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D4.2 Quick Check Policy Brief 2

*Human normal immunoglobulin in Portugal: Analysing price increases across multiple markets*

Prepared by National Authority of Medicines and Health Products (INFARMED, I.P.)

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## 1. Executive Summary

### a) Objective of the analysis

Portugal has been experiencing an increasing expenditure on human normal immunoglobulin (HNIg) in recent years due to rising volumes and exceptional price reviews granted to these medicines to overcome the problems associated with shortages.

This policy brief aims to investigate the price increases across multiple markets. We will study whether the price increase also occurred at the European level or was more pronounced in Portugal. Additionally, we will examine whether the price increase was observed for other plasma-derived products, such as human albumin (HA).

We used EURIPID data and Portuguese price information to support our study. This policy brief aims to demonstrate how EURIPID can be used beyond external reference purposes.

### b) Key messages

In Portugal, the pricing changes of medicines containing HNIg and HA diverged. Specifically, there was a noticeable rise in the price of HNIg, particularly in 2021, while HA maintained a consistent price. Comparatively, across Europe, there's a general upward trend in the pricing of both medicines. However, the escalation in HA pricing is more recent and notably more pronounced in 2023.

Even with the rise in HNIg prices, Portugal still maintains a cost per mg below the average of other countries. As for HA, its cost remains the lowest. Considering the trends seen in other countries, it's anticipated that the cost of HA in Portugal will likely increase in the coming years.

**Keywords:** Portugal; drug costs; EURIPID; human normal immunoglobulin, HNIg, human albumin, HA

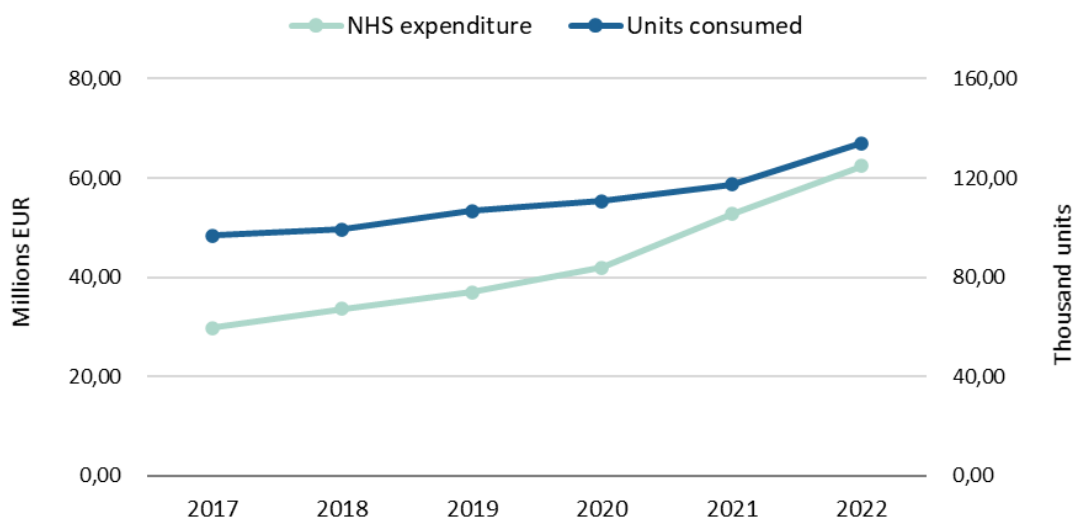
## 2. Introduction

Human normal immunoglobulin (HNIg) is a blood product used to treat a variety of conditions, including primary immunodeficiency syndromes, common variable immunodeficiency, severe combined immunodeficiency, immune thrombocytopenic purpura, among others.

HNIg is available in different formulations for intravenous or subcutaneous administration from different manufacturers.

In Portugal, the increasing use of HNIg is a national problem due to its scarcity and problems related to shortages. Between 2017 and 2022, there was an increase in the consumption of products with the respective active ingredient in public hospitals ( $\Delta + 38,5\%$ ), accompanied by an increase of public expenditure ( $\Delta + 109\%$ ). The average unit cost of these medicines also shows an increase from 308 € in 2017 to 466 € in 2022 ( $\Delta + 51\%$ ).

Figure 1 - HNIg in the NHS hospitals



In 2022, HNIg was the INN with the greatest Portuguese NHS expenditure in hospital care<sup>1</sup>.

*Table 1 - INN with highest expenditure in Portugal*

Active substances	NHS expenditure 2022	Δ €	Δ %
Human Normal Immunoglobulin	62 412 847	+ 9 729 698	+ 18,5%
Pembrolizumab	59 450 218	+ 17 189 667	+ 40,7%
Ustekinumab	37 377 178	+ 5 504 082	+ 17,3%
Tafamidis	35 657 793	+ 18 282 086	+ 105,2%
Dolutegravir + Abacavir + Lamivudine	33 881 432	- 9 709 706	- 22,3%
Lamivudine + Dolutegravir	33 417 939	+ 23 536 742	+ 238,2%
Bictegravir + Emtricitabine + Tenofovir Alafenamide	27 400 364	+ 14 229 545	+ 108,0%
Ibrutinib	26 720 047	+ 4 345 713	+ 19,4%
Nivolumab	24 839 605	- 2 833 008	- 10,2%
Daratumumab	24 469 662	+ 6 954 473	+ 39,7%
Remaining active substances	1 396 465 239	+ 103 653 599	+ 8,0%
<b>Total</b>	<b>1 762 092 325</b>	<b>+ 190 882 892</b>	<b>+ 12,1%</b>

In 2023, there is a slight stabilization of the reported average unit cost and a small increase in consumption (Δ + 3,8 %) and expenditure (Δ + 6,0 %) with this medicine.

Furthermore, there have been increasing requests for exceptional price reviews for plasma-derived products, as well as increasing notifications of drug shortages, mainly due to the lack of raw material (blood) since 2016.

The expected behaviour on price should be similar for all plasma-derived products, such as human albumin (HA). However, this is not the case in Portugal. For HA, the average unit cost reported by NHS hospitals has suffered few changes, being the same in 2023 as it was in 2017.

Based on the EURIPID database, we are trying to understand if the price increase for HNIg also happened in other European countries or if it was more pronounced in Portugal. Additionally, we are studying if there are differences between the two plasma-derived products in terms of price increases, which would be expected.

<sup>1</sup> <https://www.infarmed.pt/documents/15786/6747749/dezembro/4d35b6e0-8a53-b1a5-7c44-d4fa3c1e979e?version=1.0>

## 3. Methods/study design

### 3.1. Data sources

Pricing information is based on the EURIPID database (<https://database.euripid.eu/>) for other European Countries, and on the Portuguese medicines price information (internal data). In Portugal, hospital prices are not publicly available.

Portuguese consumption is provided by NHS hospitals (CHNM) on a monthly basis and includes the number of units of product consumed in that month and the NHS expenditure associated.

### 3.2. Search strategy

Based on Portuguese national data consumption, for the 2 selected active ingredients, i.e. Human Albumine (B05AA01) and HNIg (J06BA02), we choose the international non-proprietary name (INN) & strength with more than 90% of the consumption in value:

- Human Albumine, 10 000 mg, I.V. and
- HNIg 1 650 mg, I.M., S.C.;
- HNIg 5 000 mg, I.V.;
- HNIg 10 000 mg, I.V.; and
- HNIg 20 000 mg, I.V.

From EURIPID database we selected the **Graph “Price Evolution Graph”**, for each INN & strength identified below, with the following search criteria:

*Table 3 - Search criteria on the Price Evolution Graph*

<b>Graph</b>	Price evolution graph
<b>Date 1</b>	01-2017
<b>Date 2</b>	10-2023
<b>Exported at</b>	15-11-2023 13:57
<b>Country</b>	Austria, Belgium, Bulgaria, Czech Republic, Greece, Hungary, Italy, Lithuania, Poland, Romania, Slovenia, Slovakia, Switzerland, Spain

<b>Price type</b>	manufacturer unit price
<b>Min or Max price</b>	MAX
<b>Currency exchange</b>	non-fixed
<b>Route of Administration</b>	all (exact)
<b>INN &amp; strength</b>	immunoglobulins, normal human, for extravascular adm. 1650 mg (exact) immunoglobulins, normal human, for intravascular adm. 5000 mg (exact) immunoglobulins, normal human, for intravascular adm. 10000 mg (exact) immunoglobulins, normal human, for intravascular adm. 20000 mg (exact) Albumin 10000 mg (20%) (exact)
<b>Status</b>	All

We gathered data spanning from 2017 to 2023 for both HNIg and HA, using the manufacturer price to eliminate variations based on marketing margins. Furthermore, we specifically chose the Maximum manufacturer price to align with the focus of our analysis: determining any price hikes throughout this timeframe.

Given the extended duration (7 years), we opted against setting fixed exchange rates at the onset or conclusion of the period. Fluctuations in these rates could deviate from the prices at the time of analysis. Therefore, we employed non-fixed currency exchange rates for accuracy.

Every country was initially chosen for the study. However, Bulgaria, Lithuania, and Romania, lacking information for any of the years under examination, were subsequently excluded. Consequently, the dataset being analyzed comprises data from 12 countries: Austria, Belgium, Czech Republic, Greece, Hungary, Italy, Poland, Slovenia, Slovakia, Switzerland, Spain, along with Portugal.

From the query we identified 4 369 records plus 354 records from Portugal, in total 4 723 records.

### 3.3. Tool of collecting, modelling, and analysing searched data

As hospital pricing in Portugal isn't accessible to the public, we are unable to provide these prices to EURIPID. Consequently, we harmonized the data based on the information available in EURIPID. All gathered data was exported to Microsoft Excel®, where subsequent analyses were conducted using this software.



### 3.4. Method of analysis

We consolidated all the records, accounting for various strengths with distinct prices. To facilitate cross-country comparisons across the time span, we computed the price per mg for each country. Regarding HNIg, the price per mg was determined as the average among the four different strengths under analysis

### 3.5. Limitations

Portugal lacks confidential prices for HNIg and HA, but it's uncertain if other European countries have such confidential prices. While EURIPID includes a field indicating the presence of Managed Entry Agreements (MEA), most countries lack this information. Even in cases where MEAs exist, it's unclear whether confidential pricing is part of the negotiation. If confidential prices are involved, the comparisons made could be biased.

Because of the scarcity of volume-related data, we chose not to incorporate it into our analysis. Having more volume information accessible through EURIPID would be beneficial, as it could help us determine whether countries with higher prices also correspond to those with higher volumes.

## 4. Results

### a) Comparison for HNIg

From 2017 to 2023, prices for HNIg surged in both Portugal and across other European nations. Yet, in Portugal, they remain comparatively lower than in other countries.

Figure 3 - Cost per mg comparison for HNIg

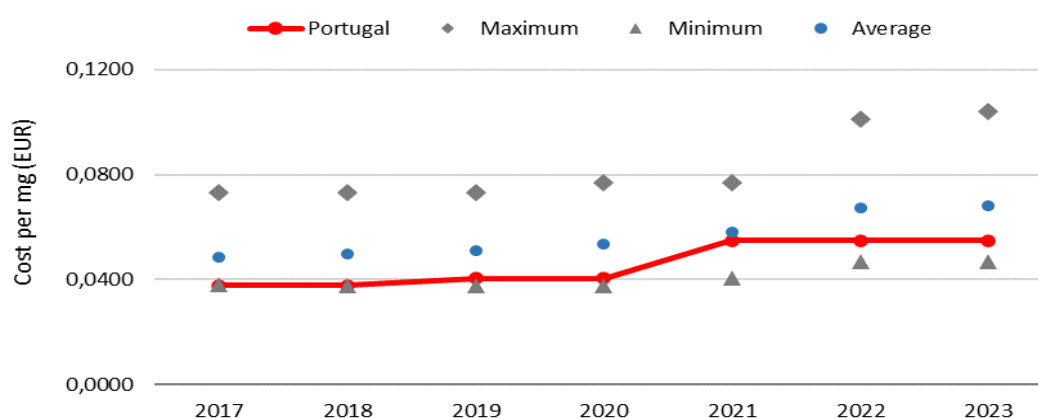
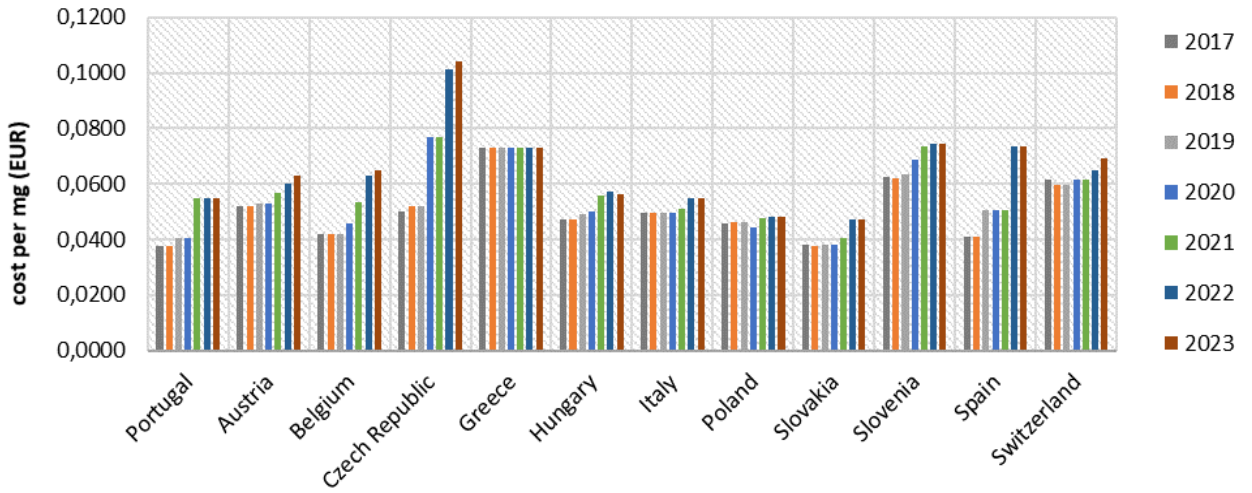


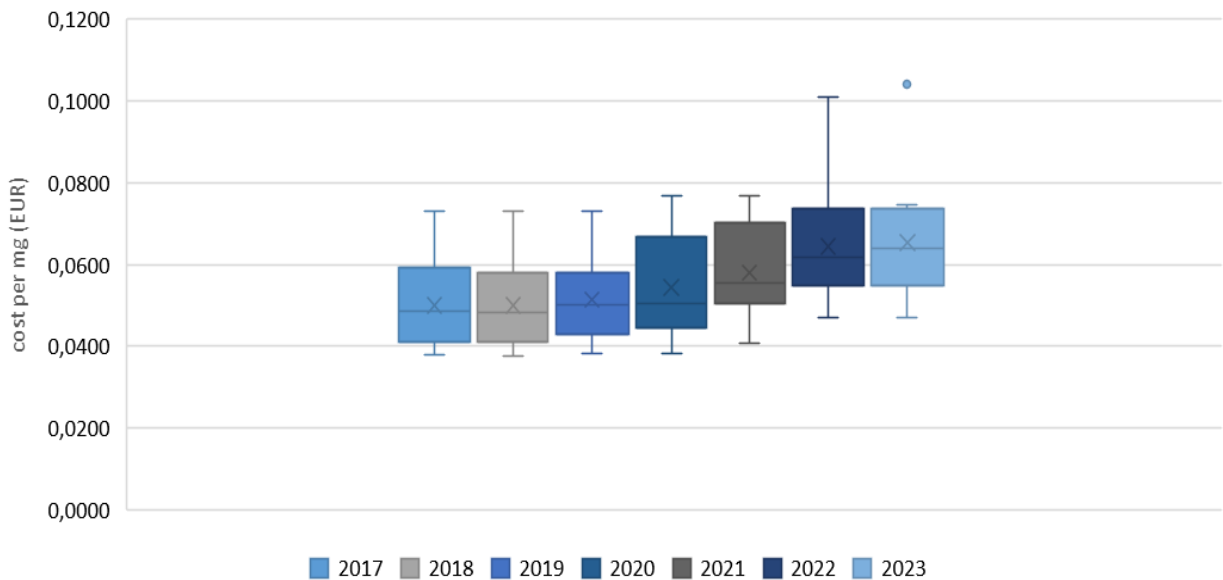
Figure 2 demonstrates a notable rise in HNIg costs in Portugal during 2021, primarily due to an exceptional price review set to remain in effect for three years. Contrastingly, for other nations, the hike is more pronounced in 2022 compared to 2021. Despite the 2021 price surge, Portugal's HNIg cost still falls below the European average. By 2023, only Slovakia and Poland boast lower costs per mg than Portugal, while Italy matches Portugal's pricing (refer to Figure 3). Notably, among the considered countries, Greece stands out for not experiencing a price increase over the years.

Figure 4 - Cost per mg in all countries for HNIg



Analyzing Figure 4 below, we noticed that median prices raised between 2020 and 2022 in the whole EURIPID region, slightly stabilizing in 2023.

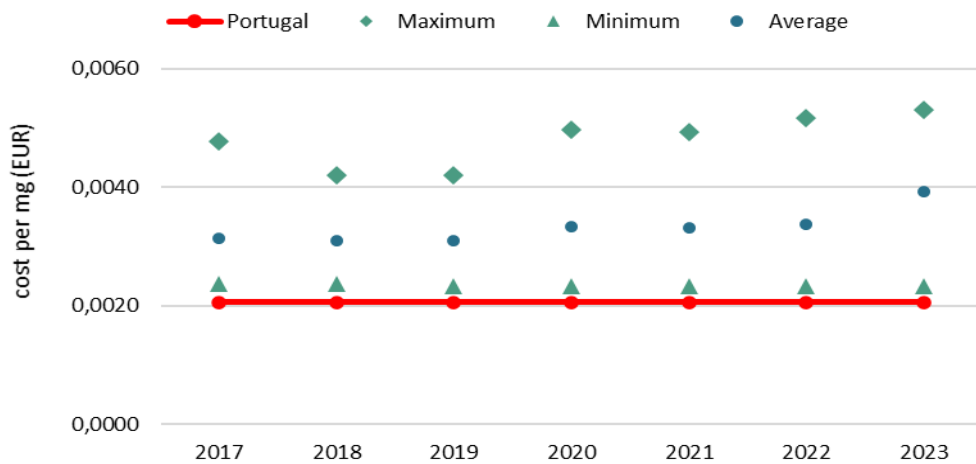
Figure 5 - Box plot of cost per mg in European Countries for HNIg



**b) Comparison for HA**

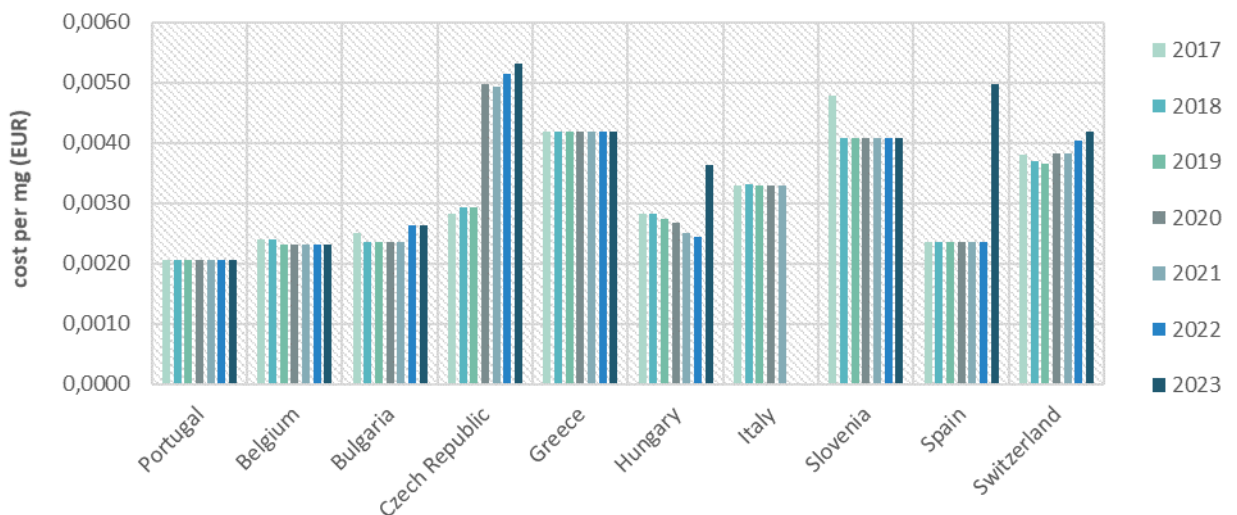
According to the data, HA price increases were lower than those for HNIg and inexistent in Portugal, that has the lowest cost per mg of all the countries in this study (Figure 5).

*Figure 6 - Cost per mg comparison for HA*



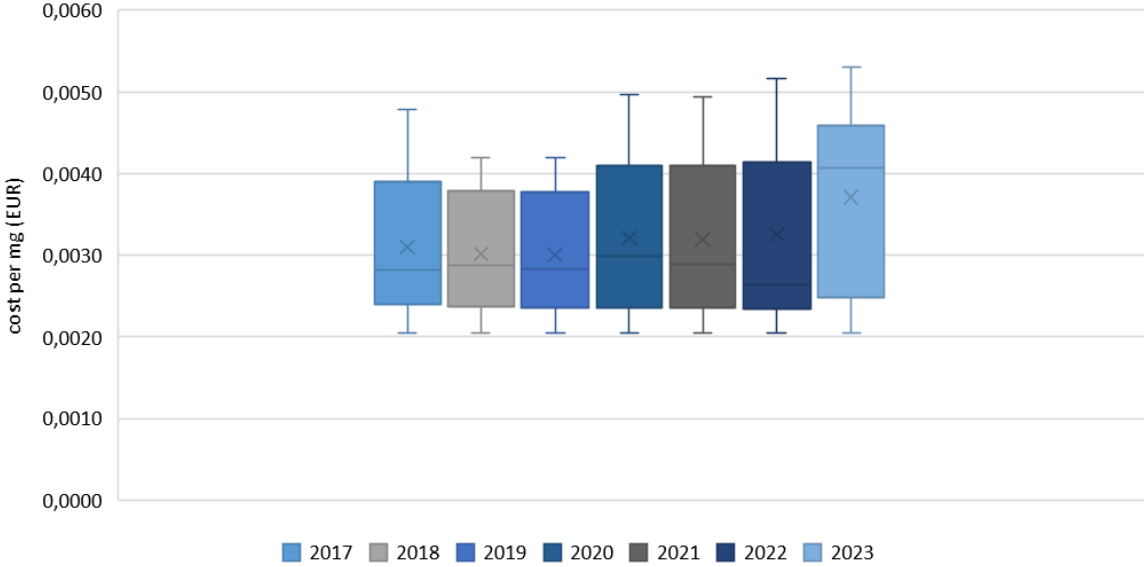
According to figure 6 below, some countries seem to have an increase in cost per mg mainly in 2023. However, unlike the evolution observed in the cost per mg of HNIg, not all countries have already had that increase.

*Figure 7 - Cost per mg in all countries for HA*



As observed in the box plot below, 2023 is the year with the biggest change. There is a bigger dispersion of prices for HA when compared to HNIg.

Figure 8 - Box plot of cost per mg in European Countries for HA



## 5. Conclusions

### a) **General conclusions**

In Portugal, the price developments of medicines containing HNIg and HA were different. An increase in the price of HNIg was observed in Portugal, notably in 2021, while no price variation occurred with HA. When compared to other European countries, there is a trend of increase in both medicines, although the increase in HA is more recent and more pronounced in 2023.

Despite the increase observed in HNIg, Portugal continues to present a cost per mg below the average of the other countries. Regarding HA, it has the lowest cost.

Given the behaviour observed in other countries, it is expected that there will also be an increase in the cost of HA in Portugal in the upcoming years.

### b) **Potential further analysis (optional)**

Considering the increasing expenditure on HNIg and the price hikes in recent years, it's necessary to monitor the evolution of these prices in other countries to ensure that the requested increases are not disproportionate compared to those occurring in European countries.

It also becomes of utmost importance to monitor the evolution of HA prices to anticipate possible increases that might occur in Portugal.

## 6. Disclaimer

The views expressed in this publication are those of the author/s and should not be attributed to EURIPID COLLABORATION and/or its funders.

## 7. List of abbreviations

HA – human albumin

HNIG – human normal immunoglobulin

MEA – Managed Entry Agreements

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