KEY ECONOMIC AND VALUE CONSIDERATIONS FOR PLASMA-DERIVED MEDICINAL PRODUCTS (PDMPS) IN EUROPE

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CHAPTER 1

ABOUT THIS PAPER

This paper aims to analyse and demonstrate the unique nature and value of PDMPs (Plasma-derived Medicinal Products) across clinical, economic, and societal dimensions, and focuses on improving Patient Access. Patient Access is viewed from two angles: formal access based on reimbursement coverage, and therapeutic access based on the availability of an optimal treatment paradigm. It also analyses key challenges that affect the full realisation of the value of PDMPs. Finally, it offers a comprehensive view of possible solutions to the identified challenges.

PDMPs are unique biological therapies derived from human plasma and are used to treat patients with rare, often genetic conditions with a high disease burden. Despite decades of effective therapeutic use in Europe, and demonstrable clinical and societal value, these treatments still face numerous Patient Access challenges pertaining to the plasma donation landscape, regulatory and reimbursement frameworks, and treatment paradigms. There is a growing clinical need of European patients for PDMPs, and considerably more plasma must be collected in Europe. As new indications arise more patients are diagnosed with diseases requiring PDMP treatment. Even when diagnosed and if therapy is available, patients often are denied adequate PDMP treatment because of therapeutic and formal Patient Access challenges. To overcome these challenges, it is necessary to form close and trust-based partnerships between industry and all healthcare stakeholders.
CHAPTER 2

EXECUTIVE SUMMARY
NATURE AND VALUE

PDMPs constitute several classes of biologic therapies, i.e. clotting factors, immunoglobulins (IgGs, including hyperimmune globulins), alpha-1 proteinase inhibitors, albumin and C1-esterase inhibitors. PDMPs share a unique nature: they are derived from human biologic material (plasma) and have a highly complex and regulated manufacturing process. Manufacturing takes 7-12 months, and constitutes the bulk of costs to companies (57 % for PDMPs compared to 14 % for small molecules pharma). PDMPs treat rare, chronic, severe, often genetic in origin, and potentially life-threatening conditions, such as primary immunodeficiencies (PID) and certain secondary immunodeficiencies (SID), bleeding disorders such as haemophilia A and haemophilia B, alpha-1 antitrypsin deficiency (AATD), hereditary angioedema (HAE), neurological diseases (e.g. chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN), Guillain-Barré Syndrome (GBS), and other orphan diseases associated with absence or malfunction of specific proteins. Individually, these diseases affect small patient populations, and PDMPs address a severe subset which often require lifelong treatment. Taken together, the therapeutic and societal impact of PDMP treatments across these diseases is extensive.

PDMPs are often the only and/or most effective therapies for the beforementioned conditions, preventing premature death, minimizing disabilities, and promoting patients’ quality of life. Since the introduction of IgGs, survival rates of patients with common variable immune deficiency (CVID) have increased from 30 % in 1979 to an almost normal life expectancy for patients without disease-related complications. In turn, clotting factors have profoundly extended the life expectancy of patients with severe haemophilia A from 19 years before 1955 to 71 years in 2001. These therapies have consistently achieved significant clinical results against primary endpoints (e.g. 80 % reduction in bleeds for haemophilia patients and over 65 % reduction in infections for patients with immune deficiencies). These results positively impact patients’ socio-economic activity and psychological well-being. They have also a much broader societal and economic benefit: comparing the time before and after the introduction of PDMPs for PIDs and haemophilia in Europe, treatments have yielded a combined health value gain (the magnitude of the socio-economic impact of PDMP treatments) of 2 Billion EUR/year. For PIDs this is approximately 1 Billion Eur/year (based on a PID population of 44,000). For severe haemophilia the figure is at least 1
Billion EUR/year (based on a severe haemophilia population of 47,000)*. In addition to the health value gains, these treatments can also prevent indirect healthcare costs in the range of 1.1 and 1.6 Billion EUR/year.* Limiting access to PDMPs often equates with denying Patient Access to the only effective therapy and reduces the concomitant socio-economic benefits.

**CHALLENGES**

**Formal Patient Access Challenges:** In Europe, many PDMP treatments are not reimbursed, or are reimbursed only for narrowly defined eligible patient populations, resulting in unacceptable inequalities geographically among patients in Europe. IgGs for PIDs are consistently reimbursed, but this is not the case for the same therapeutic class in relation to SIDs. In many countries, PDMP treatments such as Factor X, Factor XIII and Protein C, are entirely omitted from reimbursement lists. When PDMPs are reimbursed, they often face additional economic challenges, including reimbursement issues, the consequences of external reference pricing (ERP model), and/or cost-containment measures such as clawback or payback taxes. Although several countries have lifted, deferred or reduced application of these taxes, in recognition of PDMPs’ unique value and nature and unique risks to availability, there remain many others that continue to apply them. PDMP manufacturing costs are high and difficult to reduce. Thus, the continued cost-containment measures threaten the already fragile balance of the PDMP industry structure, ultimately limiting Formal Patient Access.

**Therapeutic Patient Access Challenges:** Access to optimal treatment is under pressure, particularly from procurement practices such as tendering where the decision is based on price alone. Tenders can be effective in controlling reimbursement budgets, but they are only appropriate if differences between medicines are negligible (when medicines are bioequivalent). However, this is not the case with PDMPs; they cannot be considered interchangeable because they are not required to prove bioequivalence (unlike generics or biosimilar medicines). Different brands within the same PDMP class have different tolerability profiles. Switching between them for economic reasons rather than clinical need can have adverse effects on patients. Availability of only a single PDMP brand of each class means

* Vintura analysis
not only that physicians will need to switch existing patients’ therapies, but also that they will have no choice of customising naïve patients’ treatment regimens, e.g. choosing between differentiated brand properties and routes of administration. When a procurement system contravenes the clinical guidelines and therapeutic need, this system may require adjustments to better serve the patients.

**Product Availability:** Plasma is a gift from healthy donors. Plasma collection policies and collection volumes directly impact the amount of PDMPs produced. In Europe, availability of source plasma is extremely uneven: just four countries contribute more than 55% of the total amount of plasma collected in Europe for manufacturing. Additionally, the plasma volume collected in Europe fulfils only around 63% of the European PDMP clinical need; the rest is imported from the United States (see Figure 12). It is difficult to attract enough plasma donors in Europe to meet the clinical need for patients. Source plasma donors face greater inconveniences and expenses than whole blood donors, so it is difficult to maintain the necessary donation volumes. Also, in Europe, there are fewer plasmapheresis centres than blood collection centres, and the plasmapheresis process takes significantly longer and is more burdensome. In recognition of these factors, the four countries collecting the most plasma per capita have allowed a system of monetary compensation for the donors’ inconvenience and expenses, which has proven to be singularly effective. Since the growing clinical need for PDMPs is a global phenomenon, without an increased European contribution in plasma collection, there is a high risk of falling short of meeting patients’ clinical needs.
RECOMMENDATIONS

The PDMP Ecosystem is in a fragile balance as it depends on a large number of variables: often uncertain volumes of donations, complex regulations, strict safety procedures and lengthy manufacturing processes. Additionally, heterogenous reimbursement across Europe and varied economic measures may further impact its current stability. These challenges negatively impact the end-goal of optimal Patient Access and require multi-stakeholder solutions. There are four actions that need the most urgent attention from all stakeholders:

1. **Apply effective measures, in collaboration with the private industry, to promote and grow plasma donations across Europe to fulfil the clinical need for PDMPs.**
   - Establish dedicated plasma collection (plasmapheresis) programs and outreach campaigns directed towards plasma donors in all EU Member States.
   - Allow co-existence of public and private sector owned plasma collection centres.
   - Stimulate plasma donations by allowing compensation for donors’ expenses and inconvenience related to donation.

   These items should be implemented and also addressed in the most appropriate policy frameworks at the EU Member States level or at the EU level.

2. **Ensure the broadest possible reimbursement coverage for all eligible patients to maximise clinical and socio-economic benefits.**

3. **Optimise reimbursement policies, considering Value Based Pricing such as value informed affordable pricing (VIA) models, and revise cost-containment measures in order to maintain the PDMP industry’s sustainability and improve equitable access to treatment for patients in Europe.**

4. **Revise and align procurement practices with clinical needs to ensure the right treatment for the right patient.**

With a strong partnership and open trust-based dialogue between industry, policymakers, patients and other healthcare stakeholders, these solutions can be achieved.
CHAPTER 3

VALUE OF PDMPS
3.1. UNIQUE NATURE OF PDMPS — FROM DONOR TO PATIENT

**SUMMARY**

Plasma-derived Medicinal Products (PDMPs) are a unique class of biological therapies used to treat rare and severe diseases. Unlike chemically synthesised drugs or biological medicines made by recombinant cell lines, PDMPs are the only therapies solely derived from human biological material. The entire process from plasma donation to patient is considerably more complex, labour-intensive, time-consuming and costly than that for other medicines (see Figure 1).6 Furthermore, since the starting material is human plasma, the processes for plasma donation and PDMP manufacturing are separately regulated to ensure patient and donor safety.

Thus, PDMPs are unique in a number of ways: overall value chain complexity, human-derived source material, regulations and safety procedures, manufacturing processes and costs, therapeutic value and socio-economic impact. This chapter will focus on exploring and explaining the critical steps in the PDMP value chain “from Donor to Patient”, against the background of a complex regulatory environment.
**FIGURE 1**

*Source: Burnouf 2018, PPTA analysis, Vintura analysis*

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**PDMPS**

**Steps**
- Collection of human plasma (source & recovered)
- Donor screening and testing
- Epidemiological surveillance
- Manufacturing pool virus marker testing
- Viral reduction treatments

**Quality & Safety measures**
- Inventory hold period
- Manufacturing/ Fractionation (Multi-step process)
- Batch release
- Quality, safety & potency testing

**Time**
- 7-12 months

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**SMALL MOLECULES PHARMA**

**Steps**
- Manufacturing (single step)

**Time**
- <1 month
PLASMA DONATION PROCESS

The PDMP manufacturing process starts with collection of human plasma from healthy donors. This initial phase is complex and heavily regulated by multiple authorities around the world to ensure both plasma safety and donor well-being.

Plasma can be obtained from whole blood (resulting in recovered plasma) or collected directly by apheresis (through a process called plasmapheresis, resulting in source plasma). PDMPs are mainly made from source plasma. Compared to whole blood donation, which takes 10-20 min, plasmapheresis is a longer and more laborious process, approximately 60-90 min, but it generates significantly more plasma per donation (approximately two- to three-fold more on average). In this process, the donor’s whole blood is collected and spun/centrifuged; plasma is separated/retained, and red blood cells, white blood cells and platelets are returned to the donor. This collection method is safe. Additionally, since plasma replenishes much more quickly than red blood cells do after whole blood donation, source plasma can be donated more often than whole blood.

To protect the donor’s health and well-being, there are numerous regulations in Europe concerning plasmapheresis centre requirements (quality assurance, infrastructure and personnel), as well as for the frequency and volume of donations for each donor*. In Europe donors can give on average 650-850ml of plasma per donation. However, there are significant differences between countries regarding donation frequency and upper limits for the total annual number of donations. In most countries this ranges from 20-60 times per year; however, in Austria up to 50 donations and in Germany up to 60 donations are allowed per year (PPTA analysis). Additionally, in most countries only specific institutions (predominantly public sector) are allowed to collect whole blood and plasma; e.g. in France only the Etablissement Français du Sang (EFS), in Finland the Red Cross, and in Poland only state-certified public hospitals may collect plasma. In four countries, Austria, Czechia, Germany and Hungary, both public and private institutions may collect plasma; notably, plasma donation volumes are substantially higher in these four countries (this issue is further elaborated in Chapter 4).

* The donation of blood and blood components in the European Union is governed by the principles set out in Article 20(1) of Directive 2002/98/EC. Frequency and volume requirements are regulated on a national level.
Beyond donor safety regulations, centres follow rigorous plasma quality and safety measures. The initial step in donation takes place even before source plasma is collected. In order for their donations to be used to manufacture PDMPs, individuals must pass a physical exam and a comprehensive health screening, and test negative for specific viruses. Furthermore, new donors must donate at least two times within a six months period, and each time they must successfully pass testing for transmissible diseases, before their donations can be used. If these requirements are not met, the donations cannot be used in further manufacture.

Once the second and safe donation has been made, the plasma goes into an additional inventory hold period to allow detection of any latent infections or other disqualifying conditions. If, and only if, the plasma has successfully passed all of the above tests, it can finally be used for manufacturing.

**PDMP MANUFACTURING PROCESS**

The first of many steps in the manufacturing process is the pooling of the plasma, whereby many donations are combined into a manufacturing vessel. The plasma pool itself undergoes additional pathogen testing to give added assurance of safety. Following that, therapeutic proteins are extracted from the plasma. This process is called fractionation, and, as the term suggests, it separates the plasma into different fractions. The fractions are purified, and potential pathogens are inactivated/removed. Each individual manufacturer’s process is different, resulting in variations between brands. For this reason, individual patient treatment relies on access to one brand. This is contrary to optimal treatment, because a patient’s tolerability could well differ depending on the brand of the given PDMP. Following further checks for efficacy, safety, and sterility, the batches of finished PDMP are released. The manufacturing processes require licensing by official bodies, and manufacturing sites undergo regular inspections. In addition to the abovementioned requirements, manufacturers and collectors may voluntarily adhere to industry standards such as the International Quality Plasma Program (IQPP) for plasma collection, which includes third-party evaluation of plasma donation centres, and the Quality Standards of Excellence, Assurance, and Leadership (QSEAL) program for manufacturing.
PDMP VALUE CHAIN AND ASSOCIATED COSTS

The complexity of the PDMP process impacts the time it takes from plasma donation (Donor) to treatment prescription/administration (Patient). Donor to Patient timelines can take as much as 7-12 months. With such extensive timelines, it is critical that sufficient plasma volumes are always available for fractionation. Due to the long lead times, unexpected increases in clinical need cannot be addressed in the short term, as production for PDMPs needed today started as far back as one year ago. Additionally, to ensure that the batches can be produced without interruption, manufacturers cannot rely on a single or unpredictable source of plasma (e.g. single collection centre, single country or even a single geographic region). In this regard, the PDMP value chain and the network of plasma collection and manufacturing must be global in nature, encompassing availability of plasma among different countries and regions. In short, plasma collection must be global whereas blood collection can be local.

PDMPs have an added and significant clinical/efficacy benefit that is uniquely attributable to their global nature. In the case of IgGs, for instance, it is important that the pool of plasma used in manufacturing be large (containing at least one thousand donations) and geographically diverse. This ensures that the final IgG product contains a wide spectrum of antibodies to various pathogens which, thereby, increases the resulting effectiveness of a therapy in protecting the patient against various infections. It is worth noting that the amount of plasma needed to treat just one patient for one year can be as high as 1200 donations for haemophilia. Therefore in Europe alone, millions of litres of plasma are needed annually to cover the core medical needs of the PDMP-eligible population.1

Another important complexity of the PDMP process is the issue of joint supply. In a joint supply situation, a given production process yields more than one product in fixed proportion.

In PDMP manufacturing, each litre of plasma contains clinically valuable proteins – IgGs, albumin, Factor VIII, Factor IX, alpha-1 antitrypsin, etc. – in fixed proportion. In order to recover their production costs, PDMP manufacturers strive to maximise the number of therapies they can sell from each litre of collected plasma. The specific
and fluctuating clinical need for each of these therapies – which in turn is dictated by such factors as the number of indications, the prevalence of disease states, diagnosis rates, and the lack of availability of alternatives – is a critical input to manufacturer production and pricing decisions. In response to increasing clinical need for IgGs, a PDMP manufacturer that wishes to remain economically viable cannot make a spot decision to quickly ramp up production; the manufacture must first consider how this decision will impact the production of other therapies.

The notion that it is economically crucial to manufacture multiple therapies from each litre of plasma is known as “last litre economics.” Here, the revenue generated by the first litre, from which the maximum number of products can be sold, is likely much higher than the revenue generated by the last litre, from which a more limited number of products can be sold. It is important to understand this concept because it is the exact opposite of the production process for chemical pharmaceuticals. With small molecule products, the cost of production steadily decreases with each incremental unit, and also spot decisions can be made to quickly ramp up production as needed. In contrast, for PDMPs, because of last litre economics, this law of dismissing cost does not apply contrary to other industries, and the production can eventually hit a threshold at which costs actually increase.

The PDMP manufacturing process is therefore extremely complex and labour intensive for the reasons mentioned above. Additionally, each manufacturer expends significant costs in optimising the fractionation process to extract a maximum yield for the desired therapeutic protein, and to ensure safety and efficacy. These reasons explain why starting material and manufacturing costs comprise a relatively large share of the economic profile for the fractionation stage of manufacturing PDMPs, while marketing and branding play a relatively small role compared to traditional pharmaceuticals. For PDMPs, manufacturing comprises 57 % of the total cost as opposed to only 14 % of the total cost for small molecule medicines manufacturing\(^1\) (see Figure 2).

For PDMPs, the manufacturing cost is difficult to reduce, since it is largely based on the necessary and critical measures to ensure donor and patient safety. With such a uniquely high fixed cost, it is fair to assume that the PDMP industry largely depends on a reliable reimbursement framework and long-term visibility into healthcare systems' needs in order to achieve the volumes needed to treat patients.
The unique pathway from “Donor to Patient” means that any disruptions at any stage of the process can negatively impact on production, and ultimately on Patient Access. Full understanding of the value and the uniqueness of PDMPs is vital to ensure collaborative work between all stakeholders, stability of the value chain, and safe and optimal Patient Access.
3.2. THERAPEUTIC VALUE OF PDMPS — CLINICAL LANDSCAPE

PDMPs constitute several classes of biologic therapies. These therapies are used to treat rare, chronic, severe, and potentially life-threatening conditions, often genetic in origin, such as PID, SID, bleeding disorders (e.g. haemophilia A and B), AATD, HAE, neurological diseases (e.g. CIDP, GBS and MMN), as well as a number of other orphan diseases associated with absence or malfunction of specific proteins. Other PDMPs save lives by preventing haemolytic disease of the foetus and new-born, treating critical conditions like sepsis, burns, and liver diseases, and assisting patients in recovery following exposure to certain viruses. PDMPs are often the only and/or the most effective therapies for these conditions. They prevent premature death, minimise disabilities, and promote patients’ quality of life.

Each PDMP therapy affects patients’ health through a unique mechanism of action. Clotting factors replace missing or deficient proteins, boosting clotting function, and they treat genetic bleeding disorders such as haemophilia A and B and von Willebrand disease, as well as surgical bleeding (see Figure 3).

IgGs address immune deficiencies and regulate immune dysfunction in neurological disorders (e.g. CIDP and GBS) and haematological diseases (primary immune thrombocytopenia (ITP)). Hyperimmune globulins containing higher levels of antibodies against specific pathogens are used to prevent serious infections or help faster recovery of infected patients (e.g. tetanus, rabies, hepatitis A and B, and cytomegalovirus). Anti-D immunoglobulin treatment is given to women to reduce foetal and infant mortality. Alpha-1 proteinase inhibitor is given to treat AATD (also known as genetic emphysema) to protect tissues, especially in the lung, from enzymes released by inflammatory cells. C1 esterase inhibitor is used for prevention and treatment of HAE characterised by acute and severe swellings in the arms, legs, face, airways and intestinal tract. Albumin is utilised in emergency situations to treat burns, severe infections (sepsis), and during surgeries to regulate blood volume and provide essential non-oncotic functions.

Since the treated diseases are mostly rare (though particularly severe), PDMPs are often misconstrued as providing “niche therapeutic solutions”. In reality, the value of these treatments is critically important to the treated patients - often no alternatives
are available. For conditions like PIDs, AATD, or Rh factor isoimmunisation, PDMPs are patients’ only hope for an effective treatment. For some diseases, other dedicated treatments may exist, but these are mostly secondary to PDMPs. This applies to certain bleeding disorders and other factor deficiencies as well as to SIDs, ITP and HAE.

Although the treated conditions are usually rare, taken as a whole, the patient populations that can benefit from PDMPs are extensive. For PID and certain neurological and haematological disorders alone, more than 80,000 people in Europe are estimated to be affected (see Figure 4).8,9,10 For other conditions like haemophilia and AATD, these numbers are even higher, both estimated at over 100,000 patients.11,12,13 Recognising their importance, IgGs, hyperimmune globulins (anti-D, anti-tetanus and anti-rabies) and coagulation factors FVIII and FIX (to treat haemophilia A and B, respectively) are included in the Model List of Essential Medicines for adults and children by the World Health Organization14,15, comprising medicines that satisfy the priority health care needs of the population and are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford. This enforces the critical importance for patients to have access to PDMPs. Limiting access to PDMPs often means limiting access to the only effective therapy available, with far reaching consequences from disability all the way to death.
**Figure 3**

PDMP classes and conditions treated*

*Source: Grabowski and Manning 2018, PPTA analysis*

<table>
<thead>
<tr>
<th>PDMP CLASS</th>
<th>CONDITIONS TREATED</th>
</tr>
</thead>
</table>
| **Coagulation factors:** | **• Bleeding Disorders**  
|                   |  
|                   |  • Haemophilia A and B  
|                   |  • Von Willebrand disease (VWD)  
|                   |  • Rare clotting factor deficiencies  
|                   |  • Bleeding from trauma  
|                   |  • Over dosage of anticoagulants or bleeding-causing toxic substances  
|                   |  • Liver disease  |
| **Immunoglobulins:** | **• Immunodeficiencies**  
|                   |  
|                   |  • Primary (PID)  
|                   |  • Secondary (SID)  
|                   |  
|                   |  • Neurological diseases  
|                   |  • Chronic inflammatory demyelinating polyneuropathy (CIDP)  
|                   |  • Acute inflammatory demyelinating polyneuropathy (Guillain Barré)  
|                   |  • Multifocal motor neuropathy (MMN)  
|                   |  
|                   |  • Haematological  
|                   |  • Primary immune thrombocytopenia (Idiopathic thrombocytopenic purpura) (ITP)  
|                   |  • Inflammatory diseases  
|                   |  • Kawasaki disease  |
| **Hyperimmune Globulins:** | **• Rabies, tetanus, hepatitis, cytomegalovirus, varicella-zoster virus**  
|                   |  
|                   |  • Rh factor complicated pregnancies  
|                   |  • Organ transplants  |

*The list of conditions may not be exhaustive.*
PDMP CLASS

Alpha-1 Proteinase Inhibitors:
- Protects tissues from enzymes of inflammatory cells.

Albumin:
- The major plasma protein, regulating blood volume and providing many essential non-oncotic functions.

C1-esterase inhibitor:
- Controls spontaneous activation of complement system as a part of the immune system.

CONDITIONS TREATED

- **Alpha-1 antitrypsin deficiency (AATD) (genetic emphysema)**
- Cardiac surgery
- Liver disease
- Severe infections
- Emergency and surgical medicine (shock, severe burns and during surgery)
- **Hereditary angioedema (HAE)**
Figure 4

Europe’s patient population by PDMP-treatable indication


Disease Treatment Outcome

<table>
<thead>
<tr>
<th>Disease</th>
<th>Increased Life Expectancy</th>
<th>Improved Quality of Life</th>
<th>Infection Prevention</th>
<th>Positively Modifies Disease Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prim. Immunodeficiencies (PID)</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Sec. Immunodeficiencies (SID)*</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>CIDP</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>ITP</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Haemophilia A and B</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Von Willebrand Disease (VWD)</td>
<td>✔</td>
<td>✔</td>
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</tr>
<tr>
<td>Hereditary Angioedema (HAE)</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
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<tr>
<td>Alpha-1 Antitrypsin Deficiency (AATD)</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
</tbody>
</table>

* Diverse causes e.g. infectious diseases and immunosuppressive medication – prevalence not estimated.

Note: European population estimated as 597 million, affected population calculated using prevalence mean values and prevalence for adult CIDP population.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence Details</th>
<th>Affected Population Europe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptomatic PID</strong></td>
<td>1/13,500</td>
<td>approx. 84,000</td>
</tr>
<tr>
<td><strong>CIDP</strong></td>
<td>1/200,000 in children, 1-7/100,000 in adults</td>
<td>approx. 84,000 (excluding SID)</td>
</tr>
<tr>
<td><strong>ITP</strong></td>
<td>2.68/100,000</td>
<td>approx. 118,000</td>
</tr>
<tr>
<td><strong>Haemophilia A</strong></td>
<td>25/100,000 (males)</td>
<td>approx. 118,000</td>
</tr>
<tr>
<td><strong>Haemophilia B</strong></td>
<td>5/100,000 (males)</td>
<td></td>
</tr>
<tr>
<td><strong>VWD</strong></td>
<td>1/8,500-1/50,000 (requiring treatment)</td>
<td></td>
</tr>
<tr>
<td><strong>HAE</strong></td>
<td>1-9/100,000</td>
<td>approx. 30,000</td>
</tr>
<tr>
<td><strong>AATD</strong></td>
<td>123.73/100,000</td>
<td>approx. 120,000</td>
</tr>
</tbody>
</table>
3.3. **Socio-economic impact of PDMPs — considerations**

Genetic/inborn diseases have a severe impact on a patient’s life, because they require lifelong treatment, management and monitoring. Treatment gives patients a significantly extended life expectancy and substantially improves their overall quality of life (physical and psychosocial).\(^4\),\(^5\),\(^16\),\(^17\),\(^18\) Following improved diagnosis and subsequent PDMP treatment, survival rates for CVID, the most common form of PID, have improved from 30 % in 1979 to an almost normal life expectancy for patients without disease-related complications.\(^2\) Similarly, better management of bleeding, especially using prophylaxis with FVIII, has had a tremendous impact on the life expectancy of severe haemophilia patient, which increased from 19 years before 1955 to 75+ years after 2000.\(^3\) PDMPs have also consistently proven to achieve significant clinical results against primary endpoints (e.g. over 65 % reduction in infections for patients with immune deficiencies treated with IgG and 80 % reduction in bleeds for haemophilia patients treated with FVIII).\(^4\),\(^5\) These improvements, across Europe, have effected a combined health value gain of approximately 2 Billion Eur/year.

The above health value gain figure is indicative of the magnitude of the socio-economic impact of PDMP treatments. To estimate the above figure for socio-economic impact, we used the following metrics: DALY, recovered DALY and VOLY.\(^19\)

DALY (disability-adjusted life year) is a measure for the burden of a disease caused by disability or early death when compared to an ideal health status. DALYs are calculated as the sum of the Years of Life Lost (YLL) due to premature death and the Years Lost due to Disability (YLD) for people living with the health condition and its consequences. DALY is usually expressed for a large population to measure impact at a country or regional level. For a single person, the DALY is used to measure personal burden of disease, often described via a disability weight from 0 to 1. For a person in a theoretical ideal health situation, the disability weight would be 0. For a person with severe chronic disease it could be as high as 0.7, meaning 70 % of their life (measured from the onset of the disease) is lost to disability or premature death. For PID, the DALY per year for treated patients is estimated as 0.368.\(^20\) For haemophilia the DALY depends on the severity. It reaches from 0.054 (mild) via 0.151 (moderate) to 0.197 (severe).\(^21\),\(^22\) Both conditions have a considerably higher patient DALY than many other chronic diseases, such as chronic obstructive pulmonary disease (COPD) (0.104), diabetes (0.120), back and neck pain (0.120) and depression (0.167).\(^20\)
In the same way that DALY describes the time lost due to a disease, the measure “recovered DALY” describes a regain of time following treatment that improves the health status. This estimation of recovered DALY can be done taking a historical perspective (health improvement compared to historical conditions) or counterfactually (theoretically assuming that patients would not be treated). Comparison of untreated and treated PID patients showed an improvement in the number of severe infections per year from eight to two infections. With a disability weight of 0.115 per severe infection commonly occurring in PID patients, it means that DALY for untreated PID patients is 0.920 per year. Hence, PDMP treatments effect a recovered DALY of 0.552, the difference between untreated (0.920) and treated (0.368) PID patients. For severe haemophilia, the above calculation can be approached from a different angle, namely historical and current life expectancy. After introduction of PDMP treatments, life expectancy for severe haemophilia increased from 19 to 71 years leading to a regained DALY of 0.500.

In order to translate (recovered) DALY – a time measure - to health value impact, we use VOLY (Value of a Statistical Life Year) which is estimated at €40,000. Health value impact is then calculated as the multiplication of (recovered) DALY times VOLY.

For the European PID patient population the health value is approximately 1 Billion Eur/year, based on 44,000 patients eligible for IgG. For severe haemophilia the figure is at least 1 Billion Eur/year, based on 47,000 severe haemophilia patients eligible for prophylaxis treatment with clotting factors.

In addition to a positive recovered DALY, optimal PDMP treatment is proven to significantly reduce avoidable indirect healthcare costs. In PID, this is achieved by reducing the number of annual hospitalisations and hospitalisation days, due to the decreased number of severe infections and related complications. On top of the value gains mentioned above, optimal PID treatment can prevent the total indirect cost in Europe between 1.1 and 1.6 Billion Eur/year (calculated as the number of hospital days prevented, multiplied by the average cost of hospitalisation day* and PID patient numbers).

*Estimates of cost per hospitalisation day range from 1420Eur to 2230Eur
Professor Lieven Annemans, Professor of Health Economics, faculty of Medicine and Health Sciences, Ghent University, comments:

“For severe and rare diseases with high patient burden of disease [such as PID and Haemophilia], the standard measure of cost-effectiveness is often not as meaningful as other endpoints. PDMPs potential to recover large number of DALYs and at the same time save substantial indirect costs are quite compelling arguments, both from the patient perspective and healthcare ecosystem viewpoint: both are supporting PDMPs socio-economic value.”

The socio-economic benefits calculations and assumptions outlined above clearly point to a great need and urgency to re-evaluate PDMP therapies in line with their significant socio-economic value.
CHAPTER 4
PATIENT ACCESS
CHALLENGES AND SOLUTIONS
SUMMARY

Realizing the full set of PDMP treatment benefits is conditional on overcoming multiple challenges to optimal Patient Access. Certain challenges are common across all of Europe, while others are more country-specific. Beyond geographic distribution, they can be mapped across the PDMPs’ entire value chain— from Donor to Patient. They can be further categorised into challenges pertaining either to Formal Patient Access (e.g. reimbursement coverage and plasma donation volumes and policies) or Therapeutic Patient Access (e.g. economic and clinical barriers to optimal patient treatment). The heterogenous nature of the European healthcare ecosystems means that these challenges often have unique or country-specific solutions. Achieving these solutions will require concerted efforts and closer partnerships from the broad spectrum of country-level and pan-European healthcare stakeholders (industry, policymakers, payers, clinicians and patient organisations).
ECONOMICS

4.1. REIMBURSEMENT

Reimbursement coverage varies widely by country and by disease state or therapy area (TA), and this creates severe inequalities among citizens. Even if a particular TA is reimbursed, further challenges may arise from restrictions on patients’ eligibility criteria. Reimbursement of a particular class of therapies does not always guarantee that all patients that could benefit receive this treatment under co-payment (full or partial). This, in turn, means that in some TAs, patients may bear a significant financial burden when treatments are only available when paid out-of-pocket. Exploration of the above policies and practices in key TAs and by representative countries will reveal the need to seek formal solutions or adopt existing ones from best-in-class markets and regions. In most European countries there is a specific PDMP or PDMPs, needed to treat severe and often life-threatening diseases, that is/are not reimbursed or may only be reimbursed on a case by case basis (see Figure 5). Unlike with the recently approved innovative drugs, whose reimbursement often correlates with a country’s key economic indicators such as percent GDP spent on healthcare, the PDMP reimbursement appears to be more randomised and heavily dependent on historic or legacy HTA decisions. For instance, countries often credited with fast and comprehensive reimbursement (such as Denmark, Ireland, or Finland) reimburse fewer PDMPs than relatively less affluent ones (e.g. Czechia and Greece). Additionally, few country-level payers and policymakers have updated their PDMP reimbursement lists in recent years to include either additional classes or brands. A closer look (noted in Figure 5) shows that such review may be necessary to expand and standardise Patient Access across Europe. In the EU, specifically, efforts are being made by various bodies and supra-national stakeholders (e.g. EUnetHTA) to ensure maximum and timely patient coverage with innovative molecules and technologies. Similar attention is required for the existing treatments such as PDMPs.
FIGURE 5
PDMP classes unavailable under reimbursement
Source: PPTA analysis

Note: Reimbursement situation is dynamic and can change over time.
While IgGs are reimbursed virtually everywhere in Europe, the eligible population is often defined as PID and some neurological disorders, and only in some cases SID. The situation is even more challenging with AATD (see Figure 6). Reimbursement and Patient Access to PDMPs often depend on the payer system archetype. AATD is a good example for this. While this disease modifying treatment is reimbursed by so-called “Therapeutic Referencing Archetype” in, for example, Germany, Italy, France, and Spain, it is not reimbursed in the entire “Health Economics Archetype” countries, e.g. the UK, Poland, and Sweden. When reimbursed, severe eligibility restrictions may apply (e.g. in Belgium only patients diagnosed prior to 2010 are covered). Lack of alpha-1 antitrypsin treatment reimbursement or severe restrictions thereof not only negatively impacts on a patient’s optimal treatment, but it also greatly affects the diagnostic landscape, whereby large numbers of patients with AATD are never discovered:

“Alpha-1 antitrypsin deficiency is heavily underdiagnosed – pulmonologists often do not even test for AATD, since no treatment is available. Consequently, patients for clinical trials are missing. Within COPD patients we estimate around 3-4 % alpha-1 antitrypsin deficiency patients, very few of whom are appropriately treated”
(Frank Willersinn, Alpha-1 Patient Advocacy Group, Belgium)

For other treatments, such as clotting factors for bleeding disorders and C1 esterase inhibitor in HAE, the situation is heterogenous, and similar to other PDMPs, the reimbursement coverage is not correlated to economic indicators or healthcare systems’ willingness to pay (i.e., high income countries are no more likely to reimburse these treatments than middle income ones). Such high disparities are somewhat surprising from a clinical standpoint, and as demonstrated in the socio-economic considerations, negatively impact patients’ well-being. Given the substantial societal benefit of these treatments and the relatively small affected populations, a more comprehensive reimbursement coverage should be considered to level up the current inequalities.
FIGURE 6

Alpha-1 antitrypsin reimbursement status across Europe

Source: Horvath et al: Diagnosis and management of α1-antitrypsin deficiency in Europe, ERJ Open Res 2019

Eight European countries fully reimburse Alpha-1 antitrypsin

Note: Situation is in accordance with the sourced publication but is dynamic and can change over time.
While reimbursement coverage is the primary factor of Formal Patient Access in terms of the treatments’ availability, there are also economic measures and challenges which impact both formal and Therapeutic Patient Access. Continuous cost containment measures endanger Patient Access. As part of the recent debate on “fair pricing models” or “value-based pricing”, a rethink of current payer policies is required to better account for the PDMPs’ actual value.

For many years, cost-effectiveness has been applied as a key criterion to assess whether medicines and other technologies deserve to be reimbursed within healthcare systems and what level of reimbursement is adequate. Cost-effectiveness measure, when applied to medicines used for a long time, typically means that each time these medicines are re-evaluated, an additional discount may be requested of the manufacturer. Recently, however, there is an increasingly complex debate on “what actually can be considered as cost-effective, which elements must thereby be considered, and how these can guide the pricing and reimbursement of medicines”. Indeed, “cost plus pricing” (i.e., adding a mark up to the costs of R&D and other costs), a model that is from time to time debated in Europe, aims at rewarding the R&D effort necessary to bring valuable medicines to patients. However, the discussion around this model is mainly in relation to the most recent innovative treatments or first-in-class treatments, and as such may prove less relevant for existing therapies such as PDMPs.

Given the PDMPs’ evident value to the patient, which includes life expectancy gains, recovery of DALY, and promotion of QALY, a more appropriate reimbursement evaluation model that could be considered is “value based pricing”. According to this model, the higher the value of medicine (in its broad interpretation) the higher the reimbursement level of that medicine. This means that value is not defined as “value for money” but has, in its most comprehensive version, two overarching dimensions: societal or payer willingness to pay for gaining QALY (or recovering DALY) and severity of the disease or burden of disease to the patient. With severe conditions, such as those that are treated with PDMPs, most payers are willing to pay more to gain QALY (or recover DALY) than in mild or moderately severe conditions. Over time, however, given the reimbursement pressures for PDMPs in Europe, this willingness
has diminished, irrespective of the value these treatments represent. One of the reasons for this is that payers also consider budget impact and overall affordability for the healthcare system in the prospect and emergence of new technologies and curative treatment options. With many new and high-cost treatments being launched (e.g. new technologies in oncology and other orphan diseases), many healthcare systems take a holistic approach and seek to offset these therapies' budget impact elsewhere. This affects established treatments such as PDMPs. As professor Annemans points out25, the offset need not unfairly affect one patient population over another:

“...it should be possible to reward value and at the same time account for affordability. This approach can be called “value informed, affordable pricing” (“VIA pricing”) and may become a practical approach to achieve pricing and reimbursement levels in line with societal values and preferences”.

This new “value informed, affordable pricing” (VIA) is an option to explore, because it proposes to reward value of medicine relative to the severity of patients’ disease burden, and makes QALY threshold additionally dependant on the size of patient population (i.e. budget impact)25. When the impact of an intervention on the budget is low or very low, as is the case in rare and ultra-rare conditions, the threshold value should be increased. In 2017, the NHS in England, was willing to set a threshold value of £300,000 per QALY for “exceptional” cases (although in practice the regular £100,000 threshold for very rare conditions is also applied). This model could become an option to ensure PDMPs’ “fair pricing”. That is not to say that VIA assessment could or should substantially increase PDMPs’ reimbursement levels across Europe. Rather, the application of this model in re-assessing PDMPs should better account for the unique value of PDMPS without upsetting the fragile economic balance of PDMPs’ value chain. Professor Annemans contends that this model requires further refinements to be applicable to all medicines and to accurately reflect unique circumstances, such as those in the PDMP value chain:

“...we could turn value based pricing into value informed, affordable pricing by explicitly modulating thresholds of societal willingness to pay, [and] accounting for disease severity and budget impact. A research agenda for better estimating disease severity and quantifying the trade-off between cost-effectiveness and budget impact is required".
Even without this research, but in recognition of the value of PDMPs, some countries have already modified and improved their reimbursement frameworks (e.g. Poland in 2018). Also, some healthcare systems in Europe have begun considering not only the value but also the unique nature of PDMPs in order to exempt them from additional economic pressures.

These additional economic pressures or challenges include external reference pricing (ERP model), and/or cost-containment measures such as clawback or payback taxes, supply growth taxes, or mandatory discounts. These cost-containment measures have historically been widely applied to PDMPs across Europe and have the potential for a strongly negative impact on Patient Access. In this context, the European Commission expressed significant concerns regarding payback mechanisms that negatively impact Patient Access to healthcare in its 2012 “Report on cost containment policies in public pharmaceutical spending in the EU”\(^{26}\). In the report, the Commission identified several structural downsides of payback mechanisms, such as:

- “If the target budget is set too low, manufacturers are penalised by payback for serving the actual health care needs of the population which may thereby exceed the target budget;

- payback may lower incentives for structural reforms of health care sector, as it in theory guarantees that all excess consumption as defined by target budget is paid back;

- payback may discourage introducing new medicines, if budget overshooting is an issue and the expected turnover on new pharmaceuticals must be paid back.”

Furthermore, and given that antihemophilic factor concentrates as well as IgGs are included in WHO’s List of “Essential Medicines”, reference is also made to the WHO “Guideline on Country Pharmaceutical Pricing Policies”\(^{27}\), which recommends to consider exempting essential medicines from taxation for reasons of equity and safeguarding access to adequate care.
Examples of PDMP economic cost containment measures

*Voluntary access and pricing scheme

Note: Country overview as of February 2020, regulations sensitive to change. Other countries not highlighted in this map might also apply cost-containment measures.
Compelling arguments on the unique specifics and the value of PDMPs have led several countries to either lift, defer, or reduce the application of these taxes for PDMPs. For example, Belgium and Poland exempted PDMPs from the application of a clawback like tax, Romania suspended the application of the clawback tax, and Portugal applied a reduced tax application of 2.5 % versus 14.5 % for traditional pharmaceuticals. There are, however, still many other countries that continue to apply these taxes to PDMPs as well as to any other pharmaceuticals, such as:

- Greece, with a 45 % clawback tax, Hungary with several clawback tax alike mechanisms, Bulgaria with a 10 % clawback and a supply growth tax;
- Italy with a 15.7 % payback tax applied selectively to PDMPs made with plasma collected outside of Italy (but not to PDMPs made with plasma collected in Italy);
- France applying a payback tax mechanism to PDMPs made with plasma collected outside of France from compensated donors (but applied to PDMPs made with plasma collected in France).

(See Figure 7). The examples of countries that have lifted cost-containment measures for PDMPs and the compelling arguments that take into account both the unique value and the unique nature of these therapies could become a blueprint for other markets in their economic policy towards these therapies.

4.1.3. PROCUREMENT

The final set of economic practices and policies that affects Patient Access is the way in which PDMPs are procured. It is key that policymakers and payers recognise the uniqueness and value of PDMPs which should be reflected in procurement practices. PDMPs cannot be considered as commodities such as generics and biosimilar medicines, since the starting material for PDMPs is plasma which is not an infinite source. In addition, tenders should be designed to include more (value-added) criteria instead of only being focused on price. In the heterogenous European healthcare systems, varied procurement approaches are practised; from direct procurement, through the so-called “intelligent tenders” which aim to ensure availability of diverse
medicines and brands, and “centralised, regional or hospital tenders” which typically result in availability of the “cheapest” single medicine or brand. Each procurement system has specific benefits relative to the type or class of medicines to which it applies. For medicines that are interchangeable or bioequivalent, such as generics or biosimilars, centralised tenders are an effective way of ensuring maximum availability at the lowest price and therefore benefiting the broadest patient population and minimising healthcare budget impact. For medicines that are not interchangeable, such as PDMPs for which proof of bioequivalence is not required, procurement practices should ensure that the optimal treatment is available. Treated patients must be allowed to continue on the optimal therapy, and for naive patients, alternative brands must be made available.

For PDMPs, switching can lead to lower tolerability, compliance issues, adverse effects, and potentially higher indirect costs related to treating the adverse effects. If only one product is selected in a centralised tender, when a patient is faced with tolerability or adverse event issues, there is no possibility to offer alternatives. Availability of only one PDMP brand of each class resulting from a centralised tender process means not only that physicians will need to switch existing patients’ therapies, but also that they will have no choice of customising naive patients’ treatment regimens. Additionally, each route of administration is effective in treating various conditions, and neither is superior to another. However, route selection should be based on patient tolerability and patient/physician preference, because changing the route of administration (e.g. from IV to SC and vice versa) will require patient training or support of a nurse or administration in the hospital/physician office setting instead of home. When a procurement system contravenes the clinical guidelines and therapeutic need, this system may require adjustments to better serve the patients. In other words, economic considerations should not supersede the clinical requirements and guidelines, nor should they impact patients’ quality of life.
4.2. TREATMENT

4.2.1. PATIENT AND PHYSICIAN PERSPECTIVES ON NON-INTERCHANGEABILITY

PDMP treatments within the same class are not interchangeable due to different tolerability profiles, resulting from slight variations in formulation (e.g. contents or properties) or from routes of administration available (e.g. for IgG: IVIG, SCIG, or facilitated SCIG (fSCIG)). Physicians often perform complex diagnostic procedures and try different PDMP brands and/or administration routes in order to reach the optimal effective treatment, tailored to the patient’s profile. Certain co-morbidities affect what brand within a class of treatments is the most appropriate for each patient and what is the risk profile in case such treatment option is not available (see Figure 8).28,29

In other words, limiting availability of brands/products within a treatment class (via procurement practice or otherwise) also limits a physician’s ability to find the optimal treatment regimen. Physicians may not be empowered to make optimal clinical decisions that fully benefit their patients due to budgetary constraints. Physicians report this as a significant challenge to their clinical practice:

“IgGs are widely available in Italy. In large clinics, we often have multiple IgGs to tailor the treatments. However, the big problem are tenders in the regions and macro areas; they mean effectively that only one product is available per entire region- tailoring is impossible at a clinic level and patients cannot travel to another clinic as it has the same single product. The only criterion is the price, not the clinical requirements.”

(Isabela Quinti, Physician, Italy, Sapienza University of Rome)
### Figure 8

Examples for immunoglobulin product considerations versus patient risk profile

*Sources: Gelfand *Int Immunopharm* 2006, Clarke et al. *IgNS* 2018*

<table>
<thead>
<tr>
<th>Product Consideration</th>
<th>Patient Risk Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stabilisers: Sugars &amp; Derivatives</strong></td>
<td><strong>Renal pathology</strong></td>
</tr>
<tr>
<td>- Sucrose</td>
<td></td>
</tr>
<tr>
<td>- Glucose/dextrose</td>
<td></td>
</tr>
<tr>
<td>- Maltrose</td>
<td></td>
</tr>
<tr>
<td>- Sorbitol</td>
<td></td>
</tr>
<tr>
<td><strong>Stabilisers: Amino Acids</strong></td>
<td><strong>Diabetes</strong></td>
</tr>
<tr>
<td>- L-Proline</td>
<td></td>
</tr>
<tr>
<td><strong>Immunoglobulin A</strong></td>
<td><strong>Interference with certain glucose monitoring systems in diabetic patients</strong>*</td>
</tr>
<tr>
<td><strong>Sodium</strong></td>
<td><strong>Contraindicated in hereditary fructose intolerance</strong></td>
</tr>
<tr>
<td><strong>High Osmolarity</strong></td>
<td><strong>History of hypersensitivity</strong></td>
</tr>
<tr>
<td><strong>Fluid Volume</strong></td>
<td><strong>Related metabolic disorders (hereditary hyperprolinemia)</strong></td>
</tr>
<tr>
<td><strong>Infants</strong></td>
<td><strong>Presence of anti-IgA antibody in persons with selective IgA deficiency (IgA&lt;0.05 g/L)</strong></td>
</tr>
<tr>
<td><strong>Individuals with hypertension, cardiovascular disease, kidney disease, endocrine system, adrenal gland disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Infants</strong></td>
<td><strong>History of hypersensitivity</strong></td>
</tr>
<tr>
<td><strong>Individuals with hypertension, cardiovascular disease, kidney disease, previous thrombosis and hypercoagulable state, pathologies with increased blood viscosity, central nervous system disorders, migraine or persistent headaches, hypovolemic state</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Infants</strong></td>
<td><strong>Individuals with conditions requiring fluid restrictions: cardiovascular disease (congestive heart failure), kidney, endocrine system, and adrenal gland disorders, conditions causing the release of stress hormones, treatment with corticosteroids, hyponatremia</strong></td>
</tr>
</tbody>
</table>

*Results falsely showing elevated glucose levels may lead to insulin overdosing and subsequent hypoglycaemia.*
Beyond the initial choice of treatment, based on patient profile and co-morbidities, treatment optimisation is a dynamic process, with multiple possible adjustments. Over time, patients’ responses alter due to wear-off effect, change in tolerability, diminished venous access, co-morbidities, etc. These complex therapy adjustments are illustrated in Figure 9. Similar to identifying the optimal initial treatment, they also require availability of multiple products, with multiple routes of administration.30

Finally, patients’ feedback on treatment outcomes and treatment changes, as well as the impact on patients’ overall physical and psychosocial health response, are inappropriately reflected. Patients in most European countries are required to give their “formal consent” at the initiation of the PDMP treatment. However, the character of this consent and patient involvement in therapeutic decisions varies greatly depending on the type of therapy. Clinically motivated changes to treatment are mostly consulted with patients (in most cases patients are informed and educated). Economically motivated changes (e.g. switch to new tender brand) are mostly ineffectual (i.e., original treatment no longer available), even if consulted with the patient, or in cases of the patient’s opposition. As a result, due to economic reasons, both physicians’ and patients’ perspectives are insufficiently accounted for, with detriment to the physician’s clinical practice and the patient’s well-being.
FIGURE 9

Treatment optimisation process by type of patient response


<table>
<thead>
<tr>
<th>MEDICAL JUSTIFICATION AND/OR PATIENT NEEDS</th>
<th>IVIG*</th>
<th>SCIG/fSCIG**</th>
</tr>
</thead>
</table>
| INSUFFICIENT EFFICACY (OCcurring INFECTIONS) | • Shorten interval between treatments  
• Increase the dose  
• Change product | • Shorten interval between treatments  
• Consider SCIG/fSCIG |
| WEAR-OFF EFFECT | • Shorten interval between treatments  
• Consider SCIG/fSCIG | • Shorten interval between treatments  
• Change product |
| COMORBIDITIES | • Change product  
• Change infusion conditions  
• Switch to SCIG/fSCIG | • Change product  
• Switch to IVIG |
| POOR TOLERABILITY | • Change product  
• Consider premedication  
• Consider post medication  
• Lower infusion rate  
• Switch to SCIG/fSCIG | • Change product  
• Consider premedication  
• Switch to IVIG |
| LOCAL REACTIONS (SCIG) | • Uncommon | • Change product  
• Consider topical medication  
• Switch to IVIG |
| POOR VENOUS ACCESS | • Switch to SCIG/fSCIG | • N/A |
| POOR COMPLIANCE | • Change site of care | • Change site of care  
• Switch to IVIG |
| INCONVENIENCE | • Change site of care  
• Consider or switch to SCIG/fSCIG | • Change site of care  
• Switch to IVIG |

* Intravenous immune globulin (IVIG)
** Subcutaneous immunoglobulin (SCIG); facilitated SCIG (fSCIG) – SCIG administered following injection of human recombinant hyaluronidase.
4.3. PLASMA

4.3.1. PLASMA OVERVIEW

The amount of PDMPs produced depends on the availability of the starting material - human plasma. Since the journey from donor to patient begins with plasma donation, having enough plasma for fractionation is fundamental. Considering the growing clinical need for plasma-derived treatments, global and European plasma donation volumes are low; these low volumes contribute to the fragility of the PDMP value chain. The plasma volume collected in Europe fulfils only around 63% of the European PDMP clinical need; the rest is imported from the United States (see Figure 12). There are multiple factors that influence low plasma donation levels. On the one hand, societal awareness of plasma’s importance is limited, as is the understanding of the differences between whole blood and source plasma donations. On the other hand, systemic solutions aimed at increasing plasma availability are often inadequate, ranging from relative scarcity of a dedicated plasmapheresis infrastructure, low uniformity of regulations between European countries and, finally, to ineffective measures to recognise donors’ effort and inconvenience. Although plasma collection is a global phenomenon, without increased European contribution, there is a high risk of falling short of clinical need in Europe (even with about a 40% supplementation from the United States), which ultimately affects the very availability for treatments for the European population.

"Plasma-derived Medicinal Products (PDMPs) are lifesaving therapies for a large majority of the patient communities represented by PLUS. It is of utmost importance to recognize their value and incorporate the patients’ voice in any relevant policy discussions. Patients are dependent on a stable supply of a range of PDMPs and therefore an appropriate supply of human plasma. As patient organisations, we call for global sufficiency of PDMPs as the ultimate goal of any regional effort to collect more plasma. Any measure or new policy aimed at increasing plasma collection should ensure that it is both patient- and donor-centered, with the goal to meet growing clinical needs for PDMPs.”

(Johan Prevot, representing the Platform of Plasma Protein Users (PLUS))
AWARENESS AND DONATION VOLUMES

A lack of awareness of the importance of plasma donation results in policies or regulations that affect the general population’s willingness to become plasma donors. This is reflected in huge disparities between different countries’ plasma collection volumes; for instance, with Austria collecting ten times more plasma per capita than Finland, Poland or Spain (see Figure 10, right side). Even though awareness is not the sole driver for donors’ willingness and ability to donate, it is the prerequisite.

Discrepancies in national plasma collection volumes means that only six countries in Europe account for ~80 % of all plasma donation to be used for fractionation in Europe to manufacture PDMPs (Germany, France, Italy, Austria, Czechia and Hungary) (see Figure 10 on the next page). However, since Italy, France and Spain use their collections exclusively for their own domestic clinical needs, only four countries (Austria, Czechia, Germany and Hungary) actually contribute more than 55 % of the total plasma collected in Europe for use in manufacturing PDMPs. These same four countries are the only ones which allow source plasma collection and allow for donors to be monetarily compensated. In other words, the entire European patient population is heavily dependent for their treatment on the countries that show high awareness by allowing source plasma collection and donor compensation. To further accentuate this point, a comparison of Europe with the United States reveals even greater potential to increase plasma availability- whilst the European average stands at 14 litres collected per 1,000 inhabitants; the US collects as much as 113 litres per 1,000 inhabitants.31 In the United Sates, source plasma collection and donor compensation are allowed.
Figure 10


Plasma for fractionation volume per country in Europe (source and recovered)

- **Germany**: 2962
- **France**: 892
- **Italy**: 842
- **Austria**: 265
- **Czechia**: 484
- **Hungary**: 402
- **Spain**: 373
- **Netherlands**: 327
- **Poland**: 314
- **Sweden**: 123
- **Rest of Europe**: 7977

Stars indicate 83% of Europe total.

Collected plasma can only be used for PDMPs sold in the same country.
Plasma donation per capita in Europe (litres per 1,000 inhabitants)

US: 113 litres per 1,000 inhabitants

Europe: 14 litres per 1,000 inhabitants

* Plasma collected not used for fractionation or transfusion due to the risk of Variant Creutzfeldt–Jakob disease (vCJD) transmission.
In the future, the clinical need for PDMPs, especially for human IgGs – is expected to grow (see Figure 11). More patients are correctly diagnosed, and overall standards of care and access to healthcare is improving. However, the amount of plasma currently available from Europe is not proportional to the European clinical need. Having a closer look at IgGs, European consumption is projected to increase by one third from 50.5 tons in 2017 to 67.5 tons in 2025 (Figure 12). The plasma collected in Europe can only cover 63% of this clinical need. Even with an increase of source plasma donations and improved manufacturing yield for IgGs, by 2025 the European clinical need coverage will remain low. This means that the current situation, where PDMP clinical need in Europe cannot be covered using European plasma alone, may aggravate. To fulfil the clinical need for therapies, plasma donations, both globally and locally, will need to increase.
FIGURE 11

The worldwide Polyvalent IgG market

Source: adapted from MRB as presented by Robert P. at International Plasma Protein Congress March 2019

CAGR 1988-2018: 9.7 %
FIGURE 12

Projected European Polyvalent IG consumptions (in kg)

Source: MRB reports 2017; Robert P. at PLUS conference Feb 2019

Note: Assumptions for 2025: 9% increase for Source plasma collections in Europe from 2017 to 2025, increase of yield for immunoglobulins from 4 g/L to 4.5 g/L in 2025. IgG consumption taken as proxy for clinical need for PDMPs because manufacturing is mostly optimised for IgG in the last litre.
Required plasma donations for European polyvalent IG consumption and available plasma from Europe (in l)

Source: MRB reports 2017; Robert P. at PLUS conference Feb 2019

Note: Assumptions for 2025: 9% increase for Source plasma collections in Europe from 2017 to 2025, increase of yield for immunoglobulins from 4 g/L to 4.5 g/L in 2025. IgG consumption taken as proxy for clinical need for PDMPs because manufacturing is mostly optimised for IgG in the last litre.
In order to improve donation volumes and address donors’ expenses and inconvenience, virtually all European countries offer a form of donor compensation—monetary (direct and indirect) and/or non-monetary (e.g. time off work). These compensation measures are designed to either minimise or off-set the inconvenience or to reimburse the donor’s out-of-pocket expenses (see Figure 13). As a general rule, these measures are broadly similar for both plasma and whole blood donors.

4.3.3. INFRASTRUCTURE AND REGULATIONS

The challenges to plasma donation volumes do not stem exclusively from awareness, but also depend on the need for more systemic solutions to increase willingness and ability to donate regularly.

There are significant differences across Europe concerning both the plasma donation infrastructure and the regulations concerning plasma centres’ practices. The donation infrastructure in some countries is centralised (with one single entity allowed to collect plasma), but in others it is decentralised, with multiple entities, public and/or private, entitled to run the process in coexistence (see Figure 14). In the centralised markets, plasma is mostly collected by the Red Cross or blood banks, and collection can be restricted to recovered plasma which is less volume- and frequency-efficient than source plasma collection. Austria, Czechia, Germany, and Hungary, which contribute the vast majority of European source plasma donations and have by far the highest donation volumes per capita, all allow private entities to collect plasma and offer monetary compensation for donors’ expenses and inconvenience. It is worth noting that private plasmapheresis centres adhere to the same regulations as the public ones, although private centres might additionally be certified for following voluntary industry standards (IQPP and QSEAL). There is a correlation between plasma volumes and the number of institutions allowed to collect source plasma. In general, the more decentralised the system, the greater the plasma donation volumes (exceptions include France and Spain). The correlation is even stronger for countries that allow private entities or associations to collect source plasma. In these countries the dedicated plasmapheresis centre network is more robust as evidenced by significantly higher donations per capita (Figure 10 and Figure 14).
Compensation measures for whole blood and plasma in Europe

Source: Commission staff working document on the implementation of the principle of voluntary and unpaid donation for human blood and blood components as foreseen in Directive 2002/98/EC on setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC

* Irrespective of actual costs
Figure 14

Centralised versus decentralised plasma collection

Source: Report to the Netherlands Ministry of Health, Welfare & Sport, Pharmaceutical Affairs & Medical Technology on The Results of a survey to understand the blood supply systems in Western European countries, PPTA analysis

* Plasma collected not used for fractionation or transfusion due to the risk of Variant Creutzfeldt–Jakob disease (vCJD) transmission.
Monetary compensate plasma donor expenses and inconvenience from private plasma collection centres

Source: Report to the Netherlands Ministry of Health, Welfare & Sport, Pharmaceutical Affairs & Medical Technology on The Results of a survey to understand the blood supply systems in Western European countries, PPTA analysis

* Plasma collected not used for fractionation or transfusion due to the risk of Variant Creutzfeldt–Jakob disease (vCJD) transmission.
There are also strict regulations in Europe concerning plasmapheresis centre requirements (infrastructure and personnel), as well as the frequency and volume of donations allowed for each donor (see Figure 15). Donation centres are often required by local regulation to have a physician on site, even though EU legislation does not require it. In actuality, EU legislation only requires a responsible person with a degree in medical or biological sciences and a qualified healthcare professional for the examination of the donors (2002/98/EC, Article 9 and Article 19, European Blood Directive). Next, plasmapheresis centres, with strict regulations and personnel requirements, are exclusively stationary and less widespread than the whole blood centres which can also use mobile units and/or collect in non-dedicated places such as businesses and public institutions. This means that plasma centres are less accessible for donors. Source plasma donation also takes longer than whole blood donation (10-20 minutes for whole blood versus 60-90 minutes for source plasma). For many people, this time commitment constitutes a substantial inconvenience that discourages regular source plasma donations. Additionally, since donations are regulated by the number that can be given in a specific period, e.g. every 14 days in Czechia, France, Italy, or the Netherlands, or the maximum amount of donations allowed per year, e.g. a maximum of 60 donations in Germany versus 24 in France, source plasma donors also need careful planning to integrate these intervals into their daily schedule.
**Figure 15**

Examples of regulations concerning plasma and donors in Europe

*Source: PPTA analysis*

<table>
<thead>
<tr>
<th>Country</th>
<th>Requirements for Plasma Collection Centers</th>
<th>Allowed Donation Frequency Per Donor</th>
<th>Allowed Donation Volume Per Donor/Donation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>• Physician requirement</td>
<td>• 50 per year</td>
<td>• 700 mL max</td>
</tr>
<tr>
<td>Czech Rep.</td>
<td>• Physician requirement</td>
<td>• Every 14 days</td>
<td>• 650 mL max, unless IV fluid replacement given</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• max 25 litres per year</td>
<td>• max 1.5 litres per week</td>
</tr>
<tr>
<td>France</td>
<td>• Collection by EFS for fractionation by LFB</td>
<td>• Every 2 weeks</td>
<td>• 750 mL</td>
</tr>
<tr>
<td>Germany</td>
<td>• Physician requirement</td>
<td>• 2 days between donations</td>
<td>• ≤ 60 kg: 650 mL incl. AC*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• max 60x per 12 months</td>
<td>• ≤ 80 kg: 750 mL incl. AC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• &gt; 80 kg: 850 mL incl. AC</td>
</tr>
<tr>
<td>Hungary</td>
<td>• Physician requirement</td>
<td>• 1 donation per 72 hours</td>
<td>• 850 mL max</td>
</tr>
<tr>
<td></td>
<td>• Plasma donors must donate whole blood once per year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>• Goals based on under utilization allow for “success” using non-remunerated donors</td>
<td>• Every 14 days</td>
<td>• 700 mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• max 1.5 litres per month</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• max 12 litres per year</td>
</tr>
<tr>
<td>Netherlands</td>
<td>• Collection and fractionation by Sanquin per the Blood Supply Act</td>
<td>• Every 14 days</td>
<td>• 650 mL</td>
</tr>
<tr>
<td>US</td>
<td>• State dependent physician requirements</td>
<td>• Once in a two-day period, and no more than twice in a seven-day period</td>
<td>• 110-149 lbs: 625 mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 150-174 lbs: 750 mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• ≥175 lbs: 800 mL</td>
</tr>
</tbody>
</table>

*Anticoagulant*
As shown, source plasma donors face significantly higher levels of inconvenience. In recognition of this inconvenience, some countries offer donors direct monetary compensation. In Czechia, monetary compensation for donor expenses and inconvenience from private plasma collection centres was allowed beginning in 2007. Data analysis shows that per capita donations increased from around five litres to around 45 litres per 1,000 inhabitants (see Figure 16). No other external phenomenon can be credited with this increase, since, during the same period, in other countries, donation volumes were stable. It is therefore evident that the combination of widespread and dedicated plasmapheresis centres and the modest and appropriate level of compensation are the critical factors in reaching sustainable plasma volumes relative to the clinical need for PDMPs.

“Our donors, both plasma and whole blood, receive a day off work and minor food rations. Whilst this is appreciated, many of them are aware of the straightforward system of monetary compensation that exists in Germany, and often ask if such a system could be introduced in our centre [in Poland]. It is clear to me that this measure alone would boost their willingness not only to donate plasma, but to donate it regularly”

(Bogumila Piernicka, Head of Blood and Plasma Donation Centre, Poland)

The benefits of employing private plasma collection alongside the public system and allowing monetary compensation are evident. They point to the great potential such solutions can offer to vastly improve the European plasma collection system.
FIGURE 16

Example Czechia: increase of donation after introduction of monetary compensation

4.3.4. COEXISTENCE

The presence of the private sector in Germany and Czechia shows that, given the appropriate policies and regulatory environment, the collection of plasma can grow significantly in a short period of time (Figure 16). However, some healthcare stakeholders perceive the increasing collection of plasma as a threat to the whole blood collection and public sector systems. Some feel that the increase in donations in one area (i.e. source plasma) must proportionally diminish donations in the other (i.e. whole blood), a concept called “crowding-out”, which suggests that coexistence of the two systems is incompatible. However, a detailed retrospective study in Czechia shows that no such phenomenon occurred. In Czechia, although source plasma donations increased dramatically upon the introduction of private collection centres between 2006 and 2010 (see Figure 17), the rate of whole blood donations remained entirely stable during this period and for subsequent years after the opening of many new plasma collection centers. The results of this investigation revealed that plasma donors and whole blood donors are rarely the same people and often have different demographic and social profiles. This indicates that increasing source plasma donations, even substantially, does not cause restrictions in whole blood donations. The two systems can coexist under conditions of monetary compensation and the resulting dynamic growth in source plasma collection.
Blood collection numbers and rates have remained relatively stable over the past 10 years, with neither sharp upticks nor declines. This stability in blood collection has persisted despite the opening of 10 plasma collection centers between 2007 and 2010. This same stability in blood collection has persisted despite a dramatic increase in predominantly compensated source plasma collection during the same time frame, moving from 6.8/1000 donations per person in 2006 to 63.4/1000 donations per person in 2010.

Professors Macis & Lacetera,
Johns Hopkins University and the University of Toronto (The Source Winter 2017)

...blood and plasma donors are not part of the same donor population. We observed that blood donors are on average older than plasma donors. ...On average, a blood donor donates twice a year. A plasma donor donates on average 20 times a year. This is a whole different commitment and explains why it is more appealing to the younger population.

Dr. Franz Weinauer, Medical Director
Blood Donation Service of the Bavarian Red Cross (The Source Fall 2018)
The discussions on coexistence, crowding-out, and the nature of compensation measures also have an ethical dimension. Directive 2002/98/EC (the European Blood Directive) repeatedly states that plasma (and blood) should be collected via “unpaid voluntary donations”. This phrasing has led some to make an unwarranted inference that only unpaid donations can be voluntary, and that donations given with monetary compensation lead to an unethical element of “enforcing” increased donations. This has led to further misconceptions that donor compensation contravenes the historic nature of donor motivations, stemming from solidarity and pertaining to moral duty or moral virtue. The Blood Directive does not, in fact, prohibit monetary compensation for plasma donations, and forms of compensation are offered in many European countries. (See Figure 13.) Directive 2004/23/EC – article 12 (the Directive on Tissues and Cells) even specifies that donors may receive compensation for expenses and inconveniences related to the donation. Nonetheless, the concepts of “unpaid” and “voluntary” are often misinterpreted.

Concerning “unpaid” donation: the word “unpaid” is often understood to mean, “not paying for a donor’s biologic materials”. In fact, the compensation offered to plasma donors is, firstly, not a “payment” but a compensation, and secondly, it is a compensation for the donor’s expenses and inconvenience, not for “biologic materials”. In fact, the small compensation given is a form of reimbursement and is proportional to the donor’s loss. It is not dissimilar to many other donor compensation/reimbursement practices which are common across Europe and is considered to comply with the notion of “unpaid voluntary donation”. (See Figure 13.)

Concerning “voluntary” donation: many scholars have opined on the “voluntary” nature of plasma donations. A useful breakdown of this problem is offered by James Stacey Taylor.39 It essentially boils down to two issues: first, one is concerned with whether compensation inhibits “informed consent”, and second, whether uncompensated donation is “morally superior” to compensated donation. The answers to both questions appear to be a resounding, “No”. Because in all European countries allowing direct monetary compensation, the systems of public (i.e., non-compensated) and private (i.e., compensated) donations coexist, there is no danger of inhibiting informed consent. As long as a system of uncompensated donation is
permitted to operate in the same area as a system of compensated donation, the donors have access to information concerning the level of compensation for their plasma.

This ensures “informed consent” which is a primary condition or a prerequisite of “voluntary” donation. Uncompensated donation is also not “morally superior” to compensated donation. If we consider most ethical systems, donor compensation is ethically permissible, even if not ethically required.

It is also critical to consider the need of the patient, who is often overlooked when debating the “ethics” of compensation. Guaranteeing Patient Access to optimal treatment is an intrinsic ethical dimension of this debate. If increasing plasma donations to achieve this end is inherently ethical and good, then by extension, reasonable measures that contribute to the sustainability of the plasma availability must also be considered ethical in nature. That is not to say that there is a moral imperative for all countries to adopt direct monetary compensation for donors’ expenses and inconvenience. Rather, it means that countries which do not allow coexistence of both systems have an ethical obligation to seek other ways to increase plasma donation in the years to come.
Recommendations

This paper has explored different dimensions of PDMPs’ unique nature and value and specific challenges that threaten the realisation of its full value. Existing and possible solutions have been identified that have the capacity to stabilise the fragility of the PDMP value chain and ultimately ensure optimal Patient Access, both formal and therapeutic. In order to achieve this, it is necessary to urgently take the following actions:

Apply effective measures, in collaboration with the private industry, to promote and grow plasma donations across Europe to fulfil the clinical need for PDMPs.

- There is a need for both country-level and pan-European awareness campaigns promoting the critical importance of plasma donations and its impact on patients’ well-being. This can be achieved by a joint effort from industry and patient associations as well as European governments and supra-national bodies.

- Countries should allow coexistence of both private and public plasma collection systems (such as is currently done in Austria, Czechia, Germany, and Hungary). The private investments can advance the efficiency and number of plasmapheresis centres, and, thereby, increase accessibility for donors and help to reduce the public investment required for the expansion of collection centres.

- Countries should revisit their implementation of the Blood Directive (2002/98/EC) and consider a system of reasonable and proportional monetary compensation for donors’ expenses and inconvenience. It has proven singularly effective in further increasing plasma donations in Europe, maximising benefit for patients. This model is similar to the compensation model for the donation of tissues and cells (Directive 2004/23/EC, also referred to as the European Tissues and Cells Directive).
RECOMMENDATIONS

Ensure the broadest possible reimbursement coverage for all eligible patients to maximise clinical and socio-economic benefits.

There is a need and urgency to revise reimbursement coverage in Europe to maximise patient populations that can evidently benefit from these treatments. This reimbursement coverage should be uniform for all PDMPs and recognise their use as the exclusive or primary treatment for severe and often rare diseases.

Optimise reimbursement policies, considering value based pricing such as value informed affordable pricing (VIA) models, and revise cost-containment measures such as clawback, payback, and supply growth taxes, in light of the uniqueness of the PDMP value chain, in order to maintain the PDMP industry’s sustainability and improve equitable access to treatment for patients in Europe.

- Reimbursement schemes which are specific to PDMPs should be advisable, especially in order to better align with the actual clinical and socio-economic value.

- Cost containment measures such as clawback, payback and supply growth taxes or mandatory discounts for PDMPs should be lifted/suspended in the name of the patient’s ultimate benefit.

- Revise and align procurement practices with clinical needs to ensure the right treatment for the right patient. Healthcare systems should strive to create the right conditions for physicians to fully optimise treatments for their patients. Physicians’ feedback and best-in-class clinical practices point to the need for availability of varied brands and routes of administration within the same therapeutic class to enable physicians to fully tailor treatments to the individual patient.

- European payers and policymakers may wish to revisit their procurement practices specific to PDMPs and take into account that they cannot be considered bioequivalent and interchangeable. It is worth considering a number of measures, such as tenders allowing for multiple brands to be procured or exemption of PDMPs from central tendering procedures.
Overall, despite evidence that PDMPs present high clinical and socio-economic value, significant challenges to PDMP Patient Access persist. The PDMP ecosystem is in a fragile balance. Heterogenous reimbursement coverage and policies across Europe, as well as varied economic measures, further impact its stability and, thus, optimal Patient Access.

Whether the challenges are pan-European or country-specific, formal or therapeutic, there is an utmost need and urgency to establish close and meaningful partnerships among all stakeholders, focused on value, within a sustainable framework of regulatory and clinical environment. Open and trust-based dialogue and collaboration between all interested parties and recognition of the unique properties of PDMPs are the critical enablers for the necessary changes required to sustain and improve patients’ lives.


REFERENCES


LIST OF ABBREVIATIONS

AATD  Alpha-1 Antitrypsin Deficiency
CIDP  Chronic Inflammatory Demyelinating Polyneuropathy
COPD  Chronic Obstructive Pulmonary Disease
CVID  Common Variable Immune Deficiencies
DALY  Disability-Adjusted Life Year
EFS  Etablissement Français du Sang
ERP  External Reference Pricing
EUnetHTA  European Network for Health Technology Assessment
fSCIG  Facilitated Subcutaneous Immunoglobulin
FVIII/IX/X/XIII  Clotting factor VIII/IX/X/XIII
GBS  Guillain-Barré Syndrome
GDP  Gross Domestic Product
HAE  Hereditary Angioedema
IgG  Immunoglobulin
IQPP  International Quality Plasma Program
ITP  Primary Immune Thrombocytopenia (Idiopathic Thrombocytopenic Purpura)
IVIG  Intravenous immunoglobulins
MMN  Multifocal Motor Neuropathy
PDMP  Plasma-derived Medicinal Product
PID  Primary Immunodeficiencies
PPTA  Plasma Protein Therapeutics Association
QALY  Quality-Adjusted Life Year
QSEAL  Quality Standards of Excellence, Assurance, and Leadership
SCIG  Subcutaneous Immunoglobulin
SID  Secondary Immunodeficiencies
TA  Therapy Area
VIA Pricing  Value Informed, Affordable Pricing
VOLY  Value of a Statistical Life Year
WHO  World Health Organization
YLD  Years Lost due to Disability
YLL  Years of Life Lost
WANT TO KNOW MORE?

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