

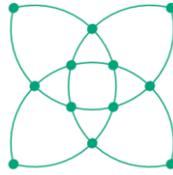
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## ASSESSMENT REPORT ON PRINT ON DEMAND LEAFLETS

February 2024



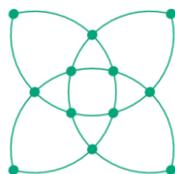
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# ASSESSMENT REPORT ON POD

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## Acronyms

**ATC-** Anatomical Therapeutic Chemical (ATC) Classification. Within this classification system, the active substances are classified in a hierarchy with five different levels.

**DDD-** Defined Daily Dose. It is the assumed average maintenance dose per day for drugs used.

**ePI-** electronic Product Information

**EU-27-** Europe Union formed by 27 countries (Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden)

**OECD-** Organization for Economic and Co-operation and Development

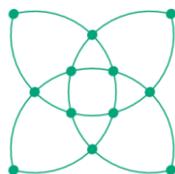
**PoD-**Print on Demand

## Executive summary

The Commission issued in 2023 a proposal for a new Directive and a new Regulation to revise and replace the existing general pharmaceutical legislation in which countries may decide whether the medicine information leaflet should be provided in paper format, electronic, or both. The proposal establishes the right of patients to ask for a printed copy of the package leaflet upon request and free of charge. The unresolved question in the Directive's proposal is: What is the total cost of the Print on Demand (PoD) leaflets?

This report provides a conservative quantification of this total cost by establishing a unit cost of a PoD leaflet in a pharmacy and estimating the total number of PoD leaflets that will be annually requested in Europe, based on a range of statistics, and reports available.

**Significant demand for PoD Leaflets considering the current level of digital skills:** While the transition to electronic Product Information (ePI) aims to reduce paper leaflets, with the current level of digital literacy across Europe, PoD will still result in a significant number of paper leaflets being printed. A substantial portion of citizens (46%) lack the digital skills needed to access ePI, requiring physical leaflets for detailed medication information. This impact will be particularly felt by the older population, aged over 65, who consume over 50% of medications and tend to have lower digital literacy according to the European Commission's Digital Economy and Society Index. This segment will drive demand for PoD leaflets substantially high.



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**Cost Implications of PoD:** Member States implementing ePI can face an estimated total PoD cost ranging from €1.680 billion to €3.495 billion annually, depending on whether leaflets are printed in black or four-color ink. The critical question is how the different national pharmaceutical/medical systems will bear this cost.

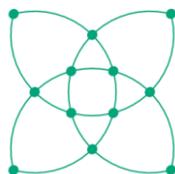
In conclusion, while ePI holds potential benefits, the significant demand for PoD leaflets due to the current limited digital literacy level of the European population makes it a regrettable substitution. The idea appears to be promising in theory, however, considering the cost implications and issues related to equitable access to medicine information, it does not make sense for an immediate adoption of ePI and thereby implementation of PoD leaflets. Addressing these challenges is crucial for a successful and inclusive transition to ePI.

### Introduction/Motivation of the report

On 26 April 2023 the Commission issued a proposal for a new Directive and a new Regulation to revise and replace the existing general pharmaceutical legislation. The Article 63 of this proposal establishes:

*'3. Member States may decide that the package leaflet shall be made available in paper format or electronically, or both. In the absence of such specific rules in a Member State, a package leaflet in paper format shall be included in the packaging of a medicinal product. If the package leaflet is only made available electronically, the patient's right to a printed copy of the package leaflet should be guaranteed upon request and free of charge and it should be ensured that the information in digital format is easily accessible to all patients.'*

Thus, the countries may decide whether the medicine information leaflet is in paper format, electronic, or both. This change should not be performed without conducting an impact assessment considering any new digital procedure has the risk of leaving behind citizens lacking digital skills. To overcome this barrier, the Directive proposal establishes the guarantee of patients' right to be provided with a printed copy of the medicine leaflet upon request and free of charge. The unresolved question in the Directive's proposal is: **What is the total cost of the Print on Demand (PoD) leaflets?** This report aims to quantify this total cost by establishing the unit cost of a PoD leaflet in a pharmacy and estimating the total number of PoD leaflets that will be requested annually in Europe.



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## Current Legal situation and new European Directives

The current EU pharmaceutical legislation includes both general and specific legislation. Directive 2001/83/EC of the European Parliament and of the Council 5 and Regulation (EC) No 726/2004 of the European Parliament and of the Council 6 (together 'general pharmaceutical legislation') lay down provisions related to medicinal products authorisation and post-authorisation requirements, pre-authorisation support schemes, regulatory incentives in terms of data and market protection, manufacturing and supply, and the European Medicines Agency (EMA). The general pharmaceutical legislation is complemented by specific legislation on medicinal products for rare diseases (Regulation (EC) No 141/2000, the 'Orphan Regulation' 7), medicinal products for children (Regulation (EC) No 1901/2006, the 'Paediatric Regulation' 8) and advanced therapy medicinal products (Regulation (EC) No 1394/2007, the 'ATMP Regulation' 9).

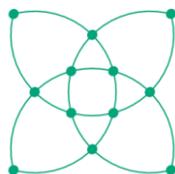
Directive 2001/83/EC, in its title V regulates package leaflets and establishes, among others:

- The inclusion in the packaging of all medicinal products of a package leaflet shall be obligatory unless all the information required (..) is directly conveyed on the outer packaging or on the immediate packaging (Article 58).
- The package leaflet must be written in clear and understandable terms for the users and be clearly legible in the official language or languages of the Member State where the medicinal product is placed on the market (Article 63).

Furthermore, and as part of the Directive, the EU Commission published guidance on labelling and the packaging insert, with key extracts below.

- Whilst there is guidance on font size (9 points), there are also stipulations for line spacing, spaces between words and the text's contrast with the background, which is influenced by paper weight, colour and will be very difficult for pharmacists to consistently meet. The leaflet must also be designed so that folding does not interfere with information -this will be an issue with on-demand printing where the leaflet will likely be folded by HCPs/patients in a variety of ways.

On 26 April 2023 the Commission issued a proposal for a new Directive and a new Regulation. Among the specific objectives of the proposal there is one related to 'making medicines more environmentally sustainable'. Article 63 seems to be aligned with this specific objective, leaving to the Member States the decision of replacing physical medical leaflets with electronic Product Information (ePI). Meanwhile, the



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proposal establishes that if the package leaflet is only made available electronically, a printed copy of the package leaflet should be guaranteed upon request of the patients and that it must be free of charge.

### Print on Demand as an alternative to regular leaflets

Under the current situation every pharmaceutical product package includes a paper leaflet folded inside it. The leaflets are printed in industrial printers that have been manufactured, calibrated and maintained precisely for this purpose. Furthermore, there are strict control measures to assure that all the leaflets are correctly printed and inserted in the right package.

In the new scenario resulting from the proposed Directive, patients could ask for a free copy of the leaflet. It is not specified who will provide this copy or how this will be done, but the most likely situation will be that pharmacy staff will print the leaflets at the request of patients when they get their prescription medicines in their pharmacy. These are the so-called Print on Demand (PoD) leaflets.

The proposed PoD will be carried out by pharmacy staff on home or office type printers, which are more prone to breakdowns and failures and require much more maintenance than industrial printers. The quality control of the PoD leaflets would have to be done manually instead of the automatic quality control of the current industrial leaflets. Furthermore, there is increased risk that the incorrect leaflet will be attached to a medicine pack than in the current situation.

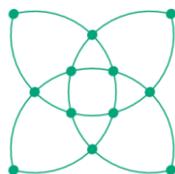
On the other hand, the current situation implies printing the leaflets of 100% of the pharmaceutical product packages sold instead of the PoD where only the leaflets requested by the consumers will be printed. The question is, **how many PoD will be requested annually and what is the unit cost in both scenarios?** Furthermore, it must be analysed the consumption of paper in terms of sustainability, as the industrial leaflets have very specific conditions (size, weight, and quality of the papers) and the PoD will use normalized A4 80gsm paper (as used by domestic printers).

### Unit cost per PoD (paper, ink, printers, workforce)

Print on Demand will have a cost constituent that must be valued in order to get a final figure that might be compared with the current inserted printed pharmaceutical information leaflets.

The unit cost per PoD leaflet shall be made up of the sum of the following items:

- Paper



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- Ink
- Printers' depreciation
- Labour cost

### *Paper*

The cost of the paper per PoD will depend on the type and amount of paper needed as well as on the paper cost. As the impressions will be done by common desktop printers, it has been assumed that the size of paper will be A4. For this analysis it has been considered a paper with a weight of 80g/m<sup>2</sup> with EU Ecolabel (DE/011/096) and Blue Angel Certification.

The average cost of the paper bought in small quantities will be 18,00 € for 2.500 sheets (3.60€/ ream of 500 sheets). Therefore, **the cost per sheet of this type of paper will be €0,0072.**

In order to estimate the amount of paper needed it has been used as an example the leaflet of a relative common prescript drug as it is Eliquis (Apixaban, see Annex I). For the layout of the text, it has been considered the regulations established within EC Directive 2001/83/EC<sup>1</sup>, where it is stipulated that for the legibility of medicinal package labelling, a minimum size of 9 of font 'Times New Roman' is required. Considering the length of the text of the previously mentioned medicament and the text layout options defined, the average size of a PoD leaflet is estimated 7 pages, resulting in 4 sheets of paper to be printed (printed both).

**All this considered, the unit cost in paper per PoD leaflet will be 0,0288€.**

### *INK COST*

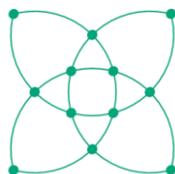
The leaflets are assumed to be printed in four colours. A 4-colour set printer toner cartridge for a laser printer costs around 170€ and can print 1.000 copies in A4 format. This means a cost per page of 0,170€.

As the number of pages of the leaflet taken as an example is 7, **the unit cost in ink per PoD leaflet will be 1,1867€.**

If the leaflets will be printed in black, it should be estimated a cost of the black toner cartridge of 80€ with which 3.000 A4 copies can be printed. This means a cost per page in ink of 0,0267 € and therefore a unit cost in ink per PoD leaflet of 0,0187€.

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<sup>1</sup> [https://www.europarl.europa.eu/doceo/document/E-8-2018-003852\\_EN.html](https://www.europarl.europa.eu/doceo/document/E-8-2018-003852_EN.html)



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### PRINTERS DEPRECIATION COST

Considering a budget price of 240€ per printer and an estimated use of 90.000 copies in its lifetime<sup>2</sup>, its depreciation cost per page will be 0,0027 €.

Therefore, the cost in printer's depreciation per average leaflet will be 0,0187€.

### LABOUR COST

The print on demand leaflets in pharmacies also imply a certain time of the pharmacy workers who will have to select the 'print leaflet' button, wait until the leaflet is printed, check that all pages are correctly printed and stapling the sheets together. The time for this process might take longer if there is less than one printer per sales spot in the pharmacy because the sellers have to check that the papers printed belong to the buyer who they are attending to. For the purpose of this report, it has been considered that **the overtime of printing a leaflet will be of one minute and a half (1'30'')** comparing with the current situation where leaflets are already printed and inside the pharmaceutical product package.

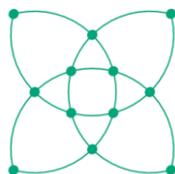
Regarding the costs assigned to the workforce, it must be considered that there are two main different types of professional profiles that work in a pharmacy: Pharmacist and Pharmacist Technician/Assistant. The workers composition of the pharmacies varies in each pharmacy, usually depending on the number of people employed in each venue (the higher the pharmacy the more rate of Technicians or Assistants per Pharmacist). For this study it has been estimated that half the workers in a pharmacy are Pharmacist and half of the workers are Technicians/Assistant whose gross salary is half the one of the Pharmacist. The cost of the labour force varies significant among the EU countries. It has been grouped the countries among 4 groups<sup>3</sup> as it is showed in Table 1.

Table 1. Workforce cost grouped by countries. Source: <https://www.salaryexpert.com/salary/job/pharmacist/>

	Average annual gross salary- Pharmacist (P)	Average annual gross salary- Technician/Assistant (T/A)	Average annual gross salary workers (50% P-50% T/A)
Group 1: North Europe countries	81.749 €	40.875 €	61.312€
Group 2: Centre Europe countries	82.072 €	41.036 €	61.554 €
Group 3: South-Mediterranean countries	55.623 €	27.812 €	41.717 €

<sup>2</sup> 5-year life expectancy-1.500 copies/month.

<sup>3</sup>Gross average salaries extracted by ERI's Salary Expert Database from 10 countries.



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Group 4: East European countries	33.374 €	16.687 €	25.031€
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Considering an average of 1.720 hours worked per year, the cost per minute will be:

Table 2. Workforce cost per minute and per leaflet.

	Gross salary per minute (€)	Gross salary per PoD Leaflet (1,5 min)
Group 1: North Europe countries	0,5941	0,8912 €
Group 2: Centre Europe countries	0,5964	0,8947 €
Group 3: South-Mediterranean countries	0,4042	0,6064 €
Group 4: East European countries	0,2425	0,3638 €

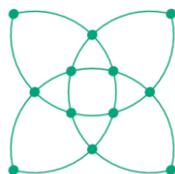
Therefore, the cost of the workforce for each PoD leaflet varies from 0,36 € to 0,89€.

### Total unit cost of a pod leaflet

Considering the above, the average cost of a leaflet PoD printed in colours will vary from 1,601 € to 2,132 €. The breakdown of costs by concept is:

Table 3. Breakdown cost for a PoD coloured leaflet

	Number of units	Unit	Unit cost	Price per leaflet
Paper	4	sheet	0,0072	0,029 €
Colour ink	7	page	0,1700	1,190 €
Printers depreciation	7	page	0,0027	0,019 €
<b>Workforce</b>				<b>0,712 €</b>
Group 1: North Europe countries	1,5	min	0,5941	0,891 €
Group 2: Centre Europe countries	1,5	min	0,5964	0,895 €
Group 3: South-Mediterranean countries	1,5	min	0,4042	0,606 €
Group 4: East European countries	1,5	min	0,2425	0,364 €
<b>TOTAL PoD cost:</b>				<b>1,949 €</b>
Group 1: North Europe countries				<b>2,129 €</b>
Group 2: Centre Europe countries				<b>2,132 €</b>
Group 3: South-Mediterranean countries				<b>1,844 €</b>
Group 4: East European countries				<b>1,601 €</b>



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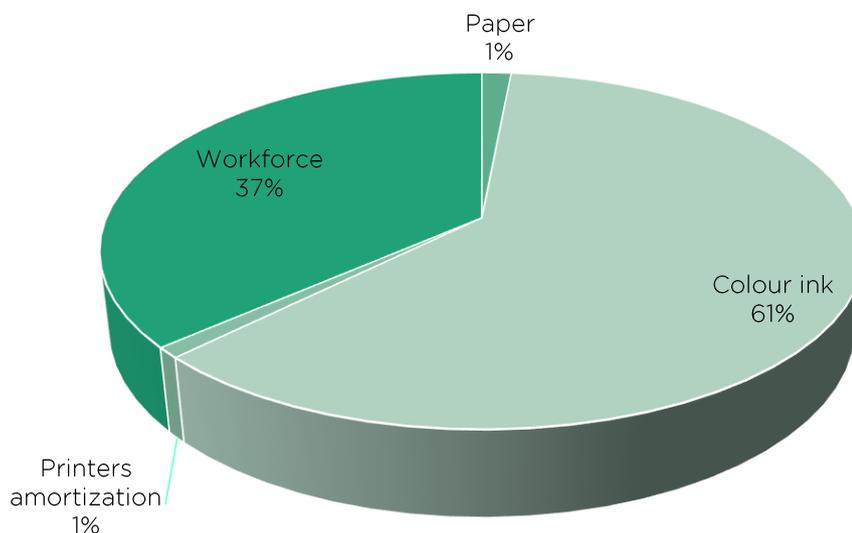
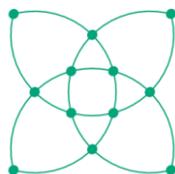


Figure 1. Breakdown of the cost of a coloured PoD

Related to the PoD leaflets printed in black, the breakdown cost by concept is:

Table 4. Breakdown cost for a PoD black leaflet

	Number of units	Unit	Unit cost	Price per leaflet
Paper	4	sheet	0,0072	0,029 €
Black ink	7	page	0,0267	0,1867 €
Printers depreciation	7	page	0,0027	0,019 €
Workforce				0,712 €
Group 1: North Europe countries	1,5	min	0,5941	0,891 €
Group 2: Centre Europe countries	1,5	min	0,5964	0,895 €
Group 3: South-Mediterranean countries	1,5	min	0,4042	0,606 €
Group 4: East European countries	1,5	min	0,2425	0,364 €
<b>TOTAL PoD cost:</b>				<b>0,9458 €</b>
Group 1: North Europe countries				1,1253 €
Group 2: Centre Europe countries				1,1288 €
Group 3: South-Mediterranean countries				0,8405 €
Group 4: East European countries				0,5979 €



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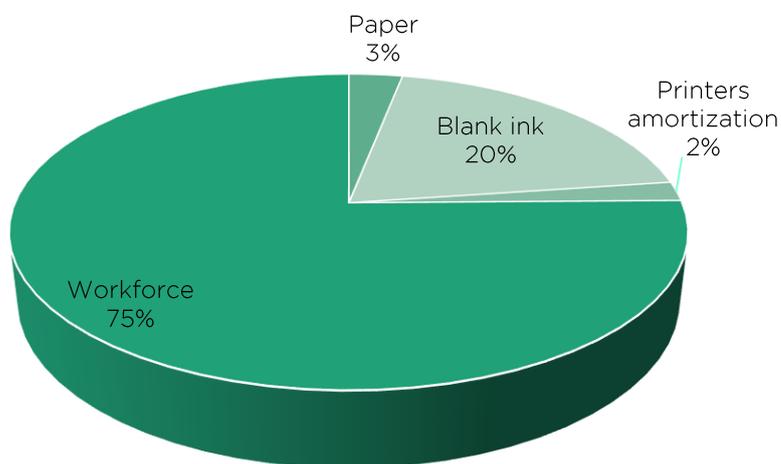


Figure 2. Breakdown of the cost of a black PoD

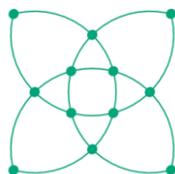
## Comparative analysis of the cost of the current situation vs the PoD

According to the pharmaceutical information leaflet print industry, the current cost of a leaflet printed on an industrial printer, folded and inside a pharmaceutical product package is 50€ per 1000 printed units, that is, 0,05€/unit. The regular leaflet paper has a density of 50g/m<sup>2</sup>. Under the current situation, every drug package has a printed leaflet, so the annual cost of this scenario is obtained by multiplying the unit cost of an industrially printed leaflet by the total number of pharmaceutical products sold in a year.

There is a significant lack of accessibility to the public data related with prescript pharmaceutical products sold in the countries of EU-27. Nevertheless, some countries do publish statistics of the total number of prescript drug packages sold, as it is the case of Spain, where the Ministry of Health reports yearly these figures<sup>4</sup>. In order to have a total figure, this report will use the data available in Spain to extrapolate to the countries where no data are available, adjusting the figures to the population of each nation and to the average level of pharmaceutical product consumed, measured in Defined Daily Dose (DDD) per 1 000 inhabitants per day. The DDD is a technical unit of measurement of the pharmaceutical product consumption and there are statistics for the majority of the European countries. It has been used the OECD Pharmaceutical Market -Pharmaceutical consumption<sup>5</sup> to have the DDD per 1 000 inhabitants per day in the majority of the Europe-27 countries. In the case of Bulgaria, Ireland, Cyprus, Malta, Poland and Romania the are

<sup>4</sup> <https://www.sanidad.gob.es/areas/farmacia/consumoMedicamentos/ATC/home.htm>

<sup>5</sup> <https://stats.oecd.org/>



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no data or the available ones are not accurate because of differences in reporting methodology or data dumping. For these countries it has been assumed a DDD per 1 000 inhabitants per day equivalent to the Europe-27 average figure<sup>6</sup>. Table 5 gathers the values of DDD per 1 000 inhabitants per day in the different countries used in this report:

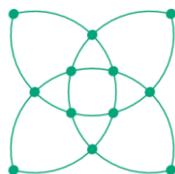
Table 5. Defined daily doses per 1.000 inhabitants per day. Source: OECD statistics.

Defined daily dose per 1 000 inhabitants per day	
EU	1.421,4
Belgium	1.222,3
Bulgaria*	1.421,4
Czechia	1.715,9
Denmark	1.533,0
Germany	1.530,9
Estonia	1.131,6
Ireland*	1.421,4
Greece	1.340,6
Spain	1.553,2
France	1.377,8
Croatia	1.263,9
Italy	1.259,6
Cyprus*	1.421,4
Latvia	1.000,5
Lithuania	1.141,7
Luxembourg	1.389,3
Hungary	1.443,7
Malta*	1.421,4
Netherlands	1.277,1
Austria	828,3
Poland*	1.421,4
Portugal	1.406,8
Romania*	1.421,4
Slovenia	1.323,9
Slovakia	1.577,2
Finland	1.857,4
Sweden	1.807,5

\*Not available data. It has been used the average figure of the rest countries with data.

This report is based on data from 2019, as recent years have been marked by the Covid-19 pandemic, which has had a significant impact on the population's consumption of medicines and therefore it wouldn't be a good reference for the

<sup>6</sup> 1.421,4 DDD per 1.000 inhabitants per day



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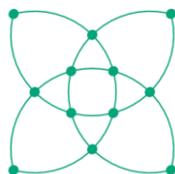
years to come. Table 6 gathers the estimated number of prescript drugs sold in 2019 in Europe-27 countries according to the above-mentioned methodology.

Table 6. Estimated prescript drugs packages sold in 2019 and cost of industrially printed leaflets.

	Number of packages sold of prescript drugs (2019)
<b>EU</b>	<b>8.574.997.515</b>
Belgium	189.164.946
Bulgaria	134.417.355
Czechia	246.877.497
Denmark	120.246.744
Germany	1.717.012.725
Estonia	20.253.398
Ireland	94.173.042
Greece	194.235.387
Spain	984.898.200
France	1.252.529.108
Croatia	69.601.913
Italy	1.017.895.008
Cyprus	16.819.339
Latvia	25.951.303
Lithuania	43.097.798
Luxembourg	11.522.256
Hungary	190.608.424
Malta	9.477.504
Netherlands	298.174.899
Austria	99.130.983
Poland	729.168.072
Portugal	195.312.757
Romania	372.803.650
Slovenia	37.218.266
Slovakia	116.135.474
Finland	138.461.439
Sweden	249.810.030

On the other hand, the PoD scenario will be assessed by multiplying the estimated unit cost per PoD leaflet per country (see section above) by the estimated number of PoD that will be requested yearly. This last figure will depend on many factors and will vary throughout time. This report considers the following factors:

- Not everybody will ask for a PoD leaflet as the information will be available electronically. Nevertheless, there are a significant number of citizens who lack



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the digital skills and that will need a physical leaflet to get the detailed information of the drugs that they, or their children, are going to consume. Eurostat gathers yearly surveys related to individual's level of digital skills sorted by group of ages and countries. For this report it has been used the latest data (2023) of the share of people that have basic or above basic overall digital skills (all five component indicators are at basic or above basic level)<sup>7</sup>.

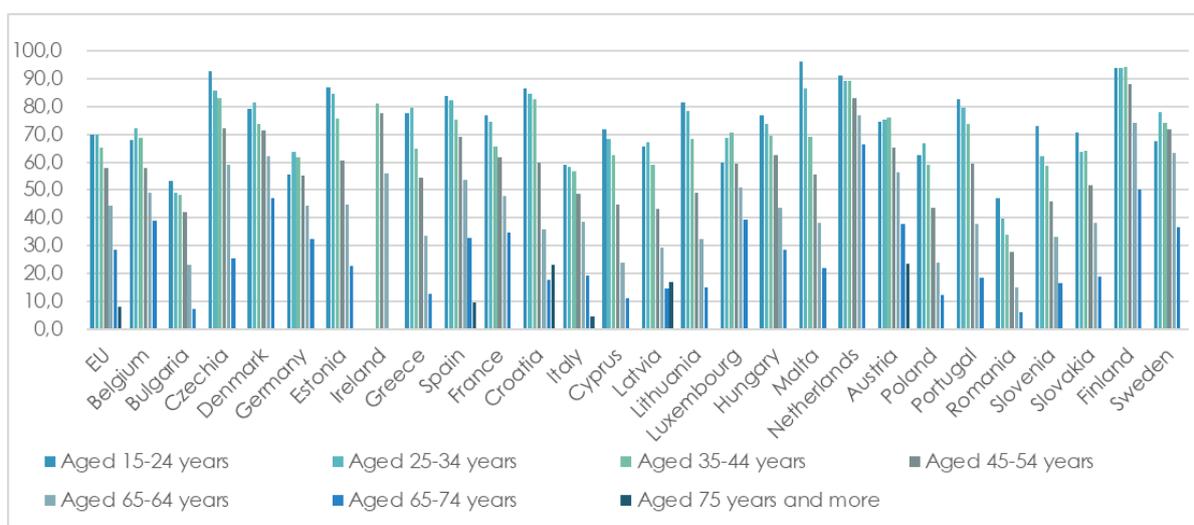
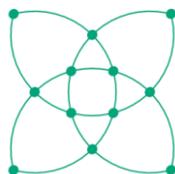


Figure 3. Individuals with basic or above basic overall digital skills (all five component indicators are at basic or above basic level). Eurostat 2023

- The rest share of citizens, the ones who do not even have a basic level of digitalization, will not be able to get the information electronically. The indicators on Figure 3 are grouped by ages differently than the group of ages used on the other statistics employed in this assessment so interpolations have been made in order to cross the data.
- The consumption of medicines is extremely correlated with the age of the consumers. Thus, it is needed to distribute the consumption between the different group of ages in order to cross it with the level of digital skills. The distribution of the pharmaceutical products consumption per age has been done considering a report on the data from BDCAP-Primary Care Clinical Database (random sample of 5 million primary care records) in Spain in 2021, where it has been published the DDD per 1 000 inhabitants per day distributed by group of

<sup>7</sup> Overall digital skills refer to five areas: information and data literacy skills, communication and collaboration skills, digital content creation skills, safety skills and problem-solving skills. Digital skills indicators are some of the key performance indicators in the context of the Digital Decade, which sets out the EU's vision for digital transformation.



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ages and sex. This 2021 report has been used because it provides this difficult to obtain information related with the DDD per group of ages of all the ATC levels.<sup>8</sup>

Table 7. DDD per 1.000 inhabitants per day per sex and group of ages. Source: BDCAP Spain 2021

Ages	Male	Female
0-14	150	126
15-34	198	415
35-64	987	1.242
>65	3.937	4.235

This data has been crossed with the population in Spain in 2021 and interpolations have been made so that the range of ages can be crossed with the ones of digitalization reports. Thus, the share of DDD consumed by the different group of ages are:

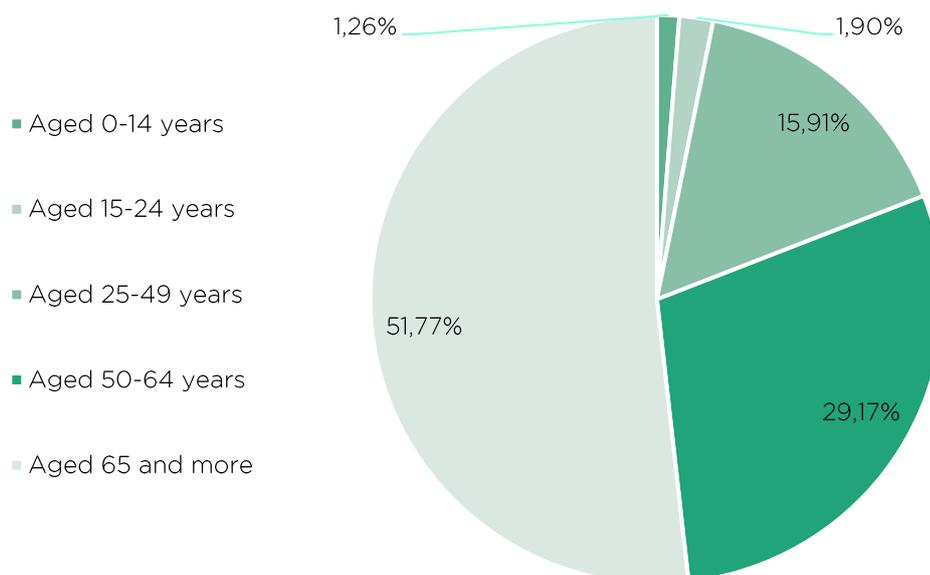


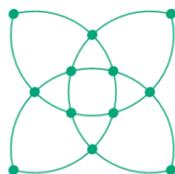
Figure 4. Share of DDD consumed by different group of ages. Source: Spanish Ministry of Health, 2021.

By applying the estimated prescript drug packages consumed yearly by country to the share of consume by group of ages, it is obtained:

Table 8. Estimated number of prescript drugs packages consumed by countries and group of ages.

	Aged 0-14 years	Aged 15-24 years	Aged 25-49 years	Aged 50-64 years	Aged 65 and more
EU	107.713.574	163.128.946	1.364.132.038	2.501.102.006	4.438.920.951
Belgium	2.376.168	3.598.634	30.092.832	55.174.456	97.922.855
Bulgaria	1.688.464	2.557.127	21.383.449	39.206.019	69.582.296

<sup>8</sup> [https://www.whocc.no/atc\\_ddd\\_index/](https://www.whocc.no/atc_ddd_index/)



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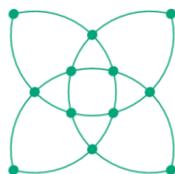
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Czechia	3.101.115	4.696.545	39.273.889	72.007.695	127.798.252
Denmark	1.510.462	2.287.549	19.129.153	35.072.823	62.246.757
Germany	21.568.004	32.664.088	273.146.676	500.807.605	888.826.352
Estonia	254.410	385.296	3.221.961	5.907.385	10.484.345
Ireland	1.182.941	1.791.528	14.981.283	27.467.808	48.749.482
Greece	2.439.859	3.695.093	30.899.451	56.653.371	100.547.613
Spain	12.371.654	18.736.496	156.680.067	287.268.989	509.840.994
France	15.733.461	23.827.850	199.255.461	365.329.909	648.382.427
Croatia	874.294	1.324.092	11.072.446	20.301.054	36.030.027
Italy	12.786.139	19.364.220	161.929.282	296.893.293	526.922.074
Cyprus	211.274	319.968	2.675.662	4.905.760	8.706.675
Latvia	325.983	493.692	4.128.398	7.569.315	13.433.914
Lithuania	541.367	819.883	6.856.105	12.570.498	22.309.944
Luxembourg	144.735	219.197	1.832.989	3.360.740	5.964.594
Hungary	2.394.300	3.626.094	30.322.465	55.595.481	98.670.084
Malta	119.050	180.298	1.507.705	2.764.339	4.906.111
Netherlands	3.745.480	5.672.416	47.434.408	86.969.802	154.352.792
Austria	1.245.219	1.885.847	15.770.005	28.913.909	51.316.003
Poland	9.159.338	13.871.540	115.997.879	212.679.214	377.460.101
Portugal	2.453.393	3.715.589	31.070.841	56.967.612	101.105.322
Romania	4.682.918	7.092.138	59.306.536	108.737.053	192.985.004
Slovenia	467.512	708.032	5.920.775	10.855.593	19.266.355
Slovakia	1.458.819	2.209.337	18.475.121	33.873.674	60.118.523
Finland	1.739.263	2.634.061	22.026.792	40.385.572	71.675.751
Sweden	3.137.952	4.752.333	39.740.404	72.863.038	129.316.303

- Crossing the shares by group of ages of citizens without digital skills with the consumption of prescript pharmacy products by group of ages, it is obtained the number of prescript pharmacy packages consumed by people with no digital skills:

Table 9. Estimated number of prescript drugs consumed by people with no digital skills and shorted by countries and group of ages.

	Aged 0-14 years*	Aged 15-24 years	Aged 25-49 years**	Aged 50-64 years***	Aged 65 and more
EU	37.163.529	50.259.528	438.517.691	1.222.046.601	3.421.474.349
Belgium	746.117	1.152.283	8.884.909	25.680.951	68.605.939
Bulgaria	874.962	1.198.014	10.972.917	26.405.254	64.349.760
Czechia	529.671	342.378	6.203.311	24.770.647	99.592.939
Denmark	394.533	476.954	4.266.757	11.691.526	38.543.154
Germany	8.284.270	14.473.458	101.951.997	250.704.287	664.253.093
Estonia	61.796	50.705	638.432	2.794.489	8.541.989
Ireland	222.511	536.742	2.817.979	9.139.913	26.252.581
Greece	853.707	826.223	8.579.233	31.745.717	89.132.385
Spain	3.071.882	3.080.280	33.490.364	110.584.197	379.331.686
France	5.413.884	5.551.889	59.627.197	165.056.053	475.243.554
Croatia	151.603	181.003	1.815.881	10.584.969	29.089.349
Italy	5.541.513	7.925.775	68.989.971	167.462.662	449.270.631



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Cyprus	79.312	90.167	925.512	3.215.726	7.793.862
Latvia	133.066	169.139	1.522.140	4.830.358	11.392.717
Lithuania	170.585	153.482	1.820.296	7.451.791	19.379.226
Luxembourg	42.263	88.424	553.838	1.503.091	4.126.915
Hungary	733.374	839.078	8.658.580	26.113.197	75.230.925
Malta	36.739	7.050	333.881	1.468.279	3.980.158
Netherlands	411.254	503.143	5.175.094	17.554.855	72.834.670
Austria	297.607	482.588	3.851.035	11.312.567	33.957.582
Poland	3.753.497	5.193.504	42.994.614	140.666.032	334.030.440
Portugal	645.488	645.026	7.247.274	29.261.414	85.454.707
Romania	3.084.638	3.745.358	37.351.257	85.516.255	180.083.894
Slovenia	193.597	191.594	2.351.436	6.560.577	16.474.851
Slovakia	524.154	649.987	6.686.146	18.606.809	50.166.589
Finland	103.486	164.102	1.321.608	7.713.644	43.150.720
Sweden	808.023	1.541.182	9.486.034	23.651.342	91.210.029

\*For the purpose of this report it has been estimated the skills of their parents (35-54 years old) See Figure 3

\*\*Average of digital skills of group 25-34 and 35-44 See Figure 3

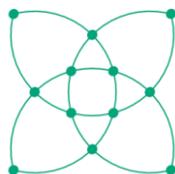
\*\*\*Average of digital skills of group 45-54 and 55-64 See Figure 3

- The majority of the medicaments are consumed in a regular basis so it can't be considered that the users will ask for a PoD every time they buy a new box. It has been applied a data extracted from IQVIA<sup>9</sup> where it is highlighted that new prescriptions are generally about **10% of overall volume**. Therefore, the 10% of Table 9 will suppose PoD leaflets, as they will be new prescriptions for which citizens will need to read the leaflet. For the rest of the drugs, the ones that are not new for the consumers it has been established that the consumers with low digital skills will ask for a PoD leaflet twice a year (once every six months) and it has been considered that a regular medication needs a consumption of one package every month. Hence, the total volume of PoD leaflet will be:

Table 10. Number of estimated PoD leaflets per group of ages and countries.

	Aged 0-14 years*	Aged 15-24 years	Aged 25-49 years**	Aged 50-64 years***	Aged 65 and more	Total of PoD
EU	9.290.882	12.564.882	109.629.423	305.511.650	855.368.587	1.292.365.425
Belgium	186.529	288.071	2.221.227	6.420.238	17.151.485	26.267.549
Bulgaria	218.740	299.504	2.743.229	6.601.313	16.087.440	25.950.227
Czechia	132.418	85.595	1.550.828	6.192.662	24.898.235	32.859.736
Denmark	98.633	119.238	1.066.689	2.922.881	9.635.789	13.843.231
Germany	2.071.068	3.618.364	25.487.999	62.676.072	166.063.273	259.916.776
Estonia	15.449	12.676	159.608	698.622	2.135.497	3.021.853

<sup>9</sup> IQVIA is a leading global provider of advanced analytics, technology solutions, and clinical research services to the life sciences industry.



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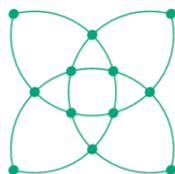
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Ireland	55.628	134.185	704.495	2.284.978	6.563.145	9.742.432
Greece	213.427	206.556	2.144.808	7.936.429	22.283.096	32.784.316
Spain	767.970	770.070	8.372.591	27.646.049	94.832.921	132.389.602
France	1.353.471	1.387.972	14.906.799	41.264.013	118.810.888	177.723.144
Croatia	37.901	45.251	453.970	2.646.242	7.272.337	10.455.702
Italy	1.385.378	1.981.444	17.247.493	41.865.665	112.317.658	174.797.638
Cyprus	19.828	22.542	231.378	803.931	1.948.466	3.026.145
Latvia	33.267	42.285	380.535	1.207.590	2.848.179	4.511.855
Lithuania	42.646	38.371	455.074	1.862.948	4.844.806	7.243.845
Luxembourg	10.566	22.106	138.459	375.773	1.031.729	1.578.633
Hungary	183.344	209.770	2.164.645	6.528.299	18.807.731	27.893.789
Malta	9.185	1.762	83.470	367.070	995.040	1.456.527
Netherlands	102.813	125.786	1.293.773	4.388.714	18.208.668	24.119.754
Austria	74.402	120.647	962.759	2.828.142	8.489.395	12.475.345
Poland	938.374	1.298.376	10.748.654	35.166.508	83.507.610	131.659.522
Portugal	161.372	161.257	1.811.818	7.315.353	21.363.677	30.813.477
Romania	771.160	936.340	9.337.814	21.379.064	45.020.974	77.445.351
Slovenia	48.399	47.898	587.859	1.640.144	4.118.713	6.443.014
Slovakia	131.038	162.497	1.671.537	4.651.702	12.541.647	19.158.421
Finland	25.872	41.026	330.402	1.928.411	10.787.680	13.113.390
Sweden	202.006	385.295	2.371.509	5.912.836	22.802.507	31.674.152

As the PoD leaflet has been estimated by countries, due to the variability of the workforce costs through the countries, the cost of the PoD will be obtained by multiplying the PoD cost per group of country by the estimated number of PoD.

Table 11. Estimation of the total cost of PoD in colour ink and in black ink.

		Cost of PoD colour per leaflet	Total cost of PoD colour leaflet (€)	Cost of PoD black per leaflet	Cost of PoD black leaflet (€)
EU		1,949 €	2.496.818.797	0,946 €	1.200.145.488
Belgium	Group 2	2,132 €	56.006.131	1,129 €	29.651.023
Bulgaria	Group 4	1,601 €	41.553.646	0,598 €	15.516.919
Czechia	Group 1	1,601 €	52.617.724	0,598 €	19.648.455
Denmark	Group 1	2,129 €	29.467.078	1,125 €	15.577.703
Germany	Group 2	2,132 €	554.179.332	1,129 €	293.396.166
Estonia	Group 1	1,601 €	4.838.840	0,598 €	1.806.915
Ireland	Group 2	2,132 €	20.772.242	1,129 €	10.997.336
Greece	Group 7	1,844 €	60.448.445	0,840 €	27.554.848
Spain	Group 7	1,844 €	244.102.867	0,840 €	111.271.966



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France	Group	2,132 €	378.930.882	1,129 €	200.615.327
Croatia	Group	1,844 €	19.278.453	0,840 €	8.787.899
Italy	Group	1,844 €	322.295.738	0,840 €	146.915.441
Cyprus	Group	1,601 €	4.845.713	0,598 €	1.809.481
Latvia	Group	1,601 €	7.224.755	0,598 €	2.697.861
Lithuania	Group	1,601 €	11.599.443	0,598 €	4.331.452
Luxembourg	Group	2,132 €	3.365.868	1,129 €	1.781.973
Hungary	Group	1,601 €	44.665.838	0,598 €	16.679.070
Malta	Group	1,844 €	2.685.576	0,840 €	1.224.194
Netherlands	Group	2,132 €	51.426.727	1,129 €	27.226.574
Austria	Group	2,132 €	26.599.200	1,129 €	14.082.270
Poland	Group	1,844 €	242.756.729	0,840 €	110.658.342
Portugal	Group	1,844 €	56.814.568	0,840 €	25.898.380
Romania	Group	1,601 €	124.011.891	0,598 €	46.308.389
Slovenia	Group	1,601 €	10.317.086	0,598 €	3.852.595
Slovakia	Group	1,601 €	30.678.046	0,598 €	11.455.764
Finland	Group 1	2,129 €	27.913.519	1,125 €	14.756.417
Sweden	Group 1	2,129 €	67.422.462	1,125 €	35.642.729

All things considered, even though the total number of leaflets printed will down from 8 575 to 1 292 million, the cost will skyrocket to a scenario where the leaflets will be PoD in the pharmacies in colour (2 497 M€) or in black ink (1 200 M€).

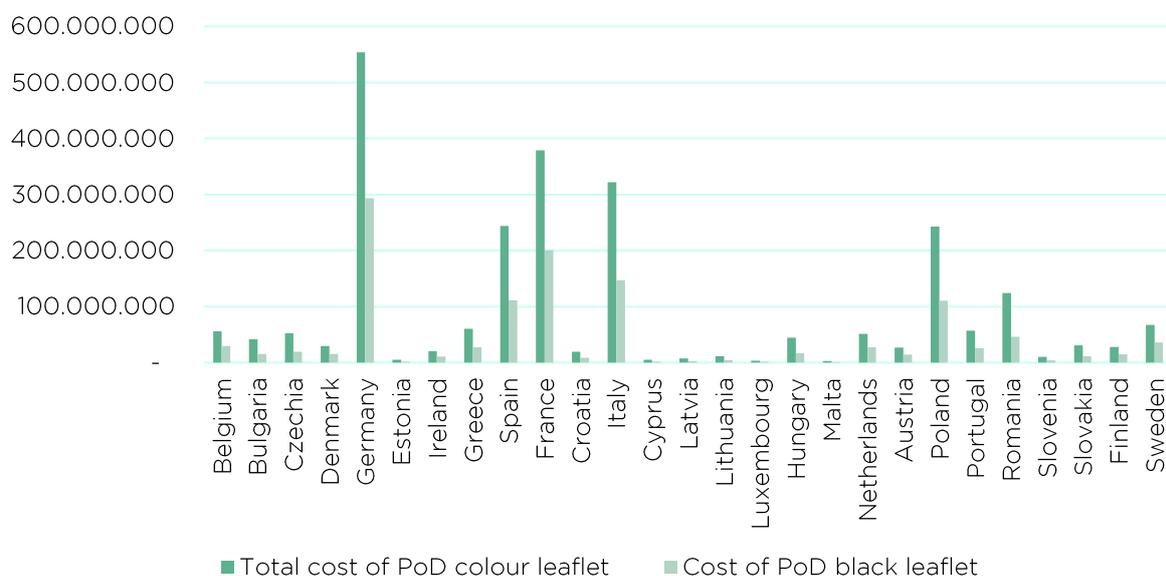
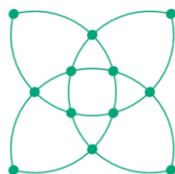


Figure 5. Bar chart of the cost of PoD in colour and in black ink vs current state



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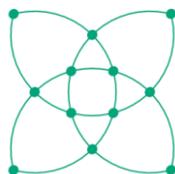
### Impact on the PoD in the pharmacies

In order to assess the impact of the PoD in the pharmacies around Europe, it has been evaluated the economic impact of the PoD scenario and divided into the total amount of pharmacies. It has been used the indicator of 'Pharmacies per 100.000 inhabitants collected in the OECD statistics.

Table 12. Economic impact of the PoD in Pharmacies

	Pharmacies per 100 000 inhabitants (2019)	Number of Pharmacies	Annual economic impact per Pharmacy (colour)	Annual economic impact per Pharmacy (black)
EU-27	31	137.790	18.120 €	8.710 €
Belgium	42	4.831	11.593 €	6.137 €
Bulgaria*	29	2.004	20.731 €	7.741 €
Czechia	23	2.464	21.358 €	7.975 €
Denmark	9	495	59.529 €	31.470 €
Germany	23	19.075	29.053 €	15.381 €
Estonia	37	494	9.802 €	3.660 €
Ireland	38	1.888	11.002 €	5.825 €
Greece	88	9.471	6.382 €	2.909 €
Spain	47	22.102	11.044 €	5.034 €
France	32	21.514	17.613 €	9.325 €
Croatia*	29	1.167	16.517 €	7.529 €
Italy	32	19.182	16.802 €	7.659 €
Cyprus*	29	251	19.321 €	7.215 €
Latvia	40	771	9.371 €	3.499 €
Lithuania*	29	800	14.498 €	5.414 €
Luxembourg	16	97	34.706 €	18.374 €
Hungary	23	2.293	19.478 €	7.273 €
Malta*	29	141	19.003 €	8.662 €
Netherlands	12	2.017	25.491 €	13.495 €
Austria	15	1.365	19.481 €	10.314 €
Poland	32	12.300	19.736 €	8.997 €
Portugal	28	2.922	19.443 €	8.863 €
Romania*	29	5.559	22.308 €	8.330 €
Slovenia	16	341	30.242 €	11.293 €
Slovakia	37	2.000	15.342 €	5.729 €
Finland	15	819	34.077 €	18.015 €
Sweden	14	1.426	47.280 €	24.994 €

\*Not available data. It has been used the EU average indicator



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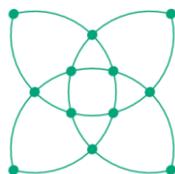
The annual economic impact per pharmacy varies widely depending on the rate of pharmacies per inhabitant (the lower the rate the bigger the impact, because they have to print leaflets for more population). The lower economic impact will be in Greece printing black leaflets (2 909 €/year per pharmacy) and the biggest impact will be in Denmark printing colour leaflets (59 529 € year per pharmacy).

It should also be noted that it is unlikely that the PoD will be provided by pharmacies at cost only. The final PoD prices, although not charged directly to the user, will likely include a profit margin. It is possible that the margins introduced will be the usual pharmacy margins, depending on the country. Taking a 40% profit margin as an average, the total price of the PoD scenario will vary from 3 495 M€ for 4-colour leaflets to 1 680 M€.

Related with the workforce needed for the PoD, the main results are gathered in Table 13

Table 13. Workforce impact of the PoD

	Equivalent hours employed in PoD	Equivalent number of Workers	Equivalent number of Workers per Pharmacy
EU-27	32.309.136	18.784	0,14
Belgium	656.689	382	0,08
Bulgaria	648.756	377	0,19
Czechia	821.493	478	0,19
Denmark	346.081	201	0,41
Germany	6.497.919	3.778	0,20
Estonia	75.546	44	0,09
Ireland	243.561	142	0,07
Greece	819.608	477	0,05
Spain	3.309.740	1.924	0,09
France	4.443.079	2.583	0,12
Croatia	261.393	152	0,13
Italy	4.369.941	2.541	0,13
Cyprus	75.654	44	0,18
Latvia	112.796	66	0,09
Lithuania	181.096	105	0,13
Luxembourg	39.466	23	0,24
Hungary	697.345	405	0,18
Malta	36.413	21	0,15
Netherlands	602.994	351	0,17
Austria	311.884	181	0,13
Poland	3.291.488	1.914	0,16
Portugal	770.337	448	0,15



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Romania	1.936.134	1.126	0,20
Slovenia	161.075	94	0,27
Slovakia	478.961	278	0,14
Finland	327.835	191	0,23
Sweden	791.854	460	0,32

The workforce related with the PoD leaflets print is equivalent to the 18 784 workers in EU-27. The impact per pharmacy is equivalent to 0,14 workers as average.

### Case study in France

In France, the LEEM (Les Entreprises du Médicament) published the results of an extensive survey, entitled "Observatoire sociétal du médicament", conducted by TNS Sofres among 2.023 people interviewed face-to-face at home in late January and early February 2011. One of the results of the study demonstrated that 86% of French people systematically read the package leaflet the first time they are prescribed a medicine. This figure drops to 44% for medicines they take regularly.

These data provide a new approach to estimating the amount of PoD needed and the costs associated with this scenario. To go further in this case study, the estimated number of packages consumed by age group according to DDD by people with low digital literacy in France is used (Table 9).

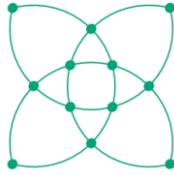
Table 14. Number of prescript drug packages consumed by group of ages

	Aged 0-14 years*	Aged 15-24 years	Aged 25-49 years**	Aged 50-64 years***	Aged 65 and more
France	5.413.883,8	5.551.889,0	59.627.196,7	165.056.053,0	475.243.553,9

Then, as it was done before, the data extracted from IQVIA is applied to new prescriptions, which are generally around 10% of total volume (and therefore 90% regular). On the number of packs newly consumed by citizens, the proportion of the 86% of people who systematically read the leaflet was applied. On the number of packs regularly consumed, a proportion of 44% was applied. It must be noted that these shares are employed only to the packages consumed by people with less than basic digital skills, because it is understood that citizens with basic or above basic digital skills will read the leaflets electronically (although it is likely that some of them prefer to ask for a PoD copy of the leaflet because of legibility issues).

Table 15. Estimation yearly of PoD by groups of age

	Aged 0-14 years*	Aged 15-24 years	Aged 25-49 years**	Aged 50-64 years***	Aged 65 and more	Total of PoD
France	2.609.492	2.676.011	28.740.309	79.557.018	229.067.393	342.650.222



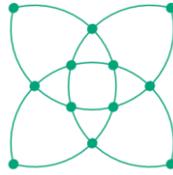
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This estimation assumes a cost of 731 M€ for the coloured PoD leaflet and 387 M€ for the black PoD leaflet.

Table 16. Annual cost of PoD and annual cost of the current system.

Cost of PoD colour per leaflet	Total cost of PoD colour leaflet	Cost of PoD black per leaflet	Cost of PoD black leaflet
2,1321	730.578.740 €	1,1288	386.786.351 €

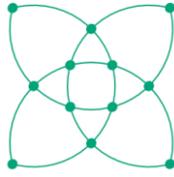


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- 'Five Things to Know about Using NBRx in your Incentive Compensation (IC) Plan' Robert Kelly, Amit Srivastava, Mark Parisi, Oct 20, 2022 <https://www.igvia.com/locations/united-states/blogs/2022/10/five-things-to-know-about-using-nbrx-in-your-incentive-compensation-ic-plan>
- 'Medication use profile by age and sex' BDCAP number 10, elaborated by the Information and Primary Attention Statistic Area. General secretary of Digital Health, Information, and Innovation of the Spanish System of Health
- 'Observatoire sociétal du médicament' Les Entreprises du Médicament (Leem)
- DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001 on the Community code relating to medicinal products for human use.



**EUROVÉRTICE**

ESPECIALISTAS EN FINANCIACIÓN EUROPEA

ANNEX 1: PRINTED LEAFLET AS AN EXAMPLE: APIXABAN

## Package leaflet: Information for the user

### Eliquis 5 mg film-coated tablets

apixaban

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What Eliquis is and what it is used for
2. What you need to know before you take Eliquis
3. How to take Eliquis
4. Possible side effects
5. How to store Eliquis
6. Contents of the pack and other information

#### **1. What Eliquis is and what it is used for**

Eliquis contains the active substance apixaban and belongs to a group of medicines called anticoagulants. This medicine helps to prevent blood clots from forming by blocking Factor Xa, which is an important component of blood clotting.

Eliquis is used in adults:

- to prevent a blood clot from forming in the heart in patients with an irregular heart beat (atrial fibrillation) and at least one additional risk factor. Blood clots may break off and travel to the brain and lead to a stroke or to other organs and prevent normal blood flow to that organ (also known as a systemic embolism). A stroke can be life-threatening and requires immediate medical attention.
- to treat blood clots in the veins of your legs (deep vein thrombosis) and in the blood vessels of your lungs (pulmonary embolism), and to prevent blood clots from re-occurring in the blood vessels of your legs and/or lungs.

#### **2. What you need to know before you take Eliquis**

##### **Do not take Eliquis if:**

- **you are allergic** to apixaban or any of the other ingredients of this medicine (listed in section 6);
- you are **bleeding excessively**;
- you have a **disease in an organ** of the body that increases the risk of serious bleeding (such as **an active or a recent ulcer** of your stomach or bowel, **recent bleeding in your brain**);
- you have a **liver disease** which leads to increased risk of bleeding (hepatic coagulopathy);
- you are **taking medicines to prevent blood clotting** (e.g., warfarin, rivaroxaban, dabigatran or heparin), except when changing anticoagulant treatment, while having a venous or arterial line and you get heparin through this line to keep it open, or if a tube is inserted into your blood vessel (catheter ablation) to treat an irregular heartbeat (arrhythmia).

##### **Warnings and precautions**

Talk to your doctor, pharmacist or nurse before you take this medicine if you have any of the following:

- an **increased risk of bleeding**, such as:
- **bleeding disorders**, including conditions resulting in reduced platelet activity;
- **very high blood pressure**, not controlled by medical treatment;
- you are older than 75 years;
- you weigh 60 kg or less;
- a **severe kidney disease or if you are on dialysis**;

**- a liver problem or a history of liver problems;**

- This medicine will be used with caution in patients with signs of altered liver function.

**- if you have a prosthetic heart valve;**

- if your doctor determines that your blood pressure is unstable or another treatment or surgical procedure to remove the blood clot from your lungs is planned.

Take special care with Eliquis

- if you know that you have a disease called antiphospholipid syndrome (a disorder of the immune system that causes an increased risk of blood clots), tell your doctor who will decide if the treatment may need to be changed.

If you need to have surgery or a procedure which may cause bleeding, your doctor might ask you to temporarily stop taking this medicine for a short while. If you are not sure whether a procedure may cause bleeding ask your doctor.

**Children and adolescents**

This medicine is not recommended in children and adolescents under 18 years of age.

**Other medicines and Eliquis**

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

Some medicines may increase the effects of Eliquis and some may decrease its effects. Your doctor will decide, if you should be treated with Eliquis when taking these medicines and how closely you should be monitored.

The following medicines may increase the effects of Eliquis and increase the chance for unwanted bleeding:

- some **medicines for fungal infections** (e.g., ketoconazole, etc.);

- some **antiviral medicines for HIV / AIDS** (e.g., ritonavir);

- other **medicines that are used to reduce blood clotting** (e.g., enoxaparin, etc.);

- **anti-inflammatory or pain medicines** (e.g., acetylsalicylic acid or naproxen). Especially, if you are older than 75 years and are taking acetylsalicylic acid, you may have an increased chance of bleeding;

- **medicines for high blood pressure or heart problems** (e.g., diltiazem);

- **antidepressant medicines called selective serotonin re-uptake inhibitors or serotonin norepinephrine re-uptake inhibitors.**

The following medicines may reduce the ability of Eliquis to help prevent blood clots from forming:

- **medicines to prevent epilepsy or seizures** (e.g., phenytoin, etc.);

- **St John's Wort** (a herbal supplement used for depression);

- **medicines to treat tuberculosis or other infections** (e.g., rifampicin).

**Pregnancy and breast-feeding**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist or nurse for advice before taking this medicine.

The effects of Eliquis on pregnancy and the unborn child are not known. You should not take this medicine if you are pregnant. **Contact your doctor immediately** if you become pregnant while taking this medicine.

It is not known if Eliquis passes into human breast milk. Ask your doctor, pharmacist or nurse for advice before taking this medicine while breast-feeding. They will advise you whether to stop breast-feeding or to stop/not start taking this medicine.

**Driving and using machines**

Eliquis has not been shown to impair your ability to drive or use machines.

**Eliquis contains lactose (a type of sugar) and sodium**

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

**3. How to take Eliquis**

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor, pharmacist or nurse if you are not sure.

**Dose**

Swallow the tablet with a drink of water. Eliquis can be taken with or without food.

Try to take the tablets at the same times every day to have the best treatment effect.

If you have difficulty swallowing the tablet whole, talk to your doctor about other ways to take Eliquis. The tablet may be crushed and mixed with water, or 5% glucose in water, or apple juice or apple puree, immediately before you take it.

**Instructions for crushing:**

- Crush the tablets with a pestle and mortar.
- Transfer all the powder carefully into a suitable container then mix the powder with a little e.g., 30 mL (2 tablespoons), water or one of the other liquids mentioned above to make a mixture.
- Swallow the mixture.
- Rinse the pestle and mortar you used for crushing the tablet and the container, with a little water or one of the other liquids (e.g., 30 mL), and swallow the rinse.

If necessary, your doctor may also give you the crushed Eliquis tablet mixed in 60 mL of water or 5% glucose in water, through a nasogastric tube.

**Take Eliquis as recommended for the following:**

To prevent a blood clot from forming in the heart in patients with an irregular heart beat and at least one additional risk factor.

The recommended dose is one tablet of Eliquis **5 mg** twice a day.

The recommended dose is one tablet of Eliquis **2.5 mg** twice a day if:

- you have **severely reduced kidney function**;
- **two or more of the following apply to you:** - your blood test results suggest poor kidney function (value of serum creatinine is 1.5 mg/dL (133 micromole/L) or greater);
- you are 80 years old or older;
- your weight is 60 kg or lower.

The recommended dose is one tablet twice a day, for example, one in the morning and one in the evening.

Your doctor will decide how long you must continue treatment for.

To treat blood clots in the veins of your legs and blood clots in the blood vessels of your lungs

The recommended dose is **two tablets** of Eliquis **5 mg** twice a day for the first 7 days, for example, two in the morning and two in the evening.

After 7 days the recommended dose is **one tablet** of Eliquis **5 mg** twice a day, for example, one in the morning and one in the evening.

For preventing blood clots from re-occurring following completion of 6 months of treatment

The recommended dose is one tablet of Eliquis **2.5 mg** twice a day for example, one in the morning and one in the evening.

Your doctor will decide how long you must continue treatment for.

**Your doctor might change your anticoagulant treatment as follows:**

- *Changing from Eliquis to anticoagulant medicines*

Stop taking Eliquis. Start treatment with the anticoagulant medicines (for example heparin) at the time you would have taken the next tablet.

- *Changing from anticoagulant medicines to Eliquis*

Stop taking the anticoagulant medicines. Start treatment with Eliquis at the time you would have had the next dose of anticoagulant medicine, then continue as normal.

- *Changing from treatment with anticoagulant containing vitamin K antagonist (e.g., warfarin) to Eliquis*

Stop taking the medicine containing a vitamin K antagonist. Your doctor needs to do blood-measurements and instruct you when to start taking Eliquis.

- *Changing from Eliquis to anticoagulant treatment containing vitamin K antagonist (e.g., warfarin).*

If your doctor tells you that you have to start taking the medicine containing a vitamin K antagonist, continue to take Eliquis for at least 2 days after your first dose of the medicine containing a vitamin K antagonist. Your doctor needs to do blood-measurements and instruct you when to stop taking Eliquis.

**Patients undergoing cardioversion**

If your abnormal heartbeat needs to be restored to normal by a procedure called cardioversion, take this medicine at the times your doctor tells you, to prevent blood clots in blood vessels in your brain and other blood vessels in your body.

**If you take more Eliquis than you should**

**Tell your doctor immediately** if you have taken more than the prescribed dose of Eliquis. Take the medicine pack with you, even if there are no tablets left.

If you take more Eliquis than recommended, you may have an increased risk of bleeding. If bleeding occurs, surgery, blood transfusions, or other treatments that may reverse anti-factor Xa activity may be required.

**If you forget to take Eliquis**

- Take the dose as soon as you remember and:
- take the next dose of Eliquis at the usual time;

- then continue as normal.

**If you are not sure what to do or have missed more than one dose**, ask your doctor, pharmacist or nurse.

#### **If you stop taking Eliquis**

Do not stop taking this medicine without talking to your doctor first, because the risk of developing a blood clot could be higher if you stop treatment too early.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

#### **4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them. The most common general side effect of this medicine is bleeding which may be potentially life threatening and require immediate medical attention.

The following side effects are known if you take Eliquis to prevent a blood clot from forming in the heart in patients with an irregular heart beat and at least one additional risk factor.

##### **Common side effects (may affect up to 1 in 10 people)**

- Bleeding including:
  - in your eyes;
  - in your stomach or bowel;
  - from your rectum;
  - blood in the urine;
  - from your nose;
  - from your gums;
  - bruising and swelling;
- Anaemia which may cause tiredness or paleness;
- Low blood pressure which may make you feel faint or have a quickened heartbeat;
- Nausea (feeling sick);
- Blood tests may show:
  - an increase in gamma-glutamyltransferase (GGT).

##### **Uncommon side effects (may affect up to 1 in 100 people)**

- Bleeding:
  - in your brain or in your spinal column;
  - in your mouth or blood in your spit when coughing;
  - into your abdomen, or from the vagina;
  - bright/red blood in the stools;
  - bleeding occurring after your operation including bruising and swelling, blood or liquid leaking from the surgical wound/incision (wound secretion) or injection site;
  - from a haemorrhoid;
  - tests showing blood in the stools or in the urine;
- Reduced number of platelets in your blood (which can affect clotting);
- Blood tests may show:
  - abnormal liver function;
  - an increase in some liver enzymes;
  - an increase in bilirubin, a breakdown product of red blood cells, which can cause yellowing of the skin and eyes.
- Skin rash;
- Itching;
- Hair loss;
- Allergic reactions (hypersensitivity) which may cause: swelling of the face, lips, mouth, tongue and/or throat and difficulty breathing. **Contact your doctor immediately** if you experience any of these symptoms.

##### **Rare side effects (may affect up to 1 in 1,000 people)**

- Bleeding:
  - in your lungs or your throat;

- into the space behind your abdominal cavity;
- into a muscle.

**Very rare side effects (may affect up to 1 in 10,000 people)**

- Skin rash which may form blisters and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) (*erythema multiforme*).

**Not known (frequency cannot be estimated from the available data)**

- Blood vessel inflammation (vasculitis) which may result in skin rash or pointed, flat, red, round spots under the skin's surface or bruising.
- Bleeding in the kidney sometimes with presence of blood in urine leading to inability of the kidneys to work properly (anticoagulant-related nephropathy).

The following side effects are known if you take Eliquis to treat or prevent re-occurrence of blood clots in the veins of your legs and blood clots in the blood vessels of your lungs.

**Common side effects (may affect up to 1 in 10 people)**

- Bleeding including:
  - from your nose;
  - from your gums;
  - blood in the urine;
  - bruising and swelling;
  - in your stomach, your bowel, from your rectum;
  - in your mouth;
  - from the vagina;
- Anaemia which may cause tiredness or paleness;
- Reduced number of platelets in your blood (which can affect clotting);
- Nausea (feeling sick);
- Skin rash;
- Blood tests may show:
  - an increase in gamma-glutamyltransferase (GGT) or alanine aminotransferase (ALT).

**Uncommon side effects (may affect up to 1 in 100 people)**

- Low blood pressure which may make you feel faint or have a quickened heartbeat;
- Bleeding:
  - in your eyes;
  - in your mouth or blood in your spit when coughing;
  - bright/red blood in the stools;
  - tests showing blood in the stools or in the urine;
  - bleeding occurring after any operation including bruising and swelling, blood or liquid leaking from the surgical wound/incision (wound secretion) or injection site;
  - from a haemorrhoid;
  - into a muscle;
- Itching;
- Hair loss;
- Allergic reactions (hypersensitivity) which may cause: swelling of the face, lips, mouth, tongue and/or throat and difficulty breathing. **Contact your doctor immediately** if you experience any of these symptoms;
- Blood tests may show:
  - abnormal liver function;
  - an increase in some liver enzymes;
  - an increase in bilirubin, a breakdown product of red blood cells, which can cause yellowing of the skin and eyes.

**Rare side effects (may affect up to 1 in 1,000 people)**

- Bleeding:
  - in your brain or in your spinal column;

- in your lungs.

### **Not known (frequency cannot be estimated from the available data)**

- Bleeding:

- into your abdomen or the space behind your abdominal cavity.

- Skin rash which may form blisters and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) (*erythema multiforme*);

- Blood vessel inflammation (vasculitis) which may result in skin rash or pointed, flat, red, round spots under the skin's surface or bruising.

- Bleeding in the kidney sometimes with presence of blood in urine leading to inability of the kidneys to work properly (anticoagulant-related nephropathy).

### **Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly (see details below). By reporting side effects you can help provide more information on the safety of this medicine.

Yellow Card Scheme

Website: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store

## **5. How to store Eliquis**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use.

These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What Eliquis contains**

• The active substance is apixaban. Each tablet contains 5 mg of apixaban.

• The other ingredients are:

- Tablet core: **lactose** (see section 2 “Eliquis contains lactose (a type of sugar) and sodium”), microcrystalline cellulose, croscarmellose sodium (see section 2 “Eliquis contains lactose (a type of sugar) and sodium”), sodium laurilsulfate, magnesium stearate (E470b);

- Film coat: **lactose monohydrate** (see section 2 “Eliquis contains lactose (a type of sugar) and sodium”), hypromellose (E464), titanium dioxide (E171), triacetin, red iron oxide (E172).

### **What Eliquis looks like and contents of the pack**

The film coated tablets are pink, oval (9.73 mm x 5.16 mm) and marked with “894” on one side and “5” on the other side.

- They come in blisters in cartons of 14, 20, 28, 56, 60, 168 and 200 film-coated tablets.

- Unit dose blisters in cartons of 100x1 film-coated tablets for delivery in hospitals are also available.

Not all pack sizes may be marketed.

### **Patient Alert Card: handling information**

Inside the Eliquis pack together with the package leaflet you will find a Patient Alert Card or your doctor might give you a similar card.

This Patient Alert Card includes information that will be helpful to you and alert other doctors that you are taking Eliquis. **You should keep this card with you at all times.**

1. Take the card.

2. Separate your language as needed (this is facilitated by the perforated edges).

3. Complete the following sections or ask your doctor to do it:

- Name:

- Birth Date:

- Indication:

- Dose : .....mg twice daily

- Doctor's Name:

- Doctor's telephone:

4. Fold the card and keep it with you at all times.

**Marketing Authorisation Holder**

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