NIHDI

Monitoring Of Reimbursement Significant Expenses

MORSE report (2021 data)

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CONTENTS

INTRODUCTION

The MORSE report aims at the financial follow-up of the expenditure for reimbursable medicinal products in relation to the adopted policy measures (including new introductions of medicines in the reimbursement scheme, saving measures, etc.) and the reporting on trends in spending on proprietary pharmaceuticals (pharmaceuticals) delivered both in public pharmacies and in hospitals.

This report examines data up to and including December 2021.

The corona pandemic (COVID-19) became apparent in 2020. It affected the consumption and the expenditure of the health insurance.

In order to evaluate NIHDI net expenditure, NIHDI data are used (Pharmanet for public pharmacies, docPH consolidated invoicing data for hospitals).

The data on the pharmaceuticals supplied during 2021 by public pharmacies are complete (Pharmanet data). Hospital data were extrapolated (DocPH 2021 data available for ten months, these are 85 % complete).

The expenditure referred to in this report is NIHDI net expenditure as invoiced to the health insurance funds (pharmaceuticals budget).
For those pharmaceuticals for which an 'Article 81/111 convention' has been concluded between the company and NIHDI, the amounts repaid to the health insurance (general health insurance budget) are not taken into account: details of the refund mechanism, set out in the annex to these conventions, are confidential.

'NIHDI net expenditure' should always be taken to mean NIHDI gross expenditure – that is, total expenditure on drugs - minus the individual patient co-payments. 'NIHDI net expenditure' does not therefore include money received under the Article 81/111 conventions. A distinct section is dedicated to the Article 81/111 conventions.

Financial monitoring is not an exact science: observations are also tested against probability factors, in the view of the internal staff (internal evaluator, case managers, Pharmanet cell, etc.).
In addition, earlier forecasts are regularly checked against real expenditure, once the data are available, to ascertain the extent of any deviations.

Several reports on pharmaceutical expenditure exist: the permanent audit, Infospot, reports from the data management department, etc. In the MORSE report, we try to process the relevant information gleaned from other sources: where deemed necessary, data from NIHDI's actuarial department were added to this report.

The main aim of these MORSE reports is to stimulate reflection and discussion. All comments are welcome!

OVERVIEW OF GLOBAL EXPENDITURE ON PHARMACEUTICALS, BROKEN DOWN INTO PUBLIC PHARMACIES AND HOSPITALS

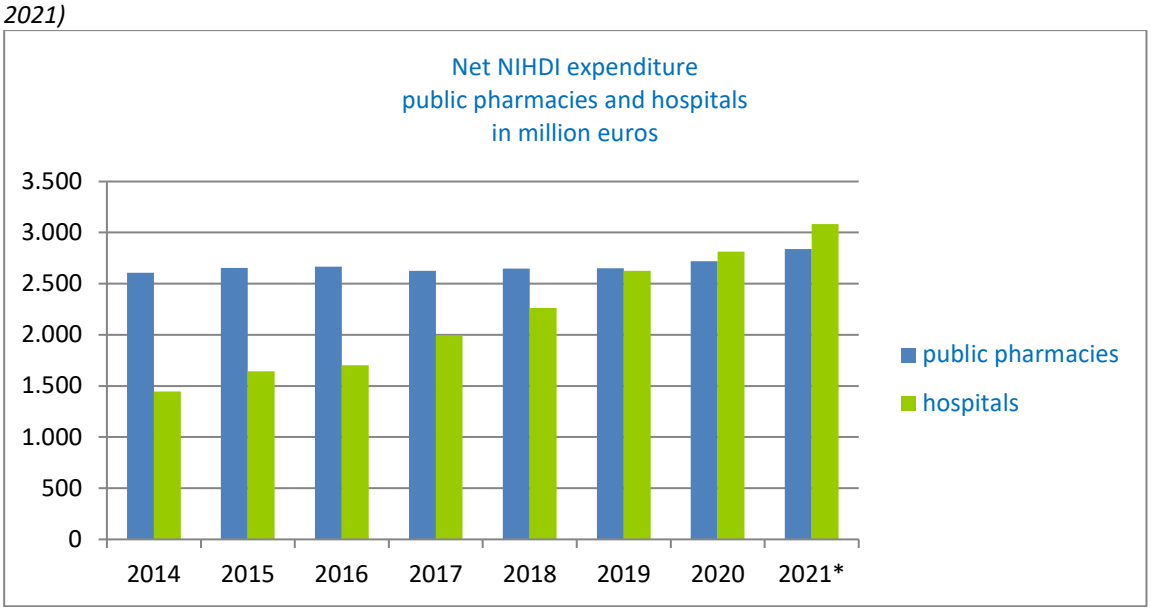
GENERAL

Table 1 : NIHDI net annual expenditure on reimbursable pharmaceuticals 2014-2021 [1]

NIHDI net expenditure x 1,000,000 €								
	2014	2015	2016	2017	2018	2019	2020	2021*
Public pharmacies	2,604.8	2,651.8	2,664.9	2,626.2	2,647.5	2,649.7	2,719.6	2,837.7
Hospitals	1,444.8	1,642.0	1,702.4	1,991.4	2,262.5	2,624.7	2,813.6	3,081.9
Total	4,049.6	4,293.7	4,367.4	4,617.6	4,910.0	5,274.3	5,533.2	5,919.7
% growth								
		2015-2014	2016-2015	2017-2015	2018-2017	2019-2018	2020-2019	2021-2020
Public pharmacies		1.8	0.5	-1.5	0.8	0.1	2.6	4.3
Hospitals		13.6	3.7	17.0	13.6	16.0	7.2	9.5
Total		6.0	1.7	5.7	6.3	7.4	4.9	7.0

*Source: Pharmanet (public pharmacies) and docPH (hospitals), * 2021 based on extrapolated docPH data*

Figure 1 : Net annual expenditure on reimbursable pharmaceuticals in public pharmacies and hospitals (2014-2021)



The global expenditure for medicinal products continues to show an upward trend. In 2021 we saw an increase in total expenditure for medicines by 7.0 %. During the years 2017, 2018 and 2019, we saw a growth figure of 6 to 7%. Growth slowed in 2020 (4.9%) and picked up again to 7.0% in 2021. Unlike in the period 2017-2019, the

[1] The figures on NIHDI net expenditure for public pharmacies are Pharmanet data. The figures on NIHDI net expenditure in hospitals come from: docPH data (NIHDI data), where total expenditure = outpatient expenditure + total expenditure on hospital admission lump sums + expenditure on hospitalised patients booked at 100% (not included in lump sum) + expenditure on hospitalised patients booked at 25% (included in lump sum).

current growth in total expenditure for medicines is due to both an increase in expenditure in public pharmacies (4.3% growth) and in hospitals (9.5% growth).

In public pharmacies we see that, the expenditure is up again after a near status quo in 2018 and 2019: a 2.6% increase in expenditure in 2020 compared to 2019 and a 4.3% increase in 2021 compared to 2020. In hospitals we can also observe an increase in expenditure in 2020 (7.2% growth) and 2021 (9.5% growth). However, this increase is less pronounced than the 14 to 17% growth observed during the period 2017-2019.

The 4.3% growth in expenditure in public pharmacies in 2021 and the 9,5% growth in expenditure in hospitals, result in a 7.0% growth in overall expenditure for pharmaceuticals. As a result, expenditure will increase to EUR 5,9 billion in 2021.

Figure 1 shows that expenditure on pharmaceuticals in hospitals makes up a growing share of overall expenditure on these products. Broadly speaking, the share of the expenditure in public pharmacies/hospitals has been equally split since 2019. In 2020, we see, for the first time, that expenditure in hospitals (narrowly) exceeds the expenditure in public pharmacies (share of hospital expenditure 50.8%). In 2021 the share of hospital expenditure rose to 52%.

Here we note the expenditure figures given in this report are figures for NIHDI net expenditure (NIHDI gross expenditure minus patient co-payments). This 'NIHDI net expenditure' does not take into account sums received under Article 81/111 conventions.

Every year, there is an increase in the share of expenditure on pharmaceuticals temporarily included in the list of reimbursable pharmaceuticals, i.e. pharmaceuticals on which an Article 81/111 convention has been concluded between the NIHDI and the company. This is due to the increasing number of conventions, larger volumes and higher prices of medicines covered by such conventions.

In 2021, as in 2020, medicines for which an Art. 81/111 agreement was entered into accounted for 35% of expenditure. In public pharmacies, a minority (13%) of the expenditure can be attributed to these medicines under contract, whereas in hospitals, this expenditure amounts to more than 50% (55% to be precise).

In comparison, in the previous two years, the share of contract medicines within public pharmacy expenditure was 10% (2019) and 11% (2020). In hospitals, their respective shares were 55% (2019) and 58% (2020).

Table 2 : Breakdown NIHDI net expenditure 2021 depending on whether or not the medicinal product falls under an Article 81/111 convention

NIHDI expenditure 2021 (in million EUR)							
	code T**	Public pharmacies		Hospital*		TOTAL	
Medicines without contract	0	2.457,2	*86,6%*	1.403,2	*45,5%*	3.860,4	*65,2%*
Medicines under contract	**1**	**380,5**	***13,4%***	**1.678,0**	***54,5%***	**2.058,6**	***34,8%***
TOTAL		2.837,7	*100,0%*	3.081,2	*100,0%*	5.9189,0	*100,0%*

*1) extrapolation based on data recorded in 2022 and 2) for lump sum medicines, the expenditure is calculated based on the real expenditure (25%) x 4 (this is a theoretical calculation of part of the expenditure for that which is covered by the lump sum)

** situation code T on 1/12/2021

In order to gain an overview of the budgetary compensation measures (a detailed analysis is not possible, due to the confidential nature of the refund mechanisms), we use the data from NIHDI's actuarial department. For completeness' sake, we report on the sums received through the annual levies on the pharmaceutical industry. The table below shows how the 81/111 receipts and levies have evolved over time.

Table 3 : Evolution of expenditure, taking account of receipts under Art. 81/111 conventions and levies (in million EUR)

	2016	2017	2018	2019	2020	2021
Recorded expenditure (*docN*) (1)	4.378,2	4.594,8	4.891,8	5.263,3	5.586,2	5.984,2
Art 81/111 receipts (2)	123,6	273,4	359,3	605,0	754,2	1.019,5
(3) = (1) minus (2)	4.254,6	4.321,4	4.532,5	4.658,2	4.832,0	4.964,7
Levies (4)	321,5	344,4	365,9	397,4	343,1	356,7
(5) = (3) min (4)	3.933,1	3.977,1	4.166,6	4.260,8	4.488,9	4.608,0

(2) Introduction of the advance system in 2017

(4) The tax reductions for the years 2020 and 2021 are only reimbursed in December 2022 and December 2023

Source: permanent audit 2022 of NIHDI's actuarial department, table 3A.1.2.9

EXPENDITURE ON PHARMACEUTICALS IN PUBLIC PHARMACIES

Table 4 : NIHDI net annual expenditure on medicines 2014-2021

	2014	2015	2016	2017	2018	2019	2020	2021
NIHDI net expenditure x 1,000,000 €	2.604,8	2.651,8	2.664,9	2.626,2	2.647,5	2.649,7	2.719,6	2.837,7

		2015-2014	2016-2015	2017-2015	2018-2017	2019-2018	2020-2019	2021-2020
% growth		1,8	0,5	-1,5	0,8	0,1	2,6	4,3

Table 5 : Top 80% of NIHDI net annual expenditure on medicines in public pharmacies

	Denomination	Growth 2020-2019	Growth 2021-2020	2021 NIHDI expenditure (in MEUR)
	Total	**2,6%**	**4,3%**	**2.837,7**
L04A	IMMUNOSUPPRESSANTS **(T)**	6,3%	7,0%	464,0
B01A	ANTITHROMBOTIC AGENTS **(T)**	4,0%	5,2%	289,9
A10B	BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS **(T)**	15,5%	12,4%	163,8
J05A	DIRECT ACTING ANTIVIRALS	-1,2%	-2,6%	139,1
R03A	ADRENERGICS, INHALANTS	2,1%	7,1%	131,3
A02B	DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)	0,4%	0,4%	103,0
B02B	VITAMIN K AND OTHER HEMOSTATICS **(T)**	23,2%	31,9%	97,2
C10A	LIPID MODIFYING AGENTS, PLAIN **(T)**	1,9%	2,0%	97,2
A10A	INSULINS AND ANALOGUES	1,6%	-2,7%	89,9
N06A	ANTIDEPRESSANTS	-1,0%	-2,8%	83,0
N05A	ANTIPSYCHOTICS	0,3%	-5,2%	80,5
N03A	ANTIEPILEPTICS	3,2%	1,0%	71,9
R03D	OTHER SYSTEMIC DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	20,0%	13,6%	62,4
N02A	OPIOIDS **(T)**	-3,1%	-0,5%	56,3
C09D	ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs), COMBINATIONS	5,1%	11,7%	45,6
C09B	ACE INHIBITORS, COMBINATIONS	6,2%	4,3%	44,1
C07A	BETA BLOCKING AGENTS **(T)**	-2,4%	-5,8%	41,8
J07B	VIRAL VACCINES	52,6%	-1,4%	39,9
M05B	DRUGS AFFECTING BONE STRUCTURE AND MINERALIZATION	-2,2%	1,1%	38,4
M01A	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS	-16,6%	2,0%	35,0
C09A	ACE INHIBITORS, PLAIN	-4,6%	-5,3%	28,9
H01C	HYPOTHALAMIC HORMONES	2,4%	0,8%	28,3
R03B	OTHER DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES, INHALANTS	-20,6%	-0,3%	25,3
J01C	BETA-LACTAM ANTIBACTERIALS, PENICILLINS	-25,9%	7,9%	23,4

(T): This ATC3 class includes 1 or more pharmaceuticals which are on the list temporarily via an Art. 81/111 convention

The overview of expenditure and growth per ATC3 class (*Table 5*) shows that **24 of the 149 classes** account for **80% of the expenditure** in public pharmacies.

ATC3 classes which include 1 or several pharmaceuticals which are temporarily on the list via an Article 81/111 convention are indicated in *Table 5* by the letter (T). The real cost to the NIHDI of these ATC3 classes may be

lower than the net expenditure reported, due to the financial compensation set out in Article 81/111 conventions.

In the public pharmacies, 13% of the expenditure is due to expenditure for medicines under contract (see *Table 2*).

Later on in this report, we look at the top 3 medicines in terms of expenditure, as well as a number of other medicine classes with interesting trends in expenditure.

We also refer to the reports on medication consumption of the Appropriate Care Unit within the Directorate for Research, Development and Quality promotion. You can consult these reports on the website: Medications – For a healthy Belgium (healthybelgium.be).

Overall, expenditure for the reimbursement of medicines in public pharmacies rose by 4.3% compared to the previous year, however we can observe underlying significant and highly divergent trends between individual classes (either strong growth, strong decrease, or trend reversals).

Figure 2 illustrates total expenditure in relation to the number of patients being treated. Expenditure and the number of patients treated remained relatively stable over the past years. In 2020 we saw a drop in the number of patients treated (-4.8% compared to 2019), while expenditure grew (+2.6%). In 2021 the rising trend continued (+4.3% compared to 2020), while the initiated downward trend for the number of patients treated reversed (+2.2% compared to 2020). These evolutions resulted in an increase in NIHDI's average expenditure per patient in 2021 to €340.7 (7.8% growth in 2020, followed by 2.1% growth in 2021).

Table 6 shows developments in the number of patients treated per ATC3 class.

Figure 2 : Evolution of NIHDI net expenditure in public pharmacies against number of (unique) patients treated

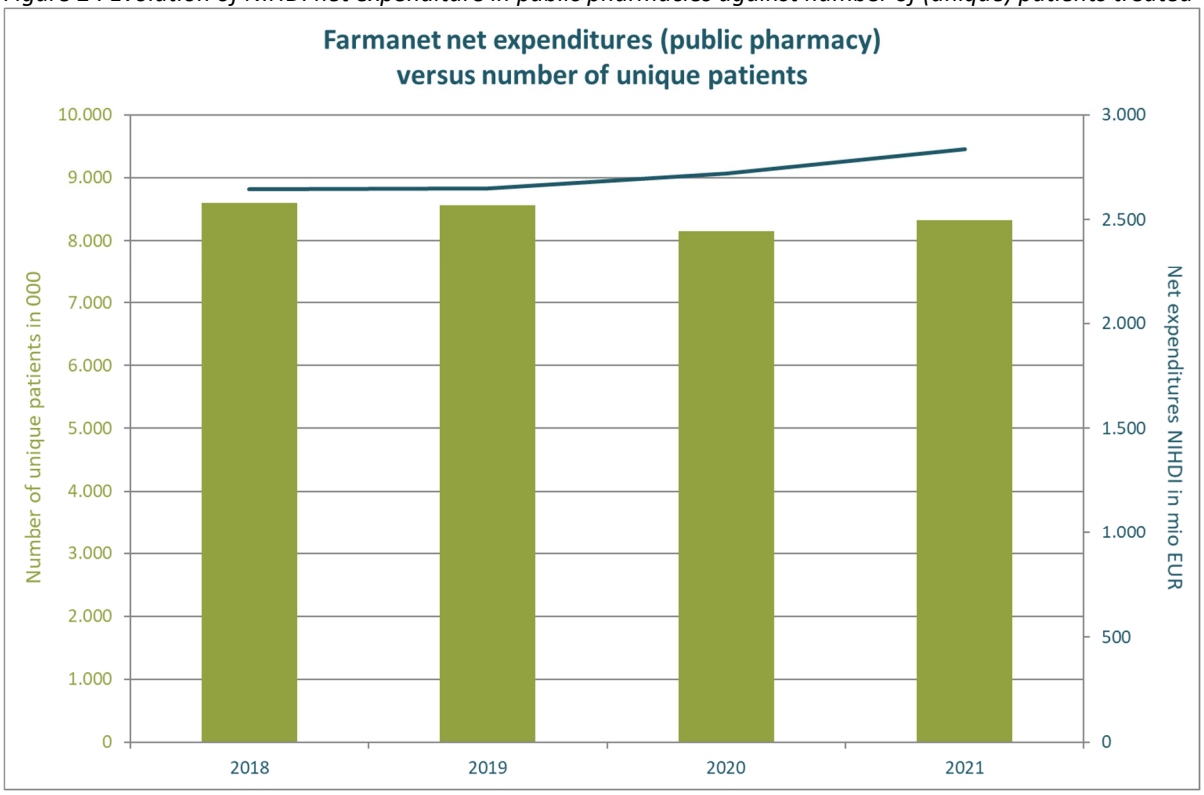


Table 6 : Evolution of number of (unique) patients treated in public pharmacies (in 000) per ATC3 class

	Denomination	Growth 2020-2019	Growth 2021-2020	Patients in 2021 (x 1000)
	Totaal	**-4,8%**	**2,2%**	**8.329,8**
L04A	IMMUNOSUPPRESSANTS **(T)**	2,4%	6,8%	133,9
B01A	ANTITHROMBOTIC AGENTS **(T)**	-2,6%	3,6%	1.565,3
A10B	BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS **(T)**	2,2%	2,7%	672,9
J05A	DIRECT ACTING ANTIVIRALS	0,6%	6,7%	41,6
R03A	ADRENERGICS, INHALANTS	-14,1%	8,7%	1.144,0
A02B	DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)	-3,5%	4,2%	2.269,6
B02B	VITAMIN K AND OTHER HEMOSTATICS **(T)**	5,8%	3,4%	0,4
C10A	LIPID MODIFYING AGENTS, PLAIN **(T)**	-0,5%	3,6%	1.611,7
A10A	INSULINS AND ANALOGUES	1,7%	1,6%	166,1
N06A	ANTIDEPRESSANTS	-0,5%	4,4%	1.272,8
N05A	ANTIPSYCHOTICS	-0,8%	1,4%	372,5
N03A	ANTIEPILEPTICS	-0,2%	5,4%	353,5
R03D	OTHER SYSTEMIC DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	-8,0%	-8,9%	144,1
N02A	OPIOIDS **(T)**	-7,1%	5,1%	1.100,5
C09D	ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs), COMBINATIONS	4,2%	6,2%	341,7
C09B	ACE INHIBITORS, COMBINATIONS	4,2%	7,4%	500,1
C07A	BETA BLOCKING AGENTS **(T)**	-0,8%	0,5%	1.299,3
J07B	VIRAL VACCINES	22,7%	-4,5%	2.145,1
M05B	DRUGS AFFECTING BONE STRUCTURE AND MINERALIZATION	-4,7%	2,1%	139,2
M01A	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS	-15,9%	2,7%	2.601,0
C09A	ACE INHIBITORS, PLAIN	-5,9%	-0,5%	534,4
H01C	HYPOTHALAMIC HORMONES	-1,2%	-1,0%	3,6
R03B	OTHER DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES, INHALANTS	-28,7%	14,6%	507,1
J01C	BETA-LACTAM ANTIBACTERIALS, PENICILLINS	-24,4%	6,6%	2.166,9

These percentages, and the relationships between them, differ from those in the table on expenditure over time (see *Table 4*). This suggests significant changes in NIHDI expenditure per patient, as illustrated in *Table 7*.

Table 7 : Evolution of average NIHDI expenditure per patient in public pharmacies, per ATC3 class

	Denomination	Growth 2020-2019	Growth 2021-2020	NIHDI expenditure per patient 2021
	Totaal	**7,8%**	**2,1%**	**340,7**
L04A	IMMUNOSUPPRESSANTS **(T)**	3,7%	0,2%	3.463,8
B01A	ANTITHROMBOTIC AGENTS **(T)**	6,8%	1,6%	185,2
A10B	BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS **(T)**	13,0%	9,5%	243,4
J05A	DIRECT ACTING ANTIVIRALS	-1,8%	-8,8%	3.341,5
R03A	ADRENERGICS, INHALANTS	18,9%	-1,4%	114,8
A02B	DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)	4,0%	-3,6%	45,4
B02B	VITAMIN K AND OTHER HEMOSTATICS **(T)**	16,5%	27,6%	245.467,6
C10A	LIPID MODIFYING AGENTS, PLAIN **(T)**	2,4%	-1,5%	60,3
A10A	INSULINS AND ANALOGUES	-0,1%	-4,3%	541,2
N06A	ANTIDEPRESSANTS	-0,5%	-6,9%	65,2
N05A	ANTIPSYCHOTICS	1,2%	-6,5%	216,1
N03A	ANTIEPILEPTICS	3,4%	-4,1%	203,5
R03D	OTHER SYSTEMIC DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	30,5%	24,7%	432,9
N02A	OPIOIDS **(T)**	4,3%	-5,3%	51,2
C09D	ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs), COMBINATIONS	0,9%	5,1%	133,5
C09B	ACE INHIBITORS, COMBINATIONS	2,0%	-2,9%	88,2
C07A	BETA BLOCKING AGENTS **(T)**	-1,7%	-6,2%	32,2
J07B	VIRAL VACCINES	24,3%	3,2%	18,6
M05B	DRUGS AFFECTING BONE STRUCTURE AND MINERALIZATION	2,6%	-1,0%	275,7
M01A	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS	-0,8%	-0,7%	13,5
C09A	ACE INHIBITORS, PLAIN	1,4%	-4,8%	54,1
H01C	HYPOTHALAMIC HORMONES	3,7%	1,9%	7.878,6
R03B	OTHER DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES, INHALANTS	11,3%	-13,0%	49,9
J01C	BETA-LACTAM ANTIBACTERIALS, PENICILLINS	-2,0%	1,2%	10,8

EXPENDITURE ON PHARMACEUTICALS IN HOSPITALS

Table 8 : NIHDI net annual expenditure on medicines 2014-2021 (docPH)

	2014	2015	2016	2017	2018	2019	2020	2021*
NIHDI net expenditure x 1,000,000 EUR	1.444,8	1.642,0	1.702,4	1.991,4	2.262,5	2.624,7	2.813,6	3.081,9

		2015-2014	2016-2015	2017-2015	2018-2017	2019-2018	2020-2019	2021-2020
growth %		13,6	3,7	17,0	13,6	16,0	7,2	9,5*

(*) extrapolation

Table 9 : Evolution of NIHDI net annual expenditure on medicines - top 80% (hospitals)

Ranking			Lump sum	ATC3		growth (%)		Total in mio EURO [2]
2019	**2020**	**2021***				**2020-2019**	**2021*-2020**	**2021***
1	1	1	No	L01F (2)	MONOCLONAL ANTIBODIES AND ANTIBODY DRUG CONJUGATES **(T)**	23,0%	11,5%	898,2
2	2	2	No	L04A	IMMUNOSUPPRESSANTS **(T)**	9,5%	5,6%	429,8
3	3	3	No	L01E (1)	PROTEIN KINASE INHIBITORS **(T)**	18,5%	6,4%	405,8
4	4	4	No	S01L	OCULAR VASCULAR DISORDER AGENTS **(T)**	0,8%	11,6%	123,9
7	5	5	No	L02B	HORMONE ANTAGONISTS AND RELATED AGENTS **(T)**	15,1%	12,2%	117,3
6	6	6	No	J06B	IMMUNOGLOBULINS	4,4%	13,4%	107,7
8	7	7	Mix	L01X (1/2)	OTHER ANTINEOPLASTIC AGENTS **(T)**	15,6%	16,2%	85,0
10	8	8	No	B02B	VITAMIN K AND OTHER HEMOSTATICS **(T)**	18,1%	13,3%	72,0
9	10	9	Yes	B05B	I.V. SOLUTIONS	-6,0%	-1,4%	54,9
29	29	10	No	R07A	OTHER RESPIRATORY SYSTEM PRODUCTS **(T)**	0,2%	379,4%	53,5
12	12	11	Mix	A16A	OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS **(T)**	-3,5%	1,6%	49,7
5	11	12	No	J05A	DIRECT ACTING ANTIVIRALS **(T)**	-41,9%	-9,1%	48,2
16	14	13	Mix	L01C	PLANT ALKALOIDS AND OTHER NATURAL PRODUCTS **(T)**	8,6%	3,3%	42,1

(T): this ATC3 class includes 1 or several pharmaceuticals which are temporarily included in the list via an Article 81/111 convention

(*) extrapolation

(1) *WHO changes ATC classification 2021: the protein kinase inhibitors were removed from class L01X and moved to a new ATC 3 class: L01E*

(2 *WHO changes ATC classification* 2022: within class L01X, monoclonal antibodies and antibody-drug conjugates were eliminated, and monoclonal antibodies and antibody-drug conjugates were moved to a new ATC 3 class, class L01F.

This overview of the (virtual) expenditure and the growth observed per ATC3 class shows that **13 of the 165 classes** account for **80 % of expenditure** on pharmaceuticals in hospitals.

ATC3 classes which include 1 or several pharmaceuticals which are temporarily on the list via an Article 81/111 convention are shown in *Table 9* by a letter (T). The real cost to the NIHDI of these ATC3 classes may be lower than the net expenditure figure given, due to the financial compensation set out in the Article 81/111 conventions.

[2] The NIHDI net expenditure per ATC 3 class is based on: docPH data (NIHDI data), where the total expenditure = expenditure outpatients (A) + expenditure booked at 100% (lump sum not included) (B) + expenditure booked at 25% (lump sum included) (C) + a theoretically calculated sum based on C (D). By adding the amount D, the expenditure is not absolute but virtual, thus allowing a ranking.

In hospitals, more than half of the expenditure (54,5%) is attributed to expenditure for medicines under contract (see *Table 2*).

In relation to the classification of NIHDI's net expenditure for medicines per ATC3 class, it needs to be noted that the WHO introduced changes in the ATC classification for class L01X (other antineoplastic agents) in 2021 and 2022. This explains why the figures for class L01X *Table 9* do not correspond to those mentioned in previous MORSE reports.
In 2021, the WHO made a change in the ATC classification system: the protein kinase inhibitors were removed from class L01X and moved to a new ATC3 class: L01E. In 2022, monoclonal antibodies and antibody-drug conjugates were eliminated and included in a new class: L01F.

Until 2020, class L01X was the class that was ranked highest year after year. In 2021, monoclonal antibodies and antibody-drug conjugates, with an expenditure of nearly 900 million euros, were ranked in first place.

In second place came immunosuppressants (L04A, 430 million euros), followed by protein kinase inhibitors (L01E).

In 2021, the expenditure for the 3 highest ranked classes, L01F, L04A and L01E, amounted to more than 1.7 billion euros or 56% of the expenditure for pharmaceuticals in hospitals. All molecules belonging to these classes are excluded from the hospital lump sum.

Whereas class L04A is ranked 2nd in the top 80% of pharmaceutical expenditure in hospitals, it is ranked 1st in the top 80% in public pharmacies (464.0 million euros in 2021). In 2019, we saw, for the first time in years, a decrease in expenditure on immunosuppressants of almost 5% in public pharmacies. This decrease was due to the commercialisation of biosimilar medicines and the associated price drop within the scope of the measure taken with regard to 'biological medicines'. However, from 2020 onwards we can observe a rise in expenditure again: by 6.3% in 2020 and by 7.0% in 2021.

In 2020, the expenditure for class L04A amounted to 464.0 million euros in public pharmacies and 429.8 million euros in hospitals. That is equal to a total expenditure of 893.8 million euros or 15,1% of the global budget for medicinal products. In comparison, in 2016, the total expenditure for class L04A was 598.01 million euros or 13.7% of the 2016 global budget for medicinal products.

Later on in the report, we discuss in more detail how spending on the top 3 medicines classes has evolved over time, and we consider several other classes of medicines where there have been interesting trends in expenditure.

EXPENDITURE ON MEDICINES IN HOSPITALS: BREAKDOWN BY TYPE OF PATIENT

BASIS

We use docPH data: consolidated invoicing data (NIHDI net expenditure), broken down by pharmaceutical packaging and type of patient (hospitalised – outpatient).
In the case of docPH data, the invoicing data for a given period refer to the period during which the medicines were delivered. DocPH data are always available at a later time, since the data for a year of delivery are selected from the data recorded for an 18-month period (the specific year and the semester following that year. In the case of the 2020 DocPH figures, the data recorded for the first half of 2021 are not yet available. The data reported are extrapolated from the recorded 2020 data (extrapolation based on about 85% of the data of the full year).

GENERAL: MEDICINES LUMP SUM

On 1 July 2006, the **medicines lump sum** was introduced for hospitalised patients in acute hospitals. In principle, all the medicines provided to these patients are covered by a fixed reimbursement scheme (lump sum).

There is, however, a list of exceptions to this principle (based on the ATC5 code).
Medicines are excluded either by law (e.g. orphan drugs, antineoplastic agents, cf Article 127(3) of the Royal Decree of 1 February 2018) or on the basis of a proposal from the 'permanent working group lump sum medicines' (if either the active substance is extremely important in medical practice and/or if the cost of the product could substantially limit its use if it were included in the lump sum).

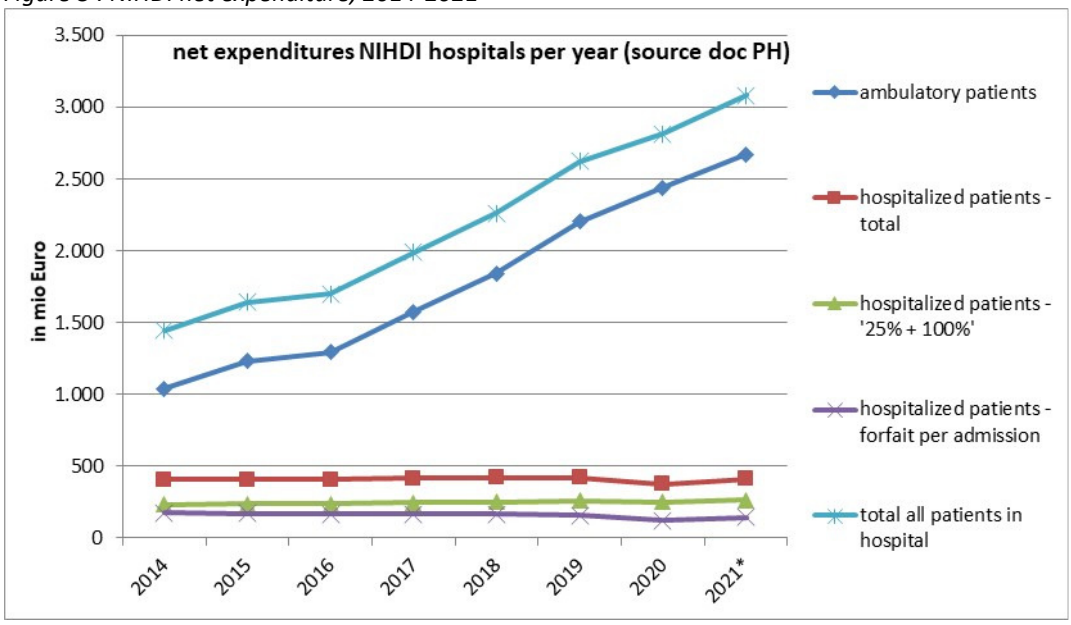
According to the legislation, for pharmaceuticals included in the lump sum, 25% of the reimbursement basis is still invoiced. The remaining part is covered by the hospitalisation lump sum (fixed amount per admission).

This partial invoicing (25% of the reimbursement basis is invoiced in the standard way, i.e. per unit used) means the actual use of medicines can be monitored without these data disappearing into a general medicines lump sum based on APRDRG (All Patients Refined Diagnosis Related Groups).

EXPENDITURE BROKEN DOWN BY PATIENT-TYPE: ANALYSIS

Plotting the annual figures per patient type gives the graph shown below.

*Figure 3 : NIHDI net expenditure, 2014-2021**



*Source: docPH, *2021 based on extrapolated data*

In 2020 and 2021 we experienced the COVID-19 pandemic resulting in periods of deferred care. This crisis has a considerable impact on the evolution of the expenditure.

When looking at the expenditure for hospitalised patients, which was stable from 2014 to 2019, we see a decrease in the expenditure of 11.3% in 2020: 22.9% less was spent on the lump sum per admission and a decrease of 4.3% can be observed in the expenditure for medicines ('25% + 100%'). In 2021, expenditure for hospitalised patients rose again by 9.7%, almost reaching the level of expenditure of 2019 (-2.7% compared to 2019). Expenditure for the fixed fee per admission rose again in 2021 by 16.9%. This means that expenditure for the fixed fee per admission did not yet reach the pre-COVID-19 pandemic level (-9.8% compared to 2019).

The rising trend for expenditure for outpatients continued, but the marked growth that could be observed in 2017, 2018 and 2019, respectively by 21.6%, 16.6% and 17.4% compared to the previous year, was less pronounced in 2020 (9.6% growth) and in 2021 (9.5% growth).
Total hospital expenditure increased in 2021 by 9.5% compared to 2020. The sharp upward curve of expenditure we observed in 2017, 2018 and 2019 (growth figure of 14 to 17%), and which was already less marked in 2020 (growth figure of 7.2%), was also tempered somewhat in 2021.

The table below (*Table 10*) shows that the share of expenditure for outpatients within total expenditure for pharmaceuticals in a hospital setting consistently increased until 2020. In 2021, we can observe a stabilisation for the first time (86.7%).
In 2021, as in 2020, expenditure for hospitalised patients amounted to less than 15% (13.3 %) of total expenditure for pharmaceuticals in a hospital setting.

Table 10 : Outpatient expenditure as a percentage of total hospital expenditure on pharmaceuticals 2014-2021 (in %)

	2014	2015	2016	2017	2018	2019	2020	2021*
Percentage of expenditure on outpatients / total expenditure hospitals	71,9%	75,2%	76,1%	79,1%	81,4%	83,9%	86,7%	86,7%

*Source docPH, * 2021 based on extrapolated data*

The national budget for lump sums (invoicing by fixed amount per admission) is set each year by the General Council. These are open-ended budget envelopes. The individual hospital receives a lump sum amount per admission, which depends on the reported case mix (based on minimum hospital data).

Table 11 shows the amounts set aside in the national budget for the medicines lump sum. The hospital lump sum has been in force since 1 July 2006. The amount earmarked in the national budget for the first year of application of the medicines lump sum (1.7.2006-30.6.2007) was 258.86 million euros. This amount has been reduced gradually over the years, and now, in the sixteenth year of the system (1.7.2021-30.6.2022) stands at 150.159 million euros.

From 1.1.2014, the price per admission is reduced to 82% of the original value if the same patient is re-admitted to the same hospital within 10 days of a previous admission. This saving measure aims to save 1.9 million euros annually.

Table 11 : Amounts set aside in the national budget for hospital admission lump sums, july 2014 - june 2022 inclusive

Period	Sum in national budget (in million EUR)
1/7/2014 - 30/6/2015	174,964
1/7/2015 - 30/6/2016	168,161
1/7/2016 – 30/6/2017	167,159
1/7/2017 – 30/6/2018	169,612
1/7/2018 – 30/6/2019	168,100
1/7/2019 – 30/6/2020	154,010
1/7/2020 – 30/6/2021	148,825
1/7/2021 – 30/6/2022	150,159

Source: data NIHDI's actuarial department

From 2015 to 2019, the number of admissions remains stable (about 1.8 million per year). Due to the COVID-19 pandemic, we can see a significant fall in the number of admissions per year in 2020 and 2021: in 2020, the number of admissions dropped to below 1.6 million (12.2% decrease in 2020 compared to 2019), and in 2021 the number rose again slightly to 1.6 million admissions per year. However, this number still implies a 9.8% drop compared to 2019, the year before the COVID-19 pandemic manifested itself. In 2021, the average amount per admission was 81.21 euros. The evolution of the average amount per admission from 2016 to 2021 is shown in the table below (*Table 12*).

Table 12 : Evolution of average amount per admission (2016 – 2021)

	2016	2017	2018	2019	2020	2021
Expenditure on admission lump sum	167,277	168,141	166,587	160,298	129,974	130,209
Number of admissions	1.789.423	1.798.581	1.775.695	1.781.763	1.564.852	1.606.404
Amount per admission	*93,48*	*93,49*	*93,82*	*89,97*	*83,06*	*81,21*

Bron: Source: data NIHDI's actuarial department (recorded data, docN), permanent audit table 3A.2.5.2

The yearly figures for the various types of expenditure are shown in the table below (*Table 13*).

Table 13 : NIHDI net expenditure 2014-2021 (in million EURO) - breakdown of hospital expenditure*

	2014	2015	2016	2017	2018	2019	2020	2021*
Outpatients [1]	**1.039,1**	**1.234,3**	**1.295,4**	**1.575,1**	**1.842,2**	**2.202,6**	**2.439,3**	**2.671,2**
Hospitalised patients, total	**405,8**	**407,7**	**407,1**	**416,3**	**420,3**	**422,1**	**374,3**	**410,7**
-Hospitalised patients, total – 25 % + 100 %[2+3]	231,8	236,9	240,0	249,3	252,3	262,4	251,3	266,8
- Admission lump sum [4]	174,0	170,7	167,1	167,0	168,0	159,6	123,1	143,9
Total hospitals	**1.444,8**	**1.642,0**	**1.702,4**	**1.991,4**	**2.262,5**	**2.624,7**	**2.813,6**	**3.081,9**

*Source: docPH, *2021 based on extrapolated data*

[1] *Outpatients*	*Medicines supplied to outpatients in the hospital, never included in the lump sum (100% reimbursement basis, actual reimbursement depends on reimbursement category)*
[2] *Hospitalised patients – 100% (NOT included in the lump sum)*	*Medicines supplied to hospitalised patients, not reimbursable as part of the lump sum because* *- the medicine is not included in the lump sum (on the list of exceptions)* *- the medicine was supplied to a patient:* *- admitted before 1.7.2006 (entry into force of the medicines lump sum)* *- admitted to a non-acute hospital* *(reimbursement basis 100%, actual reimbursement depends on reimbursement category)*
[3] *Hospitalised patients – lump sum 25 %*	*Medicines supplied to hospitalised patients in an acute hospital (date of admission since 1.7.2006), and medicine included in the lump sum* *(reimbursement = 25% of the reimbursement base rate; abolition of reimbursement depending on reimbursement category)*
[4] *Admission lump sum*	*Lump sum received by the hospital for each admission.* *This amount is revised each year and depends on the case mix reported by the hospital* (minimum hospital data).

Table 14 : Growth percentages NIHDI net expenditure period 2014-2021 - breakdown expenditure hospitals*

	2014-2013	2015-2014	2016-2015	2017-2016	2018-2017	2019-2018	2020-2019	2021*-2020
Outpatients [1]	7,5	18,8	4,9	21,6	17,0	19,6	10,7	9,5
Hospitalised patients, total	**0,3**	**0,5**	**-0,1**	**2,3**	**0,9**	**0,4**	**-11,3**	**9,7**
-Hospitalised patients, total – 25 % + 100 % [2+3]	2,7	2,2	1,3	3,9	1,2	4,0	-4,3	6,2
- Admission lump sum [4]	-2,7	-1,9	-2,2	0,0	0,5	-5,0	-22,9	16,9
Total hospitals	**5,4**	**13,6**	**3,7**	**17,0**	**13,6**	**16,0**	**7,2**	**9,5**

*Source: docPH, *2021 based on extrapolated data*

OVERVIEW OF THE EXPENDITURE FOR OTHER PHARMACEUTICAL DISPENSING IN PUBLIC PHARMACIES

IN GENERAL

In addition to the dispensing of reimbursable pharmaceuticals, there is other pharmaceutical dispensing that is reimbursed by the health insurance.

The database Pharmanet contains the data on reimbursable pharmaceutical dispensing that is reimbursed in public pharmacies.

Most of the expenditure for reimbursable pharmaceutical dispensing goes to pharmaceuticals. In 2020, the expenditure for reimbursable pharmaceuticals in public pharmacies amounted to 2.837,7 million euros (94%) compared to 203,0 million euros (7%) for other reimbursable pharmaceutical dispensing.

Table 15 : Evolution of the annual NIHDI net expenditure for reimbursable pharmaceuticals and other pharmaceutical dispensing in public pharmacies (2018-2021; in million EUR)

NIHDI net expenditure x 1,000,000 EUR				
	2018	**2019**	**2020**	**2021**
Pharmaceuticals	2.647,5	2.649,7	2.719,6	2.837,7
Other pharmaceutical dispensing	125,6	149,3	167,5	203,0
Share other pharmaceutical dispensing (%)	4,7	5,6	6,2	7,2
Growth %				
		2019-2018	**2020-2019**	**2021-2020**
Pharmaceuticals		0,1	2,6	4,3
Other pharmaceutical dispensing		18,8	12,2	21,2

Source: Pharmanet

The other pharmaceutical dispensing includes, among other things, magistral preparations, various fees (waiting fees, fees for supplying methadone, oxygen, ...), medical nutrition, dispensing within the scope of care trajectories for diabetes and chronic renal failure (strips and lancets, blood glucose meter, blood pressure monitor).

When we sort the NIHDI 2021 net expenditure by size, we see that the following 9 categories are ranked highest. These 9 categories represent 93% of the expenditure for other pharmaceutical dispensing.

Table 16 : Evolution of the annual NIHDI net expenditure for other pharmaceutical dispensing in public pharmacies, top 9 of the expenditure (2018-2021; in million EUR)

Ranking	**Category**	**2018**	**2019**	**2020**	**2021**	***Cumulative share***
	Total	*125,6*	*149,3*	*167,3*	*203,0*	*100%*
1	Magistral preparations	*63,3*	*66,5*	*65,0*	65,5	32%
2	Fee reference pharmacist function	*2,0*	*19,5*	*25,5*	36,6	50%
3	Self-catheterisation	*19,0*	*19,9*	*21,7*	22,3	61%
4	Specific reimbursement for contraceptives	*6,6*	*6,7*	*11,4*	*15,8*	69%
5	Fees and lump sums 'oxygen'	*9,1*	*9,6*	*13,8*	13,9	76%
6	Dietary nutrition	*8,0*	*8,8*	*9,6*	*9,9*	81%
7	COVID-19 self-tests	*0,0*	*0,0*	*0,0*	*9,7*	86%
8	Diabetes care pathways	*7,6*	*7,5*	*7,9*	*8,3*	90%
9	COVID-19 fast tests	*0,0*	*0,0*	*0,0*	*7,7*	93%
	Growth %					
			2019-2018	**2020-2019**	**2021-2020**	
	Totaal		*18,8*	*12,2*	*21,2*	
	Magistral preparations		5,0	-2,1	0,7	
	Fee reference pharmacist function		890,2	30,7	43,5	
	Self-catheterisation		4,6	8,9	3,1	
	Specific reimbursement for contraceptives		2,7	69,8	38,0	
	Fees and lump sums 'oxygen'		5,5	44,0	0,4	
	Dietary nutrition		10,8	8,6	3,9	
	COVID-19 self-tests		nvt	nvt	nvt	
	Diabetes care pathways		-1,6	6,2	4,9	
	COVID-19 fast tests		nvt	nvt	nvt	

In line with the section on expenditure for magistral preparations, a lump-sum intervention is provided for the fractional dispensing of methadone-based substitution treatments by the pharmacist. The evolution of this expenditure is shown in the following table.

Table 17 : Evolution of the annual NIHDI expenditure for fractional dispensing of methadone-based substitution treatments (2018-2021, in million euro)

	2018	2019	2020	2021
Recorded expenditure	3,32	3,32	3,34	3,30
Growth %	1,8	-0,2	0,7	-1,2

Source: actuarial department, permanent audit 2022

DETAILED ANALYSIS OF SEVERAL CLASSES OF DRUGS WITH SIGNIFICANT EVOLUTIONS

PUBLIC PHARMACIES

L04A – IMMUNOSUPPRESSANTS

GENERAL

Overall, NIHDI expenditure for ATC class L04A showed a rising trend in 2021 compared to 2020 and 2019, for both public pharmacies (+€55,907,866 /+13,7% compared to 2019 and +€30,350,915/+7.0% compared to 2020) and hospitals (+€58,350,449/+15,7% compared to 2019 and +€22,794,878/+5.6% compared to 2020).

Table 18 : evolution of NIHDI net annual expenditure for ATC class L04A immunosuppressants (2019 – 2021)

	Public pharmacies (euros)	Hospitals (euros)
2019	408,059,299	371,435,248
2020	433,616,249	406,990,819
2021	463,967,165	429,785,679

The annual DDD figures for class L04A show a further rising trend between 2019 and 2021, both for public pharmacies (+€4,088,193/+12.1% in 2021 compared to 2019 and +€2,162,647/+6.1% in 2021 compared to 2020) and hospitals (+€1,745,163/+17.0% compared to 2019 and +€951,816/+8.6% compared to 2020).

Table 19 : evolution of annual DDD figures for ATC class L04A immunosuppressants (2019 – 2021)

	Public pharmacies	Hospitals
2019	33,660,291	10,251,185
2020	35,585,838	11,044,531
2021	37,748,484	11,996,348

The growth in the NIHDI expenditure in public pharmacies can primarily be explained by additional indications becoming reimbursable for drugs that were already reimbursable (e.g. tofacitinib-Xeljanz®, baricitinib-Olumiant®, ustekinumab-Stelara®, ixekizumab-Taltz®, guselkumab-Tremfya®) and by new drugs becoming reimbursable (e.g. upadacitinib-Rinvoq®, filgotinib-Jyseleca®), for which the cost of a treatment per patient is also continuing to rise in comparison with earlier therapeutic options.
The greatest cost in public pharmacies in 2019 was for subclasses L04AB (adalimumab-Humira® and biosimilars and etanercept-Enbrel® and biosimilars, ...) and L04AC (ustekinumab-Stelara®, guselkumab-Tremfya®, secukinumab-Cosentyx®, ixekizumab-Taltz®, ..).

The rise in NIHDI expenditure in hospitals can mainly be explained by the extension of reimbursability of medicines that were already reimbursable, and increasing use within these new therapeutic indications. (e.g. ustekinumab-Stelara®, vedolizumab-Entyvio®, lenalidomide-Revlimid®, canakinumab-Ilaris®, …), for which the cost of a treatment per patient is also continuing to rise in comparison with earlier therapeutic options.
For example, the increase in the use of 7 molecules (vedolizumab, ocrelizumab, ustekinumab, canakinumab, lenalidomide, pirfenidone and pomalidomide) constitutes additional expenditure for the health insurance fund amounting to +€77,007,838 (+20.7%) compared to the total 2019 L04 budget for hospitals.

On the other hand, there are also products for which there was a decrease, such as tocilizumab-RoActemra® (mainly due to stock problems), eculizumab-Soliris® (price reduction by law), natalizumab-Tysabri® (price reduction by law) and alemtuzumab-Lemtrada® (shift to other options for RRMS) and fingolimod-Gilenya® (price reduction by law and generics). Overall, reimbursement for these molecules by the health insurance fund amounted to €17,724,083 less than in 2019 (-4.8% compared to the L04 budget in 2019).

The average NIHDI cost per DDD in 2021 was notably higher in hospitals (€35.8/DDD) than in public pharmacies (€12.3/DDD).

The background to the trends observed in public pharmacies and in hospitals is explained further below.

A) Public pharmacies

1) General

In 2019 NIHDI net expenditure for class L04A in public pharmacies amounted to about 408,1 million euros, which increased to about 433,6 million euros in 2020 and to about 464,0 million euros in 2021. (*Figure 4*)

The number of DDDs and the number of patients showed a rising trend during this period: the number of DDDs increased from 33.6 million in 2019 to 37.7 million in 2021, and the number of patients from 122,411 in 2019 to 133,949 in 2021. (*Figure 4*).

Figure 4 : evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2018 – 2021) for ATC class L04A immunosuppressants

Figure 5 : evolution of NIHDI net monthly expenditure (public pharmacies 2017 – 2021) for ATC class L04A immunosuppressants

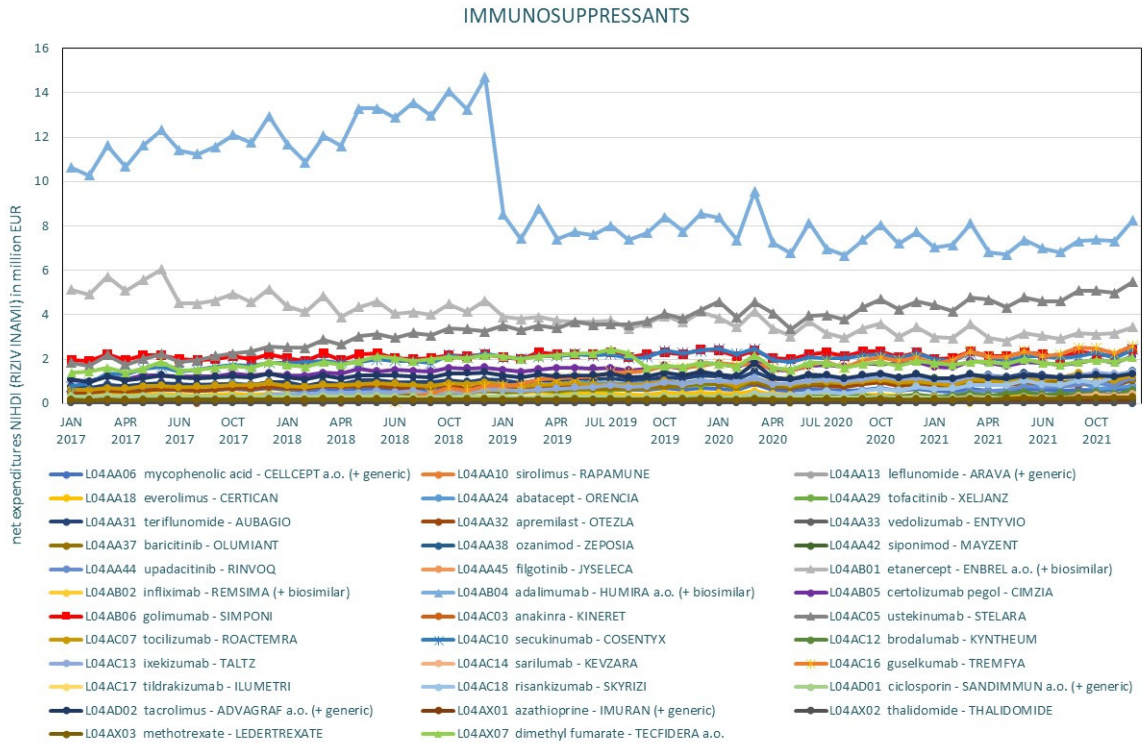


Figure 6 : evolution of number of DDDs per month (public pharmacies 2017 – 2021) for ATC class L04A immunosuppressants

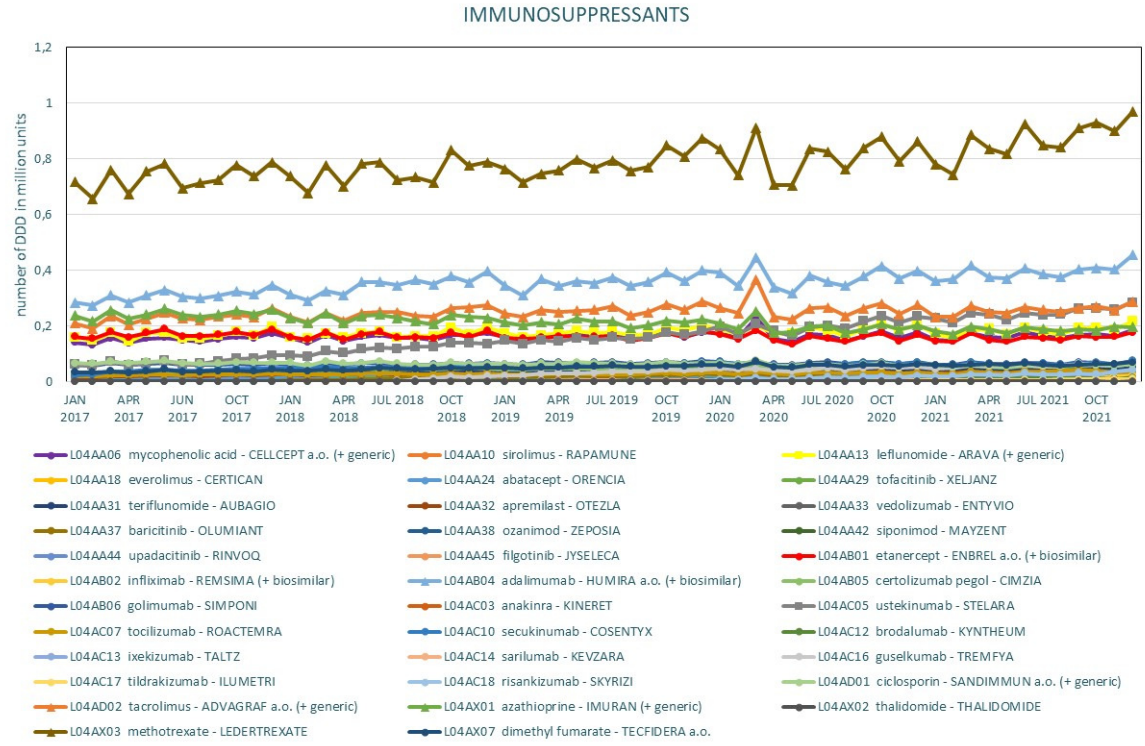
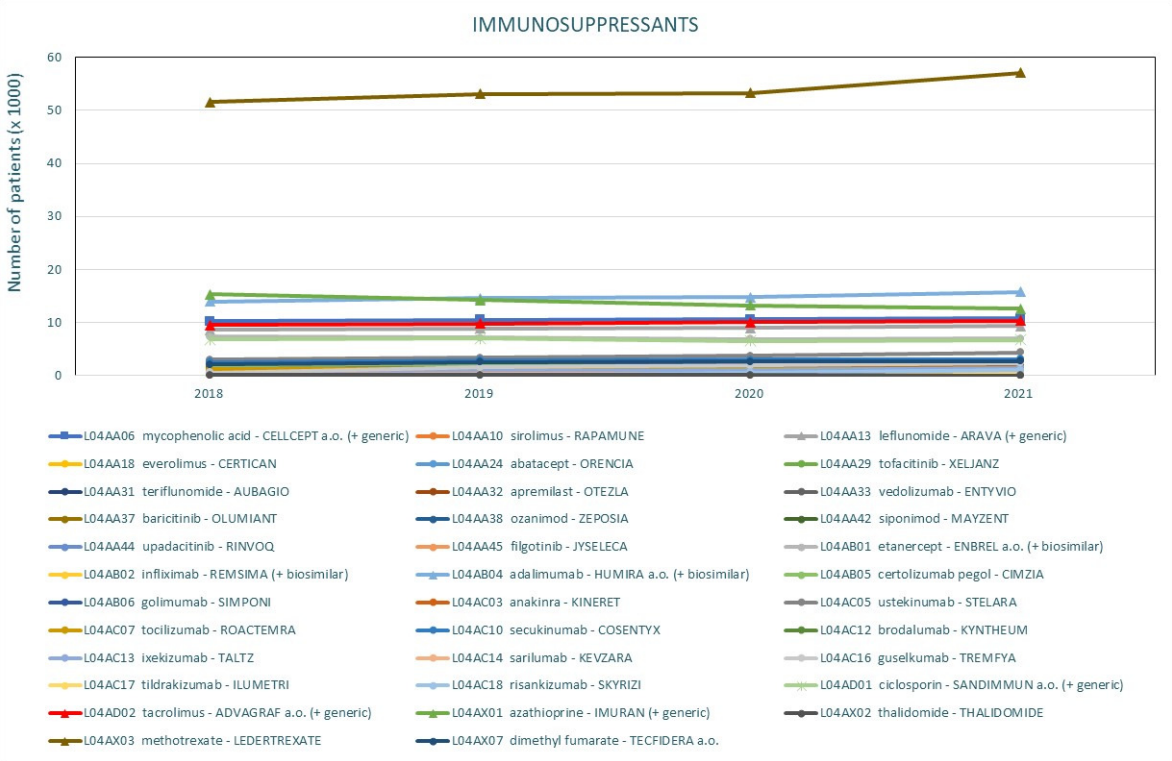


Figure 7: evolution of number of patients per year (public pharmacies 2018 – 2021) for ATC class L04A immunosuppressants



It is clear from *Figure 5* that adalimumab (Humira® and biosimilars - ATC L04AB04) accounts for the main part of NIHDI expenditure in the ATC L04A class in public pharmacies. While NIHDI net expenditure for adalimumab has fallen since 1/1/2019, due to biosimilars becoming eligible for reimbursement and the reduction in price associated with this under the 'biological medicines' measure, it still represents the largest share of the expenditure in this class.

The second most important pharmaceutical is ustekinumab (Stelara®, ATC L04AC05), for which a continuous increase in net NIHDI expenditure can be observed. The fact that Stelara became reimbursable for an additional indication, namely the treatment of ulcerative colitis, could explain the rising costs for the NIHDI.

The third most important pharmaceutical is etanercept (Enbrel® and biosimilars, ATC L04AB01). While net NIHDI expenditure for etanercept follows a downward trend due to the introduction of reimbursability for biosimilars and the resulting price reduction in the context of the 'biological medicines' measure, it still accounts for a large part of expenditure in this class.

Expressed in the number of patients (*Figure 7*) there is a very strong prevalence of Ledertrexate ® (methotrexate, ATC L04AX03), but due to the very low cost price of this molecule this has only a limited effect on the NIHDI budget.
Overall, there is a continuing upward trend in the number of patients reimbursed for drugs from class L04A in public pharmacies (*Figure 4*).

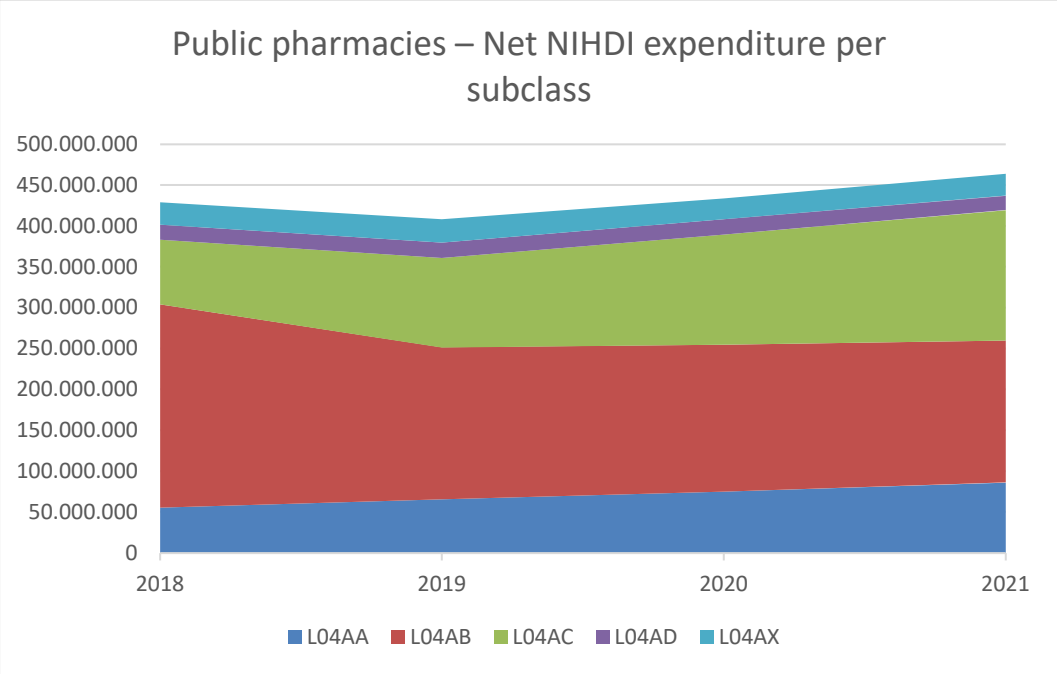
2) Analysis per subclass

The L04A class can be subdivided into different subclasses:

- L04AA (selective immunosuppressants),
- L04AB (tumour necrosis factor α inhibitors),
- L04AC (interleukin inhibitors),
- L04AD (calcineurin inhibitors),
- L04AX (other immunosuppressants).

These drugs are primarily used for the treatment of, among other things, rheumatic conditions, psoriasis, Crohn's disease, ulcerative colitis, multiple sclerosis, certain cancers and in the case of transplants.
Overall, a decrease in the NIHDI expenditure on subclass L04AB can be seen after 2018, whereas an increase can be observed in subclasses L04AA and L04AC.
(*Figure 8*).

Figure 8: NIHDI net expenditure on immunosuppressants per subclass



Subclass L04AA (selective immunosuppressants)

In public pharmacies an increase can be observed in the NIHDI net expenditure for subclass L04AA : NIHDI net expenditure in 2019 = 65.3 million euros; NIHDI net expenditure in 2020 = 74.9 million euros; NIHDI net expenditure in 2021 = 86.0 million euros.

This increase can mainly be explained by the class of janus kinase inhibitors (JAK) (+€19.8 million or +126% in 2021 compared to 2019), with reimbursement of:

- A number of new pharmaceuticals: Rinvoq® (upadacitinib, ATC L04AA44) from 1 November 2020 for the treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis, and Jyseleca® (filgotinib, ATC L04AA45) from 1 August 2021 for the treatment of rheumatoid arthritis and ulcerative colitis
- Additional reimbursed indications for the pharmaceuticals Xeljanz® (tofacitinib, ATC L04AA29), more specifically the treatment of psoriatic arthritis and ulcerative colitis and Olumiant® (baricitinib, ATC L04AA37), more specifically the treatment of atopic dermatitis.

Furthermore, an increase in NIHDI expenditure can be observed for Aubagio® (teriflunomide, ATC L04AA31) (+€1.9 million or +14.7% in 2021 compared to 2019), and for Otezla® (apremilast, ATC L04AA32) (+€0.9 million or +10.0%), due to an increase in the number of patients.

On the other hand, a decrease in NIHDI expenditure was observed for Certican® (everolimus, ATC L04AA18) (-€1.2 million or -22% in 2021 compared to 2019), and for Orencia® (abatacept, L04AA24) (-€0.5 million or -5%), due to a price reduction following savings measures relating to old medicines.

In 2016 about 26,300 patients were reimbursed for the subclass L04AA, rising to about 27,400 in 2020 and about 29,800 patients in 2021.

Subclass L04AB (tumour necrosis factor α inhibitors)

This subclass represents the largest NIHDI expenditure in public pharmacies within the L04A class, although there is a falling trend in this net NIHDI expenditure for this subclass L04AB: in 2019 this amounted to around €186.0 million, in 2020 around €179.8 million and in 2021 around €173.8 million.
This drop is due to the introduction of biosimilars and the resulting price reduction in the context of the 'biological medicines' measure. In addition, there is a growing share of biosimilars used compared to the original pharmaceuticals: in 2020, the percentage of biosimilars amounted to around 14%, increasing to 21% in 2021. Biosimilars are cheaper than the original pharmaceuticals.

The lion's share of NIHDI expenditure in ATC class L04AB in public pharmacies can be attributed to adalimumab (Humira® and biosimilars, L04AB04), followed by etanercept (Enbrel® and biosimilars, L04AB01). NIHDI expenditure for these medicines amounted to a total of €124.6 in 2021. However, NIHDI expenditure for adalimumab dropped in 2021 by €7.9 million (-8.3%) compared to 2019, and for etanercept by €7.9 million (-17.5%) compared to 2019.

On the other hand, NIHDI expenditure in public pharmacies increased for infliximab (ATC L04AB02). Before March 2021, this molecule was only available in hospitals (IV administration), but since then, it can also be administered subcutaneously (available in public pharmacies).

Despite the drop in net NIHDI expenditure in this subclass L04AB, there is still a rising trend in the number of patients that were treated with a medicine from subclass L04AB (26,069 patients in 2020, increasing to 27,593 patients in 2021).

Subclass L04AC (interleukin inhibitors)

The NIHDI net expenditure for this subclass shows a sharply increasing trend in recent years: NIHDI net expenditure in 2019 = 109.4 million euros; NIHDI net expenditure in 2020 = 134,7 million euros; NIHDI net expenditure in 2021 = 159.5 million euros.

This increase can be explained by:

- Additional indications becoming reimbursable for
    - Stelara® (ustekinumab, ATC L04AC05), more specifically the treatment of ulcerative colitis (+€13.2 million/+30% in 2021 compared to 2019)
    - Tremfya® (guselkumab, ATC L04AC16), more specifically the treatment of psoriatic artritis
    - Taltz® (ixekizumab, ATC L04AC13), more specifically the treatment of psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis (+€5.7 million/+63.7% in 2021 compared to 2019)
    - RoActemra® (tocilizumab, ATC L04AC07) for subcutaneous administration, more specifically the treatment of giant cell arteritis.

- An increasing use of RoActemra® (tocilizumab, ATC L04AC07) (+€2.6 million/+24.7% in 2021 compared to 2019) and Kevzara® (sarilumab, ATC L04AC14) (+€1.6 million/+84.3% in 2021 compared to 2019). These are interleukin-6 inhibitors that are probably increasingly used with cytokine release syndrome induced by the infusion of Kymriah® and Yescarta®, which are CAR-T therapies.
- An increasing use of Skyrizi® (risankizumab, ATC L04AC18) for the treatment of psoriasis, for which a clear increase in the number of patients can be observed.

The growth of this subclass is also noticeable in the number of patients who were reimbursed: in 2019 about 9,900 patients were reimbursed for this subclass of medicines, rising to about 12,100 in 2020 and about 14,600 patients in 2021.

Subclass L04AD (calcineurin inhibitors)

In this subclass (primarily used in the case of transplants), a slight increase in NIHDI net expenditure can be observed: in 2019 NIHDI net expenditure amounted to about €18.9 million, in 2020 about €18.8 million and in 2021 about €17.7 million.

The reduction in net NIHDI expenditure in 2021 can be explained by the price reduction in the context of the 'old medicines' measure.

The number of patients who were reimbursed in this subclass also shows a slightly increasing trend, from about 16,600 patients in 2019 to about 16,900 patients in 2021.

Subclass L04AX (other immunosuppressants)

In 2019, NIHDI expenditure in this subclass amounted to about €28.4 million, in 2020 about €25.3 million and in 2021 about €26.9 million.

The number of patients who were reimbursed in this subclass shows an increasing trend from about 69,700 patients in 2019 to about 72,300 patients in 2021 (mainly due to an increasing use of lenalidomide and pomalidomide in the treatment of multiple myeloma).

B) Hospitals

1) General

Overall NIHDI expenditure for ATC class L04A showed a rising trend in 2021 compared to 2020 and 2019 in hospitals (+€58,350,449/+15.7% compared to 2019 and +€22,794,878 /+5.6% compared to 2020), to a total of €429,785,679, which also translates into a further increase in DDD data (+€1,745,163/+17.0% compared to 2019 and +€951,816/+8.6% compared to 2020), with a total of 11,996,348 DDD. There was a slight decrease in €/DDD from 36.2 €/DDD in 2019 to 35.8 €/DDD in 2021.

The growth in NIHDI expenditure in hospitals can mainly be explained by the extension of reimbursability of medicines that were already reimbursable, and increasing use within these new therapeutic indications (e.g. ustekinumab-Stelara®, vedolizumab-Entyvio®, lenalidomide-Revlimid®, canakinumab-Ilaris®), with the cost of treatment per patient also steadily rising in comparison with earlier therapeutic options.
For example, the increase in the use of 7 molecules (vedolizumab, ocrelizumab, ustekinumab, canakinumab, lenalidomide, pirfenidone and pomalidomide) constitutes additional expenditure for the health insurance fund amounting to +€77,007,838 (+20.7%) compared to 2019.

On the other hand, there are also products for which there was a decrease, such as tocilizumab-RoActemra® administered intravenously (mainly due to stock problems), eculizumab-Soliris® (price reduction by law), natalizumab-Tysabri® (price reduction by law in the context of the 'old medicines' measure) and alemtuzumab-Lemtrada® (shift to other options for relapsing remitting multiple sclerosis (RRMS)) and fingolimod-Gilenya® (price reduction by law and generics). Overall, reimbursement for these molecules by the health insurance fund amounted to €17,724,083 less than in 2019 (-4.8%).

Figure 9: evolution of NIHDI net annual expenditure and number of DDDs (hospitals (all patients) 2012 – 2021) for ATC class L04A immunosuppressants

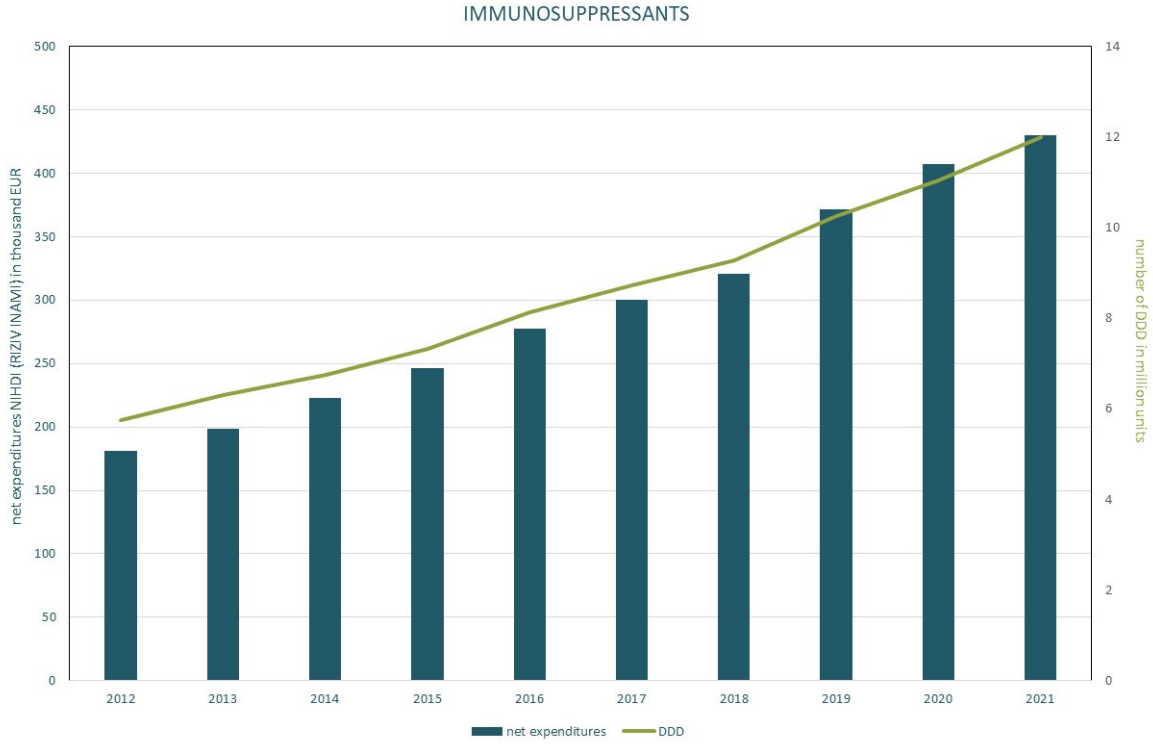


Figure 10: evolution of NIHDI net quarterly expenditure (hospitals (all patients) 2017 – 2021) for ATC class L04A immunosuppressants

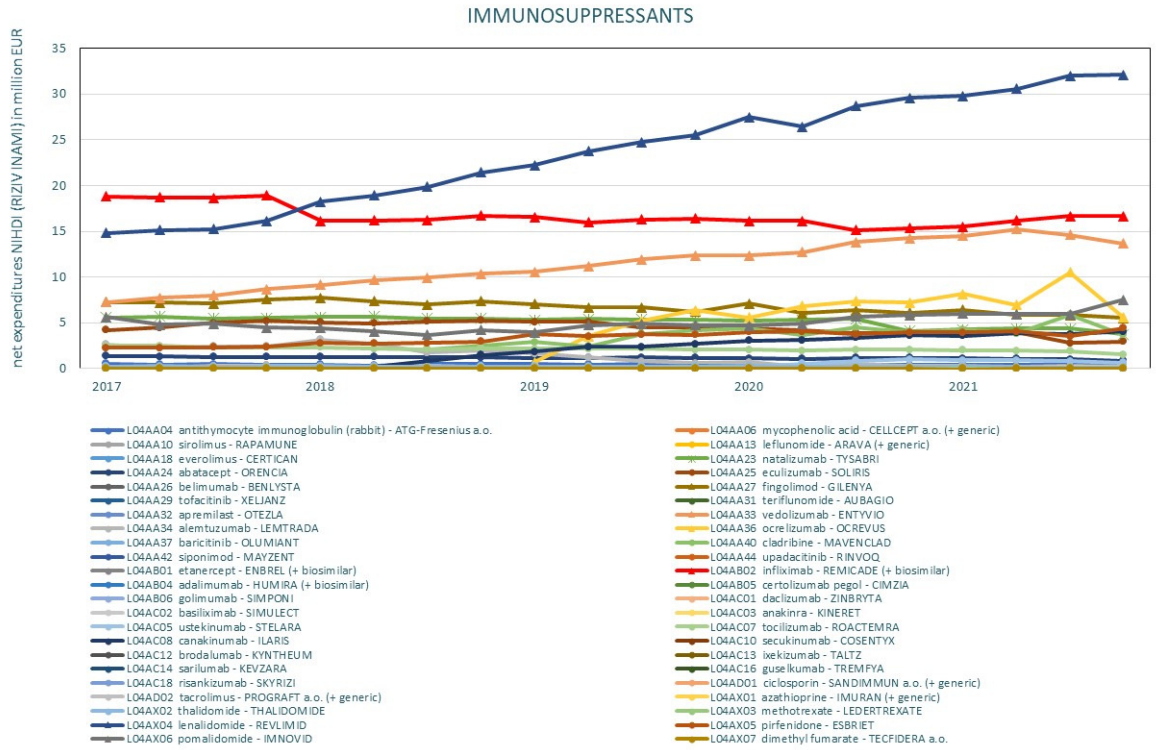


Figure 11: evolution of number of DDDs per quarter (hospitals (all patients) 2017-2021) for ATC class L04 immunosuppressants

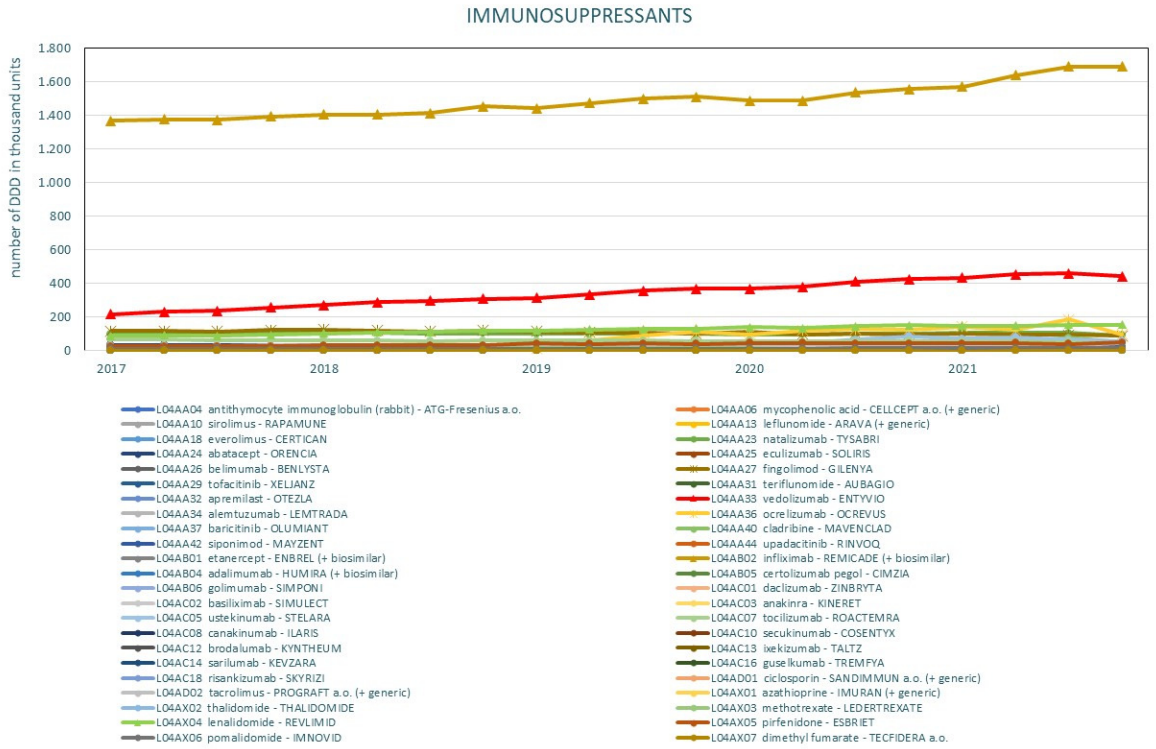


Figure 10 shows that lenalomide (Revlimid®, ATC L04AX04) accounts for the lion's share of NIHDI expenditure in ATC class L04A in hospitals, namely €124,557,475 (29%!). Moreover, NIHDI expenditure for this medicine used in the treatment of multiple myeloma (MM) and myelodysplastic syndrome (MDS) is still increasing. The registration of generics and the price reduction by law in 2022 will provide some temporary improvement in this.

The second most important molecule where expenditure in hospitals is concerned, is infliximab (Remicade® and biosimilars, ATC L04AB02) (intravenous administration), with a total of €65,032,486 (15.1%). However, NIHDI expenditure for this molecule remains stable (reimbursable for Crohn's disease, ulcerative colitis, rheumatoid arthritis, psoriasis, psoriatic arthritis, etc.)

The third most important pharmaceutical is Entyvio® (vedolizumab, ATC L04AA33), with a total of €58,082,049 (13.5%), for which a rising trend is observed (reimbursable for Crohn's disease and ulcerative colitis

On the other hand, when we look at the number of DDDs, the data show that infliximab accounts for the largest number of DDDs in hospitals, followed by vedolizumab (ATC L04AA33).

2) Analysis per subclass

Class L04A can be subdivided into various subclasses:

- L04AA (selective immunosuppressants),
- L04AB (tumour necrosis factor α inhibitors),
- L04AC (interleukin inhibitors),
- L04AD (calcineurin inhibitors),
- L04AX (other immunosuppressants).

These drugs are primarily used for the treatment of, inter alia, rheumatic conditions, psoriasis, Crohn's disease, ulcerative colitis, multiple sclerosis, certain cancers, specific immunopathology, pulmonary fibrosis and in the case of transplants.

Overall, a steep increase can be observed in the NIHDI expenditure (*Figure 12*) :

- on subclass L04AA, from €101,695,165 in 2016 to €169,265,178 in 2021 (+€67,570,014/+66.4%), or an increase by +€14,464,234 (+9.3%) from 2019 to 2021;

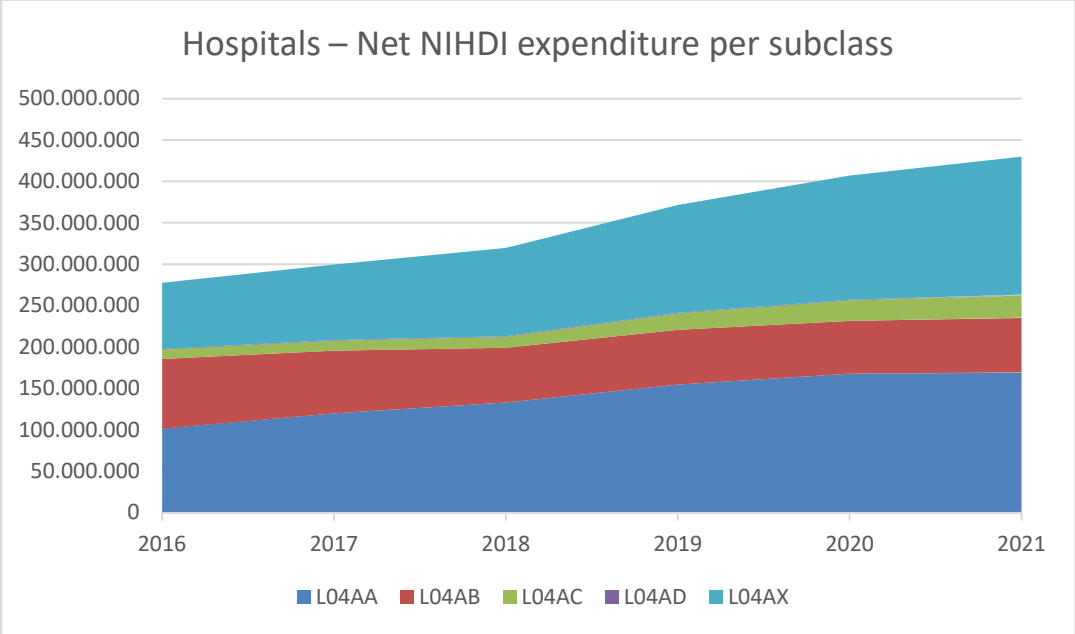
- on subclass L04AC from €10,343.926 in 2016 to €27,080,707 in 2021 (+€16,736,781/+161.8%), or an increase by +€7,560,592 (+38.7%) from 2019 to 2021;

- on subclass L04AX from €79,762,647 in 2016 to €166,698,829 in 2021 (+€86,936,181/+109.0%), or an increase by +€36,435,791 (+28.0%) from 2019 to 2021.

There has been a moderate decrease for subclass L04AD, from €740,357 in 2016 to €716,755 in 2021 (- €23,602 / -3.2%).

A steep fall can be seen in NIHDI expenditure on subclass L04AB, from €83,882,607 in 2016 to €66,022,207 in 2021 (- €17,860,399 / -21.3%).

Figure 12: NIHDI net expenditure on immunosuppressants per subclass



Subclass L04AA (selective immunosuppressants)

This subclass contains, on the one hand, oral selective immunosuppressants that are used for rheumatic disorders, multiple sclerosis or in the context of organ transplantation, which means the use of these drugs is rather limited in hospitals.
On the other hand, it also contains pharmaceuticals used in the treatment of multiple sclerosis, ulcerative colitis (UC) and Crohn's disease (CD), systemic lupus (SLE) or of paroxysmal nocturnal haemoglobinuria (PNH) and haemolytic-uraemic syndrome (aHUS).
Within subclass L04AA there has been a sharp increase in NIHDI expenditure, from €101.695.165 in 2016 to €169.265.178 in 2021 (+ €67.570.014 / +66,4%), or an increase with + €14.464.234 (+9,3%) from 2019 to 2021.

The molecules with a strongly decreasing trend of >10% compared to 2019 are:

- Mycophenolate mofetil, ATC L04AA06 (-12.8% to €288,078), anti-human T- lymphocytes obtained from rabbits (ATG), ATC L04AA04 (-12.9% to €1,741,247) which are used in the context of organ transplantation and stem cell transplantation.
- Leflunomide, ATC L04AA13 (-28.5% to €10,886) used for rheumatoid arthritis and abatacept, L04AA24 (-15.8% to €4,008,568) used for rheumatoid arthritis as well as polyarticular juvenile idiopathic arthritis (price reduction in the context of the 'old medicines' measure).
- The use of natalizumab, ATC L04AA23 (-21.8% to €16,783,423), fingolimod, ATC L04AA27 (-11.1% to €23,663,729), alemtuzumab, L04AA34 (-77.8% to €955,116) and teriflunomide, ATC L04AA31 (-12.2% to €67,427), used in the treatment of multiple sclerosis, has decreased as well. For natalizumab and alemtuzumab there were price drops in the context of the 'old medicines' measure. In addition, the potential strong immunosuppressive effect of these molecules may have played a role in the decreased use during the COVID-19 pandemic.
- As a result of the price reduction by law of eculizumab, ATC L04AA25, there is also a strong decrease in expenditure (-28.9% to €13,589,387).

The molecules with a strongly increasing trend of >10% are:

- The janus kinase inhibitors (JAK) with baricitinib, ATC L04AA37 (+375.4% to €20,630), for the treatment of rheumatoid arthritis (RA) and atopic dermatitis, and tofacitinib, ATC L04AA29 (+155.3% to €12,837), for the treatment of rheumatoid arthritis (RA) and ulcerative colitis (CU), are mainly reimbursed outside hospitals.
- Cladribine, L04AA40 (+32.2% to €17,719,741) and ocrelizumab, L04AA36 (+97.4% to €31,214,026), for the treatment of relapsing remitting multiple sclerosis (RRMS).
- Apremilast, L04AA32 (+52.9% to €33,380), an oral therapy for the treatment of psoriasis and psoriatic arthritis.
- Belimumab, L04AA26 (+50.2% to €900,929), for the treatment of systemic lupus (SLE), for which a modification was made to the reimbursement conditions.
- A sustained increase in the use of vedolizumab, L04AA33 (+26.0% to €58,082,049) for the treatment of ulcerative colitis (UC) and Crohn's disease (CD).

Subclass L04AB (tumour necrosis factor α inhibitors)

This subclass shows a steep fall in the NIHDI expenditure, from €83.882.607 in 2016 to €66.022.207 in 2021 (-21,3%), due to the introduction of biosimilars and the associated price reduction under the 'biological medicines' measure.

Infliximab, L04AB02 remains status quo (-0.3%) but still with a significant cost for health insurance of €65,032,486, which is administered intravenously and subcutaneously. On the other hand, etanercept, L004AB01, still shows a strong increase compared to 2019 (+138.9% to 147,140€), with a more limited increase for adalimumab, L04AB04 (+29.7% to 746,272€).

The TNF-α inhibitors without biosimilar products show decreases of -21.9% for certolizumab, L04AB05 (up to 10,511€) and -54.1% for golimumab, L04AB06 (up to 85,797€).

It should also be noted that, with the exception of infliximab IV (hospital only), drugs in this class are mainly reimbursed in public pharmacies (see subclass L04AB in public pharmacies).

Subclass L04AC (interleukin inhibitors)

NIHDI net expenditure on this subclass has shown a steeply increasing trend in recent years, from €10,343,926 in 2016 to €27,080,707 (+ €16,736,781 / +161.8%) in 2021.

This increase can be explained by the reimbursement of :

- A new pharmaceutical for the treatment of psoriasis in adults, risankizumab, L04AC18 (€6.035).
- Additional reimbursed indications for ustekinumab, ATC L04AC05 (€3,289,763 / +320.0%), more specifically the treatment of psoriatic artritis and ulcerative colitis.
- Anakinra, L04AC03 (€339,591 / +201.5%) for cryopyrin-associated periodic syndrome (CAPS), adult-onset Still's disease (AOSD) and systemic idiopathic juvenile arthritis (SJIA).
- A more extensive eligibility for reimbursement for cryopyrin-associated periodic syndrome (CAPS), systemic idiopathic juvenile arthritis (SJIA), familial Mediterranean fever (cr-FMF), hyperimmunoglobulin-D-syndrome (HIDS)/ mevalonate kinase deficiency (MKD) and tumour necrosis factor receptor-associated periodic syndrome (TRAPS) of canakinumab L04AC08 (€16,331,916 / +65.2%), resulting in continued increasing use.
- A new pharmaceutical for the treatment of rheumatoid arthritis (RA), sarilumab, L04AC14 (€5,120).

Molecules with decreasing trend:

- The pharmaceuticals for the treatment of psoriasis in adults ixekizumab, ATC L04AC13 (but decreasing by -22.8% compared to 2019 to €14,718) and brodalumab, ATC L04AC12 (-49.5% to €545).
- Secukinumab, ATC L04AC10 (-68.6% to €8,508), for the treatment of psoriatic arthritis and the treatment of ankylosing spondylitis.
- A slight decrease in the use of tocilizumab, L04AC07 (-14.1% to €7,379,602), mainly due to supply problems. In CAR-T treatments, tocilizumab is now also used for the prevention of cytokine storm.

Subclass L04AD (calcineurin inhibitors)

In this subclass (mainly used in relation to transplants) a slight decrease in the NIHDI net expenditure can be detected in hospitals: -6,5% in the period 2019-2021 to €716.755. Since the patients remain in hospital for only a short time after the transplant procedure, the budgetary impact is limited.

Subclass L04AX (other immunosuppressants)

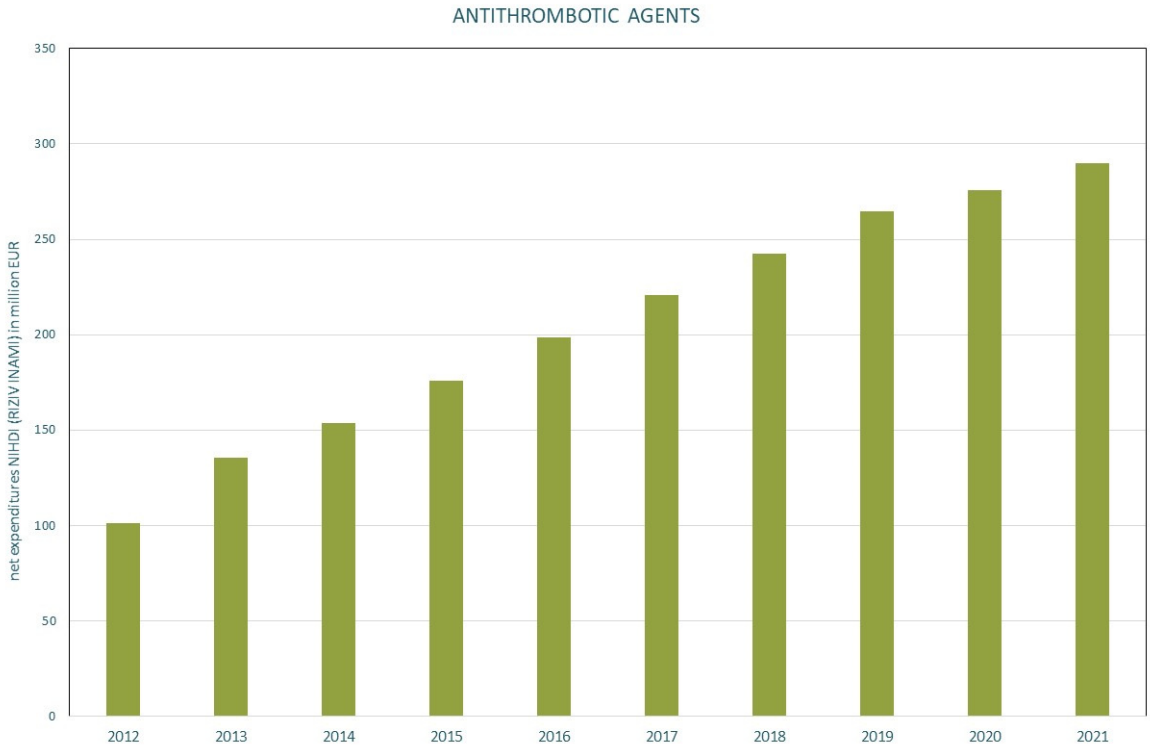
In this subclass a steep increase in NIHDI net expenditure can be detected in 2021 of +109.0% (+ €86,936,181) compared to 2016, which accounts for a total of €166,698,892 versus €79,762,647.

The increase in net NIHDI expenditure in this subclass is mainly due to, on the one hand, a strong increase versus 2019 of +29.5% for lenalidomide, ATC L04AX04 (up to €124,557,475€) for the treatment of multiple myeloma (MM), myelodysplastic syndrome (MDS) and mantle cell lymphoma (MCL), complemented by pomalidomide, ATC L04AX06 (+38.9% to €25,461,425), also in earlier treatment lines.

There is also a continued rise for pirfenidone, ATC L04AX05 (+8.2% to €15,985,856), for the treatment of idiopathic pulmonary fibrosis.

B01A – ANTITHROMBOTIC AGENTS

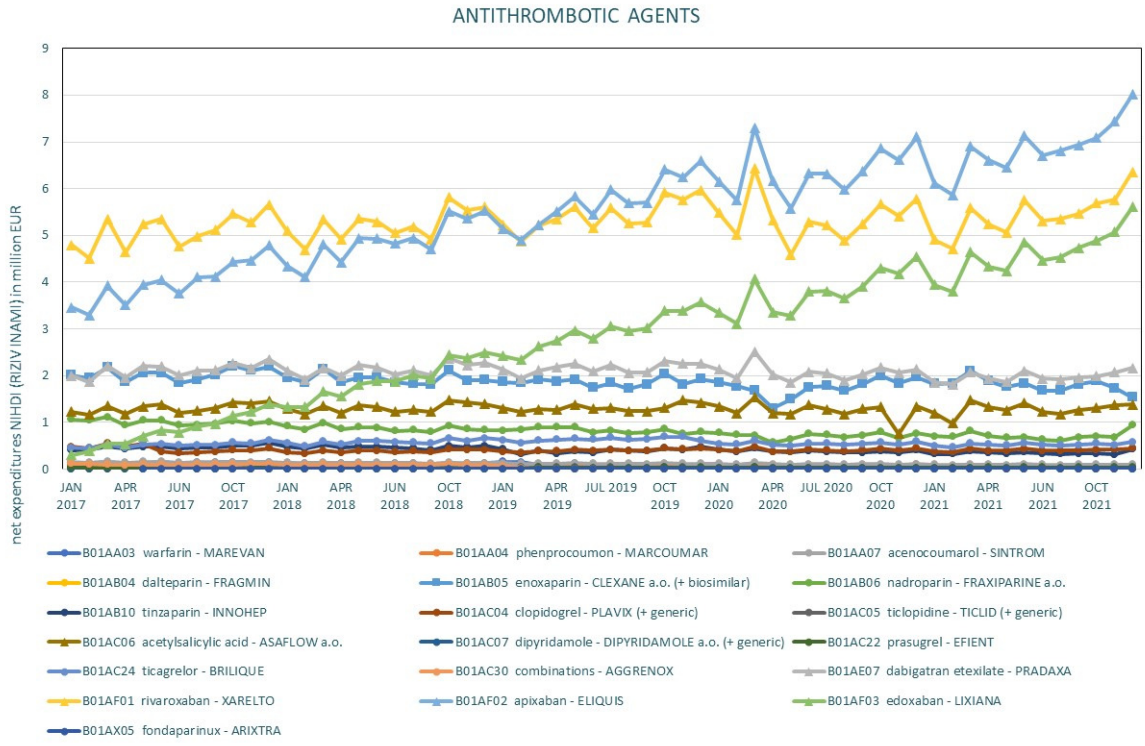
Figure 13: evolution of NIHDI net annual expenditure (public pharmacies 2012 – 2021) for ATC class B01A antithrombotic agents



Net NIHDI expenditure for antithrombotics in public pharmacies shows a steady growth. However, this growth has been less pronounced since 2019.

Antithrombotics comprise antiaggregants, anticoagulants, thrombolytics and 'others' (Cablivi® and Defitelio®).

Figure 14: evolution of NIHDI net monthly expenditure (public pharmacies 2017 – 2021) for ATC class B01A antithrombotic agents



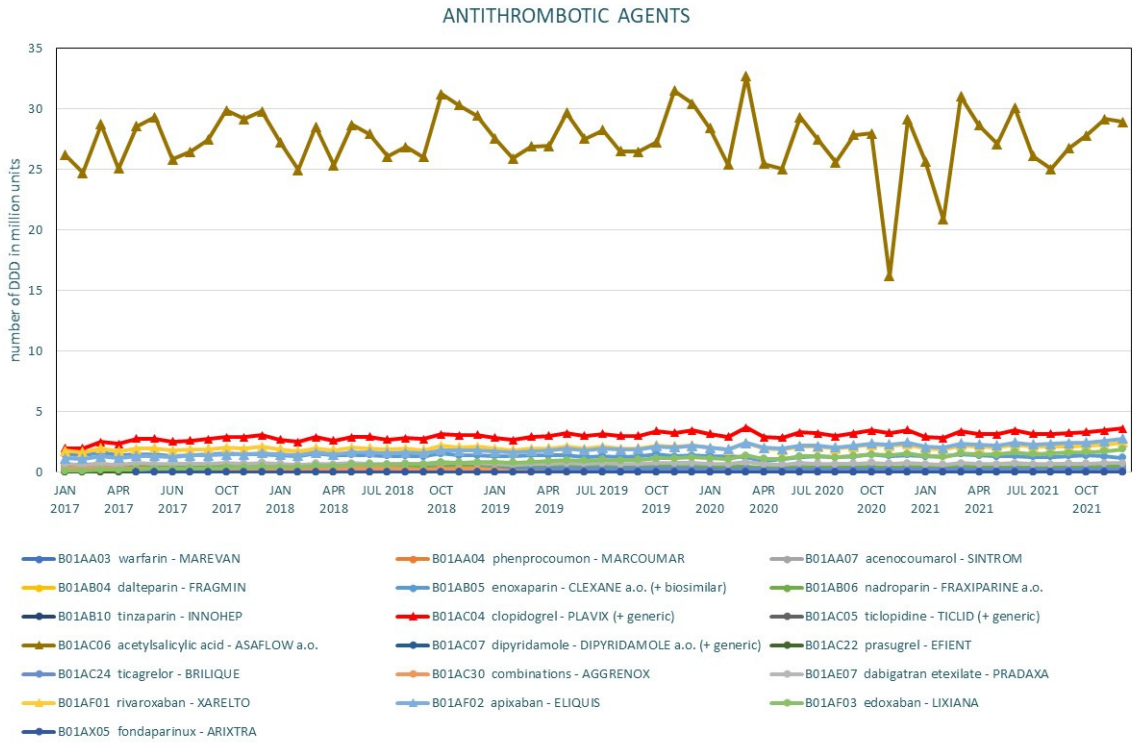
The rising cost for antithrombotics is dominated by three direct oral anticoagulants (DOACs): Xarelto®, Eliquis® and Lixiana® (factor Xa inhibitors). The cost for Pradaxa® (direct thrombin inhibitor) remains stable.

It needs to be noted here that most indications of the four DOACs are reimbursed via an agreement between the pharmaceutical company and the Institute. The figures shown here are the figures based on the list price. The actual costs for the NIHDI are confidential and are calculated on the basis of the retrocessions stipulated by the agreement.

Expenditure for the other antithrombotics remains stable.

At the start of the COVID-19 crisis, in the spring of 2020, there was a notable peak in NIHDI expenditure in public pharmacies for most antithrombotics.

Figure 15: *evolution of the number of DDDs per month (public pharmacies 2017 – 2021) for ATC class B01A antithrombotic* agents



The volumes, expressed in million DDDs, are clearly dominated by Asaflow®. However, due to the low price of Asaflow®, these volumes only result in minimal NIHDI expenditure compared to the more expensive DOACs. For the other antithrombotics, the scale (number of DDDs in million units) is so small that the increase in the volumes of DOACs is not noticeable. The evolution in the volume of the molecules other than acetylsalicylic acid within antithrombotics is shown more clearly in the figure below (*Figure 16*). Besides an increasing use of DOACs, we can see a decrease in the use of the cheap vitamin K antagonists (Marcoumar®, Sintrom® and Marevan®).

Figure 16: evolution of the number of DDDs per month (public pharmacies 2017 – 2021) for ATC class B01A antithrombotic agents *excluding acetylsalicylic acid (B01AC06)*

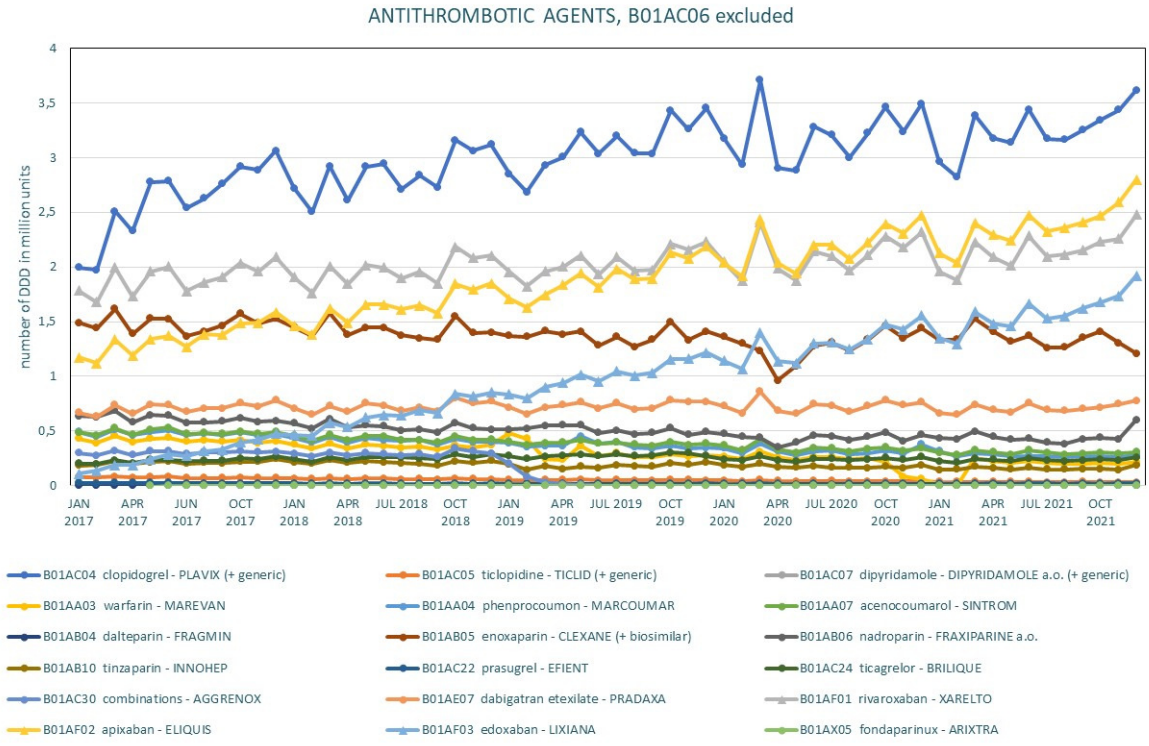
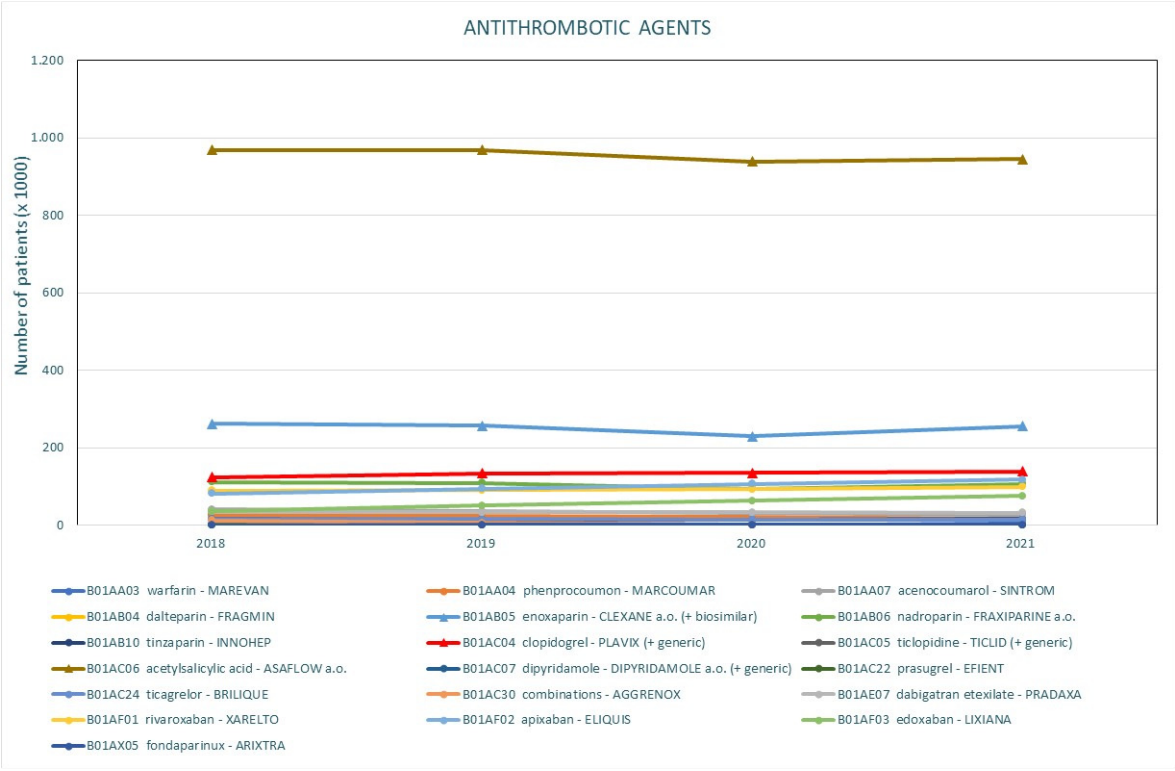
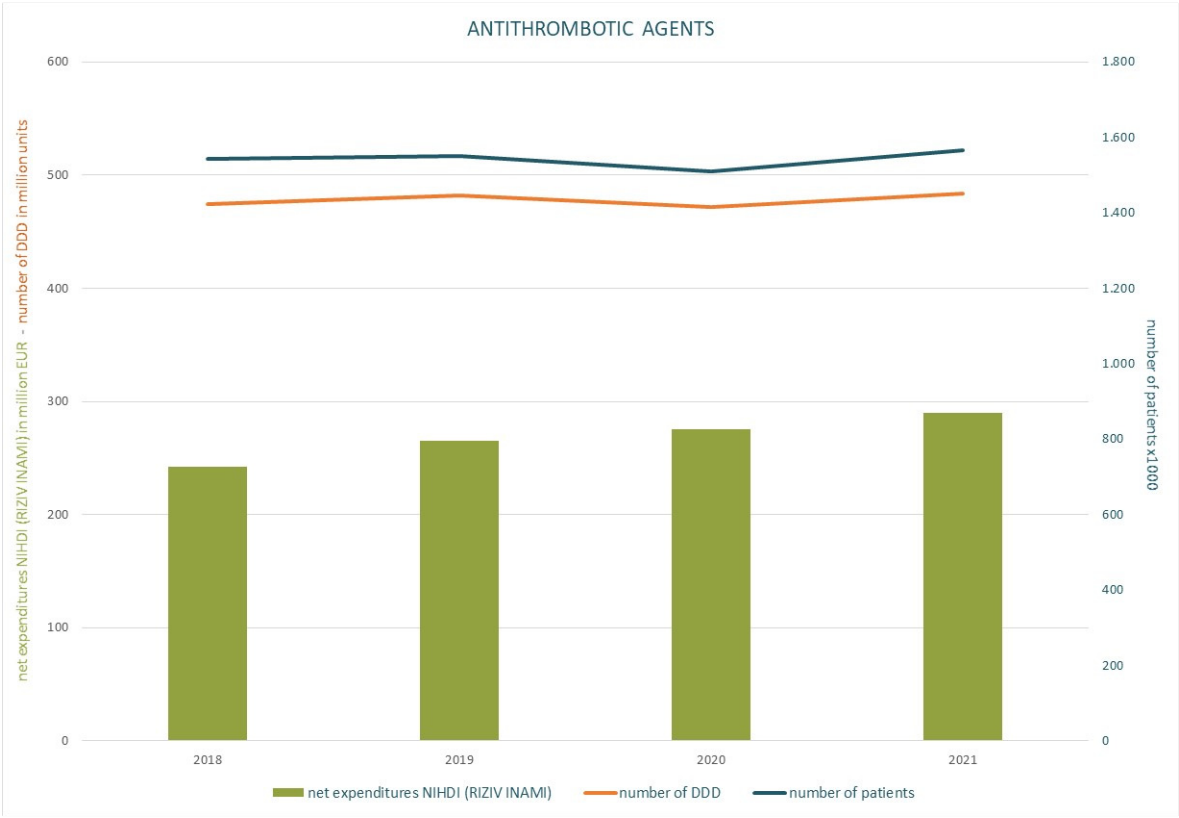


Figure 17 : evolution of the number of patients per month (public pharmacies 2018 – 2021) for ATC class B01A antithrombotic agents



Nearly a million Belgians are being treated with acetylsalicylic acid (Asaflow® and others), the most used molecule among antithrombotics. The second largest group of patients, around 250,000, is treated with Clexane®. For most medicines, use is fairly stable. An increasing trend is mainly observed for Lixiana® and Eliquis®.

Figure 18: evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2018 – 2021) for ATC class B01A antithrombotic agents



Conclusion: NIHDI expenditure in public pharmacies is rising, and amounts to nearly €300 million. The driver of this expenditure is DOACs. The increase in expenditure for DOACs may be due to the ageing of the population and consequently a higher incidence of atrial fibrillation, an extension of the number of new indications with chronic use, and a decreasing use of the cheap vitamin K antagonists (Marcoumar®, Sintrom® and Marevan®).

A10 – DRUGS USED IN DIABETES

Figure 19 shows the NIHDI expenditure in 2012-2021 for all glucose-lowering medicines for the treatment of diabetes mellitus. The data is subdivided into two subclasses: insulins and analogues, and others.

Figure 19: evolution of NIHDI net annual expenditure (public pharmacies 2012 - 2021) for ATC class A10 drugs used in diabetes

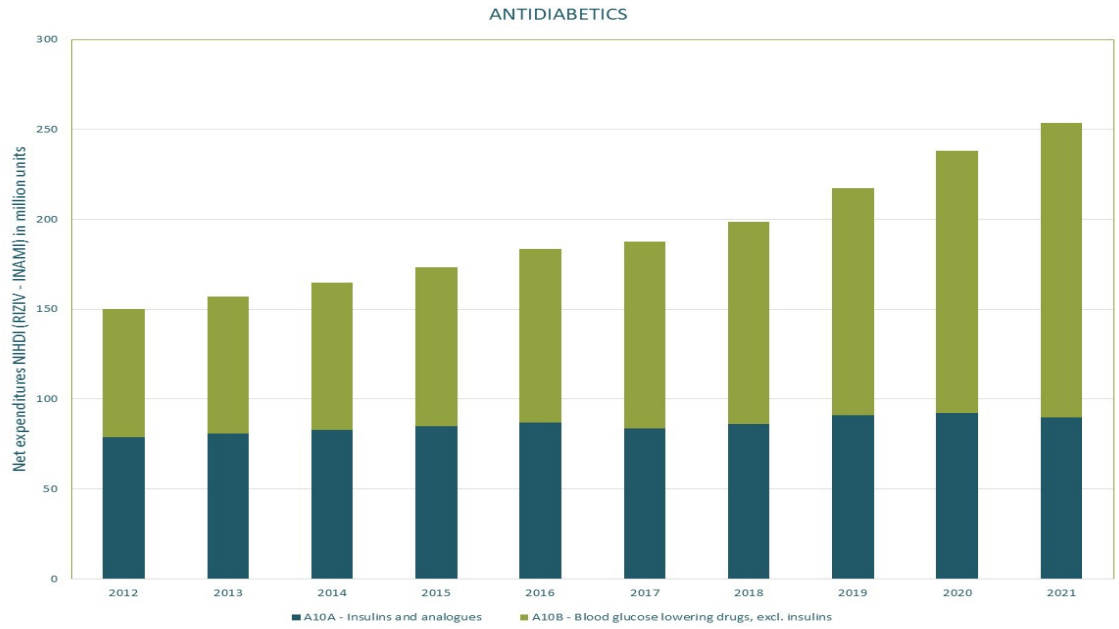
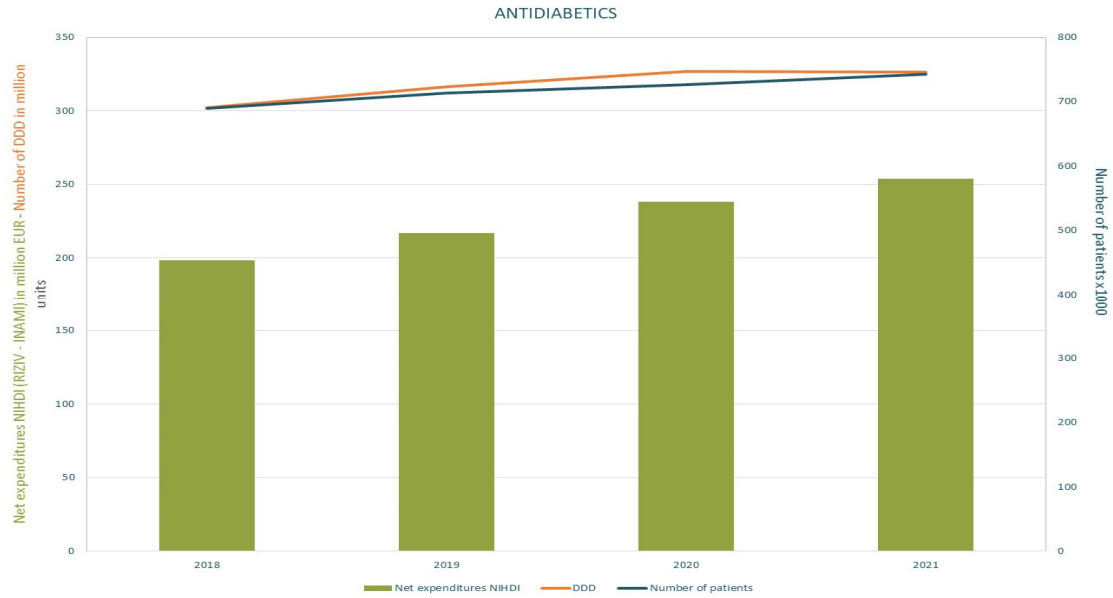


Figure 20: evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2018 – 2021) for ATC class A10 drugs used in diabetes



In the years 2018-2021 the number of diabetes patients that are treated with pharmaceuticals increased, as did the volume of medicines, expressed in DDDs, and the corresponding costs.

There are two reasons why the volume has increased:

1° the growing number of patients

2° the extension of the reimbursement criteria from 1 July 2019.

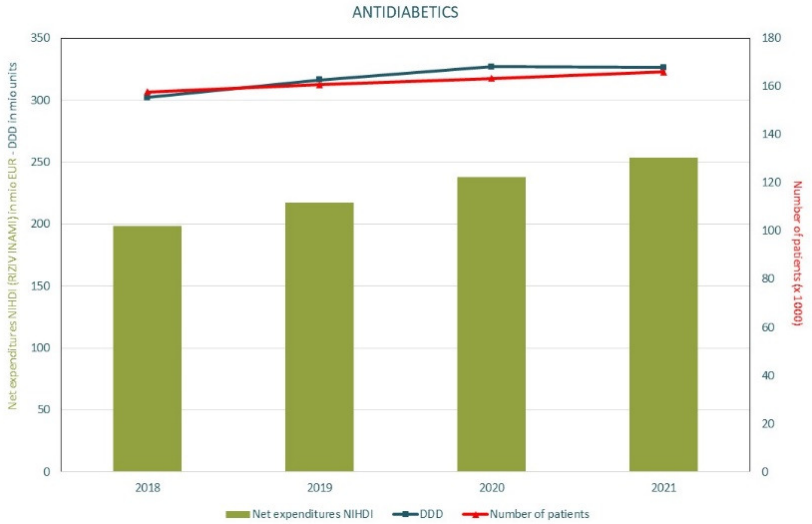
The evolution in 2020-2021 no longer shows this significant increase, with volumes expressed in DDDs even levelling out.

Figure 21: evolution of NIHDI net annual expenditure (public pharmacies 2012 – 2021) for ATC class A10A insulins and analogues

After a decrease in expenditure in 2017, presumably as a result of the advent of less expensive alternatives for insulin glargine and insulin aspart, we can see in this graph that expenditure grew again in the years 2018-2020. In 2021, expenditure decreased once more.

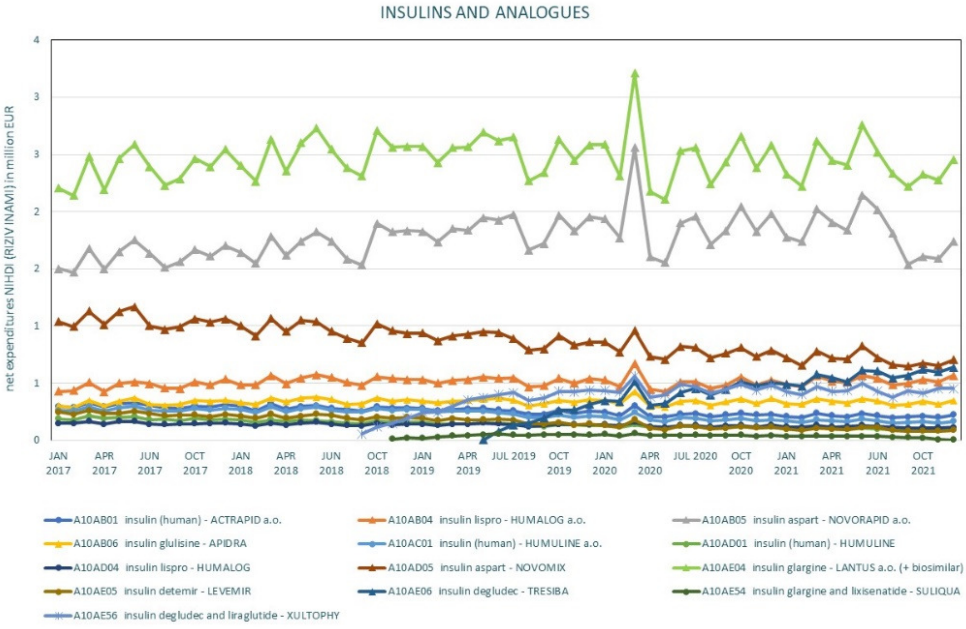
On 1 April 2019, basal insulin Tresiba® with a double dose (200 IE/ml) was included in the reimbursement list, and one month later, on 1 May 2019, basal insulin Tresiba® 100 IE/ml with the normal dose of 100 IE/ml. On 1 July 2019, the medicines based on insulin glargine (Lantus®, Abasaglar®, Toujeo®) and on insulin degludec (Tresiba®) of Chapter IV were moved to Chapter I, with the condition of a 2.2% price reduction. As a result of this change, reimbursement of this basal insulin is no longer subject to its use in a later line of treatment, and its first-line use is reimbursed. This led to an increase in expenditure in 2019 and 2020, despite the imposed price reduction of 2.2%. In 2021, expenditure for insulin decreased for the first time since 2017.

Figure 22: evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2018 – 2021) for ATC class A10A insulins and analogues



As mentioned in previous MORSE reports, the number of patients that are treated with insulin grows continuously year after year. 170,000 patients are treated with insulin in Belgium. In 2021, the volume expressed in DDDs stabilised, despite the increasing number of patients that use insulin. This suggests that the share of patients that use small amounts of insulin is now representative in the figures.

Figure 23: evolution of NIHDI net monthly expenditure (public pharmacies 2017 – 2021) for ATC class A10A insulins and analogues

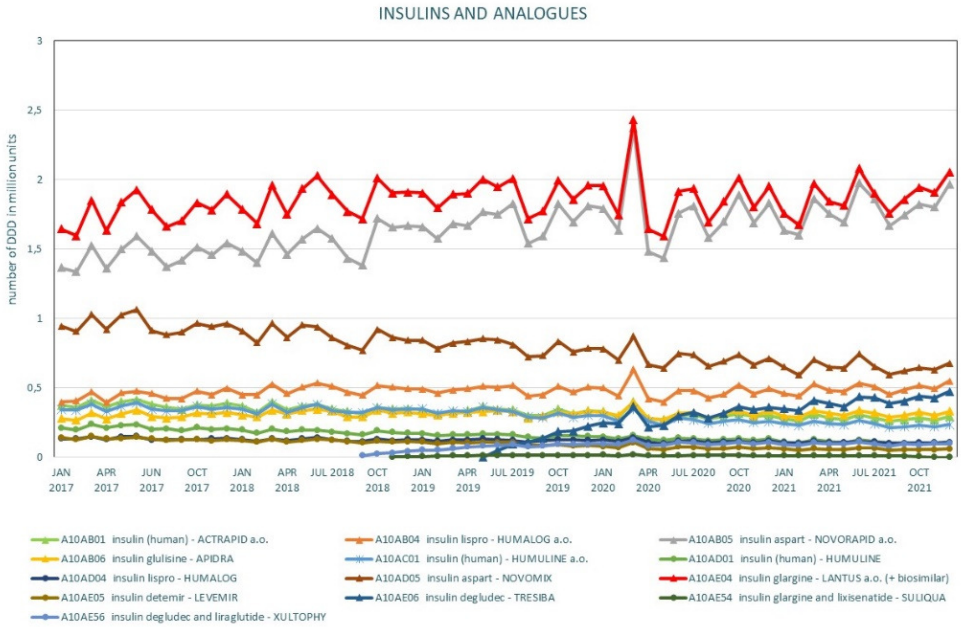


In the class of insulins and insulin analogues, expenditure for insulin degludec, the newest basal insulin, is rising. Expenditure for insulin glargine, which has been the most used basal insulin for years, has not decreased after the protection of the patent of Lantus® and the advent of biosimilars. In this context, reference must be made to the advent of the successor of Lantus®: Toujeo®, an original medicine with triple concentration. This medicine is conquering the market of insulin glargine.

For short-acting insulin, insulin aspart, an upward trend can be observed.

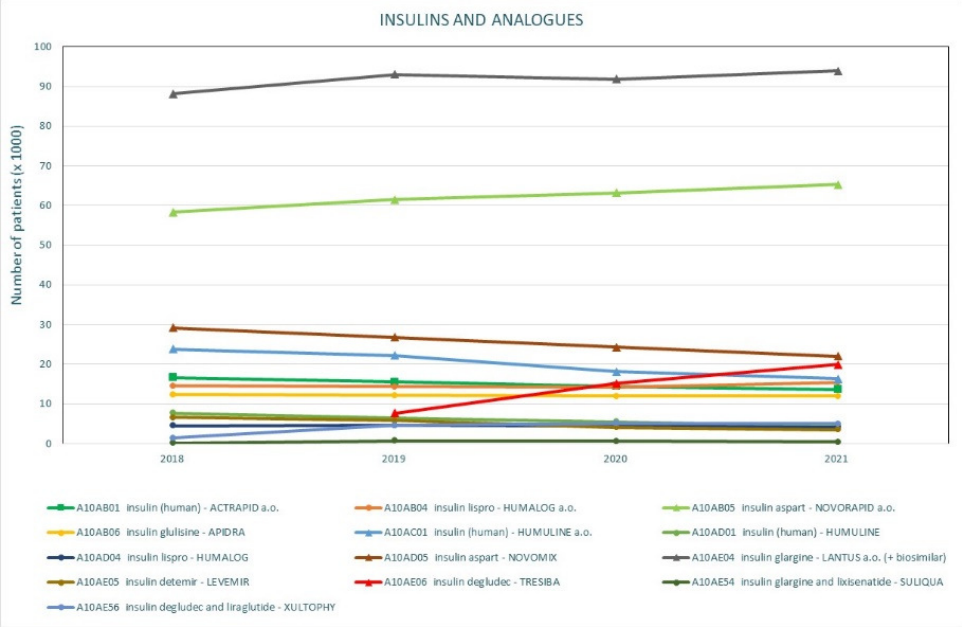
Monthly expenditure for pre-mixed insulins has decreased, a trend that can also be observed on an annual basis.

Figure 24: evolution of number of DDDs per month (public pharmacies 2017 – 2021) for ATC class A10A insulins and analogues



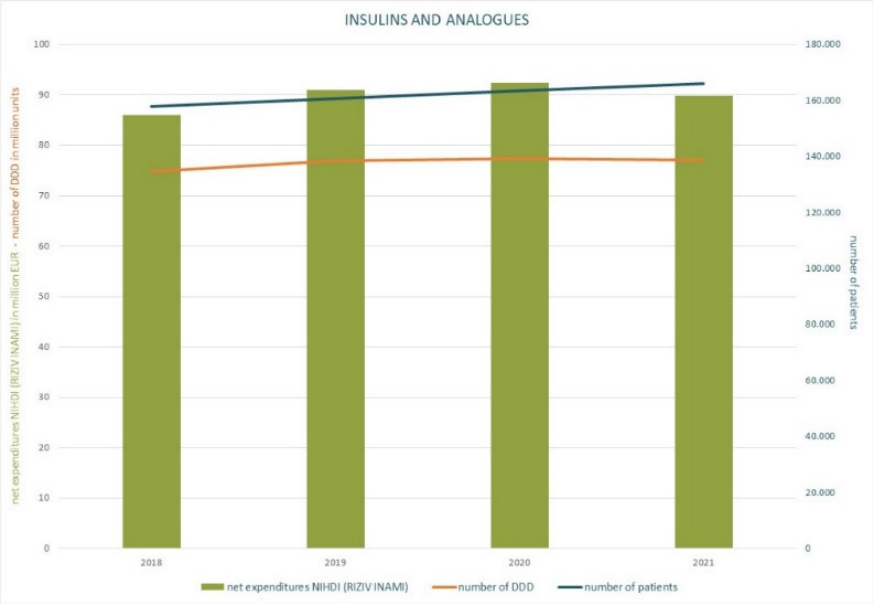
The use of insulin expressed in DDDs shows the following trends: an increase in the basal insulin glargine (mainly Toujeo®) and insulin degludec (Tresiba®). A similar increase can be observed for short-acting insulin, insulin aspart. This is used more in a basal bolus regimen and also in insulin pumps. This is parallel to a decreasing trend for the pre-mixed insulin Novomix®.

Figure 25: evolution of number of patients per year (public pharmacies 2018 – 2021) for ATC class A10A insulins and analogues



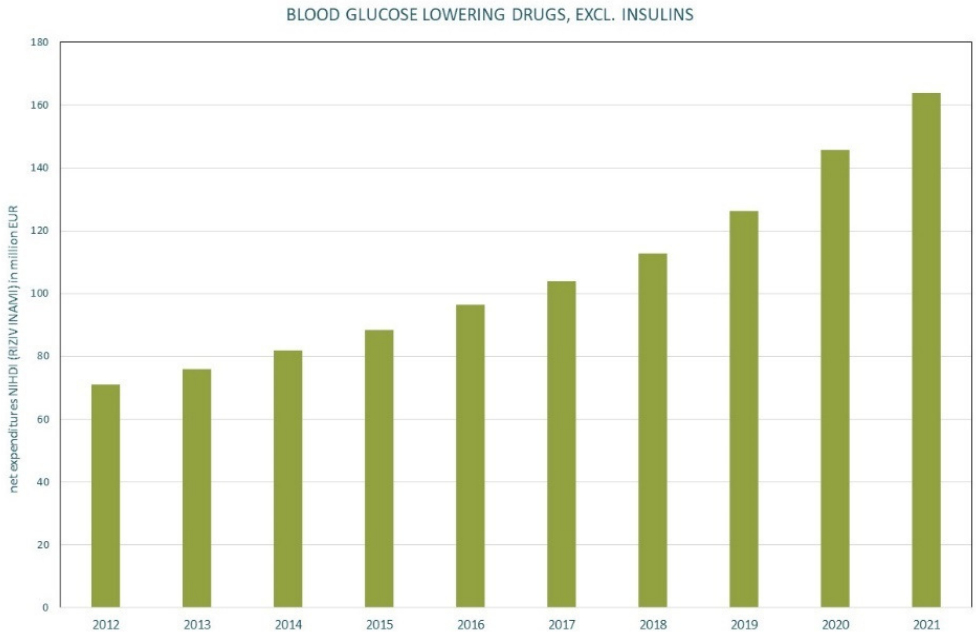
That decrease is probably related to the reimbursement since 2016 of the new pharmaceuticals Tresiba® (insulin degludec), Suliqua® (mix of insulin glargine and an incretin mimetic) and Xultophy® (mix of insulin degludec and an incretin mimetic), the use of which seems to be growing. The number of patients that are being treated with these new pharmaceuticals has risen since they were put on the market.

Figure 26: evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2018 – 2021) for ATC class A10A insulins and analogues



A10B – BLOOD GLUCOSE LOWERING DRUGS, EXCLUDING INSULINS

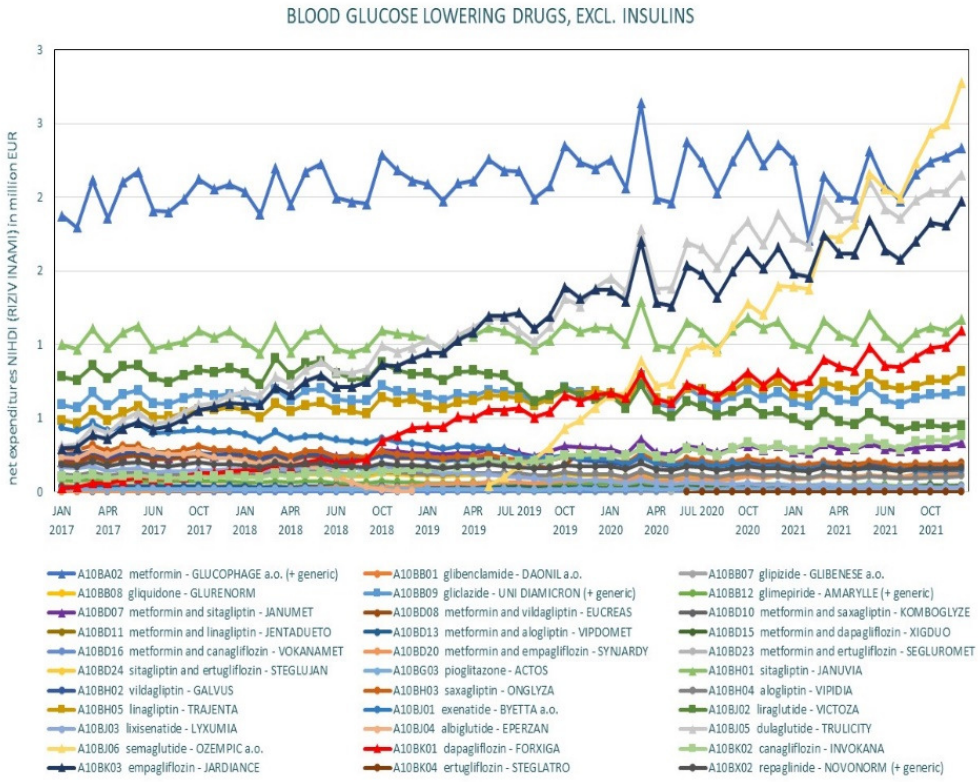
Figure 27: evolution of NIHDI net annual expenditure (public pharmacies 2012 – 2021) for ATC class A10B blood glucose lowering drugs, excluding insulins



Expenditure for antidiabetics other than insulin has risen significantly in 10 years, almost tripling. As is shown in the graphs below, this phenomenon is explained by a greater use of the two most expensive classes: the class of incretin mimetics and the class of gliflozins, whose use goes beyond their hypoglycemic activity, acting as a diuretic that is effective for respectively heart failure and renal insufficiency.

We note that among all antidiabetics other than insulin, only the class of gliflozins is reimbursed via an agreement between the manufacturer and the NIHDI. This means that the real net expenditure is lower than that shown in the graph.

Figure 28: evolution of NIHDI net monthly expenditure (public pharmacies 2017 – 20121) for ATC class A10B blood glucose lowering drugs, excluding insulins



The graph above clearly shows the fast growth in expenditure for medicines based on gliflozins (Forxiga® & Jardiance®). This growth is in part explained by the reimbursement of new indications for those pharmaceuticals (renal insufficiency and heart failure). The impact of the group-based revision of 'diabetes' of 2019, with a price reduction of 10% for incretin mimetics, is not visible because it is tempered by a greater use caused by the group-based revision of 1 July 2019, which relaxed the reimbursement criteria. Expenditure for those pharmaceuticals remains stable, with the exception of Ozempic® and Trulicity®. This is probably due to a very fast and massive use of Ozempic® (and to a lesser extent of Trulicity®) because of their supposed positive effects on the control of obesity associated with type 2 diabetes. For example, the use of Ozempic® has tripled since 2020.

Figure 29: evolution of number of DDDs per month (public pharmacies 2017 – 2021) for ATC class A10B blood glucose lowering drugs, excluding insulins

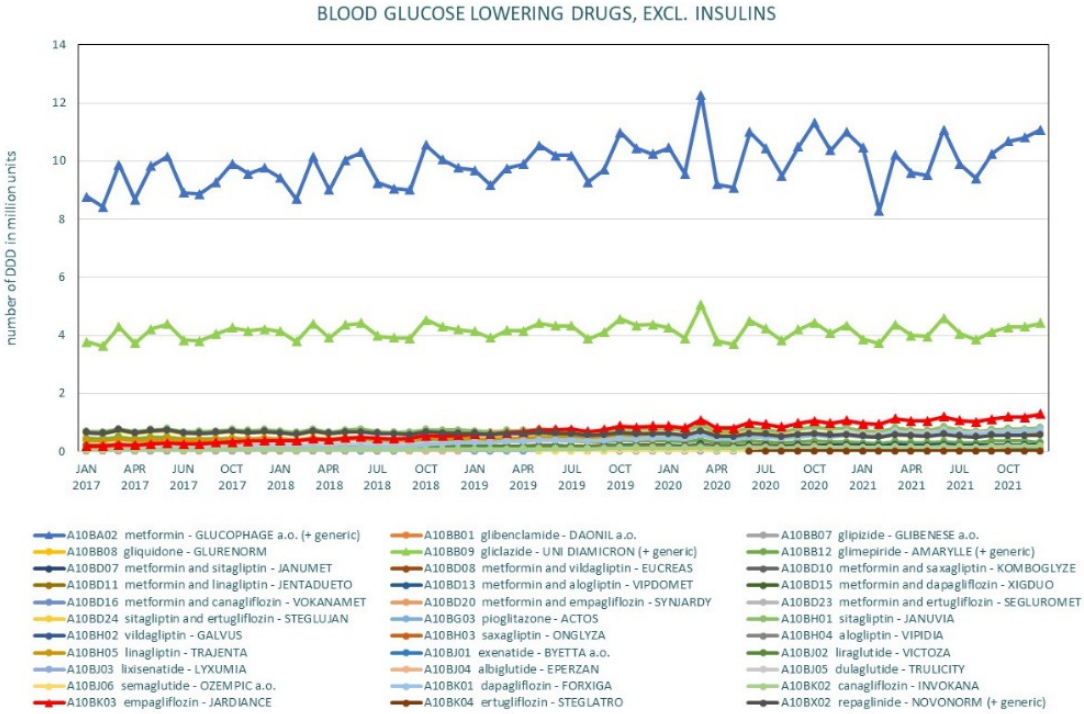


Figure 30: evolution of number of patients per year (public pharmacies 2018 – 2021) for ATC class A10B blood glucose lowering drugs, excluding insulins

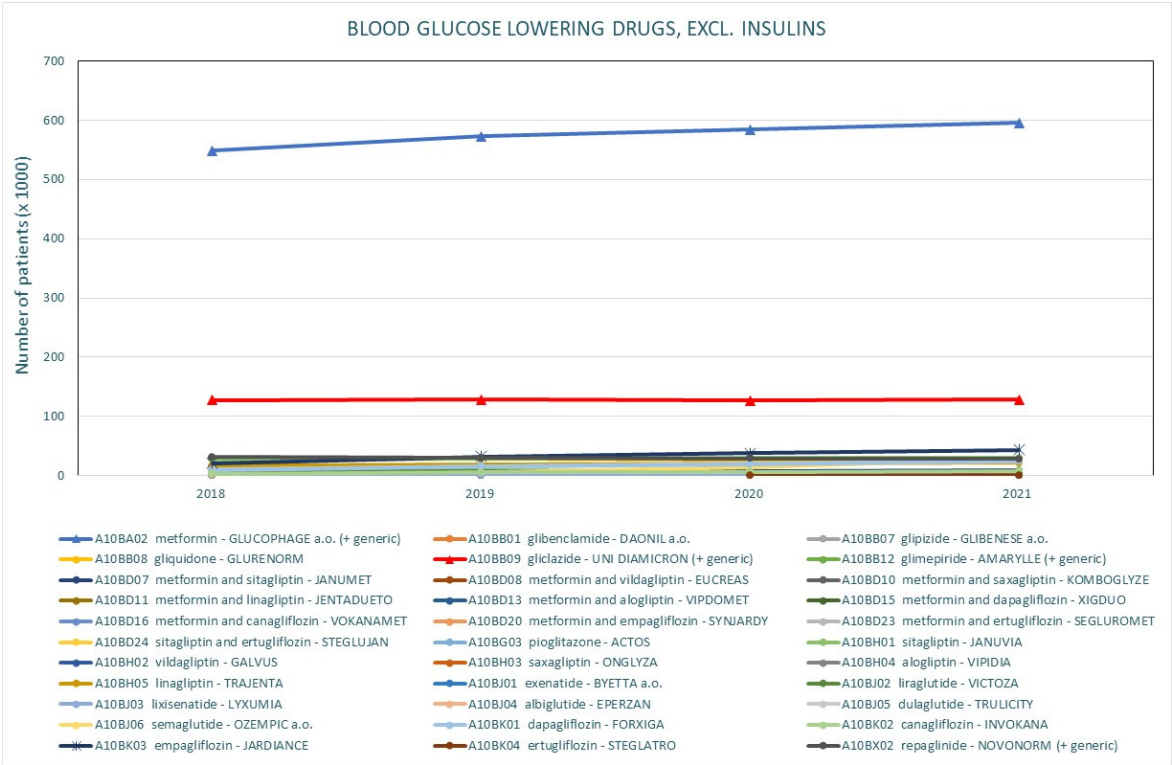
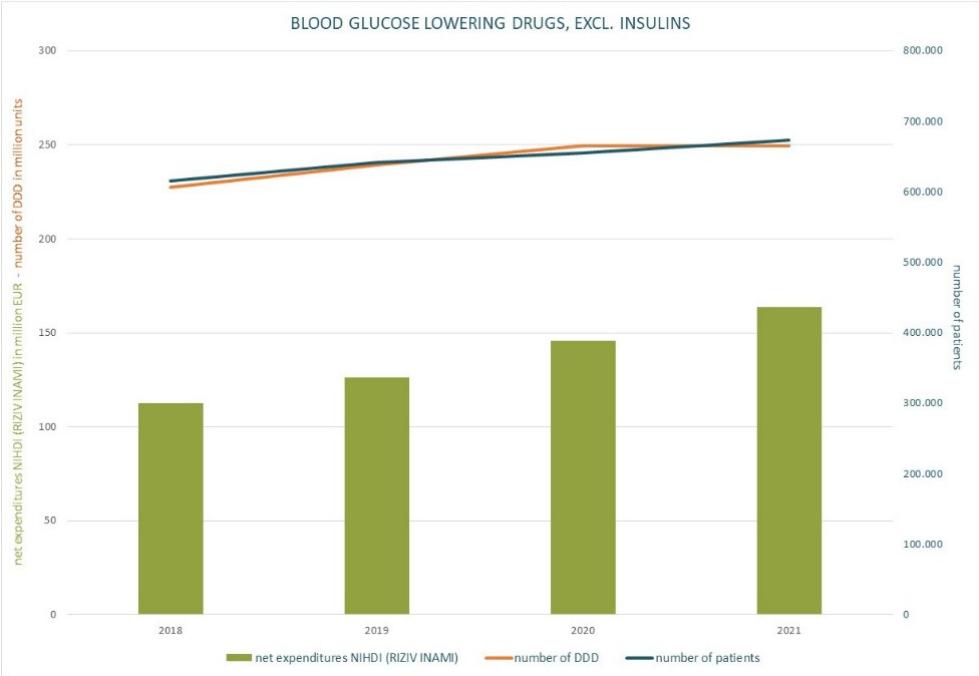


Figure 29 and *Figure 30* show that metformin remains the most used molecule, with more than 572,000 patients per year. The class of sulfonylurea derivates comes next, with approximately 165,000 patients per year, a reasonably stable figure for the past 10 years. The growth of pharmaceuticals based on gliflozins is perhaps less clearly visible here, but nevertheless involves approximately 50,000 patients per year. The reimbursement of the new indications for Jardiance® and Forxiga® (renal insufficiency and heart failure) is likely to increase the use of these pharmaceuticals even further. In other words, the last two graphs show that the significant expenditure for gliflozins today corresponds to a minority of treated patients.

Figure 31: *evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2018 – 2021) for ATC class A10B blood glucose lowering drugs, excluding insulins*



In summary, the increase in expenditure for antidiabetics other than insulin is explained by a growing number of diabetes patients that are treated with the two most expensive classes: incretin mimetics and gliflozins. In addition, gliflozins have recently been included in the reimbursement list for two indications apart from diabetes mellitus: heart failure and renal insufficiency (reimbursement category B instead of category A for diabetes patients).

The reimbursement of the new indications for gliflozins and the continued use of Ozempic® will maintain this increase in expenditure over the coming years.

R03 – DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES

GENERAL

BCFI :

For asthma and chronic obstructive pulmonary disease (COPD), the following are primarily used:

- β2-mimetics (syn. β2-agonists) short-acting or long-acting β2-mimetics
- anticholinergics (syn. parasympatholytic drugs or muscarinic receptor antagonists) short-acting or long-acting via inhalation (short/long-acting muscarinic agonists: SAMA and LAMA)
- corticosteroids (*inhaled corticosteroids: ICS*)

Limited place for:

- leukotriene receptor antagonists (only with asthma)
- theophylline
- the monoclonal antibodies used for asthma.

The GINA guidelines 2022 propose the following treatments for asthma:

The severity of asthma, the therapeutic regimen and the measure of therapeutic control in adolescents (≥12 years old) and adults is usually catalogued in 3 groups (mild, moderate and severe). The aim of an asthma treatment is to obtain good symptom control (symptoms during the day, waking up because of symptoms, SABA use, reduction of physical activity) and to minimise future exacerbations and limit adverse effects of the treatment (GINA, 2022).

Mild asthma: well-controlled asthma with step 1 or step 2 treatment, i.e.

step 1: symptomatic medication according to need (in case of complaints low dose of ICS and SABA) or low-intensity control medication (ICS and SABA are used).

step 2: daily low dose of ICS or daily leukotriene receptor antagonist (LTRA) or low dose of ICS+SABA according to need. HDM-SLIT may be added.

Moderate asthma: well-controlled asthma with step 3 treatment, i.e.

step 3: low dose of ICS-SABA or low dose of ICS-long-acting β2-agonists (LABA) or medium dose of ICS or add LTRA or HDM-SLIT

Severe asthma – controlled: asthma that requires step 4 or step 5 treatment, i.e.

step 4: medium dose of ICS+SABA or medium/high dose of ICS-LABA maintenance + rescue SABA or higher dose of ICS-LABA or add long-acting tiotropium (LAMA) or switch to higher dose of ICS. SABA according to need.

step 5: add LAMA, determine asthma phenotype, high dose of ICS+SABA or ICS+LABA, add low dose of oral corticosteroids (OCS) or LTRA or azithromycin in adults.

Severe asthma – uncontrolled: difficult to control asthma despite step 4 or step 5 therapy.

- add anti-IgE (omalizumab) in case of severe allergic asthma (IgE)
- add anti-IL-5/anti-IL5R (mepolizumab, benralizumab, reslizumab) for severe eosinophilic asthma
- add anti-IL4R (dupilumab) for severe eosinophilic/type 2 asthma
- add anti-TSLP (tezepelumab) for severe asthma

The GOLD guidelines 2022 propose the following treatments for COPD:

These guidelines for the treatment of COPD divide patients into 4 categories (A, B, C and D) based on the risk of exacerbations and the severity of the symptoms (by means of mMRC and CAT score), subdivided further into degrees 1-4 based on FEV1 percent predicted. The initial treatment for each group is outlined below:

Group A: 0-1 exacerbations in the past year, mMRC 0-1 and CAT score < 10.
A bronchodilator for inhalation will be chosen as initial treatment.

Group B: 0-1 exacerbations in the past year, mMRC ≥ 2 and CAT score ≥ 10.
A long-acting bronchodilator (anticholinergic or beta-agonist) for inhalation will be chosen as initial treatment.

Group C: ≥ 2 exacerbations or ≥ 1 leading to hospitalisation in the past year, mMRC 0-1 and CAT score < 10.
A long-acting anticholinergic for inhalation will be chosen as initial treatment.

Group D: Group C: ≥ 2 exacerbations or ≥ 1 leading to hospitalisation in the past year, mMRC ≥ 2 and CAT score ≥ 10.

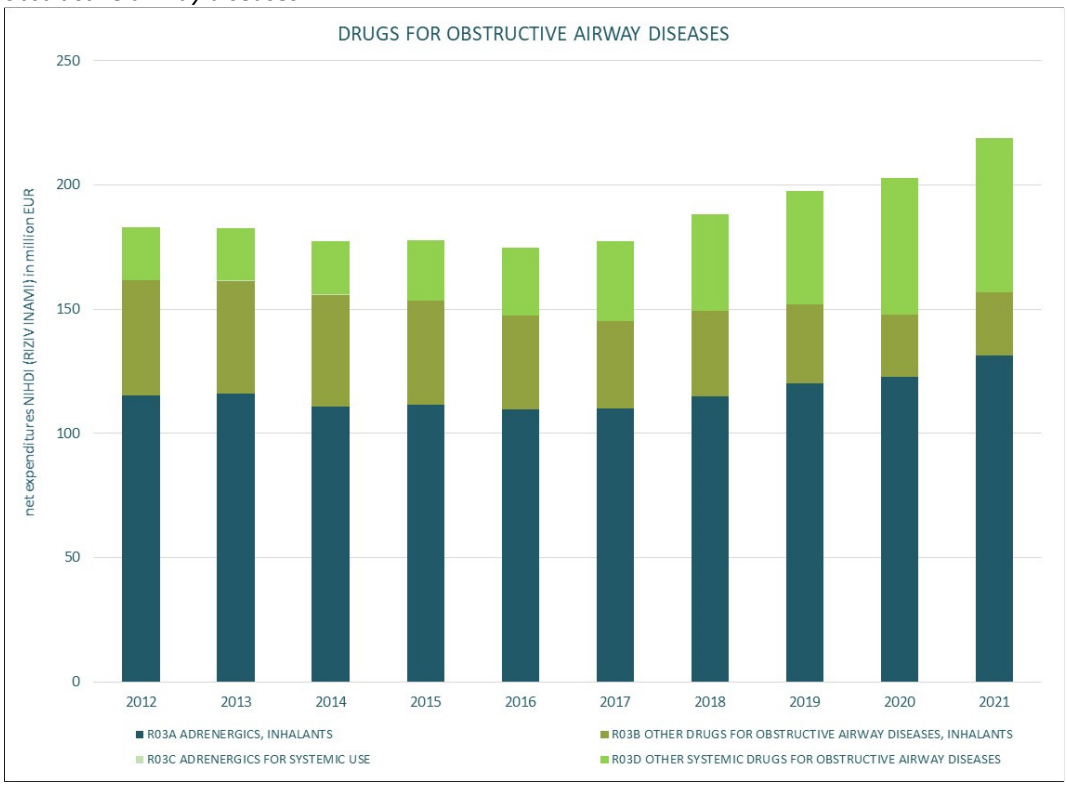
A long-acting anticholinergic will be chosen as initial treatment, or, if highly symptomatic, a combination of a long-acting anticholinergic and a long-acting beta-agonist, or, if EOS > 300, a combination of an inhaled corticoid and a long-acting beta-agonist for inhalation.

Depending on the extent of symptom control and control of exacerbations, the further pharmaceutical treatment will be determined. The three main therapeutic classes – LABAs, LAMAs and ICS – are then combined and titrated up to achieve optimal control.

Today there are no biological medicines (monoclonal antibodies) with demonstrated efficacy that are reimbursed in Belgium for the treatment of COPD.

The evolution of expenditure on ATC class R03 (per ATC4-level) is shown in Figure 32.

Figure 32: evolution of NIHDI net annual expenditure (public pharmacies 2012 - 2021) for ATC class R03 drugs for obstructive airway diseases



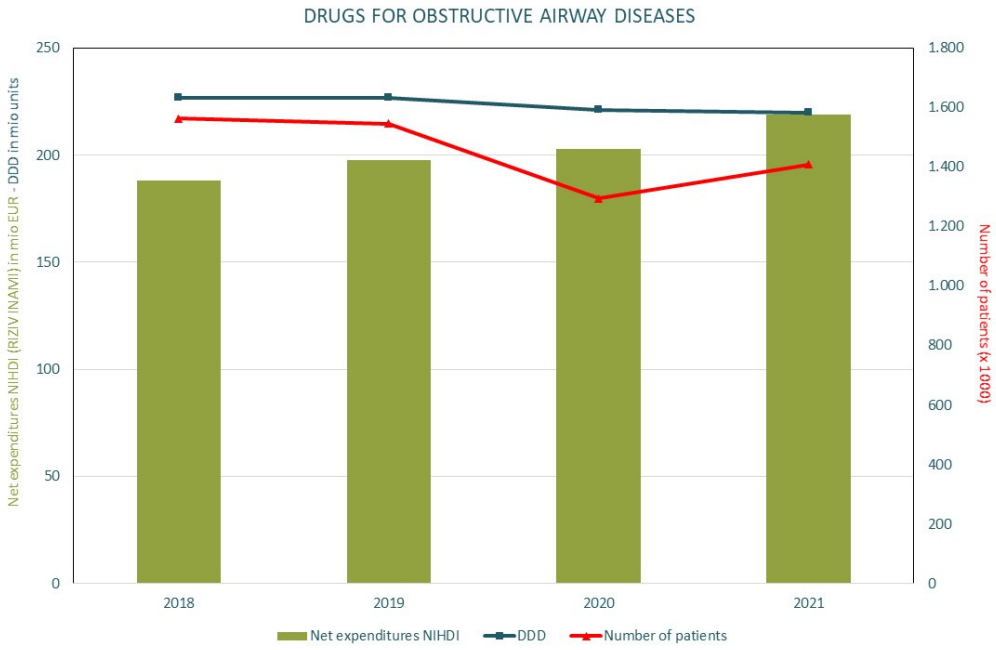
In the above graph, expenditure relating to ATC class R03C does not appear, given that such expenditure is limited (€7.700 in 2021).

Figure 32 shows that there is a relative stabilisation of NIHDI expenditure for ATC classes R03A (SABA, LAMA), R03B (ICS, LAMA) and R03C (LTRA), but also an increasing significant impact of the more recent biological therapeutic options for the treatment of asthma.

The most noteworthy development in recent years is the increase in the use of and expenditure on monoclonal antibodies in public pharmacies, more specifically with a factor 3 compared to 2012.

The vast majority of the R03-drugs are dispensed in public pharmacies, including R03DX (with the exception of reslizumab (R03DX08)). Nevertheless, around 28% of total NIHDI expenditure for biological therapy for asthma (nearly €70 million) in hospitals is covered (*Table 20*). The further development of new biological options and the possible extension of the target group of patients is likely to further enhance the growth of monoclonal antibodies in the coming years.

Figure 33: evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2018 – 2021) for ATC class R03 drugs for obstructive airway diseases



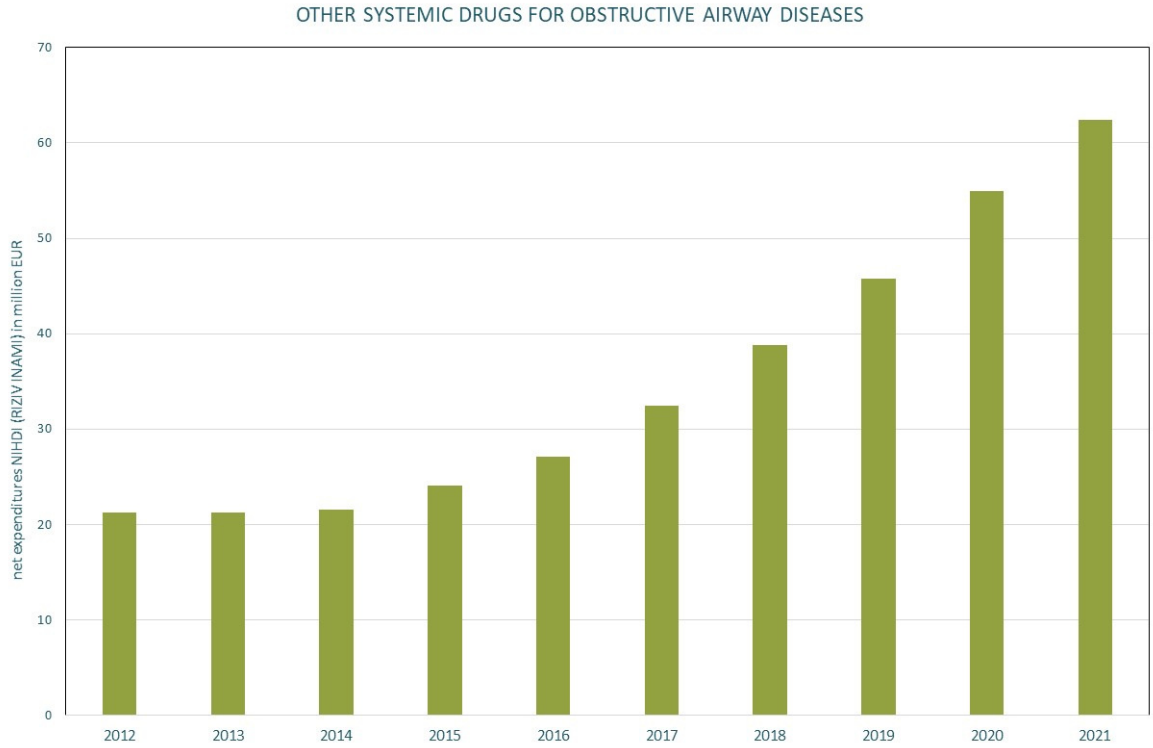
In the period 2019-2020 there was a steep drop in the number of patients, which did not translate into a proportional drop in the number of DDDs. This may be a result of less frequent doctor-patient contacts due to the vulnerability of these patients during the COVID-19 pandemic, leading to the supply of larger packages.

Specifically for ATC class R03D, the number of patients treated decreased slightly, as well as the number of DDDs. This can in part be explained by the sharp decrease in the use of LTRA (R03DC).

Table 20: net NIHDI expenditure and number of DDDs in 2021 in public pharmacies and hospitals for monoclonal antibodies (biological medicines).

R03DX – biological R\	2021		
	DDD	Net expenditures (EUR)	DDD PTY-equivalent
Outpatients	1,400,918	50,778,678	3,838
Hospitalised patients	533,079	19,218,002	1,460
Total	1,933,997	69,996,680	5,299

Figure 34: evolution of NIHDI net annual expenditure (public pharmacies 2012 - 2021) for ATC class R03D other systemic drugs for obstructive airway diseases



The evolution of expenditure per pharmacological class is illustrated in Table 21.

Table 21*: NIHDI net annual expenditure (public pharmacies) on drugs for obstructive airway diseases (ATC class R03), per pharmacological class: comparisons 2012 – 2021*

	2012		2021			
	Expenditure (€)	%	Expenditure (€)	%	Unique patients	%
Leukotriene receptor antagonists	16.416.534	9,0%	11.172.202	5,1%	131.968	9,4%
ICS	17.814.662	9,7%	12.484.915	5,7%	368.695	26,2%
ICS/LABA	87.636.357	47,9%	75.187.011	34,3%	670.664	47,6%
ICS/LABA/LAMA-		0%	22.626.765	10,3%	58.512	4,2%
LABA	8.217.948	4,5%	3.820.986	1,7%	25.221	1,8%
LAMA	23.863.150	13,1%	9.604.787	4,4%	48.456	3,4%
LAMA/LABA		0%	14.037.258	6,4%	46.379	3,3%
Monoclonal antibodies	**3.791.243**	**2,1%**	**50.796.263**	**23,2%**	**6.026**	**0,4%**
Others	1.475.151	0,8%	427.919	0,2%	10.478	0,7%
SABA	5.449.001	3,0%	5.098.228	2,3%	379.896	27,0%
SABA/ SAMA	14.026.577	7,7%	10.576.088	4,8%	241.833	17,2%
SAMA	4.147.406	2,3%	3.222.280	1,5%	208.728	14,8%
TOTAL	182.838.029	100%	219.054.701	100%	1.408.343	100%

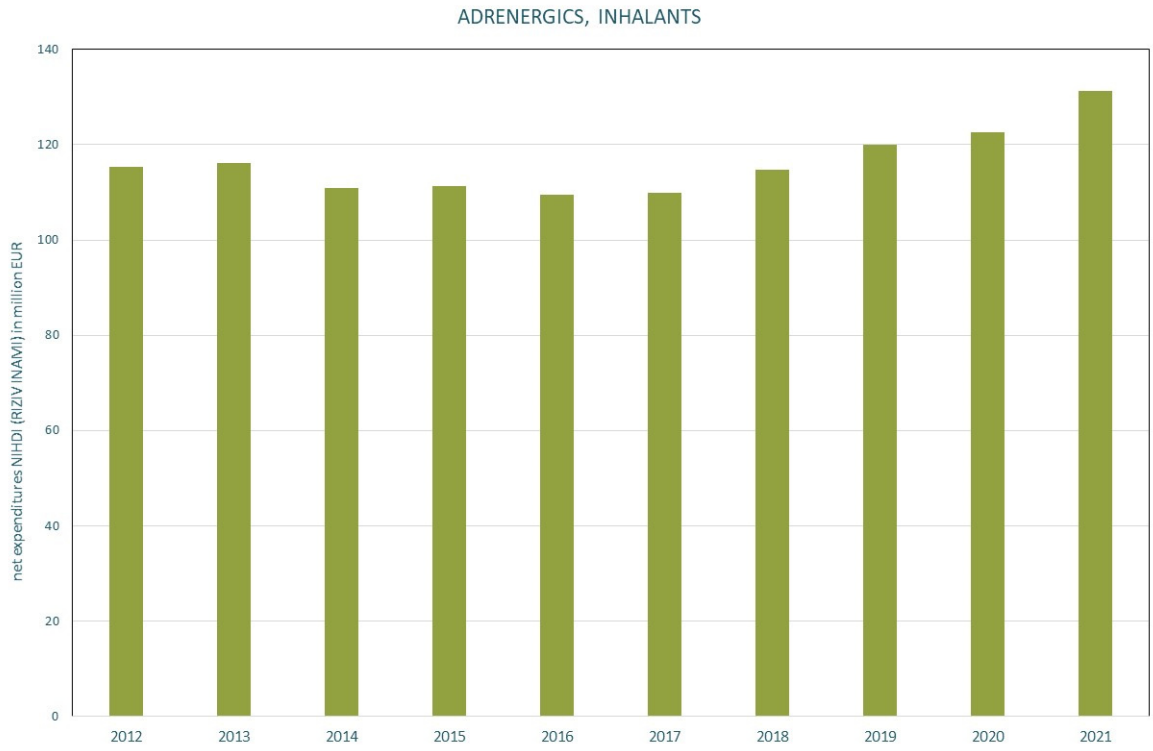
ICS: inhaled corticosteroids (R03BA)
LABA: β2- long-acting mimetics via inhalation (R03AC12 , 13, 18, 19)
LAMA: long-acting anticholinergics via inhalation (R03BB04, 05, 06, 07)
SABA: β2-short-acting mimetics via inhalation (R03AC02, 03, 04)
SAMA: short-acting anticholinergics via inhalation (R03BB01, 02)
Monoclonal antibodies: (R03DX)
Leukotriene receptor antagonists: (R03DC01, R03DC03)
Other : (R03BC01, R03CC02, R03DA04)

Fixed associations:
ICS/LABA (ATC R03AK) ICS/LABA/LAMA (ATC R03AL08, 09, 11, 12)
SABA/SAMA (ATC R03AL01, 02) LABA/LAMA (ATC R03AL03, 04, 05, 06)

The fixed combinations LABA/LAMA have been reimbursable since 2014, the fixed combinations ICS/LABA/LAMA since 2018. Since 1 April 2020, individual and combined ICS, LABAs and LAMAs for inhalation are reimbursed under Chapter I.

ADRENERGICS, INHALANTS (R03A)

Figure 35: evolution of NIHDI net annual expenditure (public pharmacies 2012 – 2021) for ATC class R03A adrenergics, inhalants



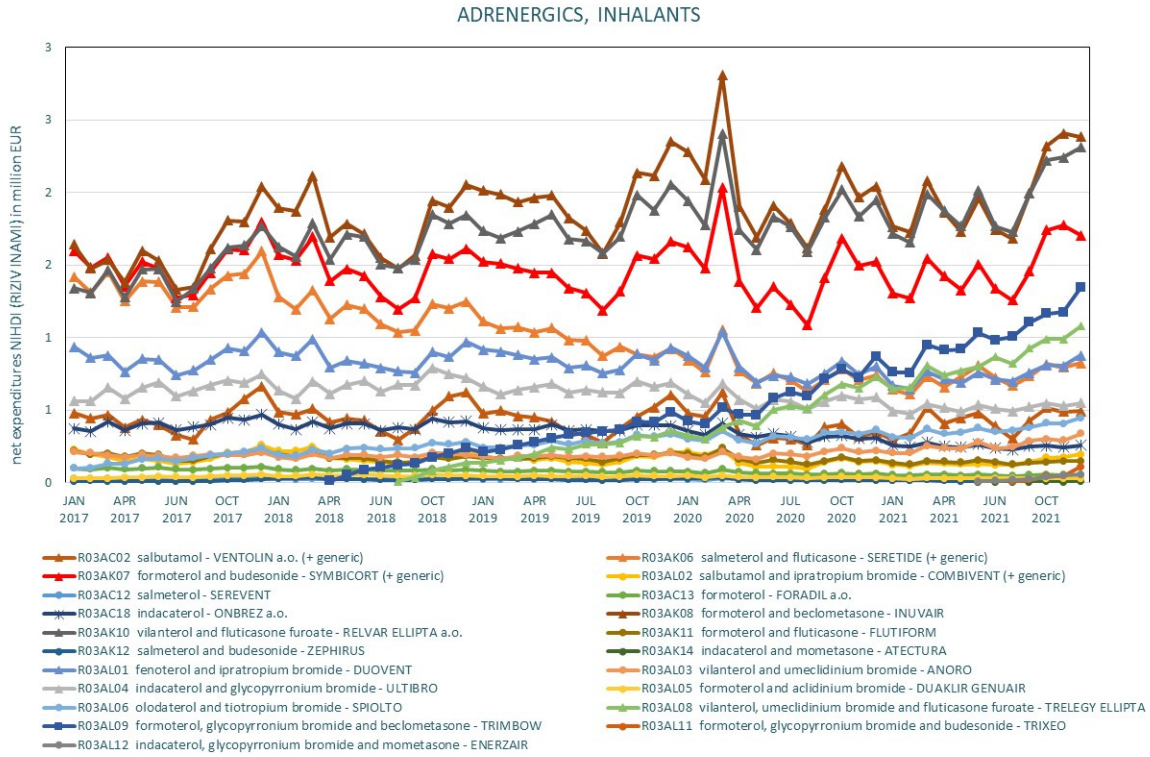
The drugs in the ATC class R03A include the short- and long-acting β2-mimetics via inhalation, as well as fixed combinations (via inhalation) in which β2-mimetics are combined with corticosteroids (ICS/LABA) and anticholinergics via inhalation (ICS/LABA/LAMA). These drugs are most commonly used for obstructive airway diseases. Various recently acquired triple combinations (LABA/LAMA/ICS) also have the indication of asthma.

Note: The WHO has not defined a DDD for ICS/LABA. The daily doses are indicated here, as specified in the package leaflet.

In 2021 a total of 1.144.000 patients took a drug from ATC class R03A (dispensed in public pharmacies); this is a stable figure in comparison with the 3 preceding years. An increase in the average number of ICS/LABA doses per patient per year explains the observed increase in the total number of doses administered. The average cost per ICS/LABA dose has fallen in recent years, so the total costs in this class of drugs are relatively stable.

After a few years of relative stability, expenditure for class R03A seems to be increasing again since 2018. Specifically for 2021, this may be due to the moving of specific medicines (LAMAs, LAMA/LABA combination preparations and LABA/LAMA/ICS tritherapy) from Chapter IV to Chapter I, as a result of which less stringent requirements need to be complied with to initiate treatment.

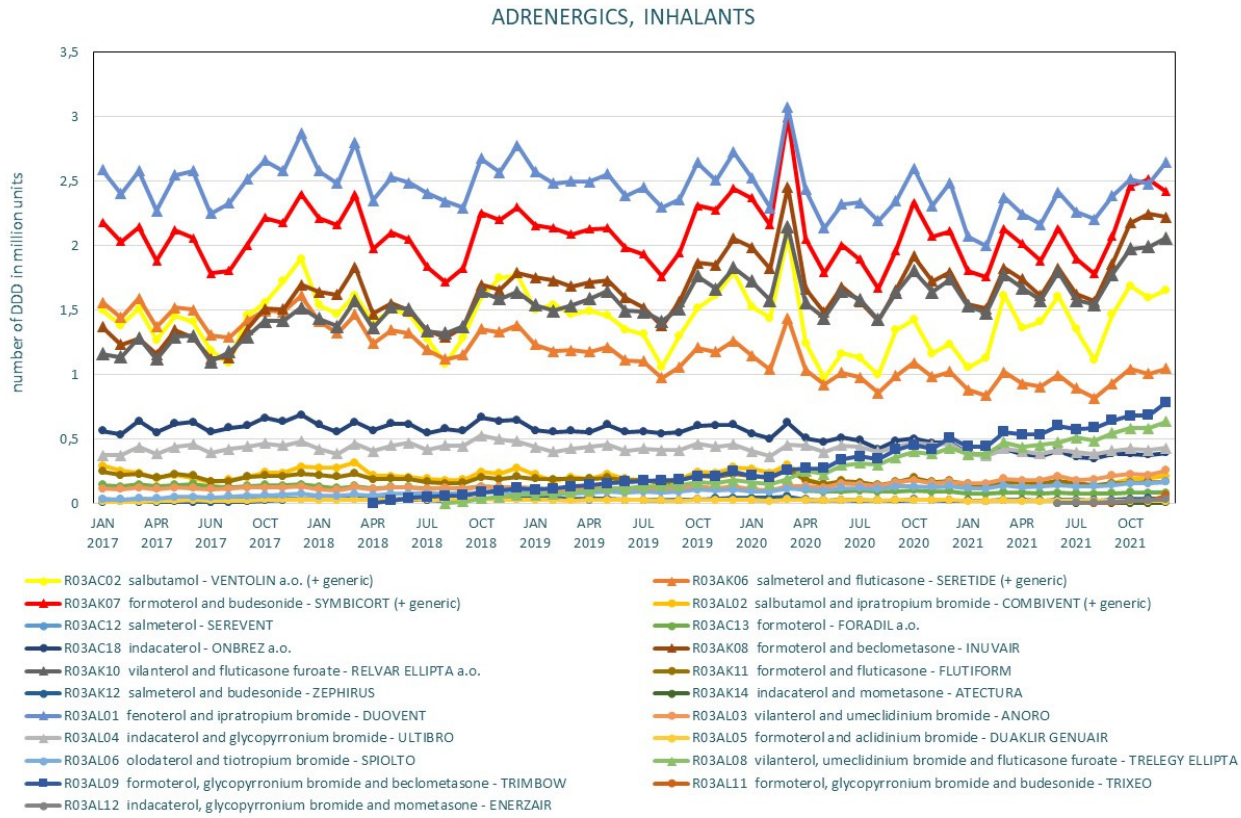
Figure 36: evolution of NIHDI net monthly expenditure (public pharmacies 2017 – 2021) for ATC class R03A adrenergics, inhalants



The figure above shows that expenditure for the three main combinations (formoterol + beclomethasone; vilanterol + fluticasone; formoterol + budenoside) has remained more or less stable. However, triple therapies are clearly on the rise, in particular the pharmaceuticals Trimbow® and Trelegy®. On 1 April 2021, all pharmaceuticals in this group were moved from Chapter IV to Chapter I, which makes it easier for doctors to start up this triple therapy. This may have contributed to the increased market share.

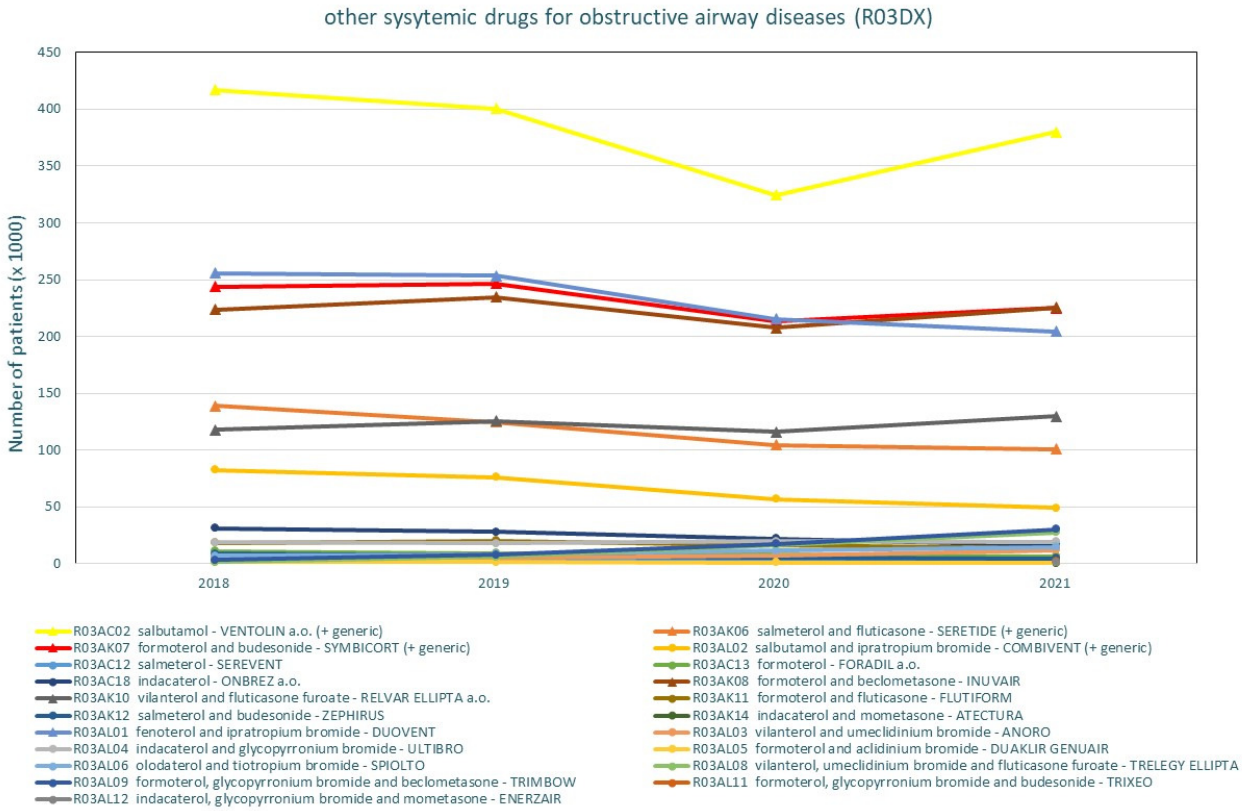
The tritherapies (ICS/LABA/LAMA, Trelegy® and Trimbow®) have been eligible for reimbursement since 2018. Since 2021, the combinations Trixeo® and Enerzair® are also available on the market. Trelegy®, Trimbow® and Trixeo® are indicated for the treatment of COPD; Enerzair® and Trimbow® are indicated for the treatment of asthma.

Figure 37: *evolution of monthly number of DDDs (public pharmacies 2018 – 2021) for ATC class R03A adrenergics, inhalants*



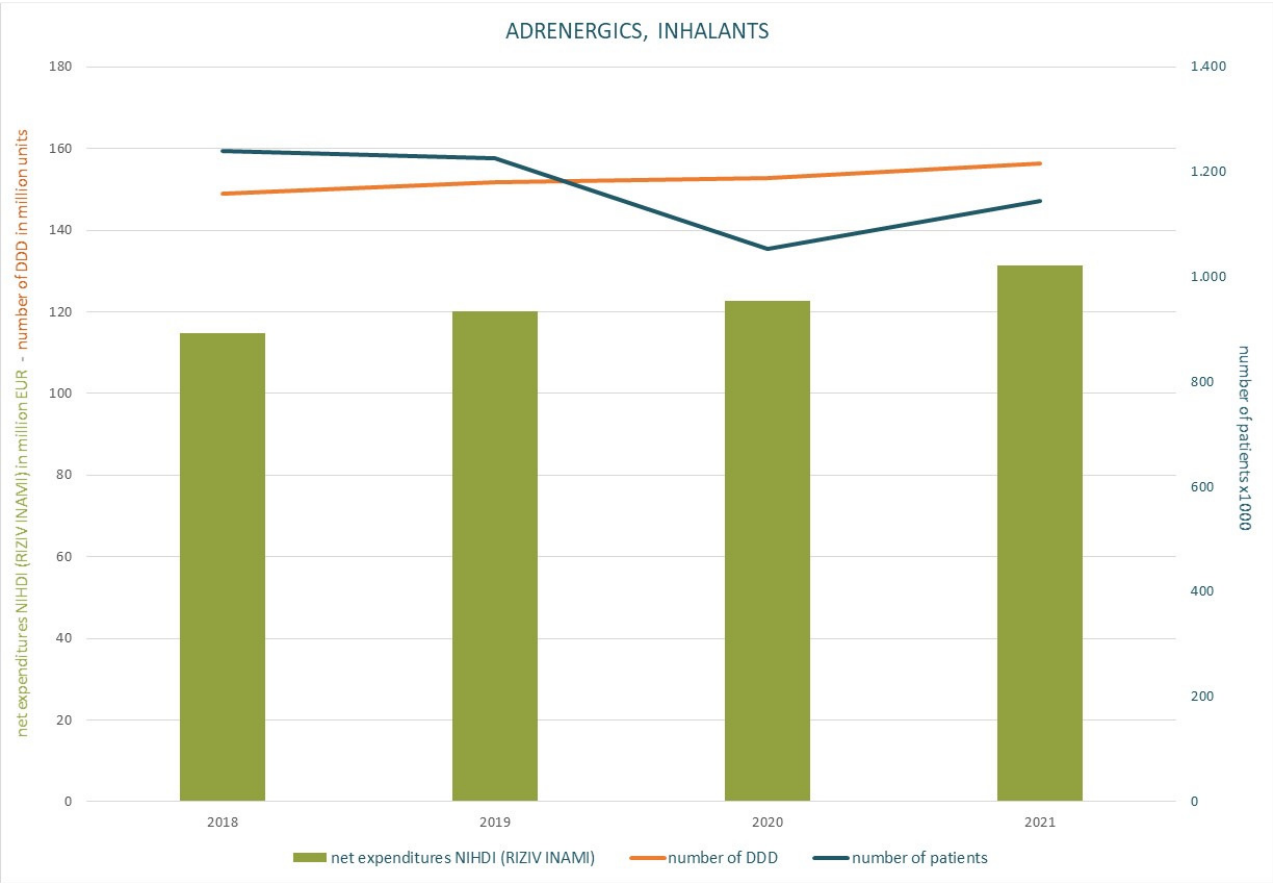
The three most frequently used pharmaceuticals in this group are Duovent®, Symbicort® (+ generics) and Inuvair®.

Figure 38: evolution of number of patients per year (public pharmacies 2018 – 2021) for ATC class R03A adrenergics, inhalants



The drug used for the greatest number of patients is salbutamol. This short-acting β2-mimetic (SABA) is used in the symptomatic treatment (if necessary) of asthma and chronic obstructive pulmonary disease (COPD). Here as well, we can see a clear effect in the number of patients in 2020. A possible hypothesis is that there was a reduced need for inhalers due to the lower transmission of respiratory infections in the population as a secondary effect of the lockdown measures and/or the increased supply of larger packages.

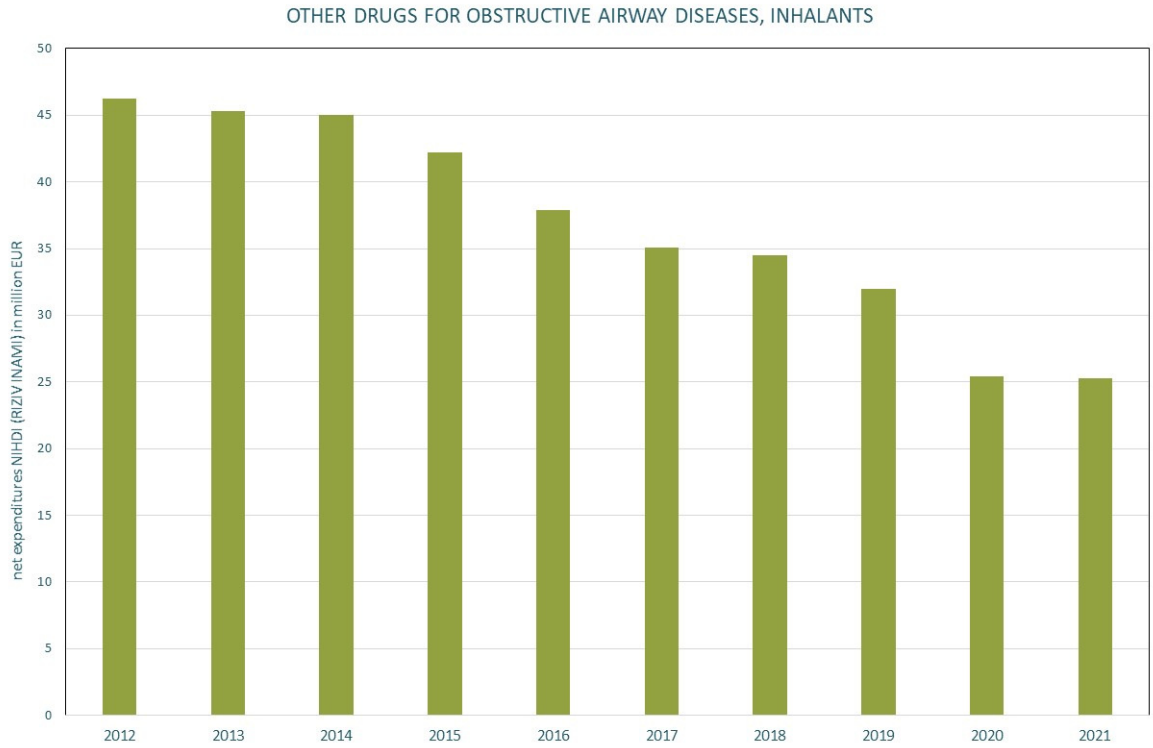
Figure 39: evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2018 – 2021) for ATC class R03A adrenergics, inhalants



However, the lower number of individual patients does not seem to have led to a decrease in the number of DDDs supplied. Given the decrease in the number of individual patients, but the increase in the number of DDDs, it is assumed that more large packages were supplied.

OTHER DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES, INHALANTS (R03B)

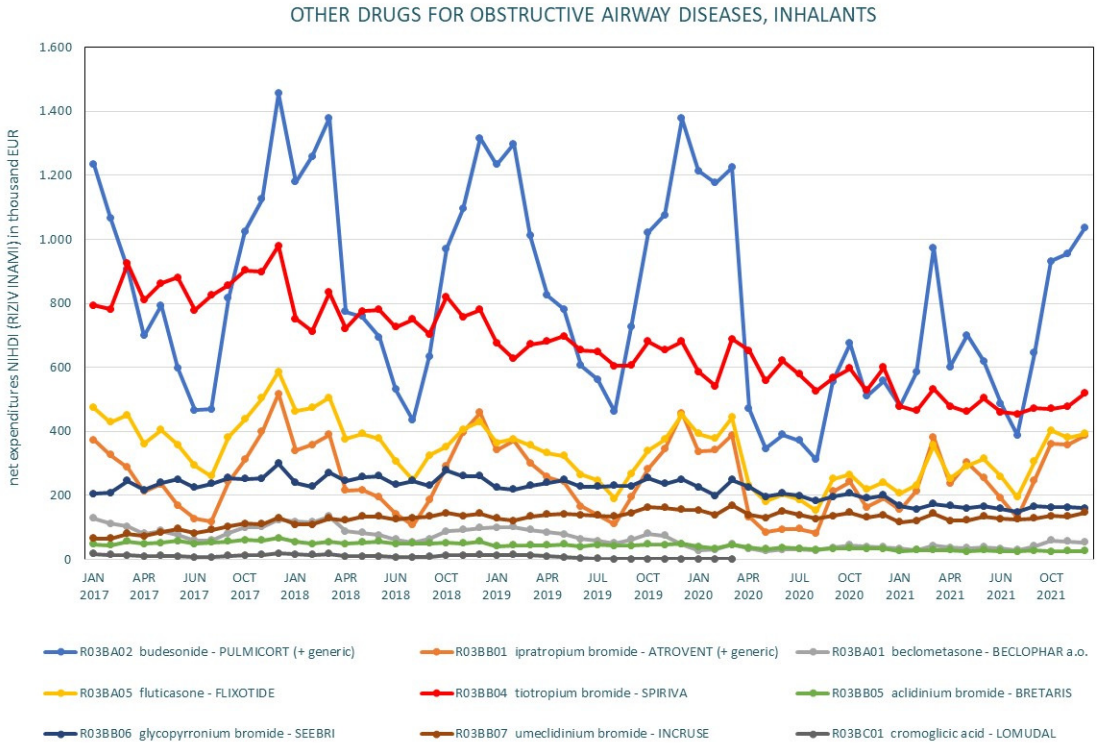
Figure 40*: evolution of NIHDI net annual expenditure (public pharmacies 2012 – 2021) for ATC class R03B, other drugs for obstructive airway diseases, inhalants*



The drugs in the ATC class R03B include the inhaled corticosteroids (ICS, R03BA) and the short-acting (SAMA) and long-acting (LAMA) anticholinergics (R03BB). ICS are, after ICS/LABA, the drugs used by the greatest number of patients: 368.600 in 2021. This is a first-line basic treatment for asthma. These drugs may exclusively be used as a last resort for COPD.

The trends observed may be partially explained by a decrease in the number of ICS DDDs per patient (a reverse trend compared to that observed for the average doses of ICS/LABA per patient). Although expenditure for 2021 is similar to that of 2020, it is too early to conclude that it will remain stable at this level.

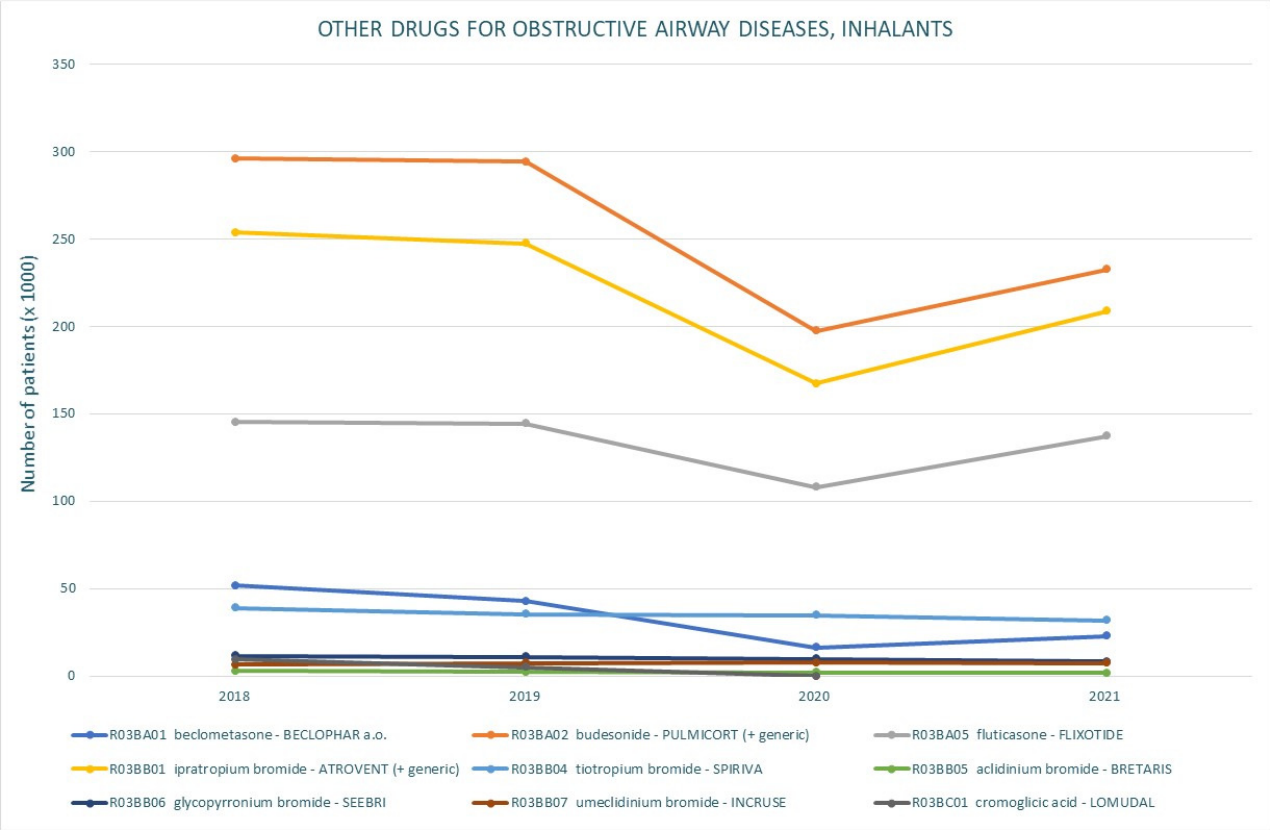
Figure 41: *evolution of NIHDI net monthly expenditure (public pharmacies 2017 – 2021) for ATC class R03B, other drugs for obstructive airway diseases, inhalants*



The seasonal trend (with winter peaks) is visible here for most pharmaceuticals used, although it was found to be significantly disrupted and less predictable in 2021. This is assumed to be the result of measures to mitigate the coronavirus crisis, as well as their use in COVID-19 patients with respiratory problems.

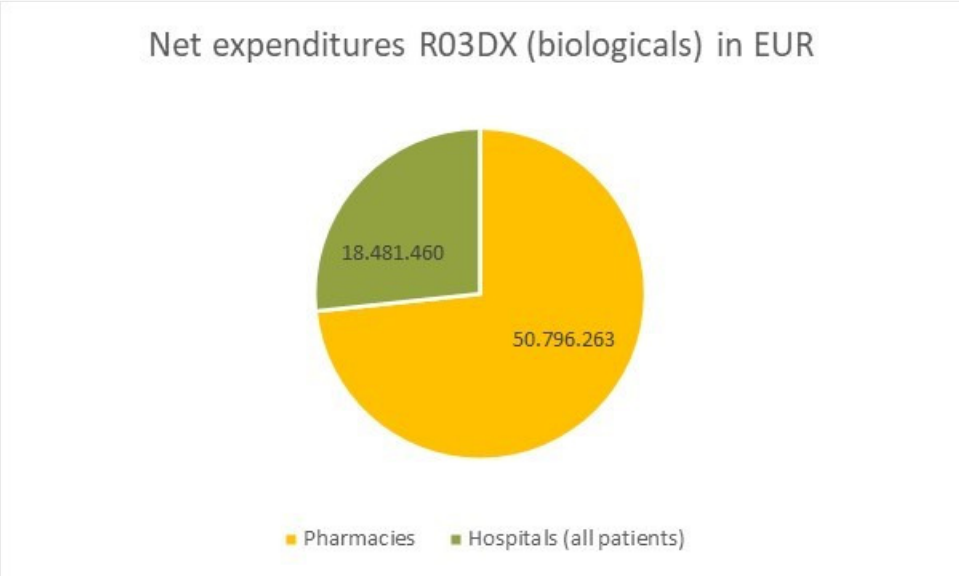
Cromoglycate (Lomudal ®) was taken off the Belgian market in 2019.

Figure 42 : *evolution of number of patients per year (public pharmacies 2018 – 2021) for ATC class R03B, other drugs for obstructive airway diseases, inhalants*



Long-acting anticholinergics (LAMA: tiotropium, aclidinium, glycopyrronium, umeclididinium) should be used as a first-line treatment for COPD. In order to encourage this use for COPD, the conditions for reimbursement were removed in 2019 (LAMA transferred from chapter IV to chapter I). Subsequently, in 2021, all inhalers were moved from Chapter IV to Chapter I as a result of a group-based revision. The precise effect of this is difficult to determine given the atypical years 2020 and 2021.

Figure 43: NIHDI net annual expenditure (public pharmacies 2012 – 2021) for ATC class R03DX other systemic drugs for obstructive airway diseases (biologicals)



The drugs in the ATC class R03D include theophylline (R03DA), the leukotriene antagonists (R03DC) and the monoclonal antibodies (R03DX); The reimbursement of the latter group of biological options is subject to strict conditions for a limited group of patients (depending on IgE content, blood eosinophils, FeNO value, severity of the asthma). Despite this limitative framework (as reflected in a limited increase of the DDD), there is still an increased use with important budgetary implications for the health insurance fund. Until 2016, only 1 molecule (omalizumab, Xolair®) was available; since then, mepolizumab (Nucala®, 2017), reslizumab (Cinquaero®, 2018) and benralizumab (Fasenra®, 2018) have been included in the reimbursement list. Omalizumab is also used for the treatment of urticaria. The further development of new biological options and the possible extension of the target group of patients is likely to further increase the use and therefore the cost for the health insurance fund in the coming years.

The use of leukotriene receptor antagonists (LTRA class of pharmaceuticals) decreased further over the past period.

Figure 44: evolution of NIHDI net monthly expenditure (public pharmacies 2017 – 2021) for ATC class R03D other systemic drugs for obstructive airway diseases

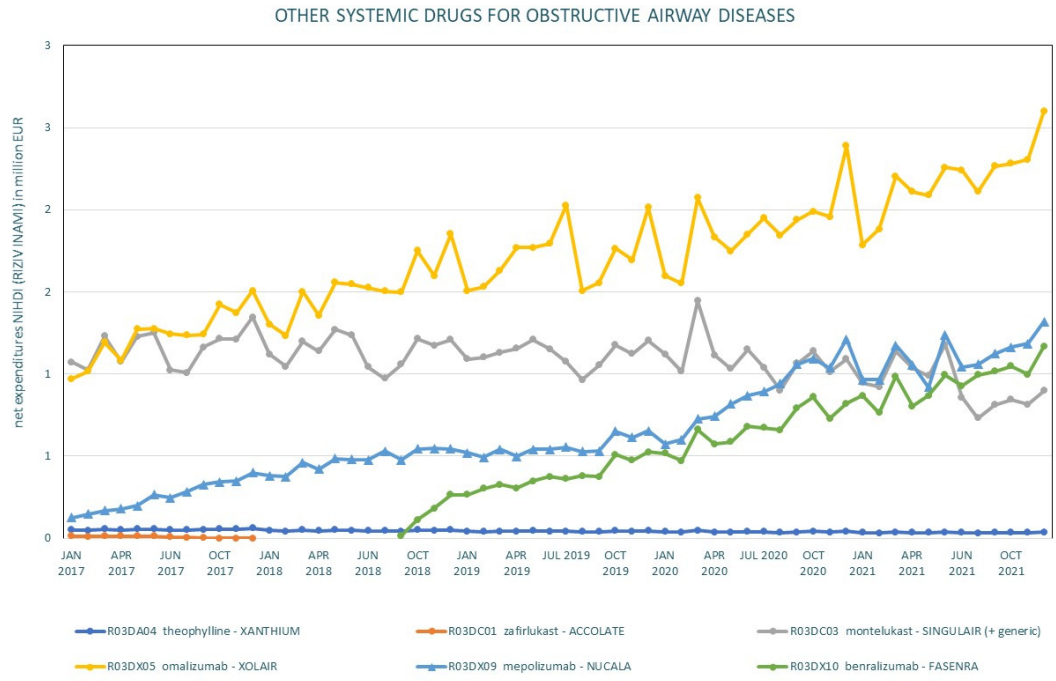


Figure 45: *evolution of number of patients per year (public pharmacies 2018 – 2021) for ATC class R03D other systemic drugs for obstructive airway diseases*

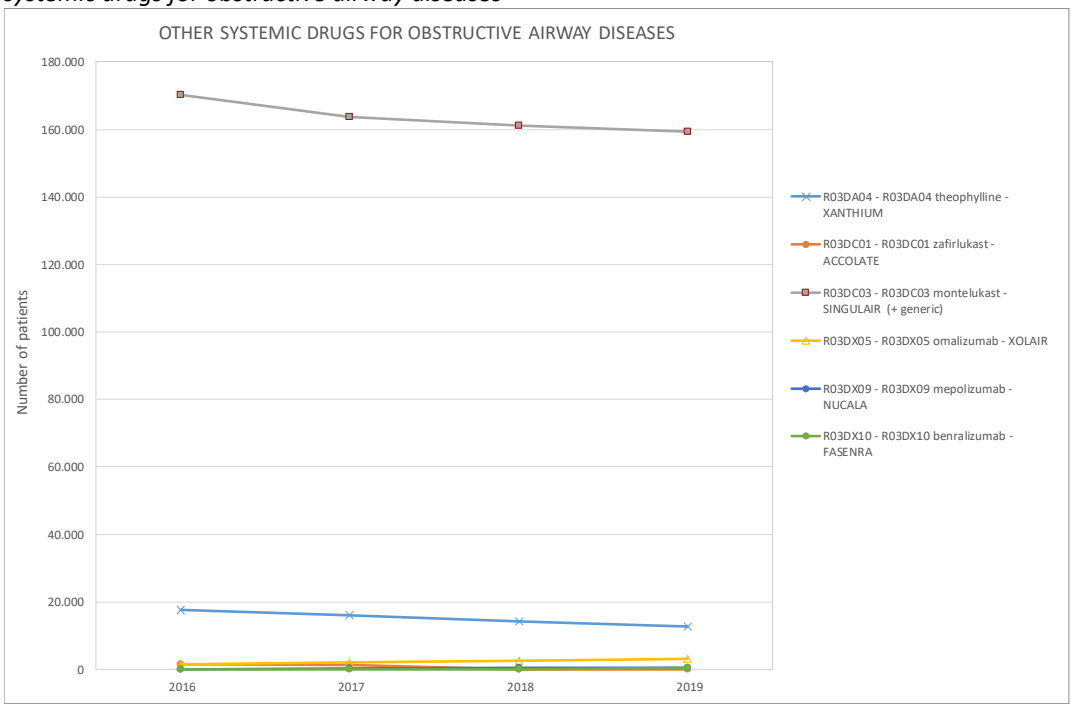


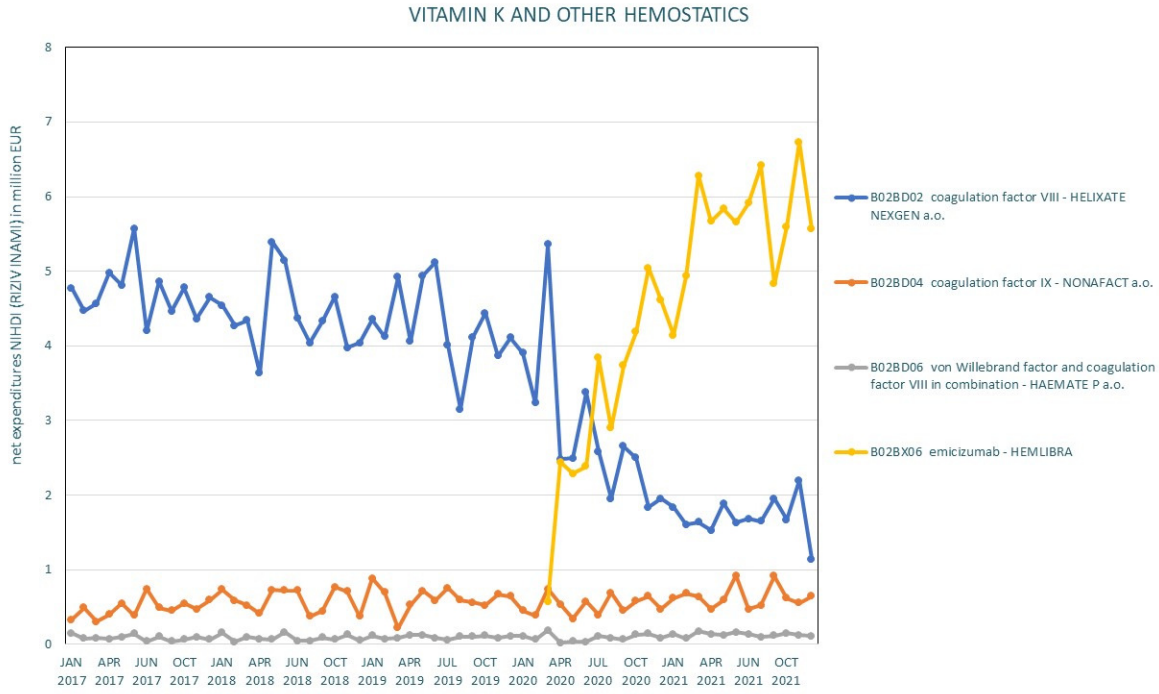
Figure 45 illustrates the fact that monoclonal antibodies, theoretically used as a last resort in severe asthma, apply to only a minority of patients.

B02B – VITAMINE K EN ANDERE HEMOSTATICA

Figure 46: evolution of NIHDI net annual expenditure (public pharmacies 2012 – 2021) for ATC class B02B vitamin K and other haemostatics

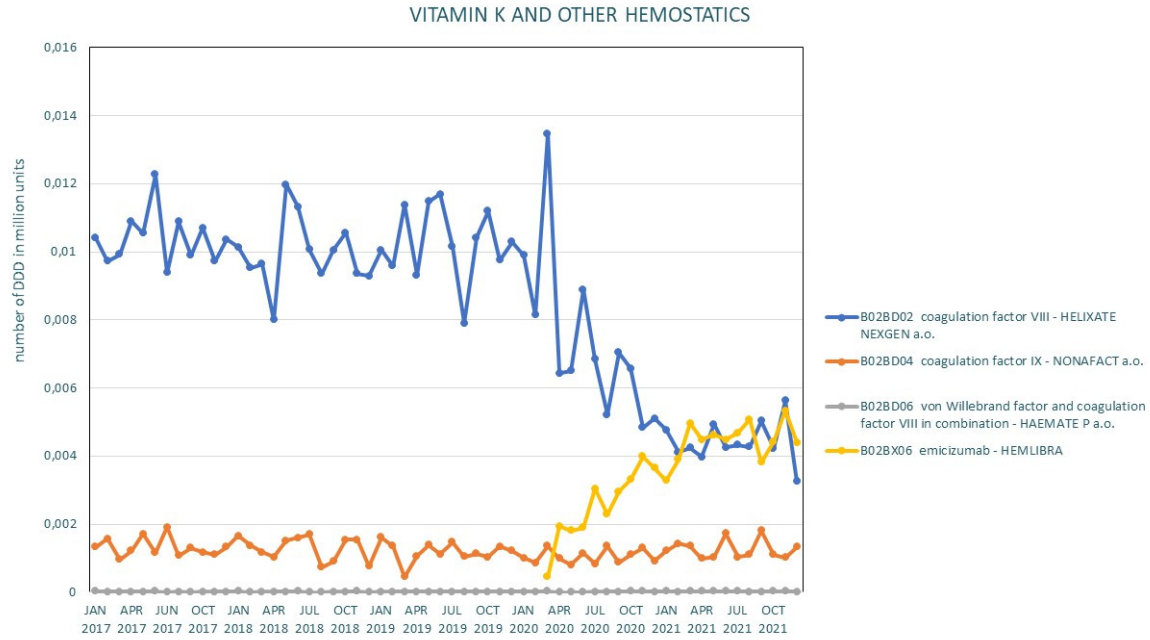
The class of pharmaceuticals under ATC code B02B comprises, where public pharmacies are concerned, pharmaceuticals for the treatment of hemophilia A, hemophilia B and von Willebrand's disease. Hospital pharmaceuticals such as fibrinogen, prothrombin complexes, thrombopoietin receptor agonists and the like are not included in public pharmacies. Expenditure has increased since 2020 and this is due to a significant use of Hemlibra®, which has been included in the reimbursement list since 1 March 2020. Hemlibra® is subject to temporary reimbursement due to an agreement between the manufacturer and the NIHDI; this means that actual expenditure is lower than that shown in the graph above.

Figure 47: evolution of NIHDI net monthly expenditure (public pharmacies 2017 – 2021) for ATC class B02B vitamin K and other haemostatics



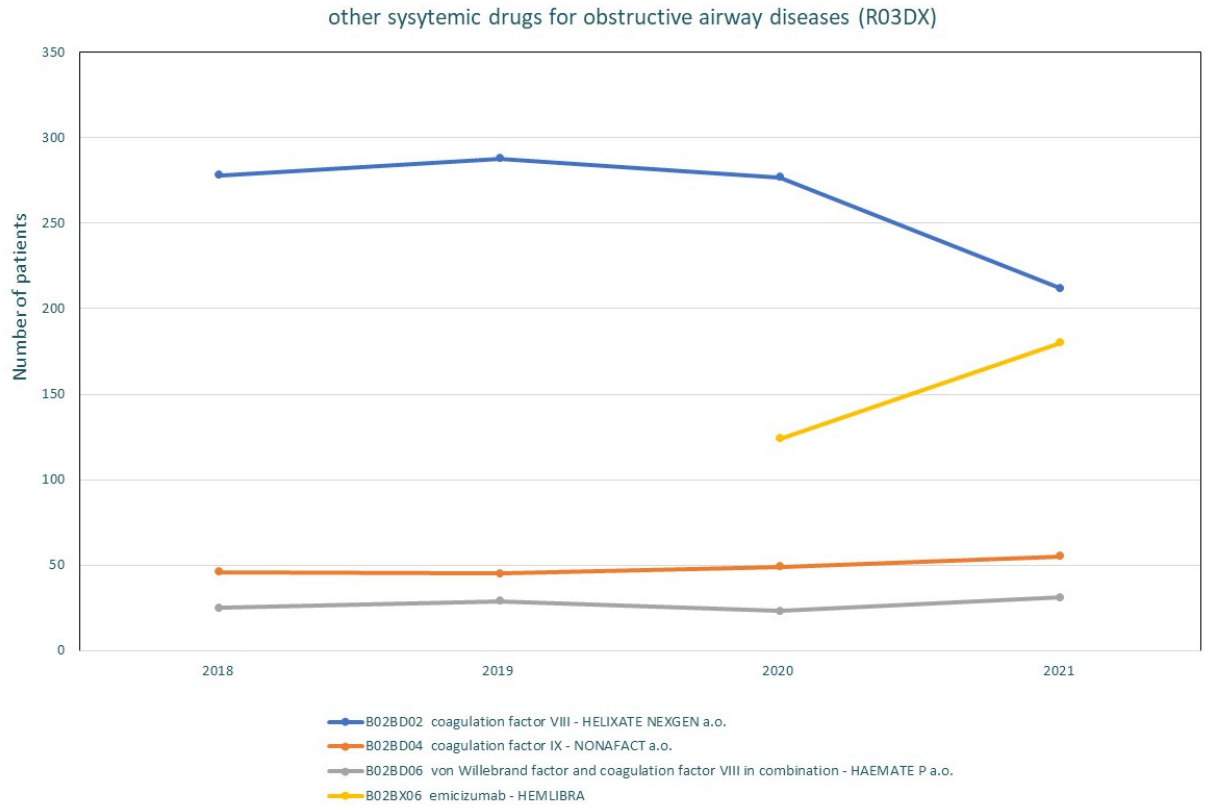
Monthly expenditure shows an increase for Hemlibra®, at the expense of other pharmaceuticals for hemophilia A, namely those with recombinant factor VIII as active substance.

Figure 48: evolution of monthly number of DDDs (public pharmacies 2018 – 2021) for ATC class B02B vitamin K and other haemostatics



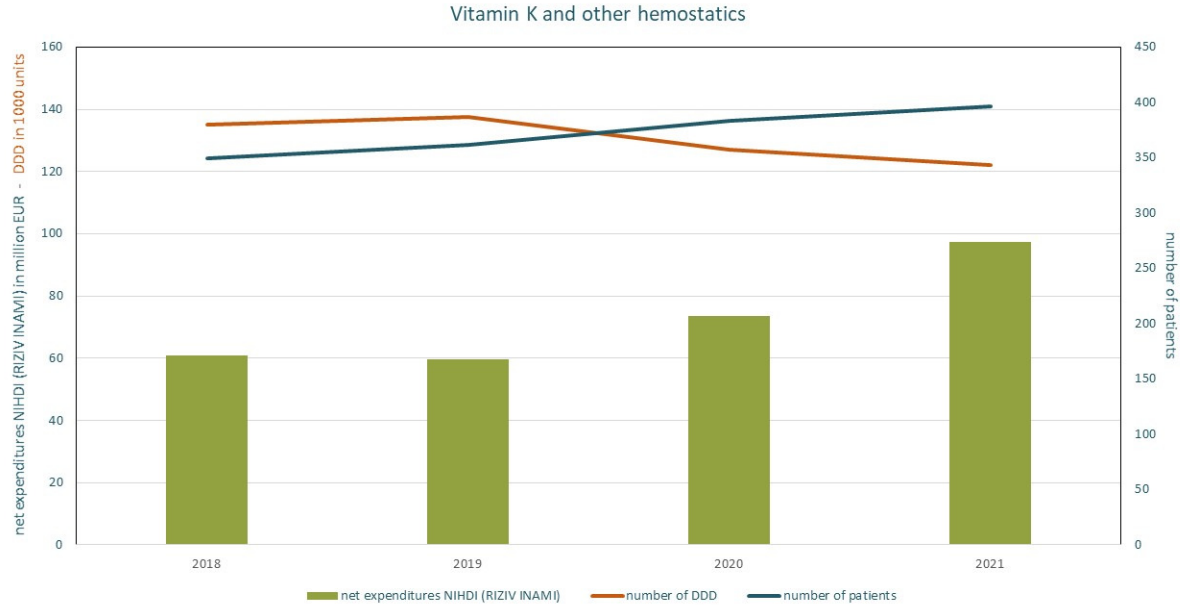
The monthly increase in DDD of Hemlibra® at the expense of a decreasing use of recombinant factor VIII confirms the trend in the expenditure graph. Hemlibra® is administered subcutaneously and has a lower administration frequency than pharmaceuticals based on recombinant factor VIII that need to be administered intravenously.

Figure 49: evolution of number of patients per year (public pharmacies 2018 – 2021) for ATC class B02B vitamin K and other haemostatics



Over the past years, the number of patients with hemophilia A, B and von Willebrand's disease has remained stable. To be clear, these are patients who collect their clotting factor replacement therapy from public pharmacies. Since Hemlibra® became reimbursable in 2020, the number of hemophilia A patients on Hemlibra® has increased; the number of patients with recombinant factor VIII has decreased since 2020. For hemophilia B and von Willebrand's disease, no change in trend can be observed since 2020, with numbers remaining stable.

Figure 50: evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2018 – 2021) for ATC class B02B vitamin K and other haemostatics



The graph above combines NIHDI expenditure in public pharmacies with patient numbers and volumes, expressed in DDD. In this graph, no other change in trend can be observed than that described above for Hemlibra®. On 1 December 2021, a group-based revision came into effect, with a number of price reductions for pharmaceuticals used in clotting disorders; this did not include Hemlibra®. Moreover, 1 month is too short to see an effect in this graph.

L01F – MONOCLONAL ANTIBODIES AND ANTIBODY DRUG CONJUGATES

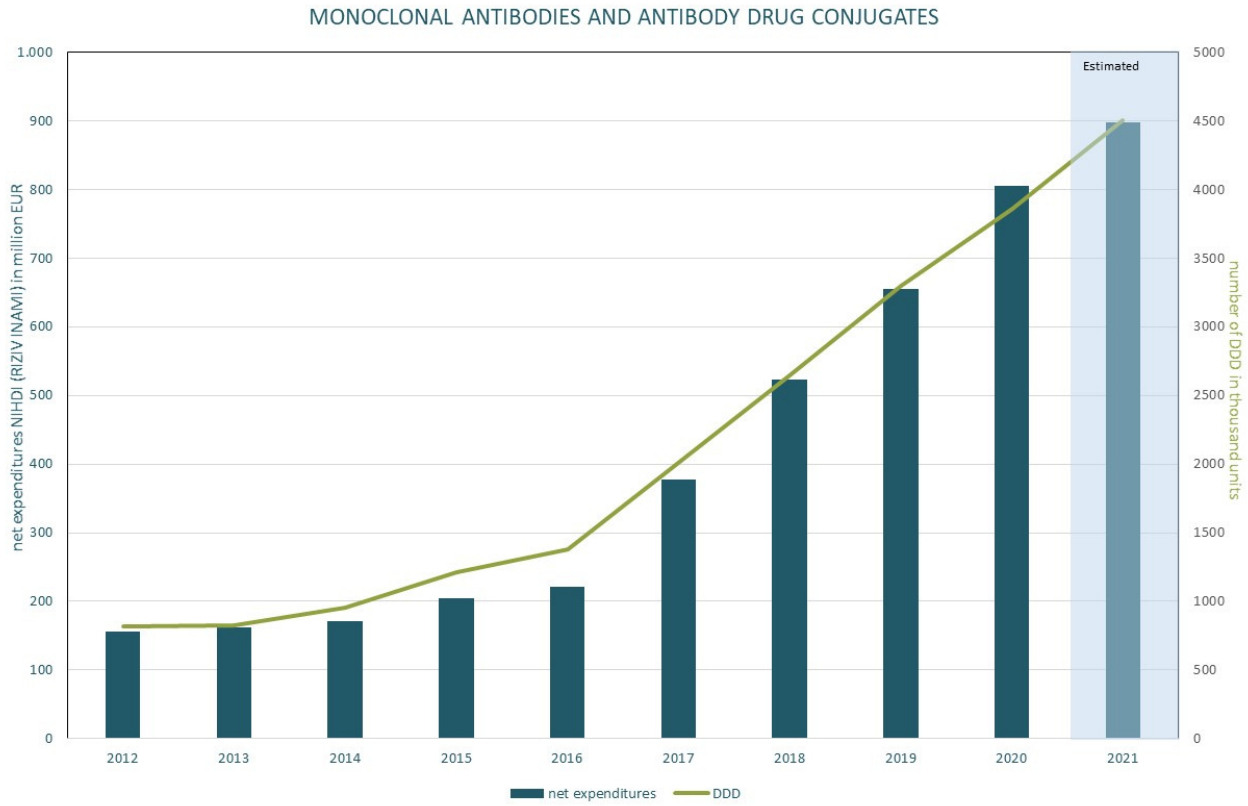
We note that the ATC code of monoclonal antibodies changed in 2022, with the elimination of class L01XC and their inclusion in the new class L01F, which explains the difference between the figures in this report and the figures in the MORSE report 2019.

For many years now, clear growth has been noticeable in both the net expenditure and the number of DDDs for ATC class L01X; in reality, that expenditure was mainly linked to monoclonal antibodies which were previously included in the subgroup L01XC. We can remark that the current class L01X, which excludes the monoclonal antibodies, shows a stable growth year after year. This is not the case for the expenditure of the new class L01F, which exclusively comprises monoclonal antibodies and antibody conjugates, which have experienced a considerable increase, but tend to decrease again:
- Tussen 2010 en 2016 waren de jaarlijkse groeipercentages ongeveer 10%
- ~71.5% in 2017 compared to 2016
- 38.8% in 2018 compared to 2017
- 25.0% in 2019 compared to 2018
- 23.0% in 2020 compared to 2019
- 11.5% in 2021 compared to 2020

The fact that net expenditure increases faster than consumption in DDDs is probably due to the fact that this class mainly comprises innovative medicines.

If we analyse *Figure 52*, we find that the highest expenditure relates to Keytruda® (pembrolizumab) and Opdivo® (nivolumab), for which expenditure has increased sharply since 2017. Since the beginning of 2017, a new system has come into force for these molecules, whereby a new indication is automatically reimbursed as soon as the EMA (European Medicines Agency) has approved the registration. This ensures that patients have access to their treatment more quickly, as it is not necessary to go through a procedure with the CRM (Commission for Reimbursement of Medicines) for each indication. This system is not only applicable for nivolumab and pembrolizumab, but for all PD(L)-1 inhibitors included in the list of reimbursable pharmaceuticals (ATC-code L01FF) including Tecentriq® (atezolizumab), Imfinzi® (durvalumab), Bavencio® (avelumab) and Libtayo® (cemiplimab). In the meantime, there are multiple indications for which PD(L)-1 inhibitors are reimbursed: renal carcinoma, urothelial carcinoma, skin carcinoma, hepatocellular carcinoma, lung carcinoma and mesothelioma, melanoma, Hodgkin lymphoma, epidermal carcinoma of the head and neck, colorectal cancer, oesophageal cancer or cancer of the gastro-oesophageal junction, stomach cancer, small intestine cancer, bile duct cancer, cervical cancer, endometrial cancer, breast cancer. Many patients are thus eligible for a treatment with one of these molecules. All these pharmaceuticals are temporarily eligible for reimbursement via a convention concluded between the company concerned and the NIHDI. It is important to emphasise that the expenditure reported here is based on the list price of these drugs. The actual costs for the NIHDI are confidential and are calculated on the basis of compensations set out in a convention between the pharmaceutical company concerned and the NIHDI.

Figure 51: evolution of NIHDI net annual expenditure and number of DDDs (hospitals (all patients) 2012 – 2021) for ATC class L01F monoclonal antibodies and antibody drug conjugates



Net expenditure and the number of DDDs of Keytruda® are very high and have been rising constantly since 2017, except in the last quarter of 2021, but that period is still an extrapolation. Opdivo® is also part of the top three where expenditure is concerned, although expenditure is clearly lower than for Keytruda®. These two pharmaceuticals represent the largest number of licensed and reimbursed indications in class L01FF.
The last molecule of the top three where expenditure is concerned is Darzalex® (daratumumab). For 2021 Darzalex® was reimbursed in monotherapy or in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone in the various indications of multiple myeloma. In 2021, an extension of reimbursable indications entered into effect for Darzalex®, which led to a new increase in expenditure and of the number of DDDs. Since that date, this pharmaceutical is also reimbursable in combination with bortezomib, melphalan and prednisone (D-VMP) in adult beneficiaries who suffer from newly diagnosed multiple myeloma and are not eligible for autologous hematopoietic stem cell transplantation.

Bevacizumab (Avastin® and biosimilars) shows a high number of DDDs, due to its many oncological indications, both in monotherapy and in combination therapy. The advent of the first biosimilar in September 2020 made it possible to reduce expenditure for bevacizumab as a result of the 'biocliff'.
Finally, the number of DDDs is also high for rituximab (Mabthera® and biosimilars), which is indicated for oncological conditions or auto-immune conditions, and for Perjeta® (pertuzumab) in several indications of breast cancer.

The increase in expenditure and DDDs of Tecentriq® found from mid 2019 can be explained by the successive reimbursement of several indications via the mechanism EMA+1: metastatic triple-negative breast cancer that has not been previously treated in combination with nab-paclitaxel, unresectable or advanced hepatocellular carcinoma that has not been treated with systemic therapy in combination with bevacizumab, and, finally, first-line treatment of metastatic non-small cell lung cancer with PD-L1+ tumours.

Figure 52: *evolution of NIHDI net quarterly expenditure (hospitals (all patients) 2017 – 2021) for ATC class L01F monoclonal antibodies and antibody drug conjugates*

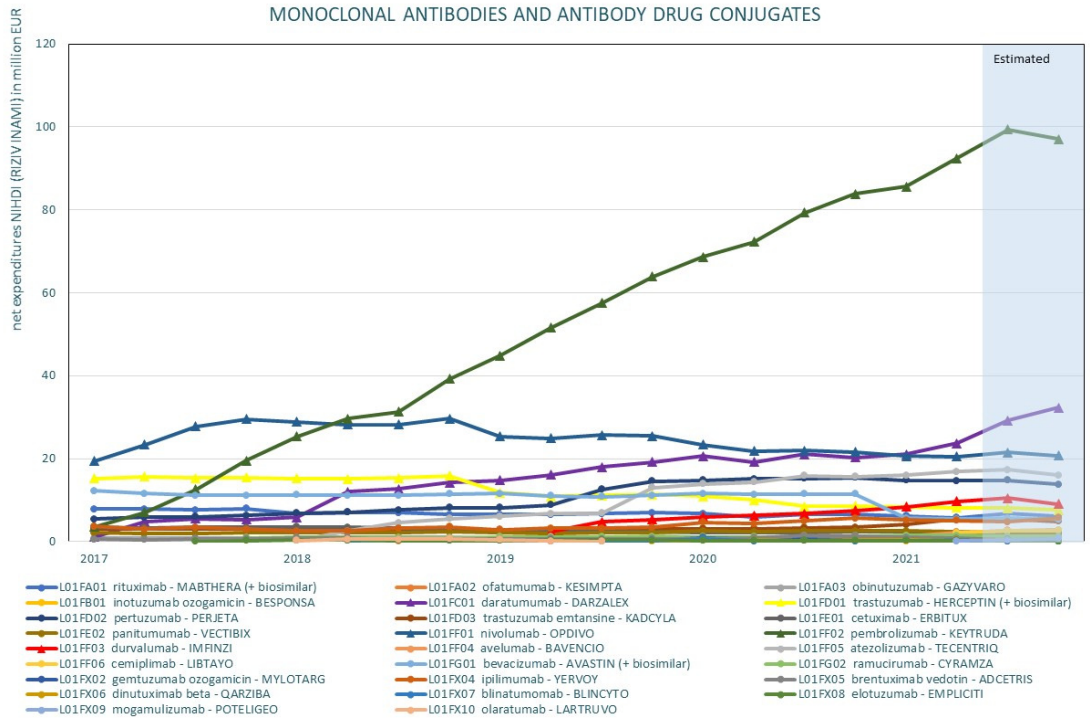
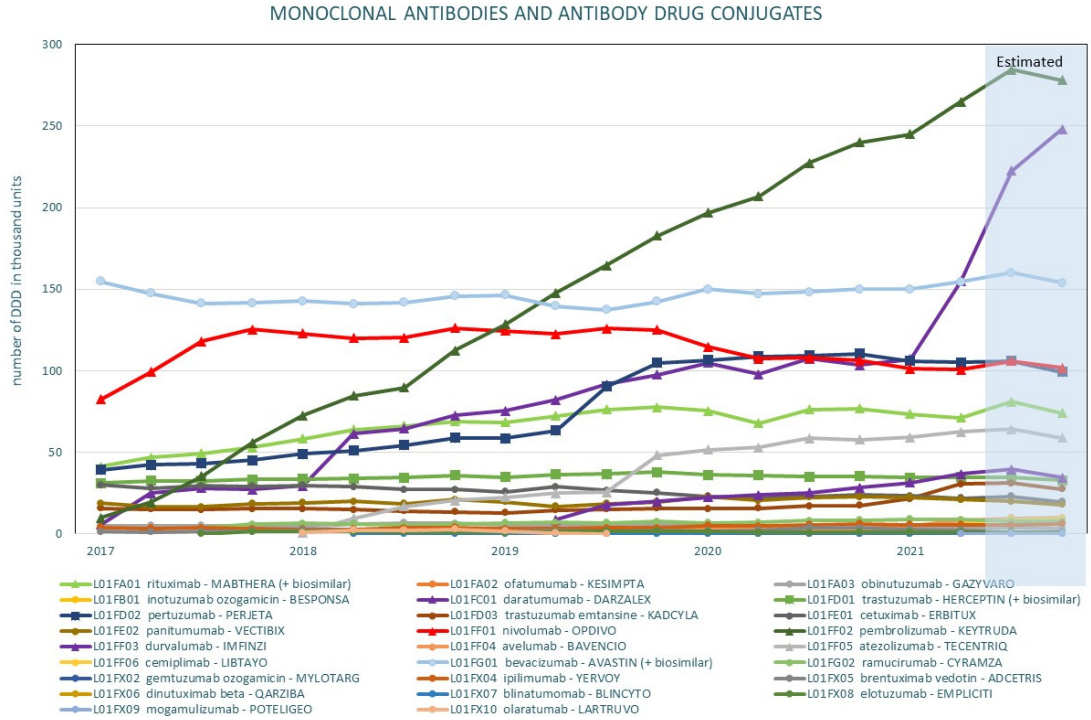


Figure 53: *evolution of number of DDDs per quarter (hospitals (all patients) 2017 – 2021) for ATC class L01F monoclonal antibodies and antibody drug conjugates*



For a detailed analysis we refer you to page 23, L04A – Immunosuppressants.

L01E – PROTEIN KINASE INHIBITORS

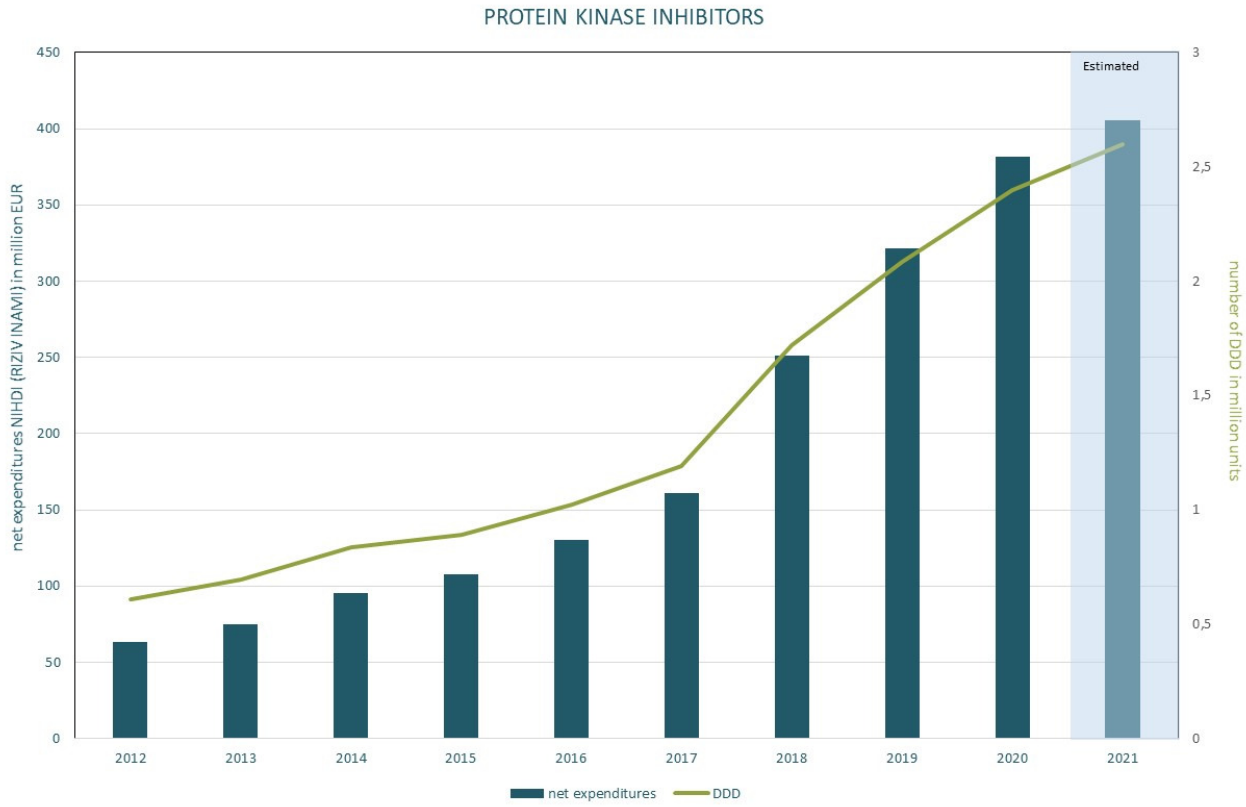
We note that the ATC code of protein kinase inhibitors changed in 2021, with the elimination of class L01XE and their inclusion in the new class L01E, which explains the difference between the figures in this report and the figures in the MORSE report 2019.

Net expenditure and the number of DDDs of ATC class L01E have been continuously rising for many years, with an important peak in 2018-2019.

Where net expenditure is concerned, the annual growth figures were as follows:

- between 10% and 20% from 2010 to 2017
- 56.2% in 2018 compared to 2017
- 28.0% in 2019 compared to 2018
- 18.5% in 2020 compared to 2019
- 6.4% in 2021 compared to 2020

Figure 54: evolution of NIHDI net annual expenditure and number of DDDs (hospitals (all patients) 2012 – 2021) for ATC class L01E protein kinase inhibitors



The peak in expenditure of 2018, linked to a high number of DDDs, can be explained in particular by the start of reimbursement of the pharmaceutical Ibrance® (palbociclib) in the treatment of advanced HR+/HER2 breast cancer, in combination with a non-steroidal aromatase inhibitor or with fulvestrant. Ibrance® is the first CDK4/6 inhibitor in the treatment of ER+/HER2 breast cancer.

For the pharmaceutical Imbruvica® (ibrutinib) expenditure and the number of DDDs are high as well. Since its inclusion in the reimbursement list in 2015, Imbruvica® has been indicated for various hemato-oncological conditions or macroglobulinemia.

Tagrisso® (osimertinib) completes this top three where expenditure is concerned. It was initially reimbursed in the second-line treatment of breast cancer with the mutation T790M. An extension of the indications in 2019

made reimbursement in the first line possible, which explains the considerable increase in expenditure for Tagrisso® from that year onwards.

These pharmaceuticals are temporarily eligible for reimbursement via a convention concluded between the company concerned and the NIHDI. It is important to emphasise that the expenditure reported here is based on the list price of these drugs. The actual costs for the NIHDI are confidential and are calculated on the basis of compensations set out in a convention between the pharmaceutical company concerned and the NIHDI.

With the exception of these three molecules, expenditure and the number of DDDs of the other pharmaceuticals in this class have remained relatively stable. Since 2018 and the reimbursement of Ibrance®, no other pharmaceutical has experienced such a peak in expenditure and number of DDDs.

Figure 55: *evolution of NIHDI net quarterly expenditure (hospitals (all patients) 2017 – 2021) for ATC class L01E protein kinase inhibitors*

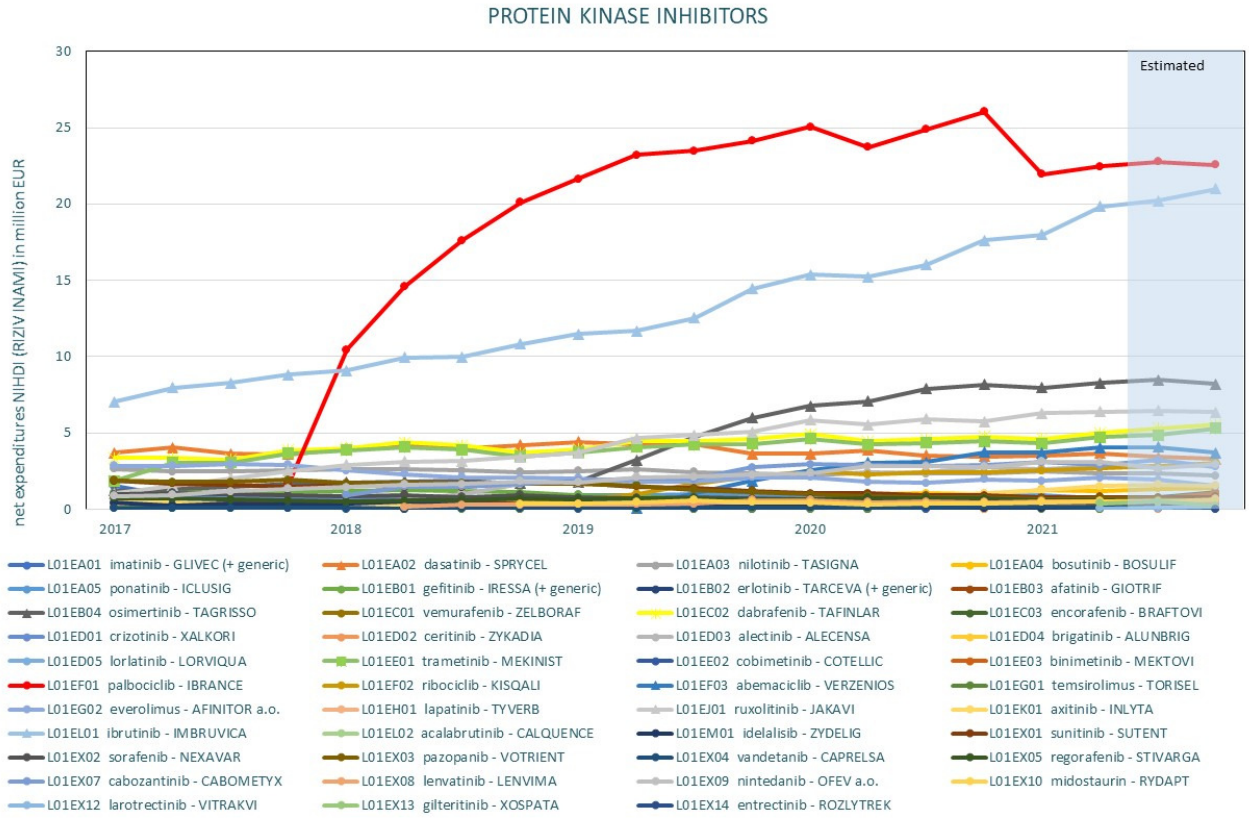


Figure 56: evolution of number of DDDs per quarter (hospitals (all patients) 2017 – 2021) for ATC class L01E protein kinase inhibitors

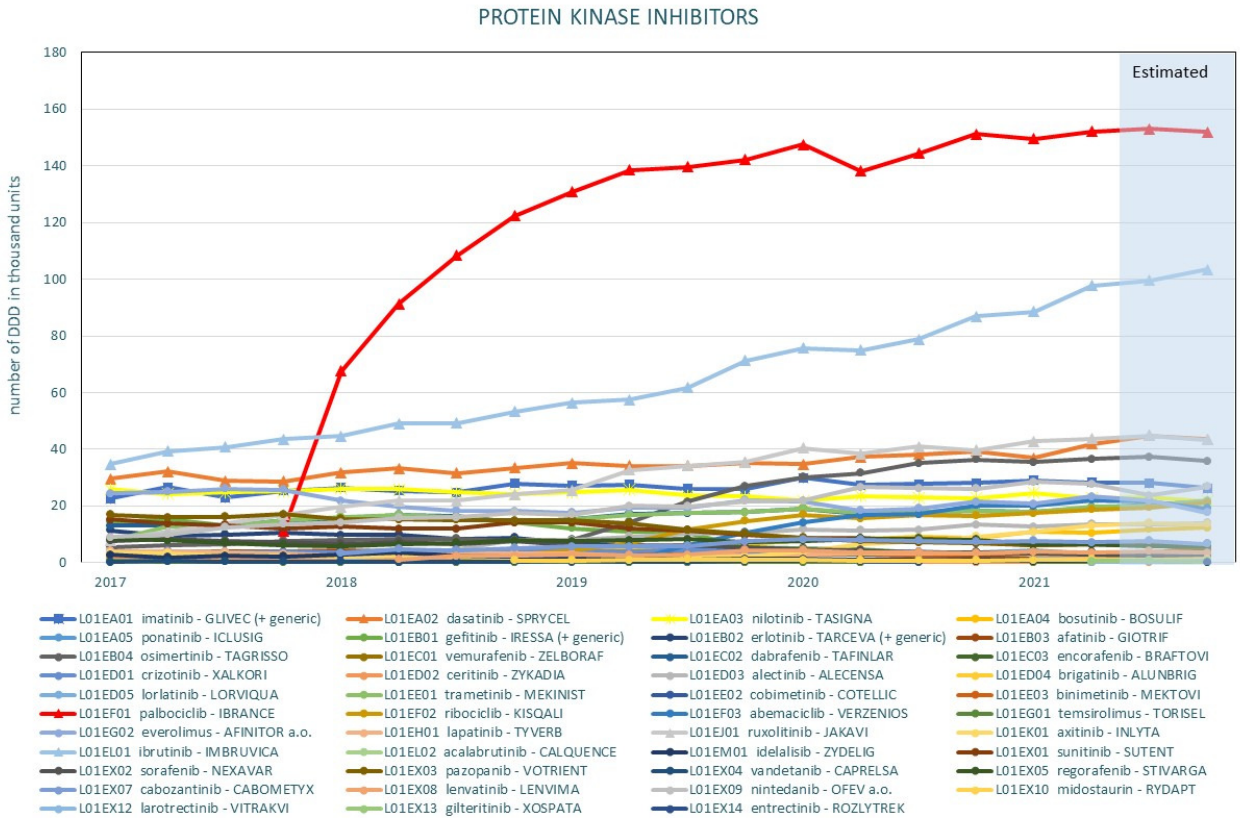
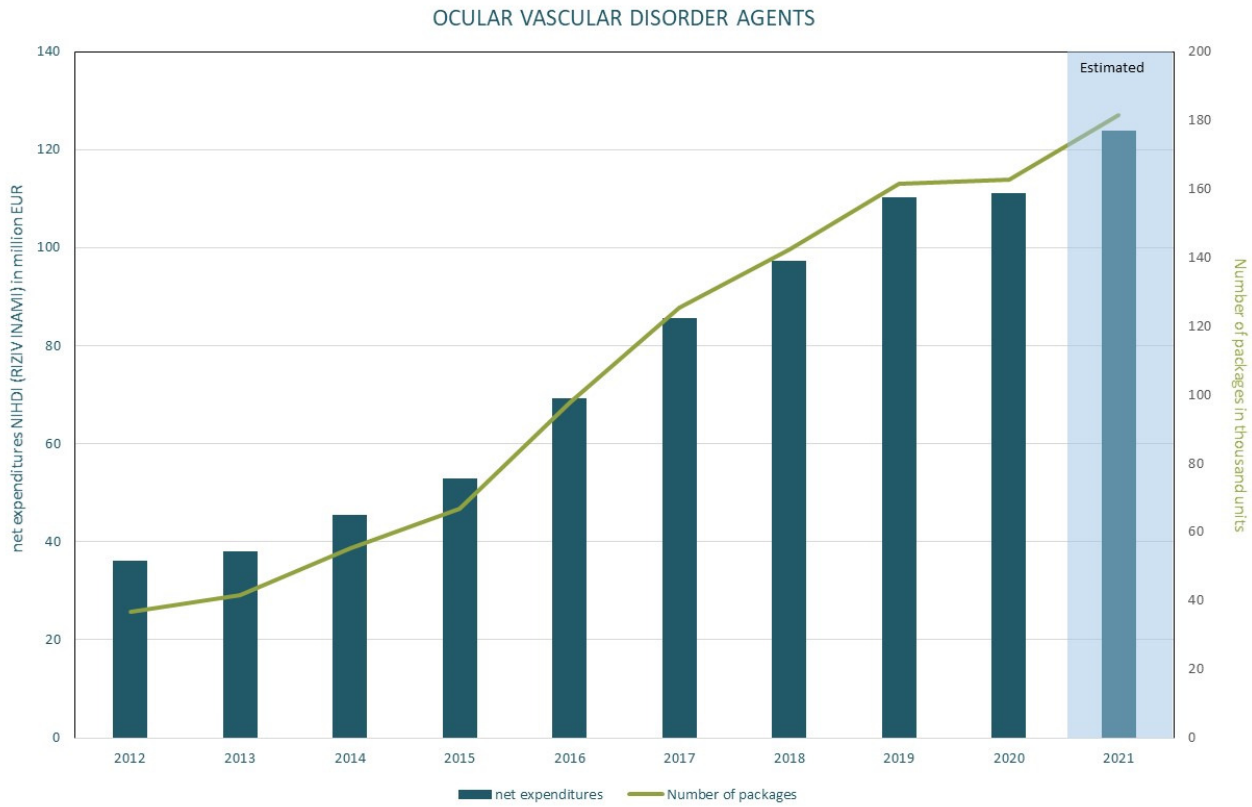


Figure 57: evolution of NIHDI net annual expenditure and number of DDDs (hospitals (all patients) 2012 – 2021) for ATC class S01L ocular vascular disorder agents

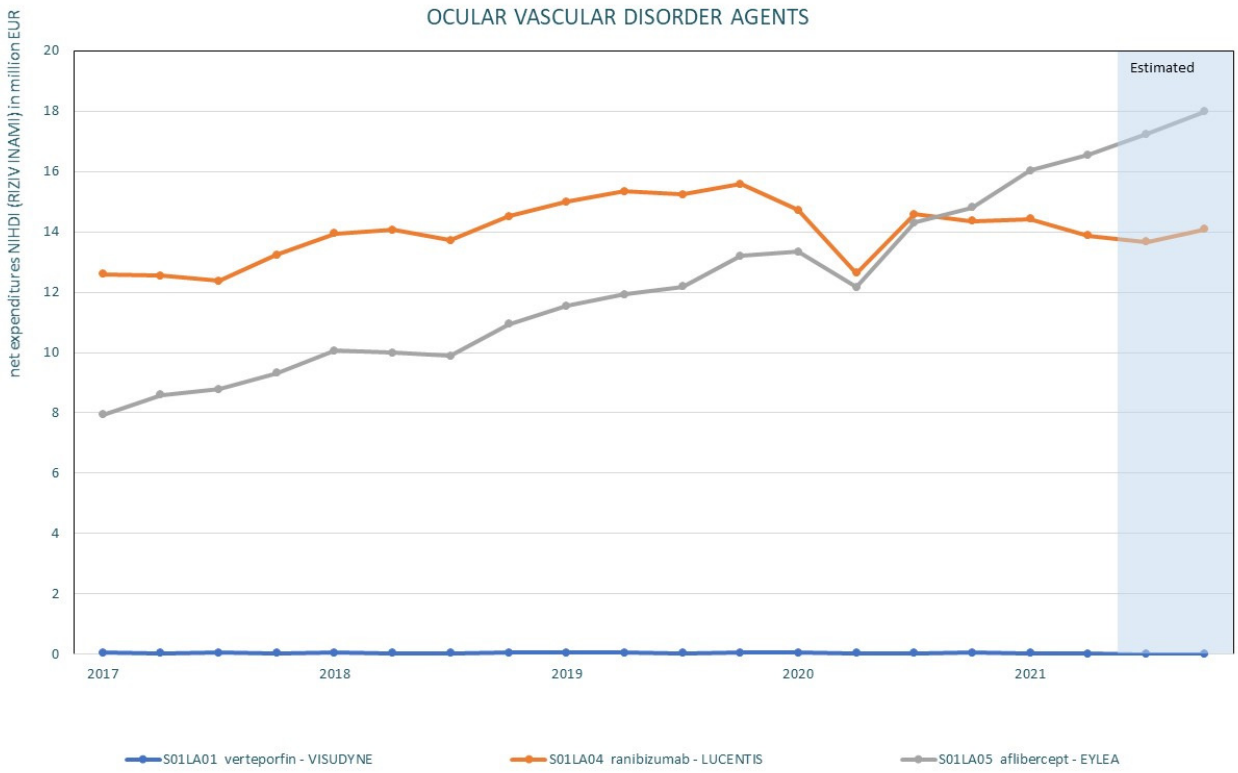


There are essentially 2 biological drugs, inhibitors of the vascular endothelial growth factor (VEGF), that are classified in class ATC S01LA ('*antineovascularisation agents*'): ranibizumab (Lucentis®, reimbursable since 2007) and aflibercept (Eylea®, reimbursable since 2013).

In hospitals there is a steady growth in 2021 of NIHDI expenditure (to > €120 million) and of the number of packages (to > 180,000) for these medicines.

Over the course of time, additional reimbursable indications have been added. These are macular oedema following central retinal vein occlusion, diabetic macular oedema, macular oedema as a result of a branch retinal vein occlusion and age-related macular degeneration. There are small differences between the reimbursable indications of both medicines. For example, unlike Lucentis®, Eylea® is also reimbursed for beneficiaries with visual impairment as a result of choroidal neovascularization in pathological myopia. This provides an explanation for the growth figures.

Figure 58: evolution of NIHDI net quarterly expenditure (hospitals (all patients) 2017 – 2021) for ATC class S01L ocular vascular disorder agents

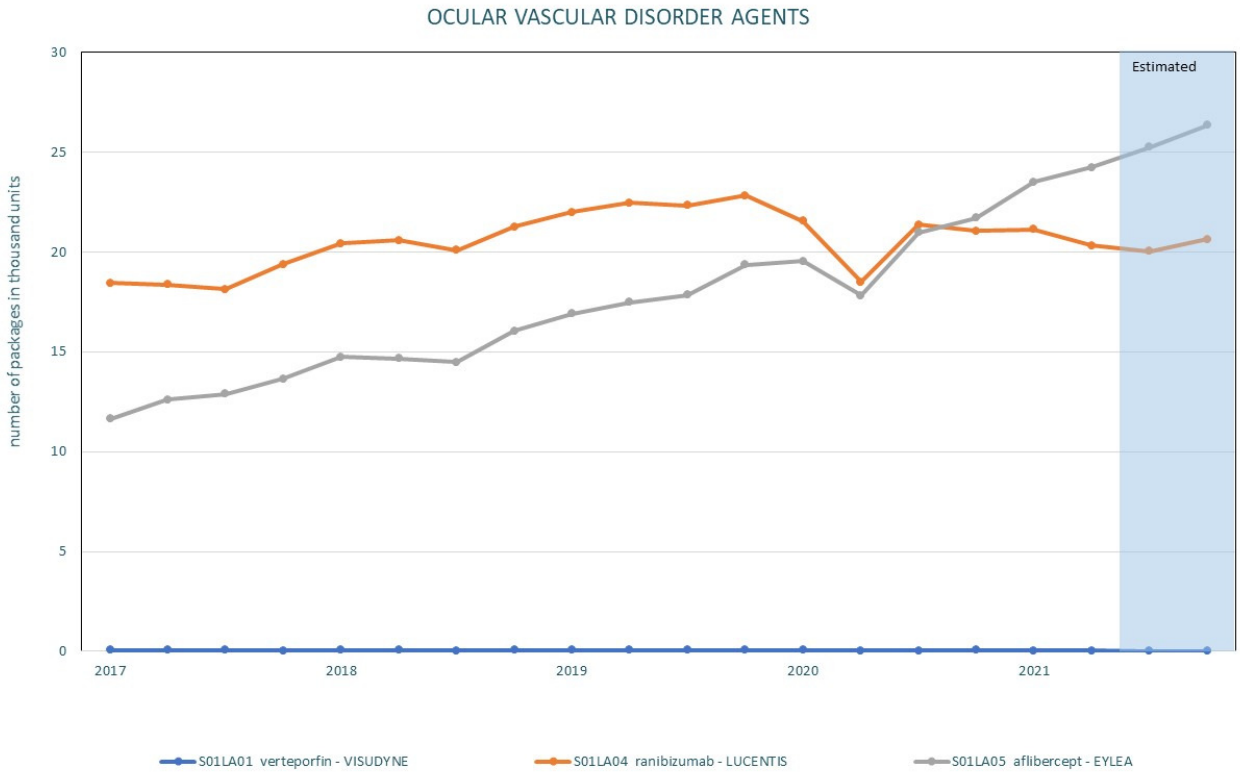


The market is dominated by Lucentis® and Eylea®. NIHDI expenditure for Visudyne® is negligible.
We see that NIHDI expenditure for Lucentis® remains stable and that it continues to rise for Eylea®, as a result of which Eylea® has been market leader since mid 2020. Previously, it was Lucentis®.

Until the end of 2021 both Eylea® as Lucentis® were temporarily reimbursable by the health insurance under a convention concluded between the NIHDI and the companies that market these drugs. The expenditure figures indicated for the health insurance take into account the 'nominal' ex-factory price of an injection vial (the dose corresponds to one injection), which is the same for the 2 products: €647. The expenditure is over-estimated because it takes no account of the confidential repayments made by the companies by virtue of these conventions. In 2022, the agreement of Lucentis® ended, followed by reimbursement at a (lower) list price. This had no influence on NIHDI expenditure until 2021.

In the spring of 2020, regular care was postponed due to the COVID-19 crisis. Furthermore, as an exceptional measure in the context of the COVID-19 crisis, from April 2020 both medicines were made available in public pharmacies. This could explain the drop in NIHDI expenditure in hospitals for this period.

Figure 59: *evolution of number of* packages *per quarter (hospitals (all patients) 2017 – 2021) for ATC class S01L ocular vascular disorder agents*



The WHO has not defined a DDD for these products. Therefore, the graph above shows the number of packages over the years. Each intraocular injection requires packaging (an injection vial or pre-filled pen). The number of packages follows the rising trend in NIHDI expenditure, given that the price of both medicines was the same until 2021.

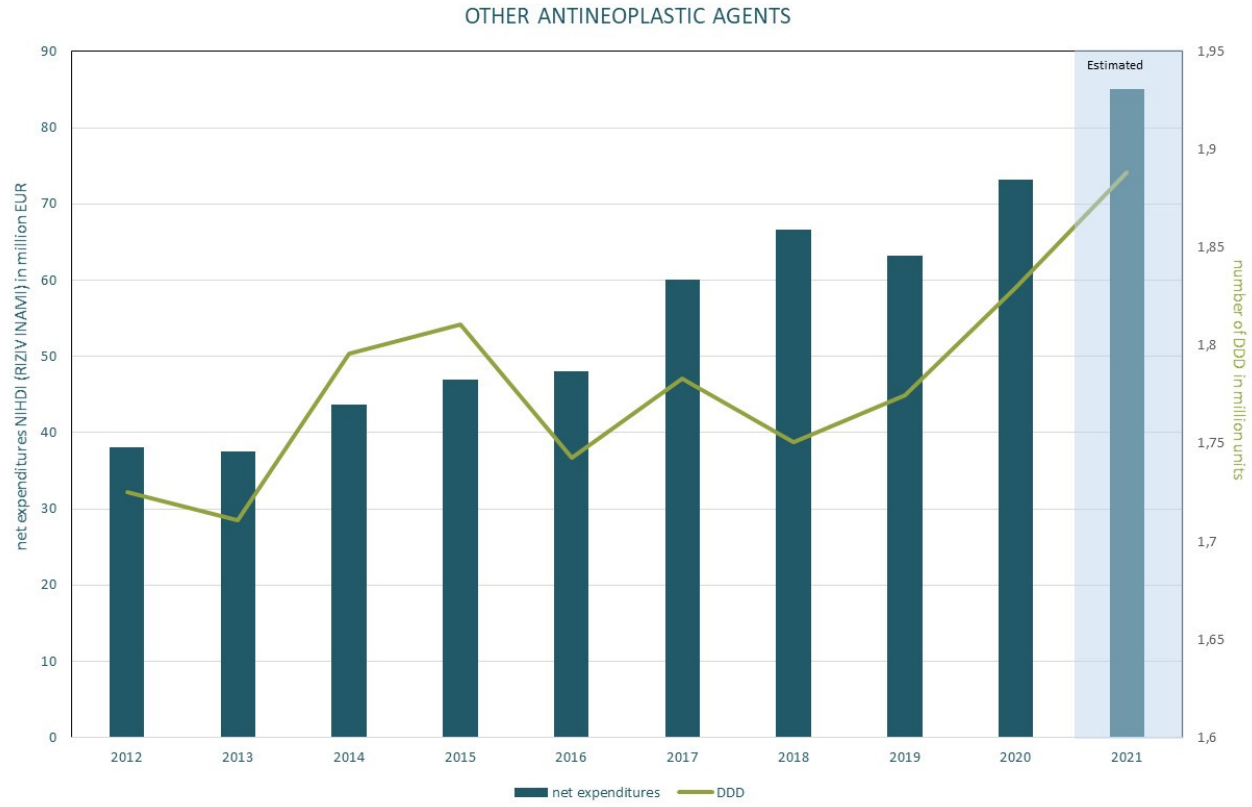
L01X – OTHER ANTINEOPLASTIC AGENTS

In ATC class L01X, the growth found in the previous years has continued, both in net expenditure and in the number of DDDs.
It needs to be noted that this class experienced a strong increase in 2017, especially where net expenditure is concerned, with an exception in 2019. Except for those two years, growth remains similar (15-20% per year):

- ~25.2% in 2017 compared to 2016
- 11.0% in 2018 compared to 2017
- 5.2% decrease in 2019 compared to 2018
- 15,6% in 2020 compared to 2019
- 16,2% in 2021 compared to 2020

We note that the ATC code of the class of protein kinase inhibitors and that of monoclonal antibodies and antibody conjugates changed in 2021 and 2022 respectively. In 2021, the subgroup L01XE was eliminated and included in the new class L01E. In 2022, the subgroup L01XC was eliminated and included in the new class L01F. This explains the difference between the figures from this report and the figures from the MORSE report 2019. Given that the new classes L01E and L01F are responsible for a significant part of the rising expenditure for that old class, this no doubt explains that the growth in expenditure remains similar each year.

Figure 60: *evolution of NIHDI net annual expenditure and number of DDDs (hospitals (all patients) 2012 – 2021) for ATC class L01X other antineoplastic agents*



Since the period of the previous report, expenditure for the pharmaceuticals Velcade® (bortezomib) and Kyprolis® (carfilzomib) has decreased sharply from 2018-2019, although Kyprolis® remains responsible for an important share of expenditure. These two pharmaceuticals are indicated in various indications of multiple myeloma.
In 2019, expenditure for Velcade® decreased sharply following the advent of the first generic, which contributed to the drop in total net expenditure that year, while the number of DDDs remained stable. This is not the case for Kyprolis®. The peak in expenditure at the end of 2017 followed by a drop in the course of 2018 can also be seen in the number of DDDs.

Expenditure for other pharmaceuticals, such as Lynparza® (olaparib), increases constantly. Since its inclusion in the reimbursement list in 2015, Lynparza® is indicated for numerous conditions, including the treatment of breast cancer, ovarian cancer, pancreatic or prostate cancer. Consequently, the number of DDDs of Lynparza® has also experienced a constant growth.

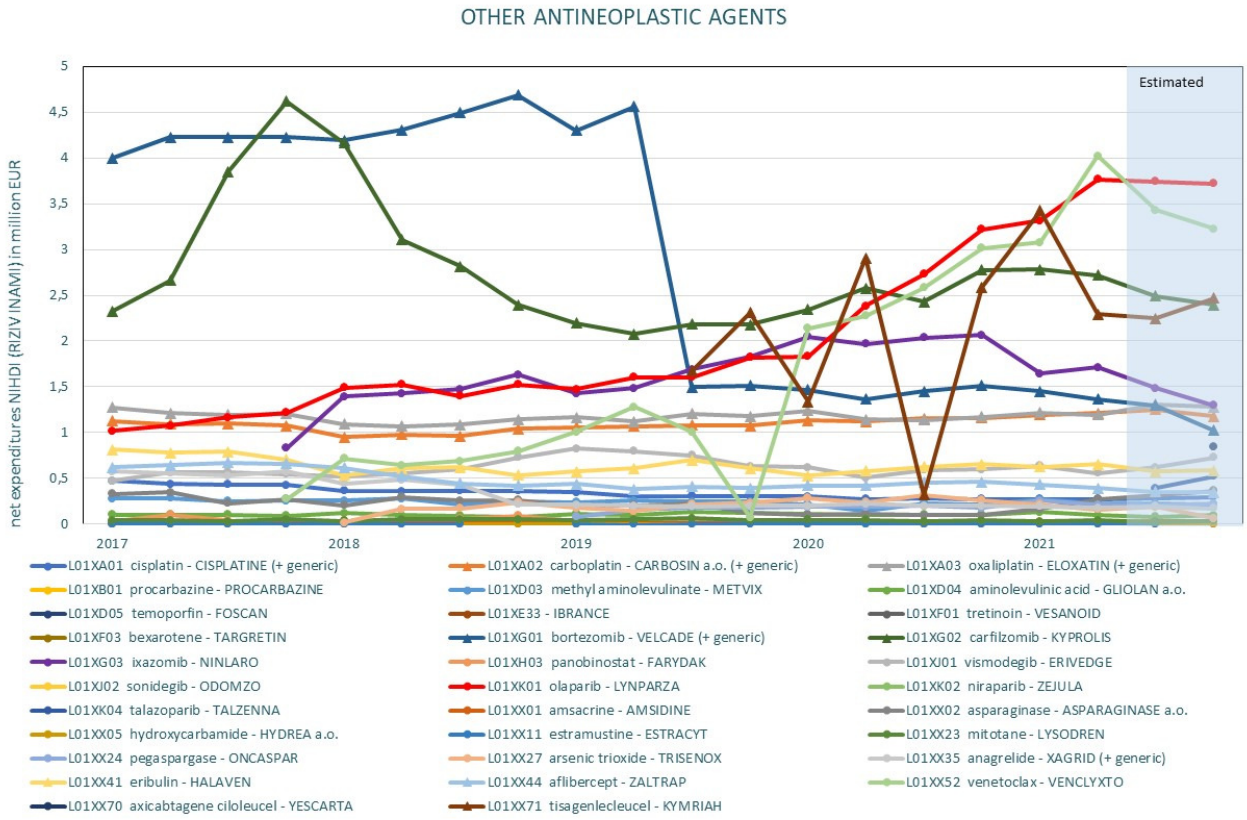
Kimryah® (tisagenleuclesel), together with Yescarta® (axicabtagene ciloceulel), is one of the first two therapies of the CAR-T type that are authorised by the European Medicines Agency. Kimryah® has been reimbursed in Belgium since 1 June 2019 and has generated high expenditure until now, although this has varied quite a lot from year to year. This can probably be explained by the fact that patients treated with Kimryah® are highly selected. Given the very high cost of this therapy, a very small variation in the number of patients treated can greatly affect expenditure. Kimryah® is indicated for various hemato-oncological conditions.
Venclyxto® (venetoclax) is also part of the top four where expenditure is concerned and is also indicated for various hemato-oncological conditions.

The last three pharmaceuticals for which expenditure is higher than €1 million per trimester are Ninlaro® (ixazomib) and pharmaceuticals containing cisplatin and carboplatin. Ninlaro® is indicated for the treatment of the progression of multiple myeloma. Platinum-based chemotherapies (oxaliplatin and carboplatin) also generate high expenditure due to their numerous indications, which is confirmed by the number of DDDs of carboplatin (see below).

The considerable increase found in 2017 may be due to the start of the reimbursement of various pharmaceuticals that generate high expenditure, such as Venclyxto® and Ninlaro®, and to the increase in expenditure for Kyprolis® and, to a lesser extent, Lynparza®.

However, it should be noted that several of these pharmaceuticals (Kyprolis®, Lynparza®, Kimryah®, Venclyxto®, Ninlaro®) are temporarily eligible for reimbursement via a convention concluded between the company concerned and the NIHDI. It is important to emphasise that the expenditure reported here is based on the list price of these drugs. The actual costs for the NIHDI are confidential and are calculated on the basis of compensations set out in a convention between the pharmaceutical company concerned and the NIHDI.

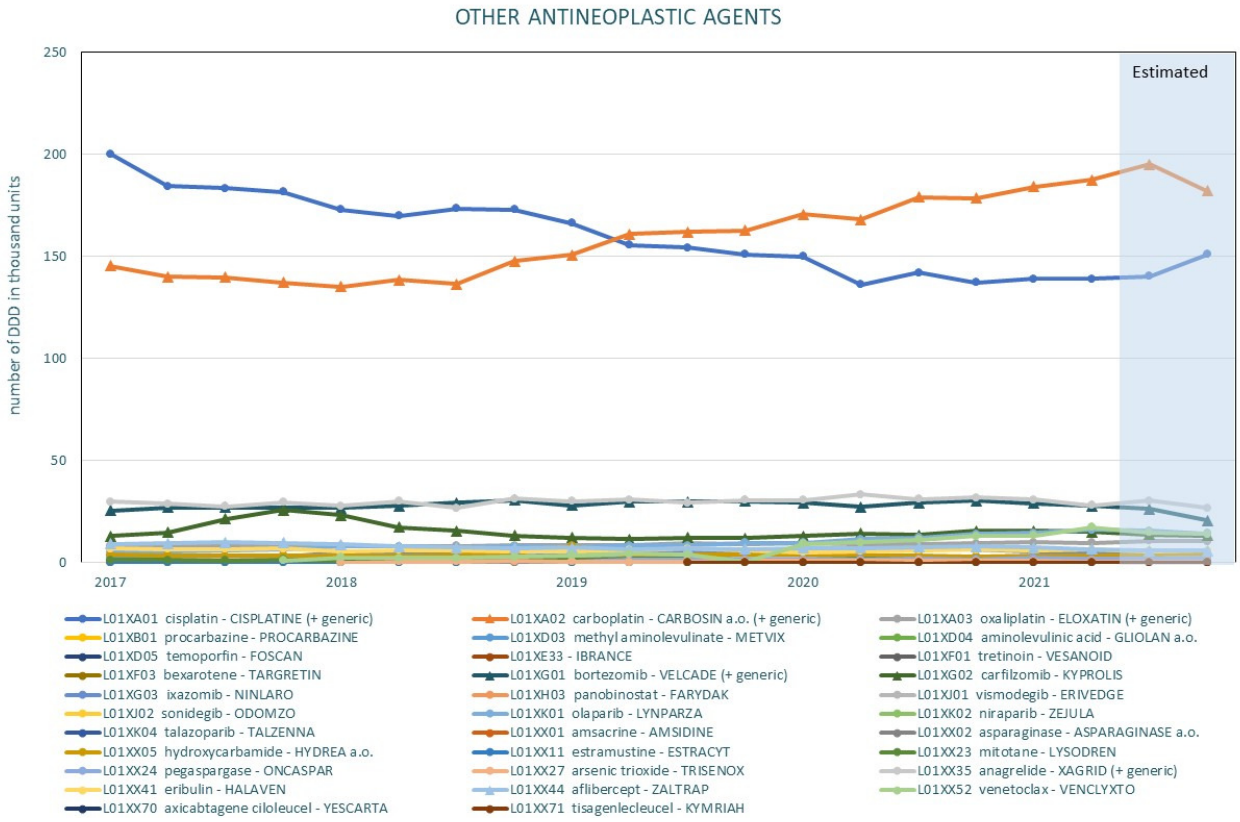
Figure 61: *evolution of NIHDI net quarterly expenditure (hospitals (all patients) 2017 – 2021) for ATC class L01X other antineoplastic agents*



As mentioned before, it is no surprise either that platinum-based chemotherapies (cisplatin and carboplatin) represent the highest numbers of DDDs, because they are administered for various indications in monotherapy or, more often, in combination therapies with new molecules.

Other pharmaceuticals, such as Kyprolis® and Velcade®, which make up a considerable share of expenditure, also represent a fairly high number of DDDs.

Figure 62: evolution of number of DDDs per quarter (hospitals (all patients) 2017 – 2021) for ATC class L01X other antineoplastic agents



R07A – OTHER RESPIRATORY SYSTEM PRODUCTS

The following medicines belong to ATC class R07A:

- Curosurf® is used in the treatment of hyaline membrane disease (Respiratory Distress Syndrome (RDS)) in newborns with a birth weight of more than 500 g.
- INOmax® is nitrogen oxide for inhalation and is used in neonates with breathing problems, or in patients of all ages after heart surgery or with pulmonary hypertension.
- Orkambi® consists of a combination of lumacaftor and ivacaftor. It is a CFTR modulator for the treatment of cystic fibrosis in patients who are homozygous for the F508del mutation.
- Symkevi® consists of a combination of tezacaftor and ivacaftor. It is a CFTR modulator for the treatment of cystic fibrosis in patients who are homozygous for the F508del mutation, or heterozygous for the F508del mutation with a residual function mutation. This medicine is invariably administered together with Kalydeco (ivacaftor).
- Kalydeco® (ivacaftor) is a CFTR modulator for the treatment of cystic fibrosis in patients with at least one gating mutation in monotherapy, or in combination with Symkevi® for the treatment of cystic fibrosis in patients who are homozygous for the F508del mutation, or heterozygous for the F508del mutation with a residual function mutation. Since recently (September 2022) it is also reimbursed in combination with Kaftrio®, but this is not reflected yet in these graphs.

Figure 63: evolution of NIHDI net annual expenditure and number of DDDs (hospitals (all patients) 2012 – 2021) for ATC class R07A other respiratory system products

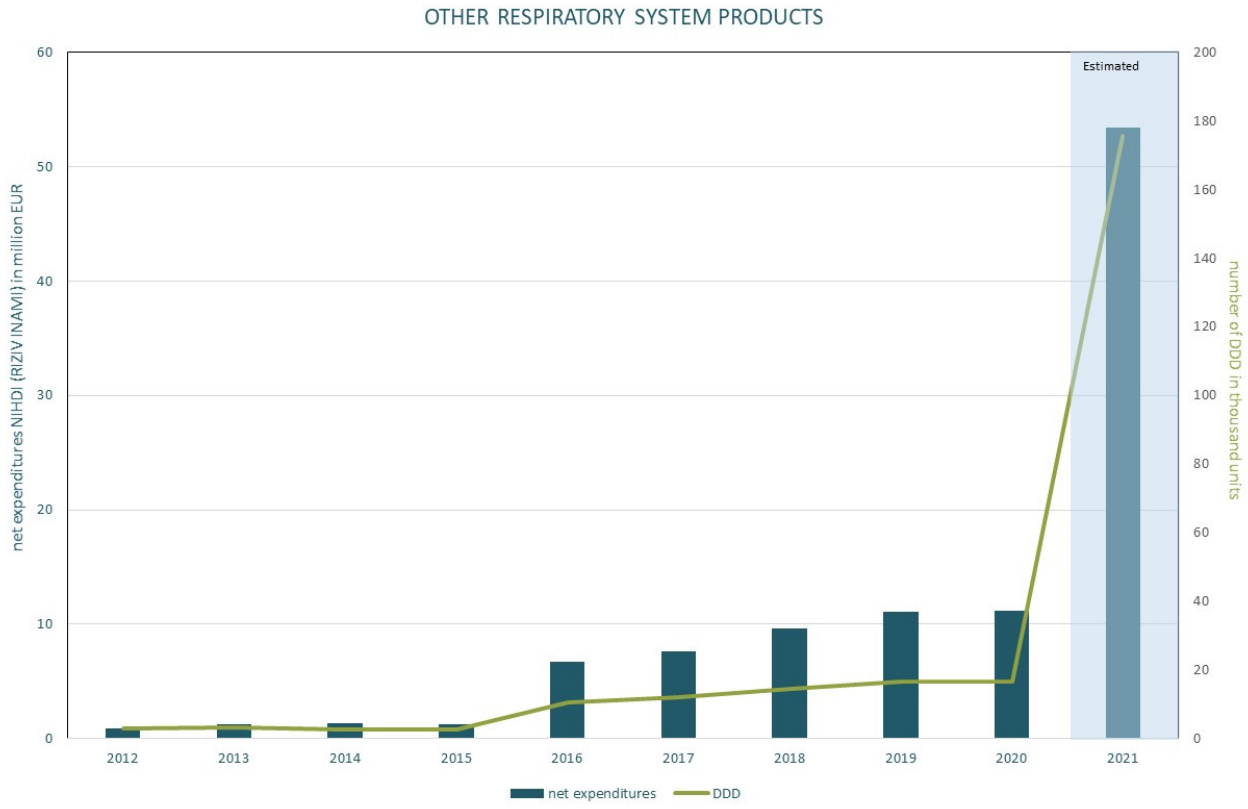
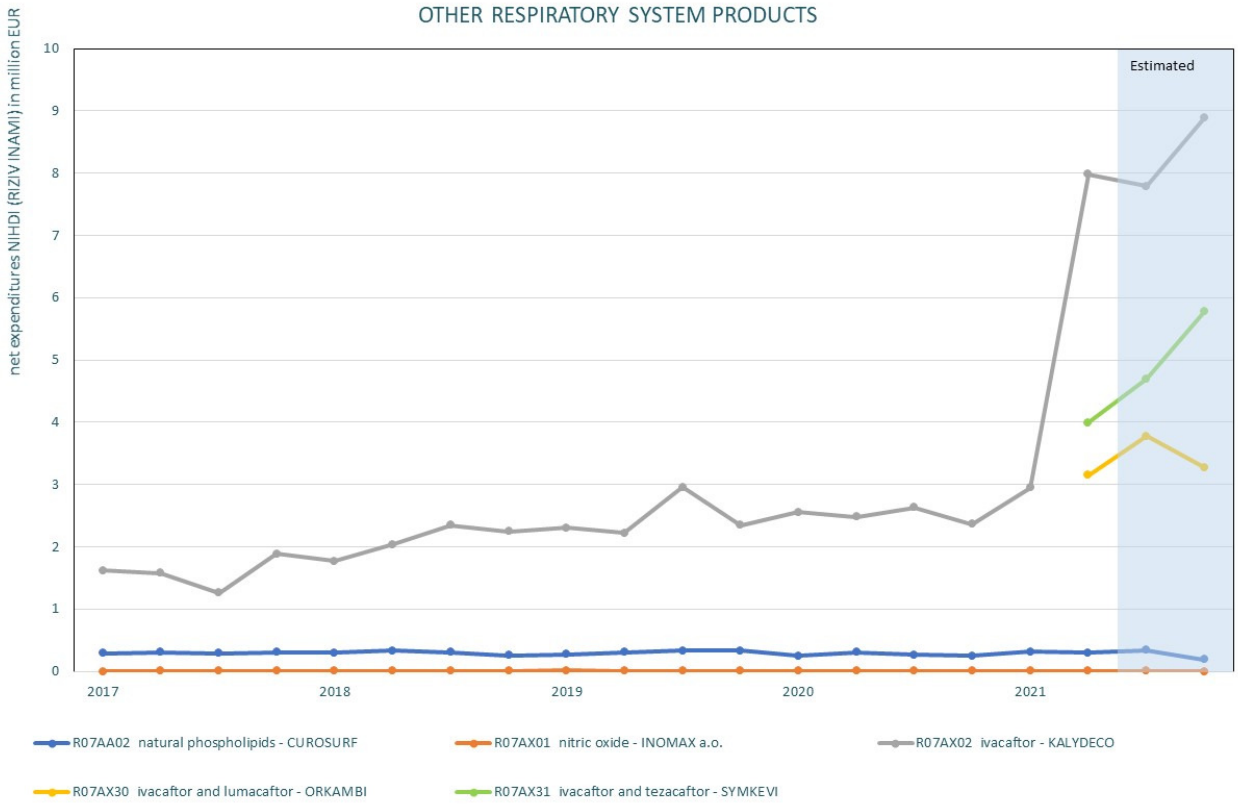


Figure 63 shows that expenditure in this class has increased sharply, first in 2016 as a result of the reimbursement of the first CFTR modulator, Kalydeco® (ivacaftor), and then an even stronger increase in 2021. The latter can also be attributed to the reimbursement of CFTR modulators, with in this case Symkevi®, in combination with Kalydeco®, which has been reimbursed since the beginning of 2021 for the treatment of cystic fibrosis in patients from the age of 12 who are homozygous for the F508del mutation, or heterozygous for the

F508del mutation with a residual function mutation. The contribution of the individual CFTR modulators is shown more clearly in Figure 64.

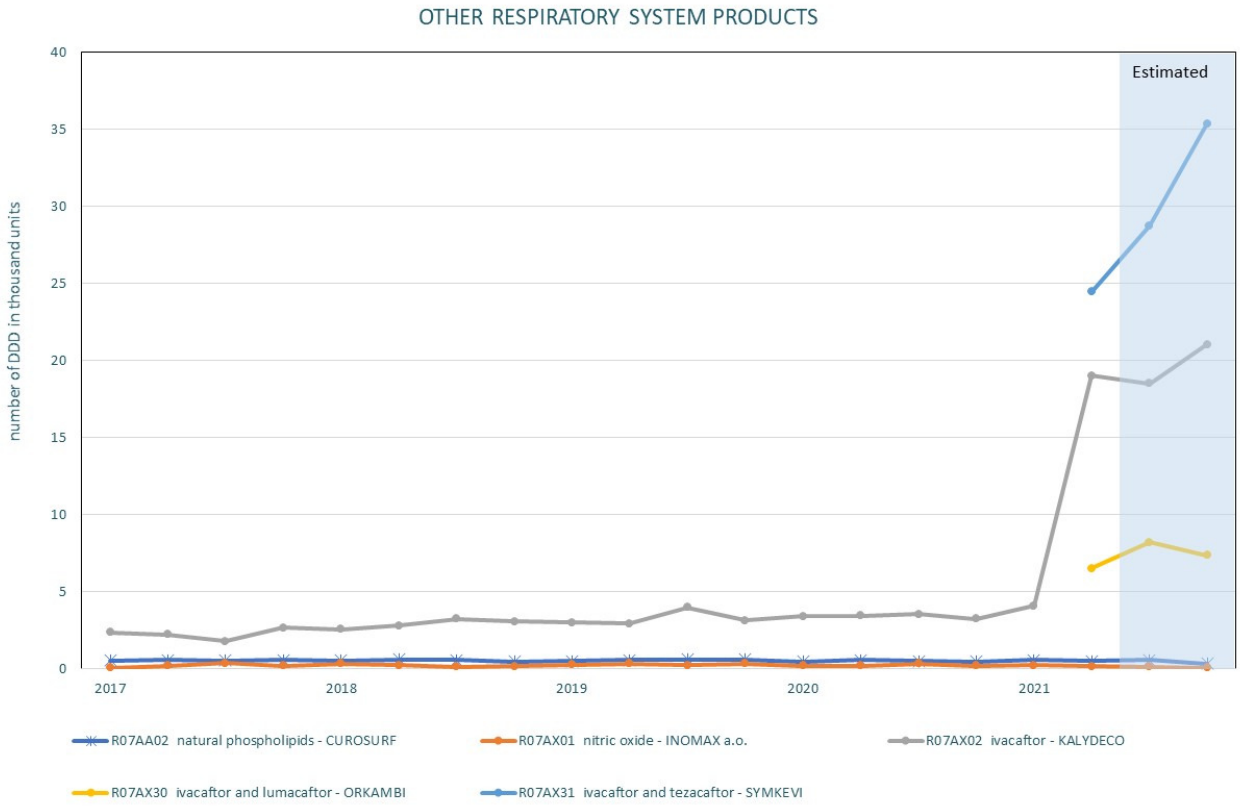
Figure 64: *evolution of NIHDI net quarterly expenditure (hospitals (all patients) 2017 – 2021) for ATC class R07A other respiratory system products*



The use of Orkambi® initially increased after its reimbursement became authorised on 1 April 2021 for homozygous patients, but decreased again in the third quarter of 2021. Also on 1 April 2021, Symkevi® 100/150mg was approved for use in patients from the age of 12 who are homozygous for F508del or heterozygous for F508del with a residual function mutation. The initial increase in the use of Orkambi®, followed by the decrease in the third quarter, may be due to the higher degree of interactions and side effects that are observed for this therapy in comparison with Symkevi® + Kalydeco®. The latter is also reimbursed for homozygous F508del patients, which means that initial Orkambi® patients may have switched to this combination therapy. The reimbursement of Symkevi® for F508del patients is clearly visible in the strong increase in expenditure for Kalydeco®.

It is important to note that all CFTR modulators are included on a temporary basis in the framework of an agreement. Thus, the real net expenditure is lower than that shown in the graphs above.

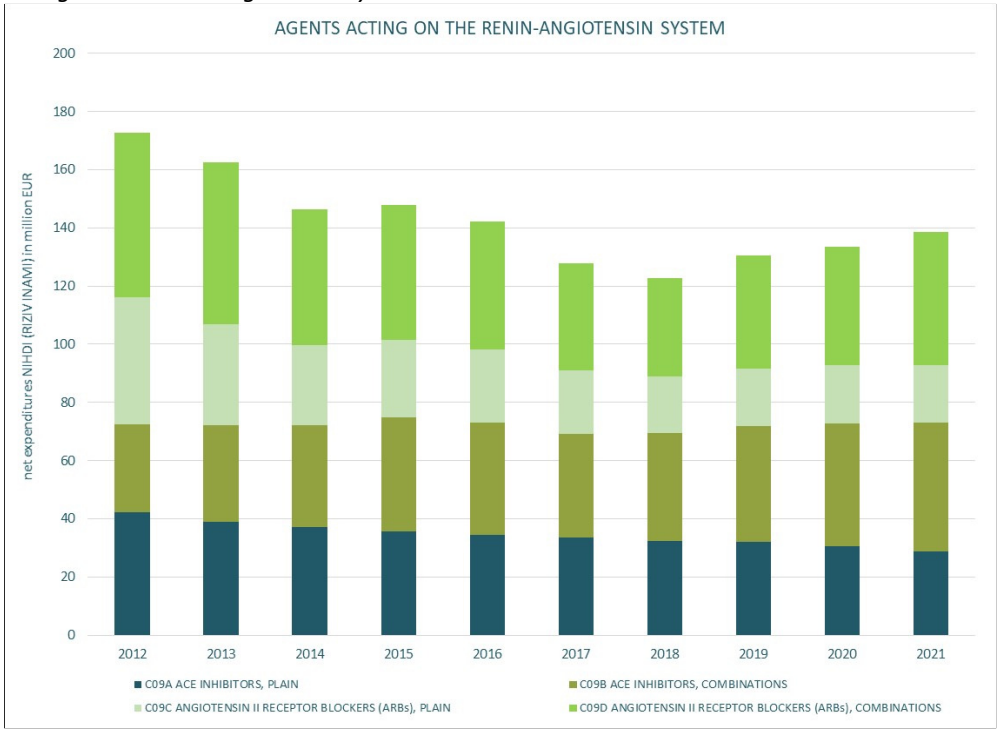
Figure 65: *evolution of number of DDDs per quarter (hospitals (all patients) 2017 – 2021) for ATC class R07A other respiratory system products*



The increased expenditure for NIHDI for CFTR modulators is also reflected in the DDDs supplied. The evolution here is similar, although the fact that the number of DDDs for Kalydeco® is lower than for Symkevi® stands out. This is due to the definition of a DDD, which was set at two a day for Kalydeco®, whereas, in practice, only one dose of Kalydeco® is administered when it is used in combination with Symkevi®. Given that the indication for Symkevi® + Kalydeco® is much greater than for Kalydeco® monotherapy, this has a great weight, which is why the share of Kalydeco® seems smaller.

C09 – AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM

Figure 66 : evolution of NIHDI net annual expenditure (public pharmacies 2012 – 2021) for ATC class C09 agents acting on the renin-angiotensin system



Expenditure on the class of agents acting on the renin-angiotensin system fell noticeably in the years up to and including 2018. Since then, we can see a continued slight increase again in expenditure on this class. What catches the eye is that ACE inhibitors have shown a very slight but consistent decrease since 2012. Combinations based on angiotensin II receptor blockers (C09D) and combinations based on ACE inhibitors (C09B) are mainly responsible for this increase.

Figure 67: evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2018 – 2021) for ATC class C09 agents acting on the renin-angiotensin system

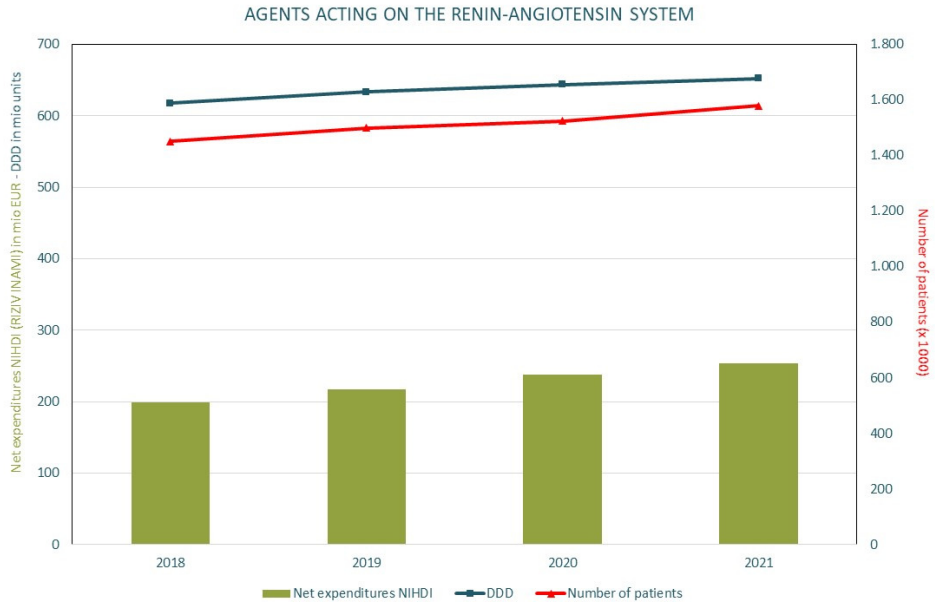


Figure 68: evolution of NIHDI net annual expenditure (public pharmacies 2012 – 2021) for ATC class C09B ACE inhibitors, combinations

Since 2012, a rising trend in expenditure can be observed for the class of ACE inhibitor-based combination preparations. There was only a slight decrease in 2016 and 2017. The cause of this was the application of the 'combicliff' for pharmaceuticals based on perindopril + amlodipine (Coveram® + generics). After 2017, we see a gradual increase again in the net annual expenditure, which continues until 2021.

Figure 69: evolution of NIHDI net monthly expenditure (public pharmacies 2017 – 2021) for ATC class C09B ACE inhibitors, combinations

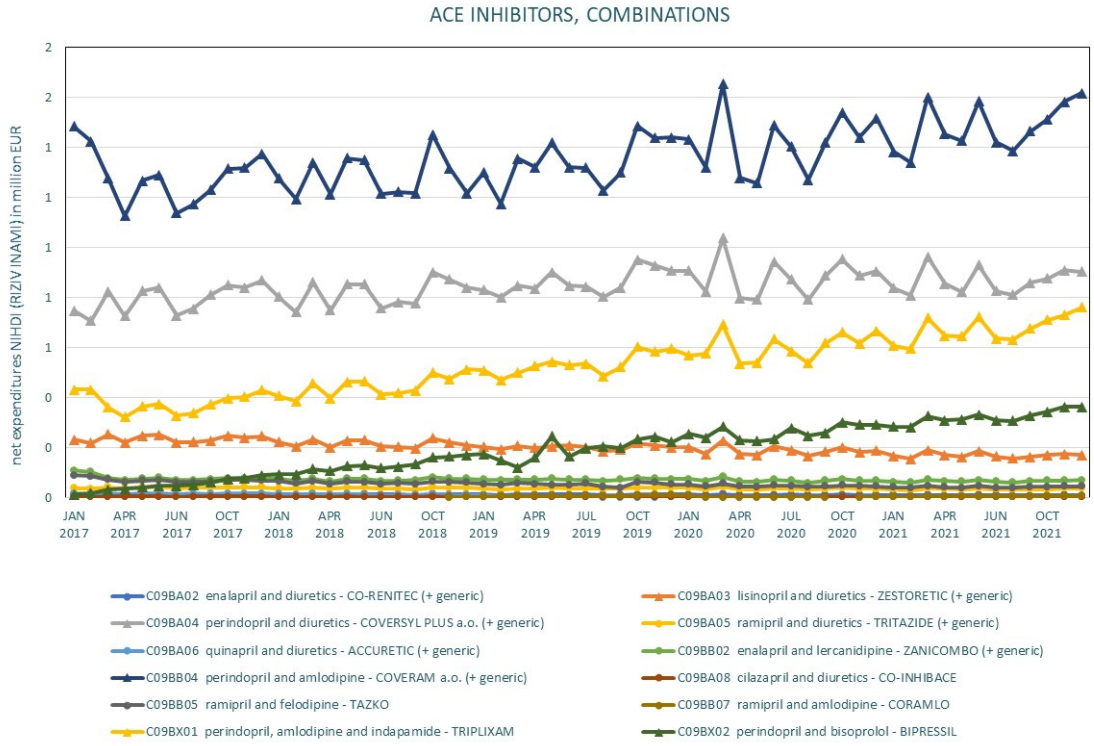


Figure 70: evolution of monthly number of DDDs (public pharmacies 2018 – 2021) for ATC class C09B ACE inhibitors, combinations

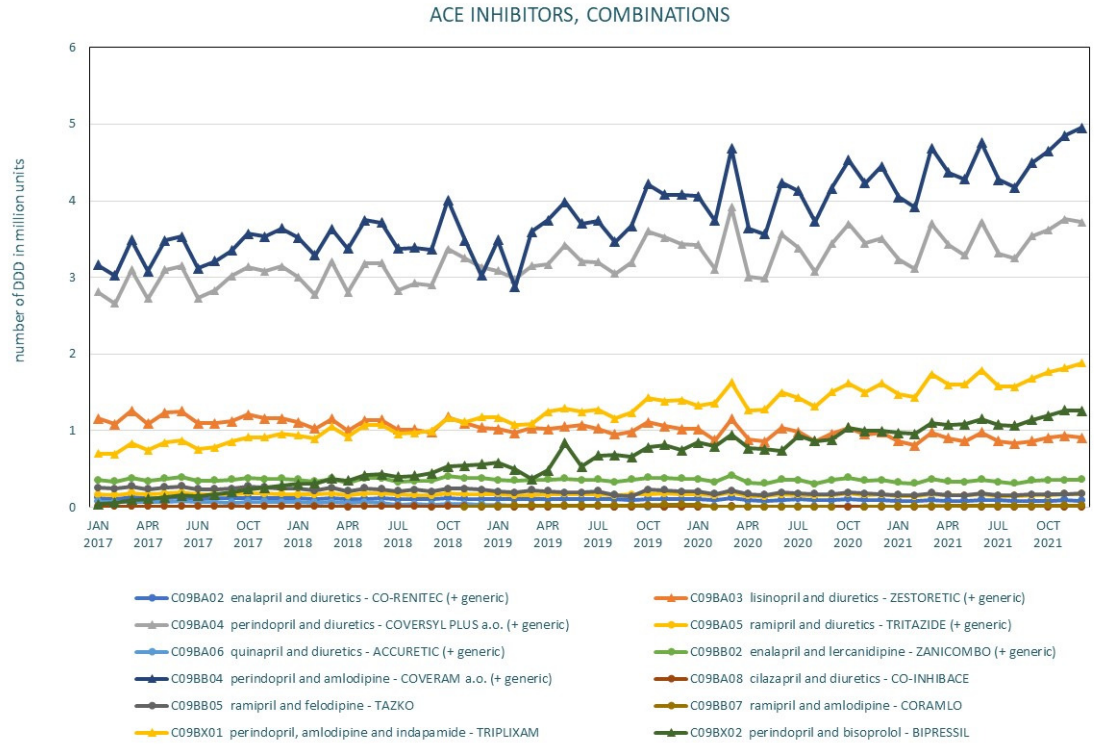
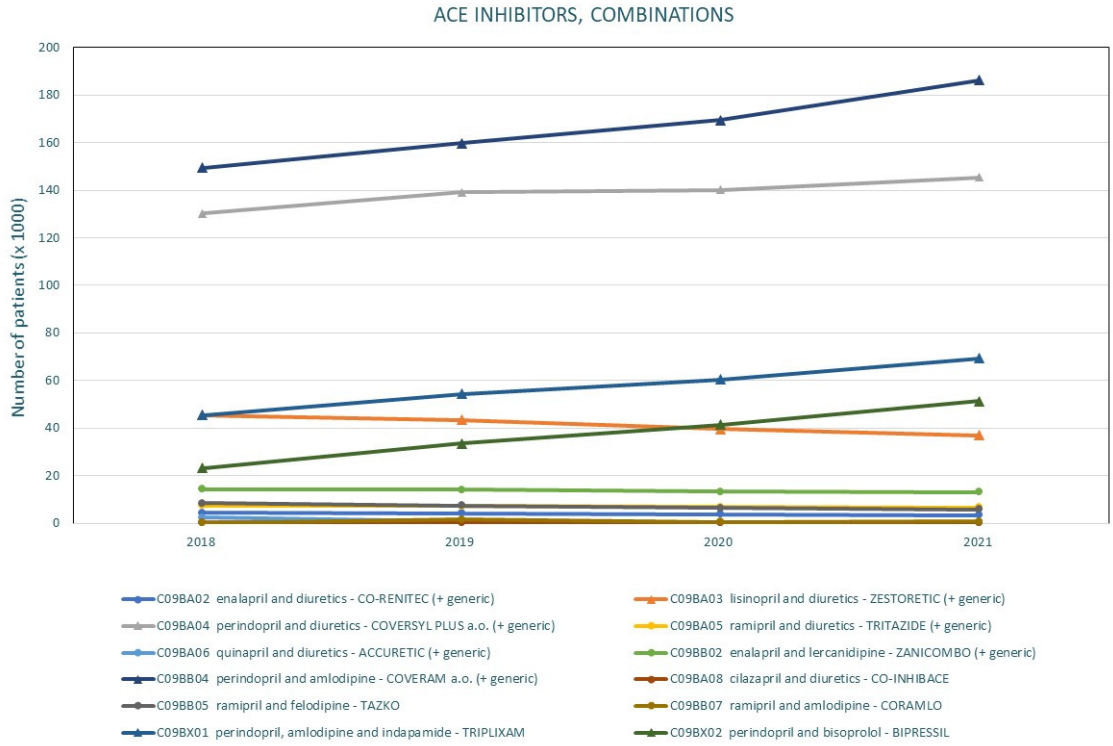
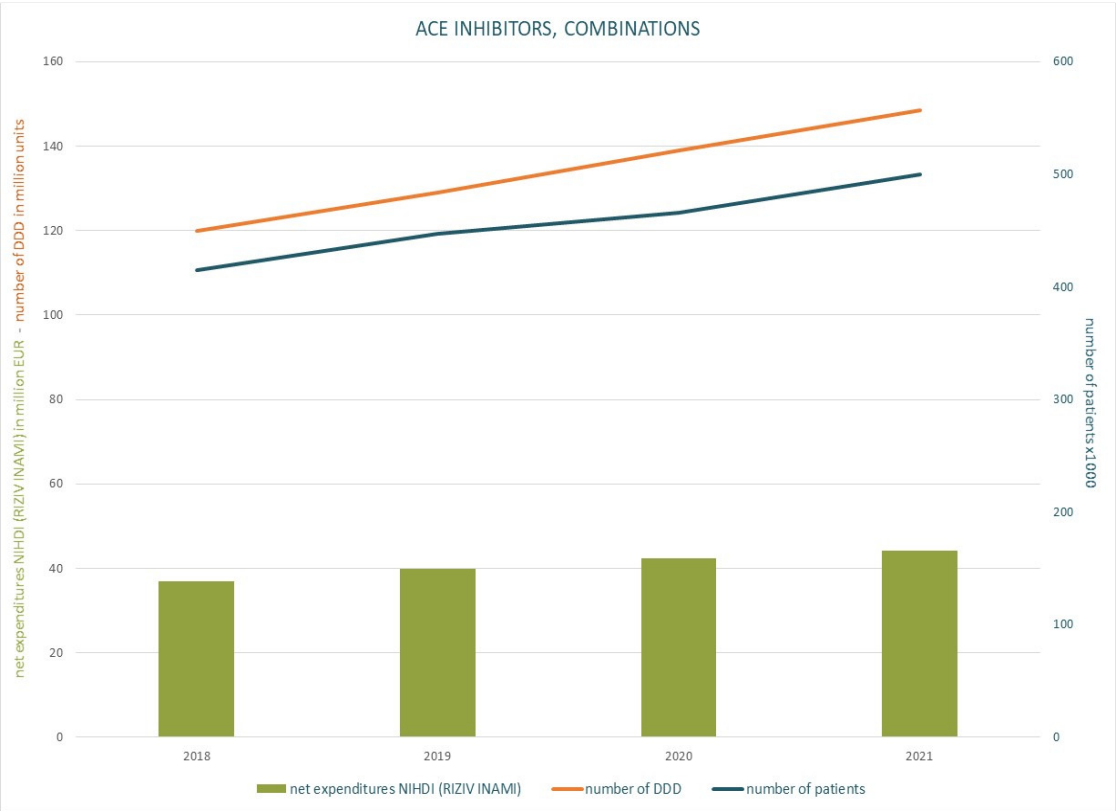


Figure 71: evolution of number of patients per year (public pharmacies 2018 – 2021) for ATC class C09B ACE inhibitors, combinations



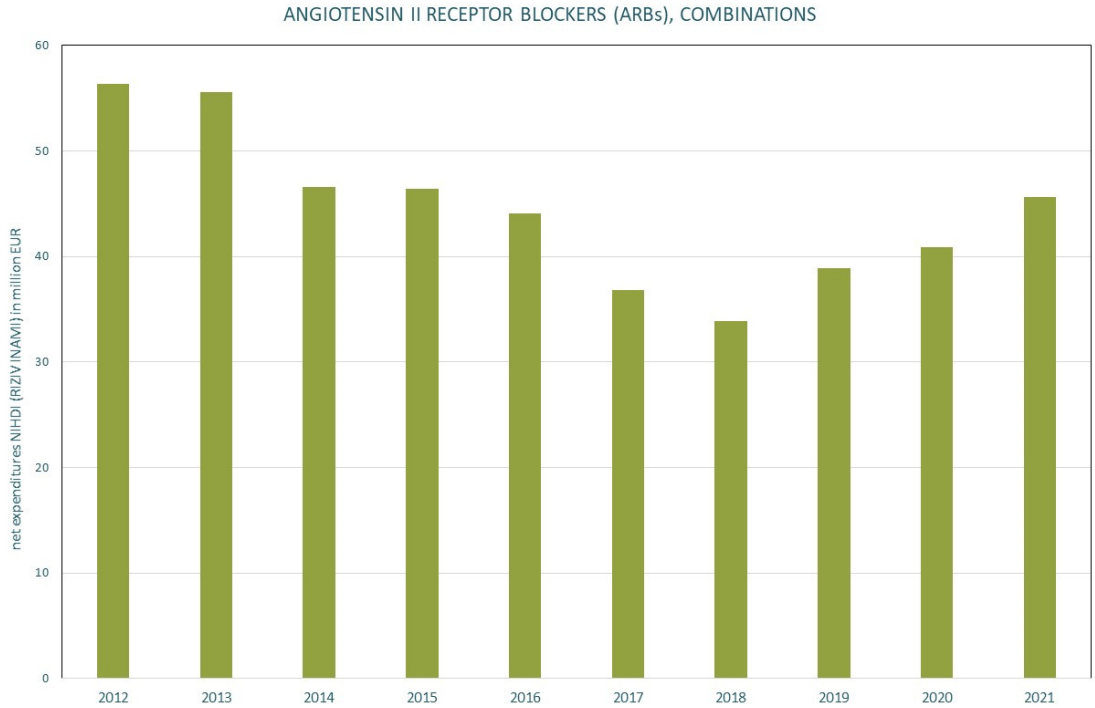
As well as a gradual increase in expenditure on perindopril + amlodipine (Coveram® + generics) and periodopril + indapamide (Coversyl plus® + generics), we can also see a clear upward trend in expenditure on the pharmaceuticals Triplixam® and Bipressil®. We can see the same trend with regard to the number of DDDs per month and the number of patients. For the pharmaceutical Zestoretic® we see a moderate decrease from 2018 onwards in expenditure, but also in the number of patients and DDDs per month.

Figure 72: evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2018 – 2021) for ATC class C09B ACE inhibitors, combinations



In conclusion, we can say that since 2018, both the expenditure, the number of patients and the number of DDDs have increased.

Figure 73: evolution of NIHDI net annual expenditure (public pharmacies 2012 – 2021) for ATC class C09D angiotensin II receptor blockers, combinations



Expenditure for the combination preparations of angiotensin II antagonists has gradually decreased since 2012. We do see however a steep fall in 2017, this is mainly due to:

- the group review of the sartans, leading to transfer of all olmesartan-based pharmaceuticals to chapter I on 1 April 2017, with the resulting 10% price reduction, and
- application, on 1 July 2017, of the reference reimbursement system and the combi-cliff to (combination) preparations based on olmesartan medoxomil, i.e., within ATC class C09D, Sevikar® (+ generics), Sevikar HCT® and Belsar plus® (+ generics). The reduction is partially offset by the steep increase in expenditure on the pharmaceutical Entresto®, which in previous years was partially reimbursed under a convention, but which has been eligible for full reimbursement since 1 June 2020.

Since 2019 there has also been an increase again in expenditure within this class. This trend continued in 2020 and 2021 and is almost entirely due to the increased expenditure on Entresto®. The pharmaceutical Entresto® has been included in the reimbursement list since 1 November 2016. Since then, expenditure for this pharmaceutical has increased, and it will continue to do so. The number of patients for this pharmaceutical is also increasing.
Following a period of stable numbers of DDDs per month from 2014 up to and including 2017, we can see a clear increase for the years 2018 up to 2021. This is largely due to the following pharmaceuticals, which have seen a definite rise in the number of patients and monthly DDDs in recent years:

- Sevikar® (+ generics): a combination based on olmesartan medoxomil and amlodipine;
- Sevikar HCT®: a combination based on olmesartan medoxomil, amlodipine and hydrochlorothiazide;
- Belsar plus® (+ generics): a combination based on olmesartan medoxomil and hydrochlorothiazide;
- Entresto®: a combination based on sacubitril and valsartan.

Figure 74: evolution of NIHDI net monthly expenditure (public pharmacies 2017 – 2021) for ATC class C09D angiotensin II receptor blockers, combinations

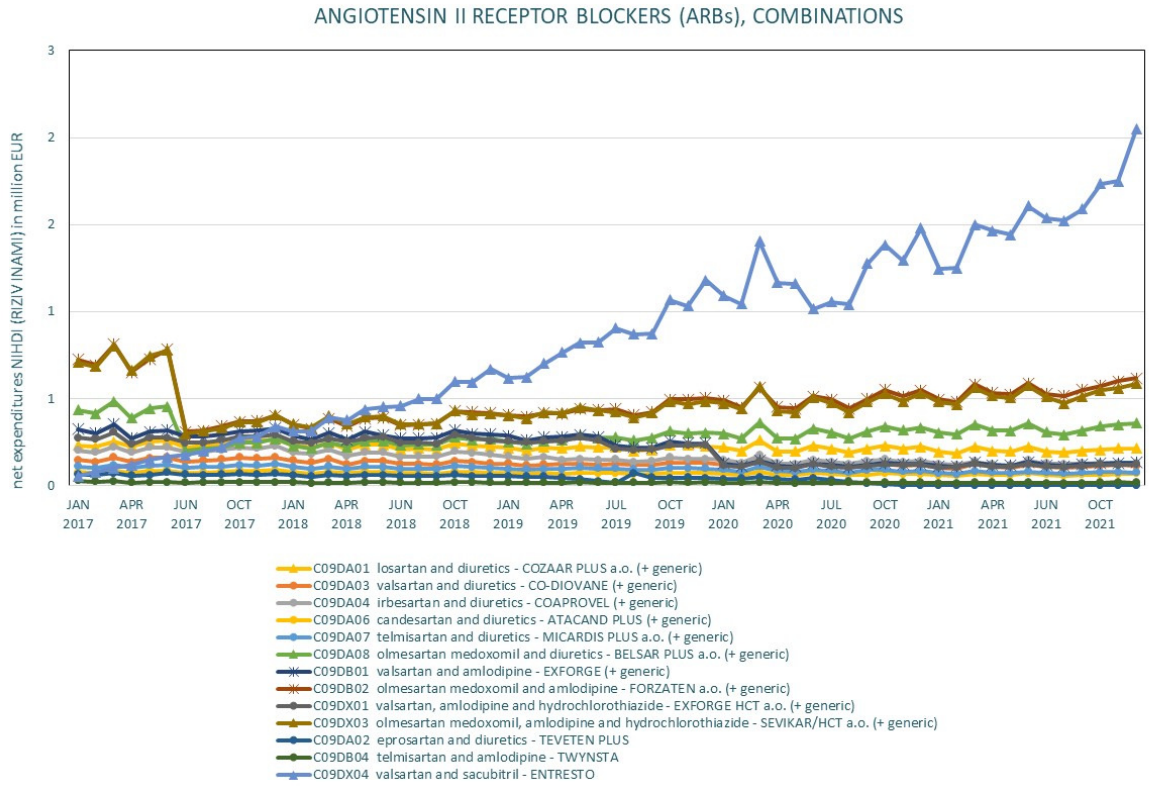


Figure 75: *evolution of monthly number of DDDs (public pharmacies 2018 – 2021) for ATC class C09D angiotensin II receptor blockers, combinations*

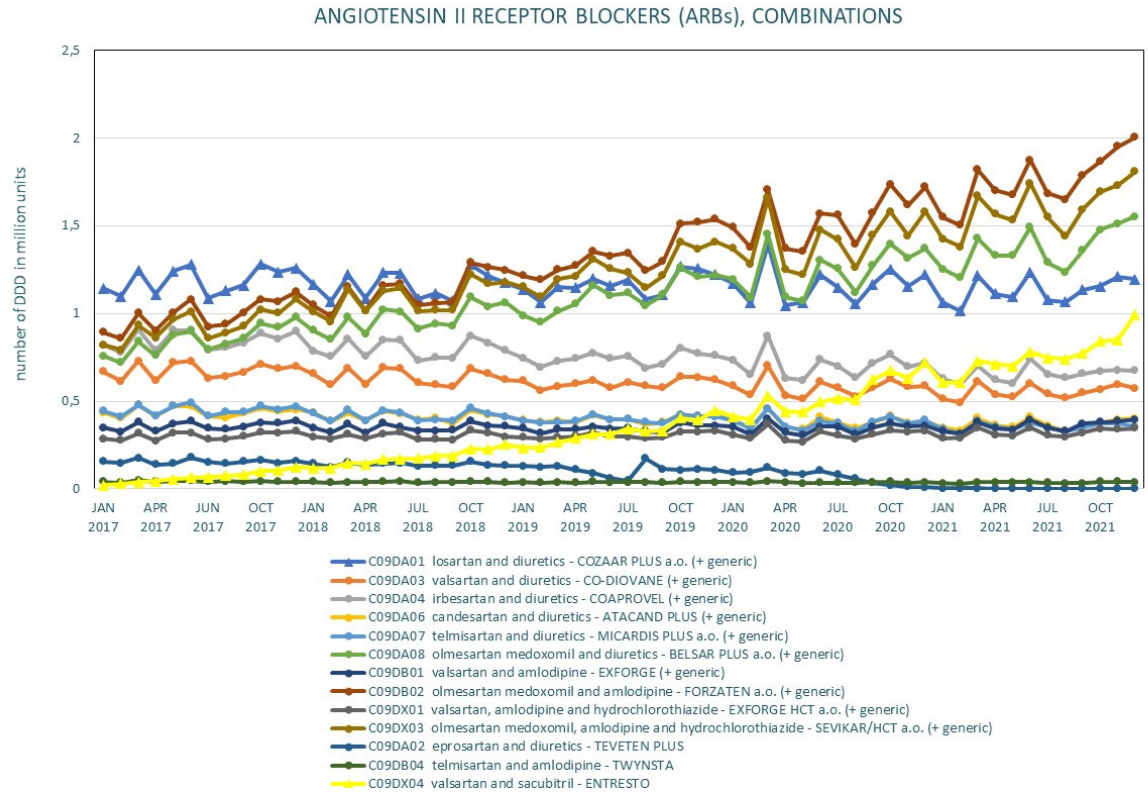


Figure 76: evolution of number of patients per year (public pharmacies 2018 – 2021) for ATC class C09D angiotensin II receptor blockers, combinations

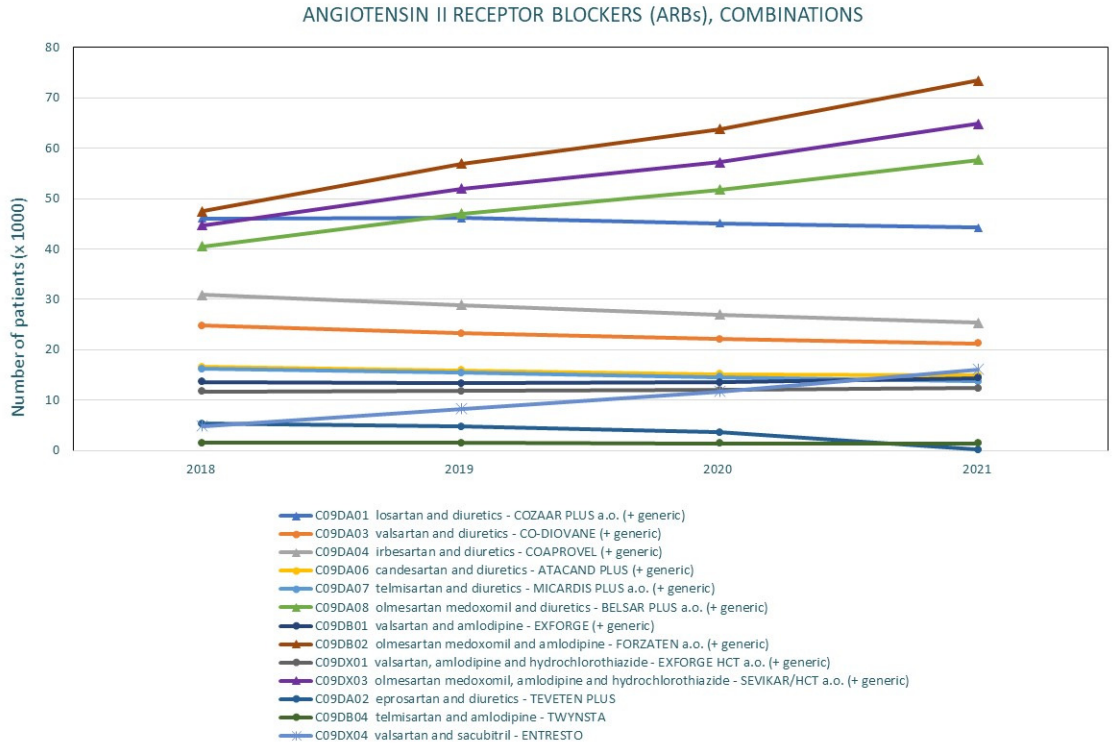
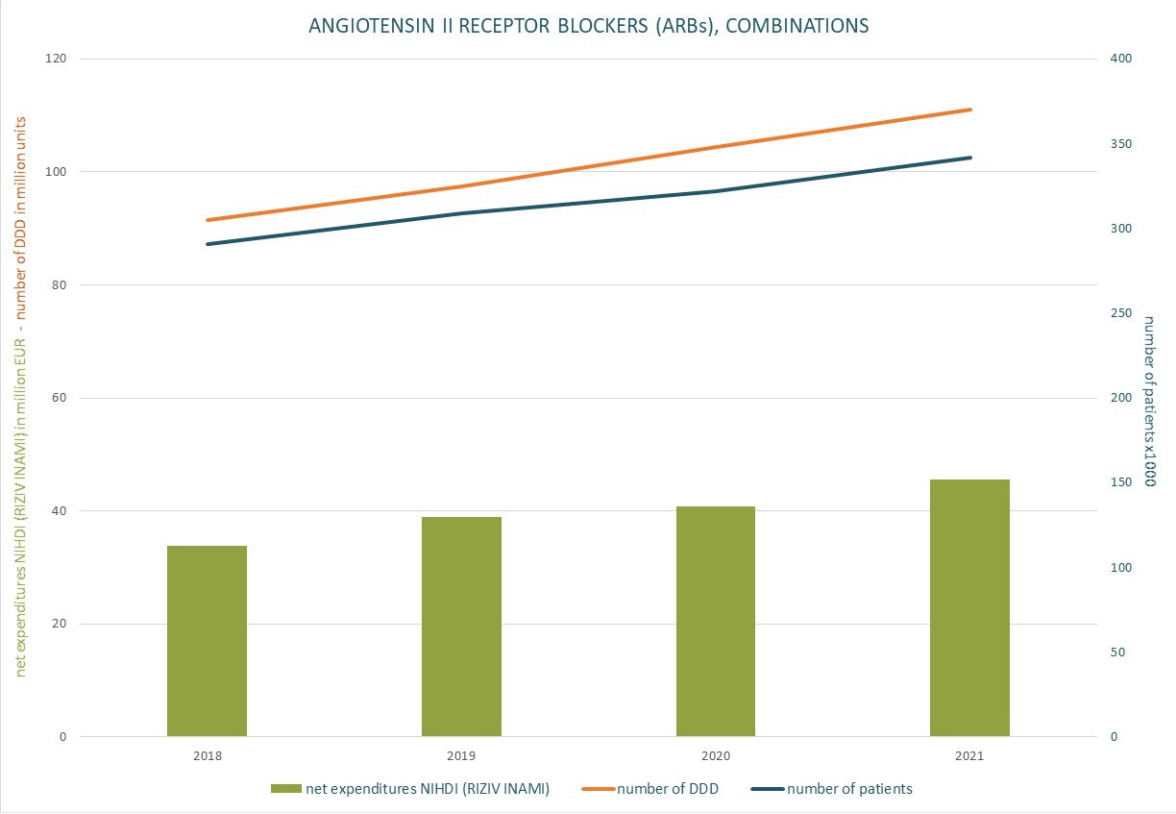
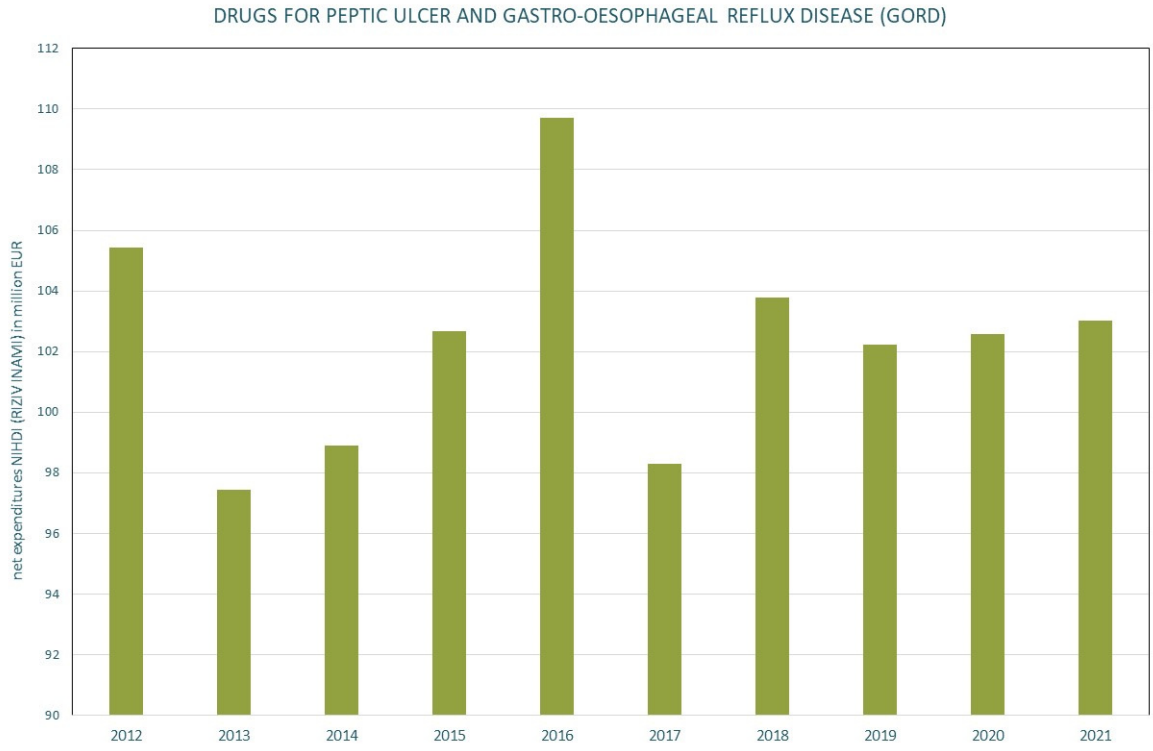


Figure 77: evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2018 – 2021) for ATC class C09D angiotensin II receptor blockers, combinations



In conclusion, we can say that since 2018, both the expenditure, the number of patients and the number of DDDs have clearly increased.

Figure 78: evolution of NIHDI net annual expenditure (public pharmacies 2012 – 2021) for ATC class A02B drugs for peptic ulcer and reflux disease



Up to and including 2016, a clear increase could be seen in the net expenditure and number of DDDs for ATC class A02B, drugs used to treat peptic ulcer and reflux disease.

In 2017, a distinct kink can be seen, both in the curve representing the number of DDDs and in the curve for net expenditure. This was due to the group review of this particular ATC class, which resulted in a number of important changes taking effect on 1 April 2017:

- Transfer from chapter II ('a posteriori' check) to chapter IV ('a priori' check) of large packages (more than 60 units) of pharmaceuticals having omeprazole, lansoprazole, pantoprazole or rabeprazole as their active substances, with reimbursement in category A for treatment of Zollinger-Ellison syndrome and post-treatment of radiofrequency ablation of the oesophageal mucus for Barrett's mucosa;
- On 1 April 2017, there was a 33% reduction in the ex-factory price of large packages of lansoprazole 30 mg - 84 tablets, 98 tablets and 100 tablets - and, since then, they are eligible for reimbursement in chapter IV.

After this, on 1 January 2017, a cost-containment measure was applied for generic pantoprazole-based pharmaceuticals. The aim of this measure was to regulate the price of generic pharmaceuticals for which the *patent cliff* was not applied on 1 January 2017, since the reference pharmaceutical was not available.

After another slight decrease in 2019, expenditure for this class has again increased gradually since 2020.

Figure 79: evolution of NIHDI net monthly expenditure (public pharmacies 2017 – 2021) for ATC class A02B drugs for peptic ulcer and reflux disease

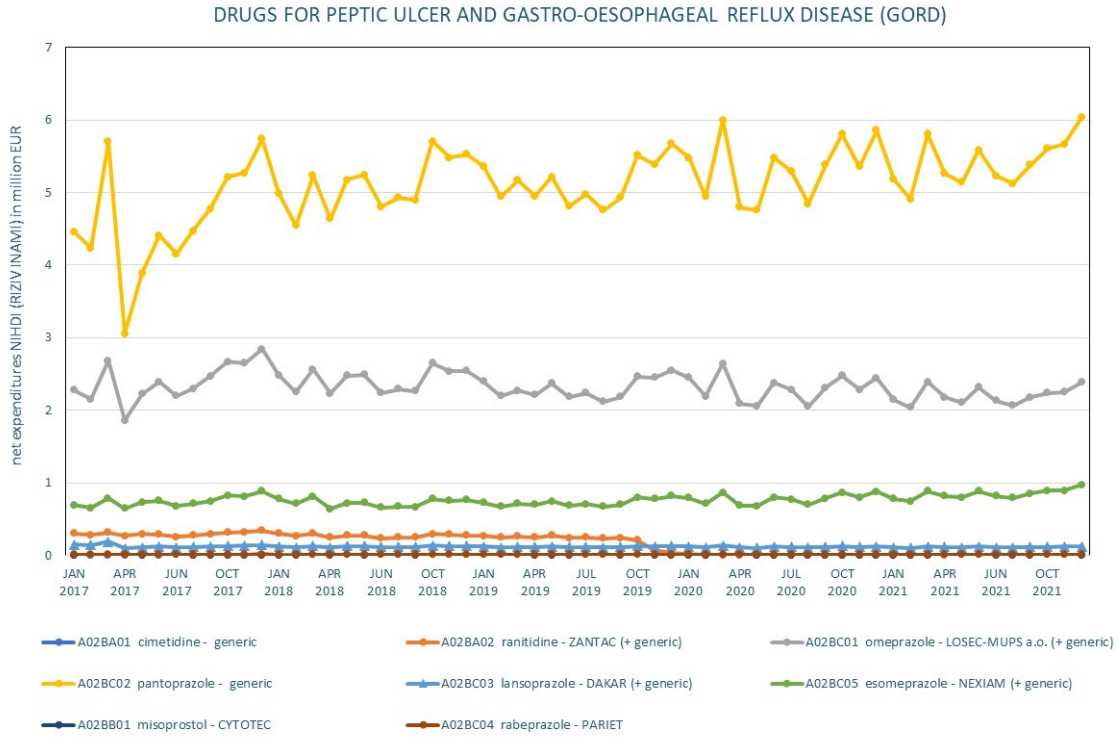


Figure 80: evolution of monthly number of DDDs (public pharmacies 2018 – 2021) for ATC class A02B drugs for peptic ulcer and reflux disease

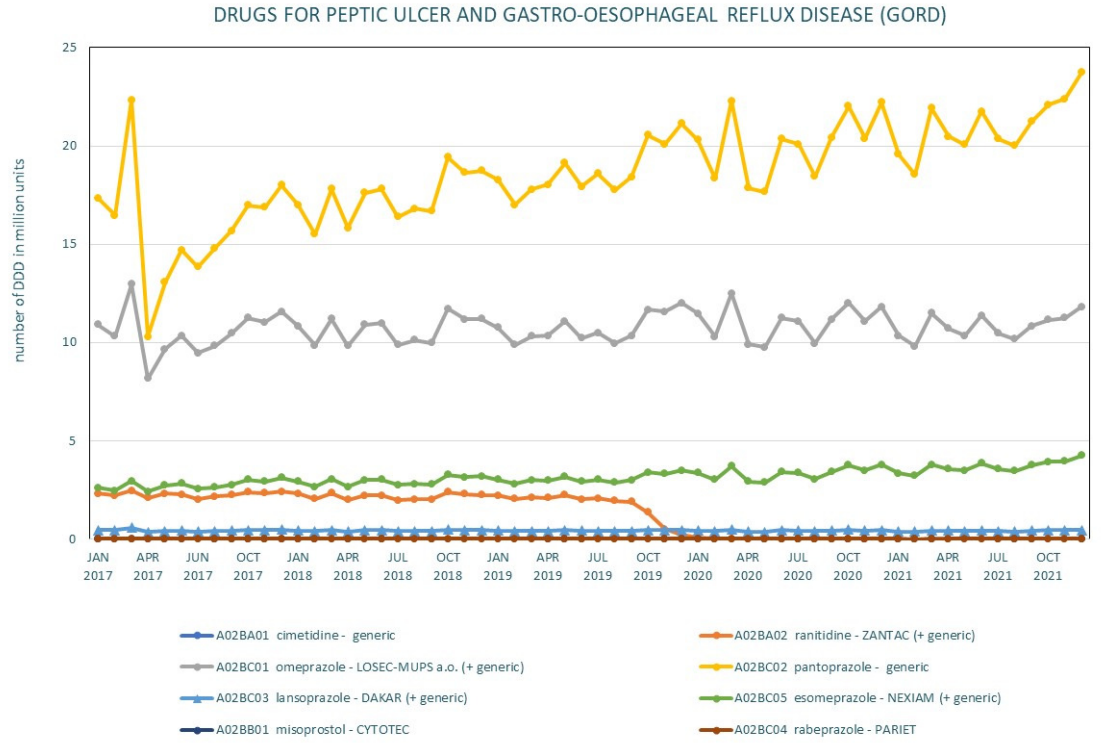
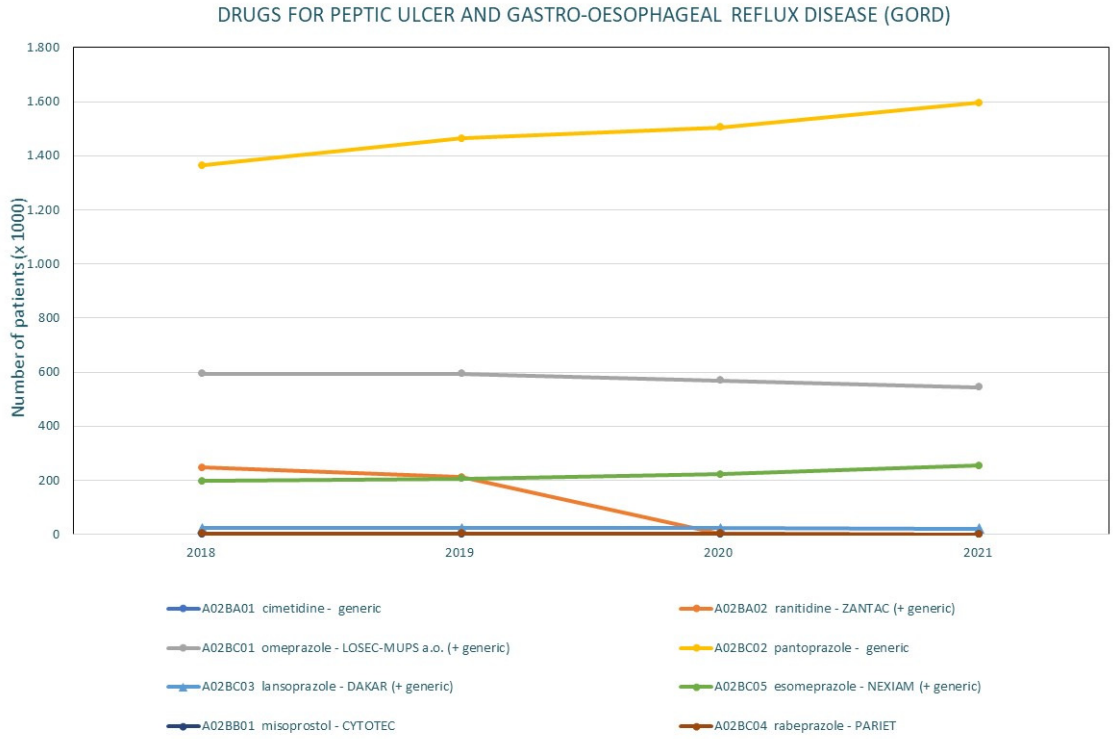


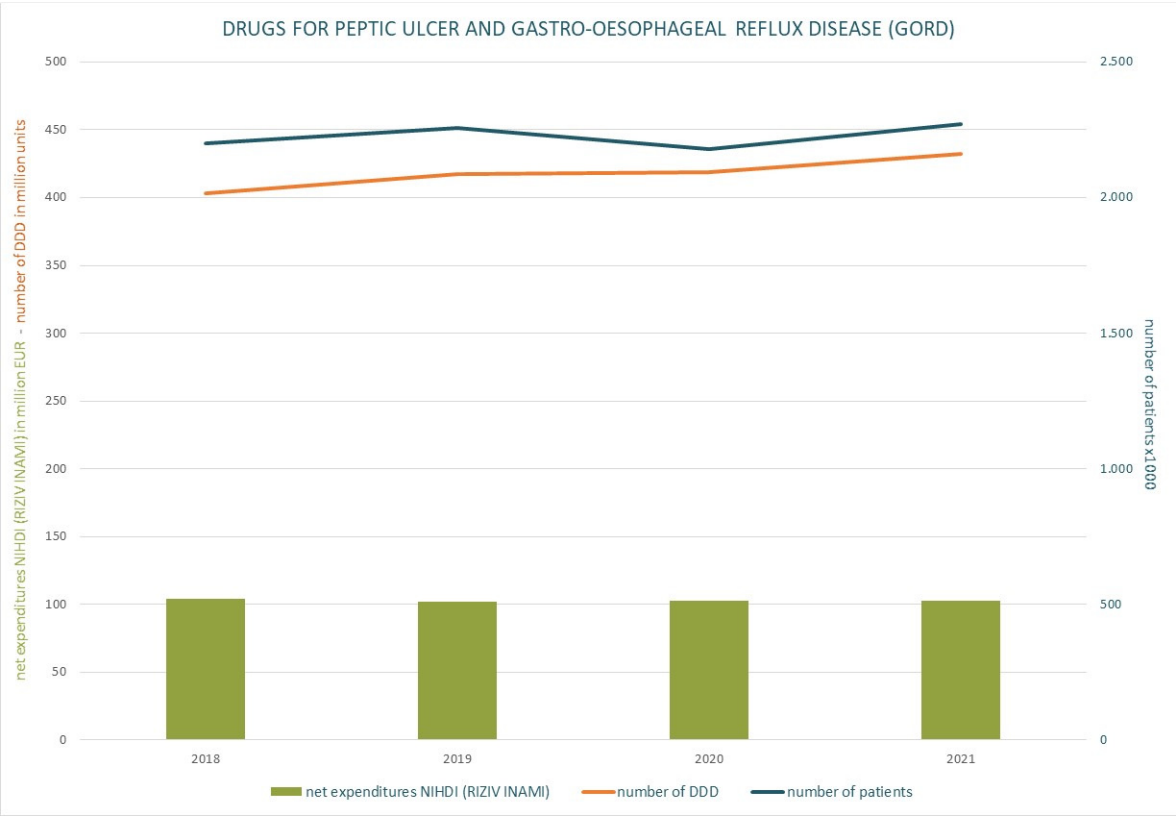
Figure 81: *evolution of number of patients per year (public pharmacies 2018 – 2021) for ATC class A02B drugs for peptic ulcer and reflux disease*



Where expenditure is concerned, but also in the number of patients and DDDs, pantoprazol and, to a lesser extent, omeprazol are the largest players. However, the number of patients using pantoprazol is increasing year after year, while the use of omeprazol decreases slightly.

Ranitidine-based medicines are no longer available on the Belgian market since September 2019. As a result, the elimination of expenditure, the number of DDDs and the patients that used ranitidine is clearly visible in all graphs above. All ranitidine-based products were recalled by the Federal Agency for Medicines and Health Products (FAMHP) because traces of impurities (NDMA) had been detected in them. Therefore, in May 2020, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) recommended to suspend sales of all ranitidine-based medicines in the European Union.

Figure 82: evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2018 – 2021) for ATC class A02B drugs for peptic ulcer and reflux disease



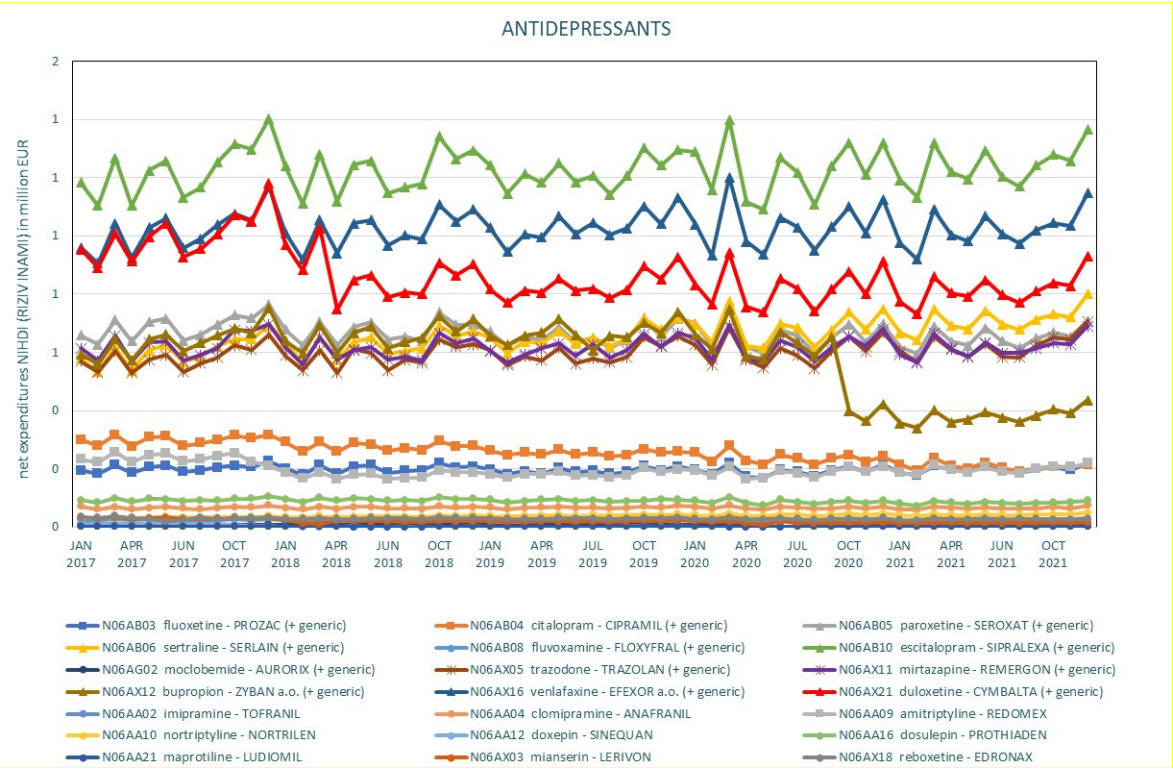
In conclusion, we can say that NIHDI expenditure for this class of medicines has remained more or less constant over the past four years, despite the slight increase in the number of patients and the number of DDDs.

N06A – ANTIDEPRESSANTS

Figure 83: evolution of NIHDI net annual expenditure (public pharmacies 2012 – 2021) for ATC class N06A antidepressants

NIHDI expenditure on the group of antidepressants has been on a downward trend for some years now. The relatively steep fall to be seen in 2015 and 2016 has clearly been levelling off since 2017. Between 2018 and 2020, expenditure remained rather stable. In 2021, a slight decrease in expenditure can be observed.

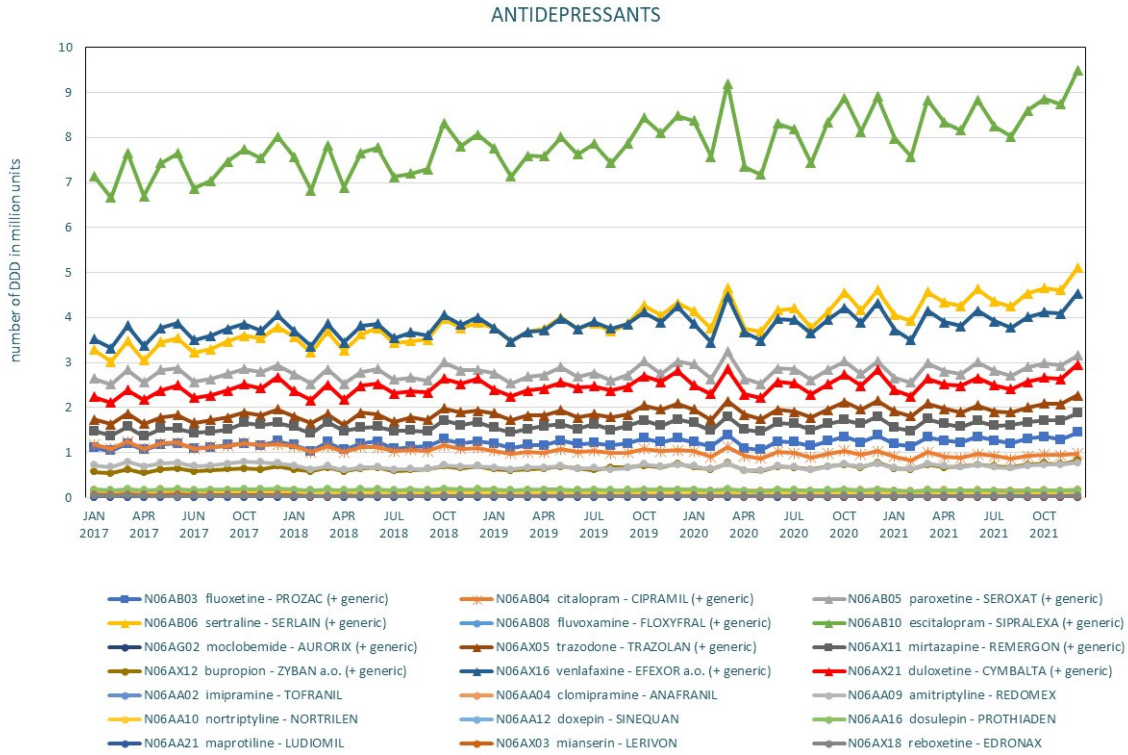
Figure 84: evolution of NIHDI net monthly expenditure (public pharmacies 2017 – 2021) for ATC class N06A antidepressants



Since 2017, escitalopram, duloxetine and venlafaxine have remained the first antidepressants where expenditure is concerned. The evolution of expenditure remains relatively stable for the different pharmaceuticals. Only for bupropion can we see a sudden drop in expenditure in 2020, although the number of DDDs remained stable. This can be explained by the advent of the generic and the opening of the reference cluster on 1 October 2020.

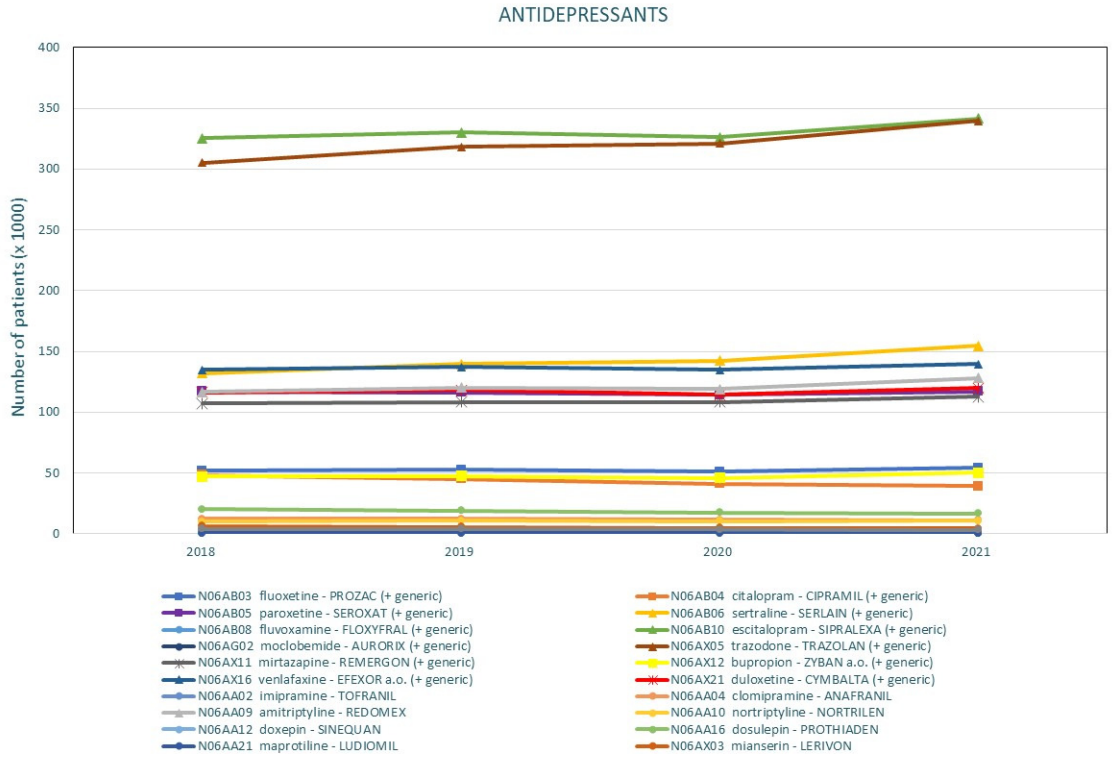
Expenditure for all pharmaceuticals experienced a peak in March 2020, which clearly indicates the start of the coronavirus pandemic. In that period, patients collected more medication from pharmacies in order to have a sufficient supply during the lockdown period, which is also reflected in the dip in April-May 2020, after the peak in March.

Figure 85: evolution of monthly number of DDDs (public pharmacies 2018 – 2021) for ATC class N06A antidepressants



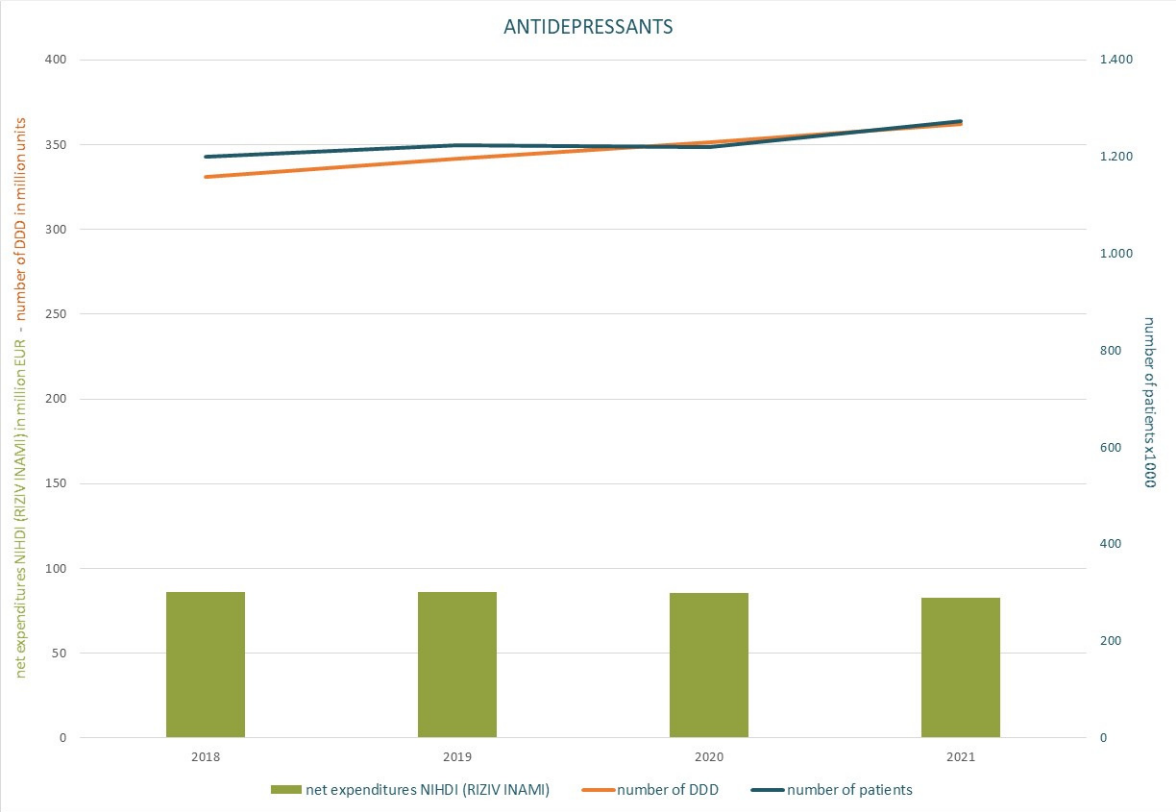
Since 2017, escitalopram has remained by far the first antidepressant where consumption is concerned. The number of DDDs per month has remained stable over the years for the different pharmaceuticals, although a slightly increasing trend in the number of DDDs can be seen for escitalopram, venlafaxine and sertraline.

Figure 86*: evolution of number of patients per year (public pharmacies 2018 – 2021) for ATC class N06A antidepressants*



In this graph as well, it is clear that escitalopram is the most used antidepressant. Where the number of patients is concerned, this number has remained relatively stable for most antidepressants. Only for trazodone can we see a slight increase since 2018.

Figure 87: evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2018 – 2021) for ATC class N06A antidepressants



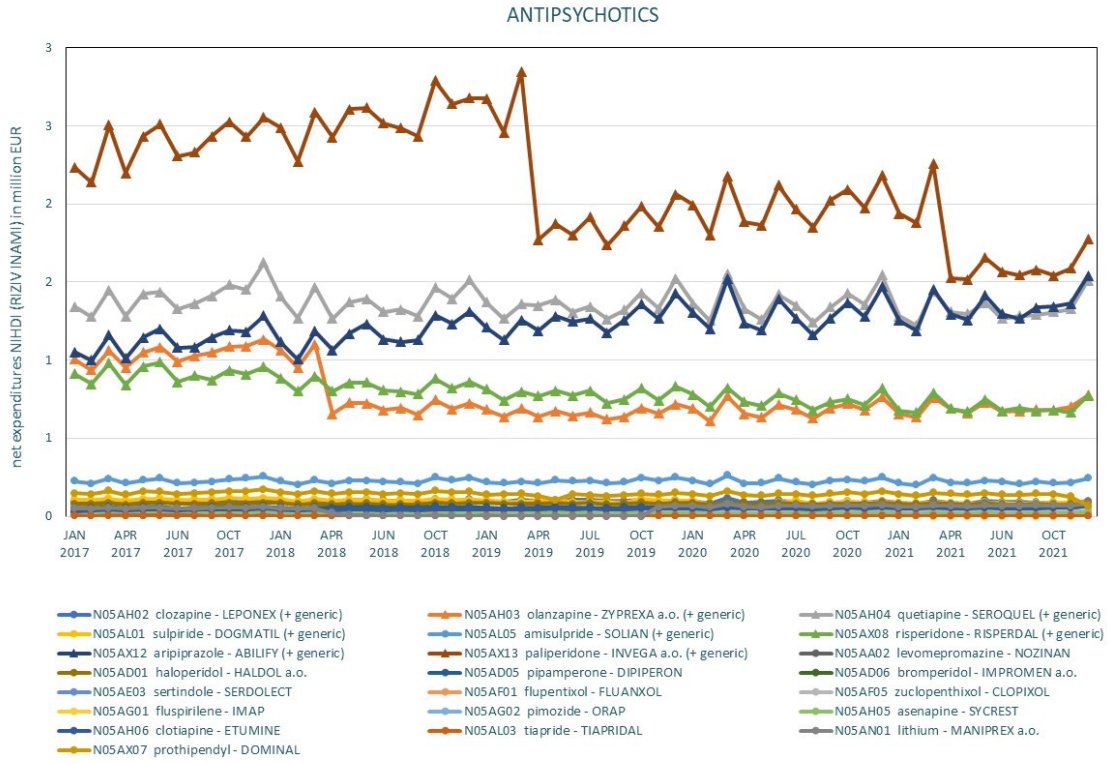
In conclusion, we can say that NIHDI expenditure has remained more or less constant over the past 4 years. The number of patients and the number of DDDs have experienced a slight increase over the past four years.

N05A – ANTIPSYCHOTICS

Figure 88: evolution of NIHDI net annual expenditure (public pharmacies 2012 – 2021) for ATC class N05A antipsychotics

NIHDI expenditure for antipsychotics have shown a general decreasing trend since 2012, which continues after a slight increase in 2015 and 2017. In 2020, expenditure remained stable, and in 2021, there was again a slight decrease in expenditure.

Figure 89: evolution of NIHDI net monthly expenditure (public pharmacies 2017 – 2021) for ATC class N05A antipsychotics



In 2018, 2019 and 2021, a drop in expenditure on antipsychotics could be seen. This drop is largely due to the reduction of expenditure on olanzapine (2018) and reduced spending on paliperidone (2019 and 2021).

Spending on olanzapine fell noticeably in April 2018. At that time, the company reduced the price of various olanzapine-based pharmaceuticals. This price reduction followed the introduction of the so-called 'ceiling prices', with a risk that more expensive packs of drugs would no longer be reimbursed.

In April 2019, the reference reimbursement system was applied to paliperidone (Invega®). The graph illustrating expenditure on this molecule shows a clear drop at this point. After that, a rising trend can be observed again in the expenditure on this molecule. However, the expenditure graph shows a clear decrease again in 2021. This is due to the application of the 'old cliff' in April 2021. Yet paliperidone still accounts for most of the expenditure on antipsychotics. Spending on aripiprazole (Abilify® and generics) has been increasing slightly since 2017, while spending on molecules based on risperidone (Risperdal® and generics) is falling slightly. Expenditure on the other antipsychotics has remained relatively stable over the last five years, apart from some seasonal peaks and the start of the COVID pandemic in march 2020.

Figure 90: evolution of monthly number of DDDs (public pharmacies 2018 – 2021) for ATC class N05A antipsychotics

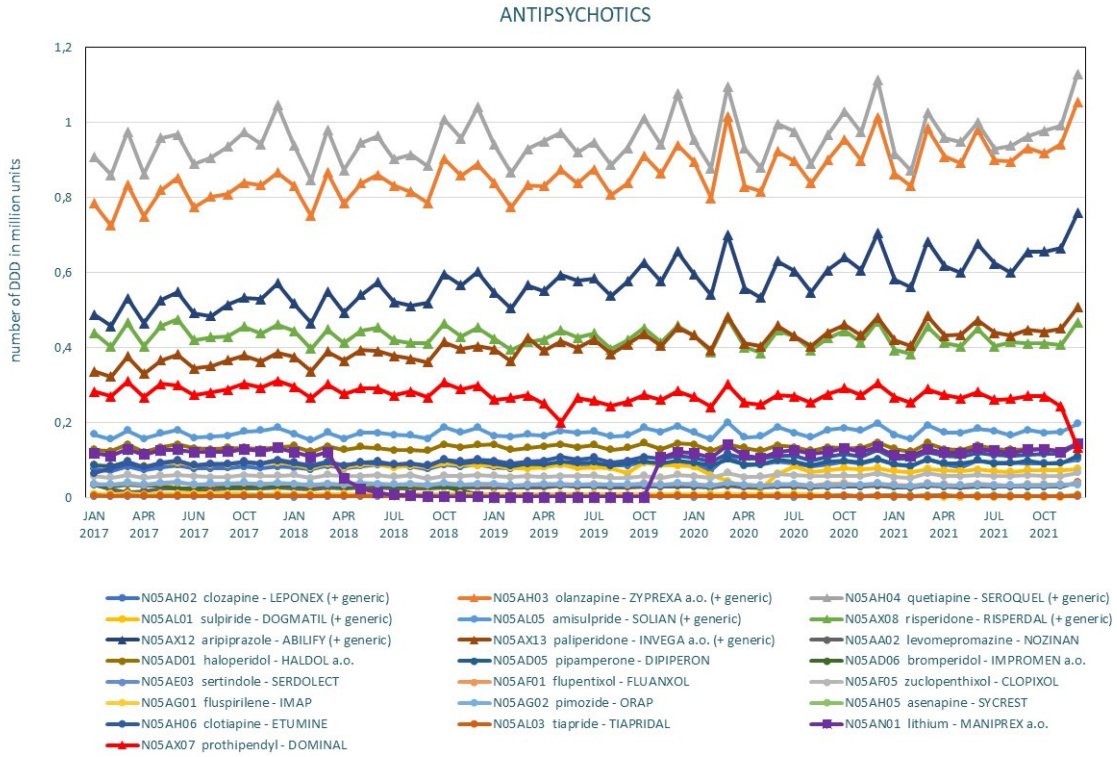
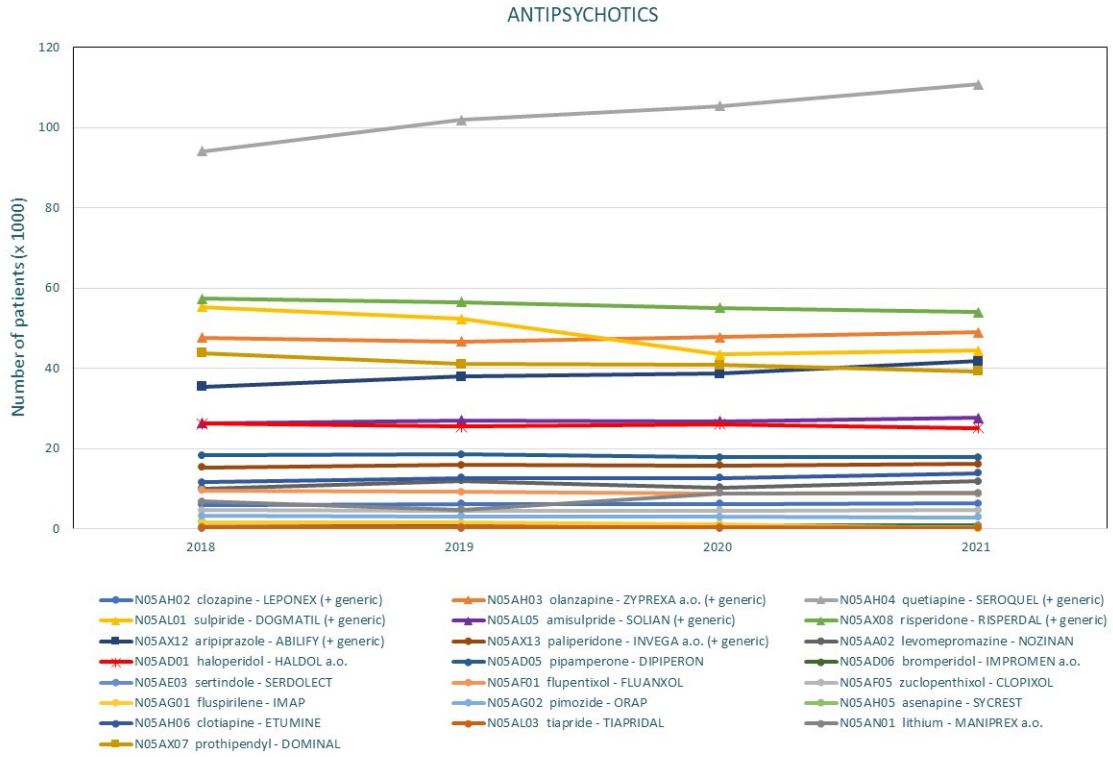
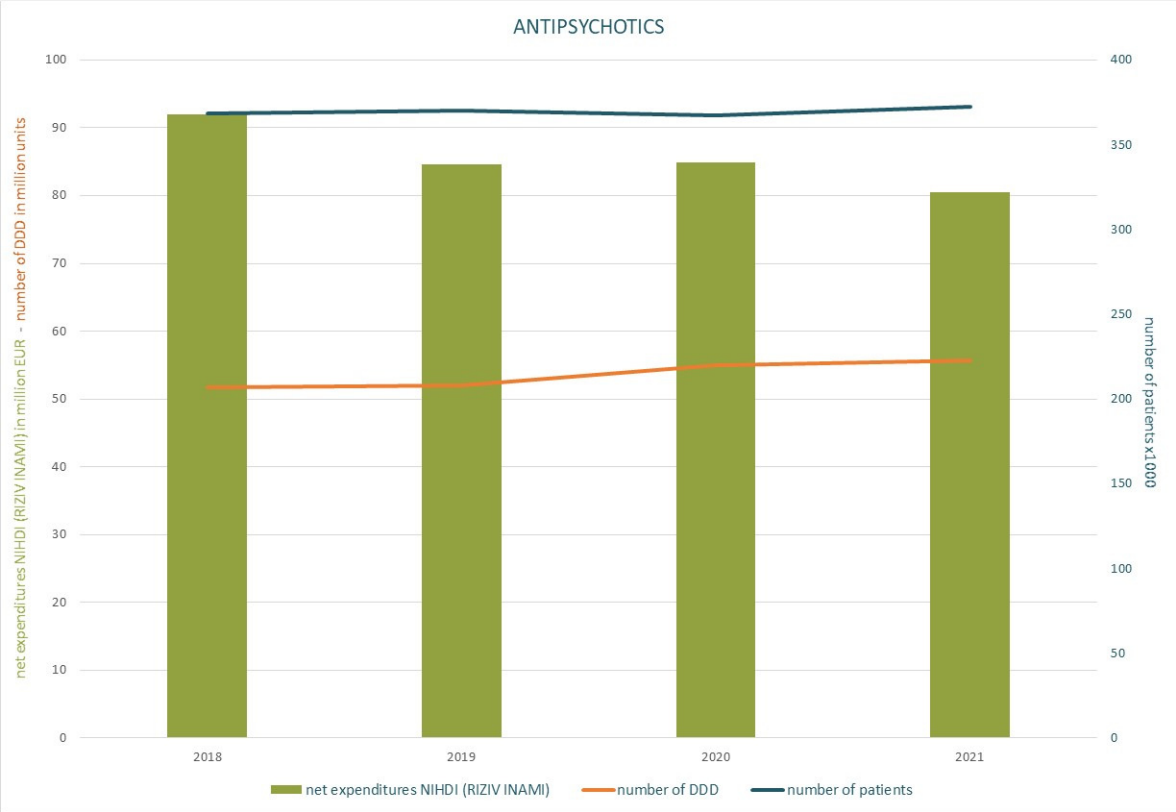


Figure 91: evolution of number of patients per year (public pharmacies 2018 – 2021) for ATC class N05A antipsychotics



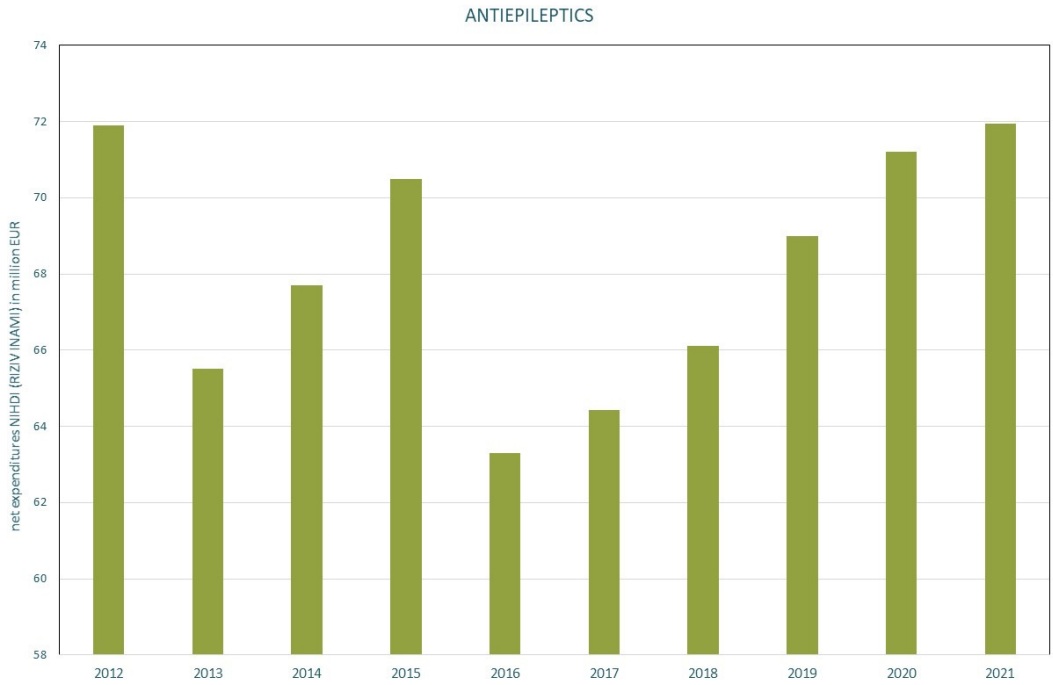
Although paliperidone accounts for a large part of the expenditure, this is not reflected in the number of patients, nor in the number of DDDs. The most used antipsychotic, both in terms of number of patients and in DDDs, is quetiapine (Seroquel ® and generics). The number of patients treated with quetiapine is increasing year by year. For the other antipsychotics, a stagnation or a slight decrease can be observed here. This decrease is most pronounced for sulpiride, risperidone and prothipendyl (Dominal®). All of this masks the increase in the number of patients for quetiapine, given that the total number of patients treated with antipsychotics remains stable.

Figure 92: *evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2018 – 2021) for ATC class N05A antipsychotics*



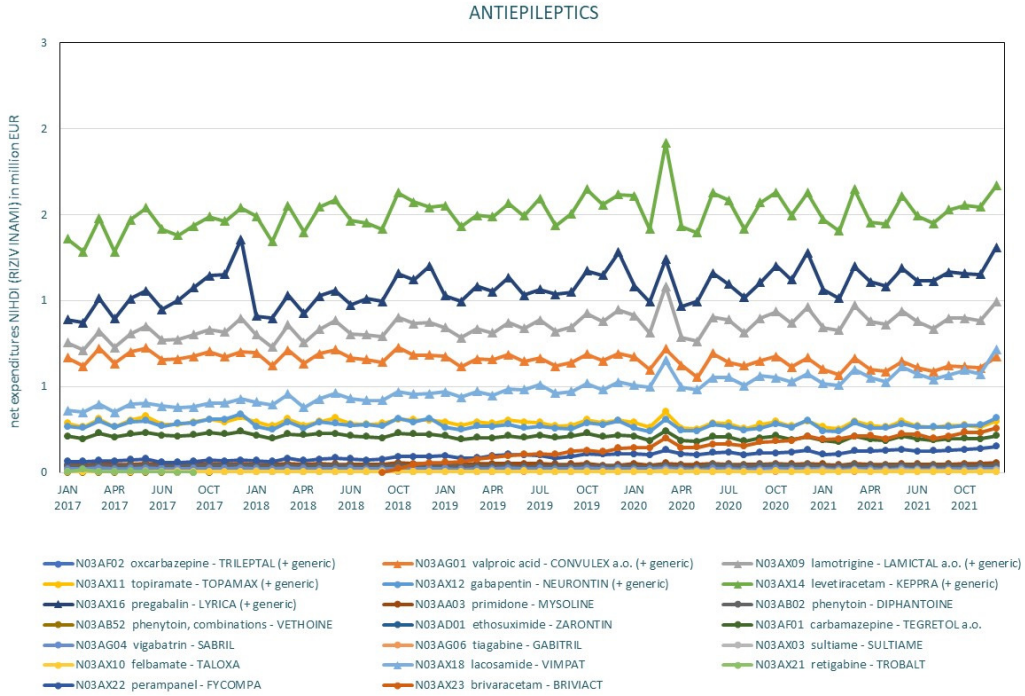
Conclusion: There have been no striking changes in the last four years in the use of antipsychotics. Both the number of patients and the number of DDDs have remained stable. Expenditure fell slightly in 2019 and 2021, due to price reductions for paliperidone: the application of the reference reimbursement system (April 2019) on the one hand, and the application of the 'old cliff' on the other hand (April 2021).

Figure 93: evolution of NIHDI net annual expenditure (public pharmacies 2012 – 2021) for ATC class N03A anti-epileptics



Expenditure on anticonvulsants has increased significantly over the past six years. This increasing trend is not caused by a specific molecule, but appears to be the accumulated result of stable to moderately increasing expenditure on most of the molecules within this group. The clear decrease in expenditure that was observed at the beginning of 2016 is due to the opening of the reference reimbursement system for pregabalin.

Figure 94: *evolution of NIHDI net monthly expenditure (public pharmacies 2017 – 2021) for ATC class N03A anti-epileptics*



Since 2017, levetiracetam (Keppra® and generics) has been the first anticonvulsant where expenditure is concerned. The evolution of expenditure has a slightly upward trend for most molecules. The clear decrease in expenditure that was observed at the beginning of 2016 for pregabalin is due to the opening of the reference reimbursement system for this molecule.

For most, a clear peak can be observed in March 2020, indicating the start of the coronavirus pandemic. During that period, patients collected more medication from pharmacies in order to have a sufficient supply during the lockdown period, which is also reflected in the slight dip in April-May 2020, after the peak in March.

Figure 95 : evolution of monthly number of DDDs (public pharmacies 2018 – 2021) for ATC class N03A anti-epileptics

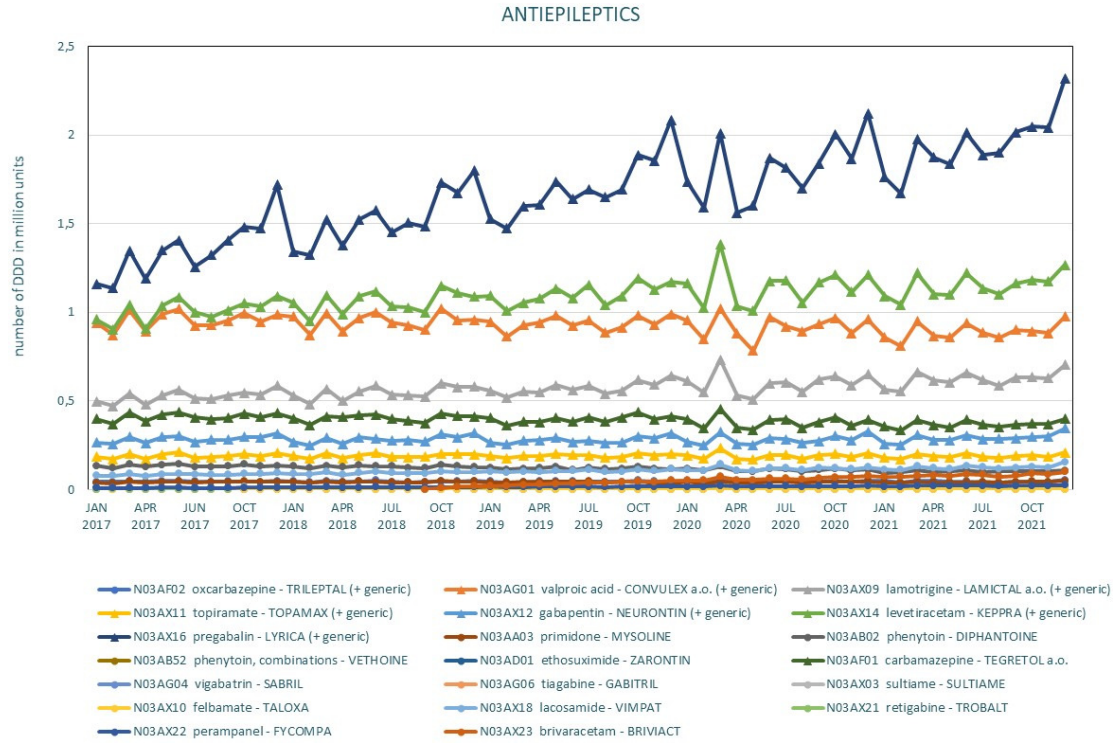
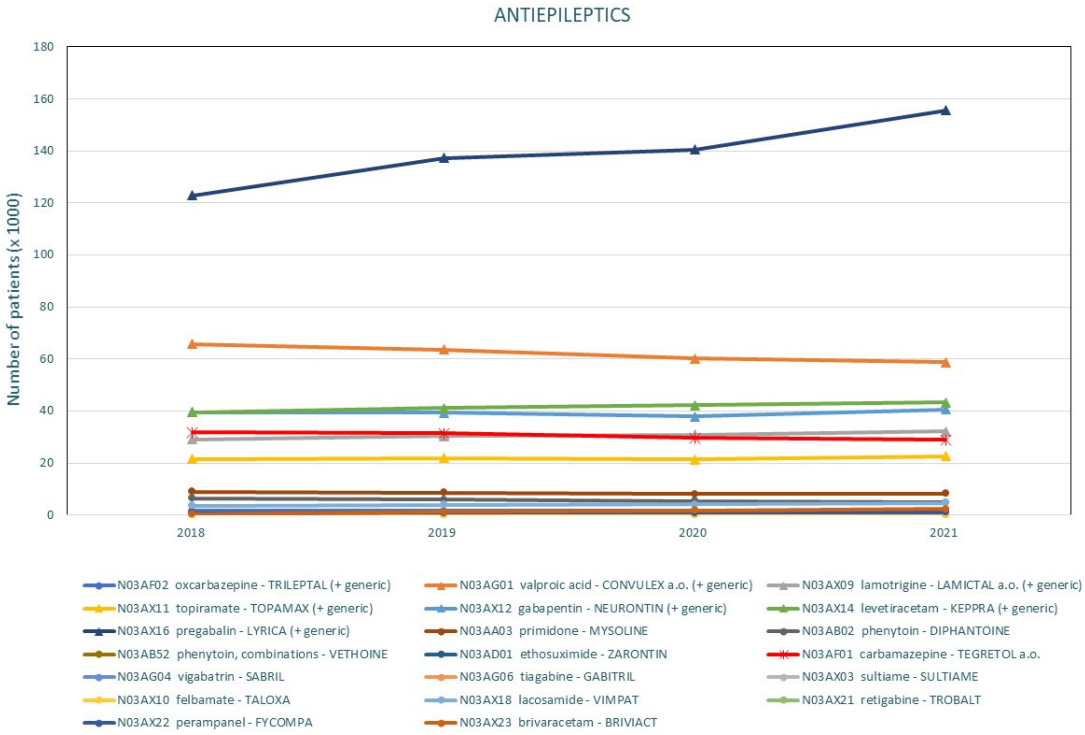


Figure 96: evolution of number of patients per year (public pharmacies 2018 – 2021) for ATC class N03A anti-epileptics



With regard tot he number of DDD and the number of patients, a very steep increase may be seen for pregabalin (Lyrica® and generics). Here, we should note that pregabalin is also indicated for other indications (anxiety disorders and neuropathic pain) and that Lyrica® has been reimbursed in chapter I since 1 September 2015. In 2021, only 1 % of patients received pregabalin in reimbursement category A (add-on treatment in patients who

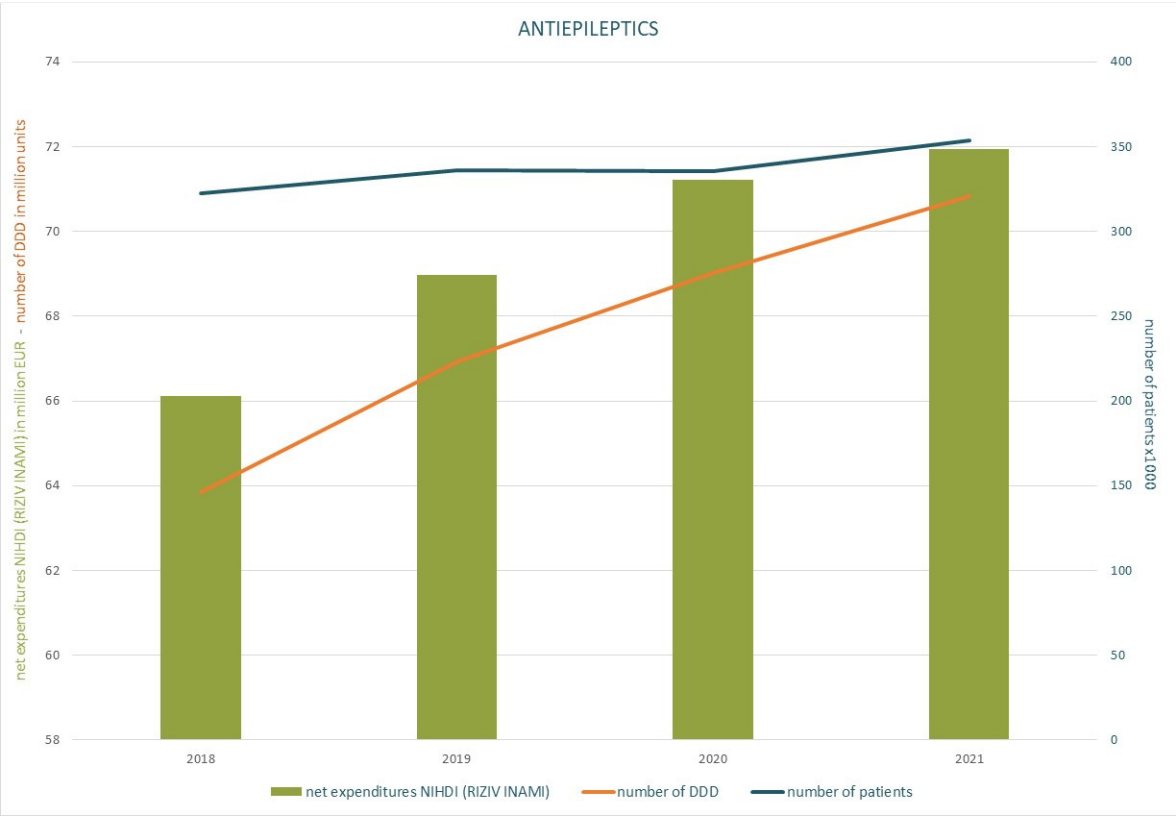
have partial seizures, if specific conditions are met, approval by the advising physician); 99 % of patients were treated with pregabalin reimbursed in reimbursement category B (chapter I).

Given the high proportion of pregabalin, a calculation based on ATC class N03A of the number of patients being treated with anti-epileptics will lead to an over-estimation. A big proportion of the patients who are being treated with Lyrica® or one of its generics will, in fact, be using this drug for an indication other than epilepsy. It is therefore difficult, on the basis of this data, to draw definitive conclusions about the number of patients being treated with anti-epileptics. We can however calculate that, leaving aside Lyrica and its generics, the number of patients receiving reimbursement for anti-epileptics, is rather stable for the period 2018-2021.

The number of patients being treated with Depakine® and its generics is experiencing a decreasing trend. The number of patients being treated with Keppra® and its generics is increasing slightly. For the other molecules, no clear trend can be seen.

The data concerning the number of DDDs reflects the trends observed regarding the number of patients. Besides a slight increase for pharmaceuticals based on levetiracetam (Keppra® and generics), the sharp increase for pregabalin is again particularly striking. The same reasoning as for the number of patients can again be followed here.

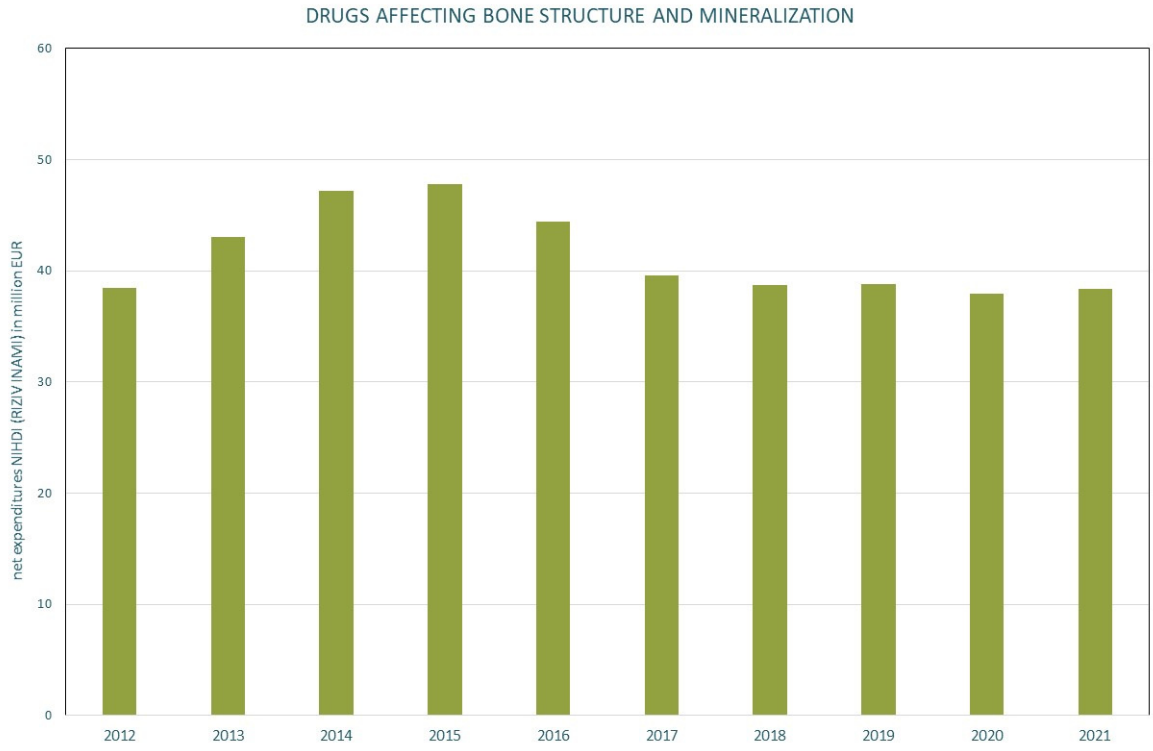
Figure 97: evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2018 – 2021) for ATC class N03A anti-epileptics



In conclusion, we can say that both NIHDI expenditure and the number of DDDs have shown a clear rising trend over the past years. The increase in the number of patients is less pronounced. Caution is needed in interpreting these trends, since pregabalin, which carries quite a heavy weighting within this group, can also be used for indications other than epilepsy.

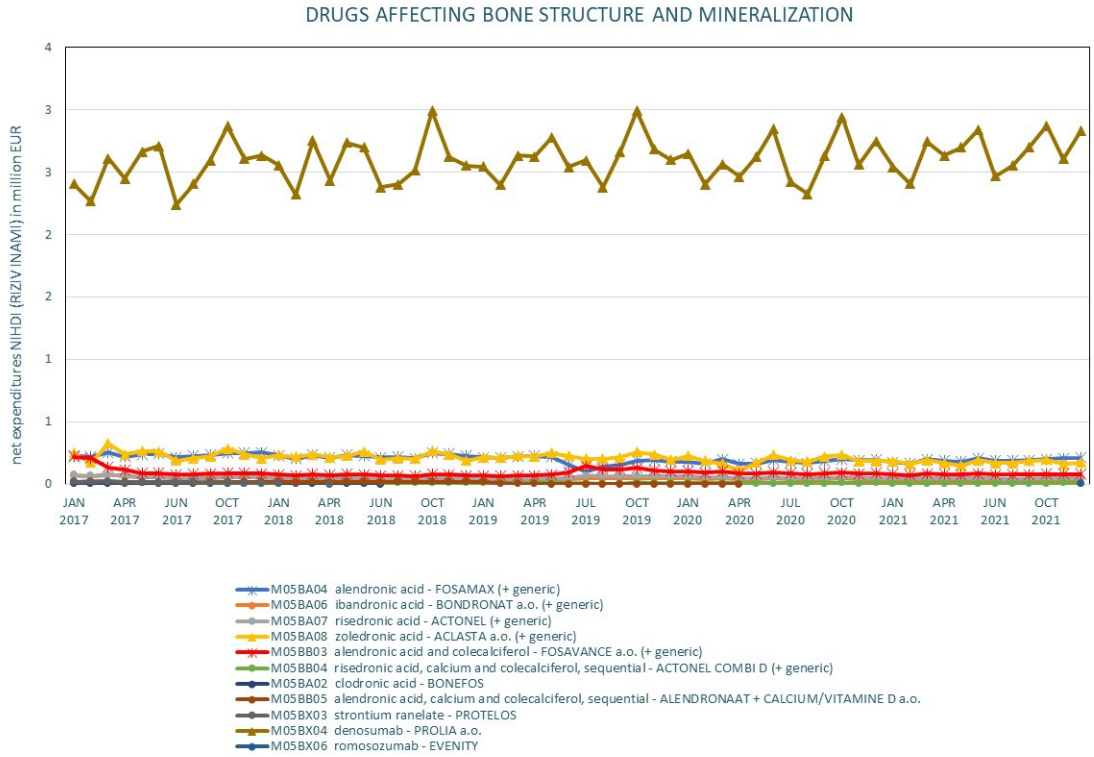
M05B – DRUGS AFFECTING BONE STRUCTURE AND MINERALIZATION

Figure 98: evolution of NIHDI net annual expenditure (public pharmacies 2012 – 2021) for ATC class M05B drugs affecting bone structure and mineralization



The fall in expenditure on drugs affecting bone structure and mineralization, which was clearly noticeable from 2015, has stabilised since 2017. Expenditure has nearly completely stabilised during the past four years.

Figure 99: evolution of NIHDI net monthly expenditure (public pharmacies 2017 – 2021) for ATC class M05B drugs affecting bone structure and mineralization



This stabilisation of expenditure on this class since 2017 can also be seen fort he individual molecules. It is striking that one molecule, namely denosumab (Prolia ® / Xgeva®), is responsible for the greatest part of the expenditure within this class.

In 2019, a temporary change in the trend can be observed in expenditure on Fosamax® (decrease) and Fosavance® (increase), which is due to the temporary unavailability of Fosamax® (see below).

Figure 100: evolution of monthly number of DDDs (public pharmacies 2018 – 2021) for ATC class M05B drugs affecting bone structure and mineralization

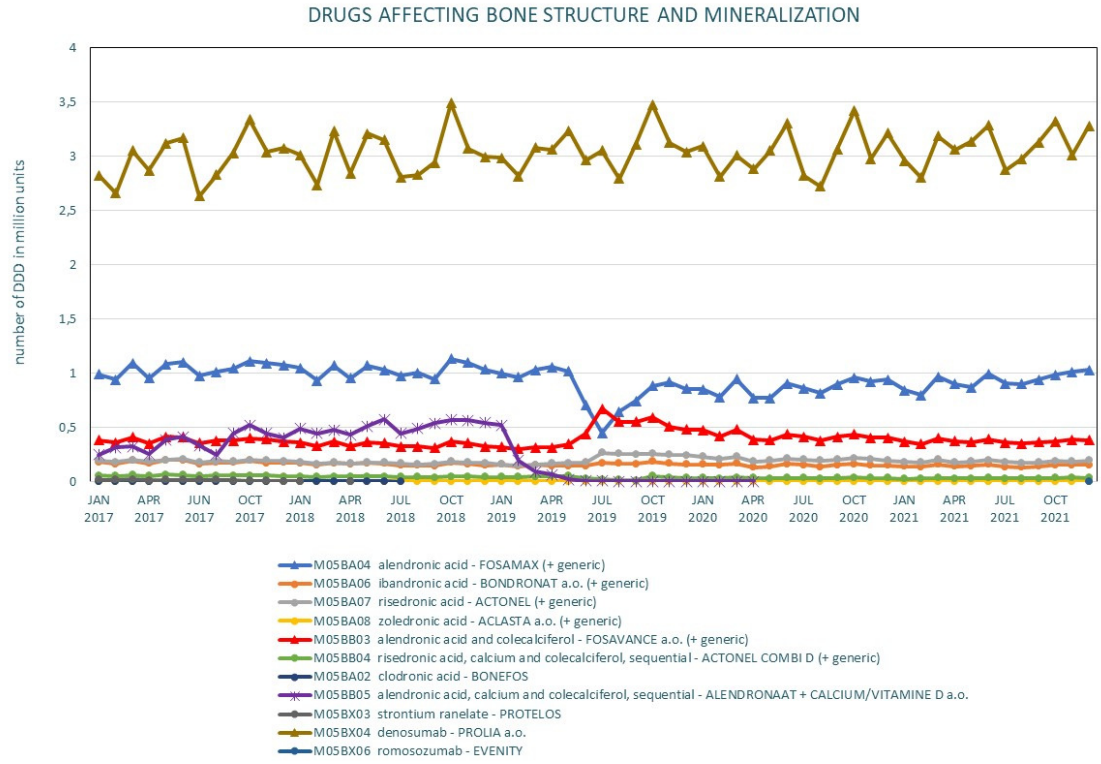
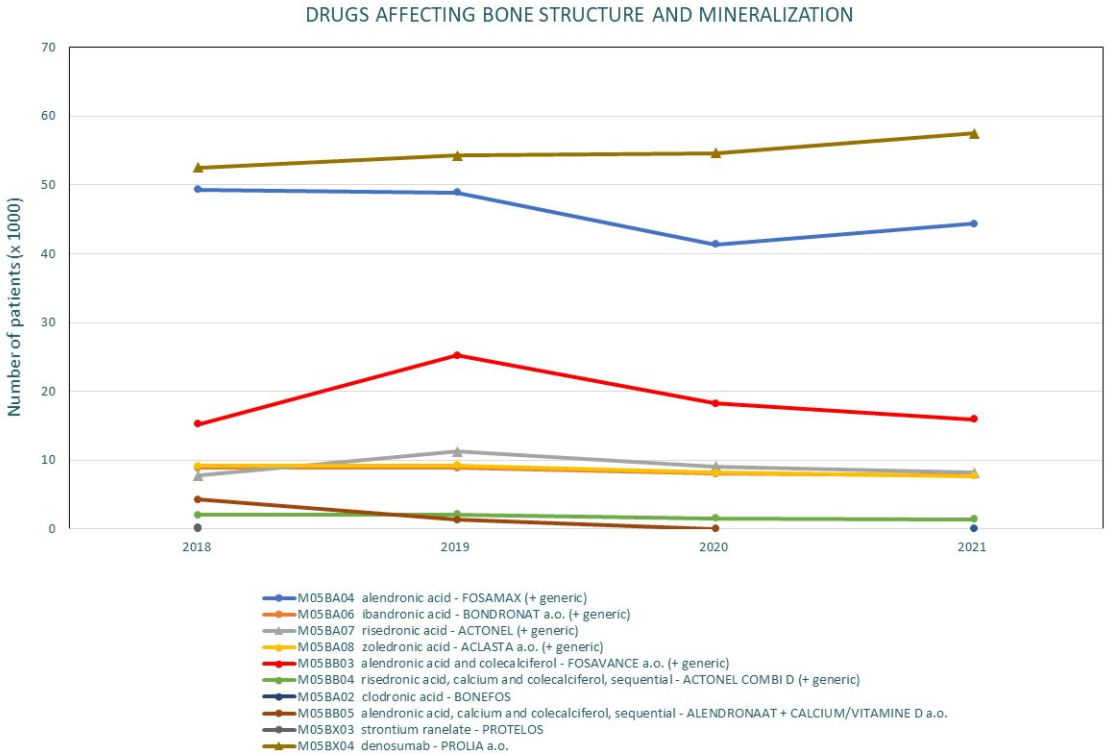
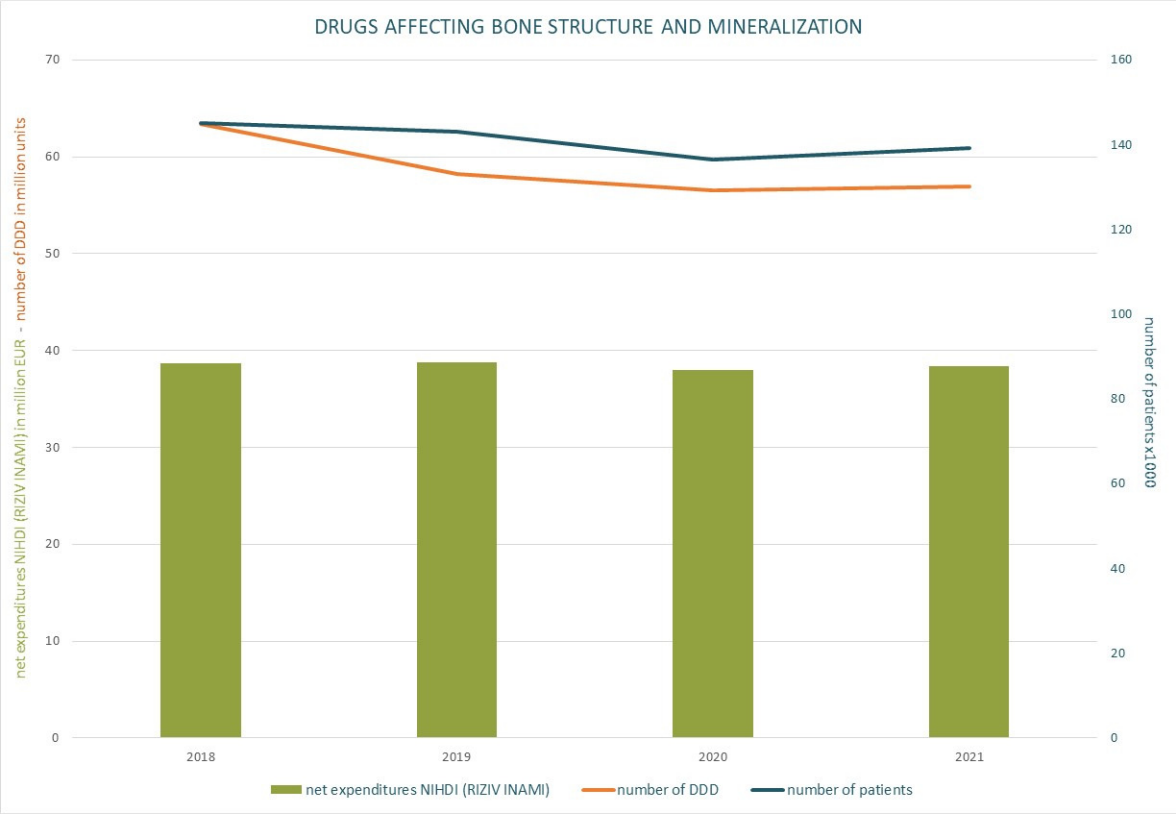


Figure 101: evolution of number of patients per year (public pharmacies 2018 – 2021) for ATC class M05B drugs affecting bone structure and mineralization



When we look at consumption in DDDs and the number of patients, we see that denosumab-based pharmaceuticals are used most, and that this use has experienced a slightly increasing trend. For the other pharmaceuticals, we see a reflection of the number of DDDs in the data for the number of patients: a clear decrease for Fosamax® in mid 2019, which is (partly) compensated by an increase for Fosavance®. This is due to a switch from Fosamax® to alternatives as a result of the temporary unavailability of Fosamax®. For Actonel® too, an increase can be seen at the same time, albeit to a lesser extent. Alenca® has not been on the market since the beginning of 2019, reflected in a drop in the number of patients to zero. For the other pharmaceuticals, the number of patients remained relatively stable.

Figure 102: evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2018 – 2021) for ATC class M05B drugs affecting bone structure and mineralization



In conclusion, we can say that NIHDI expenditure for this class of medicines has stabilised over the past four years. However, both the number of patients and the number of DDDs experienced a slight decrease, which is not reflected in expenditure. This decrease is somewhat more significant for the number of DDDs.

DOSSIERS

DOSSIER – 'ARTICLE 81/111 CONVENTIONS'

PRINCIPLE

For some new treatment options, reimbursement can involve scientific and/or budgetary uncertainties. These uncertainties may be related to the (relative) therapeutic value of the product, the cost per treatment or the overall budgetary impact of the medicine if available to the whole population. Generally, it is a combination, so there is uncertainty as to the cost benefit ratio of the new therapy.

To prevent patients being denied access to these new, sometimes very promising treatments, and to give the pharmaceutical company an opportunity to (further) prove the value of the medicine in a real-life setting, these treatments can be made temporarily eligible for reimbursement, subject to clearly specified conditions. The precise conditions to be met by the pharmaceutical company to enable this temporary reimbursement are set out in a convention. These conventions are one of the policy tools used to keep better control of the budget.

The conditions are mostly two-fold: firstly, the company is asked, during the period of temporary reimbursement, to collect additional information and evidence on specific points of uncertainty. Secondly, during this period the company shares the responsibility for the uncertainties and risks linked to reimbursement (e.g. an excessively high listing price even for someone who's responding to a treatment). In practice this means that the convention includes a budgetary compensation scheme. The risks are thus shared by the health insurance and the company.

In order to reach an agreement, negotiations take place in a working group during a number of face-to-face meetings organised by the NIHDI. This working group is made up of representatives from the pharmaceutical company, the insurance bodies (for the insurance committee), the CRM, the professional organisation representing the pharmaceutical industry, the Minister of Social Affairs, the State Secretary for the Budget and the Minister of Economic Affairs. The negotiating procedure may not take longer than 120 days. If consensus is reached within this period, a convention is signed by the NIHDI and the pharmaceutical company.

It has been possible to conclude such conventions since 2010. The relevant legislation has been amended on several occasions since then, but the key principles have remained the same. The current procedure to be followed to reach agreement on a convention is set out in Article 111 and following of the Royal Decree of 1 February 2018 concerning the procedures, terms and conditions for reimbursement by the compulsory healthcare and benefits insurance towards costs of pharmaceuticals. Before this Royal Decree came into force, the procedure to be followed was set out in Article 81 and following of the Royal Decree of 21 December 2001 concerning the procedures, terms and conditions for reimbursement by the compulsory healthcare and benefits insurance towards costs of pharmaceuticals. The terms 'Article 81/111 conventions' and 'Article 81/111 procedure' refer back to the legal basis of these conventions.

The negotiation procedure is launched on the basis of a proposal from the CRM (Article 81bis/112), or when the CRM is unable to formulate a definitive proposal with a two thirds majority (Article 81/111).

Until 1 July 2014, it was possible for a company, following a negative opinion from the CRM, to submit a request for negotiations to take place (Article 81). Since 1 February 2018, it is again possible, subject to certain conditions, for a negotiation procedure to be launched following a negative CRM opinion (Article 113).
Since 1 July 2014, companies, in certain circumstances, may submit a request for an Article 81/111 procedure for class 2 dossiers (no therapeutic added value) in cases where the reference pharmaceutical is marked on the positive list with the letter 'T'.
Since 2018, the CRM may make a proposal to begin negotiations, where reimbursement is requested, for any reference pharmaceutical on the positive list and highlighted with the letter 'T'; including, then, for generics, biosimilars, pharmaceuticals imported or distributed in parallel (Article 112).

LEGAL BASIS

Law on compulsory healthcare and benefits insurance, coordinated on 14 July 1994 - Art. 35 bis (7).

Royal Decree of 01.02.2018 concerning the procedures, terms and conditions for reimbursement by the compulsory healthcare and benefits insurance towards costs of pharmaceuticals – Articles 111 to 117 inclusive.

Law containing provisions with regard to the reimbursement of pharmaceuticals as well as the administrative costs, efficiency and transparency of insurance organisations, coordinated on 1 April 2019 - Chapter V.

BUDGETARY COMPENSATION

As described above, Article 81/111 conventions make it possible to manage the risks and uncertainties linked to the reimbursement of a new treatment. Often, this is done by means of a budgetary compensation mechanism. Most conventions are structured in such a way that the health insurance initially bears the costs of the medicine concerned. After a clearly defined period, the pharmaceutical company pays back a certain sum to the NIHDI (=budgetary compensation). The value of this budgetary compensation depends on what is stated in the convention.

Various compensation/refund mechanisms are used, either alone or in combination:

- Repayment of a percentage of the turnover resulting from the pharmaceutical in question, possibly with an individual or group ceiling applied (e.g. per therapeutic class, per indication) - any earnings in excess of this ceiling must be partially or fully repaid;
- Repayment of a set amount per unit sold, corresponding to the difference between the proposed reimbursement basis and the value, in line with the evaluation of the criteria referred to in Article 4 of the Royal Decree of 1 February 2018;
- Repayment of an amount corresponding to all or part of the difference between the expenditure foreseen and the actual expenditure on the pharmaceutical in question;
- A reduction in the reimbursement basis of (an)other pharmaceutical(s) marketed by the applicant, resulting in reduced expenditure for the health insurance on a medicine other than the pharmaceutical in question;
- Any other arrangement at the cost of the applicant which reduces expenditure.

These various forms of compensation might give the impression that these conventions are purely financial in nature. However, there is a reason for all of these mechanisms, and this reason is often science-based. The 'repayment of a percentage of the turnover' mechanism, for example, may be based on a system where the health insurance only bears the costs of patients who are deemed to have benefitted from the pharmaceutical ('outcomes-based agreement'), or maybe the costs are only reimbursed when the pharmaceutical is administered for a treatment which has been shown, with sufficient scientific proof, to be effective and safe.

The information related to the amount of a company's financial contribution and the schedule which determines how precisely the budgetary compensation is to be calculated is contained in the annex to an Article 81/111 convention. The contents of such an annex are confidential. This means that the budgetary compensation provided for each medicine or, in the case of some conventions, for each group of medicines, cannot be reflected in this MORSE report. In other words, expenditure on pharmaceuticals that are already mentioned elsewhere in this report than in *Table 3* and in this Chapter 'Article 81/11 agreements', does not take into account the compensation received by the NIHDI within the framework of Article 81/11 agreements.

RESOLVING SCIENTIFIC AND BUDGETARY INCERTAINTIES

Conventions are used to collect additional information and evidence on particular questions on which there is uncertainty. The uncertainties which the pharmaceutical company is supposed to have clarified by the time when the convention expires may be scientific and/or budgetary in nature.

These uncertainties probably partially account for the overall increase in the number of conventions seen in recent years. The CRM often reports serious uncertainty as to the therapeutic value (the dossiers often contain

immature data submitted too early to the EMA, such as phase II study results); there may also be major budgetary uncertainties (high treatment cost per patient, considerable budgetary impact due to wide target group). Although the CRM does its best to make proposals for definitive inclusion on the list of reimbursable pharmaceuticals, starting a negotiation process is often the only way to make medicines accessible to the patient in a way that the expenditure can at least be monitored.

More and more emphasis is being placed on generating evidence. Pharmaceutical companies are asked to collect data, during the term of the convention, in order to give an answer to the existing uncertainties.

It is up to the pharmaceutical companies to determine how best to clarify these uncertainties. A company may report new study-results (e.g. of a post-marketing study), or interim analyses (e.g. of an ongoing phase III study), presenting new data concerning the initial open questions.

A company may also use 'real-life data' from registers, or access information from the Common Sickness Funds Agency (IMA-AIM). The IMA can provide information from the invoiced data submitted to the insurance bodies, on, for example, the number of patients or packages per indication for one particular molecule, the duration of treatment, any concomitant medication, etc.

For a limited number of pharmaceuticals, data is collected by Sciensano, often in collaboration with the NIHDI. These are first and foremost clinical data which cannot be accessed via invoicing databases and which require specific registers to be set up or adjusted. More information can be found on the website https://www.sciensano.be/en/health-topics, consulted on 26 October 2022).
A company collects all the relevant data and produces an evaluation report, which, on expiry of the convention, is submitted to the working group responsible for the negotiations. The report is then thoroughly assessed. The working group, taking account of the data supplied and the probative force of these data, decides whether it is best to extend the convention or organise a new CRM evaluation.

In the latter case, the working group advises the company to launch a new CRM procedure using the data which became available during the time covered by the convention, so that the CRM can make a new judgment.

In conclusion, an Article 81/111 convention can offer a temporary solution to make promising therapies available to patients. However, there is always a trade-off between risks and benefits. When possibly granting a temporary reimbursement, account will be taken of the fact that the investment of public funds is sufficient so that there is no loss of social welfare if the medicine ultimately proves to be cost-effective; but also that public funds are used responsibly if it later turns out that the product has little or no benefit for patients. There must therefore also be a clear EXIT strategy where difficult choices have to be made. Without additional evidence, the medicine will no longer be reimbursed or will be reimbursed at a publicly known price that reflects the value of the medicine. After all, we must ensure that one therapy for which there is less evidence does not supplant another therapy with a better cost-benefit profile.

SOME FIGURES

The option of Article 81/111 conventions was introduced in 2010 (see also 'Principle').

However, for the presentation of the data in the MORSE report only a 10-year interval is taken into account. Thus, the information presented in this report refers to the reimbursement dossiers for which the company submitted an application to the Minister for Social Affairs to start a procedure for the conclusion of an agreement in the course of the period 2011-2021, from 26 October 2022. One request for reimbursement may cover various package sizes, or different indications for one and the same molecule. It is up to the pharmaceutical company to decide whether to submit such a joint request for reimbursement.

Number of requests to launch negotiations, and their outcomes

In the period 2011-2021 , a total of 466 requests for the launch of Article 81/111 negotiations were received by the Minister for Social Affairs.

The tables below also comprise the applications within the framework of a CRM procedure for a pharmaceutical distributed in parallel. However, until now, those CRM procedures have never led to the conclusion of an agreement.

The considerable increase in the number of applications in 2021 is no doubt the result of a double phenomenon: a) the resumption of suspended or limited activities during the COVID-19 pandemic[3]; and b) the continuous increase in the number of molecules following an Article 81/111 procedure that can be observed since the introduction of the agreement system.

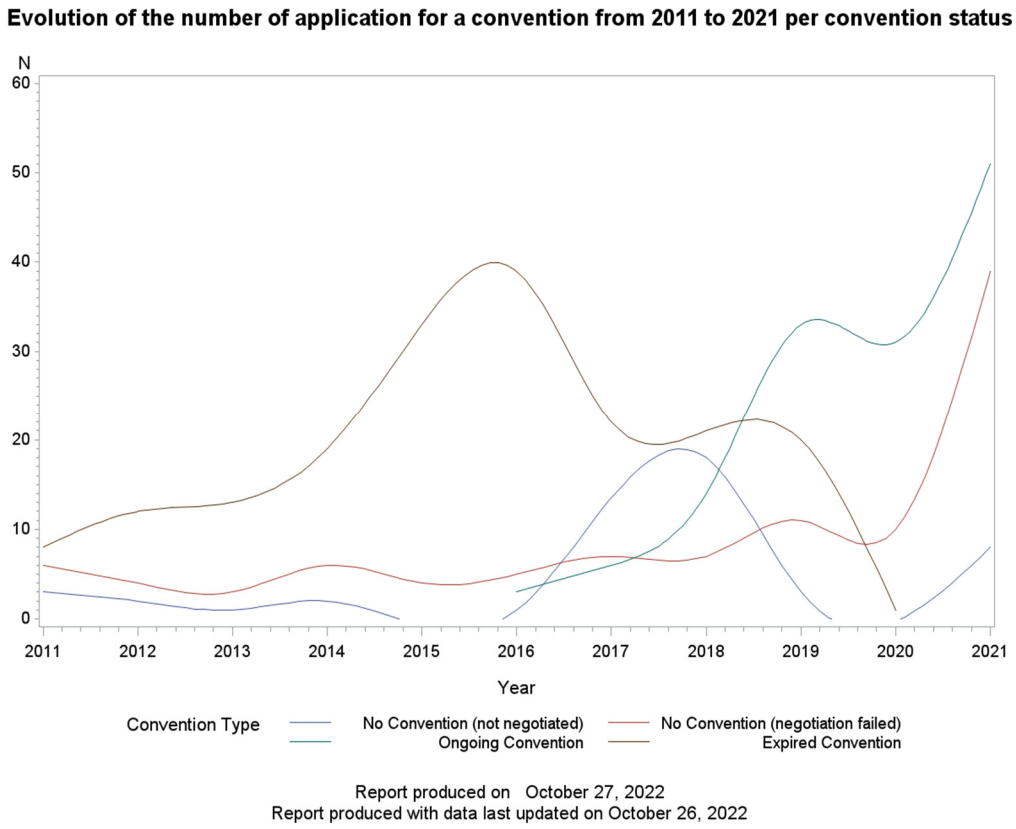
Table 22 and *Figure 103* show the status of the requests received between 2011 and 2021. Although the number of dossiers subjected to Article 81/111 has risen considerably, we also find that the number of dossiers resulting in an agreement has clearly decreased: 48% of the dossiers did not lead to an agreement. By way of comparison: the average number of non-executed agreements over all years is 31%. However, these figures must be interpreted with care, as part of the applications for an agreement directly lead to final inclusion in the reimbursement list (cf. 'No Convention', p. 136).

Table 22: Evolution of number of requests to conclude an Article 81/111 convention.

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Total
No Convention (not negotiated)	3	2	1	2	.	1	.	18	3	.	8	38
No Convention (negotiation failed)	6	4	3	6	4	5	7	7	11	10	39	102
Ongoing Convention	.	.	.	.	.	3	6	14	33	31	51	138
Expired Convention	8	12	13	19	33	39	22	21	20	1		188
Total	17	18	17	27	37	48	35	60	67	42	98	466

[3] As a reminder: due to the COVID-19 pandemic, the periods of the CRM procedures were suspended from 13 March 2020 to 1 April 2021 (RD no. 20 of 13 May 2020 introducing temporary measures in the fight against the COVID-19 pandemic and to ensure the continuity of care in the compulsory health care insurance).

Figure 103: *Evolution of number of requests to conclude an Article 81/111 convention*

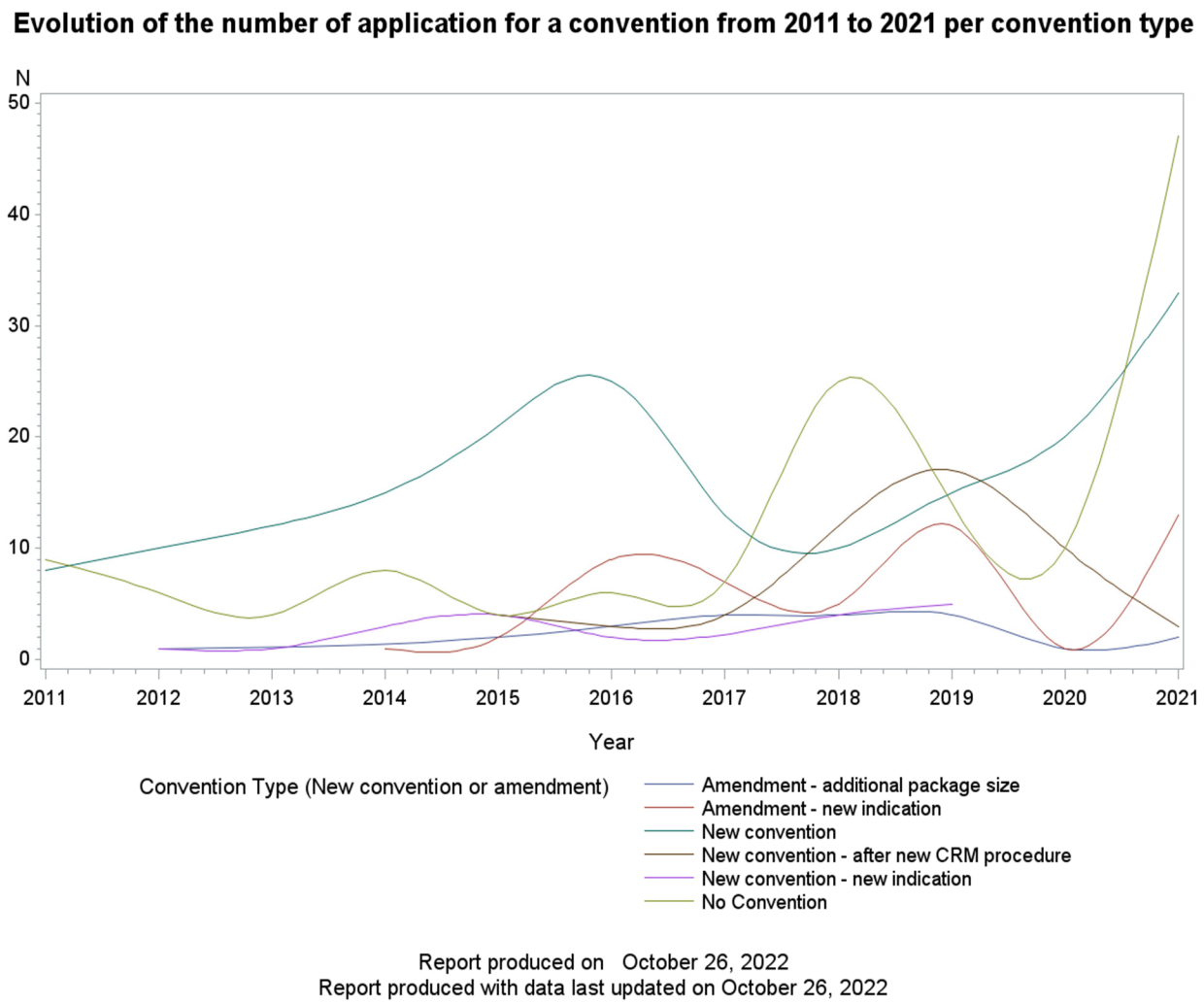


It appears in more detail from Table 23 and Figure 104 that the increasing trend does not only relate to applications to conclude conventions for new molecules. In recent years, there has been a logical increase in, firstly, the number of new conventions concluded for a molecule/indication which has already been reimbursed for a temporary period and was reassessed by the CRM; and, secondly, in the number of additional conventions concluded, or amendments to an existing convention, in the event of a new indication or a change of indication.

Table 23: Evolution of number of requests to conclude an Article 81/111 convention – details on outcomes

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Total
No Convention	9	6	4	8	4	6	7	25	14	10	47	140
Amendment - additional package size	.	1	.	.	2	3	4	4	4	1	2	21
Amendment - new indication	.	.	.	1	2	9	7	5	12	1	13	50
New convention	8	10	12	15	21	25	13	10	15	20	33	182
New convention - after new CRM procedure	.	.	.	.	4	3	4	12	17	10	3	53
New convention - new indication	.	1	1	3	4	2	.	4	5	.	.	20
Total	17	18	17	27	37	48	35	60	67	42	98	466

Figure 104: Evolution of number of requests to conclude an Article 81/111 convention – details on outcomes



Time until reimbursement (via a convention)

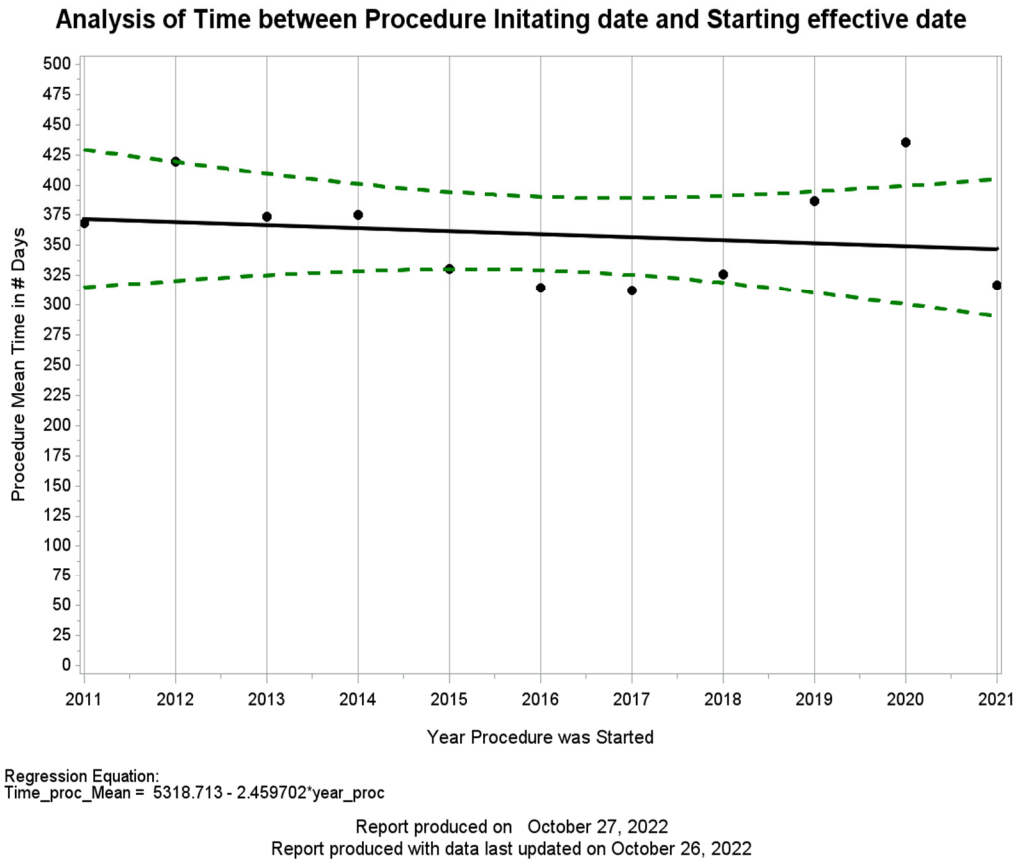
The duration of a reimbursement procedure is specified in the Royal Decree of 1 February 2018. It amounts to a maximum of 180 days. However, the reimbursement procedure (and therefore the 180-day period) may be suspended in the event of missing elements when submitting an application or in the absence of the price attribution. Furthermore, during the reimbursement procedure, the applicant may request twice a suspension of up to 90 days, and up to 120 days may be spent in the negotiation procedure to reach an agreement.

Possible suspensions are included in the number of days given in the following analysis.

It should be noted that during the COVID-19 crisis in 2020-2021, the calendar of the CRM procedures was temporarily suspended (suspension of deadlines from 13 March 2020 to 31 March 2021). This resulted in the total duration of the suspension(s) in practice often being longer than the maximum suspension periods mentioned in the Royal Decree of 1 February 2018. This is also evident from the figures for 2019 and 2020 (year in which the application was submitted to the CRM).

From 2011 to 2021, the average number of days between submission of a request for reimbursement and the entry into force of that reimbursement is 355 days.
In the case of 72 % of the conventions concluded, it took less than a year to achieve reimbursement via a convention. The shortest time between submission of the request for reimbursement and the entry into force of the reimbursement was 127 days. The longest period between submission and entry into force of the reimbursement was 688 days (i.e. ± 22,5 months); a consequence of suspensions during the procedure and the calendar halt during the COVID-19 crisis.
Gedurende de periode 2015-2018 is de tijd nodig tussen de indiening van een terugbetalingsaanvraag en het effectief in werking treden van de terugbetaling relatief stabiel gebleven (ca. 10 maanden). Aangezien overeenkomsten hoofdzakelijk worden afgesloten voor geneesmiddelen waarvoor het farmaceutisch bedrijf een therapeutische meerwaarde claimt of voor weesgeneesmiddelen, betekende de daling van ca. twee tot drie maanden ten opzichte van tien jaar geleden, een snellere toegang voor patiënten tot innovatieve geneesmiddelen. For 2019 and 2020, we notice a new increase (plus 2 months approximately) of the time between submitting the request for reimbursement and the reimbursement taking effect, that is, in all likelihood, due to the temporary suspension of the calendar for CRM procedures because of the COVID-19 crisis. Since then, the processing of the procedures has returned to the pace of the period 2015-2018. Thus, the trend in the processing time of a procedure is clearly decreasing, as illustrated in Figure *105*.

Figure 105: Evolution of time between submission of the reimbursement dossier and entry into force of reimbursement



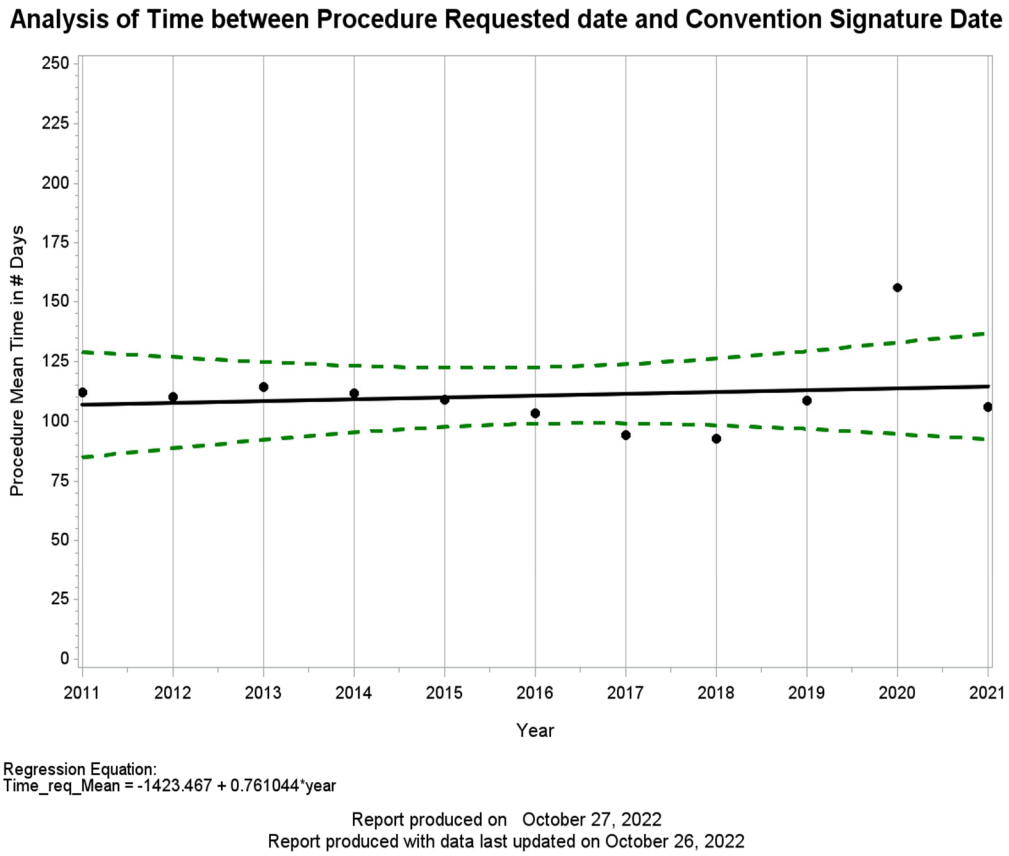
Timeframe to suspend a discussion according to Article 111, 112 or 113 of the Royal Decree of 1 February 2018

As described above, according to regulations, a maximum of 120 days may be spent on discussions to reach a possible 81/111 convention.

Due to the fact that during the COVID-19 crisis in 2020-2021, the calendar of procedures was temporarily halted, it was temporarily possible to have a suspension in the context of an Article 81/111 discussion that lasted longer than 120 days. This is also reflected in the 2019-2020 figures.

From 2011 to 2021 discussions took on average 110 days (taking into account the COVID-19 situation). According to regulations, 10 days of this period are spent on the assessment by the Minister/State Secretary for the Budget. *Figure 106* shows the evolution of this processing time in the period 2011-2021.

Figure 106 : Evolution of the time between submitting an application for an Article 81/111 convention and signing the convention (i.e. time spent on negotiations and approval of the content of the agreement by the ministers involved) per year in which the application was submitted



Expired conventions

Table 24 shows the evolution of the outcome of the agreements when they expire.

- Of the 151 conventions which have expired between 2011 and 2021, no new CRM procedure seems to have been launched for 7 of them (4,63%).
- For 25,82% (39/151) of the expired conventions, a new CRM procedure was launched and the pharmaceutical/indication was definitively included in the list of reimbursable pharmaceuticals.
- For 64,9 % (98/151) of the expired conventions, a new CRM procedure was launched and the pharmaceutical/indication was temporarily included in the list of reimbursable pharmaceuticals, via a new convention.
- In the case of 4,63 % (7/151) of the expired conventions, a new CRM procedure was launched, but the (temporary or definitive) reimbursability was not retained. As a result, the pharmaceutical/indication is no longer reimbursed.

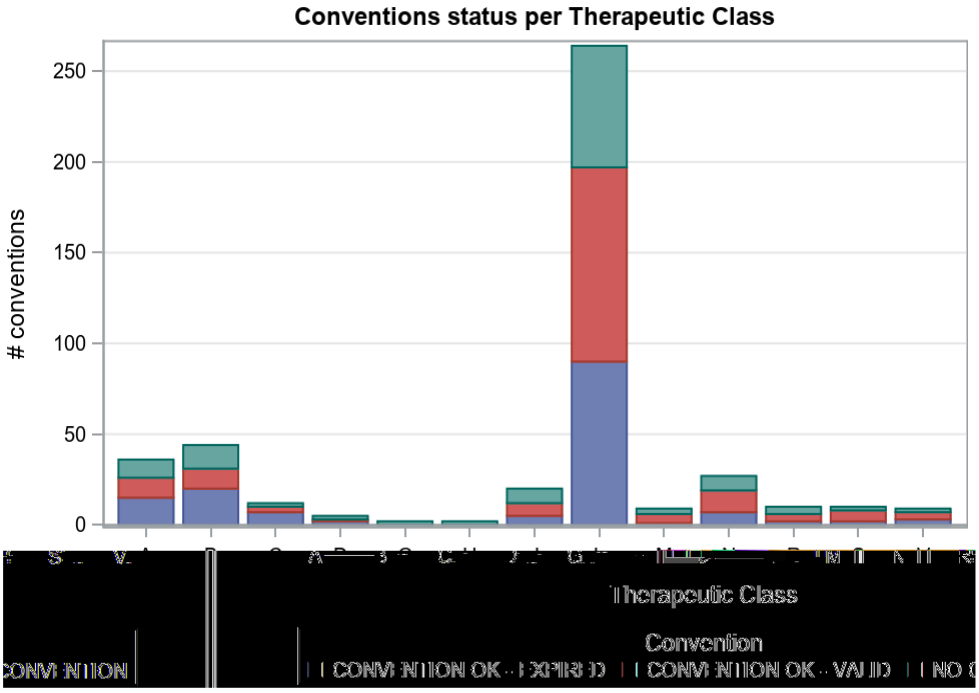
Table 24: Expired conventions – current situation

Outcome when convention is ended	Frequency	Percent
definitive listing after new CRM procedure	39	25,83
new convention after new CRM procedure	98	64,90
no reimbursement - no new CRM procedure	7	4,64
no reimbursement after new CRM procedure	7	4,64

Conventions per ATC code

Figure 107 gives an overview per ATC class (level 1) of the number of requests leading to negotiations since the introduction of this procedure.

Figure 107: Overview of requests for Article 81/111 conventions per ATC class

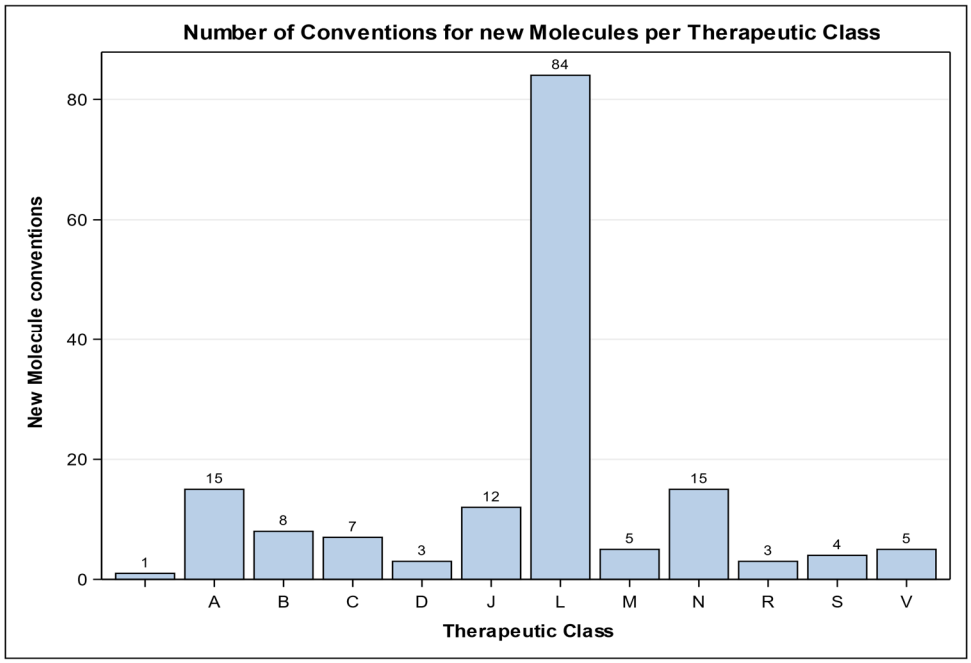


Most conventions (58,6%) were concluded for medicines in ATC class L, 'Antineoplastic and immunomodulating agents'. Next were medicines from ATC class B 'Blood and blood forming organs' (9,78%).

It should however be noted that for some pharmaceuticals, more than one indication is reimbursed by means of a convention, so for some pharmaceuticals, more than one convention may be concluded.

In terms of molecules, one or more conventions were concluded in the period 2011-2021 for 162 molecules (unique ATC code).

Figure 108: Overview of number of Article 81/111 conventions (new molecule) concluded per ATC class (2011-2021)



Conventions per status of CRM opinion

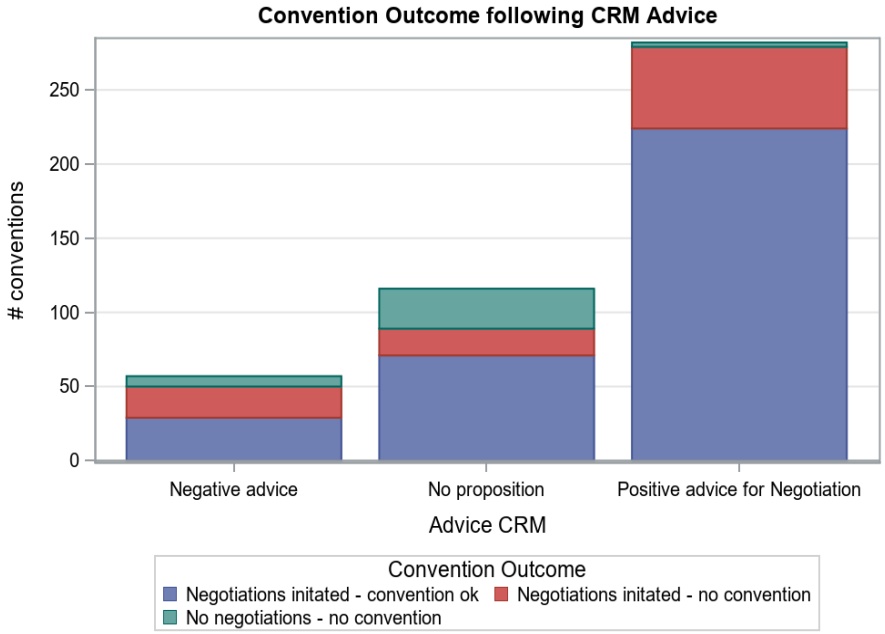
Until 1 April 2014, a company which had received a negative opinion from the CRM could submit a request to enter into negotiations. Since 1 February 2018, this has again become possible, although only after an explicit demand from the Minister for Social Affairs, asking for a company which has received a negative opinion from the CRM to be permitted to lodge a request to launch negotiations.

In 7 of the 64 cases (10.9%) where the CRM had issued a negative opinion, the start of the negotiation procedure was refused by the minister concerned. 31 of the 64 cases (48.4%) where the CRM had issued a negative opinion, eventually resulted in a convention.

A convention was concluded in 178 of the 206 cases (86.4%) where the CRM had issued a proposal to negotiate, and in 72 of the 112 cases (64.3%) on which the CRM did not issue an opinion.

In a limited number of cases, the Commission proposed to start a negotiation procedure, the company submitted an application to the Minister for Social Affairs, and the medicine was included definitively in the list of reimbursable pharmaceuticals – usually after consultation with the working group and with a price reduction. This situation is illustrated by *Figure 109* under the modality 'Negotiations Initiated – No convention'. Only once did the Minister decide before the consultations with the working group to include the medicine definitively in the list of reimbursable pharmaceuticals with a reduction in the list price (the previous MORSE reports erroneously stated that no application for an Article 81/111 procedure had been submitted for that dossier).

Figure 109: Overview of number of Article 81/111 convention requests, by status of CRM opinion



Conventions, by type of reimbursement request submitted by the pharmaceutical company

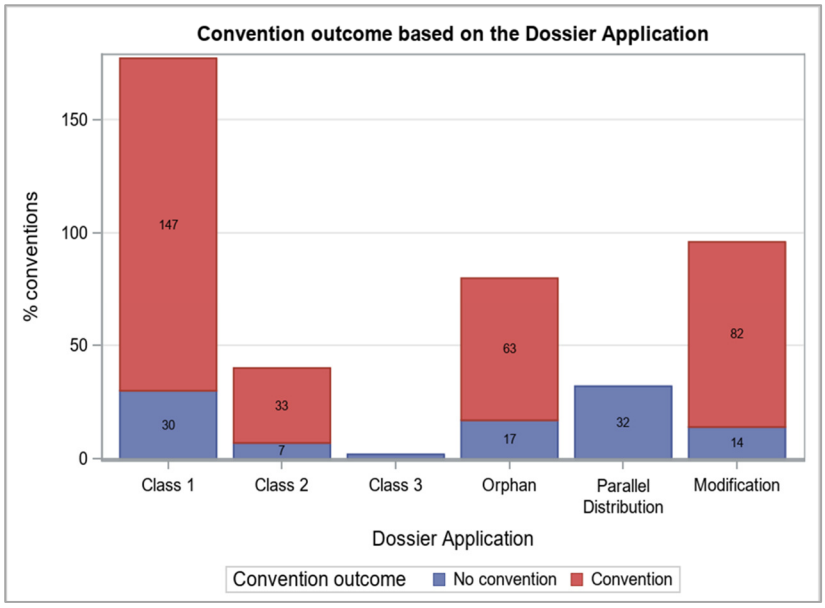
Table 25 and *Figure 110* show the number of negotiations that did or did not lead to an agreement, by type of reimbursement application. In the case of 83,05 % (147/177) of reimbursement requests for which the pharmaceutical company claims therapeutic added value ('Class 1'), a convention is concluded and temporary reimbursement takes place. For 79% (63/80) of requests regarding an orphan drug, a convention is concluded. In requests for negotiations where no claim of therapeutic added value is made ('Class 2' and 'Class 3'), the pharmaceutical is listed temporarily in 78,5 % (33/42) of the cases. In such cases, the reference pharmaceutical is also 'under contract', which probably makes it more likely that agreement will be reached. 85,4% (82/96) of requests for negotiations concerning an amendment to the reimbursement conditions result in a temporary reimbursement: either a new convention is concluded or an existing convention is amended.

In a number of cases, the request to launch negotiations was rejected by the Minister for Social Affairs; this was mainly the case for pharmaceuticals submitted as 'parallel distribution' and for which the application for an Article 81/111 procedure was not in agreement with the provisions of the RD of 1 February 2018. It is also possible that the Minister decided that the application of the company contained insufficient reasons/arguments to be able to carry out an Article 81/111 procedure and that therefore no negotiations with the working group could be launched.

Table 25: Overview of Article 81/111 convention requests, by type of reimbursement request submitted by the pharmaceutical company

	Negotiation Outcome		
Demand Category (Frequency Row Pct)	**No convention**	**Convention**	**Total**
Class 1	30 16.95	147 83.05	177
Class 2	7 17.50	33 82.50	40
Class 3	2 100.00	0 0.00	2
Orphan	17 21.25	63 78.75	80
Parallel Distribution	32 100.00	0 0.00	32
Modification	14 14.58	82 85.42	96
Total	102	325	427

Figure 110 : Overview of Article 81/111 convention requests, by type of reimbursement request submitted by the pharmaceutical company

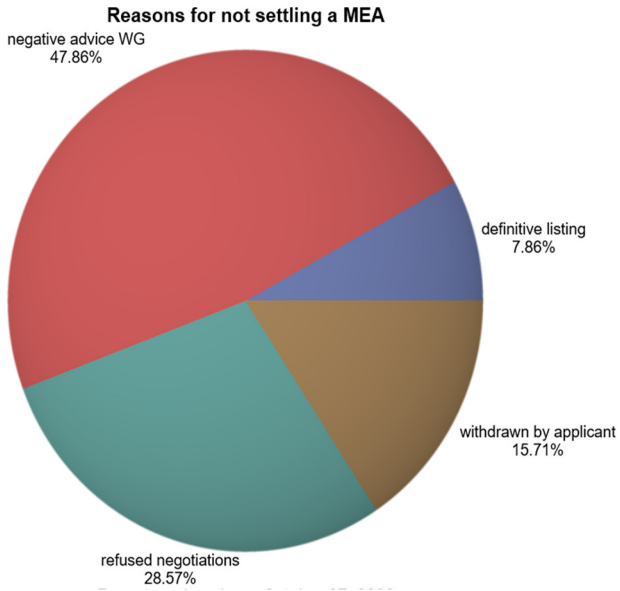


No convention

Even when the pharmaceutical company has made a request for negotiations to the Minister of Social Affairs, the procedure does not always result in a convention. *Figure 111* shows the percentages of the reasons that did not lead to the non-signature of an agreement at the end of the procedure.

- In 7,86 % of such cases the pharmaceutical is included definitively in the list of reimbursable pharmaceuticals without a convention. Often, the list price is directly reduced.
- In 28,57 % of cases, , the Minister decides that it is not the right time to start negotiations. This can be because the clinical data available are not yet mature enough to allow proper discussion of a temporary reimbursement. It is also possible that the applicant submitted an invalid application to start negotiations (submission of the application outside the timeframe mentioned in the Royal Decree of 1 February 2018 or the application does not contain the information mentioned in Article 11, 112 or 113 of the this Decree, ...)
- In 47,86 % of the cases, the working group carrying out the negotiations decides that no agreement can be reached, and informs the Minister of this.
- In about 16% of the cases, the pharmaceutical company withdraws from the negotiations in mid-procedure.

Figure 111: Overview of reasons why no convention is concluded

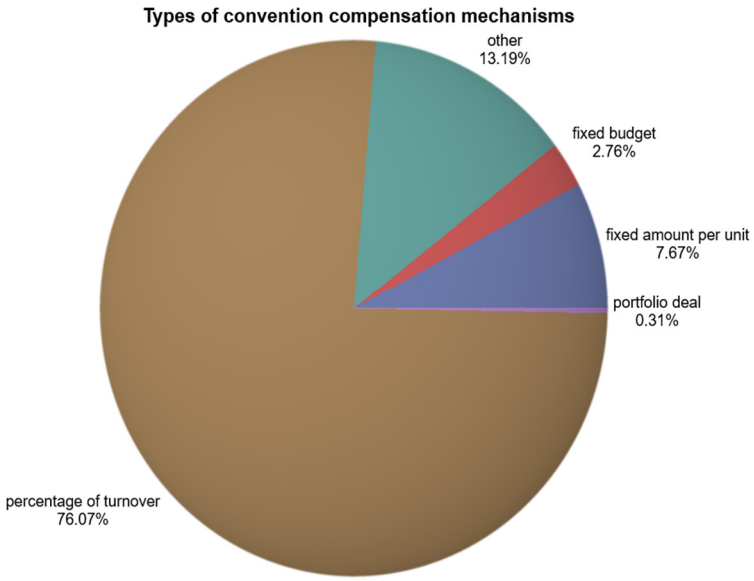


Budgetary compensation mechanism

Figure 112 shows the various budgetary mechanisms used in the context of the agreements concluded. 87% of the conventions concluded have included only one budgetary compensation mechanism.

- In most of them (76%) part of the turnover is repaid. This compensation mechanism can involve repayment of a set percentage of the turnover, or a percentage which increases by pre-determined 'tranche' of turnover. As previously explained, when setting the repayment percentage, account may also be taken of certain aspects. These include the percentage of non-responders, as seen in clinical studies, in which case the compensation mechanism can be described as 'outcomes-based' at the level of the population, insufficient evidence of efficacy or non-appropriate packaging-sizes which could result in wastage.
- In 7,7% of the conventions concluded, the applicant is required to repay a set amount per unit sold.
- In 2,76% of cases, the amount to be repaid corresponds with all or part of the difference between the forecast expenditure and the actual expenditure on the relevant pharmaceutical. For example, a pre-determined amount could be repaid, irrespective of the turnover achieved, or the company could be asked to repay anything above the predicted turnover.
- The percentage of conventions in which the compensation is achieved solely by a reduction in the price of another medicine in the applicant's portfolio is very low (0.36%). This shows that this is not the preferred compensation mechanism, possibly because of its uncertain outcome.

Figure 112: Overview of Article 81/111 convention requests, by budgetary compensation mechanism



The remaining 13,19% of the conventions concluded combined two or more compensation mechanisms.

The use of two or more compensation mechanisms in one convention is complex and logistically more difficult to follow than when one mechanism is applied. One possible advantage of combining compensation mechanisms – and specifically of combinations which include a price reduction for another product – seems to be that a higher level of compensation is possible, since the financial pressure on a company is exerted on not just one product from its portfolio. Such a system, however, also creates greater uncertainty, since it is based on forecasts not just relating to the pharmaceutical being reimbursed on a temporary basis, but also relating to the portfolio product.

Sometimes, moreover, more 'alternative' compensation mechanisms are included in conventions, such as financial compensation to optimise data collection by Sciensano, or compensation on medicines which are not in the applicant's portfolio but have a (therapeutic) link with the drug which is the subject of the convention.

To provide greater budgetary certainty, a 'cap' can be applied – mostly in combination with other compensation mechanisms: a considerable proportion of the amount above this cap has to be repaid. The 'cap' is set at a percentage of the anticipated turnover and varies between conventions, but is often set at less than 100% of the anticipated turnover.

No separate 'conventions budget', but a 'budget control mechanism'

As previously reported, there is no separate budget for pharmaceuticals which are reimbursed by virtue of a convention. Conventions are one of the medicines policy tools used to keep tighter control on the budget.

In the section below we describe the evolution over time of expenditure on medicines reimbursed via conventions under Article 81 and following (RD 21.12.2001) and Article 111 and following (new RD 1.2.2018) in Table 26, Table 27 and Figure 113. On the one hand, the situation is presented per calendar year. Given that these data are meaningful, especially in terms of bookkeeping, the situation is also shown cumulatively since the introduction of confidentiality agreements in Belgium.

The following points should be borne in mind when interpreting these figures:

- Re-calculation to report the actual 'year of provision of services'.
  Conventions are split into years T in which a refund/compensation is expected from the pharmaceutical company, based on the provisions in the conventions. The pharmaceutical company is mostly required to declare the gross turnover figures (before deduction of the budgetary refund) over a particular period covered by the convention. The conventions run from one date to another, which means that the period covered can spread over two or three calendar years, and the moment of settlement does not necessarily fall in the same calendar year as the period to which the settlement refers. Under the conventions, therefore, (gross) expenditure takes place in a given year 'T', but the repayments happen either fully or partially in the year T+1 or even later in some specific cases (e.g. if a P4P mechanism is being activated), when the company makes the declaration. The tables below contain a proportionate recalculation, to relate the turnover figures and compensation mechanisms back to the actual years in which the turnovers and refunds took place.
- We can only take account here of direct financial compensation mechanisms. Indirect compensation, via price reductions for other pharmaceuticals, is not accounted for (the compensation figures are therefore underestimated).
- With regard to the turnover figures, in some cases the full turnover for the pharmaceutical is used, including the turnover for that pharmaceutical for 'non-contracted' indications. Based on these data, one can therefore not determine a separate budget for pharmaceuticals reimbursed throught an agreement.
- Since October 2016, moreover, when new conventions are concluded or amendments made, efforts are made to collect, in year T, an amount as close as possible to the compensation (repayment) due in the year when the expenditure actually took place (year T), according to the mechanism set out in the convention, as part of the drive towards prepayment of the actual expenditure on pharmaceuticals within the health insurance system. Application of the 'prepayment' system should provide a more accurate picture of the actual net expenditure per calendar year.
- The turnover and refund figures are initially based on known data, i.e. company declarations of turnover, prepayments made, provisional and definitive settlements for expired conventions. Where the data are not known, we use estimates, which acted as a basis for the negotiations.
- All these figures refer to ex factory prices. The turnover figures correspond to the expenditure for the health insurance at ex factory prices, so take no account of expenditure on margins, fees or VAT. For practical reasons, the budgetary compensation mechanism in Article 81/111 conventions is mostly determined on the basis of turnover figures for ex factory prices. Besides, for most medicines reimbursed under an Article 81/111 convention, the share of margins and fees is low. These are often medicines which are only reimbursed when delivered by a hospital pharmacy, which means that these

margins are subject to a ceiling. The margins are therefore mostly negligible in comparison to the total cost price of these often very expensive pharmaceuticals.

- The data refer to the situation on 27/10/2022, source Pharmaceutical Policy directorate (database on follow-up of Article 81/111 conventions).

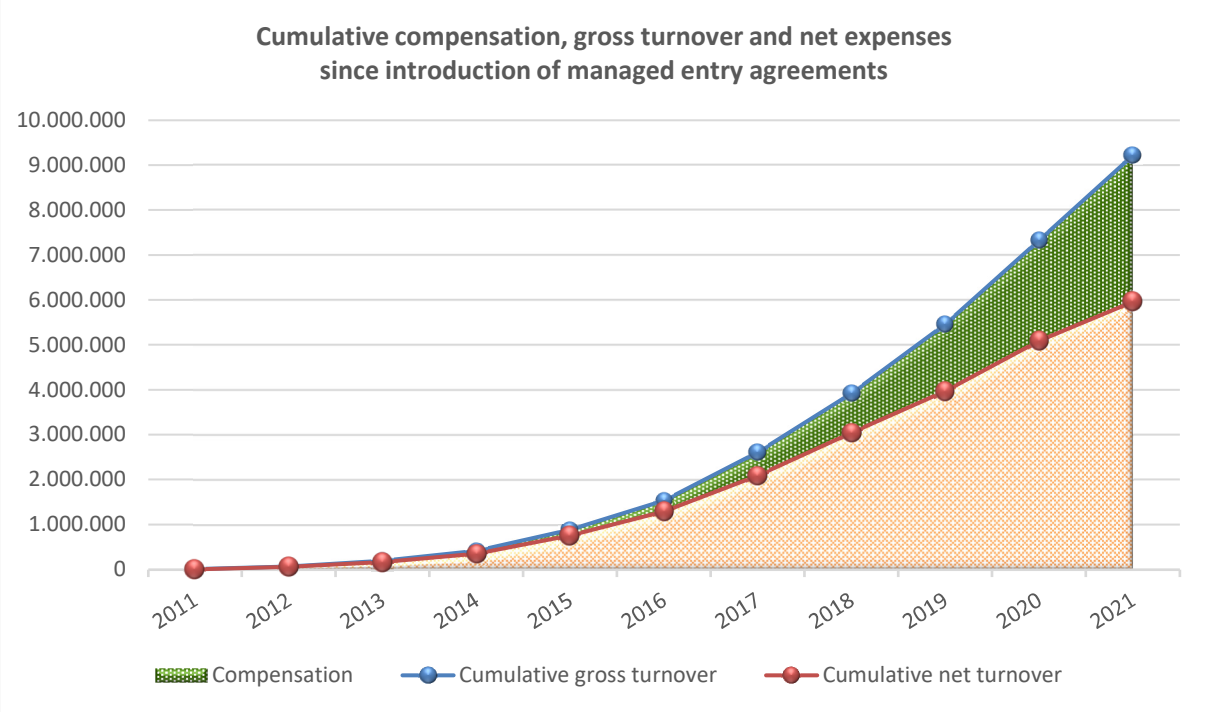
Table 26 : Overview, per year, of turnover figures, compensation and net expenditure (ex factory prices, expressed in 000 EUROS).

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Gross turnover	8.680	53.411	130.744	225.160	466.079	652.609	1.070.010	1.314.967	1.534.232	1.866.280	1.896.269
Advance	0	0	0	0	0	0	100.491	195.504	387.036	540.457	707.644
Balance	1.249	2.630	23.729	41.428	56.629	121.316	172.652	162.066	218.099	213.539	311.895
Overall compensation	1.249	2.630	23.729	41.428	56.629	121.316	273.144	357.571	605.135	753.996	1.019.539
Net turnover	7.432	50.780	107.015	183.731	409.450	531.293	796.866	957.396	929.097	1.112.284	876.731
Percentage	14.4%	4.92%	18.1%	18.4%	12.2%	18.6%	25.5%	27.2%	39.4%	40.4%	53.8%

Table 27: *Cumulative overview, per year, of turnover figures, compensation and net expenditure (ex factory prices, expressed in 000 EUROS).*

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Cumulative gross turnover	8.680	62.091	192.835	417.995	884.074	1.536.683	2.606.693	3.921.660	5.455.893	7.322.172	9.218.442
Cumulative advance	0	0	0	0	0	0	100.491	295.996	683.031	1.223.488	1.931.132
Cumulative balance	1.249	3.879	27.608	69.037	125.665	246.981	419.634	581.700	799.800	1.013.339	1.325.233
Overall compensation	1.249	3.879	27.608	69.037	125.665	246.981	520.125	877.696	1.482.831	2.236.827	3.256.366
Cumulative net turnover	7.432	58.212	165.227	348.958	758.409	1.289.702	2.086.568	3.043.964	3.973.062	5.085.346	5.962.076
Percentage	14.4%	6.25%	14.3%	16.5%	14.2%	16.1%	20.0%	22.4%	27.2%	30.5%	35.3%

Figure 113 : Overview, per year, of cumulative turnover figures, compensation and net expenditure (ex factory prices, expressed in 000 EUROS



DOSSIER – ORPHAN DRUGS

An orphan drug is a pharmaceutical product used for the diagnosis, prevention or treatment of a rare disease for which either no means of prevention, diagnosis or treatment exists, or where the medicine offers a significant benefit for patients compared to the current situation.

A rare disease is a life-threatening and/or chronically debilitating condition with a prevalence of 5 out of 10,000 people in the European Union or less (or 5,000 people or less in Belgium).

NUMBER OF PHARMACEUTICALS

The designation of orphan drug, obtained from the European Medicines Agency (EMA) via a designation process prior to registration, can however:

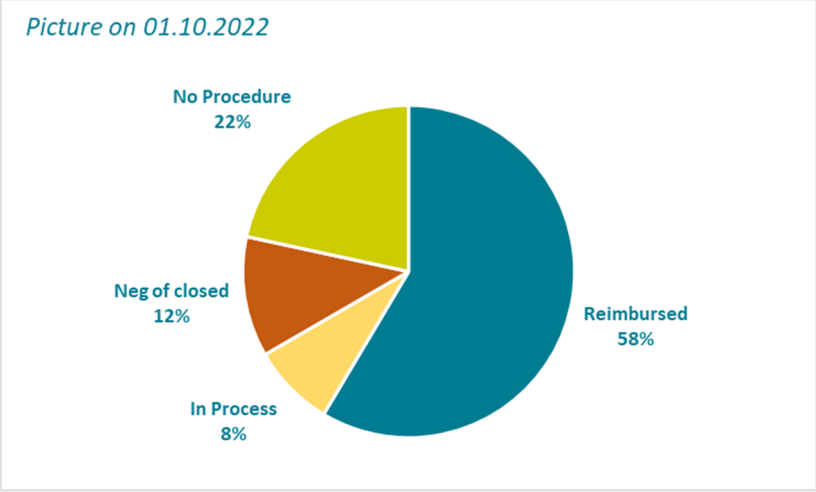
- **be withdrawn** by the company, particularly in order to extend the indications;
- **be lost** when, for example, the ten-year exclusivity expires or
- **not be obtained** if the company has not gone through the designation process.

Given these **changes in status**, it is not such an easy task to count the number of pharmaceuticals.

A good example to illustrate these difficulties are the drugs used for pulmonary arterial hypertension. The range of drugs used against this disease includes medicines which still have the status of orphan drugs, medicines without prior designation, medicines whose status of orphan drugs has been withdrawn or has expired, generic medicines, and even medicines which have been taken off the market.

On 1 October 2022, at the time of the reimbursement evaluation, there were 222 registered medicines considered as orphan drugs, or previously regarded as orphan drugs. Almost 2/3 of these pharmaceuticals were eligible for reimbursement (113 on 1 October 2022).

Figure 114 : Reimbursement status of pharmaceuticals which have, or have had, the status of orphan drugs



Overview of the distribution of the 4 scenarios:

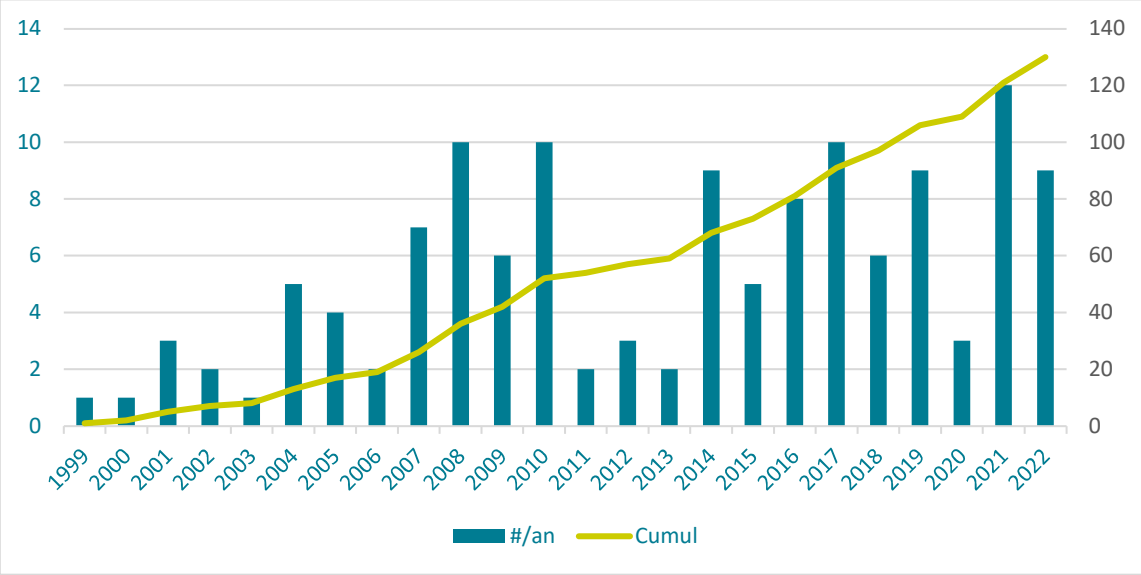
- Nearly **60%** of medicines qualified as orphan drugs are **reimbursable**.
- A little more than **10%** of these were **not accepted for reimbursement**, not only for budgetary reasons, but because alternatives exist which are often cheaper, or due to the absence of certain essential elements for the procedure.
- A little less than **10%** follow the **CRM procedure**, but
- especially for slightly over **20%** of those drugs, the company responsible did **not** file an application for inclusion in Belgian reimbursement.

With respect to the reimbursable pharmaceuticals, it is also interesting to know certain aspects of their reimbursement conditions.

Of the 130 pharmaceuticals, 3 were included in Chapter I of the list of reimbursable pharmaceuticals. In comparison with previous reports, the percentages referring to inclusion in the reimbursement list and non-submission of such an application were similar or even identical, leading to the conclusion that **98%** of orphan drugs are included either in Chapter IV or in Chapter VIII. Thus, the **prior agreement** of the consulting physician of the health insurance fund is normally required for the reimbursement of orphan drugs.

For 50 of them, or nearly 40%, reimbursement was or is still **provisional**, and for 45 a **College** of Physicians was created. For 38, both aspects are present, but these are unrelated. Their respective legal bases vary a few years, but the orphan drug status does not de facto lead to the creation of a College or the drawing up of a contract, as could be seen in the latest inclusions in reimbursement.

Figure 115 : Evolution of the number of orphan drugs eligible for reimbursement (per year and cumulative)

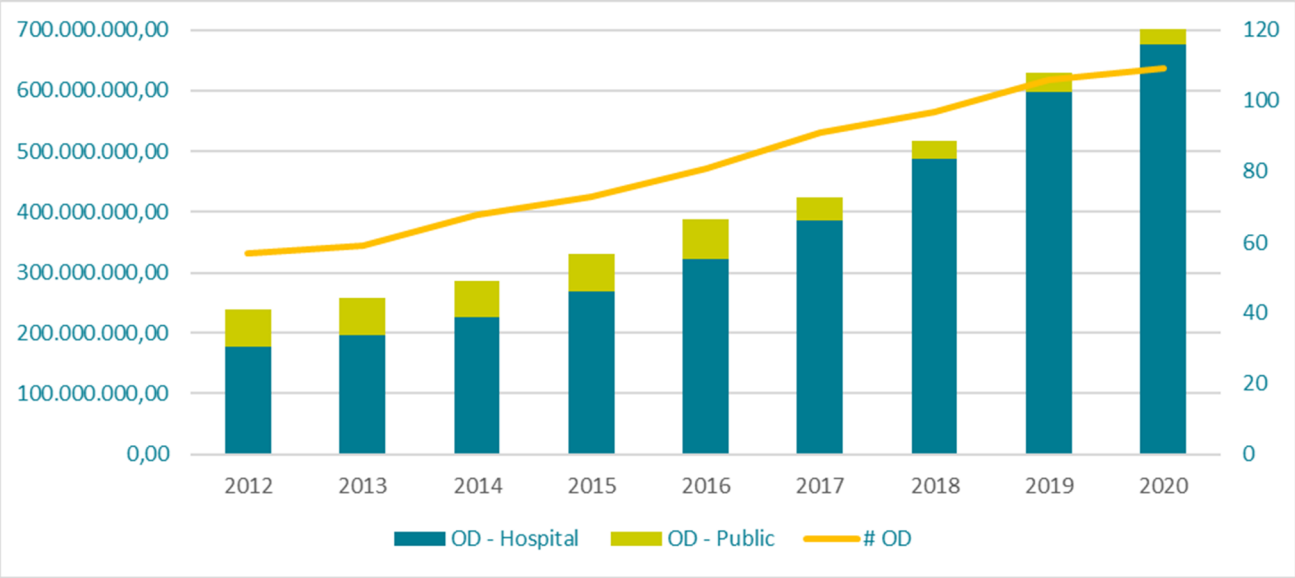


EXPENDITURE

Most orphan drugs are only eligible for reimbursement in hospitals, which explains their importance in these spending figures. In addition, they are practically all listed in Category A.

The two figures below (Figure 116 and Figure 117) show firstly the intrinsic evolution of NIHDI expenditure on orphan drugs and, secondly, the percentage which they represent in the total expenditure on reimbursable medicines.

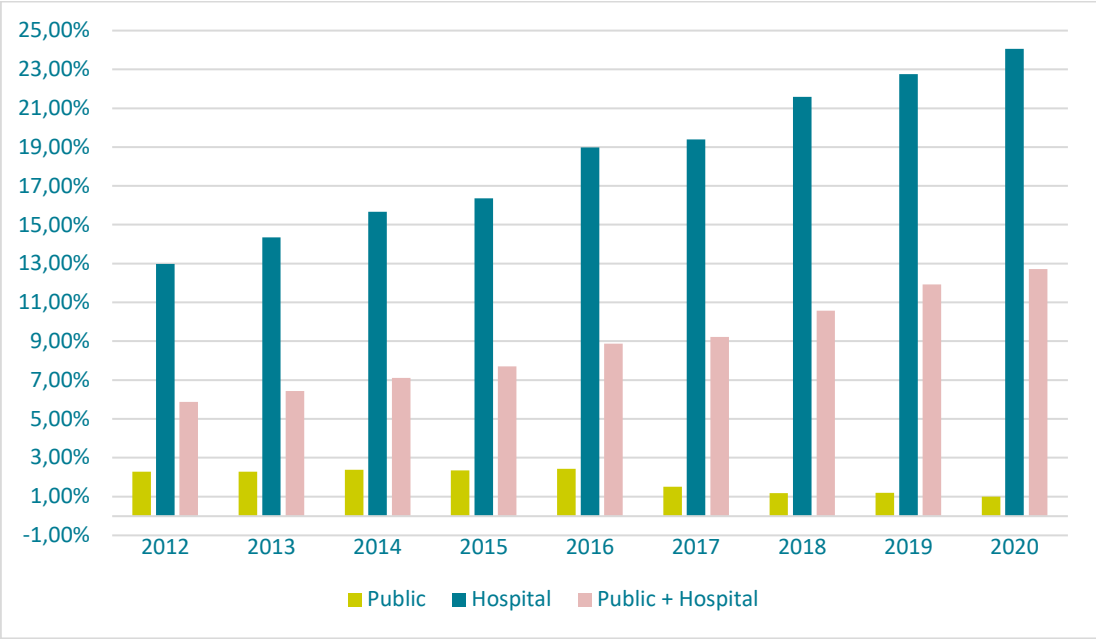
Figure 116: evolution of NIHDI net annual expenditure (public pharmacies and hospitals) and number of orphan drugs eligible for reimbursement, 2012 - 2020



Between 2012 and 2020, expenditure has evolved by a factor of 2.96, while the number of orphan drugs becoming eligible for reimbursement between these two years increased by a multiplication factor of 1.75. In summary: for a doubling of the number of medicines included in the reimbursement list, the related actual expenditure has triplicated. However, it must be noted that some pharmaceuticals are regulated by article 81/111 agreements, the modalities of which are such that actual expenditure could be lower.

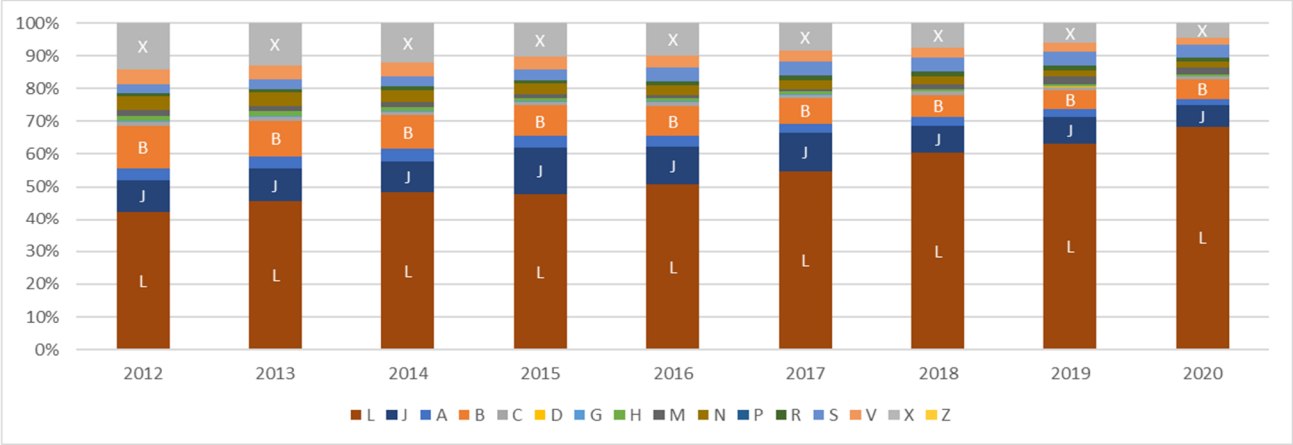
This parameter or distortion becomes smaller when the expenditure for orphan drugs is compared to total expenditure for reimbursable pharmaceuticals, given that some non-orphan drugs are also temporarily included in the reimbursement list via an agreement.

Figure 117 : orphan drugs as a percentage of NIHDI net annual expenditure, by place of delivery (public pharmacies and hospitals), 2012 - 2020



Based on Figure 117, we can roughly estimate that expenditure on pharmaceuticals with, or which previously had, the status of orphan drugs, makes up in 2020, 13% of total net expenditure on reimbursable pharmaceuticals, varying according the place of delivery, from 1% of net expenditure in public pharmacies to almost 25% of hospital expenditure.

Figure 118: Evolution of the share of the ATC classes in hospital expenditure



The class of oncological conditions, namely ATC class L, has increased from 40 to 70 percent.

On a detailed level, based on the orphan drug status, it can be determined that the increase in this class bears no relation to the granting of the orphan drug status.

Figure 119: Share of ATC class L in hospital expenditure for medicines with (OD) or without (NOD) orphan drug status, comparison of 2012 vs 2020

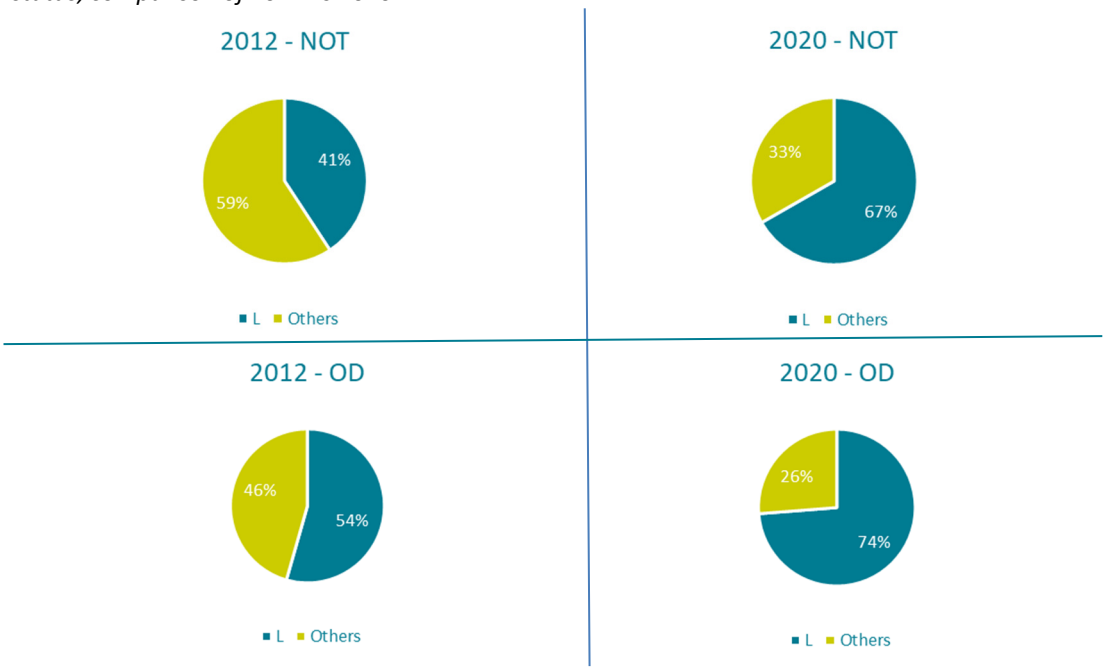


Figure 120: Evolution of hospital expenditure in the ATC classes based on orphan drug status – situation in 2017

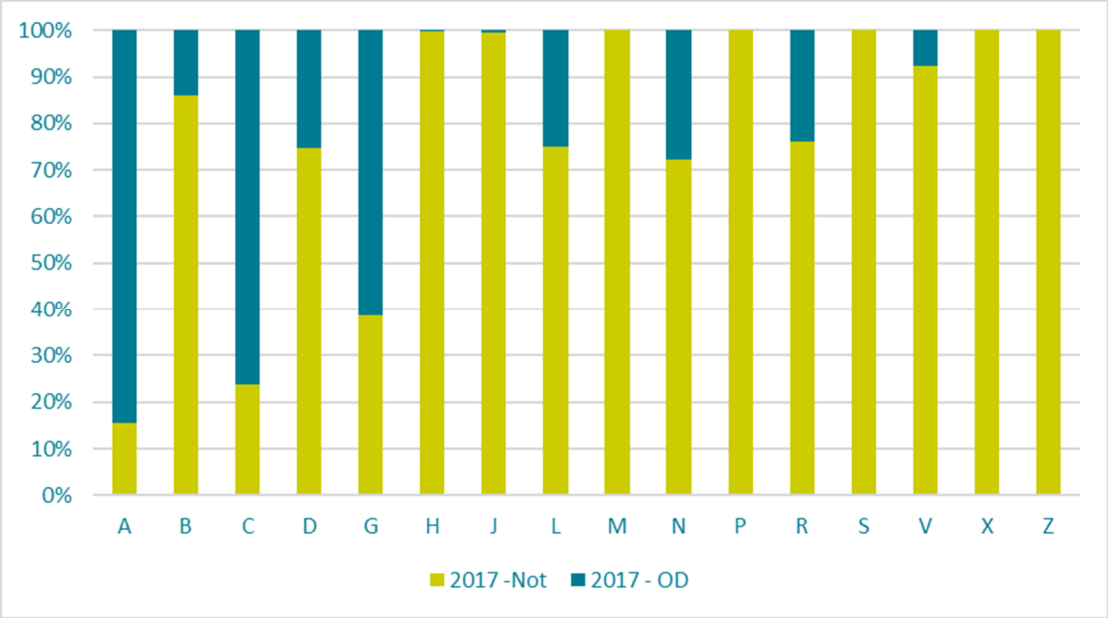
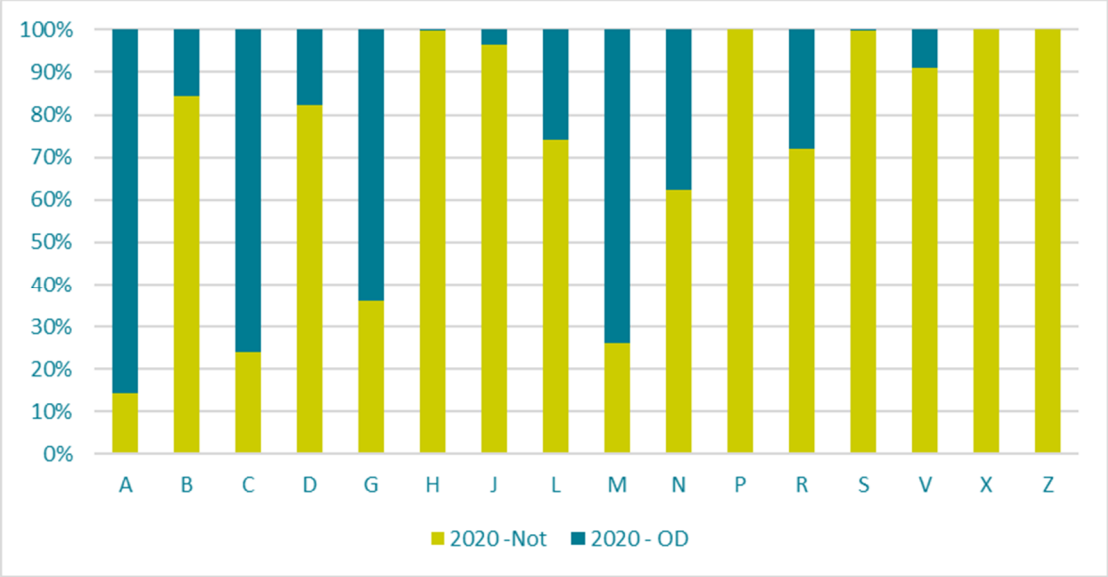


Figure 121: Evolution of hospital expenditure in the ATC classes based on orphan drug status – situation in 2020



Based on these two graphs, the balance between orphan drugs and non-orphan drugs in hospital expenditure for each ATC class has remained fairly stable. The dominance of orphan drugs in class A is normal given that this class comprises all so-called metabolic diseases, the majority of which are considered rare. The M class, which comprises products aimed at the musculoskeletal system, has experienced a therapeutic breakthrough for a form of spinal muscular atrophy, which by definition meets the criteria of rare diseases and orphan drugs. This has also led to an increase in the share of the expenditure for this organ system in all hospital expenditure by 2 to 6%.

GENERAL COMMENTS
The comments made in the 2020 report still apply :

In the field of oncology, the emergence of orphan drugs is due to the increasingly targeted characterisation of cancers, which means that patients are sub-divided into specific forms of cancer.

The high expenditure on treatments carried out on blood components is due to a number of drugs used to treat so-called rare, but well-known diseases, such as some types of haemophilia. Others are better known in the media because of their annual cost.

The treatment used for PAH is evolving from a monotherapy to a polytherapy; this means that expenditure in that area is going up, with a yearly budget per patient of around 40-50,000 euros. This cost is only, however, for this type of medicine and not for other products which are sometimes used before or after, and which do not meet the criteria for an orphan drug, namely calcium channel blockers – not to mention the medicines used if the patient is admitted to hospital and if he/she receives a transplant.

DOSSIER - THE COMMISSION FOR REIMBURSEMENT OF MEDICINES

General

In this analysis, we assess two of the variables which can be objectively measured, and which seem to be essential to enable access to new, innovative or otherwise, drugs in Belgium: the number of requests for reimbursement (dossiers) submitted, and the Commission proposals and Minister's decisions on the new medicines for which a request has been submitted.

During the evaluation and interpretation of data, a series of important elements must be borne in mind:

1. General elements

- Reimbursement of medicines in Belgium is supply-led, so reimbursement is dependent on a request for reimbursement, submitted by the pharmaceutical company. This is absolutely essential for all reimbursable pharmaceuticals and important for the speed of reimbursement of sometimes innovative new medicines.
- For orphan medicinal products and class 1 requests, the request can be submitted as soon as the applicant has received a positive opinion from the Committee for Medicinal Products for Human Use of the EMA (European Medicines Agency).
  This possibility has to date not been used that often. Between 2017 and 2021, 7,84% of class 1 requests and requests for reimbursability for orphan medicinal products were submitted on the basis of a positive opinion from the EMA's Committee for Medicinal Products for Human Use, before the marketing authorisation was granted: 8 requests in 2017, 6 requests in 2018, 3 requests in 2019, 4 requests in 2020 and 4 requests in 2021.
- On 1 April 2018, the Royal Decree of 21 December 2001, concerning the procedures, terms and conditions for contribution by mandatory insurance for healthcare and benefits towards costs of pharmaceuticals, was repealed and replaced by the Royal Decree of 1 February 2018 concerning the procedures, terms and conditions for contribution by mandatory insurance for healthcare and benefits towards costs of pharmaceuticals. This resulted in a number of changes to the Commission procedures, including the following:
  - a redefining of a number of subclasses,
  - an extension of the sorts of requests which may be processed (new inclusion of line extensions of pharmaceuticals which are already reimbursed),
  - introduction of a specific procedure for generics and copies which could qualify for a partial exemption from application of the patent cliff;
  - introduction of a specific procedure for the listing as reimbursable of the new paediatric forms of pharmaceuticals already reimbursable for adults (subclass 2C; 90-day procedure),
  - introduction of a procedure to amend the reimbursement conditions, in order specifically to extend reimbursement of a pharmaceutical already reimbursed for adults, so that it can be reimbursed for children (90-day procedure),
  - introduction of an option for companies to request the launch of negotiations with a view to concluding a convention for pharmaceuticals on which the CRM has given a negative opinion - solely on the basis of a reasoned proposal from the Minister of Social Affairs;
- In application of Article 1 of the Royal Decree no. 20 of 13 May 2020 on temporary measures in the fight against the COVID-19 pandemic and to ensure the continuity of care in the compulsory healthcare insurance (published in the Belgian Official Gazette on 19 May 2020), the calendars that determine the timeframes for the implementation of the procedures in order to modify the list of reimbursable pharmaceuticals, were suspended as from 13 March 2020. This measure was abolished by Article 1 (3) of the Royal Decree of 28 December 2020 abolishing certain temporary measures of the Royal Decree no. 20 of 13 May 2020 containing temporary measures in the fight against the COVID-19 pandemic and

to ensure the continuity of care in the compulsory healthcare insurance, and of the Royal Decree no. 21 of 14 May 2020 temporarily adapting the reimbursement conditions and administrative rules in the compulsory healthcare insurance as a result of the COVID-19 pandemic, and the calendars resumed on 1 April 2021.

2. Specific elements for this analysis

- The data reported come from the administrative database used by the secretariat of the Commission for Reimbursement of Medicines for the permanent monitoring of procedures and deadlines. For the analysis of the number of dossiers, we considered all the data on dossiers submitted between 1 January 2003 and 31 December 2022. For the analysis of the proposals of the CRM and of the decisions of the Minister for Social Affairs, all data of the administrative database entered until 6 October 2022 was taken into account.
- For this analysis, we take account only of unique dossiers. This means that, in the case of simultaneous requests lodged for various dosages/packages of pharmaceuticals, the dossiers are taken together if the company responsible, the type of dossier, the day '0' (day of the request), active substance, Commission proposal and the ministerial decision are all identical.
- This analysis does not differentiate between first requests and renewed requests (limited number), i.e. any 'unique' dossier is regarded in the analysis as a 'new dossier'.
- The analyses do not take account of dossiers dealt with purely at an administrative level, i.e. without the involvement of the Commission, where the procedure is limited to 60 days.

Number of dossiers

The number of dossiers submitted in 2020 via the CRM procedure (Royal Decree of 21 December 2001 concerning the procedures, terms and conditions for contribution by mandatory insurance for healthcare and benefits towards costs of pharmaceuticals and the Royal Decree of 1 February 2018 concerning the procedures, terms and conditions for contribution by mandatory insurance for healthcare and benefits towards costs of pharmaceuticals) is in accordance with the average annual number of dossiers submitted over the past 10 years, while the number of dossiers submitted in 2021 was higher than the average number of dossiers submitted over the past 10 years, with considerable differences between the types of requests (see Figure 122). In 2017, the number of dossiers submitted was higher than the average number of dossiers submitted each year for the last 10 years. In 2017, there was an increase in the overall number of dossiers submitted compared to 2016, largely due to a steep increase in the number of class 1 dossiers submitted, but also to an increased number of dossiers to amend the reimbursement conditions (procedures launched by a firm or by the CRM itself). In 2018, we can see that the number of dossiers submitted reached the level of 2012, and that the fall continues in 2019. The fall in numbers observed in 2019 compared to 2018 is largely due to a reduction in the number of class 2 dossiers submitted, but also to a steep fall in the number of dossiers asking to amend the reimbursement (procedures started by a company or by the CRM itself). In 2020, an increase in the overall number of dossiers submitted has been observed compared to 2019. This is mainly due to an increase in the number of dossiers submitted in class 1, an increase in the number of dossiers for admission to the reimbursement of pharmaceuticals subject to parallel import/distribution as well as an increase in the number of dossiers with a request for an increase in the reimbursement base. This increase continued in 2021, mainly as a consequence of an increase in the number of dossiers for orphan drugs, as a result of an increase in the number of dossiers submitted in class 3, and as a result of an increase in the number of dossiers for the modification of reimbursement modalities (procedures started by a company or by the CRM itself).

It should be noted that:

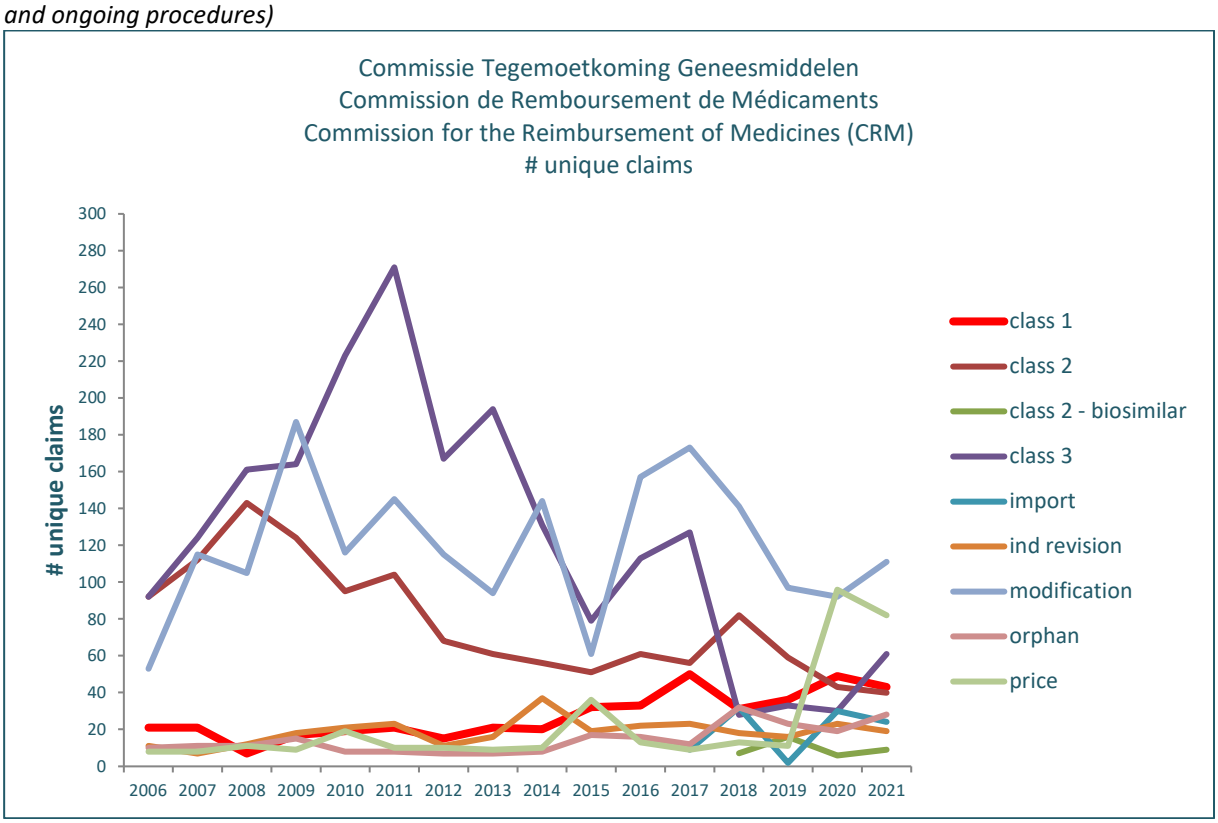
- After reaching a low point in 2008, the number of class 1 requests has grown since 2009 to 50 in 2017, 31 in 2018, 38 in 2019, 49 in 2020 and 43 in 2021.
- The number of orphan drug requests is considerably higher since 2018 than the numbers observed since 2010: between 2010 and 2014 there were 7 to 8 orphan drug requests per year, while in 2015, 2016 and 2017 the number of orphan drug requests has risen to respectively 17, 16 and 12 requests and the number of requests increased further to 32 in 2018, 23 in 2019 and 19 in 2020. In 2021, there were 28 applications for orphan drugs.
- After 5 years in which the number of applications for class 2 remained fairly stable (51 applications in 2015, 61 applications in 2016, 56 in 2017, 82 in 2018 and 59 in 2019), the number of applications decreased significantly in 2020 (43 applications in 2020). That decline continues in 2021 (40 applications in 2021).
- The number of class 3 requests – non-administrative procedure – has reached in 2018 its lowest point since entry into force of the Royal Decree concerning the procedures, terms and conditions for contribution by mandatory insurance for healthcare and benefits towards costs of pharmaceuticals (79 requests in 2015, 113 in 2016, 127 in 2017, 28 in 2018). From 2019, the number of class 3 applications - non-administrative procedure increased again: 33 applications in 2019, 30 applications in 2020 and 61 applications in 2021.
- The high number of requests to amend the reimbursement arrangements is striking in certain years, particularly in 2007, 2009, 2011, 2014, 2016, 2017 and 2018; these requests may ask for an extension of indications as well as more technical corrections. So pay attention: the figures for the second half of 2007 cover all amendments for simvastatin, with a move from category C to category B. Similarly, in 2009, there were many pricing changes for a large number of dossiers (contrast agents), administrative simplifications (transfer of sartans and ACE inhibitors to chapter I – reformulation of the reimbursement conditions to achieve greater consistency for the EPOs). In 2011, at the initiative of the CRM, the reimbursement conditions were changed for many dossiers (medicines used to treat Parkinson's disease, pharmaceuticals based on paclitaxel, etc.), and also in 2014 (docetaxel-based pharmaceuticals,

oxaliplatin, anastrozole, etc.), in 2016 (pharmaceuticals based on gemcitabine, irinotecan, growth hormones, etc.), and in 2017 (pharmaceuticals based on COX-2 selective nonsteroidal anti-inflammatory drugs, piroxicam-based pharmaceuticals, aliskiren-based pharmaceuticals, etc.).

The following were NOT added to the data:

- for 2010, 228 completed 'class 3 – administrative procedure' dossiers, nor 898 'Article 97 procedures - administrative proposals for amendments/corrections to the list';
- for 2011, 231 completed 'class 3 – administrative procedure' dossiers nor 201 'Article 97 procedures - administrative proposals for amendments/corrections to the list';
- for 2012, 214 completed 'class 3 – administrative procedure' dossiers nor 114 'Article 97 procedures - administrative proposals for amendments/corrections to the list';
- for 2013, 246 completed 'class 3 – administrative procedure' dossiers nor 373 'Article 97 procedures - administrative proposals for amendments/corrections to the list';
- for 2014, 142 completed 'class 3 – administrative procedure' dossiers nor 227 'Article 97 procedures - administrative proposals for amendments/corrections to the list';
- for 2015, 146 completed 'class 3 – administrative procedure' dossiers nor 264 'Article 97 procedures - administrative proposals for amendments/corrections to the list';
- for 2016, 109 completed 'class 3 – administrative procedure' dossiers, 55 completed 'parallel import - administrative procedure' dossiers nor 188 'Article 97 procedures - administrative proposals for amendments/corrections to the list';
- for 2017, 132 completed 'class 3 – administrative procedure' dossiers, 84 completed 'parallel import - administrative procedure' dossiers nor 344 'Article 97 procedures - administrative proposals for amendments/corrections to the list';
- for 2018, 112 completed 'class 3 – administrative procedure' dossiers, 53 completed 'parallel import - administrative procedure' dossiers nor 160 'Article 97 procedures/Article 130 - administrative proposals for amendments/corrections to the list';
- for 2019, 187 completed 'class 3/classe 2 – administrative procedure' dossiers, 22 completed 'parallel import - administrative procedure' dossiers nor 509 'Article 97/article 130 procedures - administrative proposals for amendments/corrections to the list';
- for 2020, 205 completed 'class 3/class 2 - administrative procedure' dossiers, 99 completed 'parallel introduction - administrative procedure' dossiers nor 139 'procedures Article 97/Article 130- administrative proposals for amendments/corrections to the list'.
- for 2021, 176 completed 'klasse 3/klasse 2 – administrative procedure' dossiers, 37 completed 'parallelle introduction - administrative procedure' dossiers nor 378 'procedures artikel 97/artikel 130 – administrative proposals for amendments/corrections to the list';

Figure 122: number of requests per year (unique dossiers – including completed procedures, cancelled requests and ongoing procedures)



Commission proposals and ministerial decisions

The Royal Decree of 21 December 2001 concerning the procedures, terms and conditions for reimbursement by the compulsory healthcare and benefits insurance towards costs of pharmaceuticals, states that the minister's decisions on the requests for reimbursement of new pharmaceuticals must be notified to the applicants within 180 calendar days from the day of submission of the request (day '0'), not counting any suspensions of the procedures. This is also stated in the Royal Decree of 1 February 2018 concerning the procedures, terms and conditions for reimbursement by the compulsory healthcare and benefits insurance towards costs of pharmaceuticals.

The minister decides on the basis of a proposal from the Commission for Reimbursement of Medicines, which must formulate a proposal within 150 days of the request.

The minister must not deviate from the Commission proposal, except for budgetary or social reasons, and may only take this decision him or herself if the Commission has not made a proposal within the 150 days (the company may request a suspension of the procedure at two stages: the evaluation and the proposal stage).

Since 1 July 2014, the Commission may make three types of proposal:

- a positive proposal
  or
- a negative proposal
  or
- in some cases, a proposal to launch a procedure under Article 81bis of the Royal Decree of 21 December 2001, whereby the Commission proposes to an applicant the launch of negotiations with a view to concluding a convention with the NIHDI on the temporary placing of a pharmaceutical on the list of reimbursable pharmaceuticals (or for temporary listing of a new therapeutic indication of a pharmaceutical already on the list of reimbursable pharmaceuticals). Since 1 April 2018, this type of proposal has been replaced by a proposal to launch a procedure under Article 112 of the Royal Decree of 1 February 2018. Currently, the CRM may issue such a proposal for applications submitted in class 1, applications submitted in class 2B or class 2C if the reference pharmaceutical is the subject of a contract, orphan medicinal products, applications for reimbursement for pharmaceuticals of which the reference pharmaceutical is the subject of a contract, applications for reimbursement for parallel imported or distributed pharmaceuticals of which the reference pharmaceutical is the subject of a contract, the biosimilar medicinal products of which the reference pharmaceutical is the subject of a contract, the applications for amendment of the reimbursement conditions with regard to the reimbursement of a new indication for which there is a therapeutic or social need, as well as the applications for amendment of the reimbursement conditions with regard to the extension of the reimbursement of an indication already reimbursed for adults to children for a pharmaceutical that is the subject of a contract.

The Commission proposals are adopted with a two-thirds majority – not counting abstentions during the vote. In other words, if there is no two thirds majority among those eligible to vote who have chosen NOT to abstain during the voting, either for a proposal to place a (new) medicine on the list, or NOT to place it on the list, then the Commission is deemed NOT to have made a proposal. Any member eligible to vote but who has declared a conflict of interest concerning the dossier, must not vote even though he/she is generally entitled to vote in the CRM.

Table 28 shows the frequency, in 2017-2021, of negative, positive or so-called 'Article 81bis proposals' by the Commission, for the various types of request. It also shows how often there is no two-thirds majority in favour of a proposal of these types. Annex 1 to this report contain detailed data on the various years.

It is clear that for class 1 applications and applications concerning the admission to the reimbursement of parallel imported or distributed pharmaceuticals, reaching a two-thirds majority for a proposal is more rare (there's no proposal from the Commission for 15% of class 1 applications and 40% of applications concerning the admission to the reimbursement of parallel imported or distributed pharmaceuticals).

Table 28: number of unique requests for inclusion in the list of reimbursable pharmaceuticals versus proposals by the Commission for Reimbursement of Medicines (2017-2021)

2017 – 2021									
	Positive		art.81 bis/art. 112		negative		no proposition		total
	number	%	number	%	number	%	number	%	number
class 1	32	19	89	53	22	13	25	15	168
class 2	156	72	18	8	31	14	13	6	218
class 2 – biosim	32	100	-	-	-	-	-	-	32
class 3	142	75	-	-	43	23	5	3	190
orphan	8	11	49	67	12	16	4	5	73
parallel import long	3	4	34	44	9	12	31	40	77
modification	340	72	57	12	53	11	20	4	470
Individual revision	45	49	-	-	41	45	5	5	91
price increase	135	79	-	-	23	14	12	7	170
suppression	17	57	-	-	13	43	-	-	30
exception	11	73	-	-	3	20	1	7	15
Total	921	60	247	16	250	16	116	8	1534

Table 29Table 29 shows, for the period 2017-2021 and for the various types of request, the frequency of positive proposals, proposals to launch a procedure under Article 81bis of the Royal Decree of 21 December 2001 or under Article 112 of the Royal Decree of 1 February 2018, or negative proposals followed by the Minister. For cases where the Commission did not make a proposal, we investigate how often the Minister took positive or negative decisions. Annex 1 to this report also contain detailed data on the individual years.

Table 29 : Ministerial decisions based on the CRM proposal (unique dossiers 2017-2021)

2017-2021							
	positive decision Min		negative decision Min		no decision Min (pos)		**total**
CTG CRM proposal	number	%	number	%	number	%	**number**
class 1	**129**	76,8	**39**	23,2	**0**	0,0	**168**
pos	32	100,0	0	0,0	0	0,0	32
neg	4	18,2	18	81,8	0	0,0	22
no proposition	15	60,0	10	40,0	0	0,0	25
art. 81bis/112	78	87,6	11	12,4	0	0,0	89
class 2	**200**	91,7	**17**	7,8	**1**	0,5	**218**
pos	156	100,0	0	0,0	0	0,0	156
neg	18	58,1	12	38,7	1	3,2	31
no proposition	12	92,3	1	7,7	0	0,0	13
art. 81bis/112	14	77,8	4	22,2	0	0,0	18
class 2 - biosim	**32**	100,0	**0**	0,0	0	0,0	**32**
pos	32	100,0	0	0,0	0	0,0	32
class 3	**172**	90,5	**13**	6,8	**5**	2,6	**190**
pos	141	99,3	0	0,0	1	0,7	142
neg	27	62,8	13	30,2	3	7,0	43
no proposition	4	80,0	0	0,0	1	20,0	5
parallel import Long	**3**	3,9	**74**	96,1	**0**	0,0	**77**
pos	3	100,0	0	0,0	0	0,0	3
neg	0	0,0	9	100,0	0	0,0	9
no proposition	0	0,0	31	100,0	0	0,0	31
art. 81bis/112	0	0,0	34	100,0	0	0,0	34
modification	**398**	84,5	**68**	14,4	**5**	1,1	**471**
pos	339	99,4	1	0,3	1	0,3	341
neg	8	15,1	43	81,1	2	3,8	53
no proposition	12	60,0	7	35,0	1	5	20
art. 81bis/112	39	68,4	17	29,8	1	1,8	57
orphan	**50**	68,5	**23**	31,5	**0**	0,0	**73**
pos	8	100,0	0	0,0	0	0,0	8
neg	2	16,7	10	83,3	0	0,0	12
no proposition	3	75,0	1	25,0	0	0,0	4
art. 81bis/112	37	75,5	12	24,5	0	0,0	49
ind revision	**47**	51,1	**44**	47,8	**1**	1,1	**92**
pos	45	97,8	0	0,0	1	2,2	46
neg	0	0,0	41	100,0	0	0,0	41
no proposition	2	40,0	3	60,0	0	0,0	5

price	**152**	89,4	**18**	10,6	**0**	0,0	**170**
pos	135	100,0	0	0,0	0	0,0	135
neg	7	30,4	16	69,6	0	0,0	23
no proposition	10	83,3	2	16,7	0	0,0	12
suppression	**16**	55,2	**10**	34,5	**3**	10,3	**29**
pos	15	88,2	0	0,0	2	11,8	17
neg	1	8,3	10	83,3	1	8,3	12
exception	**13**	86,7	**2**	13,3	**0**	0,0	**15**
pos	11	100,0	0	0,0	0	0,0	11
neg	1	33,3	2	66,7	0	0,0	3
no proposition	1	100,0	0	0,0	0	0,0	1
total	**1212**	79,0	**308**	20,1	**15**	1,0	**1535**

This table shows that in most cases, the Minister follows the Commission's proposals.

The Minister's decision is positive in more than 65% of the cases on which the Commission has not formulated a proposal (in 7,6% of all types of dossier).

For requests submitted in class 1, in 4 cases the Minister overruled a negative proposal from the Commission (i.e. in 18,2% of class 1 dossiers on which a negative proposal was formulated).

For requests regarding the listing of an orphan medicinal product, in 2 cases the Minister overruled a negative proposal from the Commission (i.e. in 16,7% of cases where a negative proposal was made regarding the listing of an orphan medicinal product).

ANNEX 1

CRM ACTIVITY
Overview of the results of procedures (RD 21.12.2001/RD 01.02.2018) concerning requests to amend the list of reimbursable pharmaceuticals 2017-2021

CRM PROPOSALS PER TYPE OF REQUEST

Table 30: number of unique requests for inclusion in the list of reimbursable pharmaceuticals versus proposals of the Commission for Reimbursement of Medicines (2017)

2017									
	Positive		art.81 bis/art. 112		negative		no proposition		total
	number	%	number	%	number	%	number	%	number
class 1	8	20	18	44	10	24	5	12	41
class 2	31	67	-	-	8	17	7	15	46
class 2 – biosim	-	-	-	-	-	-	-	-	-
class 3	55	63	-	-	29	33	3	3	87
orphan	2	20	6	60	1	10	1	10	10
parallel import long	-	-	-	-	8	89	1	11	9
modification	63	66	8	8	19	20	5	5	95
Individual revision	8	42	-	-	8	42	3	16	19
price increase	4	50	-	-	-	-	5	50	8
suppression	-	-	-	-	-	-	-	-	-
exception	2	40	-	-	2	40	1	20	5
Total	173	54	32	10	85	27	30	9	320

Table 31: number of unique requests for inclusion in the list of reimbursable pharmaceuticals versus proposals of the Commission for Reimbursement of Medicines (2018)

2018									
	Positive		art.81 bis/art. 112		negative		no proposition		total
	number	%	number	%	number	%	number	%	number
class 1	1	5	9	41	5	23	7	32	22
class 2	44	72	5	8	8	13	4	7	61
class 2 – biosim	6	100	-	-	-	-	-	-	6
class 3	13	68	-	-	6	32	-	-	19
orphan	2	9	14	61	5	22	2	9	23
parallel import long	1	4	-	-	-	-	24	96	25
modification	93	73	18	14	13	10	4	3	128
Individual revision	9	50	-	-	8	44	1	6	18
price increase	10	91	-	-	-	-	1	9	11
suppression	2	67	-	-	1	33	-	-	3
exception	2	100	-	-	-	-	-	-	2
Total	183	58	46	14	46	14	43	14	318

Table 32: number of unique requests for inclusion in the list of reimbursable pharmaceuticals versus proposals of the Commission for Reimbursement of Medicines (2019)

2019									
	Positive		art.81 bis/art. 112		negative		no proposition		total
	number	%	number	%	number	%	number	%	number
class 1	5	15	21	64	1	3	6	18	33
class 2	33	70	4	9	9	19	1	2	47
class 2 – biosim	13	100	-	-	-	-	-	-	13
class 3	16	73	-	-	4	18	2	9	22
orphan	2	13	12	80	1	7	-	-	15
parallel import long	-	-	-	-	1	50	1	50	2
modification	65	76	8	9	7	8	6	7	86
Individual revision	7	44	-	-	8	50	1	6	16
price increase	6	75	-	-	2	25	-	-	8
suppression	-	-	-	-	1	100	-	-	1
exception	5	100	-	-	-	-	-	-	5
Total	152	61	45	18	34	14	17	7	248

Table 33: number of unique requests for inclusion in the list of reimbursable pharmaceuticals versus proposals of the Commission for Reimbursement of Medicines (2020)

2020									
	Positive		art.81 bis/art. 112		negative		no proposition		total
	number	%	number	%	number	%	number	%	number
class 1	8	20	26	63	2	5	5	12	41
class 2	23	70	6	18	4	12	-	-	33
class 2 – biosim	5	100	-	-	-	-	-	-	5
class 3	17	89	-	-	2	11	-	-	19
orphan	2	14	9	64	3	21	-	-	14
parallel import long	1	5	18	90	-	-	1	5	20
modification	53	74	9	13	8	11	2	3	72
Individual revision	11	55	-	-	9	45	-	-	20
price increase	69	91	-	-	5	7	2	3	76
suppression	12	63	-	-	7	37	-	-	19
exception	-	-	-	-	-	-	-	-	-
Total	201	63	68	21	40	13	10	3	319

Table 34: number of unique requests for inclusion in the list of reimbursable pharmaceuticals versus proposals of the Commission for Reimbursement of Medicines (2021)

2021									
	Positive		art.81 bis/art. 112		negative		no proposition		total
	number	%	number	%	number	%	number	%	number
class 1	10	32	15	48	4	13	2	6	31
class 2	25	81	3	10	2	6	1	3	31
class 2 – biosim	8	100	-	-	-	-	-	-	8
class 3	41	95	-	-	2	5	-	-	43
orphan	-	-	8	73	2	18	1	9	11
parallel import long	1	5	16	76	-	-	4	19	21
modification	66	74	14	16	6	7	3	3	89
Individual revision	10	56	-	-	8	44	-	-	18
price increase	46	69	-	-	16	24	5	7	67
suppression	3	43	-	-	4	57	-	-	7
exception	2	67	-	-	1	33	-	-	3
Total	212	64	56	17	45	14	16	5	329

DECISIONS OF THE MINISTER based on the CRM PROPOSAL

Table 35: Ministerial decisions based on the CRM proposal (unique dossiers 2017)

2017							
	positive decision Min		negative decision Min		no decision Min (pos)		**total**
CTG CRM proposal	number	%	number	%	number	%	**number**
class 1	**27**	65,9	**14**	34,1	**0**	0,0	**41**
pos	8	100,0	0	0,0	0	0,0	8
neg	4	40,0	6	60,0	0	0,0	10
no proposition	1	20,0	4	80,0	0	0,0	5
art. 81bis/112	14	77,8	4	22,2	0	0,0	18
class 2	**41**	89,1	**4**	8,7	**1**	2,2	**46**
pos	31	100,0	0	0,0	0	0,0	31
neg	4	50,0	3	37,5	1	12,5	8
no proposition	6	85,7	1	14,3	0	0,0	7
class 3	**77**	88,5	**6**	6,9	**4**	4,6	**87**
pos	55	100,0	0	0,0	0	0,0	55
neg	20	69,0	6	20,7	3	10,3	29
no proposition	2	66,7	0	0,0	1	33,3	3
parallel import Long	**0**	0,0	**9**	100,0	**0**	0,0	**9**
neg	0	0,0	8	100,0	0	0,0	8
no proposition	0	0,0	1	100,0	0	0,0	1
modification	**72**	75,8	**19**	20,0	**4**	4,2	**95**
pos	61	96,8	1	1,6	1	1,6	63
neg	1	5,3	16	84,2	2	10,5	19
no proposition	4	80,0	1	20,0	0	0,0	5
art. 81bis/112	6	75,0	1	12,5	1	12,5	8
orphan	**9**	90,0	**1**	10,0	**0**	0,0	**10**
pos	2	100,0	0	0,0	0	0,0	2
neg	0	0,0	1	100,0	0	0,0	1
no proposition	1	100,0	0	0,0	0	0,0	1
art. 81bis/112	6	100,0	0	0,0	0	0,0	6
ind revision	**9**	47,4	**10**	52,6	**0**	0,0	**19**
pos	8	100,0	0	0,0	0	0,0	8
neg	0	0,0	8	100,0	0	0,0	8
no proposition	1	33,3	2	66,7	0	0,0	3
price	**6**	75,0	**2**	25,0	**0**	0,0	**8**
pos	4	100,0	0	0,0	0	0,0	4
no proposition	2	50,0	2	50,0	0	0,0	4

exception	**4**	80,0	**1**	20,0	**0**	0,0	**5**
pos	2	100,0	0	0,0	0	0,0	2
neg	1	50,0	1	50,0	0	0,0	2
no proposition	1	100,0	0	0,0	0	0,0	1
total	**245**	76,6	**66**	20,6	**9**	2,8	**320**

Table 36: Ministerial decisions based on the CRM proposal (unique dossiers 2018)

2018							
	positive decision Min		negative decision Min		no decision Min (pos)		**total**
CTG CRM proposal	number	%	number	%	number	%	**number**
class 1	**7**	31,8	**15**	68,2	**0**	0,0	**22**
pos	1	100,0	0	0,0	0	0,0	1
neg	0	0,0	5	100,0	0	0,0	5
no proposition	3	42,9	4	57,1	0	0,0	7
art. 81bis/112	3	33,3	6	66,7	0	0,0	9
class 2	**55**	90,2	**6**	9,8	**0**	0,0	**61**
pos	44	100,0	0	0,0	0	0,0	44
neg	6	75,0	2	25,0	0	0,0	8
no proposition	4	100,0	0	0,0	0	0,0	4
art. 81bis/112	1	20,0	4	80,0	0	0,0	5
class 2 - biosim	**6**	100,0	**0**	0,0	**0**	0,0	**6**
pos	6	100,0	0	0,0	0	0,0	6
class 3	**14**	73,7	**4**	21,1	**1**	5,3	**19**
pos	12	92,3	0	0,0	1	7,7	13
neg	2	33,3	4	66,7	0	0,0	6
parallel import Long	**1**	4,0	**24**	96,0	**0**	0,0	**25**
pos	1	100,0	0	0,0	0	0,0	1
no proposition	0	0,0	24	100,0	0	0,0	24
modification	**99**	77,3	**28**	21,9	**1**	0,8	**128**
pos	93	100,0	0	0,0	0	0,0	93
neg	2	15,4	11	84,6	0	0,0	13
no proposition	0	0,0	3	75,0	1	25,0	4
art. 81bis/112	4	22,2	14	77,8	0	0,0	18
orphan	**7**	30,4	**16**	69,6	**0**	0,0	**23**
pos	2	100,0	0	0,0	0	0,0	2
neg	0	0,0	5	100,0	0	0,0	5
no proposition	1	50,0	1	50,0	0	0,0	2
art. 81bis/112	4	28,6	10	71,4	0	0,0	14
ind revision	**9**	50,0	**9**	50,0	**0**	0,0	**18**
pos	9	100,0	0	0,0	0	0,0	9

neg	0	0,0	8	100,0	0	0,0	8
no proposition	0	0,0	1	100,0	0	0,0	1
price	**11**	100,0	**0**	0,0	**0**	0,0	**11**
pos	10	100,0	0	0,0	0	0,0	10
no proposition	1	100,0	0	0,0	0	0,0	1
suppression	**0**	0,0	**0**	0,0	**3**	100,0	**3**
pos	0	0,0	0	0,0	2	100,0	2
neg	0	0,0	0	0,0	1	100,0	1
exception	**2**	100,0	**0**	0,0	**0**	0,0	**2**
pos	2	100,0	0	0,0	0	0,0	2
total	**211**	66,4	**102**	32,1	**5**	1,6	**318**

Table 37: Ministerial decisions based on the CRM proposal (unique dossiers 2019)

2019					
	positive decision Min		negative decision Min		**total**
CTG CRM proposal	number	%	number	%	**number**
class 1	**31**	93,9	**2**	6,1	**33**
pos	5	100,0	0	0,0	5
neg	0	0,0	1	100,0	1
no proposition	5	83,3	1	16,7	6
art. 81bis/112	21	100,0	0	0,0	21
class 2	**45**	95,7	**2**	4,3	**47**
pos	33	100,0	0	0,0	33
neg	7	77,8	2	22,2	9
no proposition	1	100,0	0	0,0	1
art. 81bis/112	4	100,0	0	0,0	4
class 2 - biosim	**13**	100,0	**0**	0,0	**13**
pos	13	100,0	0	0,0	13
class 3	**19**	86,4	**3**	13,6	**22**
pos	16	100,0	0	0,0	16
neg	1	25,0	3	75,0	4
no proposition	2	100,0	0	0,0	2
parallel import Long	**0**	0,0	**2**	100,0	**2**
neg	0	0,0	1	100,0	1
no proposition	0	0,0	1	100,0	1
modification	**79**	91,9	**7**	8,1	**86**
pos	65	100,0	0	0,0	65
neg	3	42,9	4	57,1	7
no proposition	4	66,7	2	33,3	6
art. 81bis/112	7	87,5	1	12,5	8
orphan	**15**	100,0	**0**	0,0	**15**
pos	2	100,0	0	0,0	2
neg	1	100,0	0	0,0	1
art. 81bis/112	12	100,0	0	0,0	12
ind revision	**8**	50,0	**8**	50,0	**16**
pos	7	100,0	0	0,0	7
neg	0	0,0	8	100,0	8
no proposition	1	100,0	0	0,0	1
price	**6**	75,0	**2**	25,0	**8**
pos	8	100,0	0	0,0	6
neg	0	0,0	2		2
suppression	**0**	0,0	**1**	100,0	**1**

neg	0	0,0	1	100,0	1
exception	**5**	100,0	**0**	0,0	**5**
pos	5	100,0	0	0,0	5
total	**221**	89,1	**27**	10,9	**248**

Table 38: Ministerial decisions based on the CRM proposal (unique dossiers 2020)

2020							
	positive decision Min		negative decision Min		no decision Min (pos)		**total**
CTG CRM proposal	number	%	number	%	number	%	**number**
class 1	**37**	90,2	**4**	9,8	**0**	0,0	**41**
pos	8	100,0	0	0,0	0	0,0	8
neg	0	0,0	2	100,0	0	0,0	2
no proposition	4	80,0	1	20,0	0	0,0	5
art. 81bis/112	25	96,2	1	3,8	0	0,0	26
class 2	**30**	90,9	**3**	9,1	**0**	0,0	**33**
pos	23	100,0	0	0,0	0	0,0	23
neg	1	25,0	3	75,0	0	0,0	4
art. 81bis/112	6	100,0	0	0,0	0	0,0	6
class 2 - biosim	**5**	100,0	**0**	0,0	**0**	0,0	**5**
pos	5	100,0	0	0,0	0	0,0	5
class 3	**19**	100,0	**0**	0,0	0	0,0	**19**
pos	17	100,0	0	0,0	0	0,0	17
neg	2	100,0	0	0,0	0	0,0	2
parallel import Long	**1**	5,0	**19**	95,0	**0**	0,0	**20**
pos	1	100,0	0	0,0	0	0,0	1
no proposition	0	0,0	1	100,0	0	0,0	1
art. 81bis/112	0	0,0	18	100,0	0	0,0	18
modification	**64**	88,9	**8**	11,1	**0**	0,0	**72**
pos	53	100,0	0	0,0	0	0,0	53
neg	0	0,0	8	100,0	0	0,0	8
no proposition	2	100,0	0	0,0	0	0,0	2
art. 81bis/112	9	100,0	0	0,0	0	0,0	9
orphan	**10**	71,4	**4**	28,6	**0**	0,0	**14**
pos	2	100,0	0	0,0	0	0,0	2
neg	0	0,0	3	100,0	0	0,0	3
art. 81bis/112	8	88,9	1	11,1	0	0,0	9
ind revision	**11**	52,4	**9**	42,9	**1**	4,8	**21**
pos	11	91,7	0	0,0	1	8,3	12
neg	0	0,0	9	100,0	0	0,0	9
price	**72**	94,7	**4**	5,3	**0**	0,0	**76**
pos	69	100,0	0	0,0	0	0,0	69
neg	1	20,0	4	80,0	0	0,0	5

no proposition	2	100,0	0	0,0	0	0,0	2
suppression	**13**	68,4	**6**	31,6	**0**	0,0	**19**
pos	12	100,0	0	0,0	0	0,0	12
neg	1	14,3	6	85,7	0	0,0	7
total	**262**	82,1	**57**	17,9	**0**	0,0	**319**

Table 39: Ministerial decisions based on the CRM proposal (unique dossiers 2021)

2021					
	positive decision Min		negative decision Min		**total**
CTG CRM proposal	number	%	number	%	**number**
class 1	**27**	87,1	**4**	12,9	**31**
pos	10	100,0	0	0,0	10
neg	0	0,0	4	100,0	4
no proposition	2	100,0	0	0,0	2
art. 81bis/112	15	100,0	0	0,0	15
class 2	**29**	93,5	**2**	6,5	**31**
pos	25	100,0	0	0,0	25
neg	0	0,0	2	100,0	2
no proposition	1	100,0	0	0,0	1
art. 81bis/112	3	100,0	0	0,0	3
class 2 - biosim	**8**	100,0	**0**	0,0	**8**
pos	8	100,0	0	0,0	8
class 3	**43**	100,0	**0**	0,0	**43**
pos	41	100,0	0	0,0	41
neg	2	100,0	0	0,0	2
parallel import Long	**1**	4,8	**20**	95,2	**21**
pos	1	100,0	0	0,0	1
no proposition	0	0,0	4	100,0	4
art. 81bis/112	0	0,0	16	100,0	16
modification	**84**	93,3	**6**	6,7	**90**
pos	67	100,0	0	0,0	67
neg	2	33,3	4	66,7	6
no proposition	2	66,7	1	33,3	3
art. 81bis/112	13	92,9	1	7,1	14
orphan	**9**	81,8	**2**	18,2	**11**
neg	1	50,0	1	50,0	2
no proposition	1	100,0	0	0,0	1

art. 81bis/112	7	87,5	1	12,5	8
ind revision	**10**	55,6	**8**	44,4	**18**
pos	10	100,0	0	0,0	10
neg	0	0,0	8	100,0	8
price	**57**	85,1	**10**	14,9	**67**
pos	46	100,0	0	0,0	46
neg	6	37,5	10	62,5	16
no proposition	5	100,0	0	0,0	5
suppression	**3**	50,0	**3**	50,0	**6**
pos	3	100,0	0	0,0	3
neg	0	0,0	3	100,0	3
Exception	**2**	66,7	**1**	33,3	**3**
pos	2	100,0	0	0,0	2
neg	0	0,0	1	100,0	1
total	**273**	83,0	**56**	17,0	**329**

ANNEX 2

SAVINGS MEASURES 2021

Measures 2021

Application of the measures on old medicines/biological medicines

- **01.01.2021:**
  - Bevacizumab – price reduction (ex-factory price) by 40.44%
  - Laronidase – price reduction (ex-factory price) by 19.75%
  - Temsirolimus – price reduction (ex-factory price) by 19.75%
- **01.04.2021:**
  - Paliperidone – price reduction (ex-factory price) by 26.85%
  - Quinagolide – price reduction (ex-factory price) by 19.75%
- **01.07.2021:**
  - Alemtuzumab – price reduction (ex-factory price) by 19.75%
  - Eculizumab – price reduction (ex-factory price) by 26.15%
  - Pemetrexed – price reduction (ex-factory price) by 26.85%
- **01.10.2021:**
  - Abatacept – price reduction (ex-factory price) by 26.15%
  - Calcipotriol + Betamethasone – price reduction (ex-factory price) by 25.44%
  - Varenicline – price reduction (ex-factory price) by 25.44%

Application of the reference price system

- **01.01.2021:**
  - Azacitidine – price reduction (ex-factory price) by 62.97%
  - Naloxon + Buprenorphine end of combination
- **01.04.2021:**
  - Fulvestrant – price reduction (ex-factory price) by 63.85% elimination FASLODEX
  - Ambrisentan – price reduction (ex-factory price) by 63.85%
- **01.07.2021:**
  - Nitisinone – price reduction (ex-factory price) by 51.52% (27.82% for ORFADIN oral use)
  - Posaconazole – price reduction (ex-factory price) by 43.64% (23.37% for NOXAFIL for injection)

- **01.10.2021:**

  - Arsenic trioxide – price reduction (ex-factory price) by 51.52%
  - Nitisinone – price reduction (ex-factory price) by 27.82% for ORFADIN oral use
  - Pemetrexed – price reduction (ex-factory price) by 51.52%

MD INDEX (took effect on: 1 January 2021)

The basic fee for pharmacists was indexed on 1 January 2021. The amount increased from €4.33 tot €4.37 (excl. VAT).
The pharmacist's margin was also indexed by 6.54%.
The limits of the personal share were not indexed.

Savings measure (1 April 2021 MD OLD_MEASURE and MD COMBICLIFF)

Introduction of the term 'complex active substance' (non-biological pharmaceuticals composed of an active substance or several active substances that have a chemical structure that can vary, either within the same lot or between different lots of the same pharmaceutical). Application of the reference reimbursement with an exception percentage for those pharmaceuticals (-23.37% or -27.82%).

End of the patent exception for the combicliff. Price regularisation for the pharmaceuticals concerned.

Change in the reduction percentage in the framework of the 'old medicines' measure.

Elimination of the 10% bracket in the context of the monthly PRICE COMPARISON reasoning if fewer than 3 available pharmaceuticals had a lower price level than the lowest price + 5%.

Savings measure (1 September 2021 – MD REGULARISATION R non A and MO_OLD_MEASURES_PART_2)

Change in the reduction percentage in the framework of the application of the reference reimbursement for pharmaceuticals that are not exclusively reimbursable in category A (44.75% instead of 43.64%). Regularisation for the pharmaceuticals concerned.

End of the exemption for the 'old medicines' measure for the reimbursable pharmaceuticals in Chapter III and in the reimbursement groups I.10.1 (*A-2*), I.10.2 (*A-3*), V.6.3 (*Cx-1*), V.6.4 (*Cx-2*), V.8.1 (*A-11*), V.8.7 (*A-69*), VII.10 (*A-21, C-17, A-22, C-18, A-41, B-308, A-51, A-59, A-78, B-282*) and XXII (*A-38, B-189, B-190, B-192, B-196, B-197, A-47, B-323, A-106, B-326, Fb-7*). Possibility to use the EU6 price exception instead. Regularisation for the pharmaceuticals concerned.

Application of the PRICE COMPARISON reasoning for non-biological pharmaceuticals just like for biological pharmaceuticals.

Group-based revision of antihemophilic drugs (1 December 2021 – MO REVISION ASTHMA COPD)

Price reductions for some active substances (B02BB01, B02BD01, B02BD02, B02BD03, B02BD04, B02BD06, B02BD07, B02BD08, B02BD10, B02BD14 and B02BX06).

ANNEX 3

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