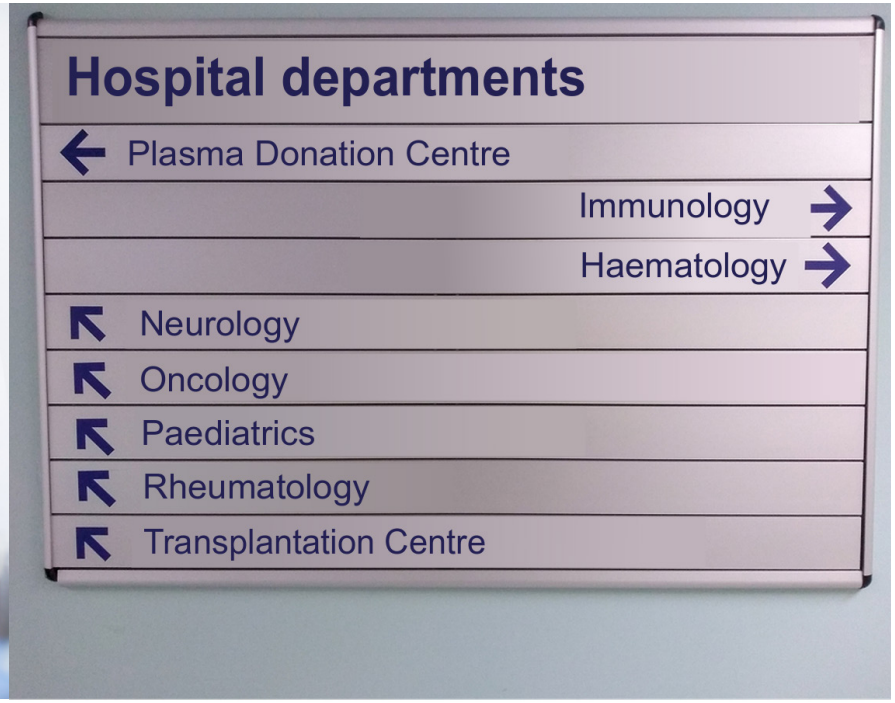
KCE REPORT 336

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



2020

KCE REPORT 336
HEALTH TECHNOLOGY ASSESSMENT

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

CHRISTOPHE DE MEESTER, JOLYCE BOURGEOIS, STEPHAN DEVRIESE, LORENA SAN MIGUEL

2020 www.kce.fgov.be

COLOPHON

Title:	Polyvalent immunoglobulins – Part 2: Use in Belgium
Authors:	Christophe De Meester (KCE), Jolyce Bourgeois (KCE), Stephan Devriese (KCE), Lorena San Miguel (KCE)
Project coordinator:	Nathalie Swartenbroekx (KCE)
Reviewers:	Marie Dauvrin (KCE); Céline Ricour (KCE)
External experts:	Frédéric Baron (CHU Liège); Véronique Bissay (UZ Brussel); Jan De Bleecker (UZ Gent / AZ St. Lucas Hospital); Kristel Claeys (UZ Leuven); Joël Daems (INAMI/RIZIV); Els Devriese (CSL.Behring); Marc Dooms (University Hospitals Leuven/Flemish Society of Hospital Pharmacists); Laure Geslin (FAGG-AFMPS); Filomeen Haerynck (UZ Gent); Ann Janssens (UZ Leuven); Annemie Lesage (FOD Volksgezondheid – SPF Santé Publique); Philippe Lewalle (Instituts Jules Bordet); Isabelle Meyts (UZ Leuven); Jean-Marc Minon (CHR de la Citadelle); Thomas De Rijdt (UZ Leuven / ABPH BVZA); Matthias Wallaert (AZ Delta); Jutte van der Werff ten Bosch (UZ Brussel/ ZNA Paola kinderziekenhuis);
External validators:	Rob Coster (NHS Improvement, England); Jean-Christophe Goffard (Hôpital Erasme, Cliniques universitaires de Bruxelles); Michel Moutschen (CHU Liège)
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
Disclaimer:	• **The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.** • **Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.** • **Finally, this report has been approved by common assent by the Executive Board.** • **Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.**
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/2020/10.273/38
ISSN:	2466-6459
Copyright:	KCE reports are published under a “by/nc/nd” Creative Commons Licence http://kce.fgov.be/content/about-copyrights-for-kce-publications.

How to refer to this document?

De Meester C, Bourgeois J, Devriese S, San Miguel L. Polyvalent immunoglobulins – Part 2: Use in Belgium. Health Technology Assessment (HTA) Brussels: Belgian Health Care Knowledge Centre (KCE). 2020. KCE Reports 336. D/2020/10.273/38.

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

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ANSM	L'Agence nationale de sécurité du médicament et des produits de santé
APB	General Pharmaceutical association
APR-DRG	All Patient Refined Diagnosis Group
ATC	Anatomical Therapeutical Classification
BPIDG	Belgian Primary ImmunoDeficiency Group
BSE	Bovine Spongiform Encephalopathy
BVZA-ABPH	Belgische vereniging van ziekenhuisapotheker - Association Belge de pharmaciens hospitaliers (Belgian Society for Hospital pharmacists)
CADTH	Canadian Agency for Drugs and Technology in Health
CAF- DCF	Central Afdeling voor Fractionering - Département Central de Fractionnement
CAGR	Compound annual growth rate
CHU	Centre Hospitalier Universitaire
CHR	Centre Hospitalier Regional
CI	Confidence Interval
CIDP	Chronic Inflammatory Demyelinating Polyneuropathy
CIVARS	Chapter IV Information Consultation System
CNK	Code nationa(a)l(e) codenummer (for all medicine and parapharmaceutical packages)
DDD	Defined Daily Dose
EMA	European Medicines Agency
EPS	Échantillon permanent-Permanente Steekproef (Permanent Sample isa representative sample of the IMA-AIM database)
ESID	European Society for Immunodeficiencies
FAMHP	Federal Agency for Medicines and Health Products

FPS	Federal Public Service
FNAIT	**Fetal and Neonatal alloimmune thrombocytopenia**
GBS	Guillain-Barré syndrome
GP	General Practitioner
ICD	International Statistical Classification of Diseases and Related Health Problems
Ig	Immunoglobulins
IMA-AIM	Intermutualistisch Agenschap - Agence intermutualiste (Agency assembling all the data of reimbursed medicines and care-acts by the seven insurance companies responsible for the national health insurance)
IPFA	International Plasma and Fractionation Association
IVIg	Intravenous immunoglobulins
KCE	Belgian Health Care Knowledge Centre
KD	Kawasaki Disease
LFB	LFB group is a French biopharmaceutical company
MDC	Major Diagnostic Category
MMN	Multifocal Motor Neuropathy
MZG-RHM	(Minimale Ziekenhuis Gegevens – Résumé Hospitalier Minimum (Minimal Hospital Data)
NGS	Next Generation Sequencing
NHS	National Health Service
NIHDI (RIZIV-INAMI)	National Institute for Health and Disability Insurance (Institut national d'assurance maladie-invalidité - Rijksinstituut voor ziekte- en invaliditeitsverzekering)
NMRC	Neuromuscular Reference Centres
RCT	Randomised Controlled Trial
PID	Primary immunodeficiency

PIT	Primary Immune ThrombocytoPenia
PPTA	Plasma Protein Therapeutics Association
SCIg	Subcutaneous Immunoglobulins
SID	Secondary immunodeficiency
TARDIS	Tool for Administrative Reimbursement Drugs Information Sharing
TCT	Technical Cell – Cellule Technique (database based on coupling of databases)
UK	United Kingdom
USA	United States of America
VAT	Value Added Tax
WHO	World Health Organisation

SCIENTIFIC REPORT

1 INTRODUCTION

1.1 Background

Immunoglobulins (Ig), also called antibodies, naturally circulate in the human blood. They are a part of the humoral immune response towards pathogens such as viruses and bacteria.

Ig, once purified from blood plasma of healthy humans, can also be used as a drug therapy. To obtain an ideal mix of circulating antibodies targeting many different pathogens, Ig are manufactured by fractioning human plasma from a pool of at least a thousand blood donors. Most of the time they are administered intravenously (IVIg), but subcutaneous use (SCIg) is emerging.[1-4] These agents were initially used as replacement therapy for patients with immune defects (primary immune deficiency), who could not adequately produce Ig to combat infections (agammaglobulinemia-hypogammaglobulinemia).[5] Since the 1980's Ig are increasingly linked to anti-inflammatory and immune modulating properties and as a result, they slowly became an important treatment option in a number of inflammatory- and autoimmune, most often rare diseases (such as Guillain Barre Syndrome, Chronic Inflammatory Demyelinating Polyneuropathy,…).[6] The exact working mechanism of Ig is not fully elucidated and therapeutic areas where they are tested are scattered over haematology neurology, dermatology, oncology, rheumatology, paediatrics. However, literature shows that evidence from high quality RCTs remains limited[7]. Although there is some variation between countries and between the various Ig products on the market, Ig are licensed for a limited list of indications (often 6 to 9 indications). Off-label use is not uncommon and appears to be recognised and accepted for some indications. A French study reported off-label use in approximately 30% of treated patients [8] and in England around 20% of patients are treated for off-label indications.[9, 10] Ig are costly medicines, with prices for one administration ranging between €1400 and

€7300[a]. Often, multiple administrations are necessary (mainly on a monthly basis for IVIg and weekly for SCIg). Therefore access to these products is highly dependent on the reimbursement policy of a country. In Belgium off-label use is not generally reimbursed by the NIHDI, although some exceptions are possible (e.g. via the Special Solidarity Fund[b] or Unmet Medical Need Programs[c]).

Worldwide, Ig use grows at an annual rate of approximately 10%.[9, 11-13] The necessary plasma to cover these needs comes, on the one hand, from the in-country (domestic) collected plasma, and on the other hand, from the international market, predominantly from the US, where 5% of the global population provides approximately 70% of the global plasma supply (for more information, see chapter 1.3 on the international market).

The growing list of potential indications, the limited evidence, the increasing use and associated cost, together with the limited supply have encouraged countries to launch initiatives encouraging appropriate use of IVIg/SCIg. Guidelines on indications to help limit non-evidence based use of IVIg/SCIg have been recently developed in collaboration with prescribers and stakeholders in Canada[14], Australia[15] and the UK[16]. In some cases, a priority list of indications to be covered in case of shortages, has been drafted and updated (e.g. in England and France[17]). In England and Australia the 'free' provision to the patient is monitored via a national application system which registers the indications and its justification, and collects some info on outcomes. Those countries have in place a national database (i.e. the National Immunoglobulin Database in England, BloodSTAR in Australia) with information per indication, summarized in annual reports, which can help in forecasting.[10, 18] For more information on these initiatives, see previous KCE report.[7]

1.2 Project scope

The Belgian authorities requested the support of KCE to offer recommendations regarding the indications in which Ig are most effective (KCE report published in February 2020[7]), as well as approximations to the required quantity of Ig needed to respond to patient needs in those indications.

Five research questions were drafted and the analysis was conducted in 2 different phases/reports. In the first phase, captured in a report published in February 2020[7], indications for Ig use were studied, based on a review of the available literature and an international comparison, while this second phase, offers a more detailed data analysis of the Belgian situation/usage of Ig in order to offer an approximation to future needs. Usage and trends are therefore, the main focus of this report.

Project research questions:

- Phase 1: adressed in report 1, published in February 2020[7]
  - Research Question 1: In what indications are intravenous and subcutaneous polyvalent Ig proven to be effective and safe?
  - Research Question 2: Are polyvalent Ig also cost-effective in those indications?
  - Research Question 3: How do the indications reimbursed in Belgium compare to those reimbursed in other countries?

[a] In Belgium, the price of one administration of IVIg (for an average weight of 75 kg), ranges between €1300 and €6600, depending on the dose used (0.4-2g/kg). For SCIg the price is slightly higher ranging from €1400 to €7300. (Prices from www.bcfi.be, consulted in April 2020).

[b] For more information on the Special Solidarity Funds in Belgium: https://www.inami.fgov.be/fr/themes/cout-remboursement/par-mutualite/fonds-solidarite/Pages/default.aspx; or https://www.inami.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/bijzonder-solidariteitsfonds/Paginas/default.aspx.

[c] For more information on Unmet Medical Need Programs in Belgium: https://www.famhp.be/en/human_use/medicines/medicines/research_development/compassionate_use_medical_need

- Phase 2:
  - Research Question 4: What are the most frequent indications for which Ig is used in Belgium?
  - Research Question 5: What is the use/consumption of Ig in Belgium, and what are the possible trends for the coming years?

1.3 International context

1.3.1 Worldwide Ig use

Great variation exists in Ig use between countries, with high users such as USA, Canada or Australia, consuming around 250-300g of Ig per 1000 inhabitants, while European countries report 100 -200 g per 1000 inhabitants. A relatively lower Ig use per 1000 inhabitants is seen in Asian countries such as Japan, China or India (see Figure 1, Figure 2 and Table 1).

Less variation exists in annual growth rates in use. Ig sales grew around 6-10% per year in Canada between the years 2014 and 2018[12], between 7 and 10% per year in Australia over the period 2014-2019[13] and approximately 10% in England in the last years[9, 19]. As we will see later on in this report, similar growth rates have been observed in Belgium.

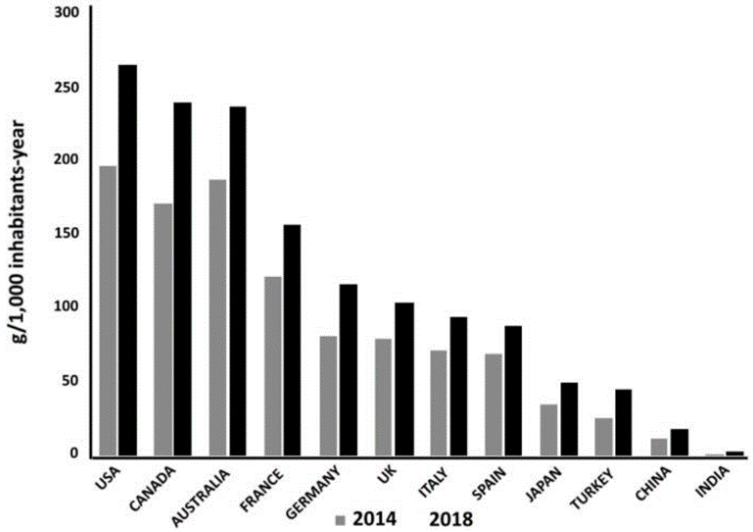
Recent forecasts published in this field, foresee a continuity in global growth for the Ig market in the next years. Thus, for the period 2018-2025, market analyst reports indicate a compound annual growth rate (CAGR) between 6% and 7%.[20-22]

Key drivers for this growth include an aging population, improved diagnostic possibilities (e.g. via innovations such as next generation sequencing - NGS) and the recognition and adoption of Ig as a valuable treatment for several immunological and neurological diseases, including some off-label indications.[21, 22] Innovations aimed at enhancing patients' comfort are also an important factor in this field (e.g. SCIg products that allow patients to follow their treatment at home, appear to be gaining acceptance).[22]

The main barriers for market expansion include the limited supply due to the scarce raw material 'plasma' and the time consuming production (around 7-10 months), and their high cost.[11, 22] Country-specific forecasts based on indication-specific databases show that in Australia, secondary and acquired immunodeficiencies, as well as chronic inflammatory demyelinating polyneuropathy (CIDP), inflammatory myopathies and myasthenia gravis are growing at a rate higher than 10% per year.[18] In England, secondary antibody deficiencies and inflammatory myopathies appear to contribute the most to the current growth in Ig use.[19]

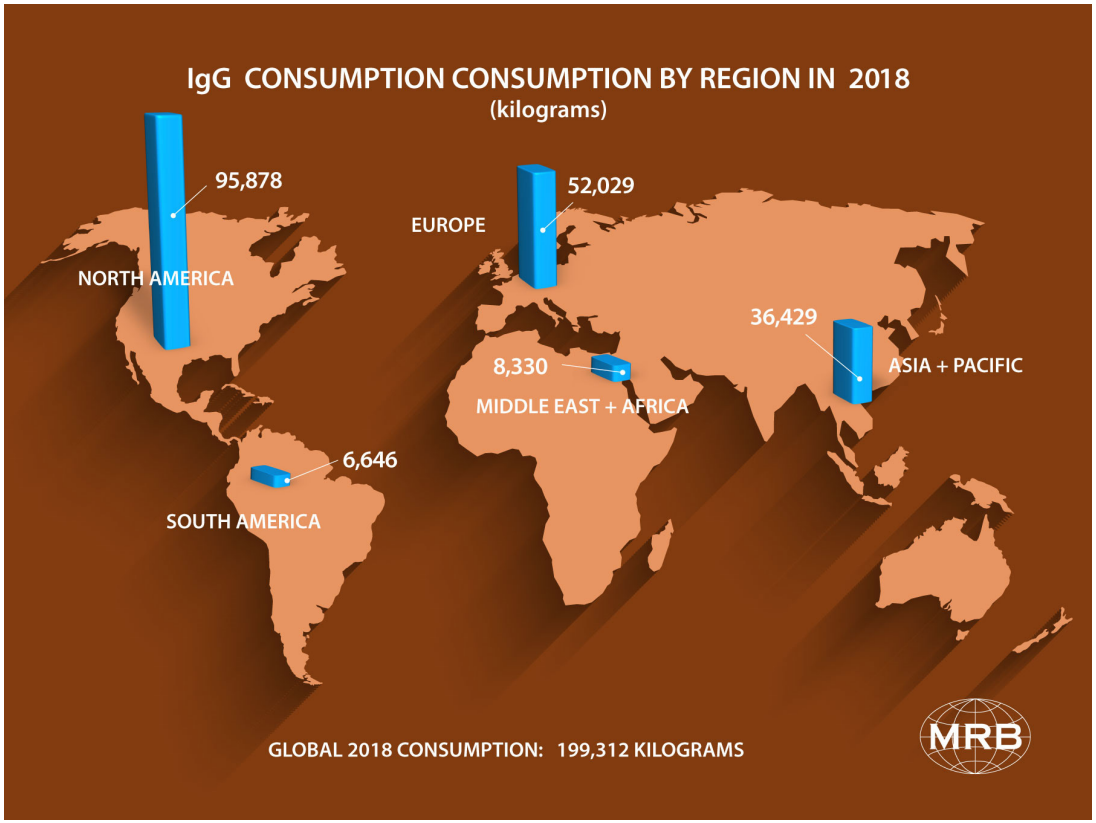
In 2018, the Canadian Agency for Drugs and Technology in Health (CADTH) examined whether there was anything on the horizon which could significantly affect the current demand for Ig (e.g. a sudden reduction in demand due to alternative treatments in certain indications not derived from plasma; or an increase in demand based on evidence that Ig could positively impact a new highly prevalent health condition such as influenza, or Alzheimer's disease). This specific study found no indication that the pattern of growth in demand for Ig would dramatically change over the medium term.[14] However, market analyst reports foresee the possibility of slower growth rates in the future due to new therapies replacing Ig (e.g. for PIT, CIDP,…) and expect an impact of the COVID pandemic on plasma products and plasma supply (see further in this report in section 1.3.4 Market Disruption and in the discussion section Trends).[23]

Figure 1 – Immunoglobulin use (2014 versus 2018) in selected countries



Source: Farrugia et al 2019[24]

Figure 2 – Ig use per continent



Source: Market Research Bureau (personal communication)

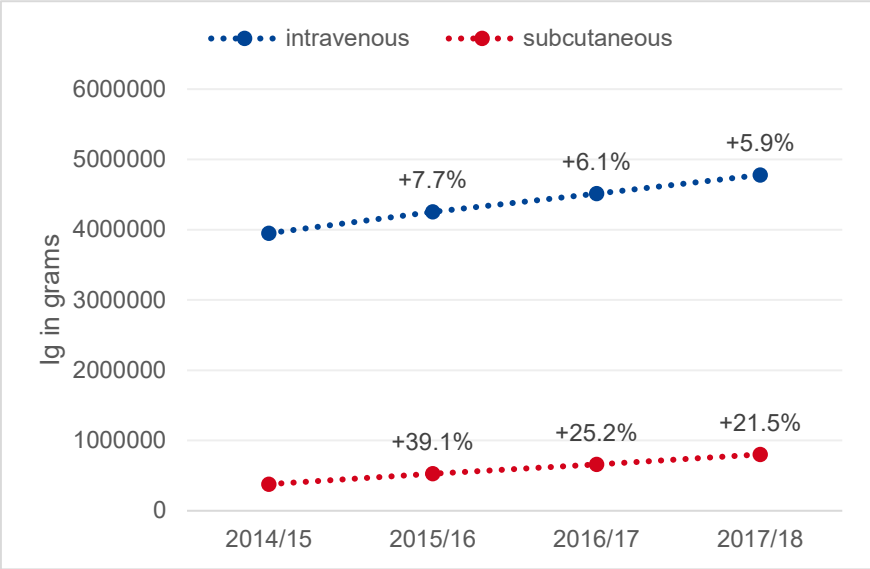
Table 1 – Ig use in selected countries

Country	Volume of Ig in kg (latest available year)*	Use per capita (latest available year)	Self-sufficiency (Ig from nationally collected plasma)
USA	100 522 (2019)[a]	306 g per 1000 population (2019)	100%[a,j]
CANADA (excluding Quebec)	5 580 (2017-2018)[b]	212 g per 1000 population (2018)	<20%[j]
AUSTRALIA	6 570 (2018-2019)[c]	250 g per 1000 population (2019)	around 50%[c]
ENGLAND (not whole UK)	6 746 (2018-2019)[d]	120 g per 1000 population (2018)	0%[d]
GERMANY	9 032 (2017)[e]	109 g per 1000 population (2017)	100%[j]
ITALY	5 500 (2017)[f]	91 g per 1000 population (2017)	77%[f]
FRANCE	8 252 (2019)[g]	127 g per 1000 population (2019)	33%[g]
NETHERLANDS	NA	NA	55%[h]
BELGIUM	2 010 (2018)[i]	175 per 1000 population (2018)	< 50%

**For most countries (USA, UK, Germany, Italy, France) figures are based on volume sold, while for Canada, Australia and Belgium, they represent reimbursed use.[a] The Plasma Protein Therapeutics Association[25]; [b] Canadian Blood Services[26]; [c] Annual report of the Australian National Blood Authority[13]; [d] The NHS England annual database report[10]; [e] The annual report of the Paul Ehrlich Insitute[27]; [f] Farruglia 2019[24]; [g] Personal communication with L'Agence nationale de sécurité du médicament et des produits de santé (ANSM); [h] Personal communication with Sanquin (organisation responsible for blood and plasma collection in the Netherlands)[28]; [i] RIZIV/INAMI (the National Institute for Health and Disability Insurance - NIHDI); [j] Report Protecting Access to immunoglobulins for Canadians[14] NA – Not available*

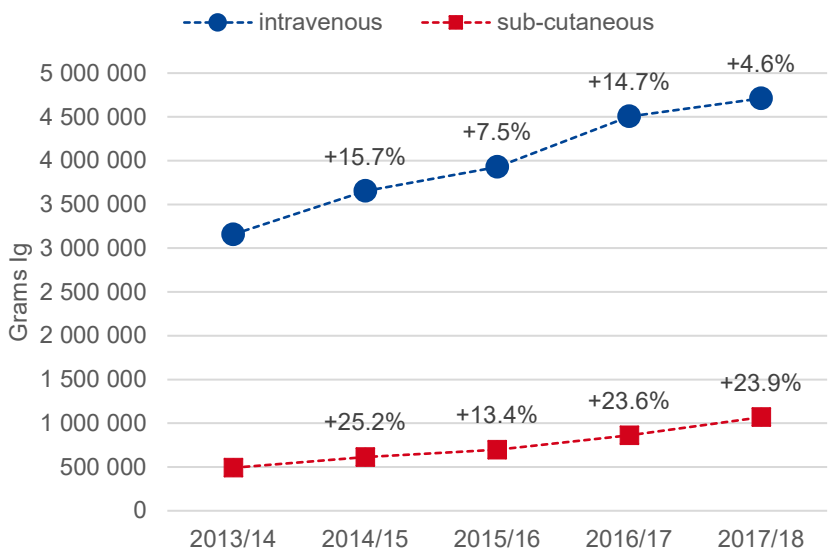
Intravenous infusions represent the most frequent type of administration and are expected to maintain their dominance in the near future. However, although the absolute volume of SCIg administration remains limited, its growth is higher compared to that of IVIg (see Figure 3 and Figure 4). This may be explained by a recent trend towards more home-based Ig administration amongst long-term users, for which SCIg are more appropriate. All economic evaluations identified in the former KCE report show that savings may be made when patients are treated with home-based SCIg instead of hospital-based IVIg. The health care costs associated with SCIg, such as the slightly higher cost per gram, the more frequent need for materials (infusion pump, syringes,…) for weekly SCIg infusions (as opposed to monthly with IVIg), and the home nursing or training/education time, appear to be somewhat lower than the costs of a monthly infusion of IVIg in a hospital setting with the associated overhead and personnel costs.[7] Nevertheless, IVIg and SCIg are not interchangeable for every indication, or every patient. The choice of administration lies with the specialist and patient, and should be based on the health and personal situation of each patient, as well as on studies showing at least non-inferiority for a given disease.

Figure 3 – Growth in Ig use per administration type in Canada*



**Excludes Quebec; Source: Canadian Blood Services[12]; Annual growth rates are shown*

Figure 4 – Growth in Ig use per administration type in England



Source: Annual UK database report [9]; Annual growth rates are shown

1.3.2 Plasma collection and self-sufficiency

As demand for Ig continues to rise, countries are putting into place measures to foresee an adequate and sustainable supply of plasma-derived products. The collection and processing of the source material, human plasma, has to be high enough to cover the existing needs. Ideally, a country strives for self-sufficiency, i.e. collecting enough plasma within the country to produce the necessary volume of Ig that could meet domestic needs. In line with the WHO and EU recommendation,[29, 30] most countries establish a voluntary non-remunerated plasma donation policy. The rationale for this position includes concerns regarding the safety of products made from the plasma of remunerated donors, ethical concerns about the commodification of human plasma, and concerns that compensation for donating plasma would diminish the commitment of volunteer donors. Notwithstanding, this topic is a much debated one, as there exists already some incentives in the voluntary, non-remunerated plasma collection (e.g. refreshments, reimbursement of travel costs and time off work).[31, 32]

Most of the in-country voluntary non-remunerated plasma collection is currently organised via not-for-profit organisations such as the Red Cross.

However, at present most countries which solely focus on non-remunerated plasma donation, depend to some degree on plasma collection from the commercial market (i.e. paid donors). Those commercial plasma donation centres are mainly located in the USA, and are often linked to a fractionator company.[33]

In the EU, commercial plasma collection is limited to a few countries which allow both paid and unpaid collection, such as Germany, Czech Republic, Hungary and Austria.[31] The plasma collection in these countries does not suffice to supply the whole of the European market and therefore, plasma from paid donors in the USA is necessary (around 35%).[34] Nevertheless. these countries allowing both paid and unpaid plasma collection have been reported to have reached self-sufficiency for plasma derived products.[14] The UK is fully dependent on imported plasma, due to the advent of the bovine spongiform encephalopathy (BSE) epidemic and variant Creutzfeldt–Jakob disease transmission, after which it was decided not to use UK plasma for the production of plasma derived products.[35] Canada collects less than 20% of their domestic plasma requirements, and depends heavily on plasma collected in the USA.[14] In Australia less than half (48%) of their domestic Ig requirements are produced from Australian blood/plasma.[13] In Italy, the self-sufficiency is relatively high, at 73% in 2017.[24] In France, 33% of the Ig sold in France are based on Ig products produced from domestically collected plasma.[d] Finally, in the Netherlands, around 55% of the plasma products, including Ig, comes from domestic plasma.[28]

To meet the expected Ig needs, both the International Plasma and Fractionation Association (IPFA) representing the non-profit sector, and the Plasma Protein Therapeutics Association (PPTA) representing the private plasma collectors and fractionators, encourage the donation of blood/plasma. To increase self-sufficiency in the long-term, the national collection of plasma donations has to increase.[31] Next to the volume of plasma collected, the fractionated amount of Ig is determined by the yield of Ig over manufacture. Large scale manufacture generally improves yields. Current modern manufacture reports Ig yields of 4.7 g/L plasma (4.8g/l for IVIg and 4.5g/l for SCIg).[24, 36] Plasma with high mean protein content can lead to higher yields, which in turn is a result of the restricted frequency of donations.[37]

In the context of these limited self-sufficiency, national arrangements have been put in place to ensure that the collected plasma is exclusively fractionated by an assigned, often local, plasma fractionator. Although there are still a few countries that have their own state-owned fractionator (such as LFB in France), this phenomenon is disappearing and national contracts are being signed with privately owned companies (CSL Behring, Grifols…) for the fractionation of the domestic plasma.

[d] Based on personal communication with L'Agence nationale de sécurité du médicament et des produits de santé (ANSM)

1.3.3 Contracting and pricing

As previously explained, the current **lack of self-sufficiency** in most countries make it necessary for them to import non-domestic Ig. There is therefore, a high **dependency on the international marke**t. Very often, countries have specific contracts in place for the fractionation of nationally collected plasma into Ig, as well as contracts for the non-domestic Ig. For example in Australia, the National blood Authority signed a contract with one fractionator for the domestic plasma (CSL Behring), while they contracted with two fractionators for the imported plasma (CSL Behring and Grifols), in order to cover for additional needs.[36] In some countries the purchase and supply of Ig is organised nationally (e.g. England, Australia, Canada).

In England, all plasma is imported and a national framework agreement is in place with eight suppliers offering, 14 different products overall.[9]

Countries apply strategic procurement processes to both protect themselves against dependency on one supplier and mitigate the risk of local production problems, which could cause product shortages.[14] Moreover, competition among companies has resulted in higher Ig yields, an increase portfolio of medicines, and a decrease in price due to fractionation, which in turn, improves a country's situation with regard to their national program for self-sufficiency in plasma-derived medicinal products.[37]

Prices vary between countries depending on the origin and price of collected plasma (domestic plasma or imported plasma) and the size of the market. When domestic plasma is processed, often specific contracts with fractionators are in place, taking into consideration the price paid by fractionating companies for the domestic plasma. Because almost every country depends to a certain extent on Ig produced from imported plasma, the price of commercial Ig is easier to compare between countries. By default, bigger markets can negotiate lower prices.[24] Thus, in 2019, the latest year for which data were available, the ex-factory prices (excl. VAT) for one gram of Ig from imported plasma ranged from a low of around €27 for IVIg, to a high of €37 for SCIg in Australia[e]. In the Netherlands, these prices of commercial products vary from €70 to €80,[f] and in England, these were mentioned to be around GBP34 per gram (≈ €38 gram) In their 2018-2019 annual report.[10] Nevertheless, these prices appear to have increased in the meantime reaching GBP45 (≈ €50) and are expected to rise again in 2021, as a result of the voluntary scheme for branded medicines pricing and access.[g] In France the ex-factory price per gram is the same for all Ig products sharing the same type of administration. Thus, for IVIg, this was €39 in 2019, and for SCIg €45.[38] In Belgium ex-factory prices have been, up to recently, relatively stable, with some small variations between products (from €42 for IVIg to €44 per gram for SCIg). However, these prices are subject to market forces, and in 2020 some product-specific price increases were implemented or pending[h].

Price negotiations and rebates in the hospitals are common practice, while these are less common outside the hospital setting (e.g. community pharmacy). In the Netherlands, recent plans have been made to limit the distribution of all Ig products to the hospital sector in order to enhance price competition, and curb the growth of Ig costs.[39]

A treatment with Ig is weight-based requiring several grams of Ig with prices varying between €1300 and €7300 for one administration[i], which makes

---

e 45 Australian dollar per gram

f Source: Farmakotherapeutisch kompas 2020- Prices reflect averages determined for medicines with the same active ingredient. Personal communication with the Ministry of Health, Welfare and Sport, indicated that important discounts are obtained on ex-factory prices in the hospital setting.

g Personal communication with a UK expert. For more information on the voluntary scheme for branded medicines pricing and access see: https://www.gov.uk/government/publications/voluntary-scheme-for-branded-medicines-pricing-and-access

h Personal communication with industry representatives, and country experts.

i In Belgium, the price of one administration for IVIg (for an average weight of 75Kg), ranges between €1300 and €6600, depending on the dose used (0.4-2g/kg). For SCIg the price is slightly higher ranging from a €1400 to €7300. (Prices from www.bcfi.be, consulted in April 2020).

patients rely on reimbursement in order to be able to afford Ig treatment, especially in cases where long-term treatment is necessary. Therefore, access to Ig remains highly dependent on the reimbursement policy of a country[11].

1.3.4 Market disruptions

When an Ig product is 'unavailable' or there is "restricted availability', or a 'shortage', pharmacists may not be able to distribute the prescribed Ig to the patient, or physicians may have to substitute, or sometimes even delay treatment or reduce doses. All of these situations may have an impact on patient care and raise important ethical considerations.[40]

In recent years, several countries experienced some supply problems for one or more IVIg or SCIg products.[10, 24, 40, 41] Worldwide, the provision of Ig is unstable. Firstly, the supply of plasma is limited. Secondly, Ig are complex biological products with production time of approximately 7 to 10 months, which can be subject to unexpected manufacturing problems or recalls.[42] Thirdly, the contracts with countries are based on forecasts, allocating a specific amount of product to that country; and therefore, when demand increases either because there are more patients requiring Ig treatment, or to make up for a product shortage, re-allocating product or increasing stock is challenging. Fourthly, manufacturers allocate their products to specific countries according to the price obtained in that market i.e. the product follows the price. This results in higher priced markets receiving preferential allocation.[24] Consulted Belgian hospital pharmacists also indicated 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. Manufacturers highlight that changes in national conditions, e.g. in reimbursement, often require them to adapt and reallocate the limited supply.[31]

In order to mitigate supply problems countries are encouraged to ensure and maintain a range of manufacturing and supplying options, and avoid focusing on only one Ig product (one contract).[14, 40, 43] Belgium has not been exempt from these product shortages, which appear to continue in the present year. More details on the Belgian situation will be offered in section 1.4 of this report.

The COVID-19 crisis is also affecting the plasma collection, mainly in the USA, which is the main exporting country. The additional need for plasma for the treatment of COVID-19 patients (convalescent plasma, hyper immune Ig derived from convalescent plasma and polyvalent IVIg) puts extra pressure on an already strained system.[44] As a result, shortages have been notified.[45]

1.4 Belgian context

Belgium is no exception and faces similar challenges to those previously described, with the collected in-country plasma not being sufficient to cover Belgian Ig needs. Since Ig are sometimes the only possible treatment for serious (sometimes life-threatening) illnesses, ensuring an adequate supply in this country is of great interest to the Belgian Health authorities. In 2014 the 'Law of 5 July 1994 on blood and blood derivatives of human origin' was updated with an article 20/1 on the self-sufficiency of plasma derivatives, including a tender procedure for fractionating the national collected plasma, and securing a national strategic stock.[46]

In 2018, a public contract was awarded for four years to a company that purchases Belgian plasma, and processes it into blood derivatives such as albumin and Ig.[47] The supply for intravenous Ig (IVIg) is expected to reach around 50% with the Belgian collected plasma. Belgian hospitals are obliged to purchase 50% of their IVIg needs via the national tender contract at a price of €38.05 per gram (VAT included). This volume is determined on the basis of reimbursed IVIg use (NIHDI data) from previous years. The FPS Public Health established a monthly monitoring of the tender procedure to follow how much Belgian plasma is being processed, and whether or not Belgian hospitals reach the 50%. The remaining 50% IVIg is contracted directly by hospitals and processed from plasma from other countries (via commercial tenders). This means that for this commercial part of IVIg, and for the total quantity of SCIg (for which no national tender is currently in place) there is high dependency on the international market.

Immunoglobulin products in Belgium are licensed to be distributed to the patient under 'restricted prescription'. For IVIg products, the distribution is restricted to the hospital setting, because the need for specific equipment and personnel for intravenous administration. SCIg products may be dispensed in a pharmacy open to the public, but the first medical prescription must be written and signed by a specialist.[48]

Reimbursement of Ig in Belgium is limited to 8 indications alongside specific requirements/criteria per indication (diagnosis, severity of illness, treatment period) (see Table 2). It is important to note that when reimbursement is approved by the National Health Insurance, no patient co-payment is necessary and that the compulsory social health insurance system in Belgium is characterised by coverage of nearly the entire population for a wide range of services. Therefore, inequalities in access to these products due to socioeconomic aspects, is likely to be very limited in those indications in which reimbursement is granted. However, only licensed indications (authorized by the EMA or the national agency FAMHP) are considered for reimbursement, and therefore, inequalities in access are more likely in off label use. Some limited funding for off-label indications is possible via an Unmet-Medical Need program or the Special Solidarity Fund, in which a commission decides on possible reimbursement for individual cases. However, even in this case, accessibility is not evident as administrative and financial barriers exist (e.g. for the Special Solidarity Fund, reimbursement is limited to 75% of the cost, with a ceiling of 1250 euro per year for adult, and the generally patient needs to pay first the treatment before reimbursement can be requested (see KCE report 327 for more details[7]). A Belgian study published in 2011 found off-label use to account for 46% of all patients treated with IVIg in the year 2007, although the methodological limitations of such study (recognised by the author) may have resulted in an overestimation.[49]

In Belgium, supply problems became more frequent since 2018 and were at that time, mostly thought to be caused by the changing Belgian market (following the introduction of the national tender procedure). Data on temporary unavailability of Ig products is available for consultation on the FAMHP website[j] where firms should report when their product cannot be supplied within three working days.[50] An overview of these data is presented in Appendix 1. In response to the supply problems observed in 2018, some government initiatives were introduced in 2019. A task force with physicians, hospital pharmacists and authorities was set up to formulate recommendations in case of shortages, i.e. to switch to SCIg when clinically possible, to prescribe rationally and only within the reimbursable indications and, specifically for hospital pharmacist, not to engage in unnecessary stocking.[51] In addition to this, reimbursement criteria were harmonized (for all IVIg products except Octagam 10% and the small packages of Nanogam® which are at present not reimbursed for streptococcal toxic shock, MMN and CIDP), allowing greater flexibility between the different brands for the 8 defined reimbursed indications (e.g. physicians can switch medication to another brand when stock ruptures occur).[52] Nevertheless, the experts consulted throughout this project, raised some concerns regarding the practical interchangeability of products, in this field, which could in some cases, be inappropriate and result in tolerability problems and inadequate treatment quality for certain patients (in particular those suffering from chronic conditions such as PID).The Federal Agency for Medicines and Health Products (FAMHP) established a system to monitor IVIg sales figures (limited to the hospital setting) of the three firms on the market selling IVIg products.

The experts consulted throughout this project indicated that shortage problems appear to continue in 2020, mainly affecting Iqymune® and Multigam® (both from the firm CAF-DCF), although not exclusively. In the national database on unavailable medicines, Iqymune® appeared several times in the period 2019/2020. As for Mutigam®, only one package size is available since March 2020. This could indicate that the firm is no longer actively commercialising Multigam®. Other products for which supply problems were noticed by hospital pharmacists, did not have an official registration of (temporary) unavailability in the FAMPH database (i.e. Privigen®, Sandoglobulin®). These temporal shortages are often a

j https://farmastatus.be/human

consequence of the strict quota/supply systems currently in place, often based on sales data from the previous years. While most of the time this gives rise to temporary supply problems, surpluses may also be possible (e.g. when a high prescriber physician leaves a hospital). A solution to this was thought to be the allowance for hospitals to re-distribute any surpluses to other hospitals in order to collaborate and avoid product stocking. Overall, hospitals pharmacists considered this lack of flexibility as an important limitation that could have a negative effect on patients' care. Thus, supply problems may impact the quality of patient care, when patients have to switch products, or postpone treatment administration. In addition, there is also the administrative burden that comes in these situations (e.g. checking available stocks, whether the reimbursement criteria are met, contacting firms, and extra communication on product availability or specifications).

To facilitate a more evidence-based practice approach in Belgium, a KCE report was already published on this subject in 2009 (KCE report 120B).[32] Similarly, recommendations by the Superior Health Council were drafted in 2010 highlighting the most appropriate indications for Ig use.[53] Consequently, some changes were made to the list of reimbursed conditions issued in January 2014, as well as in April 2017, and more recently in September 2019 (more details in KCE report 327)[7].

Table 2 – Reimbursed indications for immunoglobulin use (IVIg and SCIg) in Belgium

Reimbursed indication	Condition/ prerequisite	Validity	Product
Primary immunodeficiency syndromes (PID) **a) congenital antibody defects or combined T- and B-cell defects resulting in antibody deficiency[1]** **b) congenital Specific Polysaccharide Antibody Deficiency** **+** **recurrent clinically significant infections for which antibiotics were indicated**	1. Specialist documents laboratory results 2. Diagnosis confirmed by a doctor from BPIDG[2] 3. Specialist completes reimbursement request form[3] 4. Documentation[4] of therapy efficiency	12 months, after which clinical re-evaluation needs to be done by a doctor from BPIDG[2]	INTRAVENOUS: Iqymune ® , Multigam ®, Nanogam ®, Octagam ®, Panzyga ®[8], Privigen ®, Sandoglobuline ® SUBCUTANEOUS: Gammanorm ®, Hizentra ®
Secundary hypogammaglobulinemia due to **a) B cell malignancy (cancer) such as Multiple Myeloma or Chronic lymphocytic leukemia** **b) iatrogenic B cell deficiencies due to chemotherapy, or monoclonal antibodies** **c) allogenic or autologous hematopoietic stem cell transplantation** **+** **recurrent clinically significant infections for which antibiotics were indicated**	1. Specialist documents diagnosis 2. Specialist completes reimbursement request form[3]	12 months	INTRAVENOUS: Iqymune ® , Multigam ®, Nanogam ®, Octagam ®, Panzyga ®[8], Privigen ®, Sandoglobuline ® SUBCUTANEOUS: Gammanorm ®[7], Hizentra ®[7]
Primary thrombocytopenic purpura (PIT)		12 months	INTRAVENOUS: Iqymune ® , Multigam ®,

Reimbursed indication	Condition/ prerequisite	Validity	Product
+ **serious bleeding or risk of bleeding**	1. Specialist documents diagnosis 2. Specialist completes reimbursement request form[3]		Nanogam ®, Octagam ®, Panzyga ®[8], Privigen ®, Sandoglobuline ®
Kawasaki disease			
Syndrome Guillain Barre **+** **progressive muscle weakness/symptomatology (GBS DS)[5]**	1. Diagnosis confirmed by lumbar puncture 2. (Paediatric) neurologist or neuropsychiatrist completes reimbursement request form[3] and must prescribe the Ig		
Invasive streptococcal group A infection (streptococcal toxic shock syndrome)	1. Specialist documents diagnosis 2. Specialist completes reimbursement request form[3]	12 months	INTRAVENOUS: Iqymune ® , Multigam ®, Nanogam ®[9], Octagam ®[9], , Privigen ®, Sandoglobuline ®
Multifocal motor neuropathy (MMN) **+** **distortion daily functioning**	1. Diagnosis made in a neuromuscular reference center[6], including an electromyographic examination 2. Neurologist or neuropsychiatrist completes reimbursement request form[3]	6 months dosis max 2g/kg/3 weeks	INTRAVENOUS: Iqymune ® , Multigam ®, Nanogam ®[9], Octagam 5%®[9], Panzyga ®, Privigen ®, Sandoglobuline ®
Chronic Inflammatory Demyelinating polyradiculopathy (CIDP) **+** **distortion daily functioning** **+** **contra-indication or ineffectiveness of oral corticoid treatment**			SUBCUTANEOUS Hizentra® only as a maintenance treatment for CIDP

1: for PID, more diagnostic specifications are mentioned in the reimbursement criteria; 2: BPIDG = 'The Belgian primary immunodeficiency group' 3: For IV preparations: the reimbursement request form must be sent to the hospital pharmacy, where it is kept for the insurance doctor. For SCIg preparations: the reimbursement request form must be sent to the advisory physician from the sickness funds who issues an authorization 4: Documentation means that the physician must make a detailed report, showing that the therapy has been effective and that treatment continuation is necessary. This report must be added to the patient's medical file. 5: GBS DS: Guillain-Barre Syndrome Disability Score; a score ranging from 0 "healthy" to 6 "dead" and for which a score of ≥ 3 or a clear negative progression justifies Immunoglobulin use 6: Diagnostic criteria following the most recent guidelines of the 'European Federation of Neurological Societies'; 7: Gammanorm and Hizentra are not reimbursed for SID in case of a hematopoietic stem cell transplantation 8: Panzyga® is reimbursed for these indications but is not commercially available in Belgium;9 Octagam® 10% and the small packages of Nanogam® are not reimbursed for streptococcal toxic shock, MMN and CIDP.

Source: website of the National Institute for Health and Disability Insurance (NIHDI-RIZIV-INAMI) [52]- consulted and up to date September 2020

2 THE USE OF IMMUNOGLOBULINS IN BELGIUM

2.1 Background

This chapter aims at describing the quantities of Ig used in Belgium, how they are used (indications, doses, length of treatment), and the existing trends in consumption. This analysis will be used as input for the next phase, where 'future needs' i.e. the quantities of Ig that would be required to treat the main indications are estimated (see Chapter 3).

2.2 Methods

2.2.1 Overview of data sources consulted

No single data set containing all relevant data on patients receiving Ig treatment exists to this date in Belgium. Therefore, multiple data sources were consulted in order to offer a more complete picture. Most of the available data sources cover only reimbursed Ig use. For info on non-reimbursed or off-label use, a survey was conducted and input from experts was requested. The analysis on indications was performed via the proxy of ICD diagnostic codes (see 2.2.3.3). However these data were only centrally available for the hospital setting. Therefore it was not possible to analyse indications in the ambulatory setting Table 3 provides an overview of the data sources consulted, but details per source are described in the relevant sections of this report.

Table 3 – Overview of data sources

Type of data	Data source	Coverage	Period analysed	Setting
Sales data	Manufacturers	Global figures	2017-2019	Hospital and community
Public expenditure	RIZIV/INAMI	Reimbursed only	2010-2018	Hospital and community
Global consumption	RIZIV/INAMI	Reimbursed only	2010-2018	Hospital and community
	Hospital survey	Non-reimbursed	2017-2019	Hospital only
Consumption/product	RIZIV/INAMI	Reimbursed only	2010-2018	Hospital and community
Consumption/indication	TCT	Reimbursed only	2012-2018	Hospital only
Consumption/prescriber type	IMA data	Reimbursed only	2010-2018	Hospital and community
Consumption/type of hospital	TCT	Reimbursed only	2012-2018	Hospital only
Frequency of hospitalisations/indication	TCT	Reimbursed only	2012-2018	Hospital only
Mean dosage used/indication	TCT	Reimbursed only	2012-2018	Hospital only
Data on patient characteristics	IMA data	Reimbursed only	2010-2018	Hospital and community
Public price of Ig	RIZIV/INAMI	Reimbursed only	2010-2018	Hospital and community

2.2.2 Industry Sales data

In order to have a more general overview of Ig use in Belgium, companies with products on the Belgian market were contacted and asked to provide their sales data for the years 2017, 2018 and 2019. The FAMHP, who receive data on IVIg sales to hospitals as part of a monitoring system, was also contacted.

2.2.3 Data on Reimbursed Ig

2.2.3.1 INAMI - RIZIV aggregated data on Ig

The INAMI – RIZIV, National Institute for Health and Disability Insurance (Institut national d'assurance maladie-invalidité - Rijksinstituut voor ziekte- en invaliditeitsverzekering), is a public social security institution that manages and supervises the compulsory health care and benefits insurance in Belgium.

The INAMI – RIZIV provided KCE aggregated data per year of reimbursed drugs, dispensed in hospital and in community pharmacies, grouped by package code (CNK codes)[k]. These data show the annual expenditure for the health insurance and the number of reimbursed packages in Belgium. Data cover the period 2010-2018 for hospital pharmacies, and 2005-2018 for community pharmacies (analysis from 2010 to 2018 because of the completeness of data for this period). Extrapolations for the first semester of 2019 are available, and were used only for the purpose of analysing trends in use.

2.2.3.2 IMA – AIM

In Belgium, residents, must in principle, have a compulsory health insurance provided through one of the seven national sickness funds and funded by social security contributions. Healthcare reimbursement data are available at IMA – AIM (Intermutualistisch Agentschap – Agence Intermutualiste). IMA – AIM is a non-profit organisation that manages and analyses information on all reimbursements related to the compulsory health insurance, collected by the Belgian sickness funds. These data cover all reimbursed services, both ambulatory and in hospital (consultations, pharmaceuticals, diagnostic and therapeutic procedures), and some patient socio-demographic and socio-economic characteristics.

For the present study, data were selected according to the ATC codes (J06BA01 and J06BA02) in order to identify patients treated with Ig. Demographic characteristics, prescriber, Ig related data (date of administration, type of Ig, dose ...) and cost data were retrieved. Given the fact that these data only cover reimbursed use and that inequalities in access to these treatments when reimbursed are unlikely, a decision was made not to extract and analyse socio-economic characteristics (out of scope). The analysis here presented covered the period 2010-2018.

Selection of data

All available Ig product packages (CNK codes) with either the ATC code J06BA01 (Subcutaneous) or J06BA02 (Intravenous) were selected (see Table 4). A detailed table listing all available packaging sizes with prices is presented in appendix table 6).

[k] Code National(e) Kode: administrative identification number per medicine per packaging

Table 4 – Evolution of Ig product availability in Belgium

Name of the product	Packages- size (expressed in gram) *	Manufacturer	Reimbursed since	Years available in the market
SUBCUTANEOUS PRODUCTS				
Subcuvia	0,8g; 1,6g	Baxter	1/09/2005	2005-2013
Vivaglobin	1,6g	CSL Behring	1/09/2006	2006-2015
Gammanorm 16,5%	0,99g; 1,65g; 3,3g	Octapharma Benelux	1/12/2010 for 1.65g; 1/01/2017	2010-current*
Hizentra 20%	1g; 2g; 4g	CSL Behring	1/03/2012	2012- current
INTRAVENOUS PRODUCTS				
Gammagard	2,5g ; 4,8g; 9,6g	Baxter	1/09/1997	1997-2012*
Kiovig	1g; 2,5g; 5g; 10g; 20g, 30g	Baxter	1/09/2010; 1/11/2011 for 30g	2010-2014*
Multigam 5%	1g; 2,5g; 5g; 10g	C.A.F.-D.C.F.	1/02/2003	2003- current *
Multigam 10%	5g; 10g; 20g	C.A.F.-D.C.F.	1/06/2016	2016- 2019
Nanogam 5%	1g; 2,5g; 5g; 10g, 20g	C.A.F.-D.C.F.	1/06/2008	2008- current *
Privigen 10%	2,5g; 5g; 10g; 20g	CSL Behring	1/05/2011	2011- current
Sandoglobuline	1g, 3g, 6g	CSL Behring	1/02/1988; 1/11/1991 for 1g	1988- current *
Octagam 5%	2,5g; 5g; 10g	Octapharma Benelux	1/07/1998	1998- current
Octagam 10%	2g; 5g; 10g; 20g	Octapharma Benelux	1/09/2010	2010- current
Panzyga 10%	1g; 2,5g; 5g; 6g; 10g; 20g; 30g	Octapharma Benelux	1/09/2017	2017- 2019**
Iqymune 10%	2g; 5g; 10g; 20g	LFB Biomedicaments	1/04/2018	2018- current*

**Not all package sizes were introduced at the same time; Over the years, different products, or package sizes experienced stock ruptures (e.g. since 2019, different packages for Multigam® 5% and Iqymune®), and/or disappeared from the market (e.g. Multigam 10% in 2019); ** Panzyga® was never commercialised and since January 2020 it was withdrawn from the market)*

Source: INAMI-RIZIV website https://ondpanon.riziv.fgov.be/SSPWebApplicationPublic/nl/Public/ProductSearch (Accessed 11 May 2020) for available products and packages, and INAMI-RIZIV aggregated reimbursement data

2.2.3.3 *Technical Cell – Cellule Technique*

The "Technical Cell – Cellule Technique" (https://tct.fgov.be) created in the Law of 29 April 1996, is a common service of the RIZIV–INAMI and FPS Public Health. Its mission is to collect, link, validate and anonymize data relating to hospitals. The TCT links the Minimal Hospital Data (MZG-RHM) to the Sickness Funds hospital reimbursement data, to facilitate the study of relationships between health care insurance expenditure and the treated conditions, and the elaboration of financing rules, accreditation standards and quality conditions.

Belgian general hospitals are required to provide twice a year, a minimal data set on the administrative, medical and nursing characteristics of both inpatient and day-care stays called MZG-RHM. The data collection serves two general purposes: a) support government health policy on health care needs, epidemiology, quality of care, and financing of hospital provisions; b) support the health policy of hospitals by providing individual hospital feedback.

The MZG-RHM data collection contains information per hospital stay on several domains: medical, administrative, nursing and staffing.

For the present study, this source was used to get more detailed patient related information on the use of Ig in the hospital setting, whether it was used in day care or during a hospitalisation (inpatient) as well as information on duration of treatment. All stays having at least one CNK code for the ATC codes J06BA01 and J06BA02 were selected in order to only consider patients with Ig consumption from 2012 to 2018. Some patients had multiple stays. Demographic characteristic, Major Diagnostic Category (MDC), All Patient Refined Diagnosis Group (APR-DRG) severity of illness of the hospital stay, Ig related data (date of administration, type of Ig, dose ...) and cost data were retrieved from the TCT data.

Analysis per proxy indication:

The TCT data do not contain the indication for which reimbursed pharmaceutical products are prescribed. However, to be able to approximate possible indications, the diagnoses available for the hospital stay were cross-matched to the indications identified in our literature review.[7] We consider these diagnoses as a proxy indication. This approach has its limits, but in the absence of detailed indication-specific data, it offers an approximation to the types of pathologies for which Ig is most commonly prescribed.

To identify the indications for which Ig is used, both principal and secondary diagnoses[l] were considered. In the TCT data (2012-2014), the ICD-9-CM (International Classification of Diseases-9th Revision-Clinical Modification) diagnostic codes are used, while a move to using ICD-10-BE (International Classification of Diseases-10th Revision-Belgium) diagnostic codes was implemented from 2016 onwards.

Based on a systematic literature review performed on the clinical and economic value of Ig (presented in the previous KCE report[7]), a list of potentially interesting indications for Ig use in Belgium was drafted. This list was reviewed by clinical experts and one additional indication (ie. Antibody-mediated types of encephalitis) was included. The consulted codes for these indications, are listed in Table 5.

[l] The principal diagnosis is defined as the condition, after study, which caused the admission to the hospital. This is not necessarily what brought the patient to the emergency room. Secondary diagnoses are the conditions that coexist at the time of admission, that develop subsequently, or that affect the treatment received and/or length of stay.

Table 5 – ICD-9-CM and ICD-10-BE procedure and diagnostic codes used to identify indications for which Ig is used in Belgium

Indication	ICD-9-CM		ICD-10-BE	
OFFICIALLY REIMBURSED INDICATIONS IN BELGIUM				
1. Primary Immunodeficiency (PID)	2790	Deficiency of humoral immunity	D80	Immunodeficiency with predominantly antibody defects
	2791	Deficiency of cell-mediated immunity	D81	Combined immunodeficiencies
	2792	Combined immunity deficiency	D82	Immunodeficiency associated with other major defects
	2793	Unspecified immunity deficiency	D83	Common variable immunodeficiency
	2798	Other specified disorders involving the immune mechanism	D84	Other immunodeficiencies
	2799	Unspecified disorder of immune mechanism		
2. Secondary Immunodeficiency (SID): -Multiple Myeloma (Kahler's disease) -Chronic Lymphatic leukaemia - B cell malignancies with Bcell depletion due to chemo or monoclonal antibodies -(Allogenic) stem cell transplantation/ hematopoietic stem cell transplantation	2030	Multiple myeloma	C900	Multiple myeloma
	2041	Lymphoid leukaemia chronic	C911	Chronic lymphocytic leukaemia of B-cell type
	99685	Complications of transplanted Bone marrow	T860	Complications of bone marrow transplant
	99688	Complications of transplanted Stem cells	T865	Complications of stem cell transplant
	V4281	Organ or Tissue replaced by transplant: Bone marrow	Z9484	Stem cells transplant status
	V4282	Organ or Tissue replaced by transplant: Peripheral stem cells	Z9481	Bone marrow transplant status
			T8603	Bone marrow transplant infection
	201	Hodgkin lymphoma	C81	Hodgkin lymphoma
	2020	nodular lymphoma	C82	follicular lymphoma
	2004	mantle cell	C83	Non-follicular lymphoma
	2007	Large cell lymphoma	C85	Other specified and unspecified types of non-Hodgkin lymphoma
	2001	Lymphosarcoma	C88	Malignant immunoproliferative diseases and certain other B-cell lymphomas

		2002	Burkitt lymphoma	C901	malignant plasma cell neoplasms
		2005	Primary central nervous system lymphoma	C902	Extramedullary plasmacytoma
		2008	other named variants/other specified malignant tumours of lymphatic tissue	C903	Solitary plasmacytoma
		2733	Macroglobulinemia waldenstrom	C910	Acute lymphoblastic leukaemia
		2003	Marginal zone lymphoma	C913	Prolymphocytic leukaemia of B-cell type
		2031	malignant plasma cell neoplasms	C914	Hairy cell leukaemia
		2038	Other immunoproliferative neoplasms	C919	Lymphoid leukaemia, unspecified
		2040	Acute lymphoblastic leukaemia		
		2042	Subacute lymphoblastic leukaemia		
		2048	Other lymphoblastic leukaemia		
		2049	Unspecified lymphoblastic leukaemia		
		2024	Leukemic reticuloendotheliosis (hairy cell)		
		2028	Other lymphomas		
		2029	Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue		
3.	**Primary immune thrombocytopenia (PIT)**	28731	Immune thrombocytopenic purpura	D693	Immune thrombocytopenic purpura
4.	**Chronic inflammatory demyelinating polyneuritis (CIDP)**	35781	Chronic inflammatory demyelinating polyneuritis	G6181	Chronic inflammatory demyelinating polyneuritis
5.	**Guillain-Barré Syndrome**	3570	Acute infective polyneuritis	G610	Guillain-Barre syndrome
6.	**Kawasaki Disease**	4461	Acute febrile mucocutaneous lymph node syndrome [MCLS]	M303	Mucocutaneous lymph node syndrome [Kawasaki]
7.	**Multifocal Motor Neuropathy**	35789	Other inflammatory and toxic neuropathy	G6182	Multifocal motor neuropathy
8.	**Streptococcus toxic shock syndrome**	04082 (+0410,+0412)	Toxic shock syndrome (+Streptococcus infection in	A483 (+B950, +B951, +B952, +B953, +B954, +B955)	Toxic shock syndrome (+Streptococcus, and

		conditions classified elsewhere and of unspecified site)		Enterococcus as the cause of diseases classified elsewhere)
	0380	Streptococcal septicaemia	A40	Streptococcal sepsis
	77181	Septicaemia [sepsis] of newborn	A41	Other sepsis
			P36	Bacterial sepsis of newborn
INDICATIONS COMMONLY REIMBURSED IN OTHER COUNTRIES BUT NOT IN BELGIUM				
9. Solid Organ transplant complications	9968	Complications of transplanted organ	T86	Complications of transplanted organs and tissue
	99651	Mechanical complications due to corneal graft	D8981	graft-versus-host disease
	99652	Mechanical complication due to graft of other tissue, not elsewhere classified		
	2795	Graft-versus-host disease		
10. Haemolytic disease in newborns	773	Haemolytic disease of fetus or newborn, due to isoimmunisation	P55	Haemolytic disease of newborn
11. Myasthenia gravis	3580	Myasthenia gravis	G700	Myasthenia gravis
	3583	Lambert-Eaton syndrome (including in neoplastic disease)	G708	Other specified myoneural disorders
	7752	Neonatal myasthenia gravis	G731	Lambert-Eaton syndrome in neoplastic disease
			P940	Transient neonatal myasthenia gravis
12. FNAIT: Fetal and Neonatal alloimmune thrombocytopenia	6780	Fetal hematologic conditions	O3682	Fetal anemia and thrombocytopenia
	7761	Transient neonatal thrombocytopenia	P610	Transient neonatal thrombocytopenia
13. Von Willebrand's disease	2864	Von Willebrand's disease	D680	Von Willebrand's disease
14. Inflammatory myopathies (dermatomyositis ,polymyositis inclusion body myositis, immune-mediated necrotizing myopathy)	7103	Dermatomyositis	M33	Dermatopolymyositis
	7104	Polymyositis	M360	Dermato(poly)myositis in neoplastic disease
	359.7	Inflammatory and immune myopathies, NEC	G724	Inflammatory and immune myopathies, (inclusion body myositis and other inflammatory and immune myopathies)

15.	**Stiff-person syndrome**	33391	Stiff-person syndrome	G2582	Stiff-person syndrome
16.	**Red cell aplasia (Erythroblastopenia)**	28481 (+07983)	Red cell aplasia (acquired) (+Parvovirus B19)	D60 (+B976)	Acquired pure red cell aplasia [erythroblastopenia] (+Parvovirus as the cause of diseases classified elsewhere)
17.	**Pemphigus (vulgaris-foliculae)-immunobullous disease**	6944	Pemphigus	L100	Pemphigus vulgaris
				L102	Pemphigus foliaceous
18.	**Posttransfusion purpura**	28741	Posttransfusion purpura	D6951	Posttransfusion purpura
19.	**Antibody-mediated types of encephalitis***	32381	Other causes of encephalitis and encephalomyelitis'	G0481	Other encephalitis and encephalomyelitis

Note: Exact ICD coding was not available for all Ig indications, so some approximations (in consultation with clinical experts) were needed. Antibody-mediated types of encephalitis was included in the list of indications after consultations with experts, who thought it was an important condition to consider.

Proxy indication per hospital stay

A cross-match between the indications found in the literature and the diagnoses identified in the TCT data was performed. The following procedure to attribute one indication to each stay was pursued:

1. In the TCT data, specialists treating a patient must register a principal diagnosis. Furthermore, they can also register multiple secondary diagnoses. When one of the diagnostic codes listed in Table 5 matched a principal diagnosis, this diagnosis was retained as the proxy indication.
2. If none of the diagnostic codes listed in Table 5 matched the principal diagnosis, secondary diagnoses were considered, and when one of these matched one of ICD codes listed in Table 5, then this secondary diagnosis was retained as the proxy indication.
3. If multiple diagnostic codes in Table 5 were identified as secondary diagnoses, only the diagnosis that came first (in order) on our table was selected as the proxy indication.

Proxy indication per patient

Similarly, patients with multiple stays in the same year were attributed one proxy indication for that year to avoid double counting. If there was more than one proxy indication identified per patient, the first indication following the order indicated in Table 5 was selected.

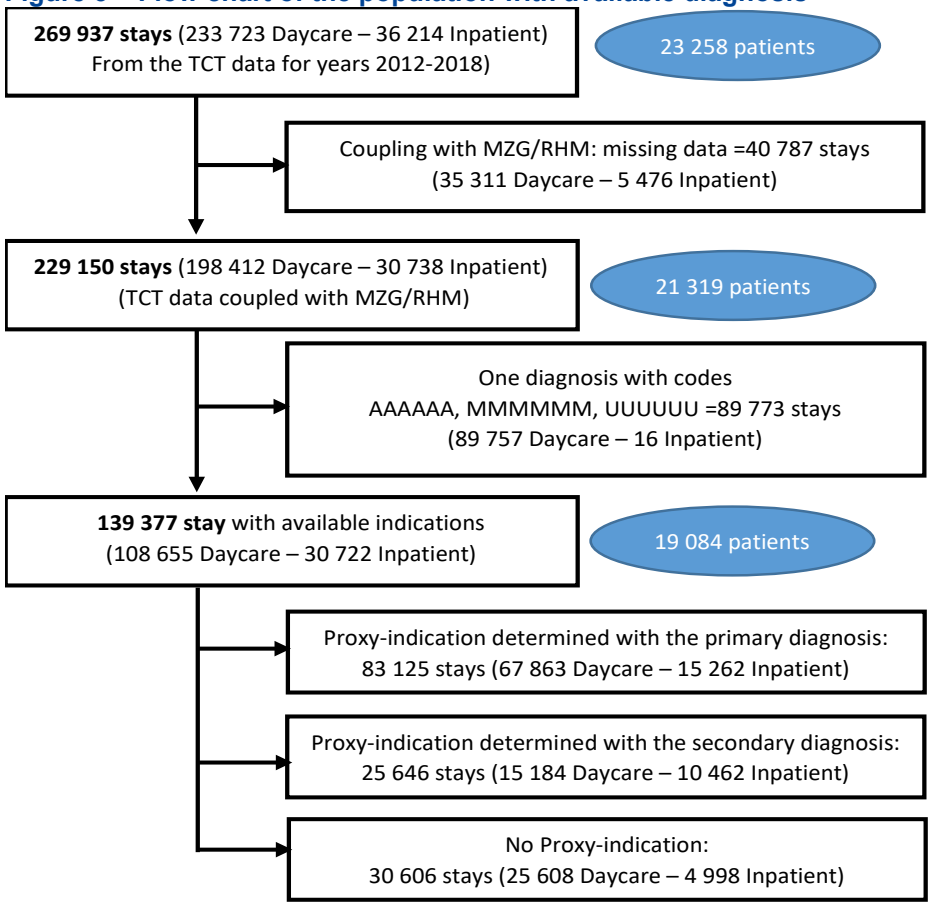
For the analysis of Ig reimbursement by hospital and by proxy indication, the year 2015 is not included as this year is not available in the TCT. Therefore, available data for this analysis include the years 2012-2014 and 2016-2018 and represents 84.9% of the initial number of stays (See Figure 5).

In a number of cases, determined by the registration rules, a diagnosis is not recorded, but a special code is registered instead. This is the case for psychiatric admissions for which a separate registration exists (“AAAAAA”), specific admissions in day-care (“MMMMMM”) and admissions in the emergency department (“UUUUUU”). Hospital stays with one of these special codes and no other, were not retained in the analysis per proxy indication. The flowchart in Figure 5 shows that approximately 50% of the originally selected stays were retained for further analysis. These selected stays captured 82.1 % of patients on Ig use, and represented 76.0% of Ig volume.

Characteristics of patients for which proxy indications could be coupled (19 084) were compared to patients for whom no coupling was possible (2235)[m] (see Figure 5). Patients with proxy indications were significantly younger than patients with no coupling (mean age was 48.5 ± 27.8 and 55.3 ± 19.6 respectively; p<0.001). More specifically, there were more patients in the age category <18 years (22.3% vs 5.1% respectively; p<0.001). Gender was also different with 54.4% of men in the group with proxy indications and 39.6% in the group where no coupling was possible (p<0.001).

[m] Age and gender information are only available in the MZG/RHM database and therefore, only for patients where a coupling between databases was possible (i.e. 21 319).

Figure 5 – Flow chart of the population with available diagnosis



Volume of Ig per proxy indication

The volume of Ig per proxy indication was calculated in three steps:

- First, for each stay, either day care or inpatient, the quantity of Ig consumed is calculated.
- Second, the stay is linked to the proxy indication of the patient. For each proxy indication, the quantity of Ig consumed is calculated for day care and inpatient stays separately. The sum of the daycare and inpatient consumption give the total quantity of Ig consumed.
- Finally, this number is divided by the number of patients who present the proxy indication, in order to have the average quantity of Ig per indication, per patient.

Status of Ig treatment

The status of Ig treatment for an indication, acute or chronic, is based on the literature (former KCE report)[7] and expert input. From the TCT database, patients were first categorised per proxy indication, and then, based on the total number of hospitalisations (day care or inpatient), (≤5; 5-10; 10-15; 15-20; 20-25 or >25). This categorisation of hospitalisations was used to check whether the TCT hospital data reflected well literature-based expectations. A limitation to this approach is that some patients are in the category <5 because of death or because they newly entered the database and therefore, insufficient follow-up data was available.

Dosage of Ig treatment

Estimations on treatment dosages differed depending on whether the treatment was considered chronic or acute. For a chronic proxy indication, the per patient Ig treatment dosage was calculated for each stay. For inpatient stays the total dosage of Ig administered over the entire hospitalisation (hospital stay) was considered, while for day-care, the dosage of each individual treatment session was captured. Only in those cases in which a patient received day care treatment for consecutive days, the total dose of Ig administered over the whole period was considered.

For acute treatment, the addition of all Ig used over the 6 months that followed the first patient visit was calculated, based on the assumption that below 6 months this would still be part of the same 'treatment'.

2.2.4 Data on non-reimbursed Ig use

All above data sources consulted covered only reimbursed indications.

In order to try to gain a general overview on Ig use, a **survey amongst Belgian hospital pharmacists** was performed in July 2020, in collaboration with the Belgian society for hospital pharmacists. In this online survey, information on the volume of Ig (in grams) which was not invoiced to the national insurance (RIZIV-INAMI) was requested. Data were requested for the years, 2017 and 2018 in order to make a comparison with the reimbursed data gathered via the previously mentioned data sources. Data for the year 2019 was also requested to ensure the most up to date information could be considered. The list of questions used can be found in appendix 8. It is important to highlight that all information received via the hospital pharmacist is limited to the hospital setting. Information on non-reimbursed use in the ambulatory sector, distributed via the community pharmacy, was not available for analysis.[n]

Another source for off-label use are the **Unmet-medical need programs and the Special Solidarity Fund**. For the Solidarity Funds, only information on the number of applications (as opposed to the number of approvals, which is confidential) and their indications could be analysed. As a proxy for the volume, the annual expenses for Ig of the Solidarity fund are also analysed.

The number of **clinical trials** in Belgium that give access to Ig for an off-label indication were searched for (search date October 12, 2020), in the following registries: Clinicaltrials.gov, clinicaltrialsregister.eu and the WHO International Clinical Trials Registry. A question on this regard was also posed to hospital pharmacists via an online survey.

This hospital pharmacist survey aimed at capturing the most recent data (2017, 2018, 2019) on non-reimbursed use, registration of indication-specific data in hospital pharmacies, and recent supply problems. Details on the hospital pharmacists' survey are presented in appendix 8. The response rate was 38%, limiting the generalisability of our results. Nevertheless, the 40 responding hospitals accounted for 53% of all reimbursed Ig use. Crude extrapolations were applied to estimate the amount of non-reimbursed use.

In addition, **sales figures of the firms were compared to the reimbursed data** for the years 2017, 2018 (2019 data of RIZIV were not yet available in September 2020). Possible differences could indicate a proxy measure for non-reimbursed use.

2.3 Results

2.3.1 Global sales of Ig

Data on volume sold by the three companies having Ig products on the market over the period 2017-2019 showed that IVIg products accounted for the largest market share (around 83% of the total Ig volume sold), with annual volumes of around 1750kg, 1780kg and 2006kg in 2017, 2018 and 2019 respectively. The volume of SCIg sold in those same years was 310kg, 353kg and 415 kg.

Over these three years, there was a clear annual increase, which was most pronounced for SCIg products intended for ambulatory care (distribution via community pharmacies) (see Table 6).

[n] The general pharmacists union (APB) was contacted for sales figures for non-reimbursed Ig use, but data are property of IQVIA (The Human Data Science Company™) and may only be used within specific contexts.

Table 6 – Sales of IVIg and SCIg (in kg) in Belgium

Year	Total volume sold (kg)	IVIg sold (kg)	SCIg sold (kg)		
	(% increase)	To hospitals (%increase)	To hospitals (% increase)	To community pharmacies (%increase)	Total (% increase)
2017	2060.67	1750.37	20.02	290.28	310.30
2018	2132.91 (3.5%)	1780.27 (1.7%)	20.99 (4.9%)	331.65 (14,3%)	352.64 (13.6%)
2019	2420.69 (13.5%)	2006.19 (12.7%)	23.66 (12.7%)	390.84 (17.8%)	414.50 (17.5%)

Source: Data based on numbers communicated by manufacturers (CSL Behring, Octapharma Benelux, C.A.F-D.C.F), and the FAMHP. Only CSL Behring and Octapharma have SCIg products on the market.

2.3.2 Reimbursed Ig use

This section covers only reimbursed use and is based on TCT and IMA - AIM data. Off-label and non-reimbursed use will be covered later on in this report (see section 2.3.4).

Reimbursed Ig in Belgium represented a total public expenditure of around 90 million euros in 2018.

Table 7 shows that overall reimbursed consumption of Ig has grown in the last years, with the exception of a stable consumption period between the years 2013 and 2014, and between 2016 and 2017, likely to have been caused by the changes in reimbursement that took place over those specific time periods (more strict criteria and the involvement of specific experts for diagnosing (details in report[7]). The overall mean increase in consumption of Ig for reimbursed indications appears to be of around 5.5% per year, with a growth of 0.7% and 6.1% in the last two years for which data are available. The growth is more predominant for SCIg.

Table 7 – Quantity of reimbursed Ig use (in kg) delivered by hospitals and community pharmacies 2010-2018

Year	Total (kg)	% increase	IVIg (kg)		SCIg (kg)			
			Delivered by hospital pharmacy	% increase	Delivered by hospital pharmacy	Delivered by community pharmacy	Total	% increase
2010	1125.9		1030.5		21.7	73.6	95.4	
2011	1255.7	11.5%	1159	12.5%	20.5	76.1	96.6	1.3%
2012	1409.4	12.2%	1293.7	11.6%	24.2	91.6	115.7	19.8%
2013	1531.4	8.7%	1395.3	7.9%	13.3	122.8	136.1	17.6%
2014	1530.6	-0.1%	1370.4	-1.8%	12.3	147.9	160.2	17.7%
2015	1690.8	10.5%	1516.4	10.7%	10.6	163.9	174.5	8.9%
2016	1881.6	11.3%	1664.5	9.8%	13	204.1	217.1	24.4%
2017	1894.6	0.7%	1661.2	-0.2%	12	221.4	233.4	7.5%
2018	2010.3	6.1%	1751.4	5.4%	12.4	246.5	258.9	10.9%

Source: INAMI-RIZIV

Reimbursed Ig delivered by hospital pharmacies included hospitalisation (inpatient and daycare), and polyclinic use. Figure 6 shows that hospital pharmacies dispense predominantly IVIg, while most SCIg use is dispensed via community pharmacies. Furthermore, the proportion of SCIg dispensed by hospital pharmacies decreased over time (from around 20% of all SCIg used in 2010 to less than 5% in 2018). The sharp decrease (from 20% to 10%) in 2012 coincided with the launch of two new SCIg products in the Belgian market: Gammanorm® and Hizentra®. It is likely to be a consequence of the current legislation, which states that it is only allowed for hospital pharmacies to dispense medicines to meet the needs of persons admitted to the care facility for treatment or an examination, and provided that the medicines are fully used for this purpose within the facility°.[54]

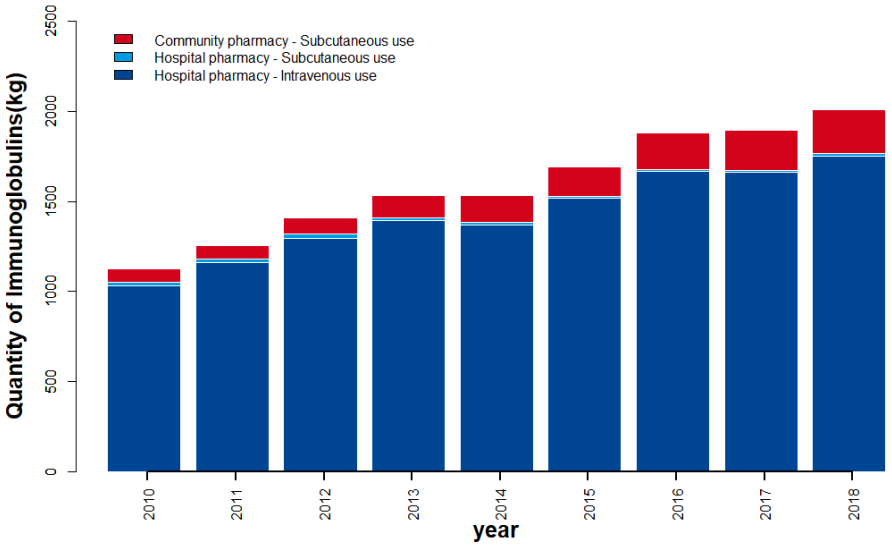
Subcutaneous use is intended to facilitate Ig administration for patients with chronic treatment (less hours of infusion, no transportation to the hospital). It can be initiated in the hospital setting, but when stable, the patient can continue at home.

Although SCIg use has experienced a steady growth from 2012, it still represents a small part of the total consumption of Ig in Belgium (≈13% in 2018). This may be explained by the reimbursement status of SCIg in this country, which until recently was limited to two indications: PID and some forms of SID. However, since September 2020, one SCIg product (i.e. Hizentra®), is also reimbursed for use in stabilized CIDP patients.

° Royal Decree of 19 October 1978. - laying down rules concerning the offices and depots of medicinal products in care facilities: http://www.ejustice.just.fgov.be/cgi_loi/change_lg.pl?language=nl&la=N&cn=1978101930&table_name=wet

Nevertheless, the clinical experts consulted throughout this project who were familiar with both IV and SCIg products highlighted that although in theory, IVIg and SCIg may be considered interchangeable, in practice patient tolerability can vary depending on the product and therefore, careful consideration should be made before switching patients (e.g. PID patients) from one administration form to the other.

Figure 6 – Evolution of reimbursed Ig use in Belgium per type of administration and setting



Source: INAMI-RIZIV

Ig delivered by hospital pharmacies, can be classified according to the setting of care where they are used: daycare, inpatient or polyclinic (see Table 8). An important note for the interpretation of the data shown in this table is that these categorisations are based on invoicing definitions. Over the period 2012-2018, hospital day-care use grew from 67.0% to 74.6%, while inpatient use decreased from 27.6% to 24.5%. Polyclinic use remained a small part of the Ig distributed by hospital pharmacies (i.e.5.4% in 2012 and 0.9% in 2018). Despite the fact that the analysed data showed some (limited) IVIg being dispensed for polyclinic/ambulant use, a consultation with experts indicated that polyclinics are not considered adequate for IVIg administration. Such consideration was made based on the need for qualified staff and adequate infrastructures, the duration of the infusion and the need to closely monitor the patient for any potential side-effects. Experts believed that the figures displayed could represented IVIg home-administration. However, no programs for IVIg treatment at home appeared to be in place in Belgium in the years analysed. A possible explanation could be the fact that, as previously stated, settings are defined based on invoicing definitions, which also changed over the period here analysed.

Table 8 – Quantity of reimbursed Ig (in kg) delivered by hospital pharmacies according to administration type

Year	Daycare		Inpatient		Polyclinic*		Total
	IV use	SC use	IV use	SC use	IV use	SC use	
2012	883.03	3.89	365.25	0.41	51.05	19.91	1323.54
2013	979.85	2.02	374.51	0.61	39.98	10.67	1407.64
2014	862.43	1.03	363.23	0.41	146.95	10.97	1385.02
2015	1082.12	0.98	424.34	0.89	6.73	8.72	1523.78
2016	1201.35	0.76	446.14	1.38	13.96	10.83	1674.43
2017	1206.09	1.03	443.36	1.12	5.85	9.85	1667.31
2018	1320.57	1.33	433.68	1.11	6.34	9.95	1772.98

*Source: TCT data. *Polyclinic use is extrapolated from the total hospital pharmacy use IMA-AIM data*

2.3.2.1 Consumption of Ig per product

Most manufacturers, with the exception of CAF – DCF which has only IVIg, have at least one IVIg and one SCIg product in the Belgian market. There is limited use of small packages and most of the time, multiple packages are distributed for one patient in order to obtain the "prescribed" dose. Over the years the proportion of small packages (<5g) increased but this is entirely due to the fact that SCIg use rose and for this administration all available package sizes are less than 5g. In 2018, packages of Ig doses <5g represented 13% of global consumption.

In the past, most Ig products came on the market via the CAF- DCF (Département Central de Fractionnement), which was initially a division of the Belgian Red Cross. However, since 2016 the CAF-DCF has become part of the French public company LFB Group[p]. Until 2014, both CAF-DCF and CSL Behring had the largest dispensed reimbursed volume on the Belgian market, but since then, CSL Behring became the largest distributor. In 2018, the market changed with the introduction of a national tender procedure for the provision of IVIg in Belgium. This contract was attributed to CSL Behring for a period of 4 years.

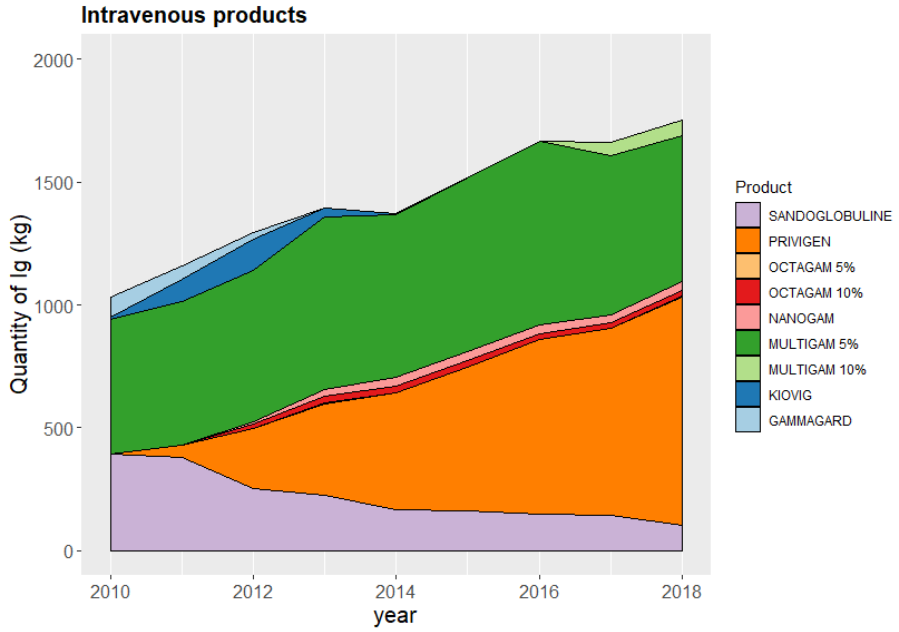
As Table 4, shows, market withdrawals and new product launches have not been rare over the last 9 years in this dynamic market. Most of the time companies launch new products, to replace 'older' ones. These newer products are, in some cases, the result of the optimization of the production process (e.g. increase yield, extra purification and quality/safety testing), while prior to 2018, (EMA harmonisation of indications), an expansion of the indications was also a motivation for new product launches. Over the last years the range of different products and suppliers decreased slightly. While prior to the year 2013, there were 4 companies on the Belgian market with a range of products (from 7 in 2010 to 12 in 2013); in 2018, there were 3 companies with 9 products in Belgium. Personal communication with manufacturers appears to confirm this trend, with more products being withdrawn from the market (CSL Behring informed that production of

[p] https://www.groupe-lfb.com/ - Accessed 12 November 2020

Sandoglobulin® is now stopped, while CAF-DCF has only one package size of Multigam® on the market as of the 1st of September 2020).

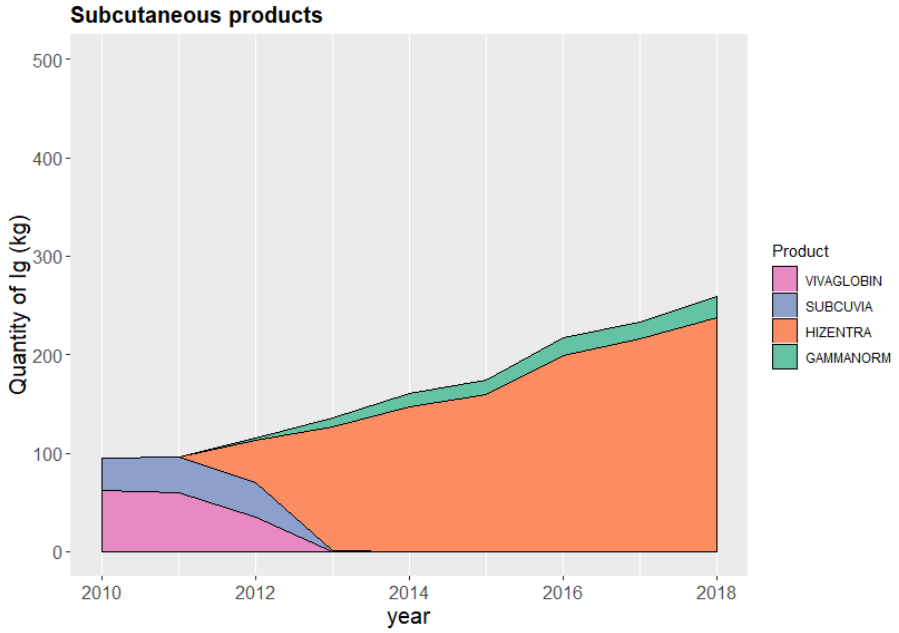
Figure 7 and Figure 8 show the evolution of the quantities of Ig delivered for the period 2010-2018 for IVIg and SCIg respectively (in Appendix 2, the details per product are shown). For reimbursed IVIg products, there appears to be some variation, but Multigam® displays the largest volume over the years. However, this market is changing (following the introduction of the tender) and currently Privigen® is the most commonly used IVIg product. The SCIg market is led by Hizentra® and to a lesser extent by Gammanorm®.

Figure 7 – Quantities of IVIg delivered for the period 2010-2018 by type of product



Source: INAMI-RIZIV

Figure 8 – Quantities of SCIg delivered for the period 2010-2018 by type of product



Source: INAMI-RIZIV

2.3.2.2 Consumption of Ig per specialty (prescriber type)

All Ig products are subject to restricted prescribing or distribution in Belgium. Thus, IVIg, can only be distributed in the hospital setting (although no specific rules exist on which medical specialties can or cannot prescribe them), while for SCIg, the first prescription must be made by a specialist, after which GPs are able to prescribe them.

When it comes to specific criteria for reimbursement, confirming diagnoses as well as reassessments are restricted to certain medical specialties or specific centres (e.g. Neuromuscular Reference Centre, BPIDG) in order to get an approval for reimbursement, but there are no limitations regarding prescribing rights, (with the only exception of GBS, for which prescribing must be made by neurologists or neuropsychiatrists).

The following section aims at identifying the type of prescribers of Ig in Belgium by using the last three digits of the NIHDI (INAMI/RIZIV) prescriber code.

Results are presented in Table 9 and Figure 9, and split by setting (hospital versus community). Because there is an important number of possible Ig indications and there are no real restrictions in terms of prescriber type (except for GBS), the table lists a large number of specialties.

An important limitation was found when looking at hospital data. Given that to this date, it is not compulsory to register the type of prescriber for inpatient care, the second largest Ig prescriber category in hospital pharmacies was the “unspecified” category (accounting for almost a quarter of all Ig hospital prescriptions in 2018). This was not a problem in the community setting, where registration of prescriber is compulsory and thus, data was more informative.

Over the years, haematologists have become the main prescribers in the hospital and community setting and in 2018 accounted for 26% of all reimbursed Ig prescriptions. The second group are the neurologists, for which there was a doubling in volume over the study period here analysed, and who prescribe predominantly in the hospital sector. In the community, in 2018, haematologist prescribing (23%) was only surpassed by GP prescribing (26%). While almost all specialists increased their prescribed volume, pneumologists decreased their volume since 2017. This could be explained by the more restricted reimbursement criteria introduced on that year for secondary immunodeficiency, in order to eliminate the possibility of prescription for chronic pulmonary disease.

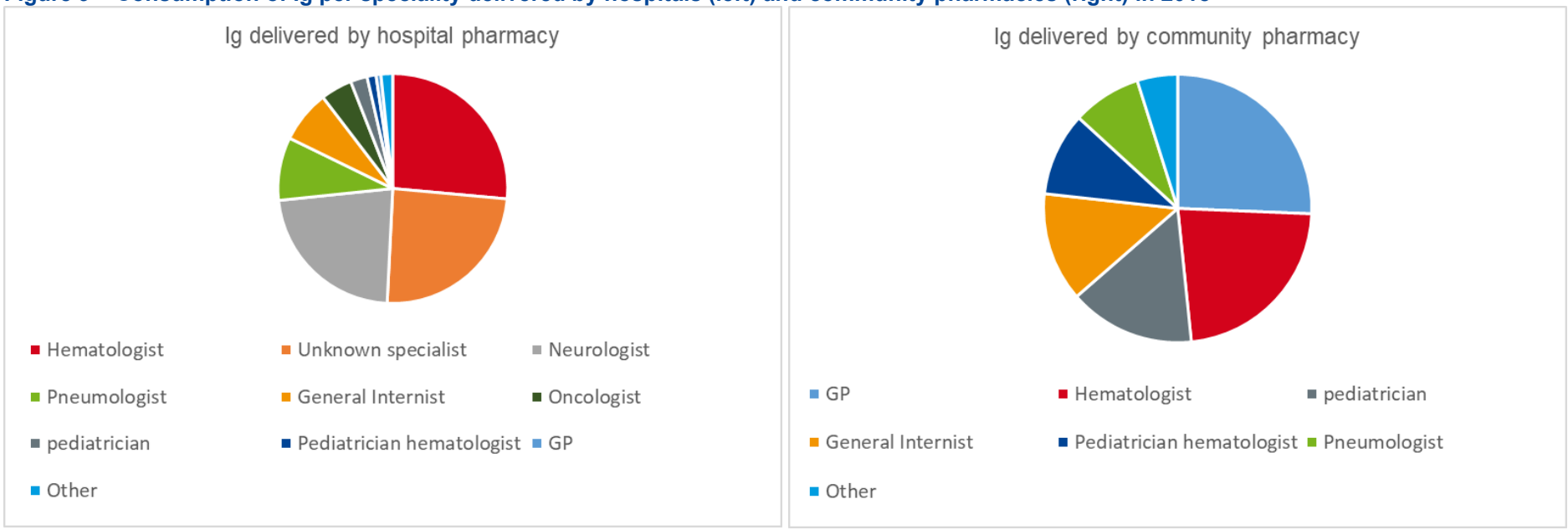
Given the high proportions of unspecified prescribers in hospital as well as the important prescription figures displayed by GPs in the community, clear conclusions on the appropriateness of prescribing could not be made.

Table 9 – Consumption of Ig (in kg) per speciality delivered by hospitals and community pharmacies (2012-2018)

	Hospital pharmacy (IVIg + SCIg)				Community pharmacy (SCIg)			
	2012	2014	2016	2018	2012	2014	2016	2018
Haematologist	295.6 (22.4%)	355.4 (25.7%)	427.1 (25.5%)	468.9 (26.4%)	10.4 (10.8%)	21.2 (14.5%)	44.5 (22.2%)	55.1 (22.7%)
Specialist – unspecified*	368.5 (27.9%)	371.8 (26.9%)	442.2 (26.4%)	431.5 (24.3%)	0.3 (0.3%)	0.3 (0.2%)	0.4 (0.2%)	0.4 (0.2%)
Neurologist	168.9 (12.8%)	200.2 (14.5%)	285.7 (17.1%)	400 (22.6%)	0.01 (0%)	0.02 (0%)	0.1 (0%)	0.1 (0.1%)
Pneumologist	212.6 (16.1%)	229.4 (16.6%)	229.9 (13.7%)	157.3 (8.9%)	19.2 (20.1%)	20.5 (14.1%)	19.4 (9.7%)	20.2 (8.3%)
General Internist	64.6 (4.9%)	52.5 (3.8%)	99.8 (0,06)	130.7 (7.4%)	6.9 (7.2%)	15 (10.3%)	23.3 (11.6%)	31.9 (13.2%)
Oncologist	81.6 (6.2%)	80.6 (5.8%)	85.7 (5.1%)	78.7 (4.4%)	3.9 (4.1%)	3.3 (2.3%)	3.4 (1.7%)	2.5 (0,01)
Paediatrician	45.9 (3.5%)	36.1 (2.6%)	34 (0,02)	41.7 (2.4%)	24 (25.1%)	24.4 (16.7%)	29.8 (14.8%)	36.9 (15.2%)
Paediatrician Haematologist	NA	9.1 (0.7%)	21.8 (1.3%)	22.5 (1.3%)	NA	5.7 (3.9%)	17.3 (8.6%)	24.4 (0,1)
GP	6.9 (0.5%)	8.5 (0.6%)	10.3 (0.6%)	12.3 (0.7%)	23.7 (24.8%)	28.3 (19.4%)	42.7 (21.3%)	62.2 (25.6%)
Emergency	1.4 (0.1%)	5.7 (0.4%)	5.4 (0.3%)	7.3 (0.4%)	0.5 (0.5%)	0.5 (0.4%)	0.04 (0%)	0.4 (0.2%)
Gastroenterologist	5.7 (0.4%)	18.6 (1.3%)	7.8 (0.5%)	6.8 (0.4%)	0 (0%)	0.1 (0%)	0.04 (0%)	0.3 (0.1%)
Dermatologist	0 (0%)	0.1 (0%)	0.1 (0%)	5.1 (0.3%)	0 (0%)	0.2 (0.2%)	0.03 (0%)	2.9 (1.2%)
Other specialist	30.5 (2.3%)	5.2 (0.4%)	9.7 (0.6%)	3.8 (0.2%)	4.6 (4.8%)	24.3 (16.7%)	18.9 (9.4%)	3.6 (1.5%)
Geriatrician	32.3 (2.4%)	4.2 (0.3%)	3.4 (0.2%)	2.4 (0.1%)	1.8 (1.9%)	0.01 (0%)	0.03 (0%)	0.3 (0.1%)
Rheumatologist	4.9 (0.4%)	4.8 (0.3%)	7.1 (0.4%)	1.7 (0.1%)	0 (0%)	0 (0%)	0.2 (0.1%)	0.1 (0)
Surgeon	0.7 (0.1%)	0.8 (0.1%)	1.1 (0.1%)	1.1 (0.1%)	0.4 (0.4%)	0.6 (0.4%)	0.3 (0.2%)	0.7 (0.3%)
Gynaecologist	1.6 (0.1%)	1.3 (0.1%)	2.1 (0.1%)	1.1 (0.1%)	0.1 (0.1%)	1.4 (0,01)	0.2 (0.1%)	0.6 (0.2%)
Foreign physician	0.1 (0%)	0.2 (0%)	0.8 (0%)	0 (0%)	0 (0%)	0 (0%)	0.02 (0)	0.01 (0)

*Source: IMA-AIM. *Specialist – Unspecified corresponds to the 0 and 9 INAMI/RIZIV prescriber code; GP: General practitioners; the total volume of Ig used for calculation of percentages is based on the IMA data. Note: in Belgium there is no official medical specialty for immunology, nor an official recognition of the qualification. A mix of different specialties, such as haematologists, paediatricians, internists, clinical geneticists, pneumologists…are part of the immunology department of a hospital. NA: not applicable*

Figure 9 – Consumption of Ig per speciality delivered by hospitals (left) and community pharmacies (right) in 2018



Source: IMA-AIM; GP: general practitioner

2.3.2.3 Consumption of Ig by patient characteristics

Over the study period (2012-2018), there was an increase in patients treated per year (11% over the entire period), though there was no continuous annual rise. The last two years for which data was available, there is a status quo (see Table 10). However, the size of the change varied greatly according to the age categories. Patients aged between 60 and 80 years represent the largest user group, and this group did rise annually. The age category of 60+ (including also 80+) represents around 50% of all the patients since 2017. The proportion of infants (<5 years) appear to have decreased in a similar magnitude to the increase observed by the proportion of children aged 5-18.

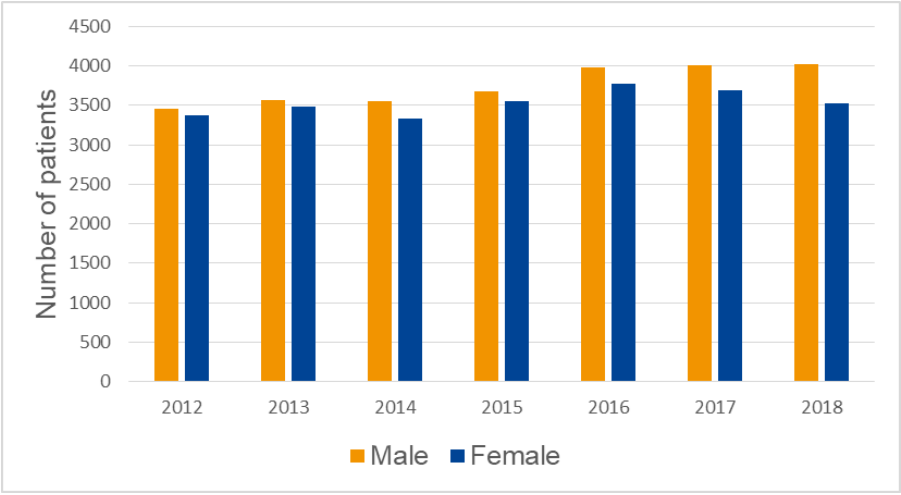
Table 10 – Number of patients using Ig per age category for the period 2012-2018

	2012	2013	2014	2015	2016	2017	2018
0-4	661 (9.7%)	609 (8.6%)	547 (7.9%)	570 (7.9%)	611 (7.9%)	549 (7.1%)	524 (6.9%)
5-17	539 (7.9%)	586 (8.3%)	582 (8.5%)	632 (8.7%)	749 (9.6%)	782 (10.2%)	842 (11.1%)
18-39	766 (11.2%)	787 (11.2%)	758 (11.0%)	798 (11.0%)	817 (10.5%)	778 (10.1%)	734 (9.7%)
40-59	1794 (26.2%)	1798 (25.5%)	1678 (24.4%)	1712 (23.7%)	1767 (22.8%)	1727 (22.4%)	1612 (21.3%)
60-79	2519 (36.9%)	2690 (38.1%)	2692 (39.1%)	2851 (39.4%)	3124 (40.2%)	3150 (40.9%)	3087 (40.9%)
≥80	556 (8.1%)	586 (8.3%)	625 (9.1%)	666 (9.2%)	697 (9.0%)	718 (9.3%)	757 (10.0%)
Total ALL	6 835	7056	6 882	7229	7 765	7704	7 556

Source: IMA-AIM

Figure 10 illustrates changes according to gender, with (limited) larger increases seen over the study period for the male population versus females.

Figure 10 – Number of patients using Ig per gender for the period 2012-2018



Source: IMA-AIM

Table 11, presents the number of patients using Ig according to the type of stay. It is important to highlight, that in this analysis, one patient can appear in different stay categories in the same year. Data shows that the number of inpatients decreased over the study period (2012-2018), while day-care and ambulatory patients increased.

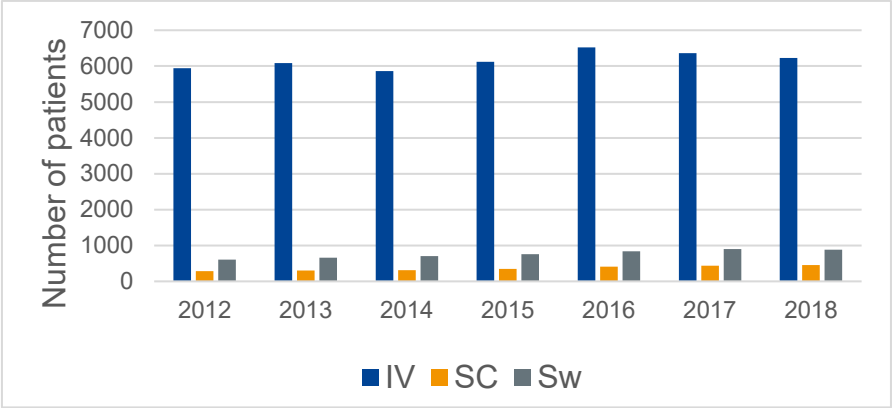
Table 11 – Number of patients using Ig (IVIg and SCIg) per stay type for years 2012-2018

	2012	2013	2014	2015	2016	2017	2018
Inpatient	3014	2927	2723	2897	3031	2787	2758
Day care*	4590	4805	4690	4893	5229	5224	5116
Community pharmacies	482	627	716	787	917	1034	1118

*Source: IMA-AIM, *Day care patients include day care, polyclinic, stays with no forfait and revalidation stays. Patients may appear in different categories within the same year and across years.*

The switch per type of Ig administration (i.e. intravenous or subcutaneous) is presented in Figure 11. The number of patients that exclusively use IVIg in one year is stable at around 6000 (6224 in 2018), while the number of patients who exclusively received SCIg increased from 288 in 2012 to 451 (+57%) in 2018. In addition, patients who switched from IVIg to SCIg during the years increased on an annual basis, from 602 patient switches in 2012 to 881 in 2018. It can be expected that these patients become full-time SCIg users and that the group of exclusively SCIg users will increase steadily over the next few years.

Figure 11 – Number of patients using Ig per type of administration for the years 2012-2018



Source: IMA-AIM; IV: patients treated exclusively with IVIg; SC patients treated exclusively with SCIg; SW: patients who switched between IVIg and SCIg during the year

The volume of Ig consumed per patient and its evolution over the study period is presented in Table 12. For patients exclusively treated with IVIg, the average annual quantity of Ig per patient increased on a yearly basis (from 204g in 2012 to 270g in 2018, a 32% increase). For patients treated exclusively with SCIg, the average quantity has marginally increased (only 10g over the 7-years analysed, which corresponds to a 5% increase). However, a closer look into this SCIg category shows that the annual quantity of SCIg dispensed via hospital pharmacies decreased, and the distribution in the community pharmacy increased. For patients who switched between IV and SC use, the average quantity of Ig per patient has also slightly increased on a yearly basis (from 243g in 2012 to 267g in 2018).

Table 12 – Average quantity of Ig in gram per patient, per year

	2012	2013	2014	2015	2016	2017	2018
All patients	207.7	216.7	222.5	233.2	241.5	244.7	266.7
IVIg patients*	204.0	215.2	220.9	233.5	241.7	246.6	270.0
SCIg patients**	210.4	206.5	208.5	200.9	212.4	210.5	220.9
Switch patients***	242.5	234.7	241.2	245.7	253.9	247.6	266.9

*Source: IMA-AIM; * exclusive IVIg treatment in a given year; ** exclusive SCIg treatment in a given year (including patients who switched between hospital and ambulatory setting); *** Switch patients are patients who received both IVIg and SCIg in a given year*

As previously seen in this report (see Table 7), the volume of SCIg in the ambulatory setting, is rising the most. Considering Ig distribution in community pharmacies is limited to SCIg, Table 11 shows that the overall number of patients in this setting also rose during this time period, while the number of patients on IVIg was rather constant. The analysis of average quantity/dosage per patient shows that SCIg patients did not increase their annual dose that much over the study period, while for IVIg patients the annual dose increased more markedly (see Table 12). In conclusion, the rather steep rise in SCIg use is more likely to be a consequence of an increase in patient numbers, while the increase in IVIg use, is more likely to be a consequence of larger annual dosages per patient combined with a small rise in the number of patients.

2.3.2.4 Consumption of Ig by hospital

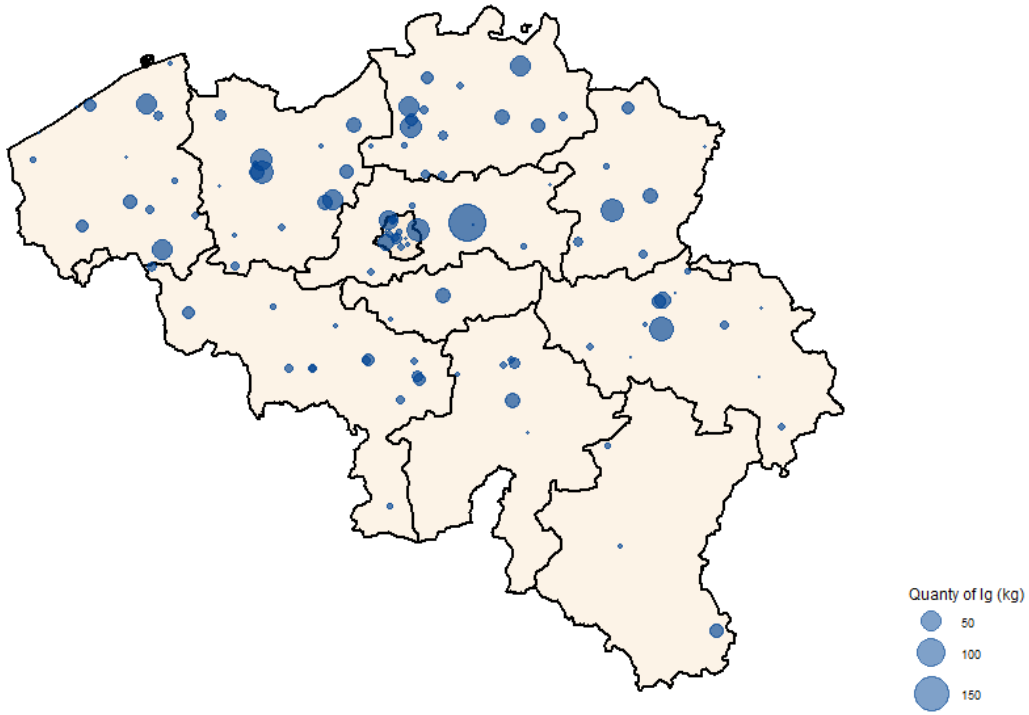
In Belgium, in the year 2018, Ig was delivered in 107 hospitals out of 115 general hospitals[q]. When looking at hospital categories, Ig use was present in all 7 academic hospitals, in all 17 general hospitals with academic character[r], in 80 out of the 82 general hospitals without academic character, and in three of the 9 specialized hospitals (e.g. revalidation centres, geriatric hospitals). The amount of Ig distributed varied greatly between hospitals. Among them, 30 delivered more than 20kg/year of Ig (3 in Brussels, 19 in Flanders and 8 in Wallonia). Among these, 9 reached an Ig volume superior to 50kg/year.

Figure 12 shows this variation of volumes between Belgian hospitals.

[q] The total number of hospitals changes from year to year due to mergers or specialised hospitals such as rehabilitation centres being transferred to the regions or communities (e.g. in 2019 there were 105 general hospitals). As the data analysis is based on year 2018, the number of hospitals of that year was used.

[r] General hospitals “with an academic character” are general hospitals that have been allocated a number of university beds. These hospitals have a specific function in terms of care, education, applied scientific research and the development of new technologies.

Figure 12 – Geographical repartition of hospitals by annual volume of Ig delivered (2018)



Source: TCT

Distribution of Ig use between hospitals in 2018

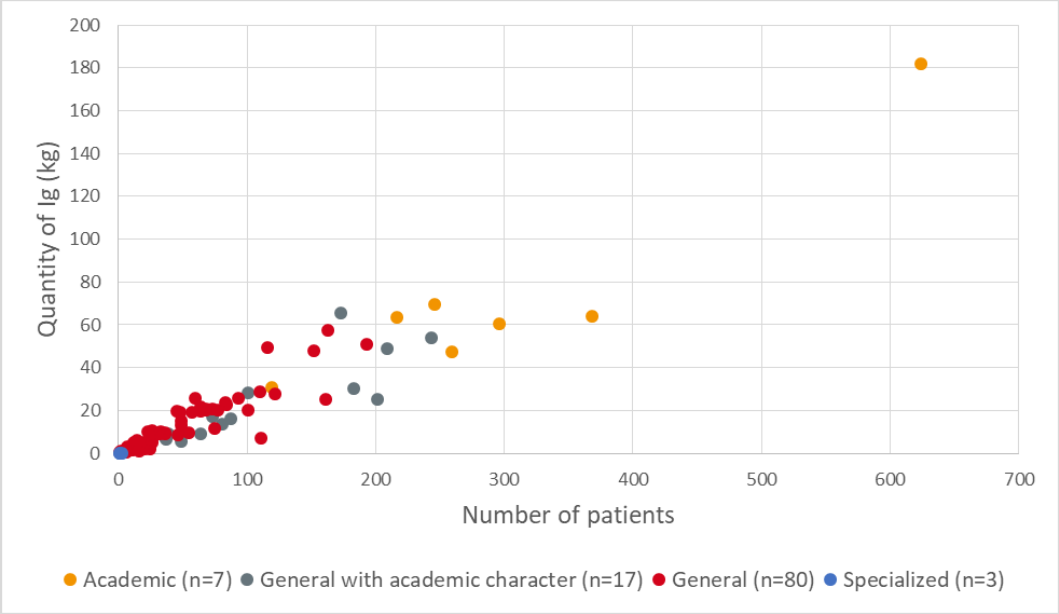
Figure 13 illustrates differences in Ig use according to the type of hospital.

In 2018, the 7 Belgian academic hospitals had the highest Ig volume, above 30 kg/year in all cases. Overall, Ig use in this type of hospital accounted for 29.8% of the total amount of Ig used in the hospital setting that year. This is in line with the proportion of patients treated with Ig in this type of hospital (30.5% in 2018). In Belgium there are 7 neuromuscular reference centres (NMRCs)[s], which are specialised centres located within an academic hospital. In these centres, a team of different medical and paramedical disciplines (neurologist, geneticist, physiotherapist, psychologist, etc.) is responsible for lifelong, continuous guidance and treatment. A relationship was once more found in these NMRCs, between the quantity of Ig used and the number of patients treated with these products.

Overall, the volume of Ig use is around three times larger in day care than in inpatient care (see Table 13).

[s] NMRCs in Belgium: UZA, UZBrussel, UCL St Luc, Erasme and HUDERF (collaboration between both hospitals), UZ Gent, UZ Leuven and CHR de la Citadelle

Figure 13 – Relationship between quantity of Ig (kg) and number of Ig treated patients by type of hospital (2018)

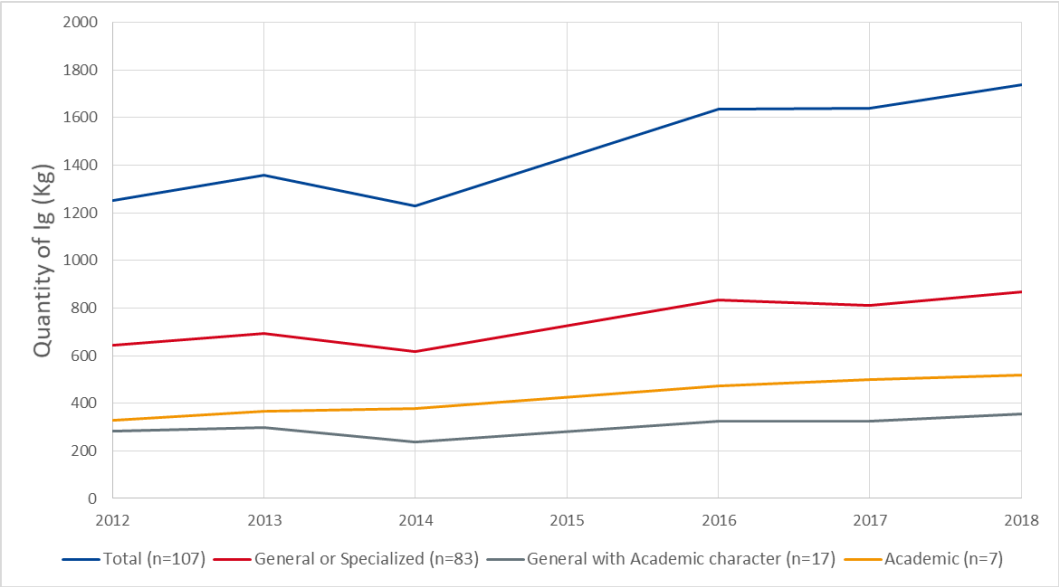


Source: TCT; Academic hospitals in Brussels: UZBrussel, UCL St Luc and Erasme; In Flanders: UZGent, UZA and KULeuven; In Wallonia: CHU-Liège. General with academic character in Brussels: Institut Jules Bordet, CHU Brugmann and CHU. St.-Pierre ; In Flanders: Jessaziekenhuis, Algemeen Ziekenhuis St.-Jan Brugge-Oostende, Ziekenhuisnetwerk Antwerpen, Ziekenhuis Oost – Limburg and Gza- Ziekenhuizen; In Wallonia: CHR De La Citadelle, CHU Ucl Namur, CHU De Charleroi, CHU Andre Vesale, CHU et Psychiatrie De Mons-Borinage, CHU Tivoli, CHR De Huy, Centre Hospitalier Epicura and Centre Hospitalier Bois De L'abbaye; Specialized hospitals: Koningin Elisabeth Instituut, Bundeling Zorginitiatieven Oostende and Revalidatieziekenhuis "Revarte".

Variability across the years (2012-2018)

The quantity of Ig used by hospitals during the last seven years differs for academic and non-academic hospitals. In 2014, there was a stabilisation in Ig consumption, but while there was a decrease of about 200kg of Ig in non-academic hospitals there was a small increase in Ig consumption in academic hospitals (see Figure 14). This may be explained by of the introduction of new reimbursement criteria in 2014. Since then, for PID patients, the diagnosis and clinical re-evaluation must be made by a physician from 'The Belgian primary immunodeficiency group' (BPIDG), recognised by the NIHDI. Most of those clinical experts (29 overall) are connected to an academic centre. Similarly, for the indication CIDP and MMN, the diagnosis and clinical re-evaluation must take place in one of the 7 NMRCs. Consequently, there was a shift/referral of eligible patients to those recognised centres.

Figure 14 – Evolution of quantity (in kg) of Ig use according to the type of hospital (period 2012-2018)



Source: TCT

The proportion of day care and inpatient stays according to academic and non-academic hospitals has evolved differently. In general or specialized hospitals, the proportion is more or less stable, moving from 74.3% in 2012 to 74.0% in 2018 for day care patients. In general hospitals with academic character and academic hospitals, the proportion of day care patients has increased from 73.9% to 80.4% and from 61.3% to 73.2% respectively in seven years, while inpatient stays decreased (see Table 13).

Table 13 – Evolution of day care and inpatient Ig use (in kg) according to the type of hospital (period 2012-2018)

		General or specialized*	General with Academic character	Academic	Total
2012	daycare	477.5 (74.3%)	208.4 (73.9%)	201.0 (61.3%)	886.9 (70.8%)
	inpatient	165.1 (25.7%)	73.4 (26.1%)	127.1 (38.7%)	365.7 (29.2%)
	total	642.6	281.8	328.2	1252.6
2013	daycare	523.5 (75.7%)	228.4 (76.9%)	229.9 (62.5%)	981.8 (72.4%)
	inpatient	168.5 (24.3%)	68.8 (23.1%)	137.8 (37.5%)	375.1 (27.6%)
	total	692.0	297.3	367.7	1356.9
2014	daycare	445.3 (72.3%)	183.0 (77.7%)	235.2 (62.5%)	863.4 (70.4%)
	inpatient	170.4 (27.7%)	52.4 (22.3%)	140.9 (37.5%)	363.6 (29.6%)
	total	615.7	235.4	376.0	1227.0
2016	daycare	617.0 (73.9%)	261.3 (80.2%)	310.2 (65.6%)	1188.4 (72.7%)
	inpatient	218.2 (26.1%)	64.7 (19.8%)	162.5 (34.4%)	445.4 (27.3%)
	total	835.2	325.9	472.7	1633.9
2017	daycare	585.7 (72.3%)	262.3 (80.4%)	347.0 (69.3%)	1195.0 (73.0%)
	inpatient	224.6 (27.7%)	63.9 (19.6%)	154.0 (30.7%)	442.5 (27.0%)
	total	810.4	326.2	500.9	1637.5
2018	daycare	642.2 (74.0%)	284.1 (80.4%)	378.6 (73.2%)	1304.8 (75.1%)
	inpatient	225.3 (26.0%)	63.9 (19.6%)	138.7 (26.8%)	433.2 (24.9%)
	total	867.5	353.3	517.3	1738.1

*Source: TCT; * Specialised hospitals are revalidation centres or geriatric hospitals*

2.3.2.5 Consumption of Ig per indication

Number of patients per year per proxy-indication

Table 14 shows the **total number of patients** on Ig per year according to proxy indication, as well as the total number of unique patients over the study period (2012-2018). This analysis is limited to hospitalised patients (inpatient or daycare) for whom linkage to diagnosis data could be performed. For around 82% of all hospitalised patients on Ig treatment, diagnostic codes were found, and were therefore included in the analysis. For more information on the methods used for linking hospital stays to indications and patients see methods 2.2.3.3 and appendix 5.

From a total of 19 084 patients receiving Ig treatment, captured in the TCT database, 2125 patients could not be linked to just one potential proxy indication, in which case, the indication with the higher frequency was selected. The most common combination was that of PID with SID (in 1626 patients) (not during the same hospitalisation, but changing ICD codes over several hospitalisations). The experts consulted throughout this research were divided on this topic. Several interpretations are possible: First of all, this could indicate that diagnosing these diseases remains challenging, and the concept of “primary” and the role of the genetic variations is not always that clear. This coupled with more strict reimbursement criteria may have resulted in inconsistent coding. Since each patient had to be linked to only one indication, to facilitate our analysis, patients with hospital stays for both PID and SID were categorised as PID patients. The second most frequent combination of diagnoses found in our dataset was SID with solid organ transplantation. Such combination was confirmed by the experts as being possible. For the purpose of our analysis, these patients were categorised as SID patients (more details on multiple indications found during our analysis are offered in appendix 7).

Table 14 – Proxy indications of patients receiving Ig during hospitalisation (inpatients and daycare)

Indication		Number of patients per year 2012	2013	2014	2016*	2017	2018	Number of unique patients
OFFICIAL REIMBURSED INDICATIONS IN BELGIUM								
• **PID**		1901 (39.0%)	2039 (41.1%)	2029 (43.3%)	2512 (44.2%)	2319 (42.7%)	2205 (40.2%)	5894
• **SID**	**- Multiple Myeloma (Kahler's disease)**	284 (5.8%)	285 (5.8%)	269 (5.7%)	333 (5.9%)	327 (6.0%)	383 (7.0%)	1100
	- - Chronic lymphocytic leukemia	183 (3.8%)	165 (3.3%)	152 (3.2%)	160 (2.8%)	170 (3.1%)	166 (3.0%)	586
	- Other	363 (7.5%)	377 (7.6%)	342 (7.3%)	391 (6.9%)	418 (7.7%)	470 (8.6%)	1625
• **PIT**		481 (9.9%)	510 (10.3%)	454 (9.7%)	527 (9.3%)	529 (9.7%)	529 (9.7%)	2414
• **CIDP**		444 (9.1%)	434 (8.8%)	432 (9.2%)	507 (8.9%)	512 (9.4%)	492 (9.0%)	1294
• **GB Syndrome**		237 (4.9%)	226 (4.6%)	212 (4.5%)	271 (4.8%)	281 (5.2%)	309 (5.6%)	1504
• **Kawasaki Disease**		107 (2.2%)	81 (1.6%)	79 (1.7%)	113 (2.0%)	86 (1.6%)	103 (1.9%)	565
• **MMN**		22 (0.5%)	22 (0.4%)	20 (0.4%)	22 (0.4%)	39 (0.7%)	37 (0.7%)	79
• **Streptococcus toxic shock syndrome**		38 (0.8%)	39 (0.8%)	29 (0.6%)	114 (2.0%)	82 (1.5%)	105 (1.9%)	387
INDICATIONS COMMONLY REIMBURSED IN OTHER COUNTRIES								
• **Solid Organ transplant rejection**		53 (1.1%)	64 (1.3%)	75 (1.6%)	72 (1.3%)	44 (0.8%)	28 (0.5%)	277
• **Hemolytic disease in newborns**		18 (0.4%)	18 (0.4%)	15 (0.3%)	17 (0.3%)	23 (0.4%)	13 (0.2%)	104
• **Myasthenia gravis**		12 (0.2%)	12 (0.2%)	15 (0.3%)	13 (0.2%)	12 (0.2%)	8 (0.1%)	57
• **FNAIT**		13 (0.3%)	14 (0.3%)	6 (0.1%)	11 (0.2%)	11 (0.2%)	8 (0.1%)	63
• **Von Willebrand's disease**		<5	<5	<5	0	0	<5	7
• **Inflammatory myopathies**		9 (0.2%)	10 (0.2%)	10 (0.2%)	13 (0.2%)	8 (0.1%)	6 (0.1%)	29
• **Stiff-person syndrome**		<5	<5	<5	0	<5	<5	<5
• **Pure Red Cell Aplasia (Erythroblastopenia)**		<5	0	0	<5	0	0	<5
• **Pemphigus (vulgaris-foliculae)-immunobullous disease**		0	<5	0	0	<5	0	<5
• **Posttransfusion purpura**		0	0	0	0	<5	0	<5
• **Antibody-mediated types of encephalitis**		6 (0.1%)	3 (0.1%)	4 (0.1%)	6 (0.1%)	9 (0.2%)	7 (0.1%)	33
• **No identified indication**		693 (14.2%)	653 (13.2%)	544 (11.6%)	605 (10.6%)	559 (10.3%)	607 (11.1%)	3056
TOTAL		4869	4956	4690	5688	5433	5479	19084

*Source: TCT; small cells replaced by <5 and totals adapted; *The year 2015 is not included as this year is not available in the MZG-RHM dataset. All patients who initiated treatment in 2015 and continued their treatment in 2016 are captured in the year 2016. PID: primary immunodeficiency, SID: secondary immunodeficiency, PIT: Primary immune thrombocytopenic, GB: Guillain-Barré, CIDP: Chronic Inflammatory Demyelinating Polyneuritis, MMN: Multifocal Motor Neuropathy, FNAIT: Fetal and neonatal alloimmune thrombocytopenia;*

From the 19 084 unique patients treated with Ig, identified in the TCT over the study period (2012-2018), 15 448 (81%) had a proxy-indication that matched one of the 8 indication groups currently reimbursed in Belgium. A further small group, accounting for just 3% of the patients analysed (580 patients) had a proxy-indication frequently recognised, and publicly funded in other countries but not reimbursed in Belgium. The remaining 3056 patients (16.0%), could not be linked to the Ig proxy indications selected from the literature. When data is analysed on a yearly basis, the proportion of patients with a linked proxy indication matching one of the indications reimbursed in Belgium appears to have grown from 83.4% in 2012 to 87.6% in 2018. Nevertheless, given the important limitations of our approach, careful interpretation of these results is needed.

Across all years, PID was the most prevalent indication representing around 42% of the overall patients per year). SID was second, and was found in around 17% of all patients. For these two proxy indications, day care was the most frequent type of hospitalisation (91.6% and 89.1% respectively).

During the study period (2012-2018), primary immune thrombocytopenia (PIT), chronic inflammatory demyelinating polyneuritis (CIDP) and Guillain-Barré syndrome (GBS) were the three most frequent proxy indications after PID and SID, accounting for 12.6%, 6.8%, and 7.9% of all patients on Ig treatment respectively. For these specific proxy indications, two thirds of patients were categorised as inpatients, versus just one third of patients who received day care. The proxy-indication Kawasaki disease (KD), toxic shock syndrome (TSS) and multifocal motor neuropathy (MMN) were present in respectively 3.0%, 2.0% and 0.4% of all patients.

Table 15 shows data on **new patients** per proxy-indication per year. It is important to note, that since 2012 which is the start of our analysis, patient numbers captured that year represent all patients available in the database and not just new patients. This explains why figures are well above those of the other years analysed. For the year 2015 data were not complete. New patients starting treatment with Ig in 2015, and continuing their treatment in 2016 are included as “new patients” in 2016. However, all patients who started an Ig treatment in 2015 for an acute indication, were not captured.

Data show that around 2500 new patients start Ig treatment every year in the hospital setting (inpatient or daycare). Around one in four of these (in 2013 29%, in 2014 29%, in 2017 25% and in 2018 23%) are diagnosed with PID. While in 2013 there were 795 PID patients starting treatment with Ig, in the more recent years the numbers have decreased to 647 and 618 new patients in 2017 and 2018 respectively. This could be explained that for PID, patients can also opt to start on subcutaneous Ig in the home setting (and are not captured in this TCT database), though often, the first administration takes place in the hospital. For an important number of the proxy indications, the number of new patients either remained relatively stable (eg. SID, PIT, CIDP), or were too few to make clear conclusions on trends (e.g. MG, haemolytic disease in newborns). For acute diseases such as GBS, KD or Toxic Shock syndrome (TSS), a slight increase in patients with Ig use can be observed over the study period. For Ig use linked to solid organ transplantation, there was a decrease in new patients, which may be explained by the better registration of SID.

An analysis of the **proportion of new patient per year over the total patient group** per indication for the same year can offer an estimation of whether treatment is chronic or acute. Thus, when the proportion of new patients compared to the overall indication-specific population in an indication is low, this means that the bulk of patients are chronic patients (e.g. PID, SID). When the proportion of new patients accounts for an important part of the overall indication-specific population, this indicates that the nature of the indication (and consequently its treatment) is more acute (e.g. GBS, KD, toxic shock).

Given the chronic nature of PID, and bearing in mind the addition of all new patients over the study period would result in 5 894 unique patients, we would expect a similar number to be treated every year (minus a small proportion of patients stopping treatment because of death, undesirable results or other reasons). However, looking at the overall number of patients being treated with Ig for PID in the year 2018, we found only 2205. The experts consulted throughout this project did find this finding surprising since, according to them, PID patients rarely stop treatment with Ig.

The **patients with no identified Ig indication** (3056 patients across the years) were patients with diagnosis of neoplasms, haematological diseases and certain disorders involving immune mechanism, diseases of the nervous system and pregnancy, childbirth and puerperium. It appears to be patients with a more acute Ig treatment (approximately 70-80% of the annual patient population is composed out of new patients). The number of new patients with Ig treatment without a registered indication has also remained relatively stable in the last years, with 529 new patients in 2013, 433 in 2014, 420 in 2017, and 456 in 2018, representing between 16% and 17% of all new users.

Table 15 – Number of new patients per year per proxy-indication

Indication	Number of new patients					
	2012[a]	2013	2014	2016[b]	2017	2018
OFFICIAL REIMBURSED INDICATIONS IN BELGIUM						
• **PID**	1901	795	696	1237	647	618
• **SID - Multiple Myeloma**	284	137	136	220	142	181
- Chronic lymphocytic leukemia	183	79	68	101	89	66
- Other	363	238	198	307	247	272
• **PIT**	481	389	332	428	396	388
• **CIDP**	444	164	146	231	176	133
• **GB Syndrome**	237	221	205	270	273	298
• **Kawasaki Disease**	107	80	77	113	86	102
• **MMN**	22	10	7	9	16	15
• **Streptococcus toxic shock syndrome**	38	37	28	112	72	100
INDICATIONS COMMONLY REIMBURSED IN OTHER COUNTRIES						
• **Solid Organ transplant rejection**	53	56	64	57	25	22
• **Hemolytic disease in newborns**	18	18	15	17	23	13
• **Myasthenia gravis**	12	11	12	9	8	5
• **FNAIT**	13	14	6	11	11	8
• **Von Willebrand's disease**	<5	<5	<5	0	0	<5
• **Inflammatory myopathies**	9	5	<5	9	<5	<5

• **Stiff-person syndrome**	<5	0	<5	0	<5	0
• **Pure Red Cell Aplasia (Erythroblastopenia)**	<5	0	0	<5	0	0
• **Pemphigus (vulgaris-foliculae)-immunobullous disease**	0	<5	0	0	<5	0
• **Posttransfusion purpura**	0	0	0	0	<5	0
• **Antibody-mediated types of encephalitis**	6	<5	<5	6	8	7
• **No identified indication**	693	529	433	525	420	456
TOTAL	4869	2789	2431	3663	2644	2688

Source: TCT; small cells have been replaced by <5 and totals adapted; [a] the year 2012 is the start of data capturing, including all the patients diagnosed in the previous years; [b] the year 2015 is not included as this year is not available in the MZG-RHM part of the data. Therefore in 2016, all patients which initiated a treatment in 2015 and continued this treatment in 2016 are included; PID: primary immunodeficiency, SID: secondary immunodeficiency, PIT: Primary immune thrombocytopenic, GB: Guillain-Barré, CIDP: Chronic Inflammatory Demyelinating Polyneuritis, MMN: Multifocal Motor Neuropathy, FNAIT: Fetal and neonatal alloimmune thrombocytopenia

2.3.2.6 Volume of Ig per year per proxy-indication

Table 16 shows the quantity of Ig per identified proxy indication per year. Note that a proxy-indication could not be linked for all reimbursed Ig used during a hospitalisation (TCT), therefore, the absolute quantities here presented per proxy-indication are sub estimations.

The largest volumes of Ig consumed are for the indication PID (≈38%), followed by CIDP (≈22%), SID (≈14%) and PIT (≈9%).

Official reimbursed indications represent 91.7% of the total volume of Ig consumed in the year 2018. Such proportion appears to be relatively stable throughout the analysed years (ranging from a low of 90.1% in 2012, to a high of 91.9% in 2017). The volume of Ig consumed, for which no indication could be linked, did not vary greatly across years with a low of 7.4% in 2016 and a high of 8.9% in 2013. Indications frequently recognised and publicly funded in other countries accounted for a low proportion of the overall volume of Ig consumed (ranging from 0.9% in 2018 to 2.2% in 2014).

Table 16 – Proxy indications of Ig delivered (in Kg) during hospitalisation per year

Indication	Quantity of Ig consumed (kg)					
	2012	2013	2014	2016[a]	2017	2018
OFFICIAL REIMBURSED INDICATIONS IN BELGIUM						
• **PID**	299.2	337.6	310.4	424.4	398.6	418.2
• **SID - Multiple Myeloma**	39.3	40.7	37.4	51.3	48.4	58.4
- Chronic lymphocytic leukemia	29.1	32.8	21.8	28.2	25.7	28.3
- Other	58.2	57.6	51.0	57.7	60.1	72.3
• **PIT**	86.8	80.2	71.8	87.1	85.9	84.3
• **CIDP**	166.2	174.0	180.8	241.1	246.7	244
• **GB Syndrome**	38.6	36.7	35.8	45.3	46.8	54.1
• **Kawasaki Disease**	3.7	3.3	3.1	5.2	2.9	4.1
• **MMN**	11.8	10.6	13.2	16.0	20.3	16.7
• **Streptococcus toxic shock syndrome**	1.5	2.5	2.5	9.7	7.8	10.4
INDICATIONS COMMONLY REIMBURSED IN OTHER COUNTRIES						
• **Solid Organ transplant rejection**	5.8	10.1	12.4	13.3	7.2	5.1
• **Hemolytic disease in newborns**	0.1	0.1	0.1	0.1	0.2	0.1
• **Myasthenia gravis**	1.7	2.0	2.6	2.4	1.7	1.6
• **FNAIT**	0.1	0.1	0.05	0.1	0.1	0.1
• **Von Willebrand's disease**	0.2	0.3	0.2	0	0	0.3
• **Inflammatory myopathies**	2.9	3.5	2.4	4.4	2.5	1.2
• **Stiff-person syndrome**	0.1	0.1	0.1	0	0.4	0.4
• **Pure Red Cell Aplasia (Erythroblastopenia)**	0.3	0	0	0.2	0	0
• **Pemphigus (vulgaris-foliculae)-immunobullous disease**	0	0.05	0	0	0.02	0
• **Posttransfusion purpura**	0	0	0	0	0.5	0
• **Antibody-mediated types of encephalitis**	0.6	0.7	0.4	1.3	1.2	0.7
• **No identified indication**	71.5	78.3	66.2	80.3	76.5	84.6
TOTAL	818.3	872.4	815.1	1069.4	1034.4	1087.6

Source: TCT; PID: primary immunodeficiency, SID: secondary immunodeficiency, PIT: Primary immune thrombocytopenic, GB: Guillain-Barré, CIDP: Chronic Inflammatory Demyelinating Polyneuritis, MMN: Multifocal Motor Neuropathy, FNAIT: Fetal and neonatal alloimmune thrombocytopenia; [a]The year 2015 is not included as this year is not available in the MZG-RHM dataset

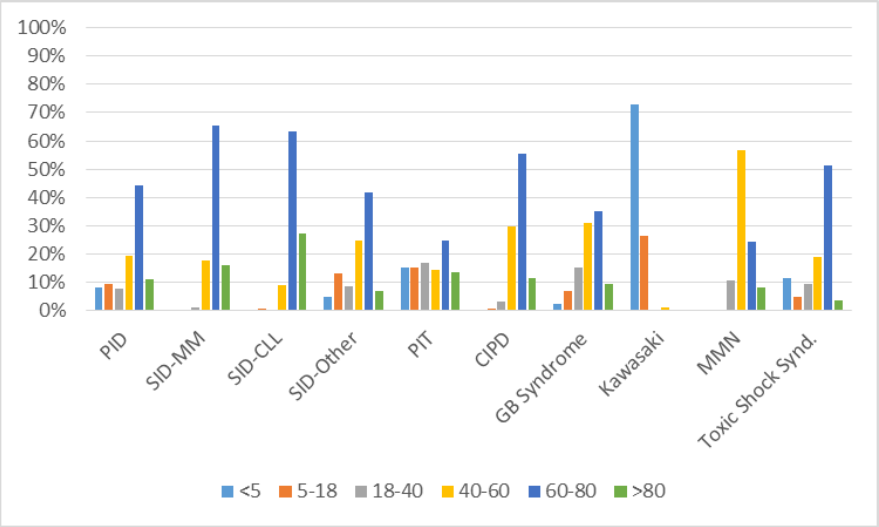
2.3.2.7 *Age and gender of patient per proxy indication*

AGE

The characteristics of the 5479 patients with a linked proxy indication for the year 2018 are presented in Figure 15. For the most prevalent diseases, i.e. PID and SID, and those linked to GBS, toxic shock syndrome and CIDP, most patients were between 60-80 years. As expected, a large majority of patients with KD, were below the age of 5. For patients linked to PIT, all age categories appeared to be equally concerned.

Consulted experts were surprised by the high proportion of 60+ patients for PID, therefore this indication group was analysed in more detail. In the year 2018, most PID patients only had a PID diagnosis (491). However, there was also an important group of patients who had both PID and SID as diagnoses (127). The latter were categorised as PID patients for the purpose of our analysis. This last group had a higher proportion of 60+ patients (72.4%), and 18,5% patients between 40 and 60 years, while the group with only a PID diagnosis (491) included younger patients, but still had around 40% of 60+ patients.

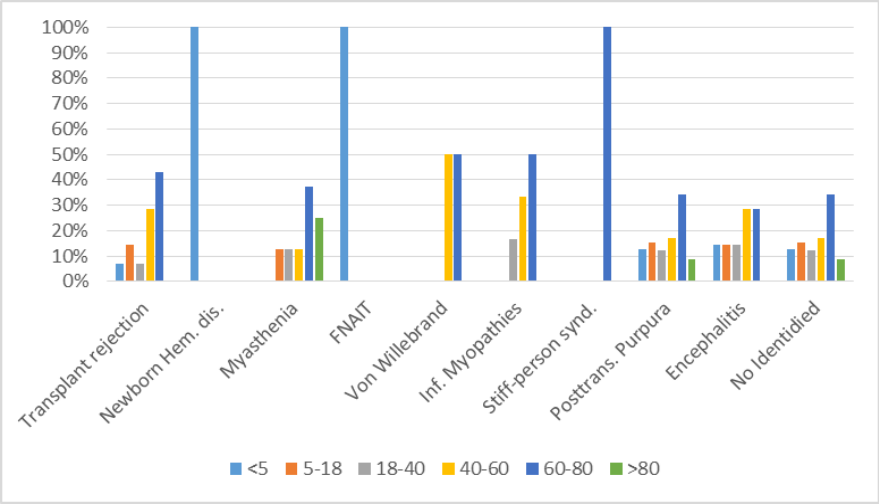
Figure 15 – Age distribution for patients with a linked proxy indication reimbursed in Belgium in 2018



Source: TCT; PID: primary immunodeficiency, SID: secondary immunodeficiency MM: multiple myeloma; CLL: - Chronic lymphocytic leukemia, PIT: Primary immune thrombocytopenic, GB: Guillain-Barré, CIDP: Chronic Inflammatory Demyelinating Polyneuritis, MMN: Multifocal Motor Neuropathy

For the patients linked with an Ig indication which is commonly reimbursed in other countries, but not in Belgium (Figure 16), it is important to note that the number of patients per indication was often less than 20. As expected, for diseases in newborns, as FNAIT and haemolytic disease in newborns, all patients were <5 years. Most patients with solid organ rejection, myasthenia gravis, Von Willebrand's disease, inflammatory myopathies, stiff-person syndrome and Antibody-mediated types of encephalitis were in the age category 40-80. Patients for which no link to an identified proxy indication could be done, appeared to fall more frequently in the 60-80 age group, with all other age categories presenting a similar distribution.

Figure 16 – Age distribution for patients with a linked proxy indication commonly reimbursed in other countries (2018)



Source: TCT; FNAIT: Fetal and neonatal alloimmune thrombocytopenia

GENDER

In 2018, the proportion of men and women was similar for PID, SID, PIT and toxic shock syndrome (with 52.5%, 55.2%, 51.0% and 51.4% of men respectively). For Guillain-Barré syndrome, CIDP and Kawasaki disease, the proportion of men was higher (58.9%, 68.7% and 66.0% respectively), while MMN appeared to be more common in women (56.8%). For the remaining of the diseases analysed, conclusions could not be made, because the number of patients per indication was less than 20. Finally, patients who could not be linked to a proxy indication, presented a similar distribution with regards to gender (53.2% of men).

2.3.2.8 Frequency of treatment per proxy indication

Length of treatment varies according to indication. When Ig is considered as a replacement therapy for people with decreased or absent production of antibodies, the treatment is chronic and patients often need lifelong Ig treatment. Nevertheless, an annual reassessment to assess the effect of Ig is required. For the Ig's property as an immunomodulation agent both acute and chronic treatments are possible. In acute indications, a single episode most often requires just one or two administrations of Ig. However, in some cases, the disease may not resolve and recurrent episodes may occur. Under such circumstances, the administration of Ig may become more chronic (e.g. PIT). For other specific indications, such as CIDP or MMN, starting with Ig and closely monitoring whether there is a positive patient's response is required, before reimbursed use can be prolonged, with regular re-assessment being necessary to justify chronic treatment.

The number of hospitalisations for the 19 084 patients with a proxy indication in Belgium over the period 2012-2018 was checked, to see if they matched well the chronic or acute nature of the different diseases considered in our analysis. The analysis was performed per type of hospitalisation.
Table 17 shows the frequency of hospitalisations (day care and/or inpatient stay) for Ig administration, for each proxy indication. For the indications considered chronic (such as PID, SID, CIDP), one could expect a high hospitalisation frequency during the timeframe 2012-2018, but half of the patients had 5 or less hospitalisations. This could be explained by the fact that not enough data points could be collected, either because some patients may have died, or because they may have been newly diagnosed patients (in particular when the first hospitalisation was in 2017 or 2018). Another possible explanation is that patients may not always be hospitalised for their treatment. This is indeed the case for those PID and SID patients, who switched to SCIg, and continued treatment in the home setting. However, for CIDP, reimbursement was not possible for patients switching to SCIg before September 2020.
For acute indications, a relatively low frequency of hospitalisations (<5) is expected. However in PIT, or solid organ transplant rejection diagnosed patients, Ig was also administered during multiple hospitals stays. This was more frequent in PIT, with 15% of patients on Ig treatment having more than

5 hospitalisations. However, this finding was not unexpected, since the literature shows that some patients with PIT may require chronic Ig administration, as the primarily acute disease can evolve to become chronic. A more chronic treatment in solid organ transplant patients could be explained by relapse problems, or by the existence of hypogammaglobulinemia.

As expected for acute, often life threatening diseases, such as toxic shock syndrome, GBS, KD, or haemolytic disease of in newborns, patients are hospitalised and Ig is administered during an inpatient hospitalisation. More information on the distribution of daycare versus inpatient care can be found in appendix 5.

For the indication CIDP, which is considered a chronic disease, 68.3% of the administration was done during inpatient hospitalisation (see appendix 5 Table 9). When confronted with this result, the experts consulted throughout this research mentioned that CIDP patients often have gait problems[55] and need to be hospitalised for practical purposes (e.g. not enough time to be transferred to day care, receive treatment and be sent home on the same day). Some of these patients may experience side effects (most often headaches) when treated too fast or may have other conditions (e.g. thromboembolic risks) that require slower infusion rates.

For other chronic diseases, such as PID and SID, Ig administration was done as daycare in 95.3% and 92.5% of cases respectively.

Table 17 – Hospitalisations per patient (day care and/or inpatient stay) treated with Ig, by indication (2012-2018)

Indication		Number of hospitalisations*						Status of Ig treatment based on literature
		≤5	5-10	10-15	15-20	20-25	>25	
OFFICIAL REIMBURSED INDICATIONS IN BELGIUM								
• **PID**		2666	995	545	351	277	1059	Chronic
• **SID**	**- Multiple Myeloma**	644	157	88	75	39	97	Chronic
	-Chronic lymphocytic leukemia	363	73	48	29	25	48	Chronic
	- Other	1096	257	114	58	36	64	Chronic
• **PIT**		2142	157	52	26	10	27	Acute (can evolve to be chronic)
• **CIDP**		729	194	90	46	39	196	Chronic
• **GB Syndrome**		1498	6	0	0	0	0	Acute
• **Kawasaki Disease**		565	0	0	0	0	0	Acute
• **MMN**		51	6	<5	<5	5	11	Chronic
• **Streptococcus toxic shock syndrome**		381	<5	<5	0	0	<5	Acute
INDICATIONS COMMONLY REIMBURSED IN OTHER COUNTRIES								
• **Solid Organ transplant rejection**		239	25	5	<5	<5	<5	Acute
• **Hemolytic disease in newborns**		104	0	0	0	0	0	Acute
• **Myasthenia gravis**		52	<5	0	<5	0	<5	Acute
• **FNAIT**		63	0	0	0	0	0	Acute
• **Von Willebrand's disease**		7	0	0	0	0	0	Acute
• **Inflammatory myopathies**		21	<5	<5	<5	0	<5	Chronic
• **Stiff-person syndrome**		<5	<5	0	0	0	0	Chronic

• **Pure Red Cell Aplasia (Erythroblastopenia)**	<5	0	0	0	0	0	Acute
• **Pemphigus (vulgaris-foliculae)-immunobullous disease**	<5	0	0	0	0	0	Acute(can evolve to be chronic)
• **Posttransfusion purpura**	<5	<5	0	0	0	0	Acute
• **Antibody-mediated types of encephalitis**	32	<5	0	0	0	0	Acute(can evolve to be chronic)
• **No identified indication**	2667	153	62	57	28	89	-

*Source: TCT; PID: primary immunodeficiency, SID: secondary immunodeficiency, PIT: Primary immune thrombocytopenic, GB: Guillain-Barré, CIDP: Chronic Inflammatory Demyelinating Polyneuritis, MMN: Multifocal Motor Neuropathy, FNAIT: Fetal and neonatal alloimmune thrombocytopenia; * In the case there were consecutive days of daycare hospitalisation, for it was not feasible to administer the prescribed dose in one session, this is counted as one hospitalisation*

2.3.2.9 Mean Ig consumed per patient per year by proxy indication

Table 18 shows the mean annual volume of Ig (in grams) per patient according to proxy indication. A CIDP and MMN patient consumes the highest volume of Ig per year (around 500g). The treatment scheme for these indications consists of administering higher doses of around 2 g/kg (for the immunomodulation effect) and once an effect is obtained, to lower the dose to 0.4 – 1g/kg every 4-6 weeks for maintenance. For PID and SID which have the same treatment scheme of one administration of 0.4g to 0.8g/kg every 3 to 4 weeks, similar annual volumes were identified. For most proxy-indications the annual dosage appeared to have rose over the study period (e.g. for PID, SID, CIDP, GBS, KD, Toxic Shock). In section 2.3.2.12, dosages per hospital stay were analysed to see whether higher dosages per stay or more frequent administrations could be the reason for this annual increase in volume.

Table 18 – Mean annual volume of Ig (in grams) per patient, according to proxy-indication (2012-2018)

Indication	Quantity of Ig consumed (g)						Change
	2012	2013	2014	2016[a]	2017	2018	2012-2018
OFFICIAL REIMBURSED INDICATIONS IN BELGIUM							
• **PID**	157.4	165.6	153.0	169.0	171.9	189.7	+21%
• **SID - Multiple Myeloma**	138.2	142.9	138.9	154.2	148.1	152.4	+10%
- Chronic lymphocytic leukemia	159.2	199.0	143.5	176.0	151.0	170.7	+7%
- Other	160.3	152.8	149.2	147.5	143.8	153.9	-4%
• **PIT**	180.5	157.2	158.2	165.2	162.5	159.4	_12%
• **CIDP**	374.3	401.0	418.4	475.5	481.9	496.0	+33%
• **GB Syndrome**	163.0	162.4	169.1	167.2	166.5	175.0	+7%
• **Kawasaki Disease**	34.6	40.4	38.7	46.2	33.9	39.8	+15%
• **MMN**	535.7*	482.5*	660.2*	725.4*	521.3	451.7	-16%
• **Streptococcus toxic shock syndrome**	38.5	63.1	86.2*	85.2	95.5	99.5	+258%
INDICATIONS COMMONLY REIMBURSED IN OTHER COUNTRIES							
• **Solid Organ transplant rejection**	109.7	158.5	165.8	184.8	164.5	180.4*	+164%
• **Hemolytic disease in newborns**	6.4*	6.6*	6.3*	6.8*	7.6*	5.6*	
• **Myasthenia gravis**	143*	167.2*	174*	185.7*	139.9*	195.7*	
• **FNAIT**	8.0*	9.3*	7.9*	8.3*	7.2*	7.2*	
• **Von Willebrand's disease**	105.0*	125.0*	85.0*	-	-	130.0*	
• **Inflammatory myopathies**	323.8*	347.1*	244.4*	334.9*	312.9*	195.0*	
• **Stiff-person syndrome**	105.0*	145.0*	72.0*	-	360.0*	360.0*	
• **Pure Red Cell Aplasia (Erythroblastopenia)**	160.0*	-	-	150.0*	-	-	
• **Pemphigus (vulgaris-foliculae)-immunobullous disease**	-	45.0*	-	-	20.0*	-	
• **Posttransfusion purpura**	-	-	-	-	235*	-	
• **Antibody-mediated types of encephalitis**	94.2*	229.0*	104.0*	209.1*	131.4*	106.8*	
• **No identified indication**	103.2	119.9	121.7	132.7	136.9	139.4	+35%

*Source: TCT; *Calculated on <30 patients. PID: primary immunodeficiency, SID: secondary immunodeficiency, PIT: Primary immune thrombocytopenic, GB: Guillain-Barré, CIDP: Chronic Inflammatory Demyelinating Polyneuritis, MMN: Multifocal Motor Neuropathy, FNAIT: Fetal and neonatal alloimmune thrombocytopenia; [a] The year 2015 is not included as this year is not available in the MZG-RHM dataset*

2.3.2.10 Dosage

To determine the volume of Ig per proxy indication for chronic treatment the average quantity by stay was estimated, while for acute proxy indications, the global quantity for a duration of 6 months was calculated (for details see the section on methods 2.2.3.3).

As shown in Table 19, the dosage per patient per stay grew for certain indications such as PID (+6.4% between 2012 and 2018), CIDP (+17.1%), GBS (+18.5%), KD (+16.9%), MMN (+12.6%) and toxic shock syndrome (+236%). The relatively large increase for toxic shock can be attributed to the shift towards more adult patients in 2018 compared to 2012 (i.e. in 2012 there were 38 patients with a mean age of 18.2 years, while in 2018 there were 105 patients with a mean age of 52.2 years). Focusing on the indications currently reimbursed in Belgium, only the dosage for SID has slightly decreased over the years (-2.6% between 2012 and 2018). For most of the indications commonly reimbursed in other countries but not in Belgium, estimations were not performed, given the very few patient cases identified. The exception was solid organ transplant rejection for which dosages per stay have increased (+29.6%) over the study period. Whether these increases in dosage per stay respond to heavier patients or different dosing schemes could not be clarified.

Overall, the number of hospital stays per patient also increased slightly over the years (see appendix 6 table 10). Per proxy indication, the picture is more variable. For example for PID and CIDP, there was an increase in the average number of stays per patient for the 2012-2018 period of 13.3% (from 5.7 to 6.5 stays) and 13.2% (from 4.5 to 5.1 stays) respectively. For other indications, there was a decrease, eg. for streptococcus toxic shock syndrome this was -23.2% (from 1.5 to 1.2 stays on average). Other indications showed more variation in their number of stays per year, e.g. solid organ transplant rejection which averages ranging from a low of 1.7 stays in 2012 to a high of 3.1 stays in 2016.

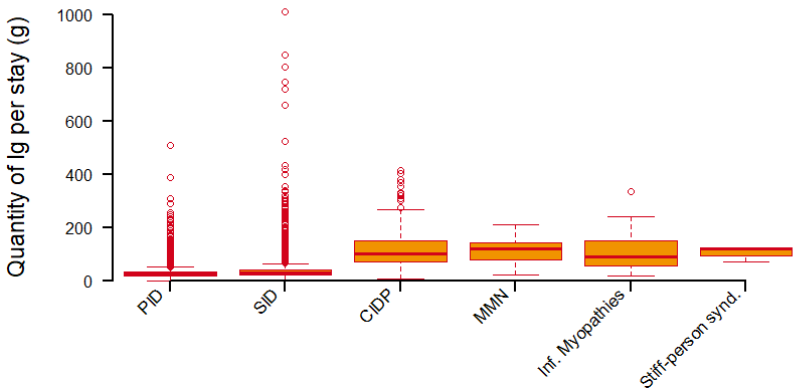
Table 19 –Average Ig (in grams) per patient per stay, according to proxy-indication (2012-2018)

Indication	Quantity of Ig consumed (g)						
	2012	2013	2014	2016*	2017	2018	% change between 2012-2018
OFFICIAL REIMBURSED INDICATIONS IN BELGIUM							
• **PID**	27.5	27.6	27.8	28.3	28.6	29.3	+6.4
• **SID - Multiple Myeloma**	29.9	30.5	31.3	29.8	31	30.8	2.7
- Chronic lymphocytic leukemia	35.1	40.2	37.5	36.9	33.2	32.6	-7.2
- Other	39.6	38.4	40.2	37	36.7	38.3	-3.2
• **PIT**	81.1	71	76.9	81.2	77.8	77	-5.0
• **CIDP**	83.3	84.1	88.8	89.6	93.2	97.5	+17.1
• **GB Syndrome**	142.6	151.7	157.2	158.5	157	169	+18.5
• **Kawasaki Disease**	33.1	39.5	36.9	44.7	33.5	38.7	+16.9
• **MMN**	87.3	98.3	99.3	99.1	107.6	98.3	+12.6
• **Streptococcus toxic shock syndrome**	25.6	47.3	62.5	72.5	71.2	86.3	+236.5
INDICATIONS COMMONLY REIMBURSED IN OTHER COUNTRIES							
• **Solid Organ transplant rejection**	63.9	63.8	71.5	59.7	74.6	82.8	+29.6
• **Hemolytic disease in newborns**	6.4	6	6.3	6.8	7.3	5.6	-
• **Myasthenia gravis**	132	66.9	84.2	65.2	62.2	74.5	-
• **FNAIT**	8	8.1	7.9	7	7.2	7.2	-
• **Von Willebrand's disease**	105	125	85			86.7	-
• **Inflammatory myopathies**	60.7	77.1	61.1	77.8	64.2	55.7	-
• **Stiff-person syndrome**	105	145	72		120	120	-
• **Pure Red Cell Aplasia (Erythroblastopenia)**	160			150			-
• **Pemphigus (vulgaris-foliculae)-immunobullous disease**		45			20		-
• **Posttransfusion purpura**					67.1		-
• **Antibody-mediated types of encephalitis**	80.7	114.5	83.2	89.6	131.4	93.4	-
• **No identified indication**	63.9	63.8	71.5	59.7	74.6	82.8	+15.8

*Source: TCT; PID: primary immunodeficiency, SID: secondary immunodeficiency, PIT: Primary immune thrombocytopenic, GB: Guillain-Barré, CIDP: Chronic Inflammatory Demyelinating Polyneuritis, MMN: Multifocal Motor Neuropathy, FNAIT: Fetal and neonatal alloimmune thrombocytopenia; * The year 2015 is not included as this year is not available in the MZG-RHM dataset*

On average for the period 2012-2018, the distributions of Ig quantities required per stay for chronic indications are shown in Figure 17. The average Ig volume per stay is lower for PID and SID (~30g of Ig) than for CIDP, MMN, stiff-person syndrome and erythroblastopenia (~110g of Ig). This could be explained by differences in the working mechanism of the administered Ig. Thus, while for PID and SID, Ig is used as replacement therapy, for CIDP, MMN, inflammatory myositis and stiff-person syndrome, Ig is used for its immunomodulatory properties, for which higher doses are recommended.

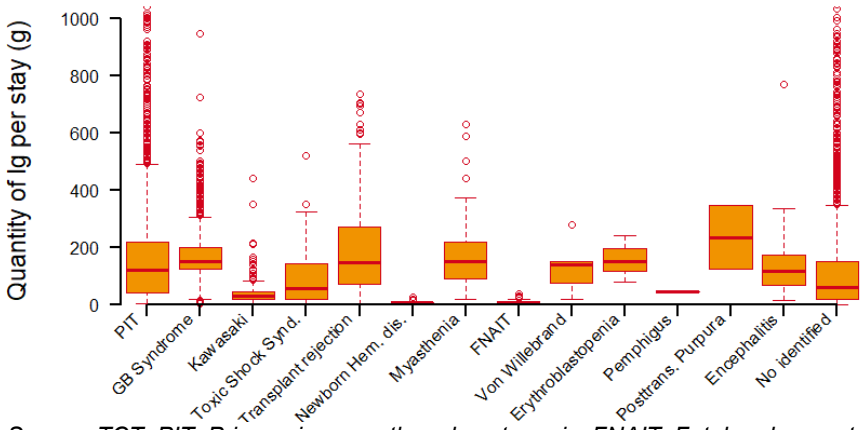
Figure 17 – Distribution of Ig quantity (in gram) by stay for chronic indications (2012- 2018)



Source: TCT; PID: primary immunodeficiency, SID: secondary immunodeficiency, CIDP: Chronic Inflammatory Demyelinating Polyneuritis, MMN: Multifocal Motor Neuropathy

Figure 18 shows distributions of Ig quantity required for acute indications. As expected, given the dependency of the recommended doses on the weight of the patient, for children diseases such as KD, haemolytic disease in newborns, or FNAIT, the quantity of Ig per stay is lower than for the other acute diseases, more prevalent in the older population (average of 17.4g of Ig for children vs 101.9 of Ig for other diseases respectively).

Figure 18 – Global distribution of Ig quantity (in gram) for acute indications per stay (2012- 2018)



Source: TCT; PIT: Primary immune thrombocytopenic, FNAIT: Fetal and neonatal alloimmune thrombocytopenia

While it is not possible to conclude something on appropriateness of dosages, as the databases did not capture the weight of the patients, one can see that often the recommended dose per administration falls within the interquartile range (25%-75%) of the quantity of Ig used by stay in Belgium. The recommended doses were derived from three main sources: The UK and Australian guidelines and the literature review undertaken during our first report on Ig (KCE report 327)[7]. A detailed table on these recommended doses and their sources is available in appendix 6. As table 20 shows, for the most common indications PID, SID, CIDP the median and even the interquartile range of the dosages per stay in Belgium are somewhat lower than the recommended dose for a 75kg adult. However for CIDP, one must also take in consideration that the recommended maintenance dosages are considerably lower.

Table 20 – Ig use per administration (in gr) compared to recommended dosage by indication (2012-2018)

Indication	Recommended dosage	Quantity consumed per administration (in gr)	
1. CHRONIC treatment: Average Ig quantity for treatment by stay		**Median**	**25%-75%**
• **PID**	0.4-0.6g/kg/3-4 weeks for IVIg and 0.1-0.15g/kg weekly or every two weeks for SCIg (≈30-45gr for IV)	26.7	[19.9;32.7]
• **SID**	0.4-0.6g/kg/3-4 weeks for IV and weekly or every two weeks for SCIg (≈30-45gr for IV)	30.0	[22.7;40.0]
• **CIDP**	Initiation: 2g/kg (over 2 days) (≈150g) Maintenance: 0,4-1g/kg (≈30-75g) every 2-6 weeks	103.2	[71.1;150.0]
• **MMN**	2g/kg (≈150g) given over 2 to 5 days and repeated after 6 weeks	120.0	[78.4;145.0]
• **Inflammatory myopathies**	Initiation: 2g/kg (≈150g) given over 2 to 5 days and repeated after 6 weeks Maintenance: 0.4-1g/kg (≈30-75g), every 4-6 weeks	90.0	[56.7;150.0]
• **Stiff-person syndrome**	Initially, max: 4g/kg (≈300g) over a 4 to 8 week period, with assessment after dosing. Maintenance: 0.4–1g/kg (≈30-75g), every 2–6 weeks	120.0	[72.0;125.0]
2. ACUTE treatment: Global Ig quantity for treatment duration < 6 months		**Median**	**25%-75%**
• **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	120.0	[40.0;220.0]
• **GB Syndrome**	2g/kg (≈150g) over 5 days. May be repeated at 14 days	150.0	[125.0;198.0]

• **Kawasaki Disease**	2g/kg in a single dose. Because it are mostly children this leads to a dosage of ≈50g. Exceptionally a second dose is needed	30.0	[20.0;45.0]
• **Toxic shock syndrome**	2g/kg in a single dose (≈150g)	55.0	[20.0;144.0]
• **Solid Organ transplant rejection**	Up to 2 g/kg (≈150g)	148.5	[70.0;272.5]
• **Hemolytic disease in newborns**	0.5g/kg over 4 hours (≈1.75g)	6.0	[3.0;7.3]
• **Myasthenia gravis**	1g/kg (≈75g). To be repeated only if there is further deterioration or no response. Patients with life threatening disease (ITU with respiratory and/ or bulbar failure) should receive 2g/kg (≈150g).	150.0	[90.0;220.0]
• **FNAIT**	Maternal: 0.5-1g/kg weekly through pregnancy. Neonatal: 1g/kg in a single dose. A 2nd dose may be given	6.0	[3.0;10.5]
• **Von Willebrand's disease**	2g/kg (≈150g)	140.0	[50.0;150.0]
• **Pure Red Cell Aplasia (Erythroblastopenia)**	1-2g/kg in divided doses over 2-5 days (≈75-150g)	150.0	[80.0;240.0]
• **Pemphigus (vulgaris-foliculae)-immunobullous disease**	Max 2g/kg per month (≈150g)	45.0	[45.0;45.0]
• **Post-transfusion purpura**	1-2g/kg in divided doses over 2-5 days (≈75-150g)	235.0	[125.0;345.0]
• **Antibody-mediated types of encephalitis**	2g/kg (≈150g) given over 2-5 days and repeated monthly for three months for initial trial	117.5	[66.0;175.0]

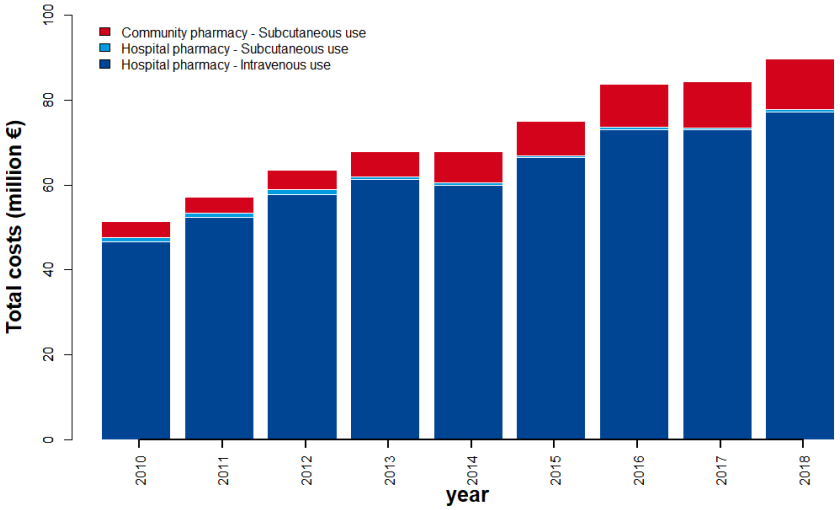
Source: TCT. PID: primary immunodeficiency, SID: secondary immunodeficiency, PIT: Primary immune thrombocytopenic, GB: Guillain-Barré syndrome, CIDP: Chronic Inflammatory Demyelinating Polyneuritis, MMN: Multifocal Motor Neuropathy, FNAIT: Fetal and neonatal alloimmune thrombocytopenia. The calculations in dosage per administration are based on the average weight of an adult person: 75 kg; the exception is Kawasaki for which the average weight of 25 was taken as it almost always concern children

2.3.3 Public Ig expenditure in Belgium

As previously stated, reimbursed Ig in Belgium represented a total public expenditure of about 90 million euros in 2018.

Figure 19 shows the growth in expenditure for the years 2010 to 2018, showing an annual increase of around 6-11% (exceptions are the years 2014 and 2017 when changes to the reimbursement system were introduced). More detailed numbers are in appendix. The growth is most pronounced for SCIg distributed in the community pharmacy (mean annual increase of 16%)

Figure 19 – Evolution of the total public expenditure in Ig delivered by hospital and community pharmacies (2010-2018)



Source: INAMI-RIZIV

The price of Ig, as for any other medication, depends on the setting where the medication is purchased:

- The ex-factory price: is the price at which manufacturers sell the pharmaceutical product to wholesalers or hospitals. This represents the maximum price, however lower prices are possible due to discounts (this is common in the hospital sector, but not in the ambulatory sector – community pharmacies). This price is also the basis for the calculation of the reimbursed prices.
- The reimbursed "inpatient" price: is the price of the Ig package delivered by the hospital pharmacy to inpatients. This price corresponds to the ex-factory price + VAT (6%)
- The reimbursed "day care" price: is the price of the Ig package delivered by the hospital pharmacy to day-care patients. This price corresponds to the ex-factory price + VAT (6%) + a fixed margin for the hospital pharmacist per package (=7.11€).
- The "reimbursed public price": is the price of the Ig delivered by community pharmacies, corresponding to the ex-factory price + VAT (6%) + margin for the wholesaler[t] + margin[u] for the pharmacist (which are partially capped per package) + delivery fee for the pharmacist (fixed per package). This reimbursed public price is only applicable for SCIg products, since IVIg are not allowed to be dispensed in community pharmacies.

A detailed table listing ex-factory and reimbursed prices per gram according to package size is presented in appendix 3.

Ex-factory prices are relatively stable at around €42 per gram for IVIg products (with a minimum and maximum of €36.02 and €56.4 per gram, for the same product (Nanogam®), depending on the package size. For SCIg products, the ex-factory price is around €44. For some Ig products (e.g. Nanogam®), the ex-factory price per gram is higher for small packages compared to larger package sizes. This was originally accepted due to the relatively higher production costs often linked to smaller packages. However, over the last years a uniform ex-factory price per gram was attributed regardless of the package size. Price adaptations, requested by the firms, have not been frequent over the period 2010-2019. Only in

[t] Wholesaler margin per package in 2020: €2.00 + 0.9% of the ex-factory price, excluding VAT, exceeding €13.33. https://economie.fgov.be/nl/themas/verkoop/prijsbeleid/gereguleerde-prijzen/geneesmiddelen-voor-menselijk

[u] Pharmacist margin per package in 2020: €3.93 + 2.16% of the ex-factory price of the medicinal product, excluding VAT, exceeding €60

February 2020 the price of Octagam®, and in August the one of Gammanorm® were increased, and more recently, a decision to increase the prices of Hizentra® and Privigen® is pending.

Reimbursed prices can differ based on the setting where Ig are dispensed, as well as on the package size. This is due to the different distribution margins which are often fixed per package (eg. €7.11 for hospital daycare), which results in a higher price per gram for smaller packages, while the purchasing price for pharmacy stays the same.

The distribution margins in the hospital pharmacy remain unchanged since 2010, whereas the distribution margins in the community pharmacy increased. Wholesaler margins decreased in 2016, but community pharmacist margins increased in 2019 and 2020 and the delivery fee per package (honorarium) increased almost on a yearly basis.

An important note to consider is that often discounts on ex-factory prices are granted in the hospital setting, while reimbursed prices are fixed. Revenues/profits in hospital pharmacies are an important pillar of general hospital financing.[56] These profits depend on the discounts they get from the firms and how they deal with distribution margins and organise deliveries. Both the national tender and the commercial tender of Ig products contribute to a significant proportion of hospital pharmacy profits. For IVIg under the national tender, a purchasing price is defined (€38,05 per gram), and the revenue for the hospital pharmacy ranges between €3.72 and €9.22 per gram. The profits made on products purchased via the commercial tender remain confidential as the sales price depends on whether or not discounts are negotiated. In the event that one firm does not supply the product at the agreed commercial tender price, other firms have to step in, but under such scenario, discounts would be rare, which could have an impact on pharmacy revenues.

A reimbursed price per gram of Ig was calculated as a ratio between the total public/reimbursed expenditure (including the different distribution fees and package sizes) and the grams of IVIg or SCIg dispensed, either via hospital pharmacies or community pharmacies, and are presented in Table 21 for the period 2010-2018. For both SCIg and IVIg products, only small variations appear to be present over the years. These can be explained mainly by differences in margins (hospital versus ambulatory) and different use of packages sizes. Over the analysed period 2010-2018, the mean public price for IVIg was around €44,26/gram, while for SCIg this was either €46,80/gram when dispensed in hospital pharmacies and €49,55/gram when dispensed via community pharmacies. Therefore, in community pharmacies, the public price of SCIg is around €2.75 /gram higher than in hospital pharmacies, due to the additional pharmacy fees for distribution.

Table 21 – Mean reimbursed (public) price per gram of Ig delivered by hospital and community pharmacies 2010-2018

Year	Price of Ig in intravenous use (€/g)	Price of Ig in subcutaneous use (€/g)	
	Hospital pharmacy	Hospital pharmacy	Community pharmacy
2010	45.24	47.01	49.67
2011	45.21	46.87	49.93
2012	44.63	46.88	50.03
2013	43.88	46.78	49.68
2014	43.75	46.83	49.68
2015	43.79	46.83	49.61
2016	43.88	46.67	49.48
2017	43.92	46.67	48.94
2018	44.05	46.63	48.93

Source: INAMI-RIZIV it is calculated based on the total public expenditure (for either all IVIg products, or all SCIg products dispensed via the hospital pharmacy or the community pharmacy) divided by the respective quantity (in grams)

2.3.4 Off-label use and non-reimbursed use

2.3.4.1 Background

Off-label use happens when a product is used for an illness/indication for which it does not have a licence (authorized by the European Medicine Agency or the national agency FAMPH). It is important to highlight that the licence is a Market Authorisation, so the initiative has to come from the company that wants to launch the medicine in the market. So when a pharmaceutical has proven to be effective for a specific illness, but the firm has not applied for a licence, the use of this particular product is considered off-label.

For the specific case of Ig, licensed indications can differ per product, but in general, for IVIg, the licensed indications are primary PID with impaired antibody production and a number of secondary immunodeficiencies (SID), PIT, GBS, KD, MMN, and CIDP. For SCIg, it is limited to PID, SID and for Hizentra®, also stabilised CIDP patients.

In 2018, the EMA harmonised their guidance for applications for marketing authorisations for IVIg, so that when a product has proven efficacy and safety in PID, a licence for SID can automatically be requested. Similarly, when a product has proven efficacy and safety in PIT, a licence for four additional indications: GBS, KD, CIPD, and MMN can automatically be requested.[57]

Off-label use and non-reimbursed use are not the same, since a country may decide whether or not off-label indications should be included in their national reimbursement policy. Moreover, the licensed indications as such are insufficient to qualify for reimbursement (eg. severity of disease being considered in some situations such as for PIT patients, for which reimbursement is not possible if there is no bleeding risk).

Countries such as France, England, Canada, and Australia make Ig available for several off-label indications (see KCE report 327[7]). Ig coverage for an indication is most often decided on the basis of the existing evidence, completed with expert opinion, considering also the severity and rarity of the illness as well as the existence (or lack) of alternative treatments. In return, Ig use in England and Australia is monitored via a national application system which registers not only the indications for which they are used, and a justification for the treatment decision, but also outcome data.

Belgium follows the general rule that only licensed medicines qualify for reimbursement by the national Health Insurance, which means for Ig that these are reimbursed for the 8 licenced indications (see Table 2 for details of reimbursement in Belgium). Though exceptions and off-label use are possible via an Unmet-Medical Need program or the Special Solidarity Fund (e.g. diseases affecting vital signs).[58] In both programs, a commission decides on possible reimbursement on an individual basis. Medical Need Programs are also possible, in which case firms cover the cost of the Ig. Clinical trials are a further potential source of access to Ig for current off-label indications.

Whereas other countries report off-label use of around 20-30% of their global use[8-10], in Belgium there is no detailed information as there is no national overview of indications. Some indication-specific information is available, though it is limited to reimbursed indications, and the data is scattered over hospital pharmacies, and in the databases of the 7 sickness funds[v]. The assumption can be made that reimbursed Ig use equals licensed indications, whereas the non-reimbursed Ig use may include licensed indications that may not fully comply with the reimbursement criteria (e.g. PIT with no bleeding risk), as well as off-label indications. In conclusion, the real magnitude of off-label Ig is difficult to estimate and information on off-label use in Belgium is only available via proxies such as the non-reimbursed Ig use.

[v] For IVIg, for reimbursement purpose, information on indications needs to be kept at the hospital pharmacy, and made available to the national health insurance (via the advisory physician of the sickness fund) upon request (a posteriori control). For SCIg, the information is available to the advisory physician of the sickness fund, because an a priori approval is necessary

2.3.4.2 Non-reimbursed use in the hospital setting

Based on the **convenience sample of responding hospital pharmacies**, 19 of the 40 responders had non-reimbursed Ig use during the years 2017, 2018, 2019. The hospitals with non-reimbursed use are bigger hospitals and had a larger volume of reimbursed Ig use compared to those who reported no non-reimbursed use.

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. Therefore, although most hospitals reported a stable proportion of non-reimbursed use, representing less than 1% of their total Ig volume dispensed (except one hospital where the non-reimbursed use represented 10%), overall, in absolute terms, there was an **increase in non-reimbursed use during those three years**. Given the proportion of reimbursed Ig use represented by the responders to our survey (the 40 responding hospitals represent 52.3% of the reimbursed Ig use), a crude extrapolation of that number could imply that the non-reimbursed Ig use in the hospital setting could equal **around 19 kg per year**, compared to an annual reimbursed Ig use of 1764kg in hospitals (RIZIV-INAMI). A limitation of 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. However, it could be the case that nonresponding hospitals have a higher or lower non-reimbursed Ig use, and therefore, our estimates could be biased.

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

Most hospital pharmacies indicated that patients pay the cost for non-reimbursed Ig **out-of-pocket**. Although they mentioned that this could also be submitted for private additional insurance. Two hospitals also specified that there are foreign patients that do not have a Belgian national insurance and therefore pay Ig out-of-pocket. Three hospitals also referred to the possibility for the prescribing physician to request 'free samples' from the firms. Legislation states that a prescriber can receive a maximum number of eight samples per medicinal product, per calendar year.[59]

Based on the number of requests for reimbursement of Ig by the **Special Solidarity Fund**, there was an increase from 2017 to 2018, but this did not continue in 2019. The number of new annual requests was, 17 in 2017, 24 in 2018 and 10 in 2019. Annual expenses for the Ig in this program have not risen in the last years either, with 255.905,03 € in 2017, 311.839,70 € in 2018 and 159.938,60 € in 2019.[w] Applications concerned mainly IVIg.

When **sales data and information on actual reimbursed Ig are compared** (all settings and types of administrations considered), there is an overall difference of 8% (= 166.1 kg) in 2017 and 6% (= 122.6 kg) in 2018.

For SCIg products used in the hospital setting: the difference between the volume of product sold to hospitals and the amount for which reimbursement was given, was 8.0 kg in 2017 and 8.6 kg in 2018. This represents around 40% of the SCIg product sold to hospitals.

For IVIg products in the hospital setting: the discrepancy is much lower, with 95% and 98% of the products sold to hospitals being filed for reimbursement in 2017 and 2018 respectively (89.2 kg in 2017 and 28.9 kg in 2018). The extent to which some hospitals may stock Ig products to face potential supply shortages is not known, and could vary greatly between hospital pharmacies. In 2019, there was a national call in the form of recommendations not to stockpile.[51]

It cannot be excluded that a part of the nonreimbursed Ig could also be a consequence of 'strict' reimbursement criteria regarding validity periods. The Belgian reimbursement period for IVIg or SCIg is fixed at either 6 months or one year (renewable), and impedes simultaneous reimbursement of Ig products. This administrative restriction could have an impact in those patients that need to switch products due to supply problems (e.g. a temporary switch from IVIg to SCIg which did not appear the best solution and for which going back to IVIg is required). Although usually, a switch (to

[w] Info based on personal communication with the Special Solidarity Funds

SCIg) is carefully planned, supply issues may force the need to switch products or administration forms.

Except the medical need program for Privigen® for treatment of bleeding in patients with acquired von Willebrand syndrome, there are no specific medical need program for Ig authorised by the FAMPH since 2017.[60]

The analysis of the clinical trials performed in Belgium showed that there were three trials on "Myasthenia Gravis" (generalised and acute myasthenia crisis) that terminated in 2018-2019.[x] In 2020 there is one clinical trial on polyvalent Ig in Belgium for the off-label indication "Diffuse Cutaneous Systemic Sclerosis", but it appears that it is withdrawn due to safety issues.[y]

Worldwide there is a growing list of ongoing studies on polyvalent Ig (see appendix 7 for an overview).

For the indication of Covid-19, there are at least 13 trials with polyvalent Ig as a treatment option[z] worldwide, though not recruiting in Belgium (see appendix 7). Although polyvalent Ig are not expected to become the standard treatment, Preliminary findings of one very small study appear to show a positive effect of IVIg on hospitalised Covid-19 patients (33 patients of which 16 received IVIg). However, this paper has not yet been peer reviewed.[61]

2.3.4.3 Non-reimbursed use in the ambulatory setting

Based on an analysis of **sales data and information on reimbursed SCIg (volume)** in the ambulatory sector, a discrepancy was found of around 25% in the volume of SCIg sold (24% 69kg in 2017 and 26% 85kg in 2018) not captured in the reimbursement data. Because it was not feasible to obtain detailed data from community pharmacies no in depth analysis could be performed in this regard to understand the possible causes of this discrepancy (use in non-reimbursed indications, parallel exports, etc).

3 REQUIREMENTS FOR IG

The objective of this exercise was to offer an approximation to the needs for Ig in Belgium over the next couple of years. Given the limitations of the existing data as well as current trends likely to have an important impact on supply/use such as the current COVID pandemic, which are not yet reflected in the available data, these estimations should just serve as illustrations and the uncertainties that come with them should always be considered.

3.1 Method

Estimations are theoretical annual Ig quantities (in gr).

Two approaches were pursued.

First, patient numbers per indication, were used in the calculations.

> Originally, epidemiological data (prevalence or incidence depending on the nature of the disease) were explored in order to estimate the size of the entire indication-specific populations for which Ig represent a possible treatment option. These data were extracted from the report performed during phase one of this research[7], where different sources such as Orphanet for the rare diseases, registries managed by Sciensano (e.g. the Belgian Neuromuscular Disease Registry)[aa], or the published literature were reviewed.
>
> An important assumption made was that not every patient suffering from a specific disease, requires Ig treatment (e.g. only those PID or SID patients who still develop infections when treated with antibiotics are eligible candidates for Ig treatment). Therefore, the number of patients requiring Ig treatment was expected to be lower than the overall number of affected patients.

---

x Clinical.trials.gov number: NCT02473952, NCT02413580 and NCT02473965

y Clinical.trials.gov number: NCT04138485

z Information on clinical trials checked on October 12, 2020

aa https://www.sciensano.be/en/belgian-neuromuscular-diseases-registry-bnmdr

However, when the epidemiological data found were compared to usage data in Belgium over the last years for which TCT data were available, it became obvious that the current registries on epidemiology did not cover an important number of indications, and in some cases (i.e. CIDP and PIT), offered a sub-estimation of the real number of patients, falling below the number of Ig users in Belgium (see Table 22).

Therefore, it was decided that the number of patients would be derived from usage data captured in the Belgian TCT database. It is important to note that these are limited to the hospital setting. The latest year for which data were available was 2018, which was therefore, used as the starting point for the estimations. Given the fact that only 81% of the overall patient population receiving Ig treatment in Belgium in 2018 could be linked to a proxy indication (n=5479), extrapolations were performed to consider the full Ig patient population of that specific year (n=6758). These extrapolations respected the proportions per indication observed in our data set.

Maximum and minimum internationally recommended doses (including actual dose per administration and frequency of administrations), were multiplied by the number of patients in order to obtain annual Ig requirements (in gr) for each indication.

A second approach was pursued in order to compare the results obtained.

This second procedure purely focused on Ig volumes consumed (in gr) over the period 2012-2018 captured in the Belgian TCT database per indication, and reflecting hospital consumption. Once more, 2018 was used as the starting point for the estimations. Overall, 61.8% of the hospital Ig consumption on that year could be link to a proxy indication, so extrapolations were performed to reflect global hospital consumption. Once more, these extrapolations respected the proportions per indication observed in our data set.

Estimations were performed in both cases for four years (2021-2024). Annual growth rates for both the number of patients and the Ig volumes consumed were derived for the period 2012-2018 and represented mean annual growth rates.

The analysis covered all indications seen in our first report[7] for which use had been identified in recent years in Belgium. Thus, the focus was not just the currently reimbursed indications, but also those commonly recognised and reimbursed in other countries.

In order to have a more global view on future needs, given the limitation of the TCT data to the hospital setting, the overall volume of Ig used in the community setting was considered, since no links between patients and indications could be performed in this setting. This overall figure was taken from INAMI/RIZIV data for the year 2018 (246.5 Kg) to which annual growth rates were applied.

3.1.1 Assumptions

A number of assumptions were made:

1st the link of patients or consumption levels to the “proxy” indications previously presented in this report, reflects “real” indications for which Ig use is needed, and all cases are correctly diagnosed.

2nd for the first approach pursuing estimations based on patient numbers, recommended doses for each indication were used, so the assumption is made that the average prescriber in Belgium follows them, and the average patient tolerates them well. Since dose is based on weight, the following assumptions were made: an adult in Belgium weights on average 75 Kg; a child weights 25 Kg and a new born 3.2 Kg. The recommended doses as well as the sources consulted are presented in appendix 6 (table 11). Maintenance doses were assumed for chronic indications.

3rd also for the first approach, recommended frequencies for Ig administration, depending on the nature of the disease, were assumed. For chronic patients, an assumption was made that patients would continue treatment throughout their entire lifetime, without interruption.

4th growth rates observed over the study period (2012-2018) both in the number of Ig patients, or in consumption (overall ambulatory consumption volumes as well as indication-specific consumption in the hospital setting) were assumed to continue a similar trend the following years (linear annual growth assumed).

Table 22 – Usage rates versus epidemiology data in Belgium

	2016		2017		2018		Rates of prevalence (chronic) and Incidence (acute) per 100 000	Sources for prevalence (for chronic) and incidence (for acute)
	N. of patients (extrap.)	Usage rate (per 100 000)*	N. of patients (extrap.)	Usage rate (per 100 000)*	N. of patients (extrap.)	Usage rate (per 100 000)*		
CHRONIC CONDITIONS								
PID (including specific antibody deficiency)	3118	27.67	2962	26.16	2720	23.91	40-100	Information of the BPIDG**
SID (including CLL, MM, hypogammaglobulinemia after HSCT)	1097	9.74	1169	10.32	1257	11.05	NA	NA
Chronic inflammatory demyelinating polyneuritis (CIDP)	629	5.59	654	5.78	607	5.33	3.32	Belgian Neuromuscular Disease Registry - Sciensano
Multifocal Motor Neuropathy (MMN)	27	0.24	50	0.44	46	0.40	0.60-9.00	Belgian Neuromuscular Disease Registry - Sciensano
Inflammatory myopathies	16	0.14	10	0.09	7	0.07	0.035-0.097	Orphanet
Stiff-person syndrome	0	0.00	5	0.05	5	0.04	NA	NA
ACUTE CONDITIONS								
Toxic shock (streptococcus-staphylococcus)	142	1.26	105	0.93	130	1.14	NA	NA
Idiopatic trombocytopenic purpura (PIT)	654	5.81	676	5.97	652	5.74	1.60-3.90	Orphanet
Guillain-Barré Syndrome	336	2.99	359	3.17	381	3.35	0.10	Belgian Neuromuscular Disease Registry - Sciensano
Kawasaki Disease	140	1.24	110	0.97	127	1.12	8.00-9.09	Orphanet
Solid Organ transplant rejection	89	0.79	56	0.50	35	0.30	NA	NA
Hemolytic disease in newborns	21	0.19	29	0.26	16	0.14	NA	NA
Myasthenia gravis	16	0.14	15	0.14	10	0.09	0.20	Belgian Neuromuscular Disease Registry - Sciensano
FNAIT	14	0.12	14	0.12	10	0.09	0.69-1.04***	From literaure (Rayment 2011)
Von Willebrand's disease	0	0.00	0	0.00	5	0.04	NA	NA

Pure red aplasia (erythroblastopenia)	5	0.04	0	0.00	0	0.00	NA	NA
Pemphigus (vulgaris-foliculae)-immunobullous disease	0	0.00	5	0.05	0	0.00	0.076-3.2	From the literature (Atzmony 2015)
Antibody-mediated types of encephalitis	7	0.07	11	0.10	9	0.08	NA	NA
Post-transfusion purpura	0	0.00	5	0.05	0	0.00	NA	NA
No identified indication	751	6.67	714	6.31	749	6.58	NA	NA
OVERALL USE	7065	62.70	6950	61.39	6764	59.46	NA	NA

*NA not applicable; BPIDG: Belgian Primary Immunodeficiency Group. *The user rates are calculated on the total Belgium population [62]11 267 910 in 2016; 11 322 088 in 2017 and 11 376 070 in 2018; ** This number is based on the website of the BPIDG https://bpidg.be/nl/pid/ . There is also an European Registry, ESID, but this only gives prevalence numbers of 2-3 per 100 000. ***Based on 1/1000-1/1500 live births and 118 000 live births in Belgium in 2018*

3.2 Results

Looking at the results obtained from deriving requirements from patient numbers and recommended doses and frequencies (see Table 23), we can see that mean requirements would be of the order of 2622 kg in 2021 and 2821 kg in 2024 in the hospital setting (3026 kg in 2021 and 3485 kg in 2024 when we include requirements for the ambulatory setting), with chronic conditions accounting for a large majority of the needs (≈89%). Most of the requirements continue to be linked to the 8 indications currently reimbursed in Belgium, although the important number of patients who could not be linked to any relevant indication, should not be neglected. Nevertheless, a part of the patients for which no indication from the list could be identified, appear to be cancer patients or patients with haematological disease, and thus, Ig treatment could potentially be for secondary hypogammaglobulinemia that may be induced by more immunosuppressing medication for cancers or auto-immune diseases. The figures obtained via this approach, appear to show an overestimation, since the estimations obtained for the year 2018 are well above the real (reimbursed) use data from the INAMI/RIZIV (2010 kg for the year 2018, versus an estimated 2702 kg based on patient numbers and recommended doses including both hospital and ambulatory use).

Although this approach was not considered appropriate given the results obtained, it raises some interesting questions regarding Ig use in this country. The overestimation may reflect lower doses in Belgium versus international recommendations, lower frequency of administrations, or more likely, the fact that an important number of chronic patients may start treatment with Ig but stop for different reasons (death, tolerability problems, lack of response to treatment, etc). A further possible reason for stopping treatment could include the use of treatment cessation strategies for certain conditions, under which once the patient is well controlled, Ig treatment may be stopped and only re-started in case of recurrence (e.g. in CIDP patients). Despite the lack of data on treatment continuation approaches, a conscious decision was made not to make any assumptions on that regard, since these would have increased the already important uncertainties that surround these estimations. A good registration system capturing, indications, and quantities consumed per patient per treatment as well as the number of yearly treatments would be necessary before clear conclusions can be made in this regard.

Table 23 – Estimations derived from patient data and recommended doses

Indication	Annual N of patients treated in BE with Ig in 2018 (extrap. from TCT hospital data)	Estimated N. of patients on Ig over period 2021-2024	Total quantity required in gr 2021	Total quantity required in gr 2022	Total quantity required in gr 2023	Total quantity required in gr 2024
1. CHRONIC treatment: Average Ig quantity for treatment by stay						
Primary Immunodeficiency (PID) TOTAL	2 720	11 793	1 139 656	1 160 228	1 181 171	1 202 492
Secondary Immunodeficiency (SID)	1 257	5 689	613 970	630 998	648 499	666 485
Chronic inflammatory demyelinating polyneuritis (CIPD)	607	2 542	450 610	455 264	459 965	464 715
Inflammatory myopathies	7	21	2 102	2 088	1 939	1 799
Multifocale Motor Neuropathy	46	262	69 580	75 361	81 622	88 403
Stiff-person syndrome	5	19	3 480	3 456	3 433	3 410
2. ACUTE treatment: Global Ig quantity for treatment duration < 6 months						
Both Toxic shock synd. & Streptococcus	130	1 094	31 637	37 222	43 792	51 522
Guillain-Barré Syndrome	381	1 805	95 931	99 584	103 377	107 315
Kawasaki Disease (children)	127	479	6 106	6 026	5 947	5 869
FNAIT or NAIT	10	27	24	22	20	19
Hemolytic disease in newborns	16	49	21	20	19	18
Myasthenia gravis	10	28	1 125	1 044	969	900
Pure red cell aplasia & Parvovirus	0	0	0	0	0	0
Von Willebrand's disease	5	19	725	720	715	710
Post-transfusion purpura	0	0	0	0	0	0
Pemphigus (vulgaris-foliculae)-immunogbullous disease	0	0	0	0	0	0
Solid Organ transplant rejection	35	84	2 644	2 361	2 108	1 883
Idiopatic trombocytopenic purpura (PIT) TOTAL	652	2 718	50 677	56 351	56 862	57 377
Antibody-mediated types of encephalitis	9	38	2 741	2 793	2 846	2 901
No identified (proxy) indication	749	2 631	150 584	155 445	160 463	165 644
HOSPITAL REQUIREMENTS			2 621 612	2 688 984	2 753 748	2 821 461
Requirements for AMBULATORY CARE			404 369	476 904	562 451	663 343
TOTAL IG VOLUME			**3 025 981**	**3 165 889**	**3 316 200**	**3 484 805**

A second approach was pursued considering usage data.

Table 24 shows the findings derived from this second approach, which are more in line with the overall figures from the RIZIV/INAMI in 2018. Overall, hospital requirements are estimated to be of 2075 kg in 2021 and of 2499 kg in 2024. Once ambulatory use is added, these needs would be of around 2480 kg in 2021 and 3162 kg in 2024.

When looking at the weight of chronic illnesses on the overall hospital requirements, we can see that these account for approximately 78% of all hospital needs. It is important to note that all use and therefore, requirements in the community setting should be linked to chronic indications, since use of Ig in this setting is limited to SCIg, and this administration type was until recently (September 2020), only reimbursed for two chronic indications (PID, SID), and since then, also as maintenance therapy for CIDP.

Most requirements are linked to officially reimbursed indications (≈92% of all hospital requirements).

In addition to the uncertainties that surround these estimates, a number of current trends not yet reflected in this data analysis, are likely to significantly affect these needs. In particular the COVID crisis is highly likely to put even more pressure on the already limited Ig supply, so product shortages already experienced in the last years are likely to increase in the near future. Despite the current lack of data, and given their importance, current trends, will be covered in our discussion.

Table 24 – Estimations derived from Belgian Ig use data

	2018 (extrap.)	2021	2022	2023	2024	Total requirements 2021-2024
OFFICIAL REIMBURSED INDICATIONS IN BE						
PID	676 699	809 042	858 677	911 356	967 268	3 546 342
SID	257 282	291 578	303 997	316 946	330 446	1 242 968
PIT	136 408	135 943	135 789	135 634	135 480	542 846
CIDP	394 822	483 777	517 678	553 955	592 773	2 148 183
GB Syndrome	87 540	104 804	111 284	118 166	125 472	459 726
Kawasaki Disease	6 634	7 062	7 211	7 363	7 518	29 155
MMN	27 023	32 509	34 576	36 773	39 110	142 968
Streptococcus toxic shock syndrome	16 828	44 811	62 110	86 087	119 321	312 328
INDICATIONS COMMONLY REIMBURSED IN OTHER COUNTRIES						
Solid Organ transplant rejection	8 252	7 826	7 688	7 553	7 421	30 488
Hemolytic disease in newborns	162	164	164	165	165	658
Myasthenia gravis	2 589	2 540	2 524	2 508	2 492	10 064
FNAIT	162	164	164	165	165	658
Von Willebrand's disease	485	601	646	693	745	2 685
Inflammatory myopathies	1 942	1 263	1 094	948	822	4 128
Stiff-person syndrome	647	1 309	1 656	2 094	2 648	7 706
Erythroblastopenia	0	0	0	0	0	0
Pemphigus (vulgaris-foliculae)-immunobullous disease	0	0	0	0	0	0
Post transfusion Purpura	0	0	0	0	0	0
Antibody-mediated types of encephalitis	1 133	1 237	1 274	1 312	1 351	5 175
No identified indication	136 893	150 584	155 445	160 463	165 644	632 136
TOTAL HOSPITAL	1 755 502	2 075 214	2 201 977	2 342 181	2 498 841	9 118 213
TOTAL VOLUME AMBULATORY CARE	246 500	404 369	476 904	562 451	663 343	2 107 068
TOTAL Ig REQUIREMENTS	**2 002 002**	**2 479 582**	**2 678 881**	**2 904 633**	**3 162 184**	**11 225 281**

3.2.1 Comparison of usage rates per indication between Belgium and England

Given the availability of detailed data for England on usage according to indications, a comparison between usage rates in England and Belgium was performed. Data for England was taken from their Ig database, launched in 2008, which includes IVIg and SCIg use both ambulatory and in the hospital setting. This database captures prospectively all NHS Ig use in England. Data entering is mandatory and reliable annual statistics are published every year in reports. Data on usage was extracted from the most recent report.[10] In order to make the Belgian data more comparable, ambulatory patients exclusively on SCIg in the year 2018 (in order to avoid double counting) were considered in the Belgian figures. From all SCIg patients, ≈19,69% are treated in hospital and thus, were excluded from our calculations, since they should already be counted for in the TCT data. The considered SCIg patients were split between the only two indications for which SCIg was reimbursed in the year analysed (i.e. PID and SID). The proportions of SID and PID patients seen in the hospital setting were respected.

Table 25 shows that overall, usage rates were higher in Belgium than in England. Differences were particularly large in the case of PID, for which Ig appear to be over 3 times more commonly used in Belgium. It is important to remember, that a number of patients in the TCT database were registered as being both PID and SID patients, and for the purpose of our analysis these, were considered to be PID patients. Whether these patients are adult PID patients, which were previously diagnosed SID, or whether these are actual SID patients is not clear.

For MMN, in Belgium proportionally less patients are treated with Ig compared to England. These differences may be due to difficulties in discerning MMN from other neuromuscular diseases at the time of diagnosis (e.g. CIDP instead of MMN).

Careful interpretation of these results should nevertheless be made, given the important limitations of the Belgian data (based on proxy indications).

Table 25 – Usage rates – comparison Belgium and England (2018 data)

	ENGLAND 2018[a] N. of patients	ENGLAND 2018 Usage rate[b] (per 100 000)	BELGIUM 2018[a] N. of patients	BELGIUM 2018 Usage rate[b] (per 100 000)
CHRONIC CONDITIONS				
Primary Immunodeficiency (PID) (including specific antibody deficiency)	4277	7.64	2967	26.08
Secondary Immunodeficiency (including CLL. MM. hypogammaglobulinemia after HSCT)	4003	7.15	1371	12.05
Chronic inflammatory demyelinating polyneuritis (CIDP)	1553	2.77	607	5.33
Multifocal Motor Neuropathy (MMN)	683	1.22	46	0.40
ACUTE CONDITIONS				
Toxic shock (streptococcus-staphylococcus)	267	0.48	130	1.14
Idiopatic trombocytopenic purpura (ITP) (acute)	1875	3.35	652	5.74
Guillain-Barré Syndrome	1030	1.84	381	3.35
Kawasaki Disease	324	0.58	127	1.12
TOTAL	14012	25.03	6281	55.22

[a] Sources: For England: annual reports Immunoglobulins database [9, 10, 19]. for Belgium TCT database;

[b] Ig usage rate per indication. based on country population – Population in England in 2018: 55 977 178 [63]. Population in Belgium in 2018: 11 376 070 [62]

4 REGISTRATION IN BELGIUM

4.1 Background

In Belgium there is no central overview on indication specific usage of Ig, though they are strictly regulated via explicit reimbursement criteria for 8 indication groups. These reimbursement criteria are specified in six different reimbursement paragraphs in the NIHDI law: four for IVIg products and two for SCIg products For reimbursed Ig, the law foresees a special application form, needed to be completed by prescribers, most often specialists. In the case of IVIg, this application form must be kept at the hospital pharmacy, and made available to the national health insurance (via the advisory physician of the sickness fund) upon request (called a posteriori control). For SCIg the application form must be sent a priori to the advisory physician of the sickness funds, to obtain an approval. Evidence that patients meet these indication-specific criteria as well as a justification for their use must be documented, and kept available for control by the advisory physician of the sickness fund. There is no central control or monitoring. For this report, indirect ways were used to derive data on indication-specific use (via diagnostic codes). Data was nevertheless limited to reimbursed use in the hospital setting.

Other countries have a more controlled system for the Ig request/application (England. Australia). They monitor via indication specific data registration, allowing frequent updates, which in turn, enable them not only to better understand changes in use and evolutions, but also to respond quickly to potential supply shortages. The country most referred to as having a good monitoring system is the UK. Already in 2008, the National Health Service developed a National Ig Database as part of their National Demand Management Programme (http://igd.mdsas.com/ig-database/). The database has time and again proved its worth during product shortages, recalls, monitoring of changes in prescribing practices and national product procurement. Annual reports provide an analysis of Ig usage across England, and annual conferences are held to discuss care of Ig patients and enhance use of the National Ig Database.

In Australia, since October 2018, a nationwide online system (i.e. BloodSTAR) to manage access to the supply of government funded Ig products was completed. The system manages the authorisation request and review processes for Ig treatment (called the Criteria for the clinical use of intravenous immunoglobulin. based on best evidence and clinical opinion). BloodSTAR was developed over a period of two and a half years and involved intensive consultation with all state and territory governments and all other stakeholders. Once developed, it was rolled out state by state across Australia over a period of two years. This national approach also enables the collection of consistent usage and outcome data to better inform funding and program requirements.

Given the importance that monitoring this scare and expensive product has, some questions were posed to stakeholders and hospital pharmacists and a short overview of their answers is offered in this section.

4.2 Method

A non-exhaustive consultation of stakeholders was conducted (RIZIV-INAMI, Sciensano, the industry, hospital pharmacists) to give input on how data-registration is currently done and how it could change in the future. As part of exploring the current situation in Belgian hospitals, an online survey was sent to hospital pharmacists. This survey posed specific questions on how indications are currently registered in the hospital (which level of detail, on paper or electronically, etc. a list of the specific questions posed is available in appendix 8). Overall, forty hospitals responded, which accounted for approximately 52% of the reimbursed Ig use in Belgium in the year 2018.

4.3 Results

Current situation for Ig

All responded hospital pharmacies reported that the mandatory application form for reimbursed Ig (attestation) is used. But the extent to which the capture of such information is digitalised largely differs between hospitals. In 14 out of the 40 centres (35%). only paper versions of the application forms for reimbursement are available at the hospital pharmacy. Nevertheless, for the majority of responders (26/40), the data are electronically available via the pharmacy software (but often required a manual input by the pharmacist, while in other systems this is directly linked to electronic prescribing).

In the vast majority of cases, only the reimbursement paragraph is registered, so details on the exact indication are generally lacking. Only in three hospital pharmacies indications were systematically registered in the pharmacy software.

Some disease-specific registries exist at a national level, such as the Belgian Neuromuscular Disease Registry (BNMDR), or at a European level, such as for PID (ESID). However, the BNMDR register does not focus on the therapeutic treatment and requires extra data-entry or coupling with Ig use information. The European register does not capture all the Belgian PID patients, as their registry is not compulsory. Stakeholders advise not to install stand-alone new registries to capture information on Ig (indications or outcome data), but use the current digitalisation wave and developed applications.

Digitalisation is in full deployment, with two projects that could potentially facilitate the registration of indications: CIVARS (Chapter IV Information Consultation System) or TARDIS (Tool for Administrative Reimbursement Drugs Information Sharing). Both are developed for reimbursed medicines. The former is merely aimed at exchanging administrative information on approval for reimbursement between prescribers, (hospital) pharmacists and the sickness funds. While the latter, allows for capturing some clinical information.

CIVARS is an eHealth 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). Physicians can request reimbursement and send an application to the insurance (advising physicians), who, in turn, can forward the authorisation or refusal. At the moment, pharmacists have a consulting role, they can consult and check whether or not there is a positive advice for reimbursement. At a later stage, the intention is that pharmacists will be able to register the prescription online.

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 (via browser), for which some experience connection problems, and in other hospitals the service is already integrated in their hospital software (most of the time linked to the electronic patient record). This means that hospital pharmacists still have to look up in the electronic patient file or in the online CIVARS application whether or not reimbursement is granted.

TARDIS is an online eHealth application allowing the recording and exchange of administrative and medical data. At the moment this is only available for anti-TNF medications for rheumatoid arthritis. TARDIS makes it possible to enter patient data in the context of certain pathologies, while at the same time requesting reimbursement for a specific treatment by filling in an online application.

For non-reimbursed Ig, there is currently no registration of indications, though such information may be available in the medical file of the patient. Stakeholders agreed that a registration of indications for which no reimbursement is requested would be informative. However they thought this should be done in an anonymous way, because often, the non-reimbursed use is linked to off-label indications.

Future possibilities

Digitalising processes in the hospital setting must be a priority as still some hospitals work only via paper. But also the interoperability between ICT systems should be facilitated (system-to-system linkage between electronic patient file, (hospital) pharmacy software, sickness funds systems).

Similar to England and Australia, Belgium could profit from a better overview on indications of Ig use. It could help to identify trends, facilitate discussion between the different stakeholders, and plan future needs.

How detailed should this data-registration be? Only for reimbursed Ig or also for non-reimbursed Ig? Only the indication or also outcome data? The latter can be helpful when there is too little clinical information on effectiveness linked to a specific Ig indication. The different options as well as the necessary steps that should be followed (legal, technical, and data protection) fall out of the scope of this report. Table 26 gives a brief, non-exhaustive summary of options.

Table 26 – Overview of possibilities for indication (or outcome) registration

What?	How?	Prerequisites
Indications for reimbursed Ig and non-reimbursed Ig	Capture indication during the prescription.	No precedent. New dataflow. new legislation
Indications for reimbursed Ig	Example CIVARS	Including a filed in which indications can be captured (predefined list of indications) and not just the reimbursement paragraph. For IVIg and SCIg. Adapt existing ZIV-legislation.
Indications and clinical information/outcome data for reimbursed Ig	Example TARDIS	Define in collaboration with clinical experts for which indications capturing outcomes is relevant and which outcomes are relevant. New legislation and agreement from the data protection authority.

5 DISCUSSION AND LIMITATIONS

The increase of Immunoglobulin use

Immunoglobulin consumption is increasing over time in Belgium at a rate similar to that seen in other countries. Thus, the overall reimbursed consumption of Ig rose from around 1126 Kg in 2010 to 2010 kg in 2018, coinciding with a national budget rise from around 50 million euro in 2010 to 90 million euro in 2018. These rises reflect an increase in both the number of patients and the annual volume of Ig used per patient.

Annual growth rates over the period 2010-2018 ranged between 6 and 12%, with the only exception of two time periods in which consumption remained practically stable: 2014 and 2017. This is probably the result of the more stringent reimbursement criteria, introduced in those two years, which appear to have had an important effect.

Overall, the use of SCIg is growing at a higher rate than IVIg, mainly due to a rise in the number of patients in the ambulatory setting (dispensed via community pharmacies), while the mean annual volume of SCIg per patient has not increased as much. In addition to this, the evolution of (public) expenditure appears to mirror that of SCIg consumption. Nevertheless, its use continues to account for a small proportion of the global Ig consumption (around 13% in 2018).

IVIg. is reserved for administration in the hospital setting due to the need for specific medical material and staff and appears to be mainly administered in the day-care hospital setting (>70% of the hospital administration), for which sometimes consecutive days of administration are necessary to obtain the prescribed dose. SCIg are predominantly administered in the home-setting, where often home nursing/training is foreseen. The analysis shows that more patients are switching to home care treatment each year.

Ig use showed a large variation between hospitals, with academic hospitals accounting for a large proportion of the overall volume of Ig used, covering also an important proportion of patients. This may be explained by the introduction of new reimbursement criteria in 2014. Since then, for PID patients, the diagnosis and clinical re-evaluation must be made by a physician from 'The Belgian primary immunodeficiency group' (BPIDG), recognised by the NIHDI. Most of those expert-clinicians (29 overall) are connected to an academic centre. Similarly, for the indication CIDP and MMN, the diagnosis and clinical re-evaluation must take place in one of the 7 NMRCs, often incorporated or linked to an academic hospital. Consequently, there was a shift/referral of eligible patients to those recognised centres.

Official reimbursed indications represent more than 90% of the total volume of Ig consumed during the analysed period (2012-2018), with PID and CIDP representing the largest volumes, respectively. Five main indications appear to account for the large majority of patients treated with Ig in the (≈ 83%) Belgian hospitals. These include PID (≈40%); SID (≈19%); PIT (10%); CIDP (9%) and GBS (6%). Although our method of using proxy-indications based on diagnostic codes has its limitations (see further), and the data cover only the hospital setting, some peculiarities were noted. A significant group of PID patients had also a SID diagnosis (but for the ease of the analysis were categorised as PID patients). A closer analysis showed that these PID-SID patients are generally speaking an older patient group (72% were 60+). The experts consulted during this research explained that in some cases, discerning adult PID from SID could be challenging (e.g. symptoms may appear at an advanced age, and the genetic causality may be found later on). These difficulties, coupled with the complex reimbursement criteria, may have resulted in inconsistent diagnostic coding.

The high proportion of unspecified prescribers (a limitation due to lack of mandatory registration in the hospital setting), impedes to make conclusions on the appropriateness of prescribing. Key prescribers appear to be haematologists, prescribing 26% of all Ig reimbursed volume in 2018. The second group are the neurologists, for which volumes prescribed doubled over the study period (2012-2018), and who prescribe predominantly in the hospital sector. The highest volume of SCIg in the community setting was prescribed by GPs in 2018.

For reimbursement to be granted, specific criteria apply that may require the confirmation of the diagnoses as well as any clinical reassessments to be restricted to either certain medical specialties or specific centres (e.g. Neuromuscular Reference Centre. BPIDG). However, there are no limitations regarding prescribing rights (with the only exception of GBS, for which prescribing must be made by neurologists or neuropsychiatrists). While there is some information captured in the reimbursement requests, these data are not centrally available, and as a consequence, it was not possible to analyse the profiles of those requesting reimbursement.

Minimum optimal dosing

Ig dosing is dependent on the weight of the patient. Strategies to limit Ig volumes include the consideration of using minimum optimal doses for patients. This means that clinicians should aim to use the lowest possible dose that achieves the appropriate clinical outcome for each patient.[64] Often, in the case of overweight, obese patients, this dose calculation is not based on the actual patient's weight but on a formula built on the ideal body weight (known as the adjusted-body weight). This approach is widely accepted and actively recommended in some countries such as Australia or Canada.[65, 66]

The NHS England recently implemented a project to reduce the recommended dose for PIT (more patients on a 1g/kg dose instead of a 2g/kg). Such strategy resulted in a considerable reduction in consumption which in turn produced cost savings (almost £5 million in 2018/19).[10]

On the basis of the limited Belgian data, the dosing schemes as well as the annual volume per patient were analysed. In general, the annual volume per patient, regardless of indication, grew annually for patients on IVIg, while for patient exclusively on SCIg, this growth was limited. However, this group of IVIg patients is made up of both patients who require dosages of 0.4 to 0.6g/kg IVIg, as a replacement treatment (PID and SID), and patients with higher immunomodulation doses of around 1 to 2g/kg (e.g. PIT, CIDP, MMN). A per-indication analysis showed that the average annual quantities per patient rose over the study period (2012-2018). Whether this is a consequence of other dosage strategies or heavier/older patients could not be clearly stated. Both dosages per administration and frequency of administrations rose. While it is not possible to conclude anything on appropriateness of dosages, as the databases did not capture the weight of the patients, one can see that often the international recommended dose per administration is reflected in the dosages per stay seen in Belgium, although for some prevalent chronic indications such as PID or SID, dosages per stay appear to be on the lower side than what one would expect from a 75 kg adult.

A comparison between the volume of Ig use in Belgium and England, shows for almost all indications a lower annual volume per patient in Belgium. Possible reasons behind this finding are difficult to discern (lower dosages, differences in patient characteristics, less frequent administrations or shorter treatments). On the other hand, the usage rate (per 100 000 population) in Belgium compared to England appears to be higher for most indications. The difference is most pronounced for PID patients (in 2018, there were 7.6 Ig treated PID patients per 100 000 population in England compared to 26 per 100 000 population in Belgium). Although the exact reasons for these findings could not be elucidated, both the finding of the relative lower volumes per patient and the larger patient numbers could indicate that in Belgium more patients start treatment with Ig but may stop it when not responding, as well as possible treat-stop-treat approaches in certain conditions where once the patient is well controlled. Ig treatment may be stopped and only re-started in case of recurrence (e.g. in CIDP patients).

As already stated in all available Ig guidelines and in the Belgian reimbursement criteria, the effect of the Ig treatment must be assessed and re-assessed, on a regular basis (every 6 months or every year). For this scarce and expensive medication, every precaution must be taken to avoid waste.

Non-reimbursed Ig use – an indicator for unmet-medical needs?

It is important to highlight that all our analyses represent only the reimbursed (publicly funded) part of Ig consumption in Belgium.

The **overall volume of non-reimbursed use and off-label use remains unknown** to this date. Some indirect ways to estimate this were explored (eg. comparison of sales data and reimbursement data, hospital pharmacist survey), leading to percentages ranging from 1% to 8% depending on the source used. But too many uncertainties hampered the interpretation of our results. Moreover, the details on indications for this non-reimbursed use are currently not captured, which impeded us from gaining an overview on possible unmet medical needs in Belgium.

Nevertheless, our (limited) findings for the hospital and community setting are described below.

For the hospital setting:

- The survey carried out among hospital pharmacists reported a non-reimbursed use of around 1% of the total Ig hospital volume. This survey captured a small increase in self-reported non-reimbursed use over the same time period. Nevertheless, as reimbursed use also increased, the proportion of non-reimbursed use over the total Ig volume consumed remained more or less stable and was not perceived by pharmacists as a possible source of future product shortages.
- The analysis of reimbursed Ig in Belgian hospitals carried out as part of our research for the period 2012- 2018, found around 10-14% of patients (around 600 patients per year) for which no relevant indication (i.e. diagnostic ICD code) could be identified. And for 1.3% to 2.7% (which represents around 120 patients per year), an ICD code for an off-label indications was found. Whether these reflect errors or incompleteness in coding/registration or reflect use in some indications for which an unmet need exists in Belgium remains unknown.
- A comparison of Ig volumes sold to hospitals and the reported reimbursed Ig hospital volumes showed discrepancies that could be considered an approximation to the quantity of non-reimbursed use in this setting. Such an analysis showed that while practically all IVIg sold to hospitals (95% in 2017 and 98% in 2018) appeared to have been filed for reimbursement, this was only 60% of the SCIg sold to the hospitals. It is important to mention that the SCIg market in hospitals is small, and that the difference between sales and reimbursed use for SCIg in this setting represents only '8 kg'. Such small differences could therefore also be a consequence of some product stocking. Based on the available data and the input from stakeholders, there is no clear conclusion on whether stockpiling may represent a problem in Belgium. The need for more flexibility to allow re-distribution of Ig products between hospitals was mentioned during our consultations.
- The Special Solidarity fund did not identify an increase in funding requests over the last three years (2017-2019), and the overall volume of requests remain to this date very low (new annual request were 17 in 2017, 24 in 2018 and 10 in 2019). It was not possible to obtain the exact volumes of Ig funded via this source.

For the ambulatory (community) setting:

Data on non-reimbursed Ig use in the ambulatory sector, are scarcer. At present, in Belgium there is no national public registration of Ig quantities distributed by community pharmacies, for non-reimbursed use. The only available data on this regard is property of a private data company (The Human Data Science Company - IQVIA).

Nevertheless, a comparison between Ig sales (to wholesalers and community pharmacies) figures and reimbursed consumption in community pharmacies showed a discrepancy of around 25% in SCIg products (representing a volume of 85kg in 2018). It is important to highlight that community use is limited to SCIg products since IVIg is reserved for the hospital setting. The extent to which the differences identified represent non-reimbursed ambulatory use, parallel exports, or (more likely) a combination of both, remains unclear.

Ig requirements

Our estimations showed that hospital requirements for the next 4 years (2021-2024) would amount to approximately 9118 Kg. Once ambulatory use is added, these needs would be of around 11 225 kg for the whole 4 year period.

As we will see in our limitations, these estimations are subject to important uncertainties mainly linked to the quality of the limited data currently available, as well as to the years it refers to (2018 being the latest year available for analysis). Assumptions had to be made on the future growth of Ig needs, but these could not take into consideration important trends which will be mentioned later on in this discussion. Nevertheless, these calculations should serve as illustrations that should be refined and adapted, as more data become available.

Trends

Enforcing growth

- Ig use is increasing, especially SCIg use in ambulatory care. For chronic diseases, the switch from IVIg to SCIg is likely to continue, which fits in the health care trend of treating patients close to (or at) their homes. The recent approval for reimbursement of the indication CIDP for the SCIg 'Hizentra®' will enforce this growth, as important dosages are used in CIDP patients. The shift from hospital to ambulatory SCIg dispensing is also likely to have an impact on the public medicines budget, as public prices are slightly higher in the community pharmacy due to the different (higher) distribution margins (pharmacist and wholesalers).
- An indication for which Ig use is likely to rise in the future is SID, as more and more immunosuppressing medication for cancers or auto-immune diseases can induce a secondary hypogammaglobulinemia. Less pronounced growth rates, but important in terms of volume, are expected for CIDP patients. In terms of off-label indications, important increases are also foreseen in myasthenia gravis and inflammatory myopathies.[13]
- Clinical trials in several diseases are ongoing. If these show positive results for Ig as a treatment, usage may go up. Either official requests for licencing could be filed, or in the absence of this, off label use may go up as there is a scientific rationale for its use.
- Use appears to grow in older adults. Thus, the proportion of patients aged over 60 increased from 45% of all patients in 2010, to 51% in 2018. This reflects the aging population, which in turn is likely to result in a higher prevalence of chronic diseases, requiring longer treatment periods.

Limiting growth

- For some indications, some alternative treatments may prove their value (e.g. eltrombopag - Revolade® for PIT). In Belgium a medical need program is ongoing since June 2020 for patients with refractory PIT (more than 6 months on other therapies including Ig). Some ongoing trials in this same field could also have an effect on future needs.
- The COVID-19 pandemic will impact the plasma supply considerably (particularly international plasma supply) and could also potentially enlarge the demand side, as clinical trials on convalescent plasma as well as polyvalent Ig are currently taken place around the world. Despite the fact that no trials on the value of polyvalent Ig are currently ongoing in Belgium, over 10 trials exploring these products are ongoing worldwide. Although polyvalent Ig are not expected to become the standard of care for COVID-19, some preliminary results linked to a small trial have shown a positive effect. Should this positive result be confirmed, or should more trials exploring polyvalent Ig start in the future, this is likely to have a (limited) impact on the consumption of Ig and could add to the existing pressures on the supply side.
- Shortages will have an impact on future use rates, but subsequent actions taken by governments, firms, hospitals and prescribers to alleviate or limit the impact of such shortages (decrease demand-side) could also have an effect on Ig availability or access.

Limitations of this research

Our data-analysis is not exempt from limitations.

As already described in our methods section, several data sources were analysed attempting to give a complete picture of the Belgian Ig use. This variety of data-sources, each with its limitations, prevented us in some cases from reaching clear conclusions. Moreover, the use of multiple partially overlapping data sources, combined with the necessary data manipulations has given rise to some small differences when confronting one source to another.

The analysis on indication-specific Ig use is limited to reimbursed Ig use in the hospital setting (daycare or inpatient), where the indication is derived from available diagnostic codes (the TCT database). There are some limitations in using the diagnosis registered in the TCT database. First of all, this is a proxy for an indication as these are diagnostic codes related to the reason of the stay and the indication for Ig as such, is not captured in the data. Not every Ig indication can be linked to a specific ICD- code. Often a grouping of several ICD codes are used to approximate the Ig indication as closely as possible. The two versions of the coding system. ICD-9 (used until 2015) and ICD-10 are not fully in accordance (see Table 5 in our methodology section). Moreover, not all hospital stays could be linked to ICD-9-CM and ICD-10-BE diagnostic codes, either because coding was missing during the coupling or because the specificity of the hospital stay did not require a diagnostic code (a psychiatric or emergency admission or some day-care hospitalisations). Consequently, around 50% of hospitalisations, predominantly daycare stays, were discarded (which represent around 18% of patients and 24% of Ig use in hospitals). Moreover, in case of patients who had more than one diagnosis, assumptions were made to link the patient to one indication, but whether our assumptions reflect or not the real indication for which Ig was prescribed cannot be assured.

Non-reimbursed use was analysed via a survey addressed to hospital pharmacist, consequently introducing some bias. Participation bias may hamper the representativeness of results. Moreover, the info on non-reimbursed use is limited to the hospital sector. In the future, if the shift to more subcutaneous use in the home setting continues, the non-reimbursed use in the ambulatory care sector could grow.

Regarding the estimations made for Ig requirements, these are based on relatively old data for which indication-specific data could be derived. As a consequence, these requirements do not reflect the current trends that we will list below and that are highly likely to have a great impact on the consumption of Ig.

Other countries such as England or Australia, which have more up to date indication specific data have forecasted an important growth for certain indications such as CIDP, inflammatory myopathies or SID. In our case, the growth of use in inflammatory myopathies in the years for which data is available was negative, but this trend may have changed in the last years. Similarly SID and CIDP have grown, but whether their growth rates in 2019 and the first half of 2020 were higher remains unknown.

Managing supply problems

Shortages appear to continue at present and are unlikely to disappear in the near future. Meanwhile, the range of products and suppliers have decreased in Belgium, often linked to the preferential distribution of the limited Ig to larger, more profitable markets. In this context, Belgium would benefit from a transparent and coherent approach to surveillance, including early warnings for potential product shortages.

Although the consideration of different strategies that could help to increase Ig supply were out of the scope of this research, it is worthwhile mentioning that most countries maintain a range of manufacturing and supplying options, and avoid focusing on only one Ig product (one contract).[14, 40, 43] Moreover, when a country wants to be less dependent on the international market, the national collection of plasma donations has to increase in order to be the closest possible to self-sufficiency.[31]

Transparency on stocks

Increasing transparency on **available stocks** could help to anticipate possible supply problems.

Other countries are facing similar challenges. The example of France serves as an illustration. Since 2008, France has in place a monthly update system for Ig stocks and needs. Based on consumption information and data received from firms that produce Ig, the ANSM publishes a monthly update on their website "*Couverture prévisionnelle des besoins en Médicaments Derivés du Sang au niveau national*".[41] A colour code indicates whether there is a risk for a shortage within 15 days, 30 days, or if there is no real threat expected for the following month. This system is the result of a collaboration between the public authorities and the pharmaceutical industry. Similar systems could be considered for Belgium.

In Belgium at present shortages at the national level are detailed in the *farmastatus* website. Nevertheless, this system only warns of shortages once a product has been already unavailable for three days. Such system does not allow for the necessary planning and adaptation that may be necessary under such circumstances. Moreover, there also shortages on a more local level, when a hospital surpasses his specific contracted quota, for which solutions should be sought.

To improve transparency on the available stocks as well as facilitating an appropriate response to specific shortages, a close collaboration between governments, manufacturers and wholesalers would be advisable (eg. discussing possibilities for strategic rotating stock).

Regarding the hospital tenders in place, pharmacists perceived as problematic the fact that requirements are based on global data of previous years that do not allow for effective quick adaptations to this dynamic market. An effort should therefore be made to improve the current forecasting methods for Ig needs. For this purpose, rapid registration of indication-specific data on usage would be necessary, in order to quantify more accurately future needs per indication. Such system would also offer more transparency.

Very few hospital pharmacists reported a problem of overstock of a specific product. Given the current lack of visibility on hospital stocks efforts to increase transparency could help to avoid waste. Moreover, initiatives that could facilitate the redistribution between hospitals of such scarce and vital products, within and outside of hospital networks, could be looked into (bearing in mind the current legal barriers, and the need for monitoring to avoid hospitals acting as distributors). In the context of supply problems, during a defined period, a legal basis could be foreseen to organise a central and controlled Ig distribution towards hospitals (and the ambulatory sector if needed). However, without clear indication-specific data, it will be particularly challenging to define the factors that should be considered to ensure a fair product distributions.

Until now there were no real shortages for SCIg products, so the ambulatory sector was less impacted. However, as this administration type is likely to grow, in the future, supply problems may arise. The current COVID - pandemic has accelerated this switch as it is deemed more appropriate to administer Ig in the home setting. Such specific SCIg shortages have already been encountered in France[67], and Octapharma recently called to temporarily stop initiating patients on their SCIg product (Gammanorm®) in Belgium. Therefore, also in the ambulatory sector, initiatives on increasing transparency should be considered.

Limiting demand

Another way to cope with a tight supply is to limit the demand. All current recommendations and reimbursement criteria highlight the need for careful consideration before starting Ig treatment for a patient (severity of the disease, approval/confirmation of diagnosis by experts...), and regular reassessment, including the consideration to wean off patients from Ig (e.g. CIDP).

In addition to recommending to use minimal optimal dosages previously covered in this section, most countries analysed in our first report implement a system of indication prioritisation to aid decision-making during shortages (more info in the KCE report 327[7]). In view of a dynamic market, regular updates are done. In France there is the list called "*Hiérarchisation des*

indications des immunoglobulines humaines en situation de forte tension d'approvisionnement". A new version of the list was published in April 2019, which is expected to be updated in order to reflect the extra pressures on the supply due to the current COVID pandemic.[68] England is also currently revising its commissioning criteria for Ig.[16]

With the exceptions of the indications in which the use of Ig is well established and those for which RCT evidence is available, rankings appear to differ from one country to another. This is due to the fact that in those cases in which limited evidence is available (not uncommon, given the rare nature of some of these diseases), national experts were consulted and involved in drafting priority lists.

To this date, there are no such decision aids/priority lists in Belgium. However, in the Belgian legislation there is already a possibility to draw such a priority list.[46] A challenge for our country is the fact that it is uncommon to consider off-label indications which could appear on a list next to, or even ranked between, licenced indications. However, in order to offer a more complete picture, and avoid neglecting undetected unmet needs, the inclusion of off-label indications, ranking them on the basis on the unmet medical need tool explained in the first series of recommendations based on the first part of this research (KCE report 327[7]) could be considered. As drafting such a list including all relevant criteria could be time-consuming, building on the work done in other countries, as well as on the opinion of national experts could be considered.

Ethical considerations

Despite the fact that ethical considerations were out of the scope of this project, it is important to highlight that aside from the widely discussed ethical issues already touched upon in the first part of this report and in more detail in the KCE report from 2009[32], linked to plasma donation (e.g. should remuneration be considered to increase the number of plasma donors?), other important ethical considerations are worthwhile mentioning.

First, the difficulties experienced by prescribers when confronted with patients suffering from a severe condition that may not be responding well to Ig treatment, but for which no other treatment alternatives exist. Stopping treatment in patients under such circumstances may be considered appropriate, given the high prices and the scarcity of Ig, but the decision is clearly not an easy one to make. Second, some off-label indications for which Ig is used in other countries can be very rare or very severe, so a decision on the appropriateness of considering Ig for such patients would need to be made, often based on very scarce evidence, data and experience. Moreover, when considering non-reimbursed use, the financial impact to the patient, in particular, when considering treatment with expensive products such as Ig, should not be neglected, and inequalities in access to care are likely to emerge. Third, these decisions on who should or should not be offered Ig treatment can become even more difficult during shortages, since during those periods delaying treatment, lowering doses or considering other treatment alternatives may not always be an appropriate option for an individual patient.

A further ethical consideration which adds to the difficulties previously mentioned, has already been described in a recent Canadian report.[14] This is linked to the fact that in most countries (and Belgium is not an exception), the split between reimbursement authorisations and prescription rights often result in specialists granting reimbursement, having to make decisions without having been in contact with the patient. Under these circumstances, refusing authorisation, against the opinion of colleagues who consider a specific treatment as a good option for their patients, may not be an easy choice.

Other findings

A number of important points were identified throughout this research.

The input captured via our survey and questionnaires for hospital pharmacists and experts made it clear that Ig products and different administration types (IV and SCIg) are not fully interchangeable, and that in some specific patients or situations, a switch would not be appropriate and could even have a negative impact on the care of the patient (e.g. tolerability problems). In addition to this, they highlighted that total harmonisation in terms of reimbursement in the indications of Ig products is lacking (e.g. Octagam® 10% and some Nanogam® 5% packages), which could make a product switch more challenging in case of real shortages.

Multiple public institutions are currently monitoring and supervising Ig use in this country, although the information currently captured via their systems remains partial (NIHDI, FAMHP, FPS) and their collaboration is organised on an ad hoc basis. Considering Ig is an expensive medicine, subject to shortages, a more pro-active monitoring could help guiding policy decisions in a more timely matter.

REFERENCES

1. Abolhassani H, Sadaghiani MS, Aghamohammadi A, Ochs HD, Rezaei N. Home-based subcutaneous immunoglobulin versus hospital-based intravenous immunoglobulin in treatment of primary antibody deficiencies: systematic review and meta analysis. Journal of Clinical Immunology. 2012;32(6):1180-92.
2. Berger M, Cupps TR, Fauci AS. Immunoglobulin replacement therapy by slow subcutaneous infusion. Ann Intern Med. 1980;93(1):55-6.
3. Lingman-Framme J, Fasth A. Subcutaneous immunoglobulin for primary and secondary immunodeficiencies: an evidence-based review. Drugs. 2013;73(12):1307-19.
4. van Schaik IN, Bril V, van Geloven N, Hartung HP, Lewis RA, Sobue G, et al. Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol. 2018;17(1):35-46.
5. Bruton OC. Agammaglobulinemia. Pediatrics. 1952;9(6):722-8.
6. Imbach P, Barandun S, d'Apuzzo V, Baumgartner C, Hirt A, Morell A, et al. High-dose intravenous gammaglobulin for idiopathic thrombocytopenic purpura in childhood. Lancet. 1981;1(8232):1228-31.
7. Bourgeois J, Fairon N, San Miguel L. Polyvalent immunoglobulins – Part 1: A rapid review Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE); 2019 02/2020. KCE Reports 327 Available from: https://kce.fgov.be/sites/default/files/atoms/files/KCE_327_Polyvalent_Immunoglobulines_Report.pdf
8. L'Observatoire des médicaments ddmedlitO. Immunoglobulines humaines normales intraveineuses et sous-cutanées: bilan des utilisations dans les établissements de santé d'Ile-de-France. 2017. Available from: http://www.omedit-idf.fr/wp-content/uploads/2018/04/Rapport-IGHN-2017VF.pdf

9. NHS England. Immunoglobulin Database: annual report 2017/2018. 2018. Available from: http://igd.mdsas.com/wp-content/uploads/ImmunoglobulinDatabaseReport201718_v1.pdf

10. NHS England. Immunoglobulin Database: annual report 2018/19. 2019. Available from: http://igd.mdsas.com/wp-content/uploads/ImmunoglobulinDatabaseAnnualReport201819.pdf

11. Garraud O. Injectable immunoglobulins, immunodeficiency and off-label clinical trials, source plasma and ethical concerns and debates. Transfus Apher Sci. 2019;58(4):529-30.

12. Canadian Blood Services. Immune Globulin 5 year trend in grams: intravenous and subcutaneous [Web page].2020 [cited May 29, 2020]. Available from: https://blood.ca/sites/default/files/Immune_Globulin_5_Year_Trend_by_Grams_2018_2019.pdf

13. National Blood Authority Australia. Annual Report: Issues of Immunoglobulin products, 2014-15 to 2018-19 [Web page].2020 [cited May 29, 2020]. Available from: https://www.blood.gov.au/pubs/1819report/part-2-annual-performance/objective-1-secure-supply-blood-and-blood-products.html

14. Health Canada. Protecting access to immune globulins for canadians. 2018. Available from: http://publications.gc.ca/collections/collection_2018/sc-hc/H22-4-12-2018-eng.pdf

15. National Blood Authority Australia. National Immunoglobulin Governance Program [Web page].2019 [cited 20/03/19]. Available from: https://www.blood.gov.au/Ig-program

16. NHS England. Updated Commissioning Criteria for the use of therapeutic Immunoglobulin (Ig) in immunology, haematology, neurology and infectious diseases in England. 2019 Available from: http://igd.mdsas.com/wp-content/uploads/NHSE_Commissioning_Criteria_for_the_use_of_Ig_V1.4_November_2019.pdf

17. L'Agence nationale de sécurité du médicament et des produits de santé (ANSM). Hiérarchisation des indications des immunoglobulines humaines polyvalentes 2019 Available from: https://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Utilisation-des-immunoglobulines-humaines-polyvalentes-Ig-dans-un-contexte-de-tensions-d-approvisionnement-point-sur-les-actions-mises-en-aeuvre-Point-d-Information

18. National Blood Authority Australia. National report on the ussue and use of Immunoglobulin (Ig): Annual Report 2017/18 2018. Available from: https://www.blood.gov.au/system/files/Report-on-the-Issues-and-Use-of-Ig-2017-18%20FINAL.pdf

19. NHS England. Immunoglobulin Database: annual report 2016/17. 2017. Available from: http://igd.mdsas.com/wp-content/uploads/ImmunoglobulinDatabaseReport201617.pdf

20. Fortune Business Insights. Market Research Report: Immunoglobulins [Web page].2019 [cited June 18, 2020]. Available from: https://www.fortunebusinessinsights.com/industry-reports/immunoglobulins-market-100571

21. Allied Market Research. Intravenous Immunoglobulin Market Overview [Web page].2019 [cited June 18, 2020]. Available from: https://www.alliedmarketresearch.com/intravenous-immunoglobulin-IVIG-market

22. Market Research Bureau. Forecast of the Global Immunoglobulin (IgG) Market 2023 [Web page].2020 [cited 3 June, 2020]. Available from: https://marketingresearchbureau.com/list-of-reports/worldwide-immunoglobulin-igg-forecast-2023/

23. Market Research Bureau. Plasma Supply into the Future. In: Proceedings of Workshop on Plasma Collection - European Blood Alliance and International Plasma and Fractionation Association;

2020; Amsterdam. Available from: https://ipfa.nl/wp-content/uploads/2019/08/1_5_ROBERT-Robert_IPFA-EBA_January14_Dispatch.pptx-FINAL-READY-FOR-PUBLICATION.pdf

24. Farrugia A, Grazzini G, Quinti I, Candura F, Profili S, Liumbruno GM. The growing importance of achieving national self-sufficiency in immunoglobulin in Italy. The emergence of a national imperative. Blood Transfus. 2019;17(6):449-58.

25. Plasma Protein Therapeutics Association. Immune Globulin (Ig) Monthly U.S. Distribution from Feb 19 to Jan 20 [Web page].2020 [cited May 29, 2020]. Available from: https://www.pptaglobal.org/safety-quality/north-america-programs/north-america-data-program

26. Canadian Blood Services. Immune Globulin 5 year trend by population 2014-2019 [Web page].2020 [cited May 29, 2020]. Available from: https://blood.ca/en/hospital-services/products/plasma-protein-products

27. Moog R. The plasma supply in Germany. Transfus Apher Sci. 2019;58(6):102668.

28. Dutch Minister for Medical Care. Recent development at Sanquin Plasma Products BV,. 2020 Available from: https://www.tweedekamer.nl/kamerstukken/brieven_regering/detail?id=2020Z18624&did=2020D40251

29. WHO. Towards 100% voluntary blood donation: A global framework for action. 2010. Available from: https://www.who.int/bloodsafety/publications/9789241599696/en/

30. DIRECTIVE 2002/98/EC setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood componentsand amending Directive 2001/83/EC, 2003. Available from: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:033:0030:0040:EN:PDF

31. EU Commission. Creative Ceutical Report: EU-wide overview of the market of blood, blood components and plasma derivatives 2015. Available from: https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/20150408_cc_report_en.pdf

32. Léonard C HG, Senn A, Huybrechts M. How to ensure self-sufficiency of stable plasma derivatives in Belgium ? Health Services Research (HSR). Bruxelles: Centre fédéral d'expertise des soins de santé (KCE). . 2009;KCE Reports 120B. D/2009/10.273/58.

33. Plasma Protein Therapeutics Association (PPTA). Donating Plasma [Web page]. [cited 25 October 2020]. Available from: https://www.donatingplasma.org/

34. Plasma Protein Therapeutics Association. Risks Decreasing European Plasma Collection [Web page].2020. Available from: https://www.pptaglobal.org/media-and-information/press-releases/1075-new-edition-of-edqm-blood-guide-risks-decreasing-european-plasma-collection

35. Millar CM, Connor N, Dolan G, Lee CA, Makris M, Wilde J, et al. Risk reduction strategies for variant Creutzfeldt-Jakob disease transmission by UK plasma products and their impact on patients with inherited bleeding disorders. Haemophilia. 2010;16(2):305-15.

36. National Blood Authority Australia. Annual Report 2016-2017: Australian Fractionation Agreement. 2020. Available from: https://www.blood.gov.au/pubs/1617report.v2/part-2-annual-performance/objective-1-secure-supply-blood-and-blood-products.html

37. De Angelis V, Breda A. Trends in Plasma Toll Fractionation for Self Sufficiency of Plasma-Derived Medicinal Products in Italy. Transfus Med Hemother. 2019;46(4):232-8.

38. Les prix de cession hors taxes aux établissements de santé pour les spécialités Immunoglobulins intraveneuses, Journal officiel

2018. Available from: Avis relatif aux prix de spécialités pharmaceutiques publiés en application des articles L. 162-16-5 et L. 162-16-6 du code de la sécurité sociale

39. Dutch Minister for Medical Care. Medicines policy progress letter,. 2019 Available from: https://www.rijksoverheid.nl/documenten/kamerstukken/2018/12/20/kamerbrief-over-voortgangsbrief-geneesmiddelenbeleid

40. Food and Drug Administration. Information About Immune Globulin (Human) Product Shortage [Web page].2019 [cited June 08, 2020]. Available from: https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/information-about-immune-globulin-human-product-shortage

41. L'Agence nationale de sécurité du médicament et des produits de santé (ANSM). Couverture prévisionnelle des besoins en médicaments dérivés du plasma sanguin au niveau national [Web page].2019. Available from: https://www.ansm.sante.fr/Dossiers/Medicaments-derives-du-sang/Situation-des-approvisionnements2/(offset)/0#

42. Plasma Protein Therapeutics Association. The Global Journey of Plasma [Web page].2019 [cited June 08, 2020]. Available from: https://www.pptaglobal.org/images/IVIG/Global_journey_of_plasma.pdf

43. EuropaBio. White paper on Public Procurement of Biological Medicines. 2015. Available from: https://www.europabio.org/sites/default/files/europabio_white_paper_on_public_procurement_of_biological_medicines_final.pdf

44. Hartmann J, Klein HG. Supply and demand for plasma-derived medicinal products - A critical reassessment amid the COVID-19 pandemic. Transfusion. 2020.

45. L'Agence nationale de sécurité du médicament et des produits de santé (ANSM). Tensions d'approvisionnements du marché français en immunoglobulines humaines-COVID19. 2020 Available from: https://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/L-ANSM-reunit-un-comite-d-experts-consacre-a-la-disponibilite-des-immunoglobulines-humaines-pour-les-patients-Point-d-information

46. Art. 20/1. incorporated in the Law of 5 JULI 1994. - Wet betreffende bloed en bloedderivaten van menselijke oorsprong. , Belgisch Staatsblad, Moniteur Belge 2014. Available from: http://www.ejustice.just.fgov.be/cgi_loi/change_lg.pl?language=nl&la=N&cn=1994070545&table_name=wet

47. Federal Public Service Health FcsaE. Order agreement in execution of public tendering with regard to the delivery of plasma derivatives to hospitals. 2018

48. FAMHP. Additional conditions for the delivery or prescription of medicinal products in the new online medicines database [Web page].Brussels: Federal Agency for Medicines and Health Products,;2018 [cited 1 October 2020]. Available from: https://www.fagg.be/nl/news/afleveringswijze_van_geneesmiddelen_in_de_nieuwe_online_geneesmiddelendatabank

49. Simoens S. Pharmacoeconomics of immunoglobulins in primary immunodeficiency. Expert Review of Pharmacoeconomics & Outcomes Research. 2009;9(4):375-86.

50. Law of 20 December 2019 amending various legislations as regards shortages of medicinal products, Belgisch Staatsblad-Moniteur Belge 3 February 2020. Available from: http://www.ejustice.just.fgov.be/cgi_loi/change_lg.pl?language=nl&la=N&table_name=wet&cn=2019122051

51. FAMHP. Limited Availability of Immunoglobulins: recommendations to hospital pharmacists and physician-specialists [Web page]. FAMPH,;2019 [cited 9/10/2019]. Available from: https://www.fagg.be/nl/news/beperkte_beschikbaarheid_van_intraveneuze_immunoglobulines_aanbevelingen_ter_attentie_van_de

52. NIHDI. Immunoglobulins: changes in reimbursment as from 1st of September 2019 [Web page].2019 [cited June 18, 2020]. Available from: https://www.inami.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/specialiteiten/wijzigingen/Paginas/immuglobulines.aspx#.XZ3r_0YzaUl

53. Superior Health Council. Recommended indications for administering immunoglobulins. 2010. No 8366

54. Royal Decree of 19 October 1978. - laying down rules concerning the offices and depots of medicinal products in care facilities, Belgisch Staatsblad-Moniteur belge 31 October 1978. Available from: http://www.ejustice.just.fgov.be/cgi_loi/change_lg.pl?language=nl&la=N&cn=1978101930&table_name=wet

55. Bozovic I, Peric S, Basta I, Rakocevic-Stojanovic V, Lavrnic D, Stevic Z, et al. Prospective analysis of gait characteristics in chronic inflammatory demyelinating polyradiculoneuropathy. J Clin Neurosci. 2020;80:6-10.

56. Belfius Bank. MAHA-analyse 2018. 25e editie sectoranalyse van de algemene en universitaire ziekenhuizen in België; 2019.

57. European Medicine Agency. Guideline on the clinical evaluation of human normal immunoglobulin for intravenous administation (IVIg). 2018 Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-human-normal-immunoglobulin-intravenous-administration-ivig-rev-3_en.pdf

58. Vannieuwenhuysen C, Slegers P, Neyt M, Hulstaert F, Stordeur S, Cleemput I, et al. Towards a better managed off-label use of drugs Health Services Research (HSR). Brussels: Belgian Health Care Knowledge Centre (KCE); 2015 29/09/2015. KCE Reports 252 Available from: http://kce.fgov.be/sites/default/files/page_documents/KCE_252_Off-label%20drugs_Report.pdf

59. Royal decree of 11 January 1993 laying down the conditions under which medicines for human use may be handed over in the form of samples., Belgisch Staatsblad-Moniteur belge 30 January 1993. Available from: http://www.ejustice.just.fgov.be/cgi_loi/change_lg.pl?language=nl&la=N&cn=1993011140&table_name=wet

60. FAMHP. Compassionate Use-Medical Need Programs [Web page].Brussels: FAMHP;2020 [cited 25 October 2020]. Available from: https://www.fagg-afmps.be/nl/MENSELIJK_gebruik/geneesmiddelen/geneesmiddelen/onderzoek_ontwikkeling/gebruik_in_schrijnende_63

61. Sakoulas G., Geriak M., Kullar R., Greenwood K., et al. Intravenous Immunoglobulin (IVIG) Significantly Reduces Respiratory Morbidity in COVID-19 Pneumonia: A Prospective Randomized Trial. 2020.

62. STATBEL. Structure of the Population [Web page].2020 [cited 26 June 2020]. Available from: https://statbel.fgov.be/nl/themas/bevolking/structuur-van-de-bevolking#panel-12

63. Office for National statistics. Annual population estimates [Web page].2020 [cited 26 June 2020]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2019estimates

64. Rajabally YA, Afzal S. Clinical and economic comparison of an individualised immunoglobulin protocol vs. standard dosing for chronic inflammatory demyelinating polyneuropathy. J Neurol. 2019;266(2):461-7.

65. Alberta Health Services. Ig dose calculator - Canada (Alberta) [Web page].2020 [cited 12 November 2020]. Available from: https://www.albertahealthservices.ca/webapps/labservices/IVIG_Dosing_Calculator.htm

66. National Blood Authority Australia. BloodSTAR calculator for adjusting Ig dose for ideal body weight [Web page].Australia: NBA;2020 [cited 16 November 2020]. Available from: https://www.blood.gov.au/bloodstar-calculator-adjusting-ig-dose-ideal-body-weight

67. l'Agence nationale de sécurité du médicament et des produits de santé (ANSM). Tension d'approvisionnement de SCIg "Gammanorm". 2020.

68. L'Agence nationale de sécurité du médicament et des produits de santé (ANSM). L'ANSM demande aux professionnels de santé de respecter la hiérarchisation des indications 2020 Available from: https://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/L-ANSM-demande-aux-professionnels-de-sante-de-respecter-la-hierarchisation-des-indications-des-immunoglobulines-humaines-normales-IgHN-Point-d-information