1.1 Number of notifications of temporarily unavailable packs of medicines for human use with a critical impact (S-28)

1.1.1 Documentation sheet

Description	**Primary indicator** • Yearly number of notifications of temporarily unavailable packs of medicines for human use with a critical impact **Secondary indicators** 1. Yearly number of notifications of temporarily unavailable packs of medicines for human use (all types of impact) 2. Yearly average duration of unavailability of packs of medicines for human use 3. Monthly share of packs of medicines for human use with a notification of temporary unavailability
Calculation	**Primary indicator** • Number of notifications of temporarily unavailable packs of medicines for human use with critical impact. The year of the notification's start date was used when counting the annual number of notifications. **Secondary indicator:** 1. Yearly number of notifications of temporarily unavailable packs of medicines for human use (all types of impact) • Number of notifications of temporarily unavailable packs of medicines for human use (all types of impact). The year of the notification's start date was used when counting the annual number of notifications. 2. Yearly average duration of unavailability of packs of medicines for human use • Average duration of unavailability of packs of medicines for human use. The year of the notification's start date was used when calculting the annual average duration. 3. Share of packs of medicines for human use with a notification of temporary unavailability Numerator: Number of notifications of temporarily unavailable packs of medicines for human use (all types of impact). All the months covered by the notification were used when counting the monthly number of notifications. Denominator: Average number of commercialised packs of medicines for human use per month. As data on the number of commercialised packs of medicines for human use was provided (through personnel communication) for several dates per month between April 2019 and August 2023, the average number per month was used.
Rationale	Recently, medicine shortages have become increasingly common in a number of countries, including Belgium, and the COVID-19 pandemic has exacerbated this issue.[1] The increasing frequency of supply interruptions and medicine shortages may impact the capacity of the health

	system to provide sufficient medicines. The Pharmaceutical Strategy for Europe, adopted in November 2020, includes addressing medicine shortages under the pillar of crisis preparedness and response.[2] Belgium applies the EU-definition of medicine shortage, which is: a shortage of a medicinal product for human or veterinary use occurs when supply does not meet demand at a national level. A medicine shortage can be both temporary or permanent (i.e. withdrawal from the market). The indicator presented here focuses on temporary disruption. A medicine maybe temporarily unavailable for a variety of reasons, including: unavailability of the active ingredient, unavailability of an excipient, delay in production, delay in the release of the final product, logistical problems, increased demand, Falsified Medicines Directive[a] – serialization, import and export authorisation in application, recall, force majeure, patent litigation, or distributional issues.[3] In Belgium, a medicine is considered to be unavailable when the marketing authorisation holder is not able to deliver the totality of an ordered quantity for public service obligations within three working days.[4] Medicine shortages can have a direct impact on health service delivery and thus on patients' health outcomes. Since December 2019, the Federal Agency for Medicines and Health Products (FAGG – AFMPS) publishes periods of unavailability, interruptions and discontinuations of commercialisation of medicines for human and veterinary use on PharmaStatus.[3] Marketing authorisation holders are obliged to notify the FAGG – AFMPS about temporary unavailability of medicine. Expected shortages need to be notified not less than two months prior and six months prior for reimbursed medicines in case of a definitive stop of the commercialisation. The minimum duration of shortage requiring notification is three working days. On the PharmaStatus notification website, shortage notifications are classified by their impact on patients. A given shortage notification for a given Anatomical Therapeutic Chemical (ATC) or active substance does not necessarily constitute a shortage that impacts patients, as this depends on the availability of appropriate alternatives in sufficient quantities, and the nature and seriousness of the condition being treated. The lists of medicines are updated daily based on reports from marketing authorisation holders or parallel distributors. The electronic alerts on medicine shortages are fed directly into the electronic prescribing system to alert prescribers at the time of prescribing.
Primary data source	FAGG – AFMPS
Technical definitions	Notifications of temporarily unavailable packs of medicines for human use are summarized as "shortage notifications" in the text. Temporarily unavailable packs of medicine concern packs that are notified as unavailable for no more than one year (otherwise it is considered as an interruption of commercialisation). One notification is defined by the combination of brand/strength/form/pack size. Thus, a temporary unavailability affecting different pack sizes for the same combination of brand/strength/form will lead to separate notifications. Temporarily unavailable packs of medicines with a critical impact concern packs of medicines for which no solution is available (no alternative, no import possible, etc.): • Critical unavailability or impact: concerns packs of medicines without solutions and for which the duration of unavailability is more than one month. Besides critical impact, the FAGG – AFMPS also identified the following impact: • Under evaluation: The evaluation of the impact of the supply problem is ongoing.

[a] The Falsified Medicines Directive (Directive 2011/62/EU), in application since 02/01/2013, introduces harmonised European measures to fight medicine falsifications and ensure that medicines are safe and that the trade in medicines is rigorously controlled. Measures include: obligatory safety features – a unique identifier and an anti-tampering device - on the outer packaging of medicines, a common, EU-wide logo to identify legal online pharmacies, tougher rules on import of active pharmaceutical ingredients, and strengthened record-keeping requirements for wholesale distributors.

	• Short-term unavailability: concerns packs of medicines for which the duration of unavailability is less than one month. This should not be a problem as there is enough stock in circulation (i.e. at the wholesaler or pharmacy). • At least three alternatives available: availability of at least three alternatives that simultaneously meet the following criteria: the same active ingredient; the same desired dose; the same route of administration; the same pharmaceutical form for certain medicines (same pharmacological characteristics, e.g. extended or modified release). • Non-vital unavailable drug: medicine that is not essential for life. • One or two alternatives available: availability of one or two alternatives that simultaneously meet the following criteria: the same active ingredient; the same desired dose; the same route of administration; the same pharmaceutical form for certain medicines (same pharmacological characteristics, e.g. extended or modified release). • Adaptation of the treatment possible: alternative with a different active ingredient, magistral preparation or route of administration is possible. • Derogation approved, but batches not yet available (import possible by the company, medicinal product soon available): the company involved has received a derogation to import certain batches of the medicinal product. The imported medicinal product will soon be available. • Derogation improved and batches available (import possible by the company): the company involved has been granted a derogation to import certain batches of the medicinal product. The imported medicinal product is available from the pharmacist and under the same reimbursement conditions. • Import possible by the pharmacist: if there is no equivalent medicine or medicine to treat the same indication available (and marketed) in Belgium, the pharmacist may import a medicine on the basis of a medical prescription and a doctor's certificate. Data on therapeutic code were missing for 56 notifications between 2015 and 2022. Thus, these notifications were excluded from analyses by therapeutic area.
Limitations	An increase in the number of shortage notifications does not necessarily indicate an increase in the unavailability situations themselves, but an increase in the reports of unavailability.[3] Indeed, the FAGG – AFMPS is raising awareness among marketing authorisation holders and parallel distributors of the importance of reporting unavailability, and the Law of 20 December 2019 clarified and tightened the reporting requirement. Since April 2021, pharmacists and wholesaler-distributors can make a notification of a suspected shortage for a medicinal product that is notified as "available (again)" or if the end date of the unavailability is exceeded. This is also a possible reason for an increase in the reports of unavailability since April 2021. The correctness of the list of temporary unavailable medicines is dependent on the readiness of pharmaceutical companies to share the relevant information and to do this in due time. This indicator is based on the unavailable packs and not on the unavailable medicines. Moreover, the results are based on absolute data, and do not take into account the number of authorised medicines marketed overall and in each therapeutic class. Consequently, results may over- or underestimate the issue of medicine shortages in some therapeutic classes, because some therapeutic classes may have more or less marketed medicines in them than in other classes. Information on the impact of medicine shortage on patients was provided more systematically starting in November 2019, thus results by impact were only analysed for the years 2020 to 2022. As information in the PharmaStatus website was available until 31/06/2022, results for the year 2022 are not directly comparable to results for years 2020 and 2021.

	Data on the number of commercialised packs of medicines for human use did not include packs with an interruption of commercialisation, which should also be counted as commercialised packs.
International comparability	International data on the number of shortage notifications with a critical impact (principal indicator) were not available. The OECD compares data on shortage of medicines across 14 OECD countries, using all notifications of actual or expected shortages with an actual (or anticipated) start date between 1 January 2017 and 31 December 2019.[1] Comparability of data between countries is affected by the different classification of "units" of a shortage notification and timing of notification across countries. Some countries, such as Belgium, Iceland and Canada, report shortages at a very detailed level (pack-size) while others report shortages by brand/strength/form or brand/form. The different classifications used may artificially inflate differences across countries since the same shortage information could lead to one or several notifications. Furthermore, the number of shortage notification may reflect differences in reporting enforcement (e.g. application of sanctions, voluntary reporting) and type of medicines for which notifications are published (e.g. only important/essential medicines).
Performance dimensions	Sustainability, Accessibility
Related indicators	
Reviewer	Sophie Bruneel, Lara Wellens and Ann Van Den Broucke (FAGG – AFMPS)

1.1.2 Results

Belgium

Figure 1 illustrates that the number of notifications of temporarily unavailable packs of medicines for human use, hereafter referred to as 'shortage notifications' increased over time from 621 in 2015 to 3 044 in 2022, reflecting the strengthening and increased monitoring of medicine shortages over time. The average duration of a shortage notification decreased over time from 123 days in 2015 to 51 days in 2022. In the period 2015-2022, approximately 40% of all notifications were concentrated in two main therapeutic areas: the nervous system (ATC group N) and the cardiovascular system (ATC group C, see Table 1 and Figure 2). More precisely, 25% of notifications were related to medicines targeting the nervous system, 16% for the cardiovascular system and 10% for the alimentary tract and metabolism in 2022 (see Table 1). Between 2015 and 2019, the main reasons for the unavailability of packs of medicines were: delay in the release of the end product and production problems, accounting for 63% and 23% of notifications on average, respectively (see Table 2 and Figure 3). Since 2020[b], the main reasons are delay in production (47% in 2022), increased demand (19% in 2022) and other mixed reasons (19% in 2022).

Regarding the impact of shortages on patients, 37% of notifications in 2022 were for medicine pack sizes with at least three alternatives available, 30% of notifications were for pack sizes with short-term unavailability and 10% of notifications were for pack sizes for which it was possible to adapt the treatment (see Figure 4, Table 3). Only 1% of notifications in 2022 were for pack sizes with critical impact.

[b] The reasons for the unavailability of packs of medicines changed before and after 2020, as they were reviewed for the launch of PharmaStatus at the end of 2019.

Figure 1 – Total number and average duration of shortage notifications in 2015-2022

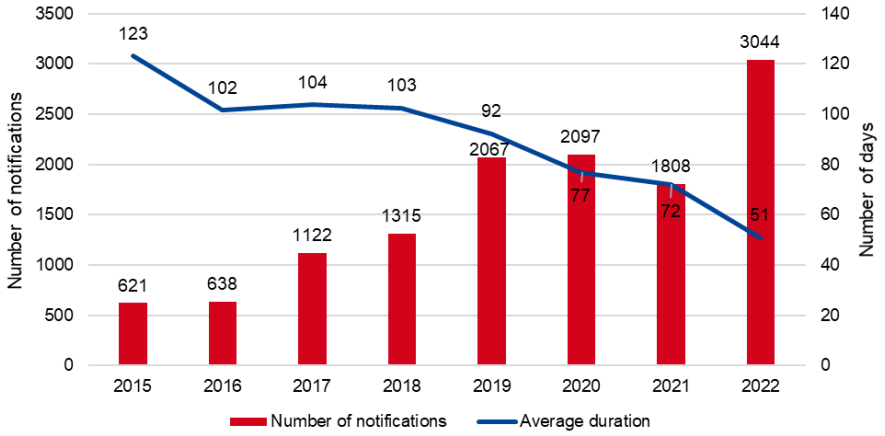
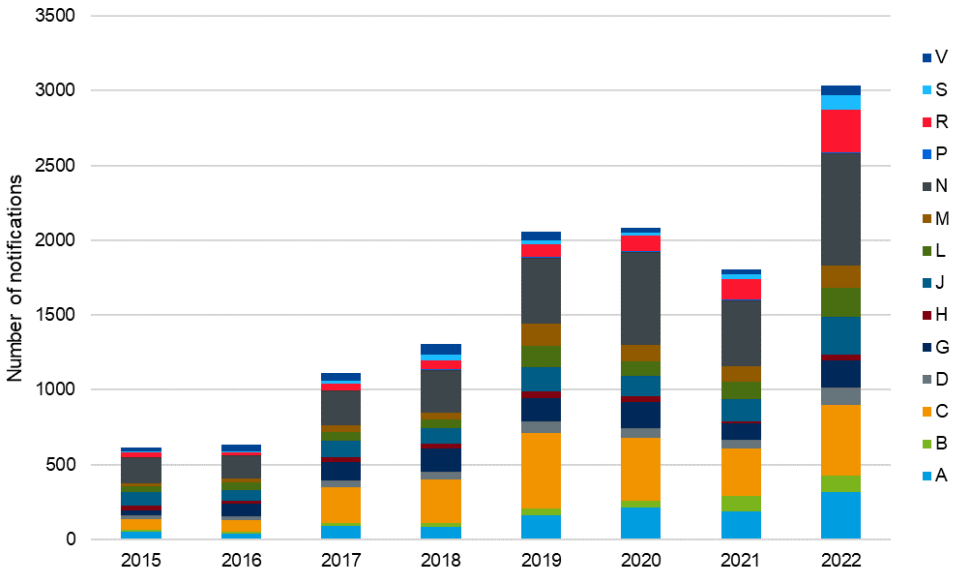


Figure 2 – Number of shortage notifications by therapeutic area (ATC level-1 code)



Note: A: Alimentary tract and metabolism; B: Blood and blood forming organs; C: Cardiovascular system; D: Dermatologicals; G: Genito urinary system and sex hormones; H: Systemic hormonal preparations, excl. sex hormones and insulins; J: Antiinfectives for systemic use; L: Antineoplastic and immunomodulating agents; M: Musculo-skeletal system; N: Nervous system; P: Antiparasitic products, insecticides and repellents; R: Respiratory system; S: Sensory organs; V: Various.

Table 1 – Number and share of shortage notifications by therapeutic area in 2015-2022

Year		A Alimentary tract and metabolism	B Blood and blood forming organs	C Cardiovascular system	D Dermatologicals	G Genito urinary system and sex hormones	H Systemic hormonal preparations,	J Antiinfectives for systemic use	L Antineoplastic and immunomodulatin	M Musculo-skeletal system	N Nervous system	P Antiparasitic products, insecticides and	R Respiratory system	S Sensory organs	V Various
2015 (n=617)	Number	49	19	66	31	29	35	87	40	22	171	1	32	7	28
	Share	8%	3%	11%	5%	5%	6%	14%	6%	4%	28%	0%	5%	1%	5%
2016 (n=634)	Number	36	16	80	22	84	23	70	52	25	153	4	16	8	45
	Share	6%	3%	13%	3%	13%	4%	11%	8%	4%	24%	1%	3%	1%	7%
2017 (n=1113)	Number	89	22	236	47	123	31	112	61	44	229	3	48	15	53
	Share	8%	2%	21%	4%	11%	3%	10%	5%	4%	21%	0%	4%	1%	5%
2018 (n=1307)	Number	86	22	293	51	157	31	102	61	48	284	3	61	34	74
	Share	7%	2%	22%	4%	12%	2%	8%	5%	4%	22%	0%	5%	3%	6%
2019 (n=2059)	Number	164	46	505	73	160	39	166	143	150	438	7	85	26	57
	Share	8%	2%	25%	4%	8%	2%	8%	7%	7%	21%	0%	4%	1%	3%
2020 (n=2086)	Number	211	49	419	63	178	35	140	99	107	621	4	104	20	36
	Share	10%	2%	20%	3%	9%	2%	7%	5%	5%	30%	0%	5%	1%	2%
2021 (n=1803)	Number	188	104	316	59	108	16	150	117	100	442	7	135	28	33
	Share	10%	6%	18%	3%	6%	1%	8%	6%	6%	25%	0%	7%	2%	2%
2022 (n=3037)	Number	318	108	471	121	181	38	251	196	148	747	9	284	96	69
	Share	10%	4%	16%	4%	6%	1%	8%	6%	5%	25%	0%	9%	3%	2%

Figure 3 – Number of shortage notifications by supply problem reason

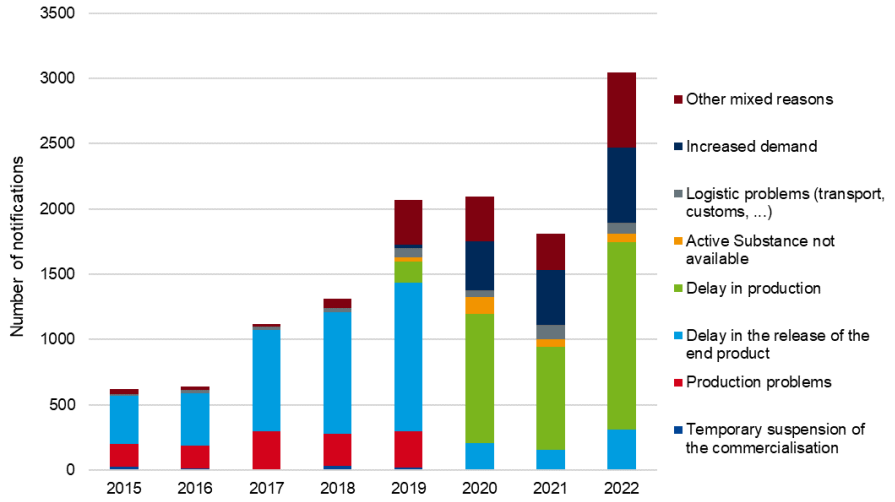


Figure 4 – Number of shortage notifications by supply problem impact (2020-2021)

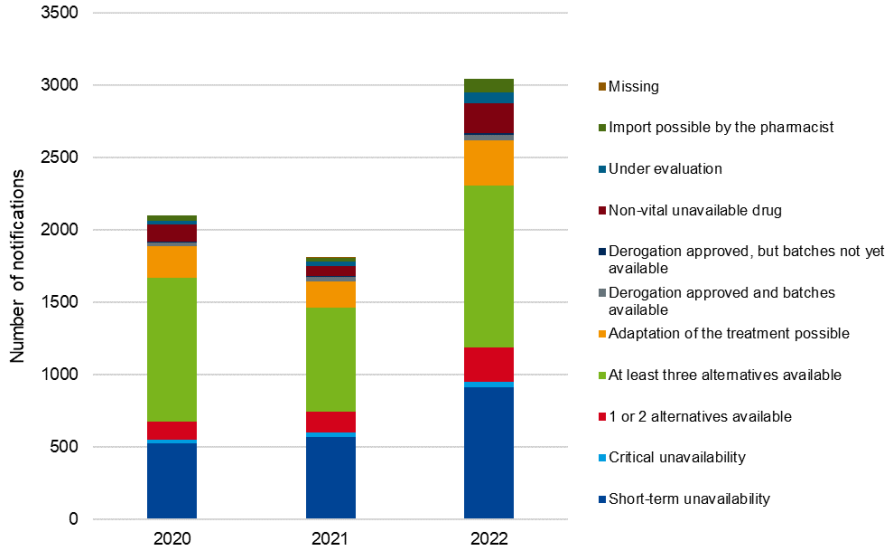


Table 2 – Number and share of shortage notifications by supply problem reason in 2015-2022

Year		Temporary suspension of the commercialisation	Production problems[1]	Delay in the release of the end product	Delay in production	Active substance not available	Logistic problems	Increased demand	Other mixed reasons[2]
2015	Number	28	176	364	0	0	17	0	36
(n=621)	Share (%)	5	28	59	0	0	3	0	6
2016	Number	11	180	398	0	0	25	0	24
(n=638)	Share (%)	2	28	62	0	0	4	0	4
2017	Number	10	291	774	0	0	23	0	24
(n=1 122)	Share (%)	1	26	69	0	0	2	0	2
2018	Number	30	247	931	0	0	31	0	76
(n=1 315)	Share (%)	2	19	71	0	0	2	0	6
2019	Number	19	281	1139	161	33	71	24	339
(n=1 315)	Share (%)	1	14	55	8	2	3	1	16
2020	Number	0	0	208	991	125	54	374	345
(n=2 067)	Share (%)	0	0	10	47	6	3	18	16
2021	Number	0	0	157	789	54	113	417	278
(n=2 097)	Share (%)	0	0	9	44	3	6	23	15
2022	Number	0	0	308	1439	66	81	578	572
(n=3 044)	Share (%)	0	0	10	47	2	3	19	19

[1] This supply problem reason was removed after the launch of PharmaStatus at the end of 2019.

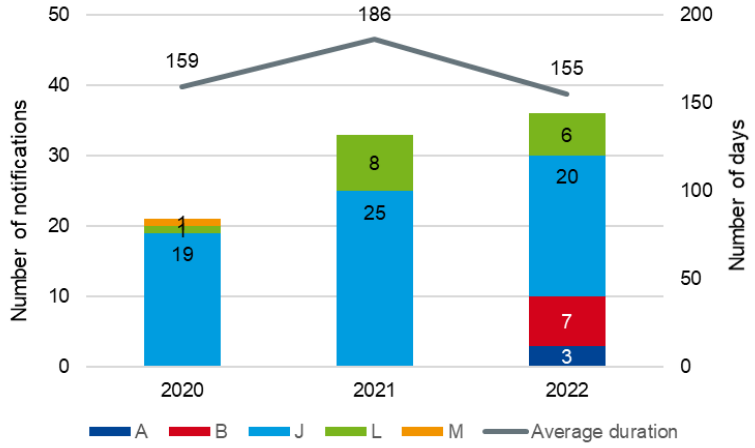
[2] Other mixed reasons include: excipient not available, recall, packaging problems, patent, Falsified Medicines Directive - Serialisation, patent protection, Brexit, application ongoing for import and export license, force majeure, other reason and reason unknown.

Table 3 – Number and share of shortage notifications by supply problem impact in 2020-2022

Year		Short-term unavailability	Critical unavailability	1 or 2 alternatives available	At least three alternatives available	Adaptation of the treatment possible	Derogation approved and batches available	Derogation approved, but batches not yet available	Non-vital unavailable drug	Under evaluation	Import possible by the pharmacist	Missing
2020 (n=2 097)	Number	526	21	123	999	216	27	5	122	25	33	0
	Share (%)	25	1	6	48	10	1	0	6	1	2	0
2021 (n=1 808)	Number	567	33	141	718	186	31	4	69	31	27	1
	Share (%)	31	2	8	40	10	2	0	4	2	1	0
2022 (n=3 044)	Number	911	36	240	1116	315	40	13	206	75	92	0
	Share (%)	30	1	8	37	10	1	0	7	2	3	0

When focusing on notifications with a critical impact on patients, i.e. critical unavailability, we observe that the number of notifications increased from 21 to 36 for those with critical impact (see Figure 5). The average duration for notifications with critical impact increased from 159 days in 2020 to 186 days in 2021, to return to 155 days in 2022. In 2022, 56% of notifications for pack sizes with critical impact were for immunoglobulins (ATC group J: antiinfectives for systemic use), 19% for enzymes (ATC group B: blood and blood forming organs), 17% for antineoplastic and immunomodulating agents (ATC group L) and 8% for glucagon-like peptide-1 (GLP-1) analogues (ATC group A; see Table 4).

Figure 5 – Total number and average duration of shortage notifications with critical impact and by therapeutic area (ATC level-1 code) in 2020-2022



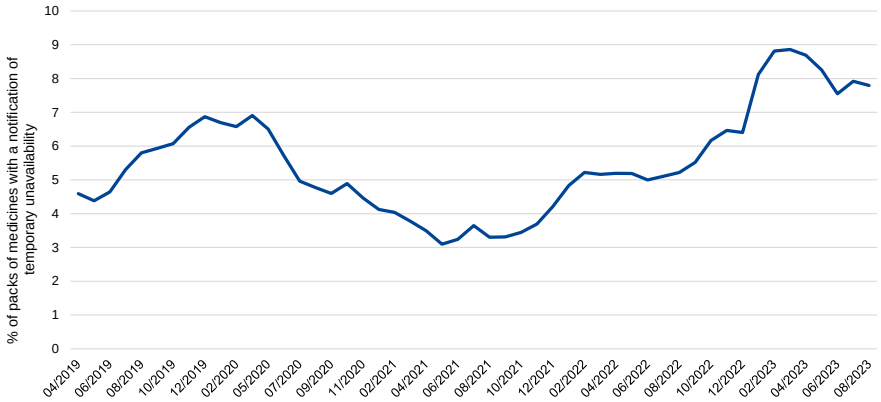
Note: only data for years 2020-2022 were presented as information on the supply problem impact was only systematically reported since November 2019.

Table 4 – Number and share of shortage notifications with critical impact by therapeutic area in 2020-2022

Year		Alimentary tract and metabolism	Blood and blood forming organs	Antiinfectives for systemic use					Antineoplastic and immunomodulating agents			Musculo-skeletal system
		A10BJ	B01AD	J01CA	J06BA	J07AL	J07BB	J07BM	L01DC	L03AX	L04AC	M03AC
		Glucagon-like peptide-1 (GLP-1) analogues	Enzymes	Penicillins with extended spectrum	Immunoglobulins	Pneumococcal vaccines	Influenza vaccines	Papillomavirus vaccines	Other cytotoxic antibiotics	Other immunostimulants	Interleukin inhibitors	Other quaternary ammonium compounds
2020 (n=21)	Number	0	0	0	15	0	2	0	0	1	0	1
	Share	0%	0%	0%	71%	0%	10%	0%	0%	5%	0%	5%
2021 (n=33)	Number	0	0	0	25	0	0	0	1	0	7	0
	Share	0%	0%	0%	76%	0%	0%	0%	3%	0%	21%	0%
2022 (n=36)	Number	3	7	0	20	0	0	0	2	1	3	0
	Share	8%	19%	0%	56%	0%	0%	0%	6%	3%	8%	0%

The monthly share of packs of medicines for human use with a notification of temporary unavailability increased between June 2019 (4.6%) and March 2020 (5.7%), and increased again starting in June 2021 (see Figure 6). In August 2023, reports of temporarily unavailable packs of medicines for human use represented, on average, 7.8% of the total number of packs for human use placed on the market in Belgium.

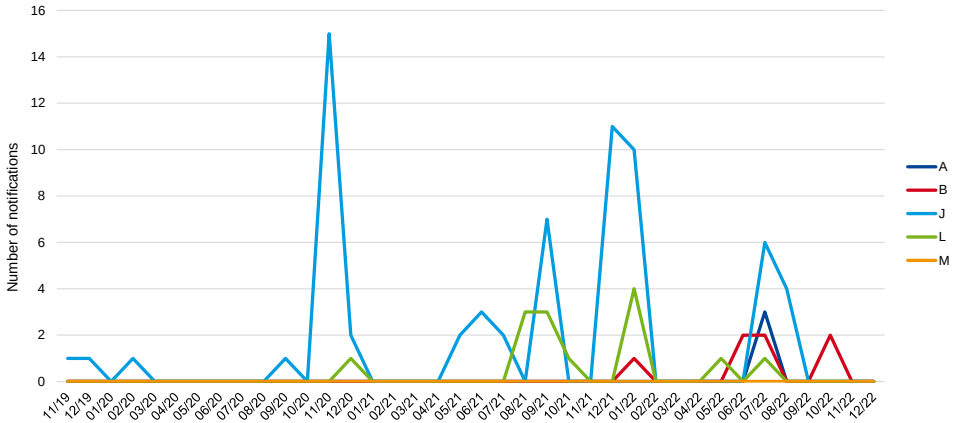
Figure 6 – Monthly share of packs of medicines for human use with a notification of temporary unavailability in 2019-2023



Impact of the COVID-19 pandemic

Since October 2020, shortages of immunoglobulins, more precisely subcutaneous immunoglobulins (SCIgs), have been reported in Belgium (see Figure 7). The shortages affected several products, including Gammanorm®, Gamunex®, Hizentra®, Iqymune® and Octagam®. The main reasons for this are the reduced collection of plasma around the world, the ever increasing need for immunoglobulins, and the dependence on plasma from other countries.[5] The COVID-19 crisis affected the plasma collection, especially in the USA which is the main exporting country. The additional need for plasma to treat COVID-19 patients (convalescent plasma, hyperimmune globulins derived from convalescent plasma and polyvalent intravenous immunoglobulins) put extra pressure on an already strained system.[6]

Figure 7 – Number of shortage notifications with critical impact by therapeutic area (ATC level-1 code) between November 2019 and December 2022



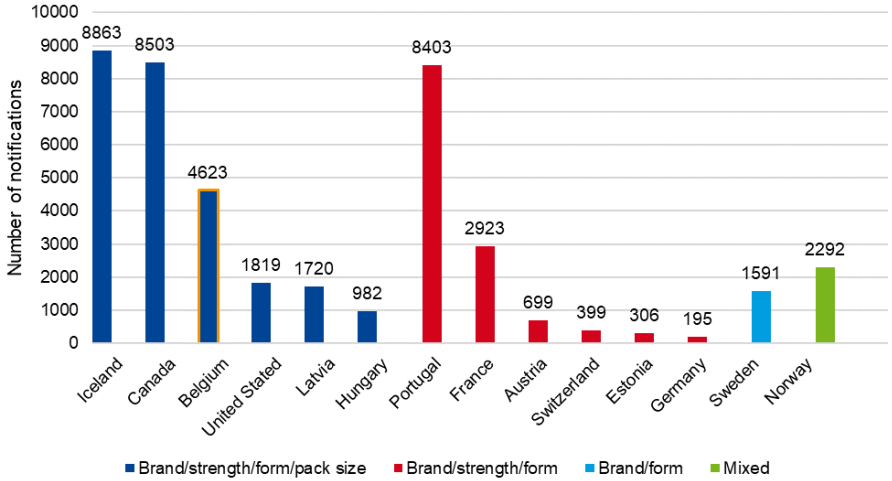
International

In 2017-2019, the number of notifications per country ranged from 195 in Germany to 8 863 in Iceland, with Belgium reporting the fourth highest number of notifications (n=4 623) among 14 OECD countries (see Figure 8). Results should nevertheless be interpreted with caution and the large variations across countries reflect both differences in notification practices and in the occurrence of shortages at national level (see the documentation sheet).

Although the distribution of shortage notifications by therapeutic area was not uniform across countries, in the majority of countries, including Belgium, medicines targeting the nervous system and the cardiovascular system were the most frequently subject to shortage notifications (each accounting for approximately 20% on average, see Table 5).

Furthermore, internationally, no information was available on the impact of medicine shortages on patients. Consequently, it was not possible to identify shortages that substantially impacted patients, such as those with critical unavailability in Belgium.

Figure 8 – Total number of notifications in 14 OECD countries (2017-2019)



Note: the difference between the total number of notifications in Belgium reported in this report (n=4 590 in 2017-2019) and the one reported by the OECD (n=4 623) is likely to be due to an updated version of the data being used in this report. *Source: OECD Health Working Paper No. 137.*[1]

Table 5 – Share (%) of shortage notifications by therapeutic area in 14 OECD countries (2017-2019)

Country	N Nervous system	C Cardiovascular system	J Antiinfectives for systemic use	A Alimentary tract and metabolism	L Antineoplastic and immunomodulating agents	G Genito urinary system and sex hormones	M Musculo-skeletal system	B Blood and blood forming organs	V Various drug classes	R Respiratory system	D Dermatologicals	H Systemic hormonal preparations, excl. sex hormones and insulins	S Sensory organs	X Missing/unknown ATC codes	P Antiparasitic products, insecticides and repellents
Austria	15	21	14	9	7	9	5	4	1	4	5	2	2	3	0
Belgium	21	23	8	8	6	10	5	2	4	4	4	2	2	0	0
Canada	28	25	8	9	5	6	4	3	2	2	4	2	2	1	0
Estonia	18	21	10	8	12	8	6	3	0	3	5	4	2	0	0
France	19	20	15	7	10	3	4	9	2	2	1	4	3	1	1
Germany	24	34	10	7	6	2	3	4	1	1	1	8	1	0	0
Hungary	13	12	7	7	7	4	4	10	27	3	2	2	1	1	0
Iceland	27	10	10	9	7	5	4	5	3	7	5	3	4	0	1
Latvia	20	19	10	10	8	6	6	4	2	6	4	2	4	0	0
Norway	20	14	11	12	6	7	6	4	2	6	5	3	2	1	0
Portugal	27	25	8	7	5	6	6	3	2	3	2	1	1	3	0
Sweden	24	9	9	9	7	10	5	6	2	5	5	3	5	0	1
Switzerland	11	7	50	2	20	0	1	4	4	0	0	1	1	0	0
United States	34	19	6	12	4	3	5	3	5	2	3	1	2	0	1

Note: Therapeutic areas are based on Anatomical Therapeutic Chemical (ATC) level-1 codes, ordered left to right according to the distribution across OECD countries.
Source: OECD Health Working Paper No. 137.

Key points

- **The number of notifications of temporarily unavailable packs of medicines for human use (i.e. shortage notifications) increased from 621 in 2015 to 3 044 in 2022, which likely reflects improved monitoring of medicine shortages over time. The average duration of a notification decreased from 123 days in 2015 to 51 days in 2022.**
- **In 2022, 37% of shortage notifications were for medicines with at least three alternatives available, 30% were for medicines with short-term unavailability and only 1% for medicines with critical impact.**
- **Between 2020 and 2022, there was an increase in the number of notifications with critical impact (from 21 to 36). The average duration of notifications with critical impact was 155 days in 2022.**
- **In 2022, immunoglobulins accounted for 56% of notifications for medicines with critical impact.**
- **Although the total number of shortage notifications varied greatly across OECD countries in 2015-2017, medicines targeting the nervous system and the cardiovascular system accounted for the largest share of notifications in most countries, including Belgium. However, the comparison of data across OECD countries should be done with caution due to differences in reporting practices.**

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