Monitoring Of Reimbursement Significant Expenses

MORSE

2020 Report

(2019 data)

CONTENTS

INTRODUCTION

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

This report examines data up to and including December 2019.

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

The data on the pharmaceutical specialties supplied during 2019 by public pharmacies are complete (Farmanet data). Hospital data were extrapolated (DocPH 2019 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 (pharmaceutical specialties budget).
For those pharmaceutical specialties 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 minus the individual patient co-payments. 'NIHDI net expenditure' does not therefore include money received under the Article 81/111 conventions.

When discussing the measures taken, we refer to historical background data (reference reimbursement system, 'old medicines' measures, group reviews, price reductions, shifts to chapter I-II/IV, etc.), as recorded by the administration, and to the administrative database used to manage individual dossiers (introduction of new medicines, changes to reimbursement s
conditions, etc.).

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, Farmanet 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 the Permanent Audit 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 PHARMACEUTICAL SPECIALTIES, BROKEN DOWN INTO PUBLIC PHARMACIES AND HOSPITALS

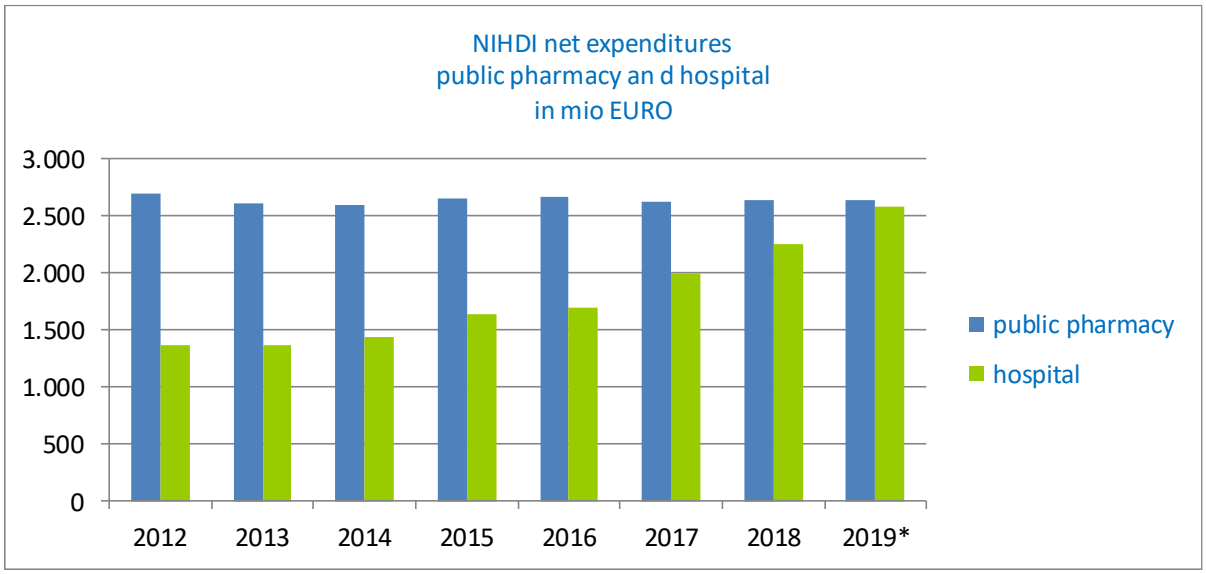
GENERAL

Table 1: NIHDI net annual expenditure on medicines 2012 – 2019 [1]

NIHDI net expenditure x 1,000,000 €								
	2012	2013	2014	2015	2016	2017	2018	2019*
Public pharmacies	2,692.9	2,619.3	2,604.8	2,651.8	2,665.0	2,626.3	2,647.6	2,647.3
Hospitals	1,367.0	1,371.4	1,444.8	1,642.0	1,702.4	1,991.4	2,255.1	2,579.7
Total	4,059.8	3,990.7	4,049.6	4,293.7	4,367.4	4,617.7	4,902.6	5,227.0
% Growth								
		'12- '13	'13- '14	'14- '15	'15- '16	'16- '17	'17- '18	'18- '19
Public pharmacies		-2.7	-0.6	1.8	0.5	-1.5	0.8	0.0
Hospitals		0.3	5.4	13.6	3.7	17.0	13.2	14.4*
Total		-1.7	1.5	6.0	1.7	5.7	6.2	6.6*

*Source: Farmanet (public pharmacies) and docPH (hospitals), * 2019 based on extrapolated docPH data*

Figure1: NIHDI net annual expenditure on reimbursable pharmaceutical specialties in public pharmacies and hospitals (2012 – 2019)



In the last three years (2017, 2018, 2019), overall expenditure on medicines has risen by about 6% every year. In 2019, this expenditure exceeded 5 billion euros (5.2 billion).

[1] The figures on NIHDI net expenditure for public pharmacies are Farmanet 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).

For public pharmacy expenditure, we see few fluctuations during the period 2012-2019: over this period, expenditure is 2.6-2.7 billion euros. Hospital expenditure, however, shows a clear upward trend over the same period. In the last three years – 2017, 2018 and 2019 – there have been increases of 17%, 13.2% and 14.4% respectively.
The stabilisation of public pharmacy expenditure in 2019 (0%) and the growth in hospital expenditure (14.4%) have resulted in an overall growth in expenditure on pharmaceutical specialties of 6.6% in 2019.

Figure 1 shows that expenditure on pharmaceutical specialties in hospitals makes up a growing share of overall expenditure on these products. In 2019, this expenditure in hospitals made up just under half of overall expenditure (49.4%).

Her 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 pharmaceutical specialties temporarily included in the list of reimbursable pharmaceutical specialties, i.e. specialties 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 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 the permanent audit. 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 2: evolution of expenditure, taking account of receipts under Art. 81/111 conventions and levies (in 000 euro)

	2014	2015	2016	2017	2018	2019
Recorded expenditure (1)	4,033,476	4,277,705	4,378,171	4,594,786	4,891,838	5.263.274
Art 81/111 receipts (2)	41,346	54,516	123,556	273,351	359,310	605,043
(3) = (1) minus (2)	3,992,130	4,223,189	4,254,615	4,321,435	4,532,528	4,658,231
Levies (4)	223,896	281,085	321,517	344,371	399,283	431,510
(5) = (3) minus (4)	3,768,234	3,942,104	3,933,098	3,977,064	4,133,245	4,226,721

source: docN; permanent audit October 2020, table 3A.1.2.9

EXPENDITURE ON PHARMACEUTICAL SPECIALTIES IN PUBLIC PHARMACIES

Table 3: NIHDI net annual expenditure on medicines 2012– 2019

	2012	2013	2014	2015	2016	2017	2018	2019
NIHDI net expenditure x 1,000,000 €	2,692.9	2,619.3	2,604.8	2,651.8	2,665.0	2,626.3	2,647.6	2,647.3

		2012-2013	2013-2014	2014-2015	2015-2016	2016-2017	2017-2018	2018-2019
% growth		-2.7	-0.6	1.8	0.5	-1.5	0.8	0.0

Table 4: top 80% of NIHDI net annual expenditure on medicines in public pharmacies

	Denomination	Growth 2018 - 2017	Growth 2019 - 2018	2019 NIHDI expenditure (in mill EUR)
	Total	0.8%	0.0%	2,647.3
L04A	IMMUNOSUPPRESSANTS	14.6%	-4.9%	407.9
B01A	ANTITHROMBOTIC AGENTS **(T)**	9.9%	9.0%	264.2
J05A	DIRECT ACTING ANTIVIRALS	6.8%	-3.2%	144.4
A10B	HYPOGLYCEMIC DRUGS WITH THE EXCEPTION OF INSULINS **(T)**	8.3%	11.9%	126.1
R03A	ADRENERGICS, INHALANTS	4.4%	4.5%	119.9
A02B	TREATMENTS FOR PEPTIC ULCER AND REFLUX DISEASE	5.6%	-1.6%	102.2
C10A	HYPOLIPIDEMIC DRUGS, SIMPLE **(T)**	-27.6%	-10.7%	93.4
A10A	INSULINS AND ANALOGUES	2.9%	5.7%	90.9
N06A	ANTIDEPRESSANTS	-3.0%	-0.3%	86.2
N05A	ANTIPSYCHOTICS (NEUROLEPTICS)	-2.7%	-8.1%	84.5
N03A	ANTI-EPILEPTIC DRUGS	2.6%	4.2%	68.9
B02B	VITAMIN K AND OTHER HAEMOSTATICS	-3.9%	-1.7%	59.8
N02A	OPIOIDS **(T)**	-4.5%	-1.1%	58.4
R03D	OTHER SYSTEMIC DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	19.5%	17.9%	45.7
C07A	BETA BLOCKERS. SIMPLE **(T)**	-5.0%	-3.5%	45.4
M01A	NON-STEROIDAL ANTI-INFLAMMATORY AND ANTI-RHEUMATIC DRUGS	-6.3%	-5.9%	41.2
C09B	ACE INHIBITORS. COMBINATIONS	4.0%	7.6%	39.8
C09D	ANGIOTENSIN II RECEPTOR BLOCKERS. COMBINATIONS **(T)**	-7.9%	14.6%	38.8
M05B	DRUGS AFFECTING BONE STRUCTURE AND MINERALIZATION	-2.1%	0.0%	38.7
C09A	ACE INHIBITORS. SIMPLE	-3.4%	-1.4%	32.0
R03B	OTHER INHALED DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	-1.8%	-7.4%	31.9
J01C	BETA-LACTAM ANTIBIOTICS. PENICILLINS	-12.1%	-5.4%	29.3
L03A	IMMUNOSTIMULANTS	-10.8%	-14.6%	28.5
H01C	HYPOTHALAMUS HORMONES	4.7%	0.9%	27.4
J07B	ANTIVIRAL VACCINES	3.1%	1.4%	26.5

(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 4) shows that **25 of the 152 classes** account for **80% of the expenditure** in public pharmacies**.**

ATC3 classes which include 1 or several pharmaceutical specialties which are temporarily on the list via an Article 81/111 convention are indicated in Table 4 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.

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: overall, expenditure on reimbursement of medicines delivered in public pharmacies has stabilised in recent years, yet we can observe underlying significant and highly divergent trends between individual classes (strong growth, rapid fall in expenditure, or trend reversals).

Figure 2 illustrates total expenditure in relation to the number of patients being treated. In 2019, expenditure remained at the same level as the previous year (- 0.01%). The number of patients treated also remained more or less the same (- 0.36%). Table 5 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

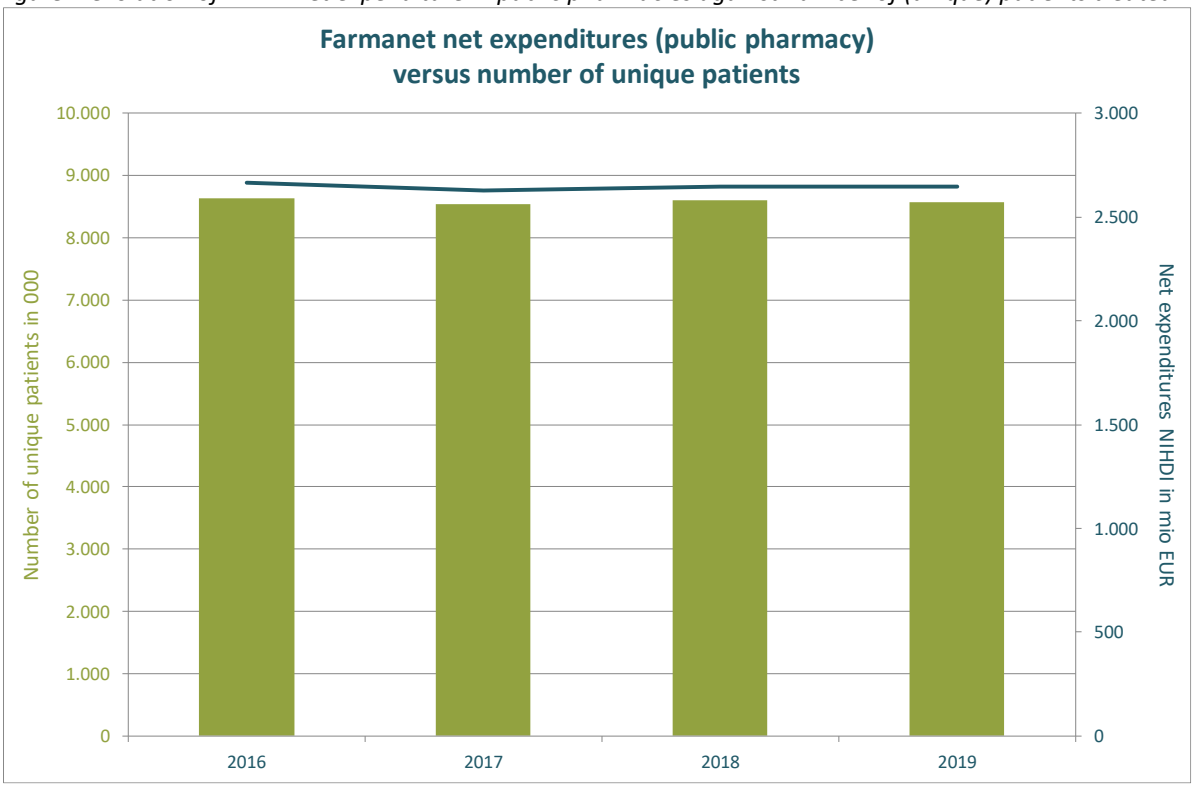


Table 5: evolution of number of (unique) patients treated in public pharmacies (in 000) per ATC3 class

	Denomination	Growth 2018 - 2017	Growth 2019 - 2018	Patients in 2019 (x 1000)
	Total	0.6%	-0.4%	8,564.9
L04A	IMMUNOSUPPRESSANTS	4.4%	4.6%	122.4
B01A	ANTITHROMBOTIC AGENTS	1.4%	0.5%	1,550.5
J05A	DIRECT ACTING ANTIVIRALS	11.3%	7.1%	38.7
A10B	HYPOGLYCEMIC DRUGS EXCLUDING INSULINS	2.4%	4.2%	641.2
R03A	ADRENERGICS, INHALANTS	4.4%	-1.2%	1,225.1
A02B	DRUGS FOR PEPTIC ULCER AND REFLUX DISEASE	3.0%	2.6%	2,257.6
C10A	HYPOLIPIDEMIC DRUGS, SIMPLE	0.2%	1.0%	1,563.0
A10A	INSULINS AND ANALOGUES	1.3%	1.8%	160.7
N06A	ANTIDEPRESSANTS	0.1%	1.9%	1,224.5
N05A	ANTIPSYCHOTICS (NEUROLEPTICS)	-0.5%	0.4%	370.0
N03A	ANTI-EPILEPTIC DRUGS	4.5%	4.2%	335.9
B02B	VITAMIN K AND OTHER HAEMOSTATICS	2.3%	3.7%	0.4
N02A	OPIOIDS	1.1%	1.0%	1,126.2
R03D	OTHER SYSTEMIC DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	-2.1%	-1.4%	171.9
C07A	BETA BLOCKERS. SIMPLE	-0.6%	0.8%	1,303.2
M01A	NON-STEROIDAL ANTI-INFLAMMATORY AND ANTI-RHEUMATIC DRUGS	-1.0%	-1.5%	3,011.8
C09B	ACE INHIBITORS. COMBINATIONS	5.7%	7.7%	447.0
C09D	ANGIOTENSIN II RECEPTOR BLOCKERS. COMBINATIONS	3.4%	6.2%	308.7
M05B	DRUGS AFFECTING BONE STRUCTURE AND MINERALIZATION	-3.0%	-1.5%	143.0
C09A	ACE INHIBITORS. SIMPLE	-1.4%	1.5%	570.8
R03B	OTHER INHALED DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	3.3%	-3.5%	620.1
J01C	BETA-LACTAM ANTIBIOTICS. PENICILLINS	1.4%	-2.4%	2,688.2
L03A	IMMUNOSTIMULANTS	-9.0%	-12.2%	4.2
H01C	HYPOTHALAMUS HORMONES	1.6%	2.5%	3.7
J07B	ANTIVIRAL VACCINES	2.7%	0.9%	1,827.9

These percentages, and the relationships between them, differ from those in the table on expenditure over time (see Table 3). This suggests significant changes in NIHDI expenditure per patient, as illustrated in Table 6.

Table 6: evolution of average NIHDI expenditure per patient in public pharmacies, per ATC3 class

	Denomination	Growth 2018 - 2017	Growth 2019 - 2018	NIHDI expenditure per patient 2019
	Total	0.2%	0.3%	309.1
L04A	IMMUNOSUPPRESSANTS	9.8%	-9.1%	3,331.8
B01A	ANTITHROMBOTIC AGENTS	8.4%	8.4%	170.4
J05A	DIRECT ACTING ANTIVIRALS	-4.0%	-9.6%	3,733.8
A10B	HYPOGLYCEMIC DRUGS EXCLUDING INSULINS	5.8%	7.4%	196.6
R03A	ADRENERGICS, INHALANTS	-0.1%	5.8%	97.9
A02B	DRUGS FOR PEPTIC ULCER AND REFLUX DISEASE	2.5%	-4.1%	45.3
C10A	HYPOLIPIDEMIC DRUGS, SIMPLE	-27.8%	-11.6%	59.7
A10A	INSULINS AND ANALOGUES	1.6%	3.8%	565.8
N06A	ANTIDEPRESSANTS	-3.1%	-2.1%	70.4

N05A	ANTIPSYCHOTICS (NEUROLEPTICS)	-2.2%	-8.5%	228.4
N03A	ANTI-EPILEPTIC DRUGS	-1.8%	0.0%	205.2
B02B	VITAMIN K AND OTHER HAEMOSTATICS	-6.1%	-5.2%	165,198.3
N02A	OPIOIDS	-5.6%	-2.1%	51.9
R03D	OTHER SYSTEMIC DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	22.0%	19.6%	265.9
C07A	BETA BLOCKERS. SIMPLE	-4.5%	-4.3%	34.9
M01A	NON-STEROIDAL ANTI-INFLAMMATORY AND ANTI-RHEUMATIC DRUGS	-5.3%	-4.6%	13.7
C09B	ACE INHIBITORS. COMBINATIONS	-1.6%	-0.1%	89.1
C09D	ANGIOTENSIN II RECEPTOR BLOCKERS. COMBINATIONS	-10.9%	8.0%	125.7
M05B	DRUGS INFLUENCING BONE STRUCTURE AND MINERALIZATION	1.0%	1.6%	271.0
C09A	ACE INHIBITORS. SIMPLE	-2.1%	-2.8%	56.0
R03B	OTHER DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	-4.9%	-4.1%	51.5
J01C	BETA-LACTAM ANTIBIOTICS. PENICILLINS	-13.3%	-3.0%	10.9
L03A	IMMUNOSTIMULANTS	-2.0%	-2.7%	6,830.3
H01C	HYPOTHALAMUS HORMONES	3.0%	-1.5%	7,457.4
J07B	ANTIVIRAL VACCINES	0.4%	0.5%	14.5

EXPENDITURE ON PHARMACEUTICAL SPECIALTIES IN HOSPITALS

Table 7: NIHDI net annual expenditure on medicines 2012 – 2019 (doc PH)

	2012	2013	2014	2015	2016	2017	2018	2019*
NIHDI net expenditure x 1,000,000 €	1,367.0	1,371.4	1,444.8	1,642.0	1,702.4	1,991.4	2,255.1	2,579.7

		2012-2013	2013-2014	2014-2015	2015-2016	2016-2017	2017-2018	2018-2019
growth %		0.3	5.4	13.6	3.7	17.0	13.2	14.4*

(*) extrapolation

Table 8: evolution of NIHDI net annual expenditure on medicines - top 80 % (hospitals)

Ranking			Lump sum	ATC 3		growth (%)		growth (%)	total in million EUROS [2]
2017	**2018**	**2019***				**2018-2017**		**2019*-2018**	**2019***
1	1	1	No	L01X	OTHER ANTINEOPLASTIC AGENTS **(T)**	39.9%		21.4%	1,024.0
2	2	2	No	L04A	IMMUNOSUPPRESSANTS **(T)**	6.6%		14.5%	366.1
4	3	3	No	S01L	OCULAR VASCULAR DISORDER AGENTS **(T)**	13.4%		14.9%	111.5
3	6	4	No	J05A	DIRECT ACTING ANTIVIRALS **(T)**	-43.1%		44.4%	92.3
5	4	5	No	J06B	IMMUNOGLOBULINS	5.2%		4.2%	88.9
7	5	6	No	L02B	HORMONE ANTAGONISTS AND RELATED AGENTS **(T)**	20.3%		27.4%	86.7
6	7	7	Yes	B05B	I.V. SOLUTIONS	0.4%		-1.4%	58.6
8	8	8	No	B02B	VITAMIN K AND OTHER HAEMOSTATICS **(T)**	-3.3%		-4.6%	51.5
10	10	9	No	L01B	ANTIMETABOLITES **(T)**	2.8%		10.6%	51.1
9	9	10	Mix	A16A	OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS	5.3%		-4.8%	48.2
11	11	11	No	L03A	IMMUNOSTIMULANTS	5.3%		13.1%	47.3
58	20	12	No	M09A	OTHER DRUGS FOR DISORDERS OF THE MUSCULO-SKELETAL SYSTEM **(T)**	1460.1%		136.1%	45.7

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

This overview of the (virtual) expenditure and the growth observed per ATC3 class shows that **12 of the 164 classes** account for **80 % of expenditure** on pharmaceutical specialties in hospitals.

ATC3 classes which include 1 or several pharmaceutical specialties which are temporarily on the list via an Article 81/111 convention are shown in Table 8 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 figures on NIHDI net expenditure per ATC3 class are based on: doc PH data (NIHDI data), whereby total expenditure = outpatient expenditure (A) + expenditure booked at 100% (not included in the lump sum) (B) + expenditure booked at 25% (included in the lump sum) (C) + a theoretical calculated amount based on C (D). Because of component (D), these figures do not show absolute expenditure, but rather virtual expenditure enabling a ranking of the classes.

Table 8 shows that the two top ranked classes in 2019, L01X and L04A, were also top of the list in 2017 and 2018. Expenditure on both these classes is still rising year on year.
In 2019, then, NIHDI expenditure on class L01X rose to more than 1 billion euros, or nearly 40% of expenditure in hospitals. Expenditure on class L04A rose in 2019 to 366 million euros.

In hospitals, more than half the expenditure (54%) went to pay for pharmaceutical specialties in 2 classes: L01X (other antineoplastic agents) and L04A (immunosuppressants). None of the molecules belonging to these classes are covered by the hospital lump sum.

While class L04A is in second place in the top 80% of expenditure on medicines in hospitals, it is in first place in the top 80% spending in public pharmacies (407.9 million euros in 2019). In 2019, however, for the first time in years, we see that expenditure in public pharmacies on immunosuppressants fell, by nearly 5%. This is due to the entry on the market of biosimilar drugs, with the resulting drop in prices, under the 'biological medicines' measure.

In 2019, expenditure on class L04A amounted to 407.9 million euros in public pharmacies and 366.1 million euros in hospitals, i.e. total expenditure of 774.0 million euros, or 14.81 % of the total medicines budget. By way of comparison, in 2016, total expenditure on class L04A amounted to 598.01 million euros, or 13.7% of the total 2016 medicines budget.

Later on in the report, we discuss in more detail how spending on the top 3 medicines classes – L01X, L04A, and S01L – has evolved over time, and we consider several other classes of medicines where there have been interesting trends in expenditure (R03D, J05A and L02B).

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 doc PH data, the invoicing data for a given period refer to the period during which the medicines were **delivered**. Doc PH 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 2019 Doc PH figures, the data recorded for the first half of 2020 are not yet available. The data reported are extrapolated from the recorded 2019 data (complete for 85%).

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 sheme (lump sum).

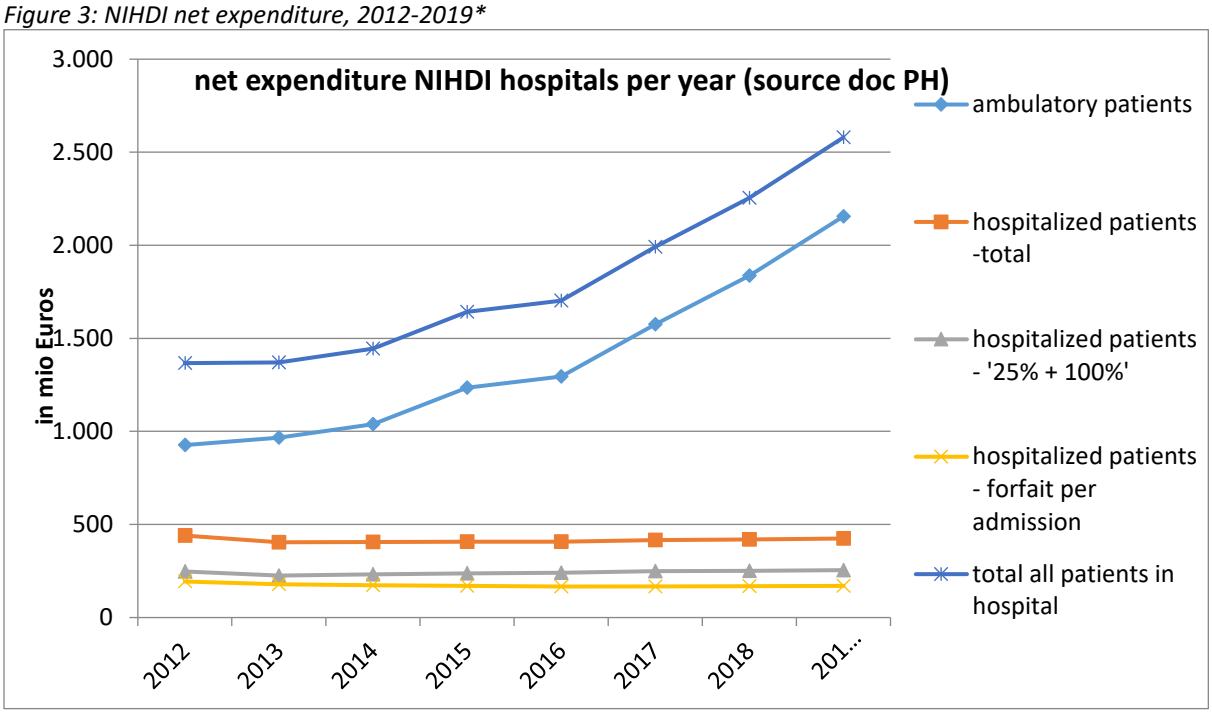
There is, however, a list of exceptions to this principle (based on the ATC5 code).
Medicines are excluded either by law (e.g. orphan drugs, antineoplastic agents, etc. cf. Article 127(3) of the Royal Decree of 1.02.2018) or on the basis of a proposal from the 'permanent working group lump sum medicines' (if either the active ingredient 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 pharmaceutical specialties 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

*Figure 3: NIHDI net expenditure, 2012-2019**



*Source doc PH, * 2019 based on extrapolated data*

Plotting the annual figures per type of patient gives the above graph (**Error! Reference source not found.**).

In 2006, overall hospital expenditure on medicines was just below a billion euros. In 2019, this figure has risen by a factor of more than 2.5, to 2.58 billion euros. Since 2014, expenditure on hospitalised patients has been stable (424 million in 2019). The significant increase in expenditure on ambulatory patients (outpatients) seen in 2015 (18.8% growth compared to 2014) was repeated in 2017, 2018 and 2019, with growth of 21.6%, 16.6% and 17.4% respectively compared to the previous year.

The table below (Table 9) shows that the share of expenditure on outpatients out of the total hospital expenditure on pharmaceutical specialties is growing year on year.
In 2019, this share has risen to 83.6%. In 2019, expenditure on hospitalised patients accounted for less than a fifth (16.4%) of the total hospital expenditure on medicines.

Table 9: Outpatient expenditure as a percentage of total hospital expenditure on pharmaceutical specialties 2012-2019 (in %)

	2012	2013	2014	2015	2016	2017	2018	2019*
Percentage of expenditure on outpatients / total expenditure hospitals	67.8%	70.5%	71.9%	75.2%	76.1%	79.1%	81.4%	83.6%

*Source: docPH, * 2019 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 10 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 fourteenth year of the system (1/7/2019 – 30/6/2020) stands at 154.01 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 savings measure aims to save 1.9 million euros annually.

Table 10: amounts set aside in the national budget for hospital admission lump sums, July 2012 - June 2020 inclusive

Period	Sum in national budget (in million euros)
1/7/2012 - 30/6/2013	180.873
1/7/2013 - 30/6/2014	172.865
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

Source: permanent audit, October 2020

Every year there are 1.7-1.8 million hospital admissions. In 2019, the average amount per admission was 89.97 euros. The table below (Table 11) shows how the average amount per admission has evolved over the period 2014-2019.

Table 11: evolution of average amount per admission (2014 – 2019)

	2014	2015	2016	2017	2018	2019
Expenditure on admission lump sum	171,992,000	173,386,000	167,277,000	168,141,000	166,587,000	160,298,000
Number of admissions	1,739,624	1,763,104	1,789,423	1,798,581	1,775,695	1,781,763
Amount per admission	*98.87*	*98.34*	*93.48*	*93.49*	*93.82*	*89.97*

Source: permanent audit, October 2020, table 3A. 1.5.2. (recorded data, docN)

The yearly figures for the various types of expenditure are shown in the table below (Table 12).

Table 12: NIHDI net expenditure 2012-2019 (in million EUROS) – breakdown of hospital expenditure*

	2012	2013	2014	2015	2016	2017	2018	2019*
Outpatients[1]	**926.6**	**966.9**	**1,039.1**	**1,234.3**	**1,295.4**	**1,575.1**	**1,835.9**	**2,155.5**
Hospitalised patients, total	**440.3**	**404.5**	**405.8**	**407.7**	**407.1**	**416.3**	**419.1**	**424.2**
Hospitalised patients – 25% + 100%[2+3]	*246.8*	*225.6*	*231.8*	*236.9*	*240.0*	*249.3*	*251.4*	*254.6*
Admission lump sum[4]	*193.5*	*178.9*	*174.0*	*170.7*	*167.1*	*167.0*	*167.7*	*169.6*
Total hospitals	**1,367.0**	**1,371.4**	**1,444.8**	**1,642.0**	**1,702.4**	**1,991.4**	**2,255.1**	**2,579.7**

*Source: docPH, * 2019 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 suppied to a patient:* *- admitted before 1.07.2006 (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 1.07.2006), 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).

DETAILED ANALYSIS OF SEVERAL CLASSES OF DRUGS (PUBLIC PHARMACIES AND HOSPITALS)

TOP 3 NIHDI EXPENDITURE IN PUBLIC PHARMACIES

L04A – IMMUNOSUPPRESSANTS

GENERAL

Globally speaking, the NIHDI expenditure for the ATC class L04A shows a further upward trend in 2019 versus 2018 in hospitals (+€46,302,548 / +14.5%), but a decrease from 2019 in public pharmacies (-€21,130,075 / -4.9%).

Table 13: evolution of NIHDI net annual expenditure for ATC class L04A immunosuppressants (2017 – 2019)

	Public pharmacies (euros)	Hospitals (euros)
2017	374,263,905	300,124,458
2018	428,982,388	319,819,871
2019	407,852,313	366,122,419

In contrast to the NIHDI expenditure there is, globally, a further upward trend in the annual DDD figures for class L04A in 2019 as compared with 2018, both in hospitals (+829,539 / +8.9%) and in public pharmacies (+2,139,070 / +6.8%).

Table 14: evolution of annual DDD figures for ATC class L04A immunosuppressants (2017 – 2019)

	Public pharmacies	Hospitals
2017	29,237,677	8,727,777
2018	31,503,034	9,275,216
2019	33,642,104	10,104,809

The growth in the NIHDI expenditure in hospitals can primarily be explained by additional indications becoming reimbursable for drugs that were already reimbursable (e.g. lenalidomide-Revlimid®, canakinumab-Ilaris®) and by new drugs becoming reimbursable (e.g. ocrelizumab-Ocrevus®, cladribine-Mavenclad®), for which the cost of a treatment per patient is also continuing to rise in comparison with earlier therapeutic options.
The highest cost in hospitals in 2019 was accounted for by the subclasses L04AA (vedolizumab-Entyvio®, eculizumab-Soliris®, natalizumab-Tysabri®, fingolimof-Gilenya®, cladribine-Mavenclad®, ocrelizumab-Ocrevus®, etc.) and L04AX (lenalidomide-Revlimid®, pomalidomide-Imnovid®, pirfenidone-Esbriet®, etc.).

The decrease in the NIHDI-expenditure in 2019 in public pharmacies is primarily due to the reduction in the price of specialties based on adalimumab and on etanercept because of the introduction of biosimilar specialties and the price reduction associated with this under the 'biological medicines' measure.

The greatest cost in public pharmacies in 2019 was for subclasses L04AB (adalimumab-Humira® and the biosimilar specialties and etanercept-Enbrel® and the biosimilar specialties, ...) and L04AC (ustekinumab-Stelara®, secukinumab-Cosentyx®, ixekizumab-Taltz®, brodalumab-Kyntheum®, etc.).

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

A) Public pharmacies

1) *General*

In 2017 NIHDI net expenditure for class L04A in public pharmacies amounted to about 374.3 million euros, which increased to about 429.0 million in 2018. From 2019 a decrease has been noticeable in the NIHDI net expenditure for class L04A in public pharmacies, down to 407.9 million in 2019 (Figure 4).

The decrease in NIHDI net expenditure for class L04A in 2019 is not noticeable in the number of DDDs: the number of DDDs rose from 31.5 million in 2018 to 33.6 million in 2019 (Figure 4).

Figure 4: evolution of NIHDI net annual expenditure and number of DDDs (public pharmacies 2010 – 2019) for ATC class L04A immunosuppressants

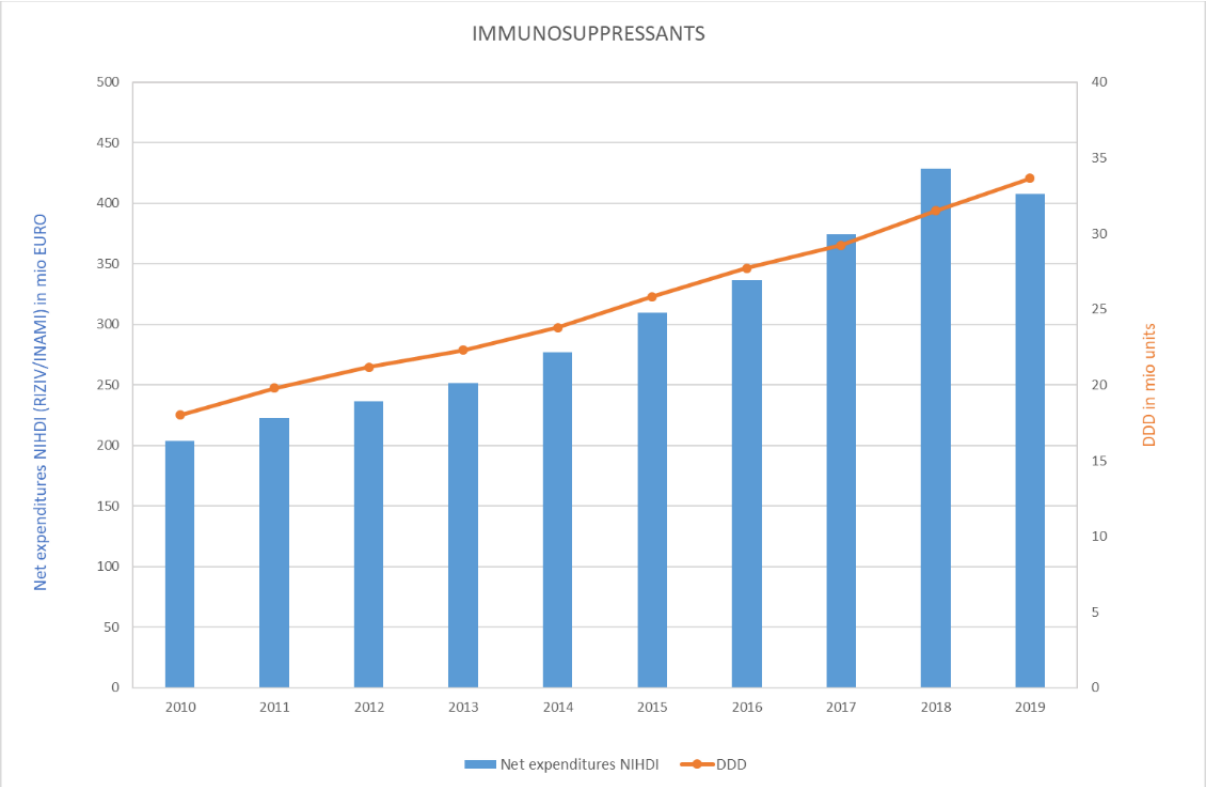


Figure 5: evolution of NIHDI net monthly expenditure (public pharmacies 2015 – 2019) for ATC class L04A immunosuppressants

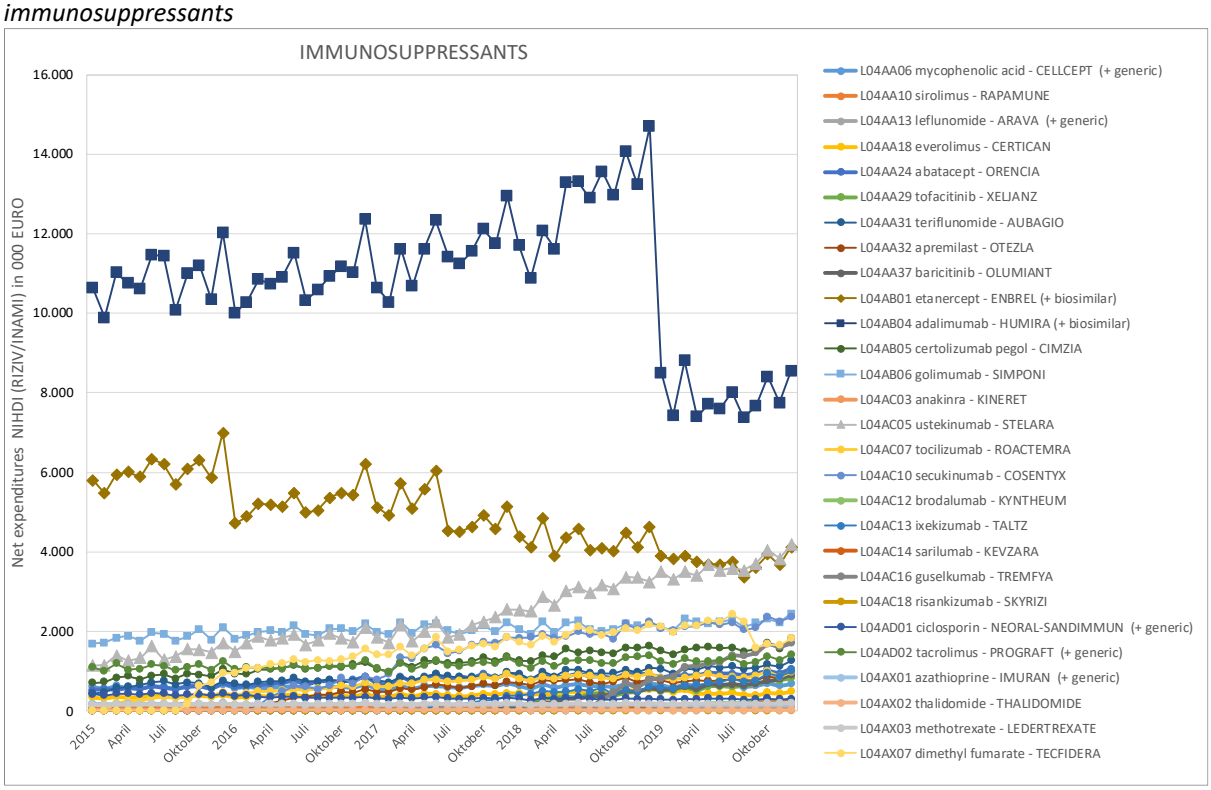


Figure 6: evolution of number of DDDs per month (public pharmacies 2015 – 2019) for ATC class L04A immunosuppressants

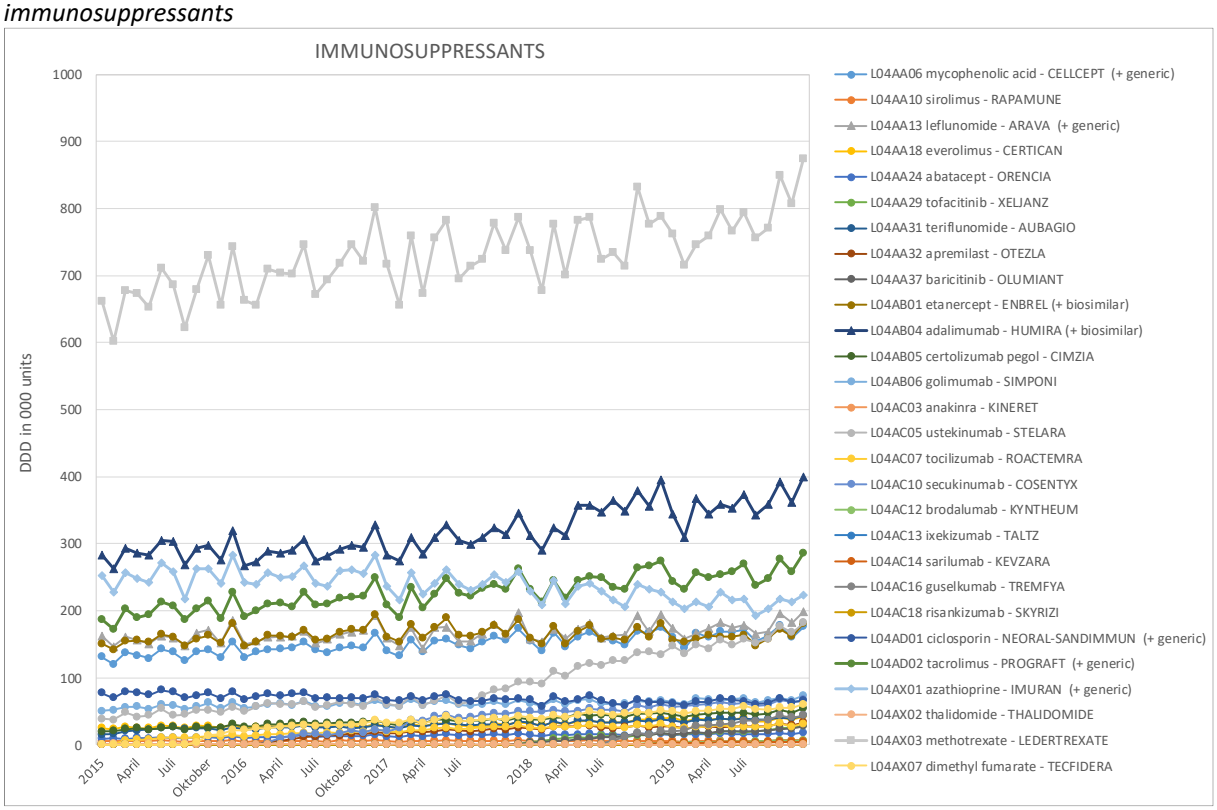


Figure 7: evolution of number of patients per year (public pharmacies 2016 – 2019) for ATC class L04A immunosuppressants

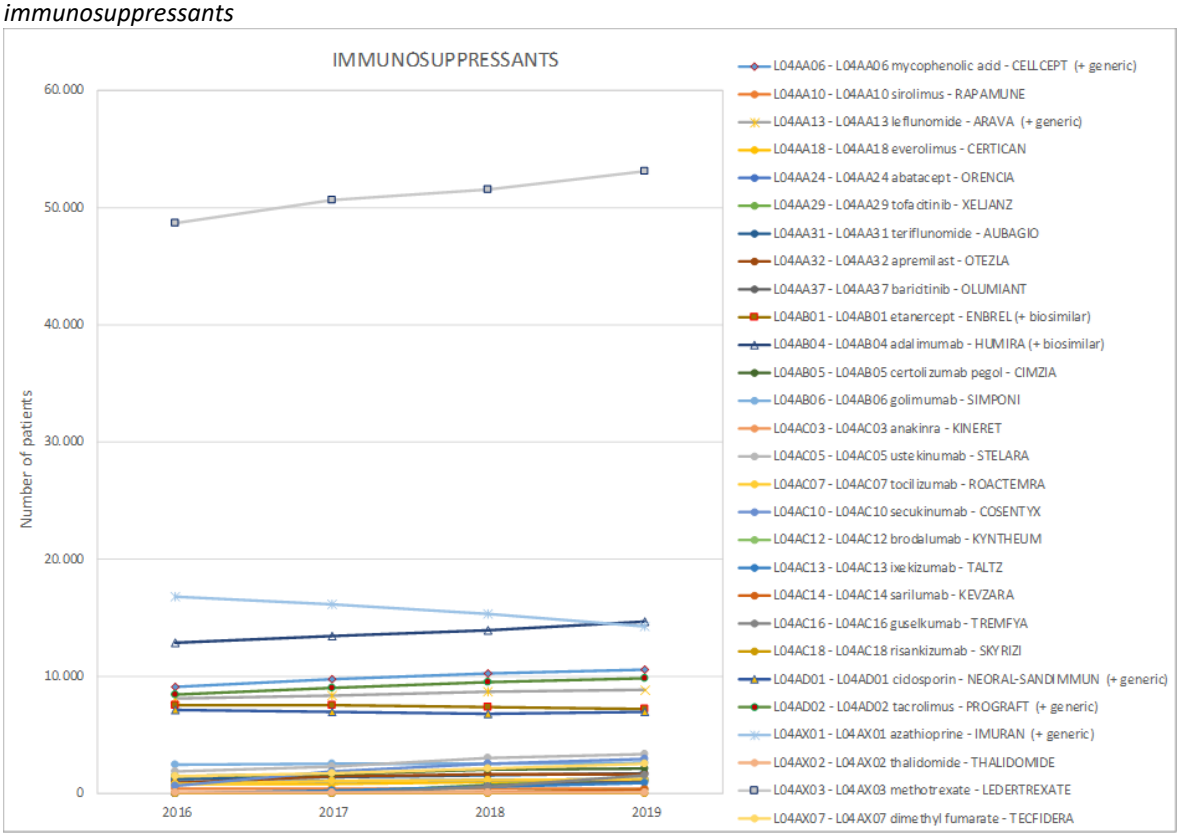
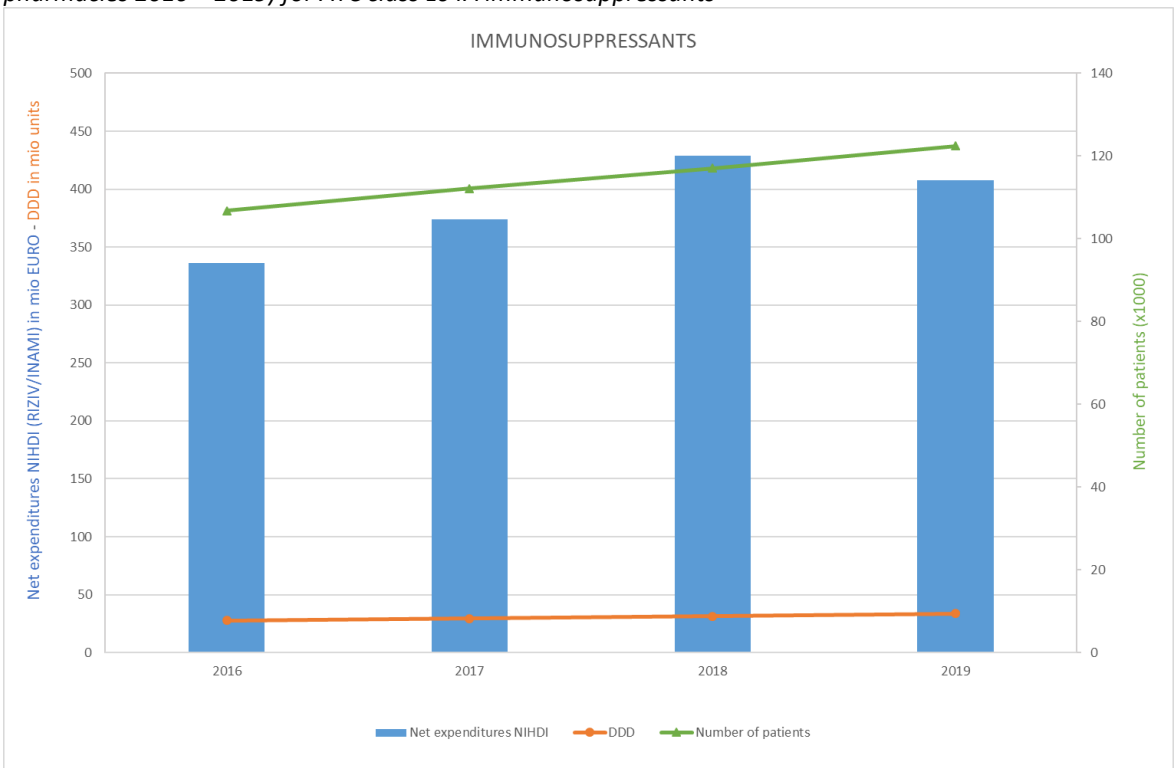


Figure 8: evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2016 – 2019) for ATC class L04A immunosuppressants



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 biosimilar specialties 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 specialty is etanercept (Enbrel® and biosimilars - ATC L04AB01), with a decrease in NIHDI expenditure due to a biosimilar specialty becoming eligible for reimbursement and the reduction in price associated with this under the 'biological medicines' measure. Nevertheless, NIHDI expenditure on this active component seems to be stabilising in 2019.

The third most important specialty is Stelara® (ustekinumab – ATC L04AC05), for which an increase in expenditure can be noted since July 2018: at that time, Stelara ® was reimbursable for the treatment of psoriasis in adults, for the treatment of psoriasis in adolescents and for the treatment of psoriatic arthritis in adults.

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 8).

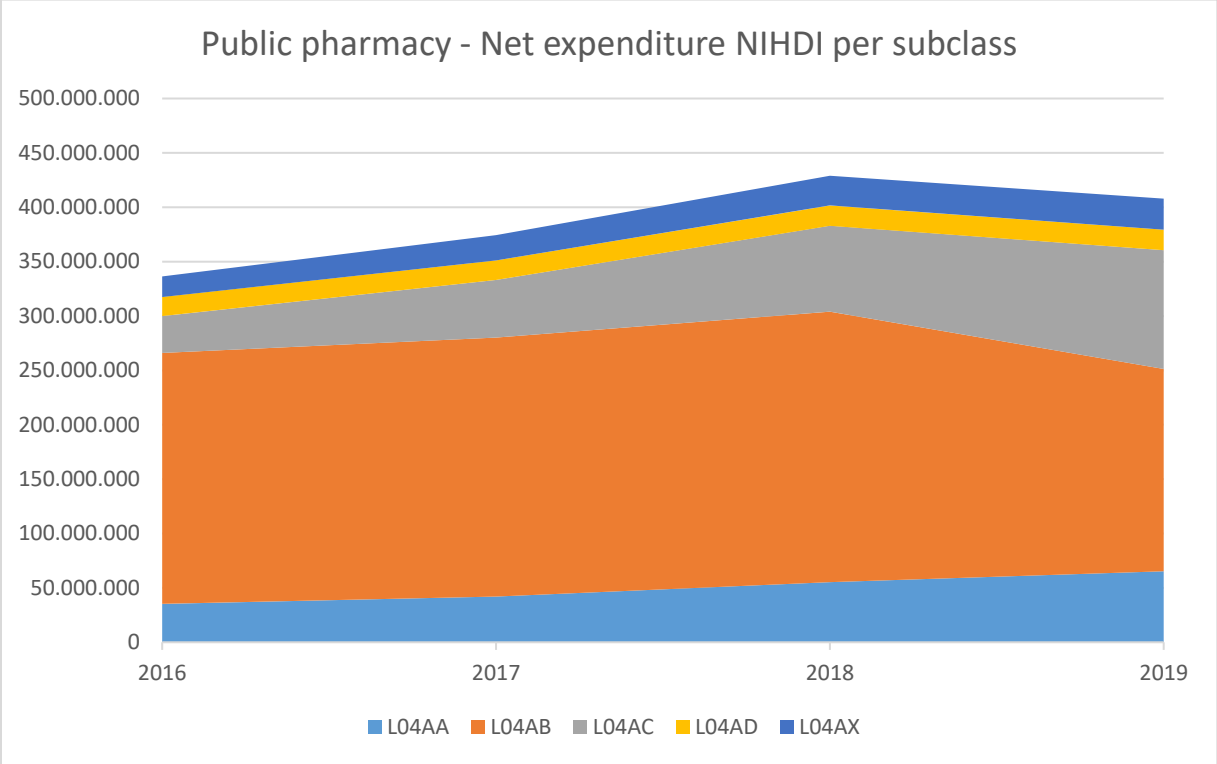
2) Analysis per subclass

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, L04AC and L04AX.

Figure 9: 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 from 2016 until the present (NIHDI net expenditure in 2016 = 35.4 million euros; NIHDI net expenditure in 2017 = 4.0 million euros; NIHDI net expenditure in 2018 = 55.3 million euros; NIHDI net expenditure in 2019 = 65.3 million euros). This increase can be explained by the reimbursement of:

- A new class of drugs, the janus kinase inhibitors (JAK) with the specialties Olumiant® (baricitinib, ATC L04AA37) and Xeljanz® (tofacitinib, ATC L04AA29), from November 2017 for the treatment of rheumatoid arthritis (RA),
- the specialty Aubagio® (teriflunomide, ATC L04AA31), for the treatment of relapsing remitting multiple sclerosis (RRMS), for which more patients were treated than anticipated.

In 2016 about 20,700 patients were reimbursed for this subclass of drugs, rising to about 22,400 in 2017, about 24,700 in 2018 and about 26,300 patients in 2019.

Subclass L04AB (tumour necrosis factor α inhibitors)

This subclass accounts for most NIHDI net expenditure in public pharmacies. In 2016 this amounted to about 230.7 million euros, increasing in 2017 to 238.2 million euros and in 2018 to 248.6 million euros. After that, NIHDI net expenditure for this subclass fell to 186.0 million euros in 2019.
Further discussion of this subclass follows under point 3 below.

Subclass L04AC (interleukin inhibitors)

The NIHDI net expenditure for this subclass shows a sharply increasing trend in recent years: NIHDI net expenditure in 2016 = 33.9 million euros; NIHDI net expenditure in 2017 = 53.0 million euros; NIHDI net expenditure in 2018 = 79.1 million euros; NIHDI net expenditure in 2019 = 109.3 million euros.

This increase can be explained by the reimbursement of:

- A number of new specialties for the treatment of psoriasis in adults: from 1 March 2017 the specialty Taltz® (ixekizumab, ATC L04AC13), and from 1 July 2018 the specialties Kyntheum® (brodalumab, ATC L04AC12) and Tremfya® (guselkumab, ATC L04AC16)
- A new specialty Kevzara® (sarilumab, ATC L04AC14) from 1 February 2018 for the treatment of rheumatoid arthritis
- Additional reimbursed indications for the specialty Cosentyx® (secukinumab, ATC L04AC10) from 1 February 2017, more specifically the treatment of psoriatic arthritis and the treatment of ankylosing spondylitis
- Additional reimbursed indications for the specialty Stelara® (ustekinumab, ATC L04AC05) from 1 December 2015, more specifically the treatment of psoriatic arthritis. Especially since 2018, steep growth has been noticeable in the NIHDI net expenditure for Stelara®.

The growth of this subclass is also noticeable in the number of patients who were reimbursed: in 2016 about 3,200 patients were reimbursed for this subclass of medicines, rising to about 5,200 in 2017, about 7,500 in 2018 and about 9,900 patients in 2019.

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 2016 NIHDI net expenditure amounted to about 17.5 million euros, in 2017 about 17.8 million euros, in 2018 about 18.6 million euros and in 2019 about 18.9 million euros.

The number of patients who were reimbursed in this subclass also shows a slightly increasing trend, from about 15,400 patients in 2016 to about 16,700 patients in 2019.

Subclass L04AX (other immunosuppressants)

In this subclass an increase in NIHDI net expenditure can be observed: in 2016 NIHDI net expenditure amounted to about 19.0 million euros, in 2017 about 23.3 million euros, in 2018 about 27.4 million euros and in 2019 about 28.4 million euros.
The increase in the NIHDI net expenditure in this subclass is due to the specialty Tecfidera® (dimethylfumarate, ATC L04AX07), for the treatment of relapsing remitting multiple sclerosis (RRMS). For this specialty a convention was concluded between the company and the NIHDI.

The number of patients who were reimbursed in this subclass also shows a slightly increasing trend, from about 65,300 patients in 2016 to about 69,700 patients in 2019.

3) Subclass L04AB (tumour necrosis factor α inhibitors)

This subclass accounts for the highest NIHDI net expenditure in public pharmacies.
In public pharmacies this subclass comprises 4 active components: etanercept (Enbrel® and biosimilars), adalimumab (Humira® and biosimiliars), certolizumab pegol (Cimzia®) and golimumab (Simponi®).

These 4 active components are considered in greater detail below:

Etanercept (ATC L04AB01)

Enbrel® was reimbursable in 2016 for the treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis, juvenile psoriatic arthritis, enthesitis-related juvenile arthritis and non-radiographic axial spondyloarthritis.

The NIHDI net expenditure for etanercept decreased between 2016 and 2019 year on year from 63.1 million euros in 2016 to 45.2 million euros in 2019. Since 1 September 2016, a biosimilar of etanercept has also been reimbursable, which meant that from 1 July 2017 the reimbursement basis for Enbrel® fell, under the 'biological

medicines' measure. Furthermore, this fall is also due to the fact that the reimbursement basis of the specialty Enbrel® was reduced further on 1/1/2019, after 15 years of being reimbursable (the so-called 'old medicines' price reduction).
The figures also show that in 2019 the share of biosimilars in relation to the original specialty amounted to 14%/86%.

A slightly decreasing trend may also be observed in the number of patients receiving a reimbursed treatment with etanercept, (from about 7,500 patients in 2016 to about 7,200 patients in 2019).

Adalimumab (ATC L04AB04)
Adalimumab represents the greatest NIHDI cost within subclass L04AB in public pharmacies.

Humira® was reimbursable in 2016 for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, psoriasis, polyarticular juvenile idiopathic arthritis, ulcerative colitis, non-radiographic axial spondyloarthritis and hidradenitis suppurativa. On 1 July 2017, the following reimbursable indications were added: plaque psoriasis in children, Crohn's disease in children and enthesitis-related juvenile arthritis, on 1 September 2017 uveitis in adults and on 1 November 2018 juvenile uveitis in children.

The NIHDI net expenditure for adalimumab rose between 2016 and 2018 year on year to 154.3 million euros in 2018. In 2019, however, the NIHDI net expenditure fell to 95.2 million euros. This fall is due to the fact that the reimbursement basis of the specialty Humira® was reduced on 1/1/2019 after 12 years of being reimbursable (the so-called 'old medicines' price reduction). Since 1 October 2018, biosimilars of adalimumab have also been reimbursable, which meant that from 1 January 2019 the reimbursement basis of Humira® fell even further under the 'biological medicines' measure.
The figures show that the share of biosimilars in relation to the original specialties amounted to 5%/95% in 2019. The share of biosimilars for adalimumab is smaller than that for etanercept, but can possibly be explained by the fact that biosimilar drugs for adalimumab have not yet been available for as long.

The number of patients receiving a reimbursed treatment with adalimumab continues to show an upward trend (from about 12,900 patients in 2016 to 14,000 patients in 2019).

Certolizumab pegol (Cimzia®, ATC L04AB05)
Cimzia® was reimbursable in 2016 for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis. From 1 May 2019 the treatment of psoriasis was added to this.

The NIHDI net expenditure on Cimzia® continued to rise from 12.9 million euros in 2016 to 18.9 million euros in 2019.

Also, the number of patients receiving a reimbursed treatment with Cimzia® has increased in line with the increase in expenditure, from about 1,400 patients in 2016 to 2,100 patients in 2019.

Golimumab (Simponi®, ATC L04AB06)
Simponi® was reimbursable in 2016 for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and ulcerative colitis.

The NIHDI net expenditure for Simponi® continued to rise from 23.9 million euros in 2016 to 26.69 million euros in 2019.

Also, the increase in the number of patients receiving a reimbursed treatment with Simponi® is in line with the increase in expenditure: from about 2,400 patients in 2016 to 2,600 patients in 2019.

B) Hospitals

1) *General*

In 2017 the NIHDI net expenditure for class L04A used in hospitals amounted to about 300.1 million euros, rising to 319.8 million in 2018 and to 366.1 million in 2019. This is an increase of +65.9 million euros compared to 2017 (+22.0%) and of +46.3 million euros compared to 2018 (+14.5%) (Figure 10).

Expressed in the number of DDDs, 10.1 million DDDs were reimbursed in hospitals, which is an increase of 1.3 million compared with 2017 (+15.8%) or of 0.8 million compared with 2018 (+8.9%) (Figure 10).

Figure 10: evolution of NIHDI net annual expenditure and number of DDDs (hospitals (all patients) 2010 – 2019) for ATC class L04A immunosuppressants

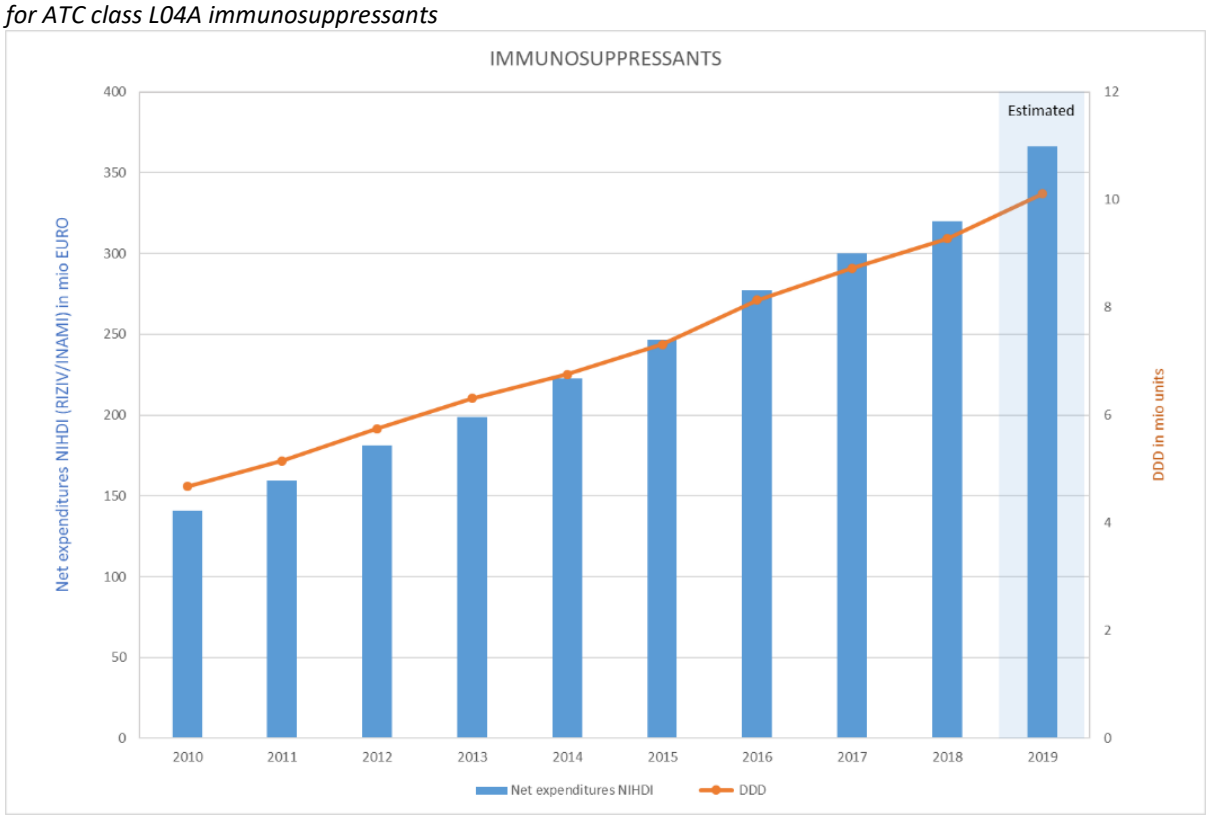


Figure 11: evolution of NIHDI net quarterly expenditure (hospitals (all patients) 2015 – 2019) for ATC class L04A immunosuppressants

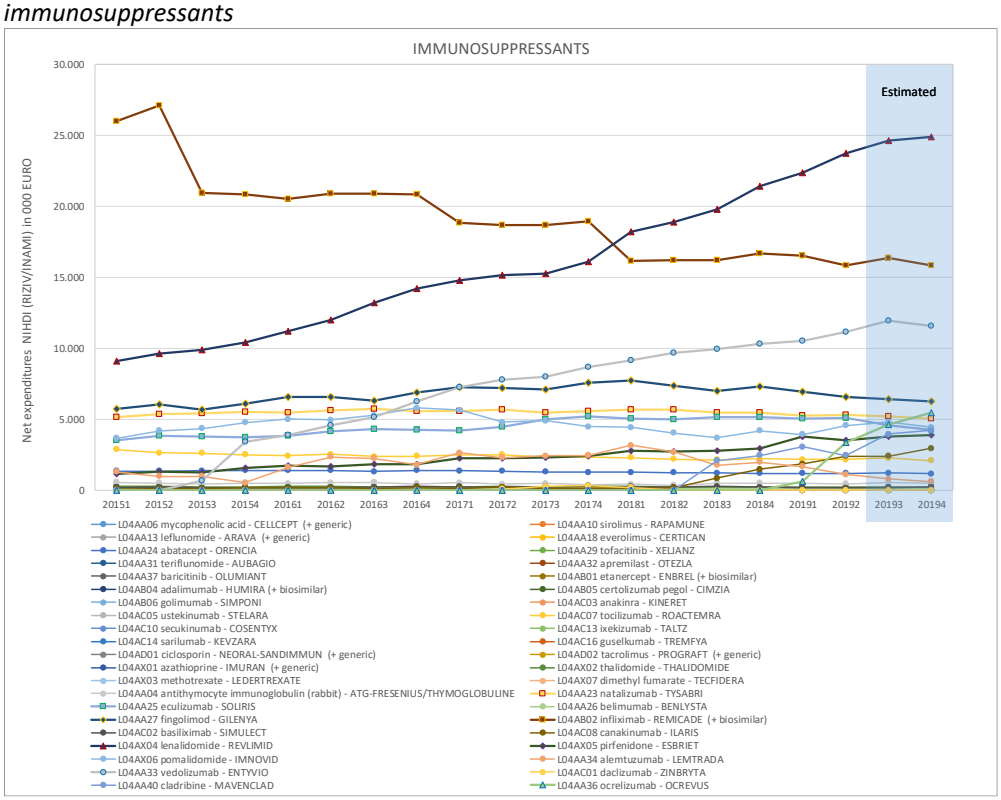
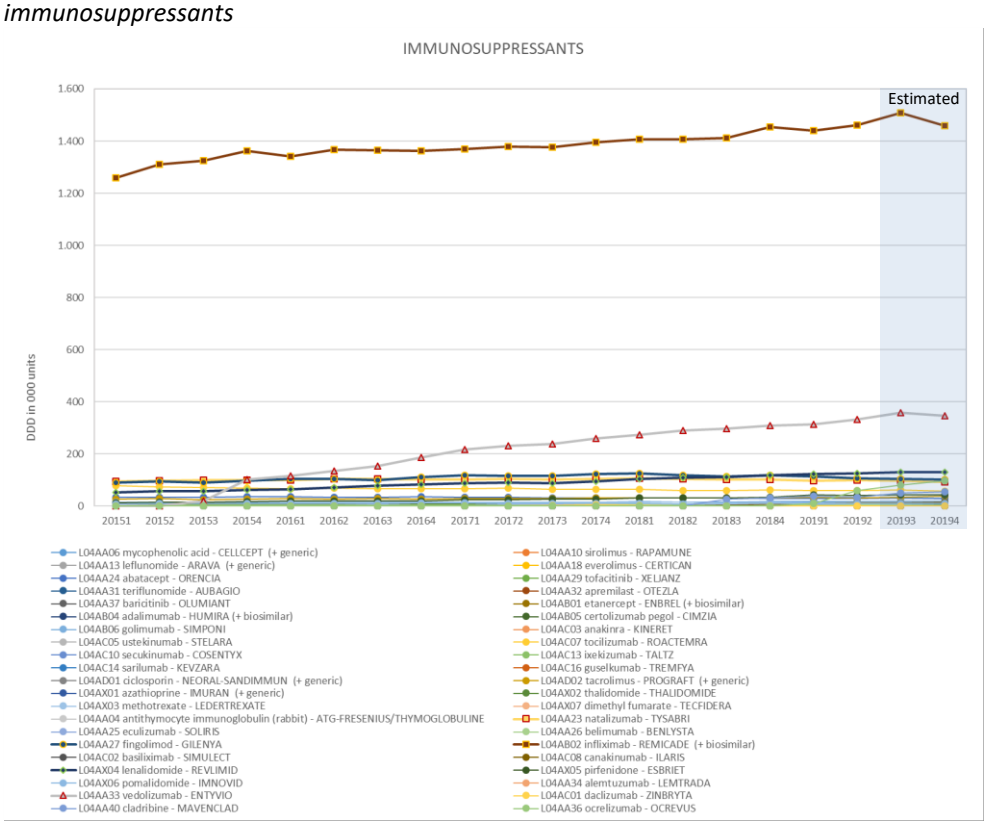


Figure 12: evolution of number of DDDs per quarter (hospitals (all patients) 2015-2016) for ATC class L04 immunosuppressants



As shown in Figure 11, the highest expenditure within the ATC L04A class is that for lenalidomide-Revlimid®, for which there has been a very strong sustained increase in use since 2015 for patients with multiple myeloma (MM), myelodysplastic syndrome (MDS) and relapsed or refractory mantle cell lymphoma (MCL).

A second strong climber is vedolizumab-Entyvio®, which is used increasingly for the treatment of ulcerative colitis (UC) and Crohn's disease (CD).

Thirdly, there are 2 specialties for the treatment of multiple sclerosis, use of which has increased strongly: ocrelizumab-Ocrevus® and cladribine-Mavenclad®.

A fourth strong climber is canakinumab-Ilaris®, for the treatment of a few specific disorders of the immune system such as cryopyrin-associated periodic syndrome (CAPS), colchicine resistant-Familial Mediterranean Fever (cr-FMF), hyperimmunoglobulin-D-syndrome (HIDS), mevalonate kinase deficiency (MKD), tumour necrosis factor receptor-associated periodic syndrome (TRAPS) and rheumatic pathology (systemic juvenile idiopathic arthritis (SJIA)).

By contrast, there has been a significant fall in the costs for infliximab-Remicade® and the biosimilar specialties, due to the introduction of biosimilar specialties and the associated price reduction under the 'biological medicines' measure.

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).

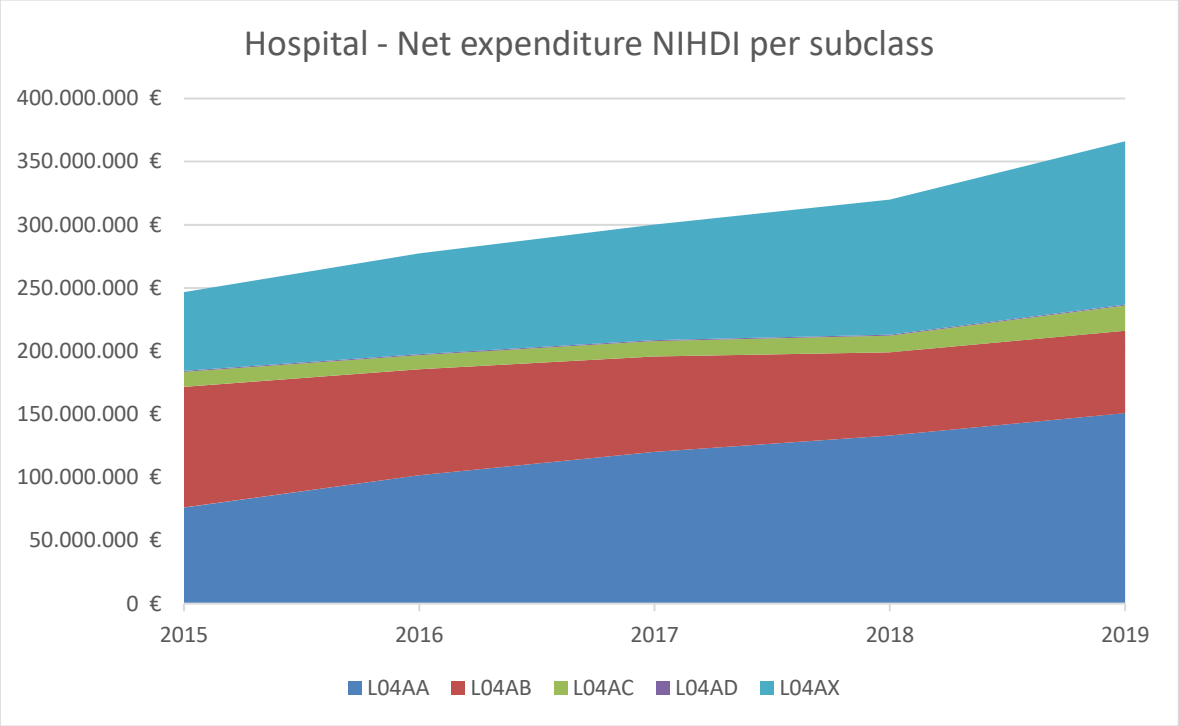
These drugs are primarily used for the treatment of, inter alia, rheumatic conditions, psoriasis, Crohn's disease, ulcerative colitis, multiple sclerosis, certain cancers, specific immunopathology, pulmonary fibrosis and in the case of transplants.

Overall, a steep increase can be observed in the NIHDI expenditure on subclass L04AA, from €76,161,879 in 2015 to €150,887,429 in 2019 (+98.1%), on subclass L04AC from €11.862.774 in 2015 to €19.856.536 in 2019 (+67.4%) and on subclass L04AX from €62,343,746 in 2015 to €129,360,130 in 2019 (+107.5%).

There has been a moderate increase for subclass L04AD, from €779,035 in 2015 to €800,479 in 2019 (+2.8%).

A steep fall can be seen in NIHDI expenditure on subclass L04AB, from €95,524,381 in 2015 to €65,217,843 in 2019 (-31.7%).

Figure 13: 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 specialties 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 €76,161,879 in 2015 to €150,887,429 in 2019 (+98.1%)

The molecules with a decreasing trend are:

- Mycophenolate mofetil, ATC L04AA06 (-8.2%), sirolimus, ATC L04AA10 (-44.9%) and anti-human T-lymphocytes obtained from rabbits (ATG), ATC L04AA04 (-0.7%) which are used in the context of organ transplantation.
- Leflunomide, ATC L04AA13 (-18.2%) used for rheumatoid arthritis and abatacept, L04AA24 (-12.7%) used for rheumatoid arthritis as well as polyarticular juvenile idiopathic arthritis.
- The use of natalizumab, ATC L04AA23, used for the treatment of multiple sclerosis, is also decreasing.

The molecules with an increasing trend are:

- Everolimus, L04AA18, which is used in the context of organ transplantation and is comparable to sirolimus in terms of positioning.
- A new class of drugs, the janus kinase inhibitors (JAK) with baricitinib, ATC L04AA37 (€1,936) and tofacitinib, ATC L04AA29 (€6,103), from November 2017 for the treatment of rheumatoid arthritis (RA).
- Teriflunomide, ATC L04AA31 (+77.6%), fingolimod, ATC L04AA27 (+11.2%), alemtuzumab, L04AA34 (+9.8%) and the very recent molecules cladribine, L04AA40 (€13,654,364) and ocrelizumab, L04AA36 (€14,096,871) for the treatment of relapsing remitting multiple sclerosis (RRMS).
- Apremilast, L04AA32 (€24,872), an oral therapy for the treatment of psoriasis and psoriatic arthritis, with more patients being treated than anticipated.
- Eculizumab, L04AA25 (+27.6%) for the treatment of paroxysmal nocturnal haemoglobinuria (PNH) and haemolytic-uraemic syndrome (aHUS).
- Belimumab, L04AA26 (+8.1%) for the treatment of systemic lupus (SLE).
- There has been a very steep increase in the use of vedolizumab, L04AA33 (+1,014.7%) 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 €95,524,381 in 2015 to €65,217,843 in 2019 (-31.7%), due to the introduction of biosimilar specialties and the associated price reduction under the 'biological medicines' measure.
This has resulted in a steep fall in the NIHDI cost for infliximab, L04AB02 (-32.0%), which is exclusively administered intravenously.
In the case of the subcutaneously administered TNF-α inhibitors, we see a steep decrease of etanercept, L004AB01 (-73.6%) due to an earlier introduction of biosimilar specialties, whereas this effect is not yet visible for adalimumab, L04AB04 (+4.2%).
The TNF-α inhibitors without biosimilar specialties still show an increase of +44.7% for certolizumab, L04AB05 and even of +1,417.6% for golimumab, L04AB06.

For the specific eligibility for reimbursement of the specialties in this class, please refer to point 3 of the section on public pharmacies.

Subclass L04AC (interleukin inhibitors)

NIHDI net expenditure on this subclass has shown a steeply increasing trend in recent years, from €11,862,774 in 2015 to €19,856,538 (+67.4%) in 2019.

This increase can be explained by the reimbursement of:

- A number of new specialties for the treatment of psoriasis in adults: from 1 March 2017 ixekizumab, ATC L04AC13 (€148,259), and from 1 July 2018 brodalumab, ATC L04AC12 and guselkumab, ATC L04AC16 (€4,247).
- Additional reimbursed indications for secukinumab, ATC L04AC10 (€27,580) from 1 February 2017, more specifically the treatment of psoriatic arthritis and the treatment of ankylosing spondylitis.
- Additional reimbursed indications for ustekinumab, ATC L04AC05 (+2,285.0%) from 1 December 2015, more specifically the treatment of psoriatic arthritis.
- The eligibility for reimbursement of anakinra, L04AC03 (€112,187) 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 (+2,006.2%), resulting in steeply increasing use.
- A slight decrease in the use of tociluzumab, L04AC07 (-18.6%).
- A stable situation for the use of basiliximab, L04AC02 (0.1%), used in the context of organ transplants.

Subclass L04AD (calcineurin inhibitors)

In this subclass (mainly used in relation to transplants) a slight increase in the NIHDI net expenditure can be detected in hospitals: +2,8%. Since the patients remain in hospital for only a short time after the transplant procedure, the budgetary impact is limited to €800,479 in 2019.

Subclass L04AX (other immunosuppressants)

In this subclass a steep increase in NIHDI net expenditure can be detected in 2019: +107.5% compared with 2015, - €129,360,130 versus €62,343,746.
The increase in NIHDI net expenditure in this subclass is mainly due to, on the one hand, a steep 145.1% increase for lenalidomide, ATC L04AX04, for the treatment of multiple myeloma (MM), myelodysplastic syndrome (MDS) and mantle cell lymphoma (MCL), and, on the other hand, a steep increase of 182.4% for pirfenidone, ATC L04AX05 for the treatment of idiopathic pulmonary fibrosis.
The use of pomalidomide, ATC L04AX06 (4.5%), for the treatment of multiple myeloma (MM), has remained relatively stable.

After a fall in expenditure in 2010, 2011 and 2012, linked to the entry onto the market of generic forms of clopidogrel (Plavix®) in 2010, the total net expenditure for antithrombotic agents once again experienced significant and steady growth from 2013 (Figure 14). This growth can be explained by prasugrel and ticagrelor being brought onto the market, but above all by the reimbursement of the new oral anticoagulants (NOACs; also called Direct Oral Anticoagulants (DOACs)), namely dabigatran (Pradaxa®), rivaroxaban (Xarelto®), apixaban (Eliquis®) and eloxaban (Lixiana®), for ever broader indications. These new indications are leading not only to an increase in the number of patients, but also to a significant growth in expenditure on these 4 drugs, with slower growth for Pradaxa® (Figure 15). This is probably explained by the fact that more patients with chronic atrial fibrillation are being treated than in the past. The posology of these new indications indeed involves a lengthy treatment compared to the maximum duration of treatment of 5 weeks for the indication already reimbursed previously (primary prevention after major orthopaedic surgery).

The number of patients being treated with vitamin K-antagonists (Marcoumar®, Marevan® and Sintrom®) has been falling steadily since 2013 and will from the end of 2016 be lower than the number of patients being treated with an NOAC (Figure 16). The costs for the NIHDI of these two classes of drugs are however very different, both in terms of the total costs and the cost price per patient and per month. It is important to emphasise that the expenditure on the NOACs is based on the list price of these drugs. The actual costs for the NIHDI are confidential and must be calculated on the basis of the refunds set out in a convention concluded between the pharmaceutical company concerned and the NIHDI.

The number of patients and DDDs and the NIHDI expenditure per month on the class of antithrombotic agents experienced a constant and similar evolution between 2016 and 2019 (Figure 19).
Furthermore, the costs for the NIHDI for acetylsalicylic acid have remained stable since 2015 (Figure 15). This follows a period of strong growth in expenditure during the period 2010 -2014 (an increase of 50%). The number of DDDs increased in this period (2010-2014) by almost 25%. In 2015, the number of DDDs increased further and then levelled off (Figure 18). The number of patients being treated with acetylsalicylic acid amounts to almost 1 million. This number has been stable in recent years (the period 2016-2019) (Figure 17). Given that acetylsalicylic acid is the least expensive treatment option per patient and per month in the group of antithrombotic agents, the cost price also remains minimal compared to that of the NOACs despite the fact that the number of patients being treated with acetylsalicylic acid is significantly higher.

Figure 14: evolution of NIHDI net annual expenditure and number of DDDs (public pharmacies 2010 – 2019) for ATC class B01A antithrombotic agents

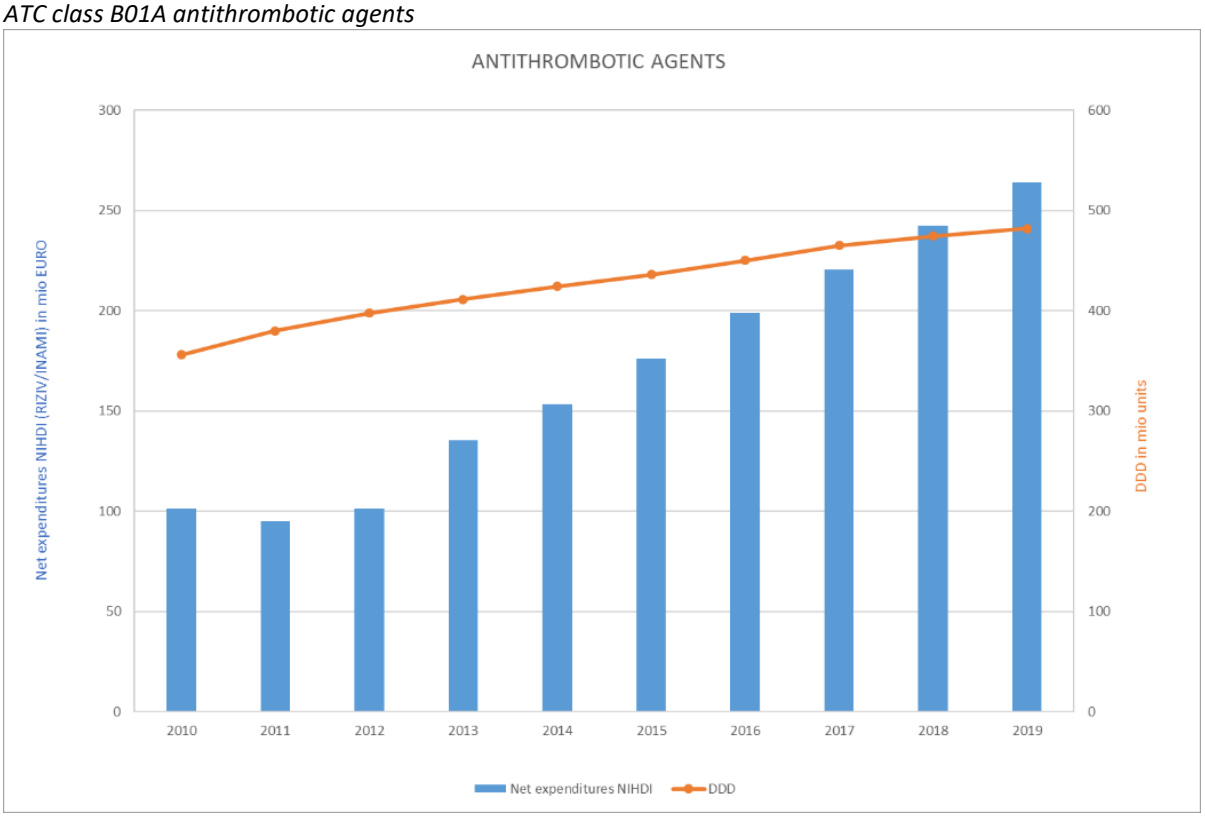


Figure 15: evolution of NIHDI net monthly expenditure (public pharmacies 2015 – 2019) for ATC class B01A antithrombotic agents

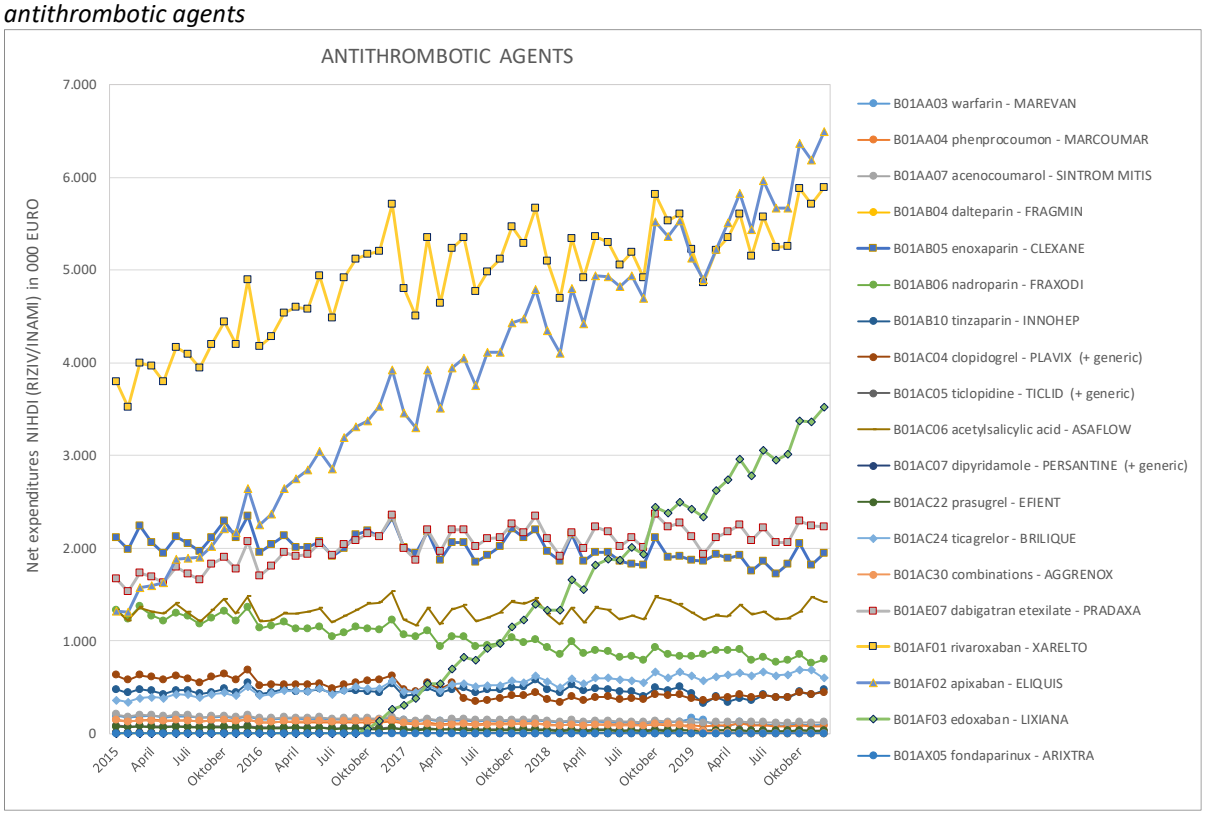


Figure 16: evolution of number of patients per month (public pharmacies 2016 – 2019) for vitamin K antagonists (ATC class B01AA) versus direct oral anticoagulants (ATC class B01AE + B01AF)

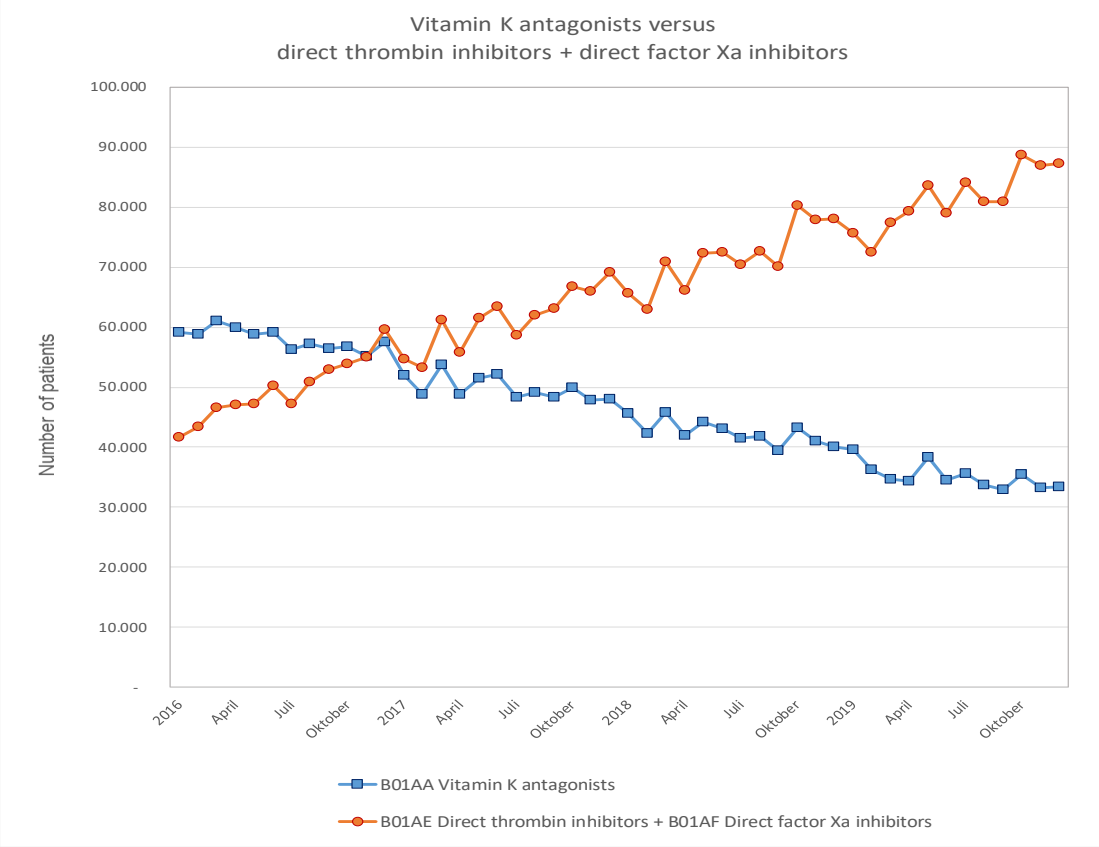


Figure 17: evolution of number of patients per month (public pharmacies 2016 – 2019) for ATC class B01A antithrombotic agents

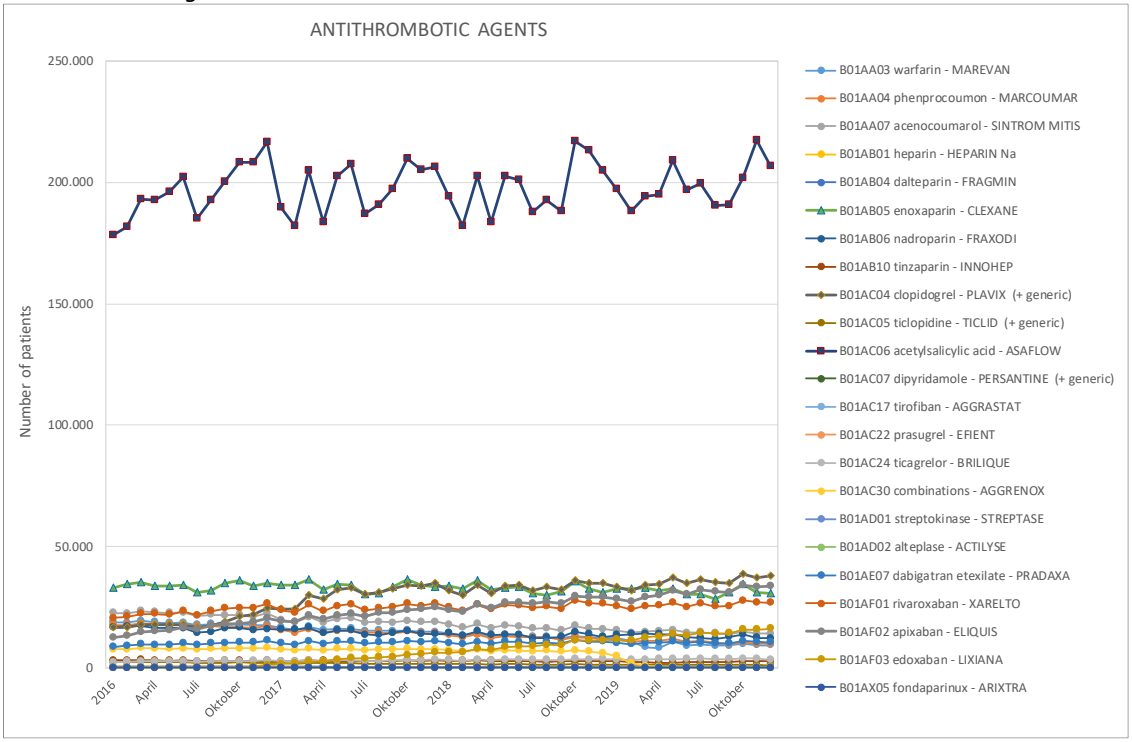


Figure 18: evolution number of DDDs per month (public pharmacies 2015 – 2019) for ATC class B01A antithrombotic agents

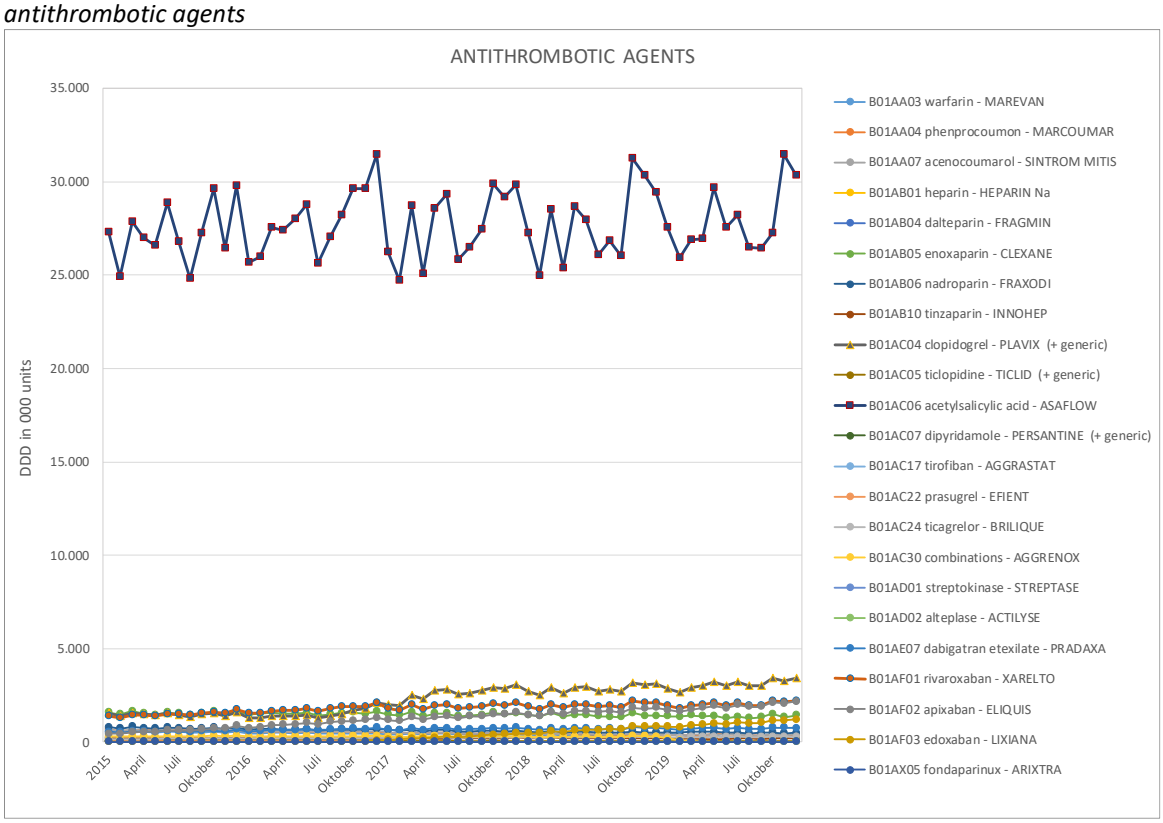
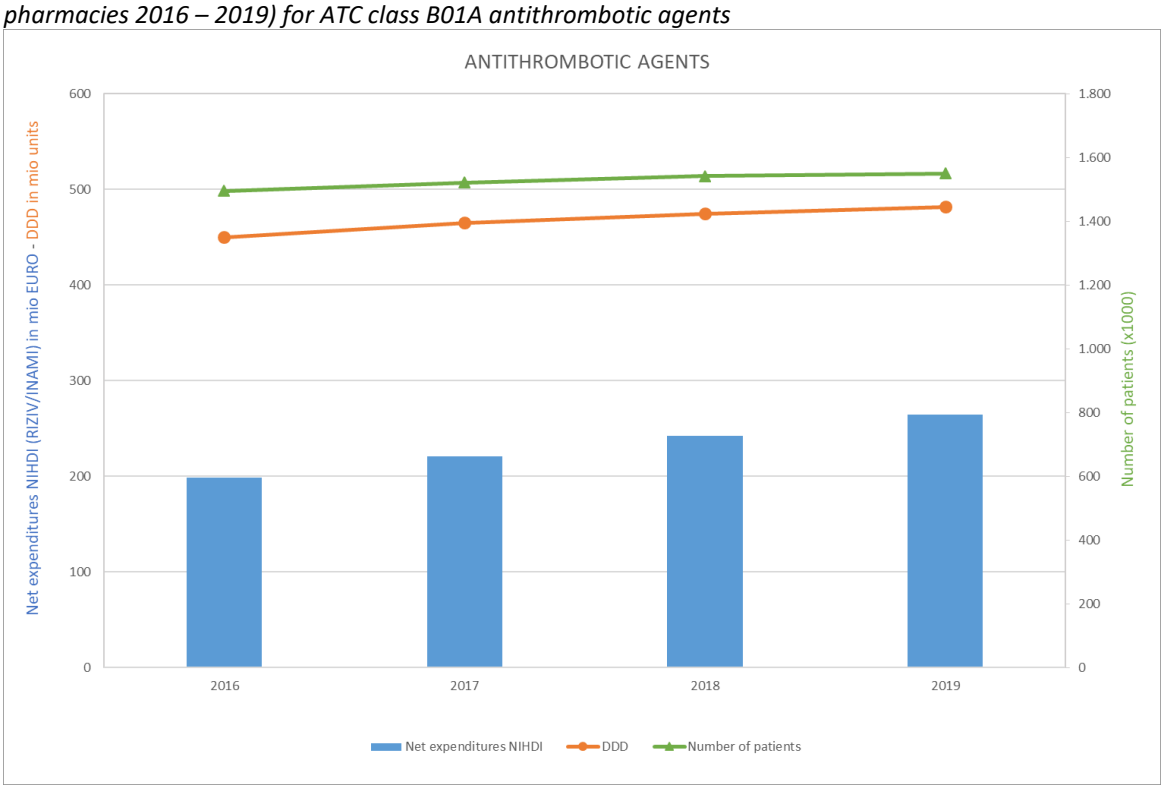


Figure 19: evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2016 – 2019) for ATC class B01A antithrombotic agents



J05A - DIRECT ACTING ANTIVIRALS

GENERAL

Table 15: evolution of NIHDI net annual expenditure for ATC class J05A direct acting antivirals (2017 – 2019)

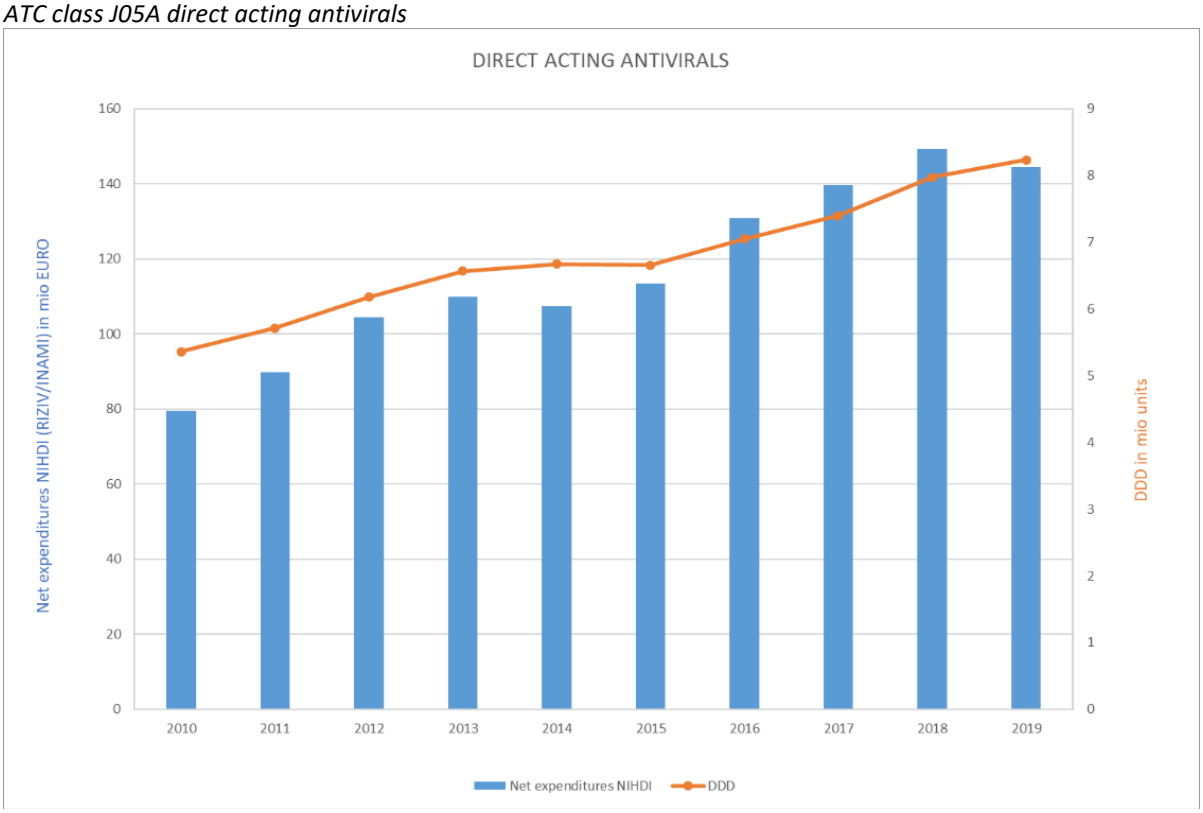
	Public pharmacies (euros)	Hospitals (euros)
2017	139,704,231	112,226,115
2018	149,234,670	63,877,175
2019	144,435,297	92,257,495

The ATC-class J05A includes the drugs used for the treatment of HIV, hepatitis, herpes and cytomegalovirus (CMV). In 2018, expenditure on this group reached a peak in the public pharmacies, whereas the expenditure fell in hospitals. Two trends are therefore noticeable.

On the one hand, in the public pharmacies, expenditure for this group decreased after 2018 due to the arrival of generic specialties of the antivirals and due to decreases in the price of the 'old' antivirals.
On the other hand, in 2018 a fall in expenditure in hospitals was noticeable, after an expansion of the target group for hepatitis C-inhibitors in 2017. There were expansions of the target group in 2015, 2017 and 2019. As a consequence of this progressive broadening of the conditions for reimbursement, a ripple effect can be observed: a peak in the year in question and a fall in the following year.

A) PUBLIC PHARMACIES

Figure 20: evolution of NIHDI net annual expenditure and number of DDDs (public pharmacies 2010 – 2019) for ATC class J05A direct acting antivirals



Overall, the number of treatments with antivirals has increased, both as expressed in the number of DDDs (volume) and in the number of patients.
However, the expenditure on this group of drugs in public pharmacies decreased after 2018. The drop in expenditure can be explained by the arrival and the increasing use of generic specialties of the antivirals and by the reductions in the price of the 'old' antivirals.
There have therefore been price reductions for the following antivirals (as single preparations and in combination preparations) under the 'old medicines' or the 'biological medicines' measures:

- Ritonavir + lopinavir — price reduction on 01.01.2017
- Valganciclor (anti-cytomegalovirus) — price reduction on 01.01.2017
- Emtricitabine — price reduction on 01.01.2018
- Enfuvirtide — price reduction on 01.07.2018
- Tipranavir — price reduction on 01.01.2019
- Atazanavir — price reduction on 01.04.2019

On 01.10.2019 the price of fosamprenavir and of the hepatitis B inhibitor entecavir fell, but these price reductions are too recent to provide an explanation for the trend in the graphs above.

In addition, the following antivirals (as single preparations and in combination preparations) fell in price as a result of the opening of the reference cluster due to the arrival of generic specialties of these drugs:

- Abavacir + lamivudine — price reduction on 01.10.2017
- Tenofovir disoproxil — price reduction on 01.10.2017
- Valganciclovir (anti-cytomegalovirus) — price reduction on 01.10.2017
- Emtricitabine + tenofovir disoproxil — price reduction on 01.01.2019
- Darunavir — price reduction on 01.07.2019

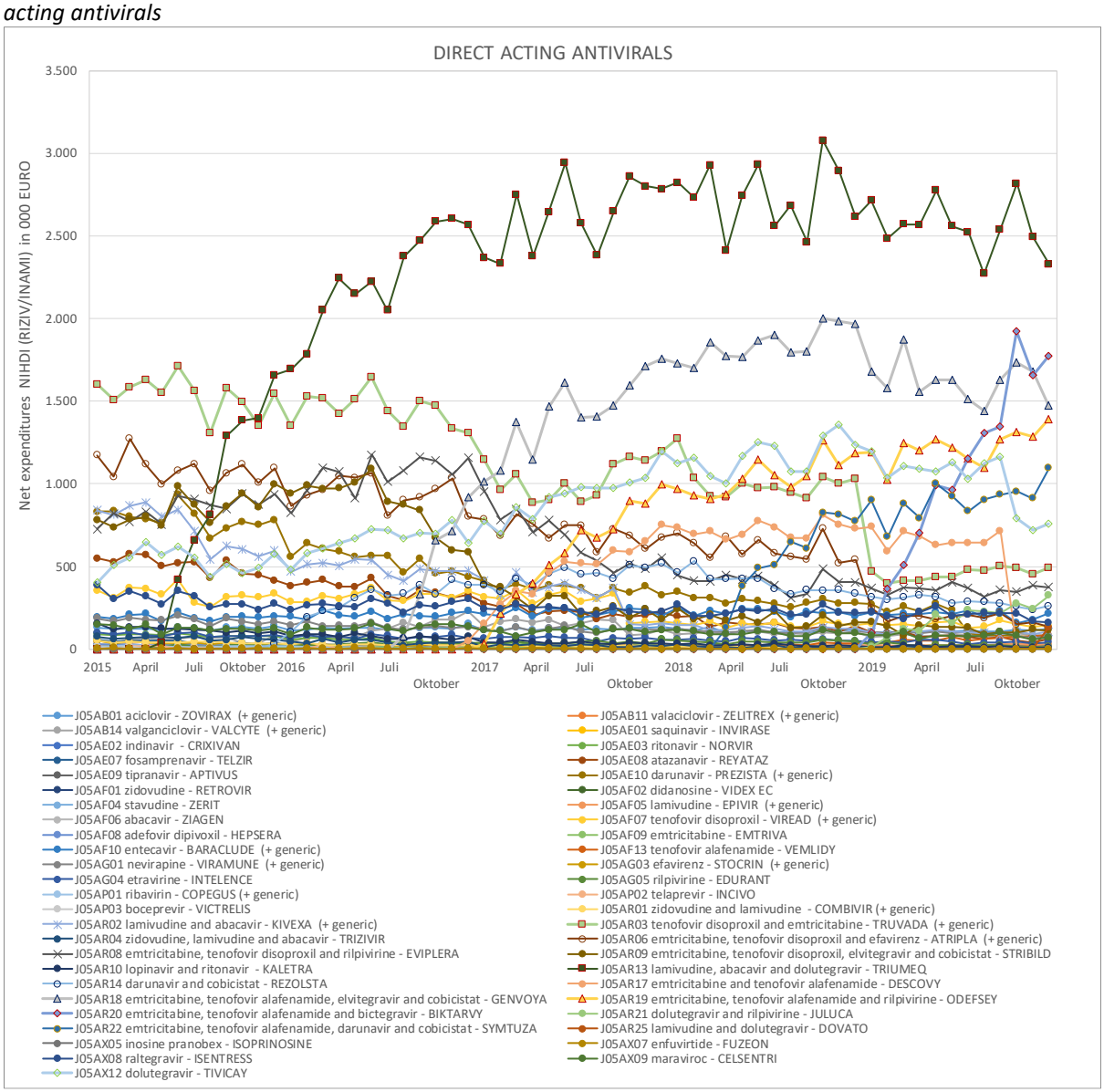
The price reductions of emtricitabine + tenofovir disoproxil + efavirenz on 1 October 2019 are too recent to provide an explanation for the trend in the graphs above.

Note that the new prophylactic indication for the pharmaceutical specialty Truvada®, abbreviated as PrEP, has been reimbursed since 1 June 2017, and that on 1 October 2017 the cluster of the tenofovir disoproxil specialties (Viread ® mono; Truvada ®, Atripla ®, Eviplera ®, Stribild ® combinations) opened, yet not for those of the recent tenofovir alafenamide salt (Vemlidy ®, Emlidy ® mono; Descovy ®, Odefsey ®, Genvoya ®).

Finally, in 2019 there was a group review of the antivirals, with price reductions that took effect on 1 October 2019. However, the effect of these price reductions is not yet visible in the figures. The pharmaceutical specialties that fell in price due to the outcome of the group review are Truvada®, Atripla®, Descovy® and Viread®, which are no longer reimbursed for the HIV indication although they still are for the hepatitis B indication.

Finally, in 2019 there was a group review of the antivirals, with price reductions that took effect on 1 October 2019. However, the effect of these price reductions is not yet visible in the figures. The pharmaceutical specialties that fell in price due to the outcome of the group review are Truvada®, Atripla®, Descovy® and Viread®, which is no longer reimbursed for the HIV indication although it still is for the hepatitis B indication.

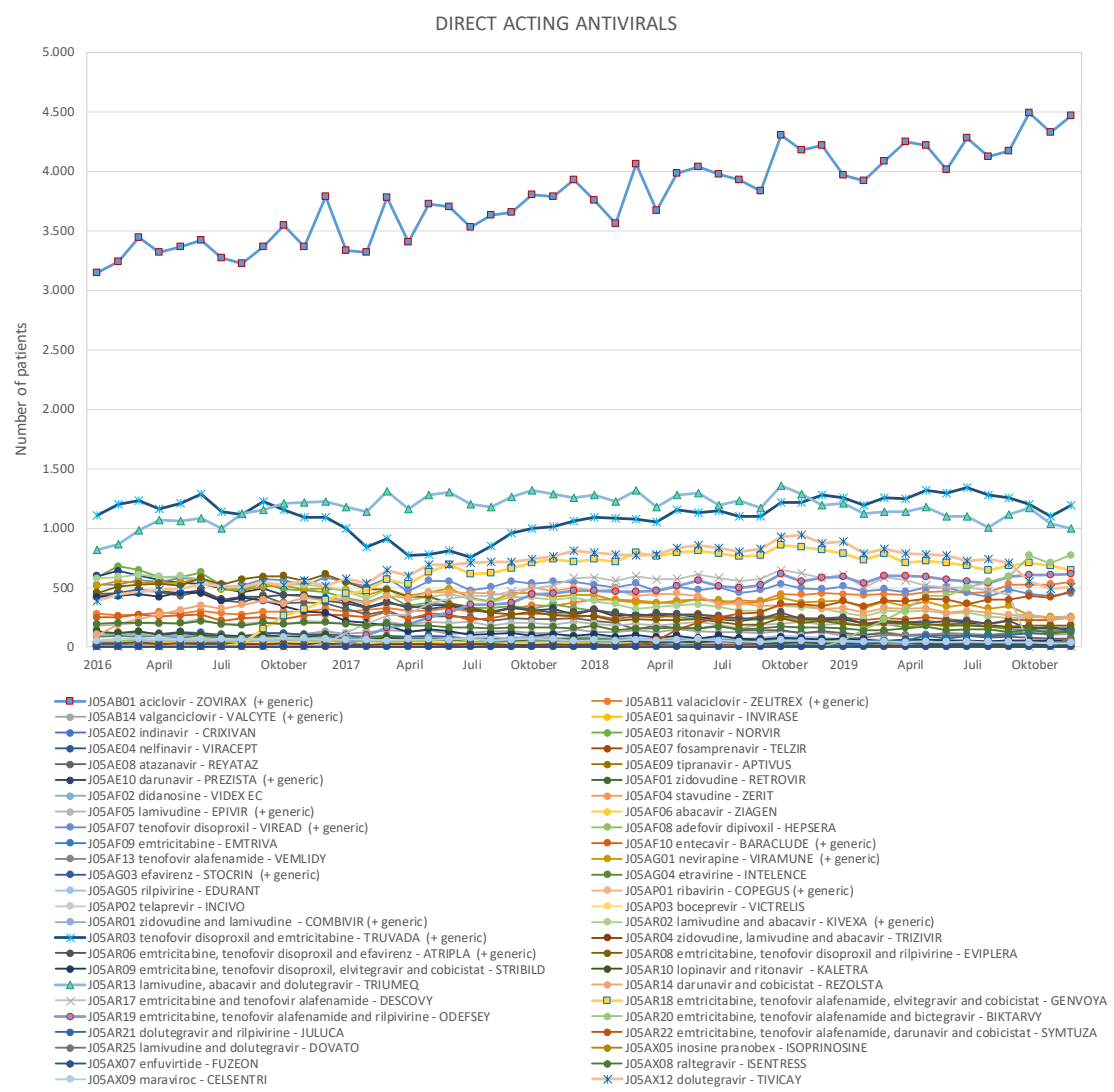
Figure 21: evolution of NIHDI net monthly expenditure (public pharmacies 2015 – 2019) for ATC class J05A direct acting antivirals



The greatest and most striking increase in expenditure is due to the pharmaceutical specialty Triumeq® (a fixed association of 3 antivirals, namely lamivudine + abacavir + dolutegravir). The antivirals with the new tenofovir salt, the tenofovir alafanemide, namely Genvoya®, Biktarvy® and Symtuza®, are also responsible for an increase in expenditure.

In addition, we see that the monthly expenditure for the pharmaceutical specialty Tivicay® increased for a time but now shows a downward trend.

Figure 22: evolution of number of patients per month (public pharmacies 2016 – 2019) for ATC class J05A direct acting antivirals

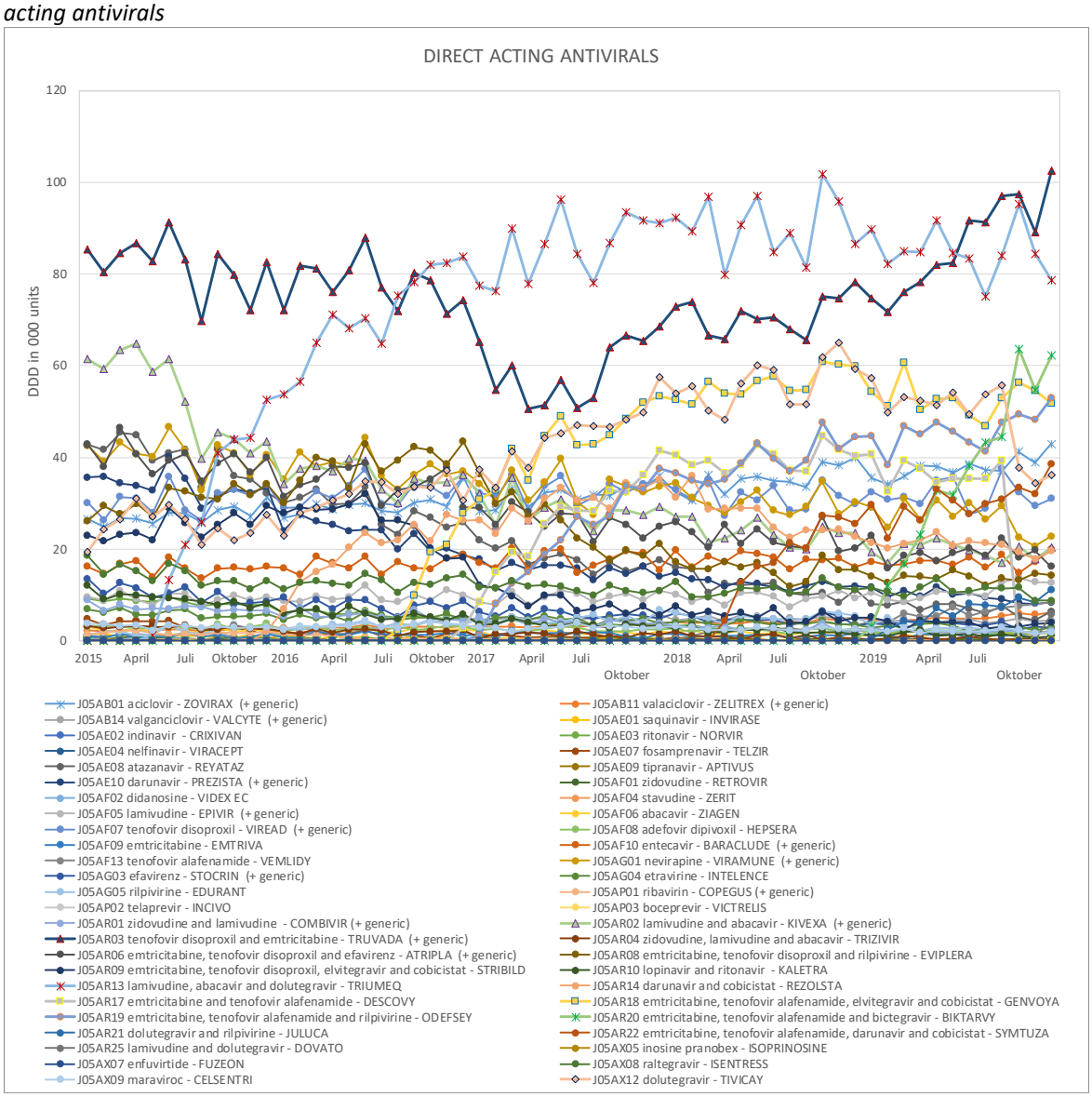


The graph above shows that the largest group of patients being treated with an antiviral are being treated for the herpes simplex virus. This requires the use of the pharmaceutical specialty Zovirax® (virus-inhibitor aciclovir). 15,692 patients are treated each year with Zovirax®.
Another, quite large group of patients being treated with antivirals are the HIV patients. On an annual basis, there are probably about 17,000 patients under medical supervision (source: Final 2018 AIDS Report of 18 November 2019, Sciensano). In the graph by month above, this group of patients is divided up because these patients are treated with different molecules, always in combinations.

The same Sciensano report shows that, between 1 June 2017 and 31 December 2018, 2,412 people were treated prophylactically with the pharmaceutical specialty Truvada® as part of a PrEP programme. In the graph by month above, an increasing use of Truvada® is visible from the second half of 2017.

The most-used antiviral, in terms of the number of patients, is the pharmaceutical specialty Triumeq®, which was overtaken by Truvada® at the end of 2019. The explanation for this is prophylactic treatment with Truvada® as part of a PrEP programme, as indicated above.

Figure 23: evolution of number of DDDs per month (public pharmacies 2015 – 2019) for ATC class J05A direct acting antivirals

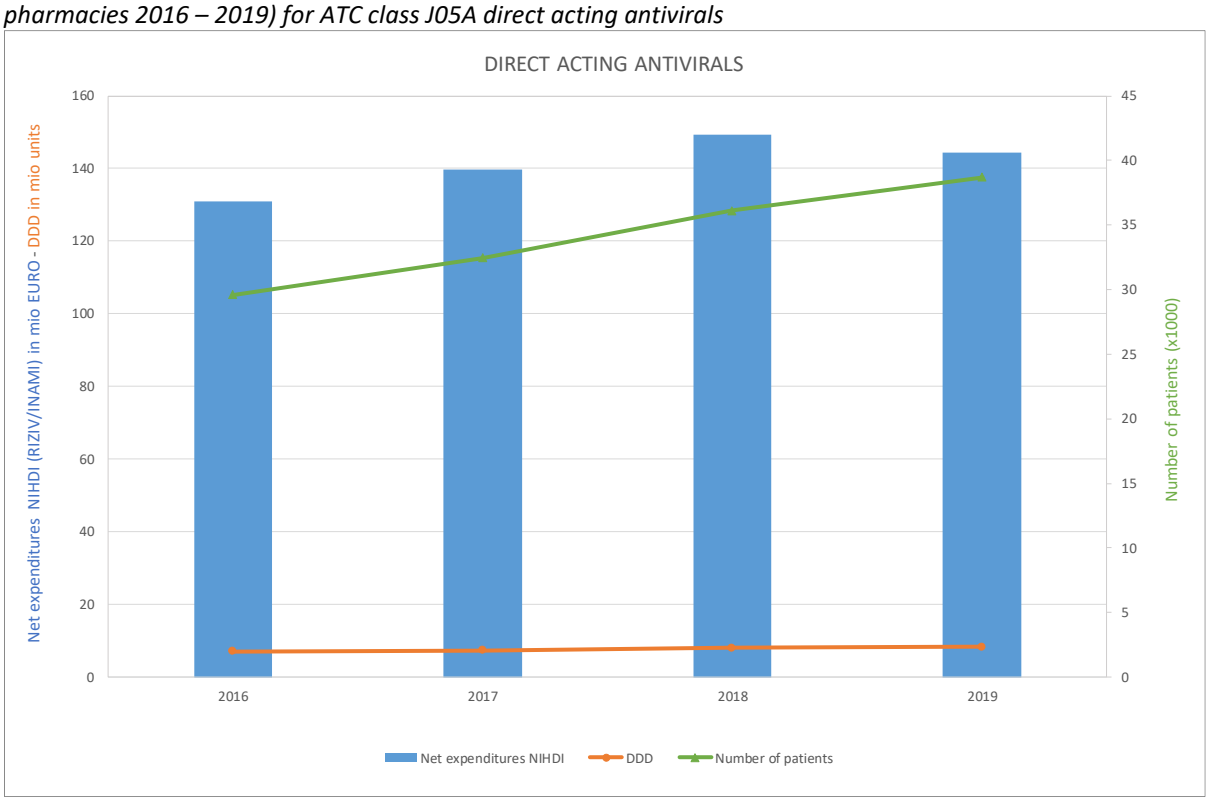


This graph, showing the evolution of the number of DDDs per month of direct acting antivirals, shows similar trends to the previous graph, which shows the evolution of the number of patients per month for this group of drugs:

- Increasing use of the pharmaceutical specialty Triumeq® (the most-used drug within the class)
- Increasing use of the pharmaceutical specialty Truvada® (from the second half of 2017 due to the PrEP programme)
- A shift in use of the pharmaceutical specialties with the old tenofovir disoproxil salt to the new tenofovir alafenamide salt, for example Genvoya®, Biktarvy® and Symtuza®.

The virus-inhibitor aciclovir, shown in the previous graph as the most used drug in terms of the number of patients per month, is only found in the peloton here. The explanation for this is that aciclovir is not usually administered chronically, so there are fewer DDDs for 1 treatment, by contrast with the other ongoing antiviral treatments.

Figure 24: evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2016 – 2019) for ATC class J05A direct acting antivirals

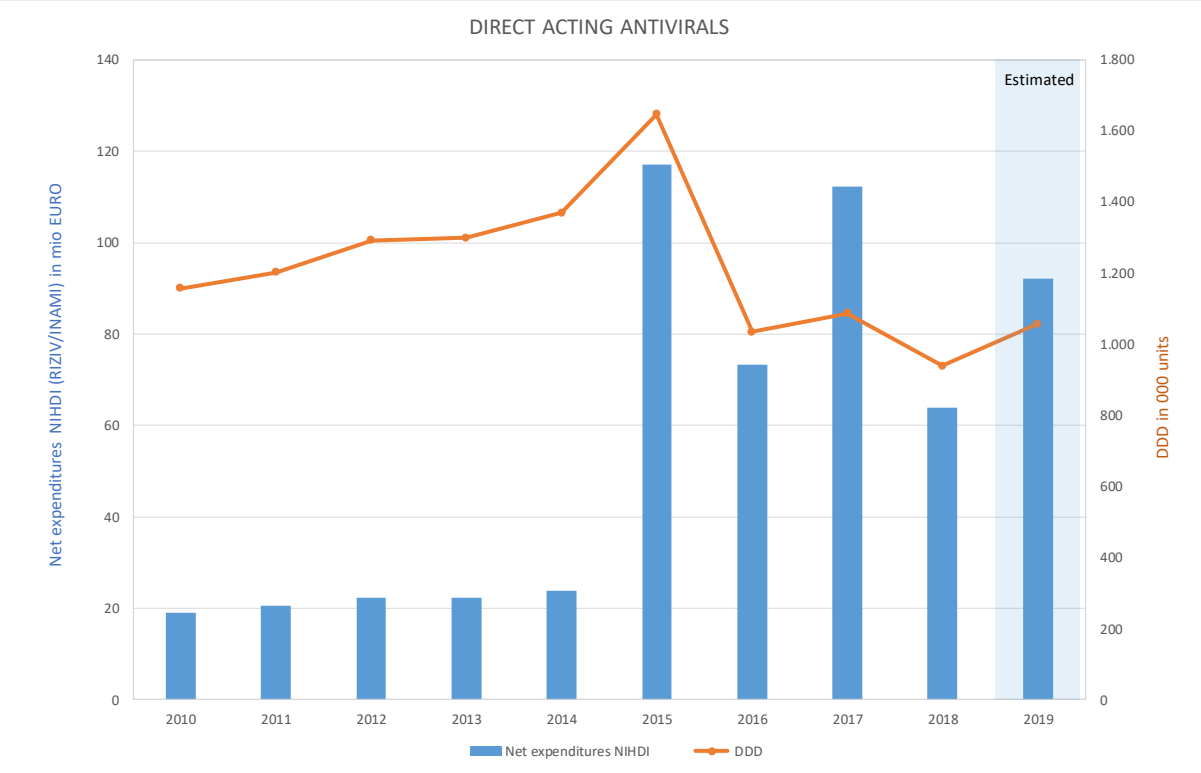


This graph shows the trends in expenditure in public pharmacies for ATC class J05A, direct acting antivirals, as discussed in general in the summary:

- An increase in the number of DDDs and in the number of patients treated (see also Figure 20).
- A peak in expenditure in 2018 followed by a fall in expenditure.

B) Hospitals

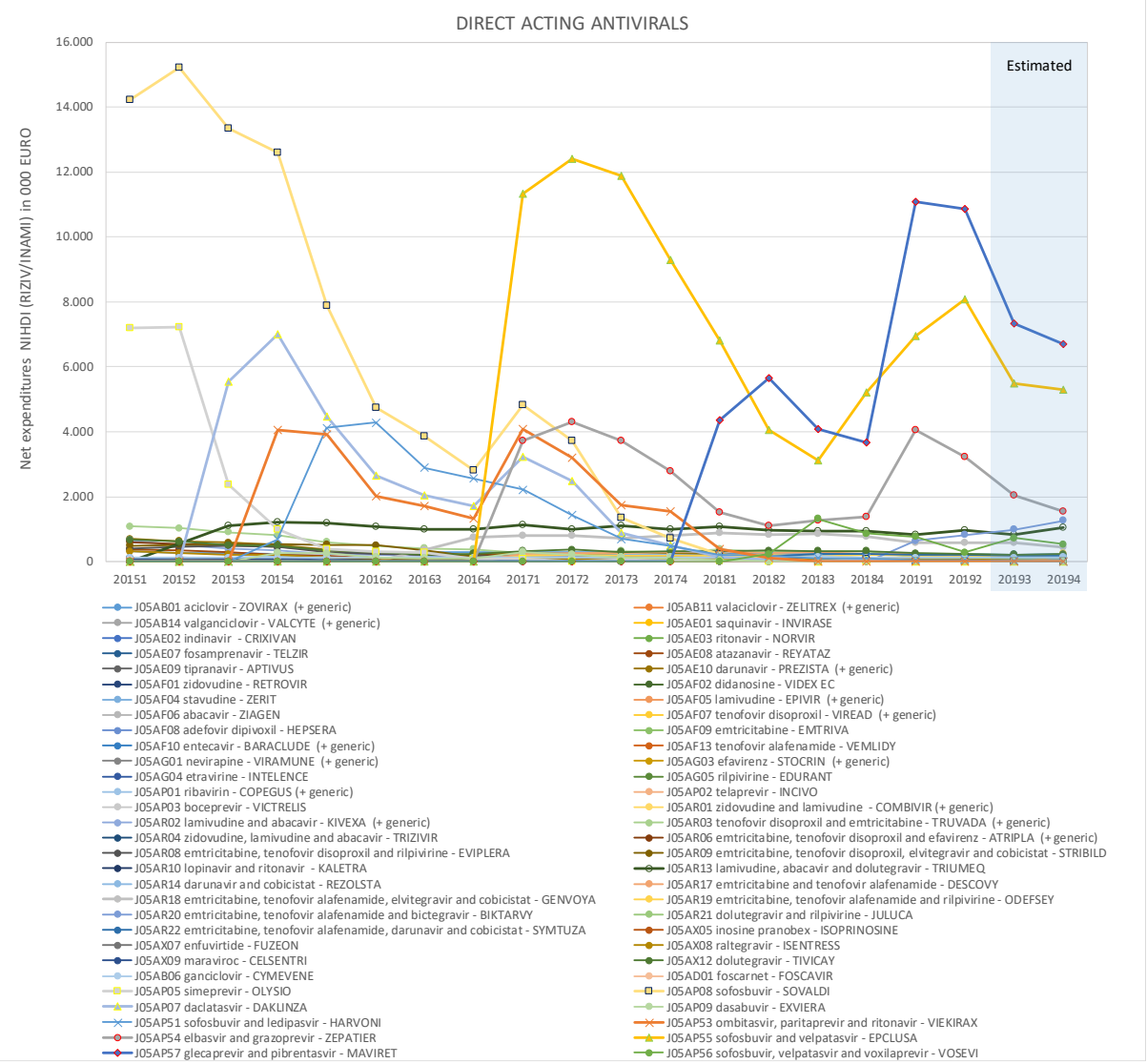
Figure 25: evolution of NIHDI net annual expenditure and number of DDDs (hospitals (all patients) 2010 – 2019) for ATC class J05A direct acting antivirals



The trends for HIV-infected patients treated with medication via the public pharmacies (see above) also apply in hospitals.

However, the illustration of these trends is distorted in the graph above by the anti-hepatitis C treatments which, in recent years, have been prescribed and reimbursed exclusively in hospitals. Since 1 January 2015, direct acting antivirals for hepatitis C – interferon-free regimens – are reimbursed, which has led to a surge in the number of DDDs and in expenditure. Reimbursement of these drugs was extended on 1 January 2017 and once again on 1 January 2019. This ripple effect is also visible in the graph above.

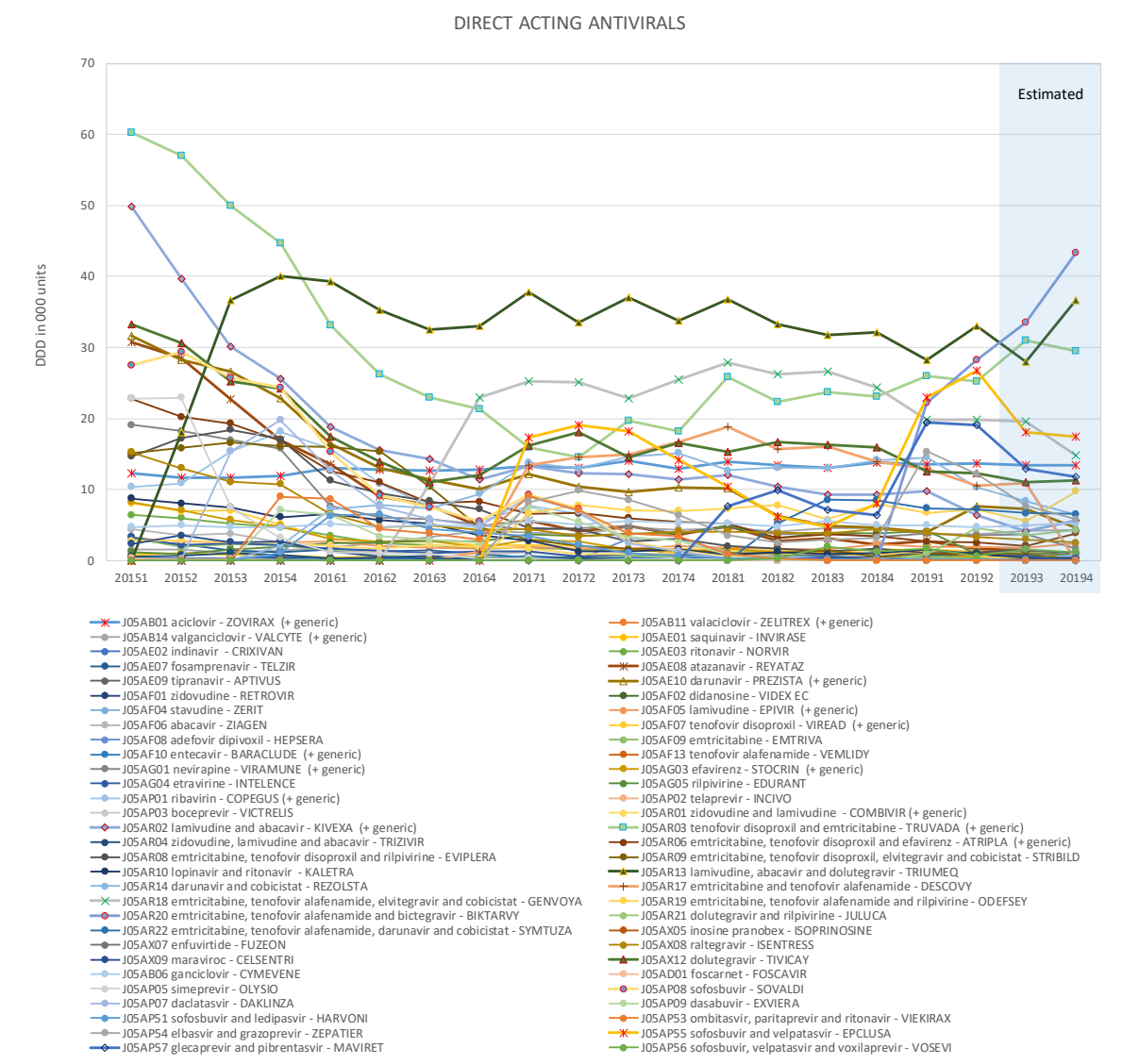
Figure 26: evolution of NIHDI net quarterly expenditure (hospitals (all patients) 2015 – 2019) for ATC class J05A direct acting antivirals



The ripple effect as a result of the ever-wider access to treatment with a hepatitis C virus-inhibitor (in 2015, 2017 and 2019), visible in the previous graph, is also present here; a second movement, however, is also visible - the short lifespan of these virus-inhibitors on the Belgian market.

For example, the pharmaceutical specialty Sovaldi®, the first hepatitis C virus-inhibitor, experienced a peak in 2015-2016 and then fell sharply, yet not to zero because this specialty was still included in other treatment schedules. First there was the rise and then downturn of the pharmaceutical specialties Olysio® and Daklinza®, then the rise and downturn of the pharmaceutical specialties Viekirax® and Exviera®, then the breakthrough of the pharmaceutical specialty Epclusa® (a combination preparation with Sovaldi® as one of the components) which fell for a time after the breakthrough, and finally there was the breakthrough of the pharmaceutical specialty Maviret® and to a lesser extent that of the pharmaceutical specialty Zepatier®.

Figure 27: evolution of number of DDDs per quarter (hospitals (all patients) 2015 – 2019) for ATC class J05A direct acting antivirals



In the graph above, which shows the number of DDDs per quarter in the hospitals, it is striking that hepatitis C inhibitors do not account for the highest number of DDDs. In the course of the months in 2019, the only curve which stands out is for the pharmaceutical specialty Epclusa®.

This graph primarily shows the trends for HIV-inhibitors, already discussed, notably a decrease in the number of DDDs for the pharmaceutical specialties Truvada® and Kivexa® and an increase, month on month, of the number of DDDs for the specialties Triumec,® Genvoya® and Biktarvy®.

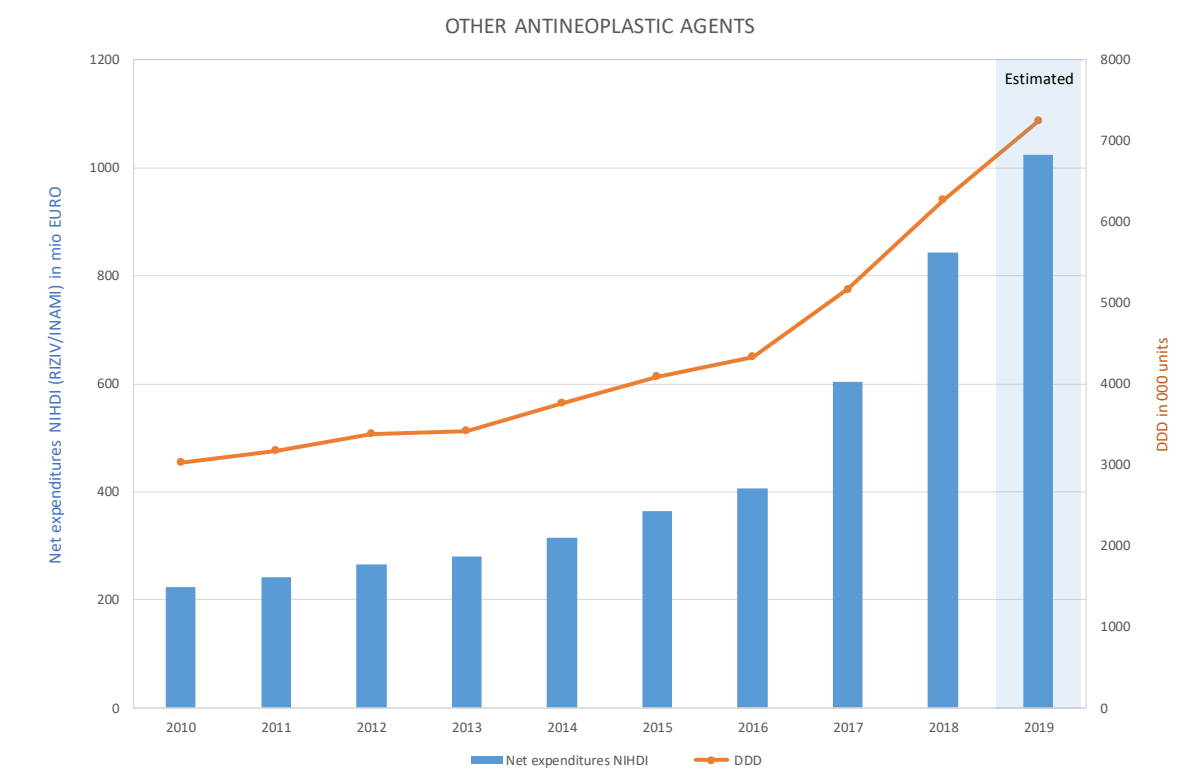
L01X – OTHER ANTINEOPLASTIC AGENTS

For many years now, clear growth has been noticeable in both the net expenditure and the number of DDDs for ATC class L01X. This growth has increased strikingly since 2017, particularly net expenditure. Whereas the annual growth percentages were about 10% between 2010 and 2016, we are seeing much higher growth percentages in recent years:

- 49% in 2017 versus 2016
- 40% in 2018 versus 2017
- 21% in 2019 versus 2018

The fact that net expenditure is increasing faster than the usage in DDDs is probably due to the fact that this class mainly contains innovative drugs.

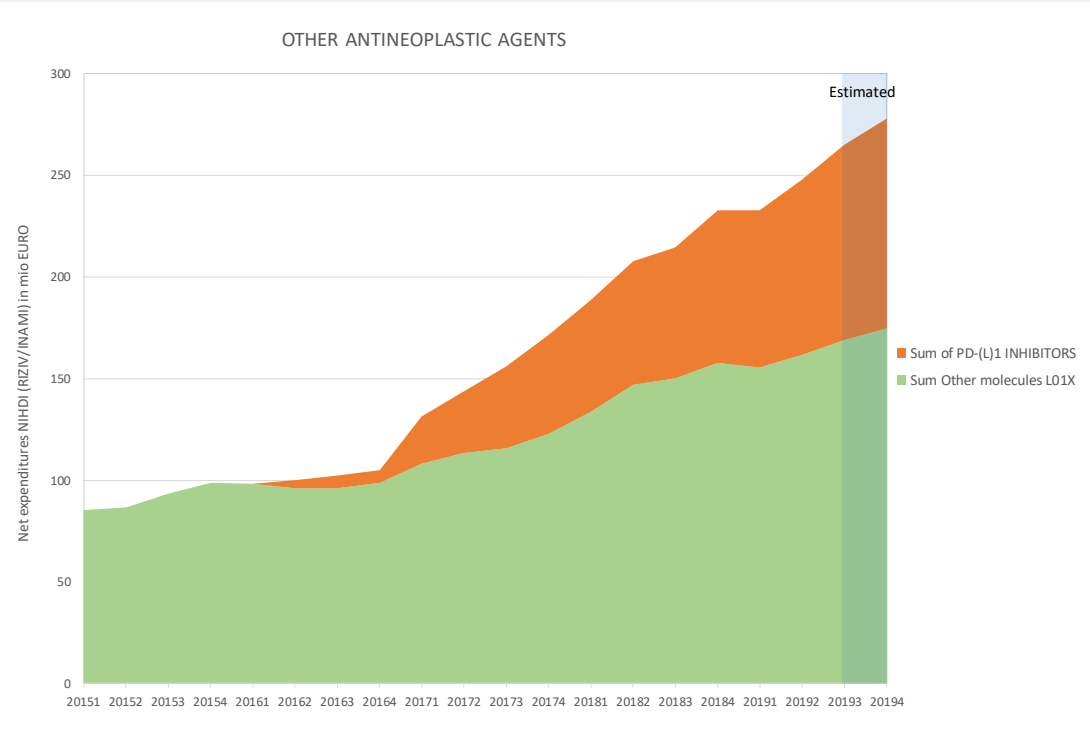
Figure 28: evolution of NIHDI net annual expenditure and number of DDDs (hospitals (all patients) 2010 – 2019) for ATC class L01X other antineoplastic agents



What is striking in the NIHDI net expenditure on 'other antineoplastic agents', is that a number of new molecules have come onto the market and are responsible for a significant part of the expenditure.

We see that 2 molecules, nivolumab (Opdivo®) and pembrolizumab (Keytruda®), experienced strong growth at the beginning of 2017. Both molecules had already been included in the list of reimbursable pharmaceutical specialties in the 2nd quarter of 2016, both in the indication 'advanced melanoma in adult patients'. 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 pharmaceutical specialties. In the meantime, (October 2020) there are 8 sorts of tumours for which PD(L)-1 inhibitors are reimbursed, so that many patients are also eligible for a treatment with one of these molecules. For an overview of the indications registered by the EMA, we refer you to the overview table included in annex 3 of this report. All these specialties 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 29: evolution of NIHDI net annual expenditure (hospitals (all patients) 2010 – 2019) for ATC class L01X other antineoplastic agents: PD-(L)1-inhibitors versus other molecules



Another molecule that accounts for a significant part of the expenditure in ATC-class L01X, is palbociclib. The specialty based on palbociclib, Ibrance®, has been reimbursed since 01/12/2017 for the treatment of women with hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer. Palbociclib was the first of the so-called CDK4/6 inhibitors to be reimbursed in Belgium; in the meantime, two other molecules are reimbursed in the same indication: ribociclib or Kisqali® and abemaciclib or Verzenios®. In Belgium, breast cancer is the most common tumour in women, and just over 2,300 patients received reimbursement for their CDK4/6 inhibitor in 2018.

A fourth molecule that has had remarkable growth in recent years is daratumumab (Darzalex ®). Darzalex® was originally only reimbursed in monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, for whom the previous treatment consisted of a proteasome inhibitor and an immunomodulating drug and who have shown a progression of the disease at the time of the last treatment; this was the case from 1 March 2017. On 1 March 2018 there was an extension of indication for Darzalex®, resulting in a further increase in expenditure. Since that date, this specialty is also reimbursable in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have had at least 1 earlier treatment.

Just like nivolumab and pembrolizumab, these last two molecules are also temporarily included in the list of reimbursable pharmaceutical specialties, on the basis of a convention concluded between the company and the NIHDI. This is the case for all specialties that form part of the top 10 net expenditures for ATC class L01X, with the exception of Herceptin®, Mabthera® and certain indications of Avastin®.

Until 2016, Herceptin® (trastuzumab) accounted for the most significant part of the expenditure on 'other antineoplastic agents' in hospitals. We see that the expenditure on Herceptin® has now been largely overtaken by the molecules mentioned above. In addition, Herceptin® has undergone various price reductions over the past years:

- On 01/01/2018: application of the 'old medicines' measure as a result of the fact that Herceptin® had been reimbursed for 15 years. The ex-factory price fell by 2.41%.
- On 01/01/2019: application of the 'biocliff' principle as a result of effective availability of a biosimilar on the market, with a resulting 15% reduction in the ex-factory price.

Figure 30: evolution of NIHDI net quarterly expenditure (hospitals (all patients) 2015 – 2019) for ATC class L01X other antineoplastic agents – Top 10

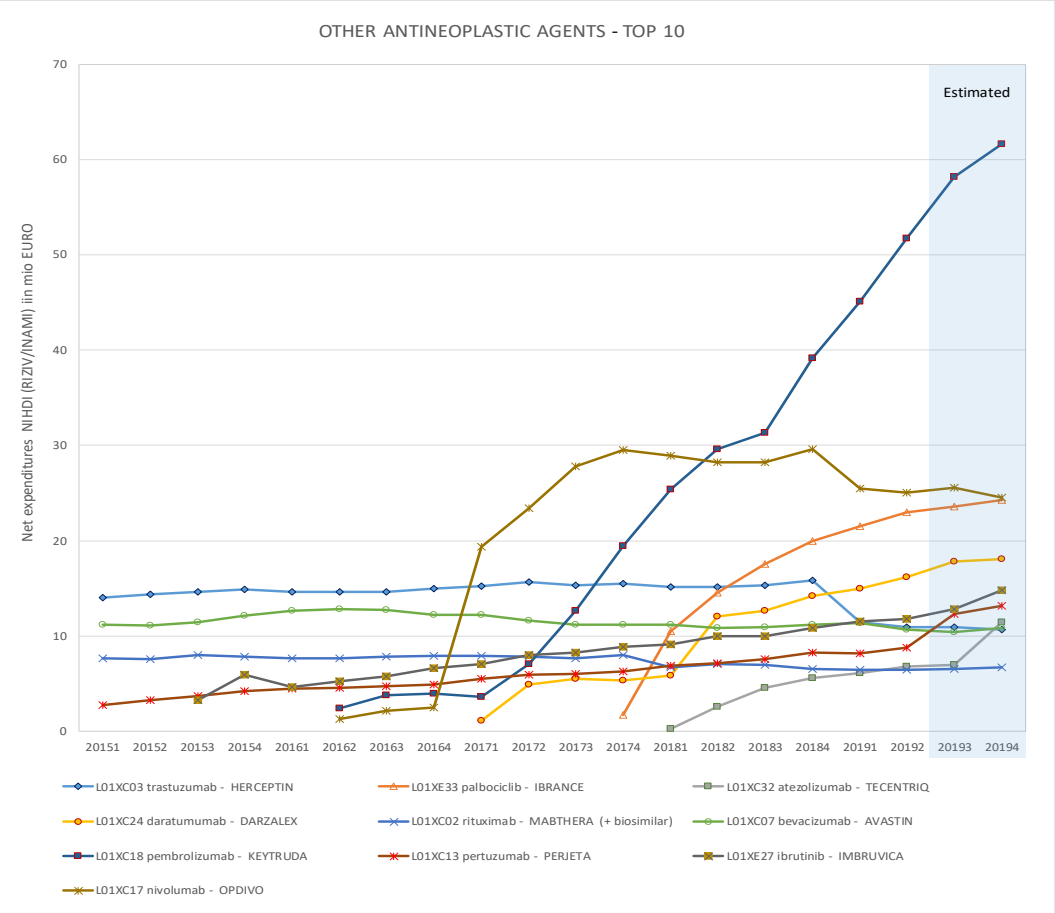
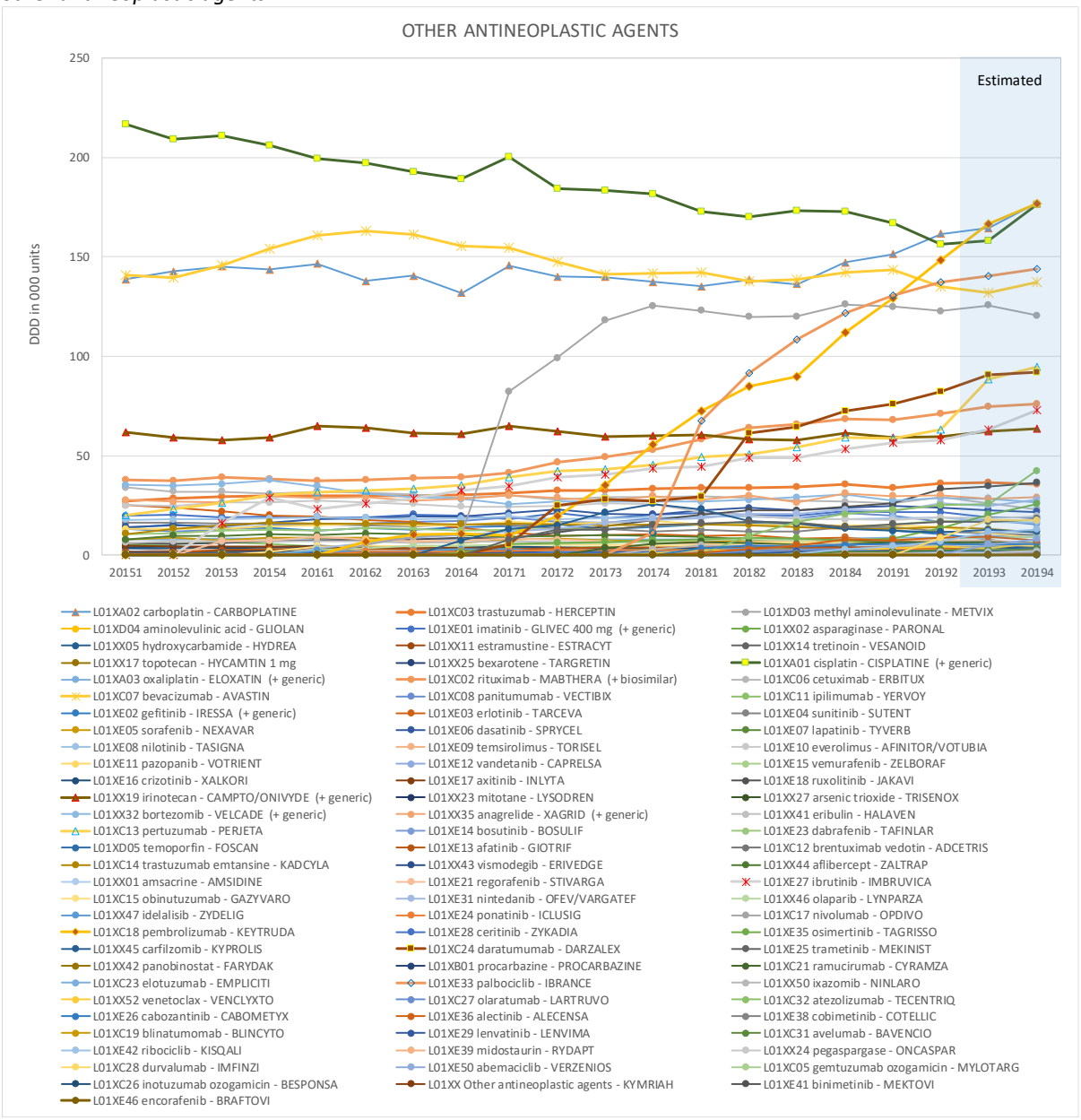


Figure 31: evolution of number of DDDs per quarter (hospitals (all patients) 2015 – 2019) for ATC class L01X other antineoplastic agents

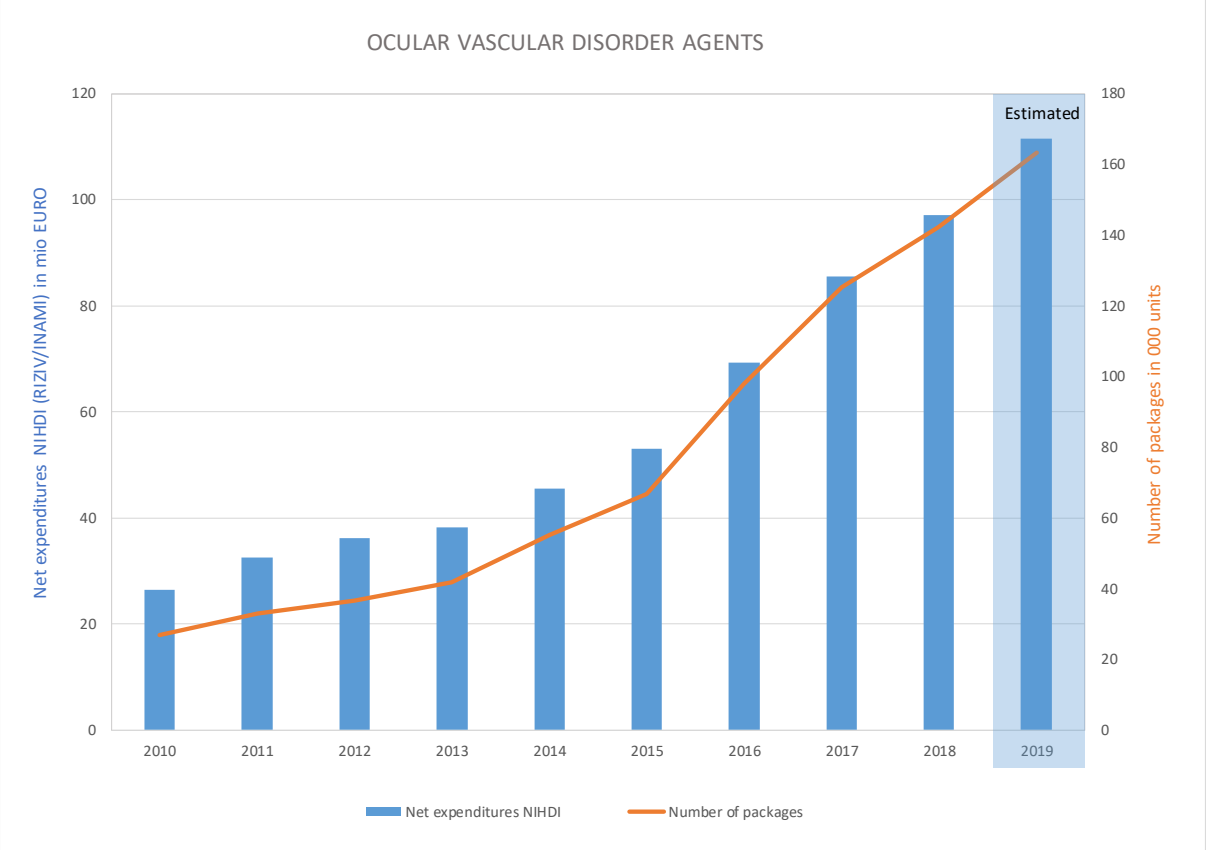


For a detailed analysis we refer you to page 19, L04A – Immunosuppressants.

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).
The first indication that became reimbursable was neovascular (wet) age-related macular degeneration.

Figure 32: evolution of NIHDI net annual expenditure and number of packages (hospitals (all patients) 2010 – 2019) for ATC class S01L ocular vascular disorder agents



The WHO has not defined a DDD for these products. Each intraocular injection requires packaging (an injection vial or pre-filled pen).

The following factors help to explain the increase in the use of these molecules during the past years:

- Over the course of time, a gradual addition of new reimbursable indications: (in chronological order) macular oedema following central retinal vein occlusion, diabetic macular oedema, macular oedema as a result of a branch retinal vein occlusion, loss of visual acuity as a result of the neovascular choroidal form.
- The indications for the treatment of age-related macular degeneration, eligible for reimbursement, were extended in 2014; in 2016 there was a lifting of the restrictions imposed by the health insurance on the number of reimbursable injections and the duration of the treatment.

With regard to the evolution of expenditure, we identify various price reductions related to the extension of the reimbursable indications. Since 2016, Eylea ® and Lucentis ® have been 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.

The following graphs show the breakdown per product (expenditure and number of units used).

Figure 33: evolution of NIHDI net quarterly expenditure (hospitals (all patients) 2015 – 2019) for ATC class S01L ocular vascular disorder agents

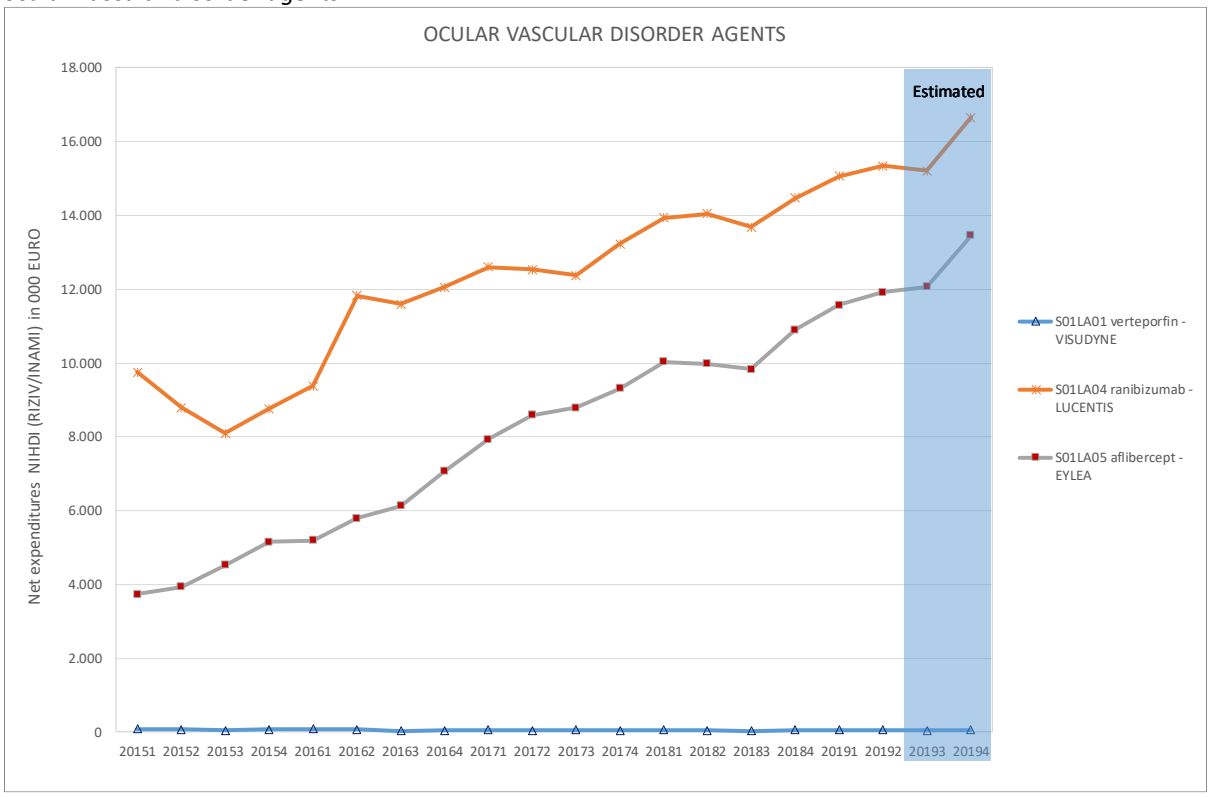
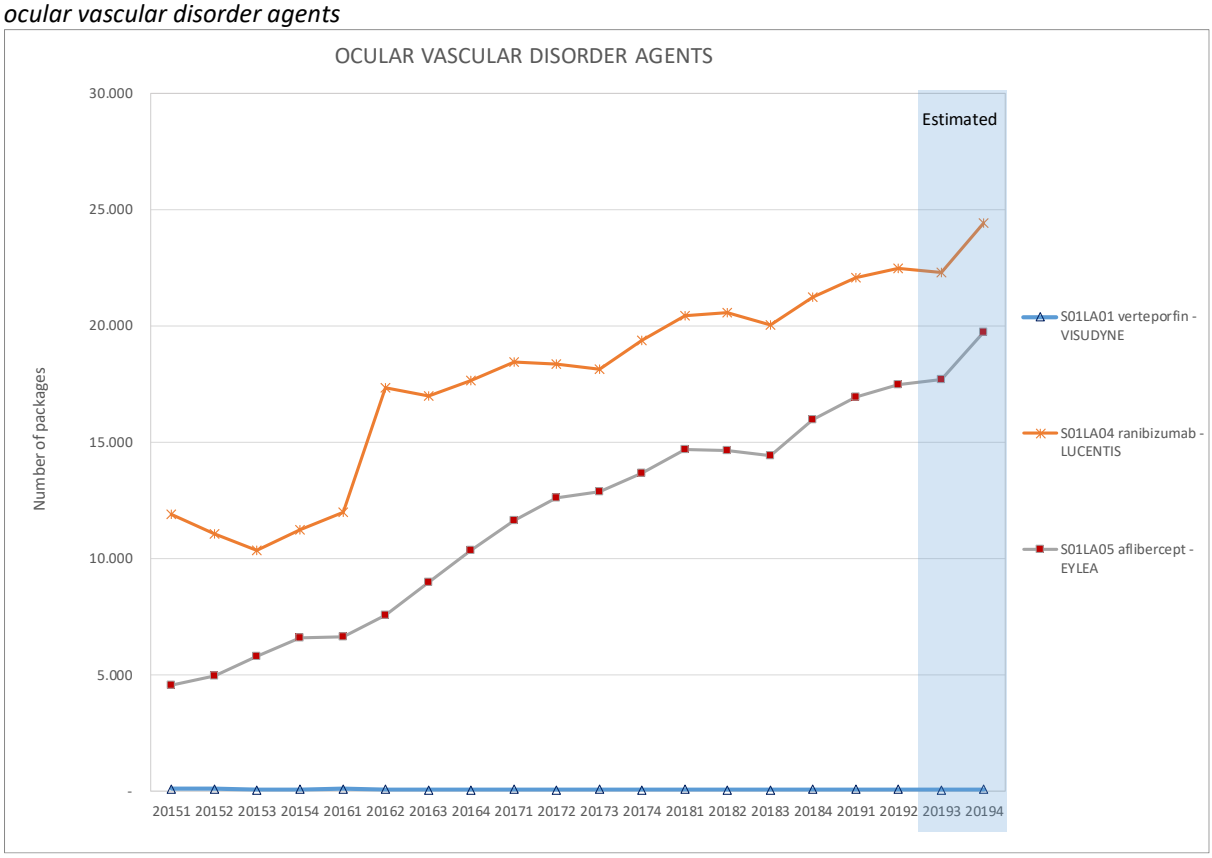


Figure 34: evolution of number of packages per quarter (hospitals (all patients) 2015 – 2019) for ATC class S01L ocular vascular disorder agents



Other groups with significant evolutions

A10 – DRUGS USED IN DIABETES

Figure 35: evolution of NIHDI net annual expenditure (public pharmacies 2010 - 2019) for ATC class A10 drugs used in diabetes

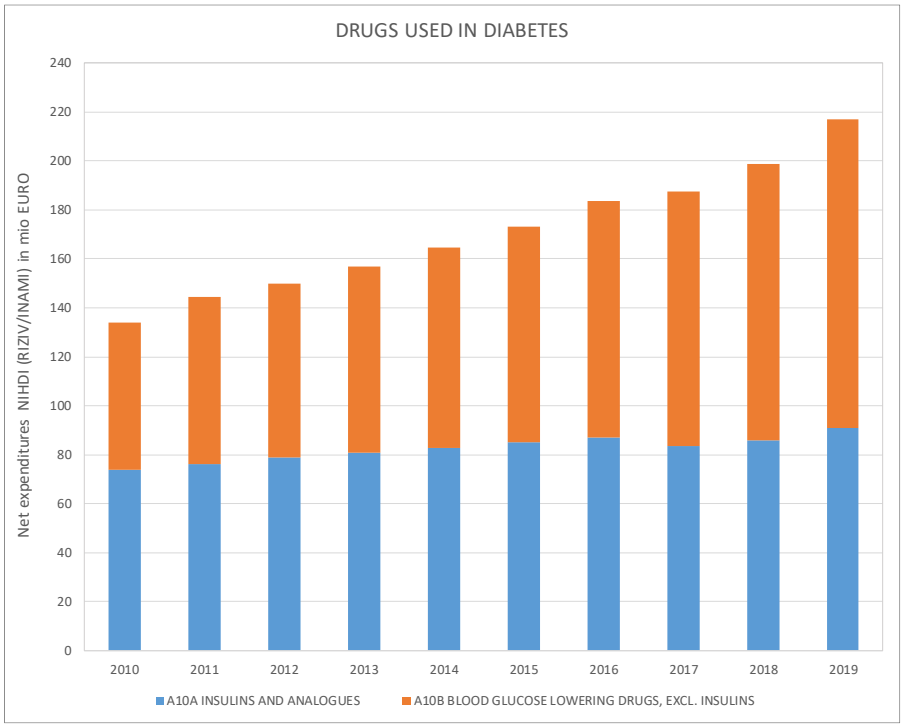
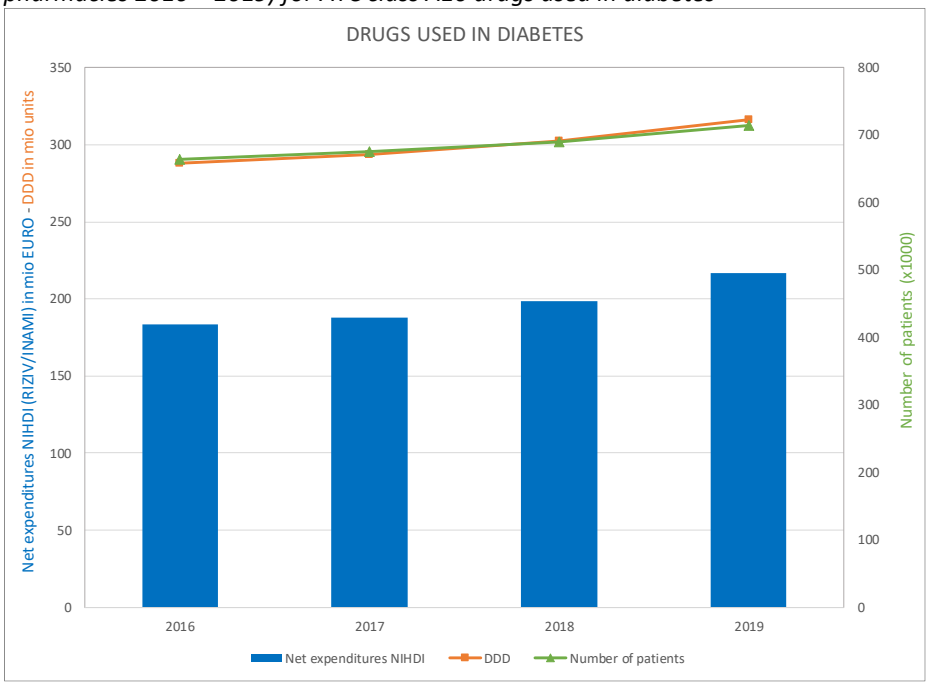


Figure 36: evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2016 – 2019) for ATC class A10 drugs used in diabetes



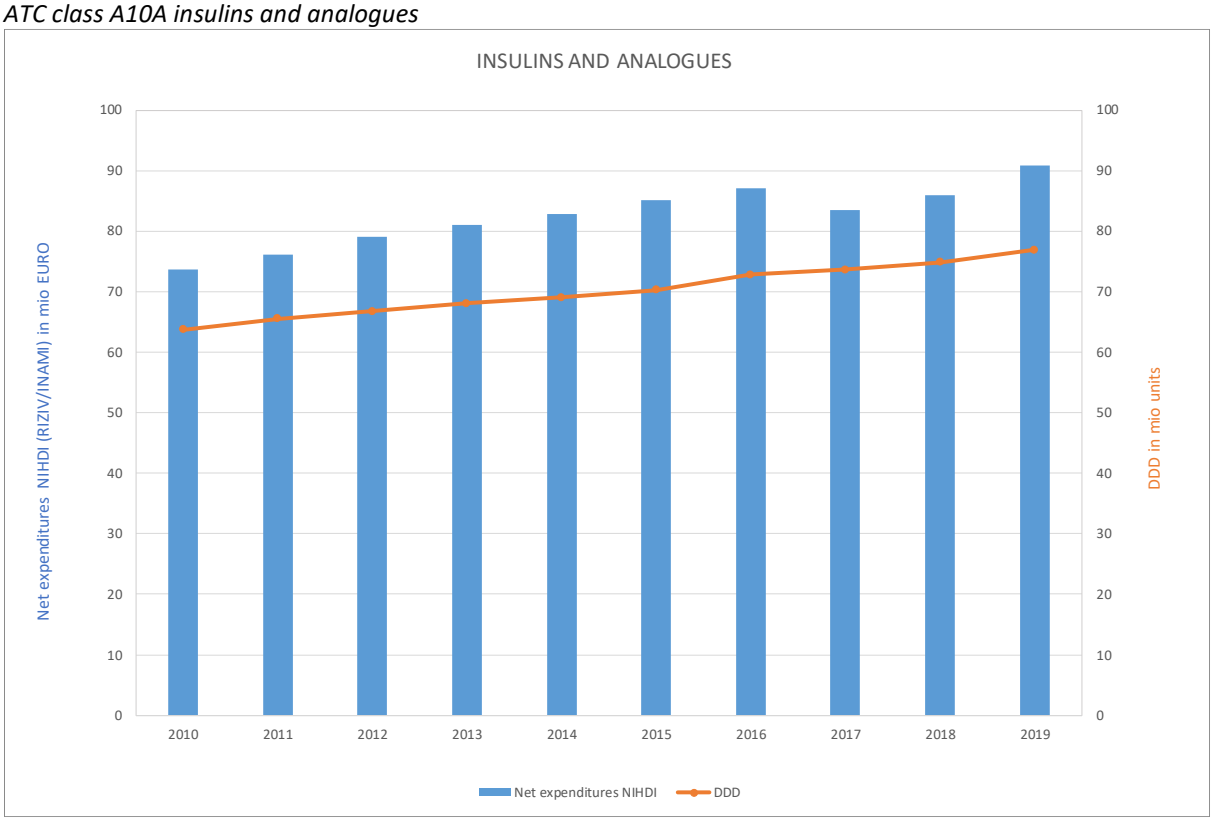
The general increase in the expenditure on drugs used in diabetes goes hand in hand with the increase in the number of patients, but is also explained by the use of more expensive drugs, for example from the class of incretin mimetics or gliflozins.

NIHDI net expenditure on insulin and insulin-analogues decreased slightly between 2016 and 2017 but since then has continued to increase moderately and steadily. The arrival of cheaper competitors of long-acting insulin-analogues (notably insulin glargine and insulin aspart) should explain this reduction.

The increase in NIHDI net expenditure is higher for oral treatments and incretin mimetics; however, the specialties in the gliflozins class are all temporarily included in the list of reimbursable drugs, via conventions. The actual net expenditure is therefore lower than indicated in the graph.

A10A - INSULINS AND ANALOGUES

Figure 37: evolution of NIHDI net annual expenditure and number of DDDs (public pharmacies 2010 – 2019) for ATC class A10A insulins and analogues



The Commission for Reimbursement of Medicines estimated in 2016 and 2017 that the arrival of competitors for insulin glargine and insulin aspart respectively would lead to savings, which can be seen in the graph above.

Figure 38: evolution of NIHDI net monthly expenditure (public pharmacies 2015 – 2019) for ATC class A10A insulins and analogues

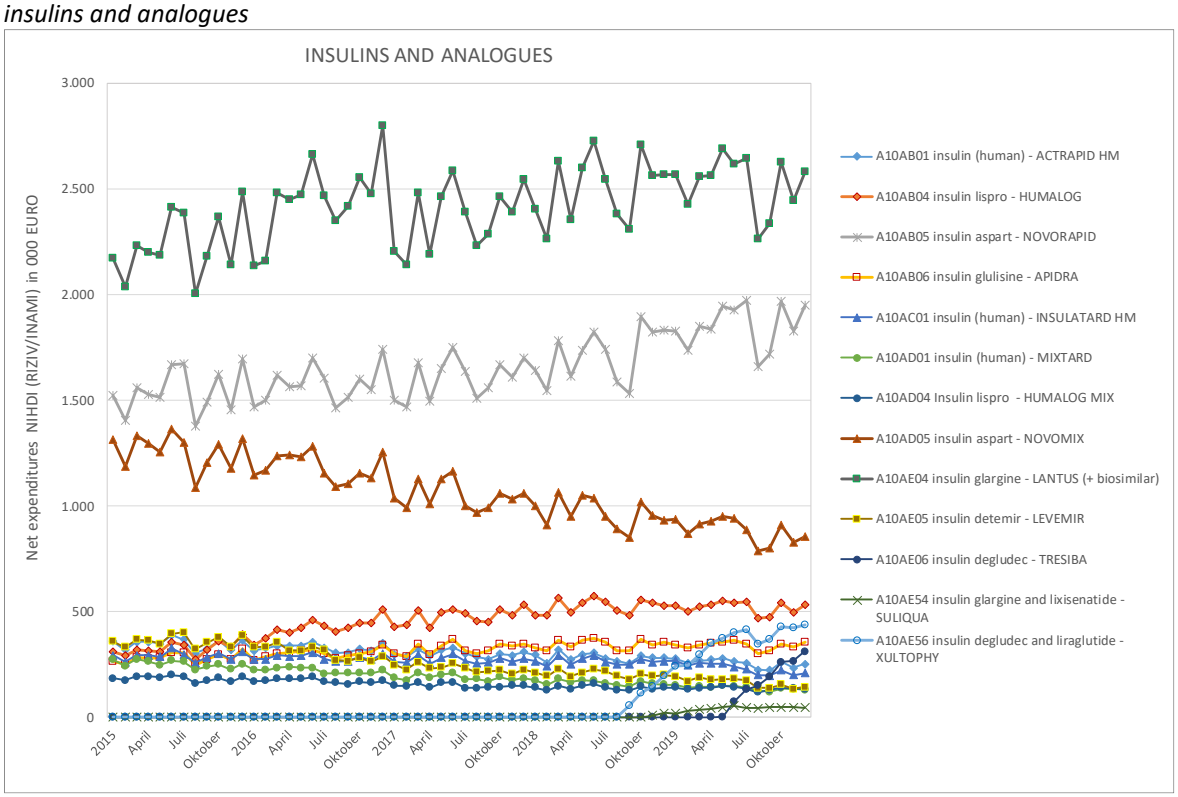


Figure 39: evolution of number of DDDs per month (public pharmacies 2015 – 2019) for ATC class A10A insulins and analogues

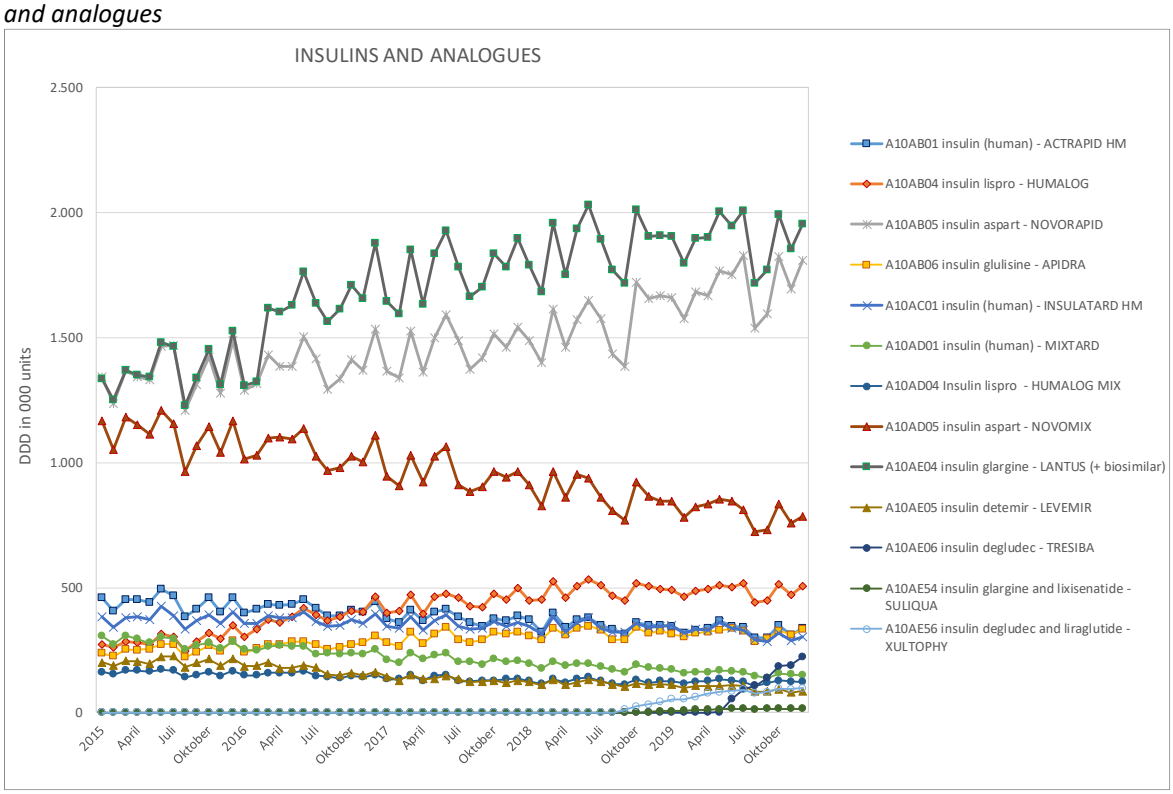
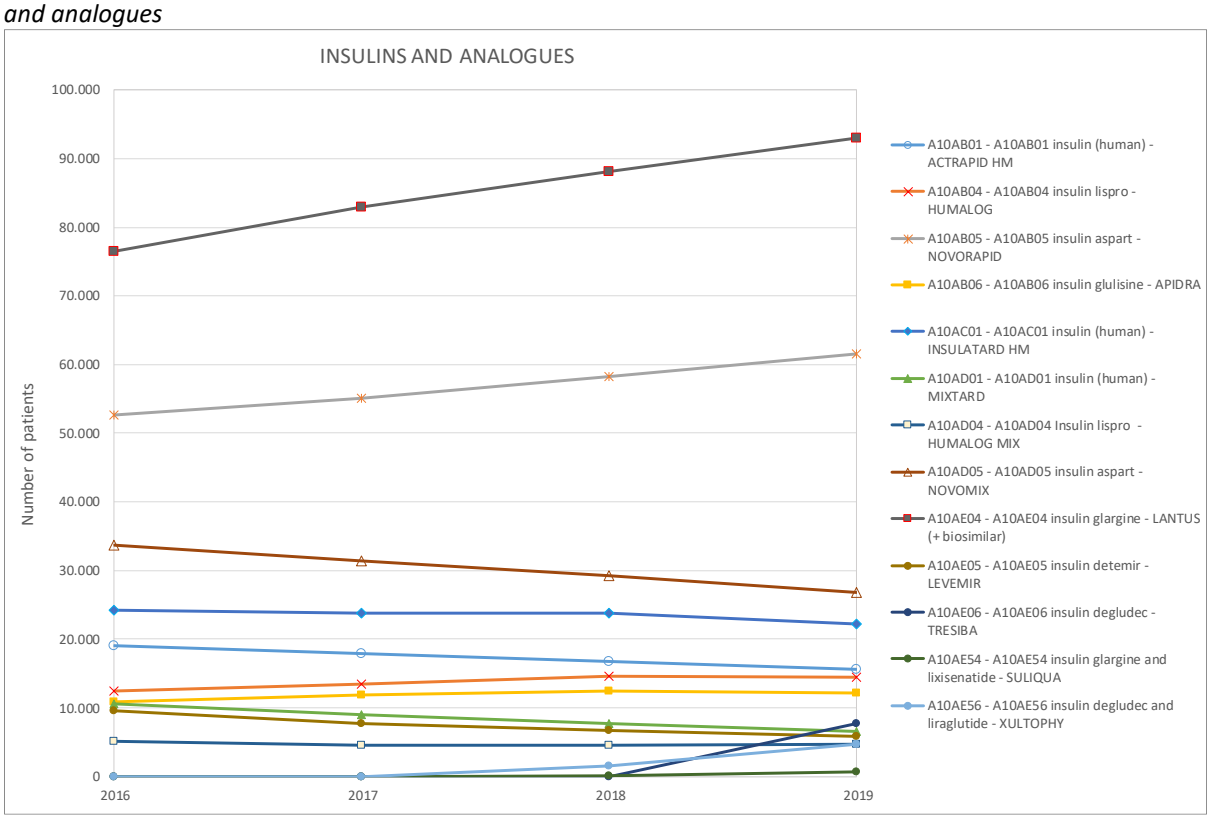


Figure 40: evolution of number of patients per year (public pharmacies 2016 – 2019) for ATC class A10A insulins and analogues



The 3 tables above show a fall in the use of pre-mixed insulin preparations (Novomix® for example).

Three new specialties have become reimbursable since the previous MORSE-report (2018 report, 2016 data): Tresiba® (insulin degludec), Suliqua® (mix of insulin glargine and an incretin mimetic) and Xultophy® (mix of an insulin degludec and an incretin mimetic).

Figure 41: evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2016 – 2019) for ATC class A10A insulins and analogues

A10B - BLOOD GLUCOSE LOWERING DRUGS, EXCLUDING INSULINS

The graph below shows that the NIHDI net expenditure on oral treatments and incretin mimetics has been increasing steadily since 2010. It also indicates that the costs per DDD have been increasing significantly since 2014, which can be explained by the arrival of more expensive drugs, such as those from the class of incretin mimetics or gliflozins. With regard to the gliflozins, all specialties are temporarily eligible for reimbursement via conventions. The actual net expenditure is therefore lower than indicated in the graph.

Figure 42: evolution of NIHDI net annual expenditure and number of DDDs (public pharmacies 2010 – 2019) for ATC class A10B blood glucose lowering drugs, excluding insulins

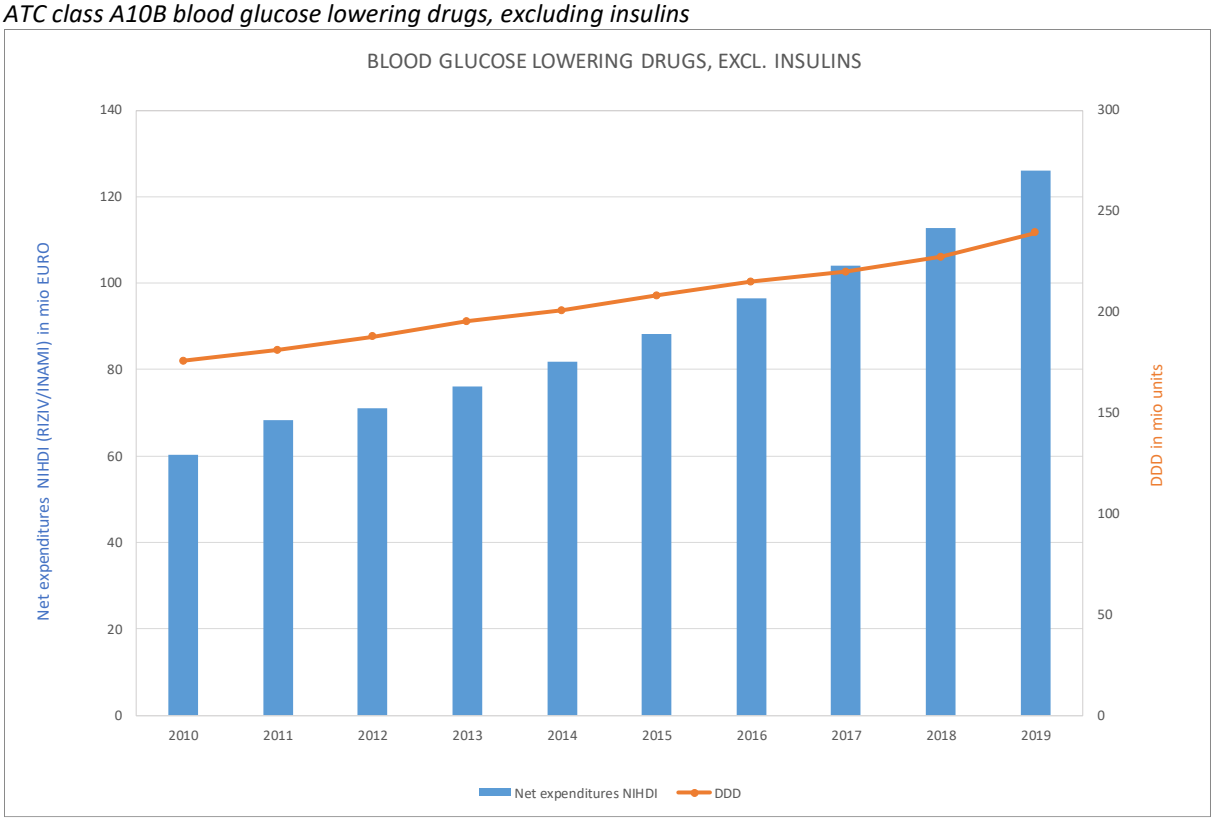
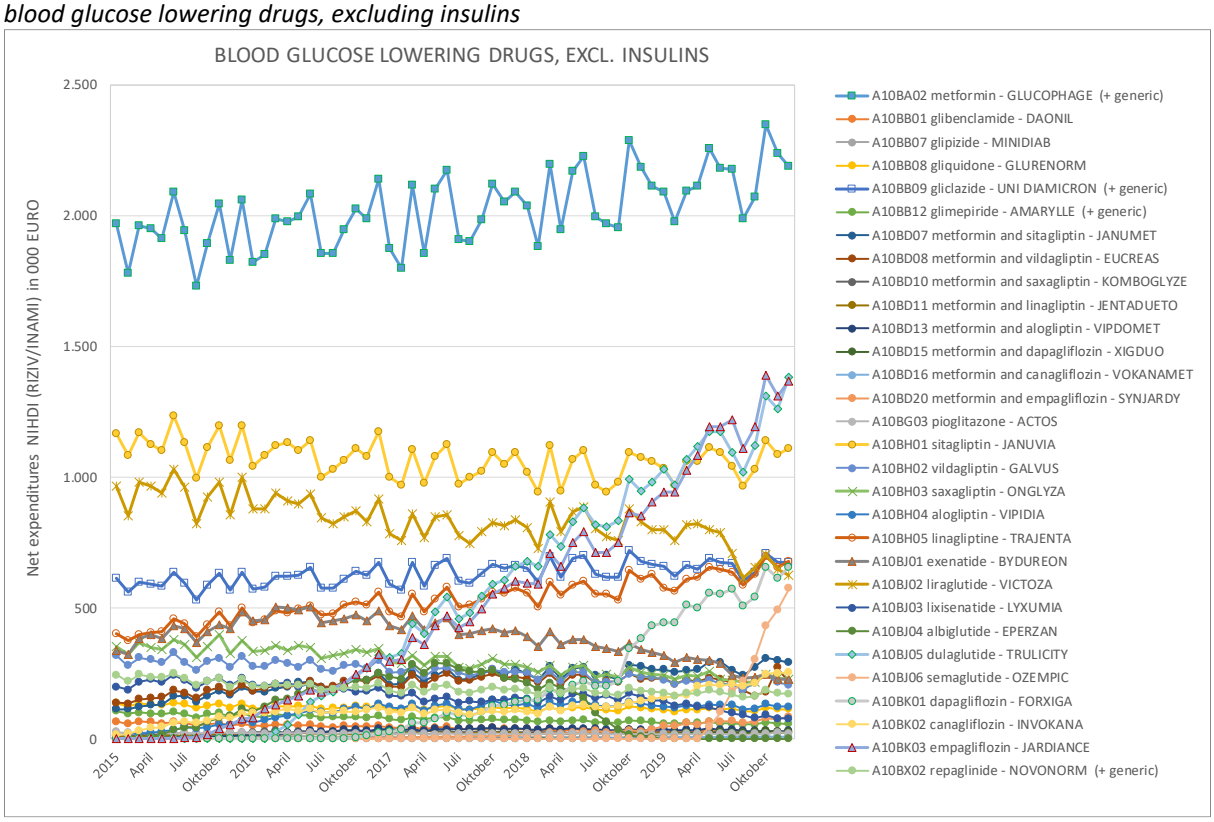


Figure 43: evolution of NIHDI net monthly expenditure (public pharmacies 2015 – 2019) for ATC class A10B blood glucose lowering drugs, excluding insulins



The graph above clearly shows the rapid increase in expenditure on drugs based on gliflozins (Forxiga® & Jardiance®, for example), which cost more than certain incretin mimetics. We can also see an increase in expenditure on the latter, except Victoza® (probably in favour of Ozempic®). The prices of incretin mimetics have decreased by 10% since 1 July 2019 as a result of the group diabetes review: a fall in expenditure should therefore be observable in a following analysis.

Figure 44: evolution of number of DDDs per month (public pharmacies 2015 – 2019) for ATC class A10B blood glucose lowering drugs, excluding insulins

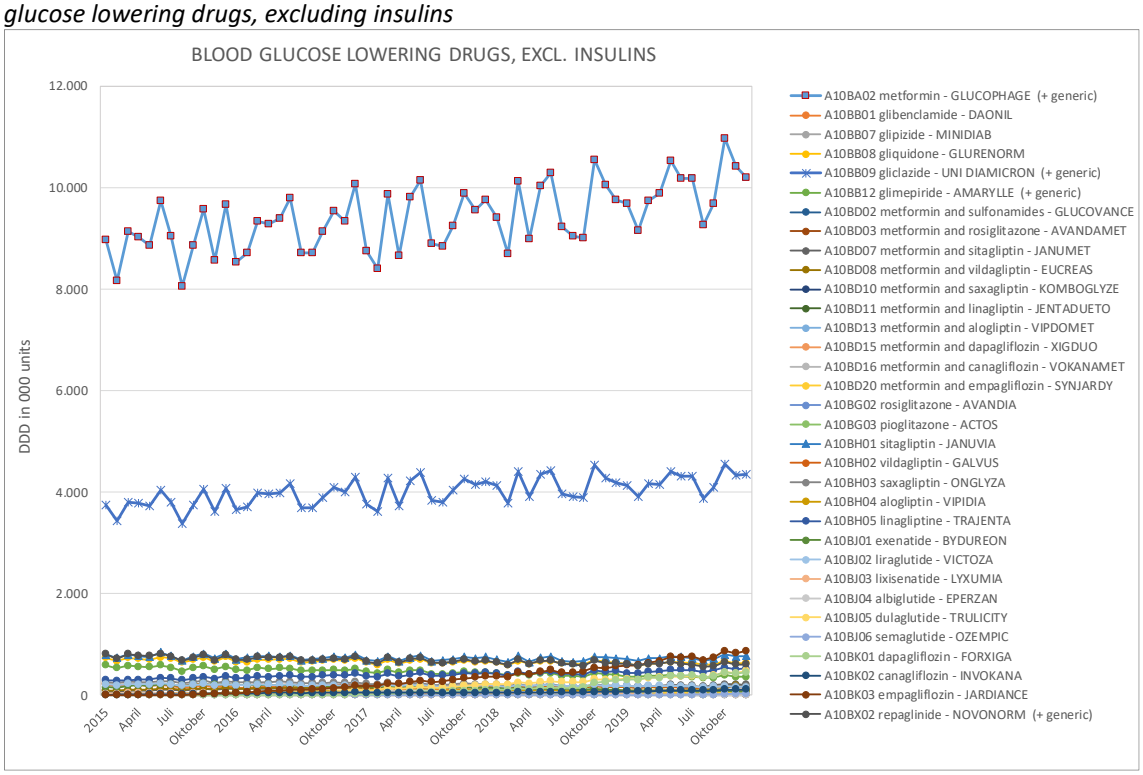
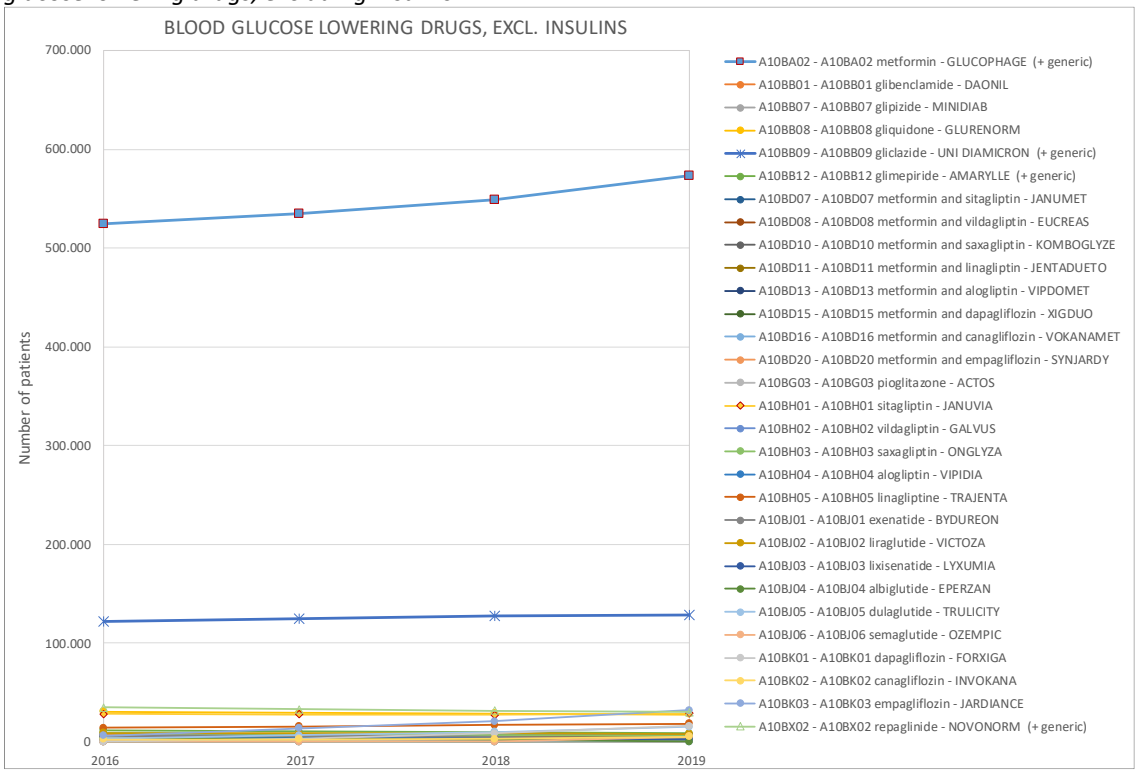
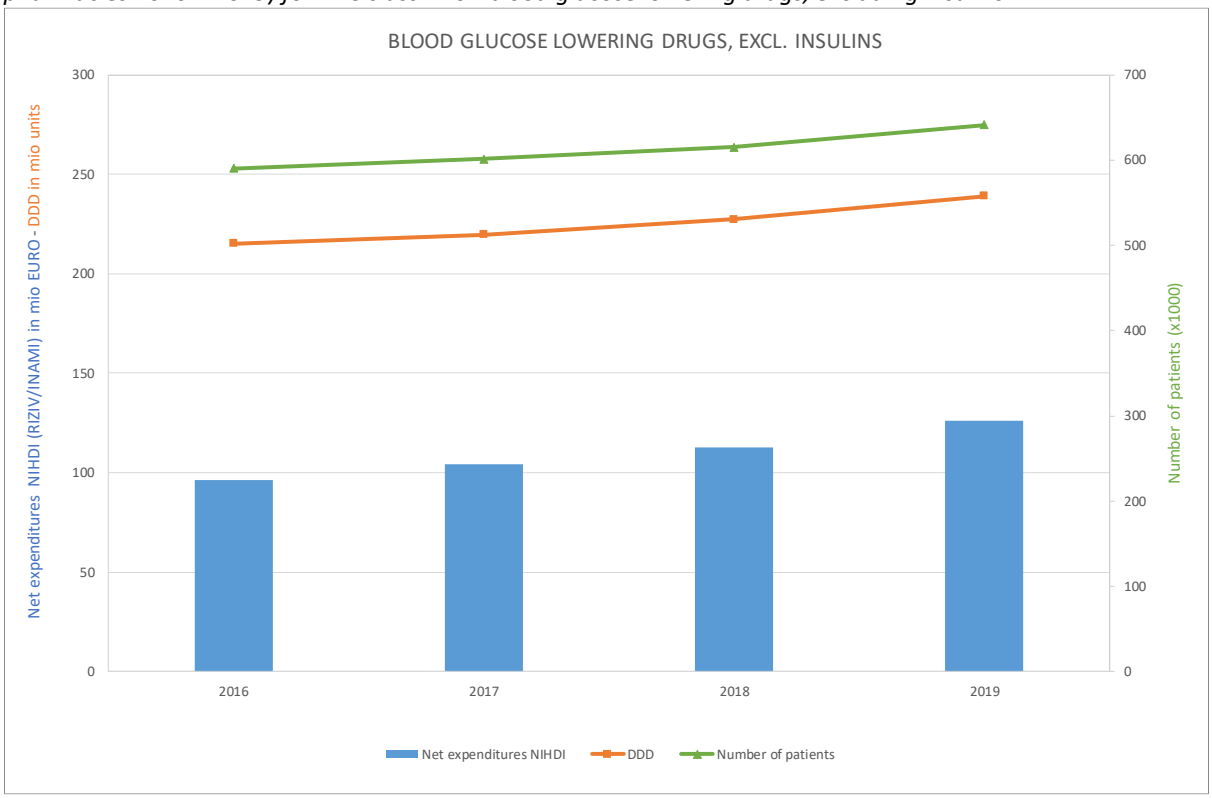


Figure 45: evolution of number of patients per year (public pharmacies 2016 – 2019) for ATC class A10B blood glucose lowering drugs, excluding insulins



The last 2 graphs 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 specialties based on gliflozins is perhaps less clearly visible here, but nevertheless involves approximately 50,000 patients per year.

Figure 46: evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2016 – 2019) for ATC class A10B blood glucose lowering drugs, excluding insulins



R03 – DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES

GENERAL

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

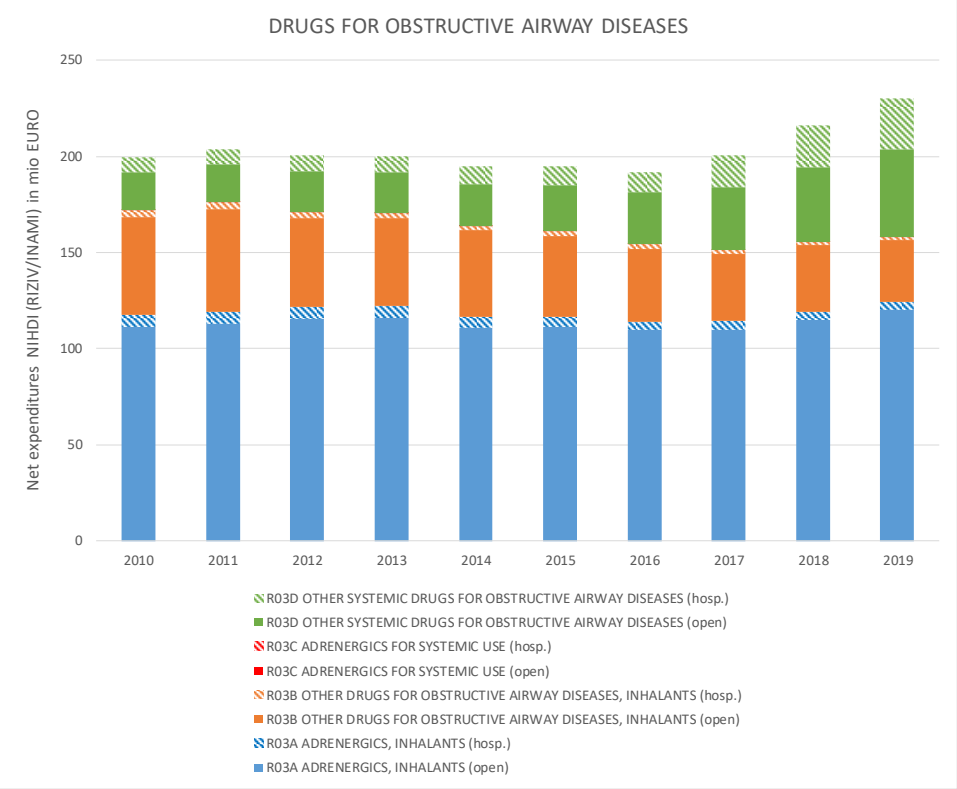
- β2-mimetics (syn. β2-agonists) short-acting or long-acting β2-mimetics via inhalation (short/long acting β2 agonist: *SABA and LABA)*
- anticholinergics (syn. parasympatholytic drugs or muscarinic receptor antagonists) short-acting or long-acting via inhalation (*short/long-acting muscarinic agonists*: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

Limited place for:

- theophylline
- cromoglicic acid (exclusively for use for asthma, no longer available in Belgium since 2019)
- the monoclonal antibodies used for asthma.

The evolution of expenditure on ATC class R03 (per ATC4-level) is shown in Figure 47.

*Figure 47: evolution of NIHDI net annual expenditure (public pharmacies **and hospitals** (all patients) 2010 - 2019) 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 (€ 30,767 in 2019).

The vast majority of the R03-drugs are dispensed in public pharmacies, with the exception of monoclonal antibodies (R0DX). The number of patients (1,546,130 unique patients, public pharmacies 2019) has remained relatively stable over the past years, as is true, in general, for the price of inhaled drugs.

The most noteworthy development in recent years is the increase in the use of and expenditure on monoclonal antibodies. 45% of the expenditure on these drugs (injectable) in 2019 was incurred by hospital pharmacies that primarily dispense these drugs to outpatients.

The evolution of expenditure per pharmacological class is illustrated in Table 16.

Table 16: NIHDI net annual expenditure (public pharmacies) on drugs for obstructive airway diseases (ATC class R03), per pharmacological class: comparisons 2010 – 2019

	2010		2019			
	Expenditure (€)	%	Expenditure (€)	%	Unique patients	%
Leukotriene receptor antagonists	16,756,604	9%	13,440,951	7%	159,344	10%
ICS	17,570,273	10%	15,743,897	8%	455,002	29%
ICS/LABA	88,370,804	48%	76,158,370	39%	721,396	47%
ICS/LABA/LAMA-		0%	6,906,972	3%	13,461	1%
LABA	4,245,857	2%	5,673,896	3%	40,425	3%
LAMA	28,389,205	16%	12,915,591	7%	55,405	4%
LAMA/LABA		0%	13,865,348	7%	32,469	2%
Monoclonal antibodies	2,102,714	1%	31,766,702	16%	3,983	0,3%
Others	1,671,490	1%	595,392	0%	19,227	1%
SABA	4,848,874	3%	5,192,761	3%	400,315	26%
SABA/ SAMA	13,933,948	8%	12,132,320	6%	309,989	20%
SAMA	4,390,404	2%	3,206,881	2%	247,250	16%
TOTAL	182,280,172	100%	197,599,082	100%	1,546,130	100%

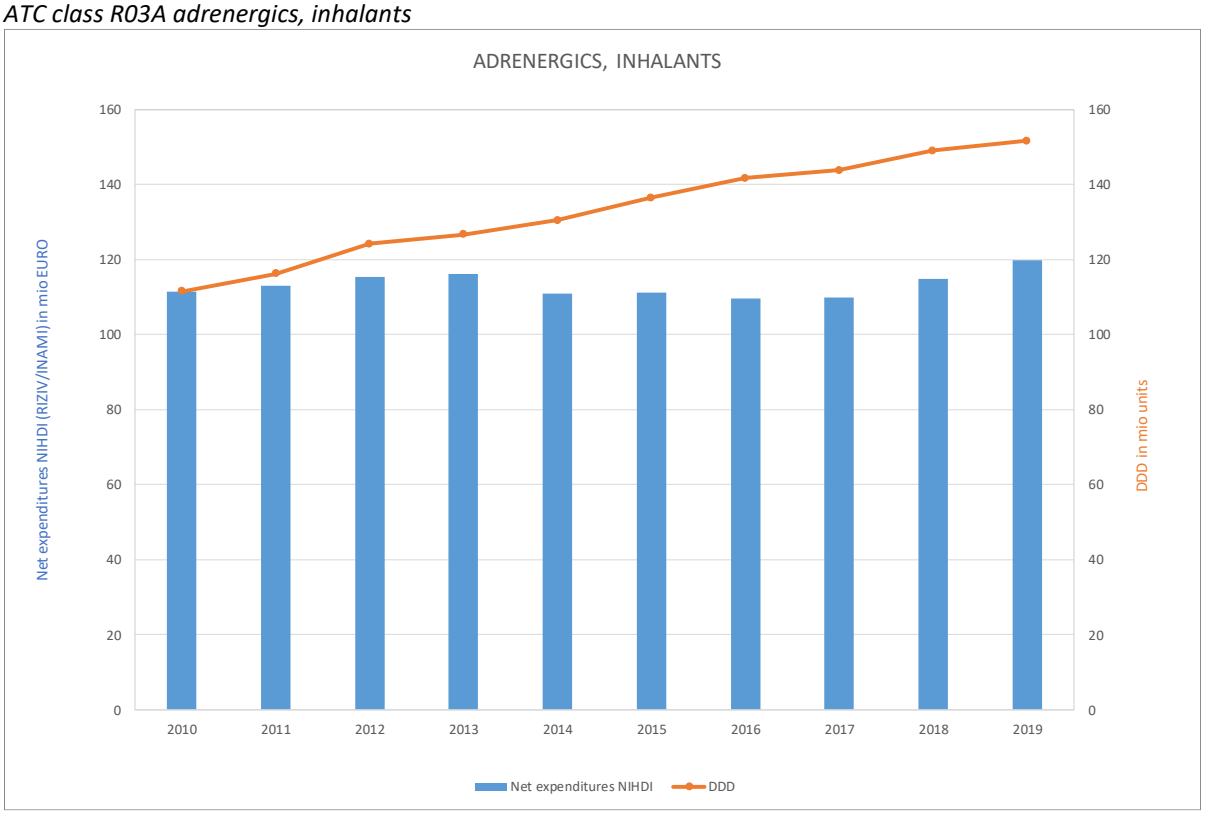
Leukotriene receptor antagonists (ATC R03DC03)
ICS: inhaled corticosteroids (R03BA)
LABA: β2- long-acting mimetics via inhalation (R03AC12, 13, 18, 19)
LAMA long-acting anticholinergics via inhalation (R03BB04, 05, 06, 07)
SABA: β2-short-acting mimetics via inhalation (R03AC02, 03, 04)
SAMA: short-acting anticholinergics via inhalation (R03AL01, 02)
Monoclonal antibodies (R03DX). Expenditure in public pharmacies makes up 55% of the total.
Fixed associations:
ICS/LABA (ATC R03AK)
ICS/LABA/LAMA (ATC R03AL08, 09)
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.

In 2019 the total expenditure (public pharmacies and hospital pharmacies) on monoclonal antibodies (ATC class R03DX) amounted to more than 58 million euros. (NB: this expenditure includes spending on omalizumab for the treatment of urticaria; in 2017 the expenditure for this indication was estimated at 5,000,000 euro, based on the Xolair® study[3])

[3] Verhamme, K., Lucet,C., Van Meerhaeghe,A., Brusselle,G., Lambert,ML. Real life effectiveness of omalizumab in difficult-to-treat versus severe asthma: a national cohort study in Belgium, European Respiratory Journal open research, November 25th 2019; 5 (4)

Figure 48: evolution of NIHDI net annual expenditure and number of DDDs (public pharmacies 2010 – 2019) for ATC class R03A adrenergics, inhalants

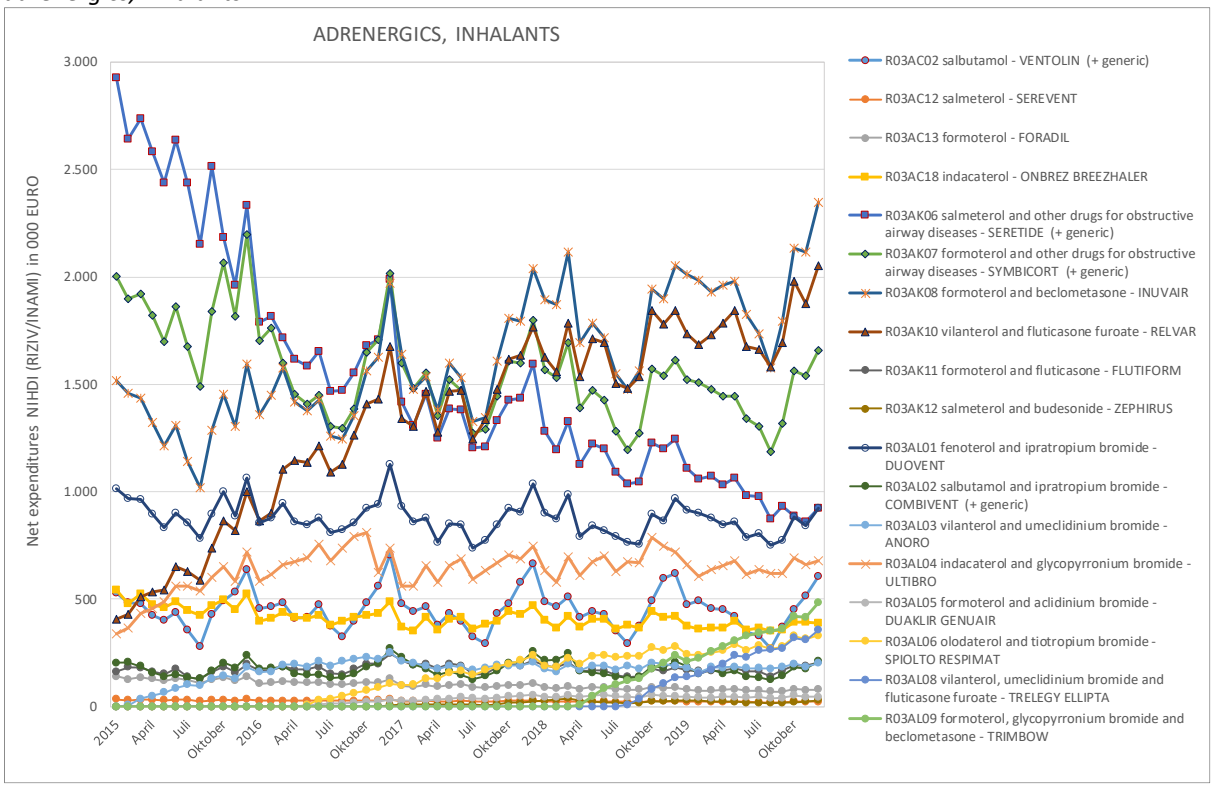


The drugs in the ATC class R03A include the short- and long-acting β2-mimetics via inhalation, as well as fixed combinations (via inhalation) in which β2-mimetics are combined with corticosteroids (ICS/LABA) and anticholinergics via inhalation (ICS/LABA/LAMA). These drugs are most commonly used for obstructive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

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

In 2019 a total of 1,225,100 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.

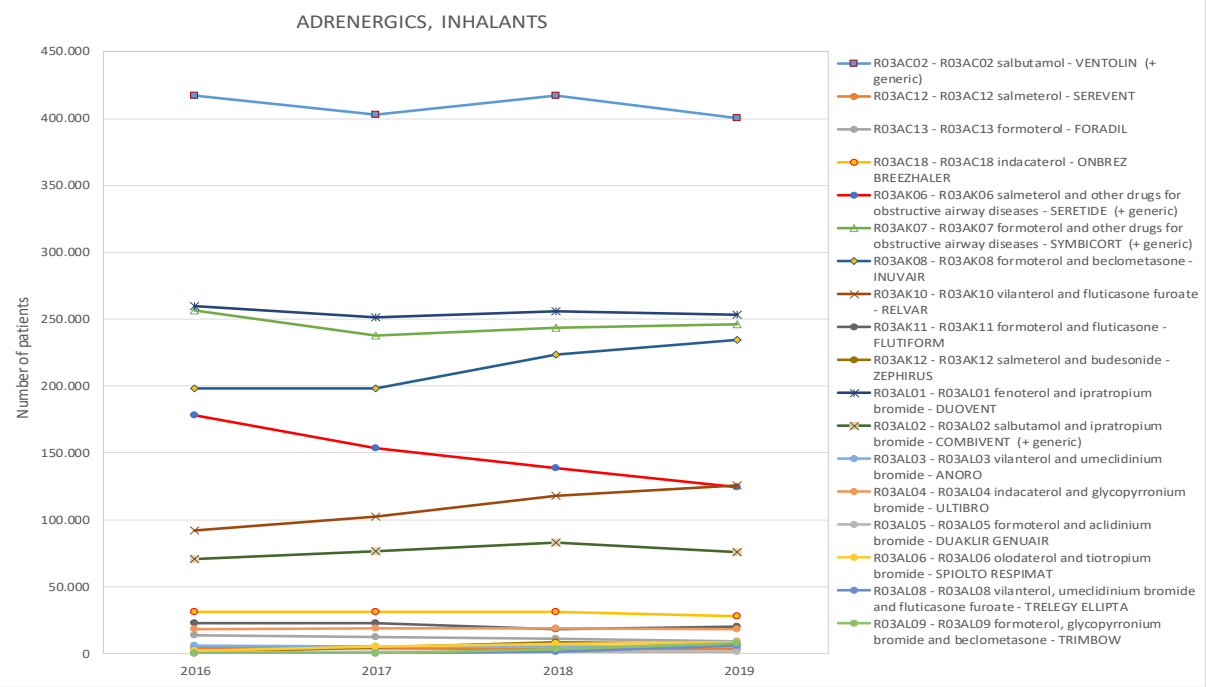
Figure 49: evolution of NIHDI net monthly expenditure (public pharmacies 2015 – 2019) for ATC class R03A adrenergics, inhalants



The 'top 3 expenditures' of the drugs in the ATC R03A class relate to fixed combinations of inhaled corticosteroids and long-acting betamimetics (ICS/LABA, R03AK).

The tritherapies (ICS/LABA/LAMA, Trelegy® and Trimbow®) have been eligible for reimbursement since 2018.

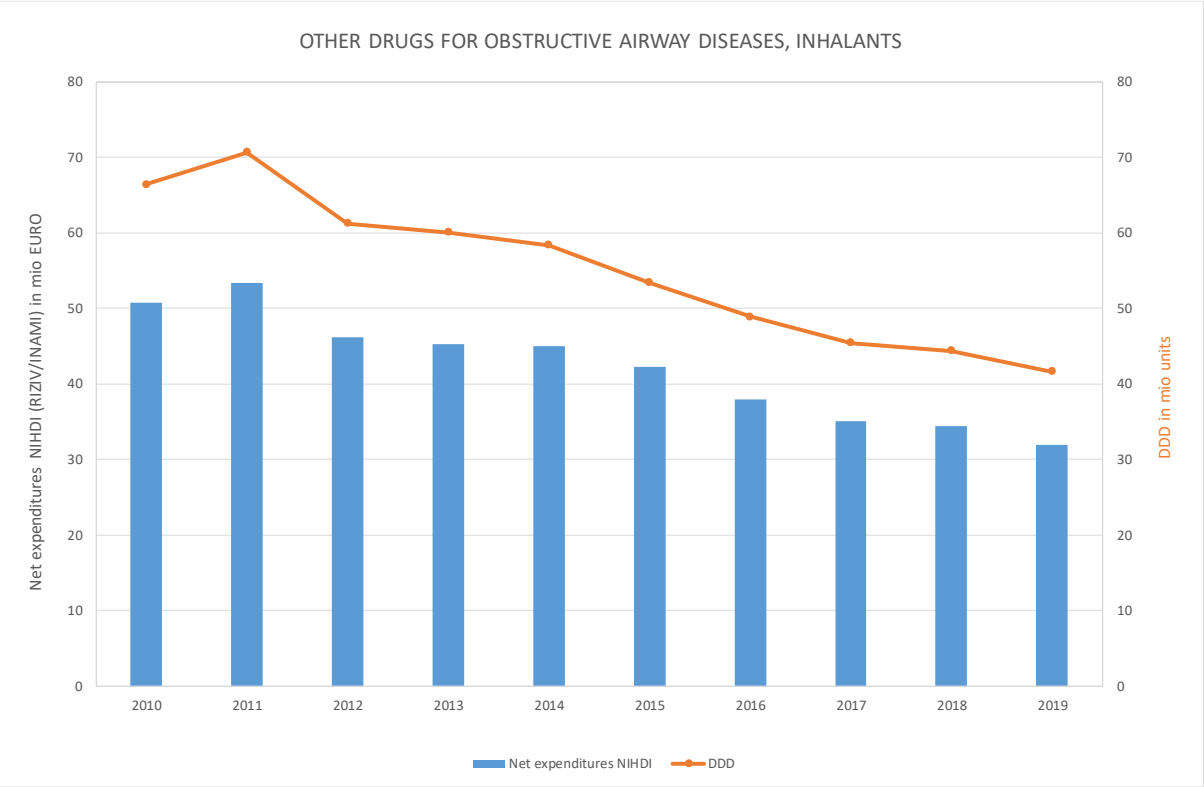
Figure 50: evolution of number of patients per year (public pharmacies 2016 – 2019) for ATC class R03A adrenergics, inhalants



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).

R03B - OTHER DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES, INHALANTS

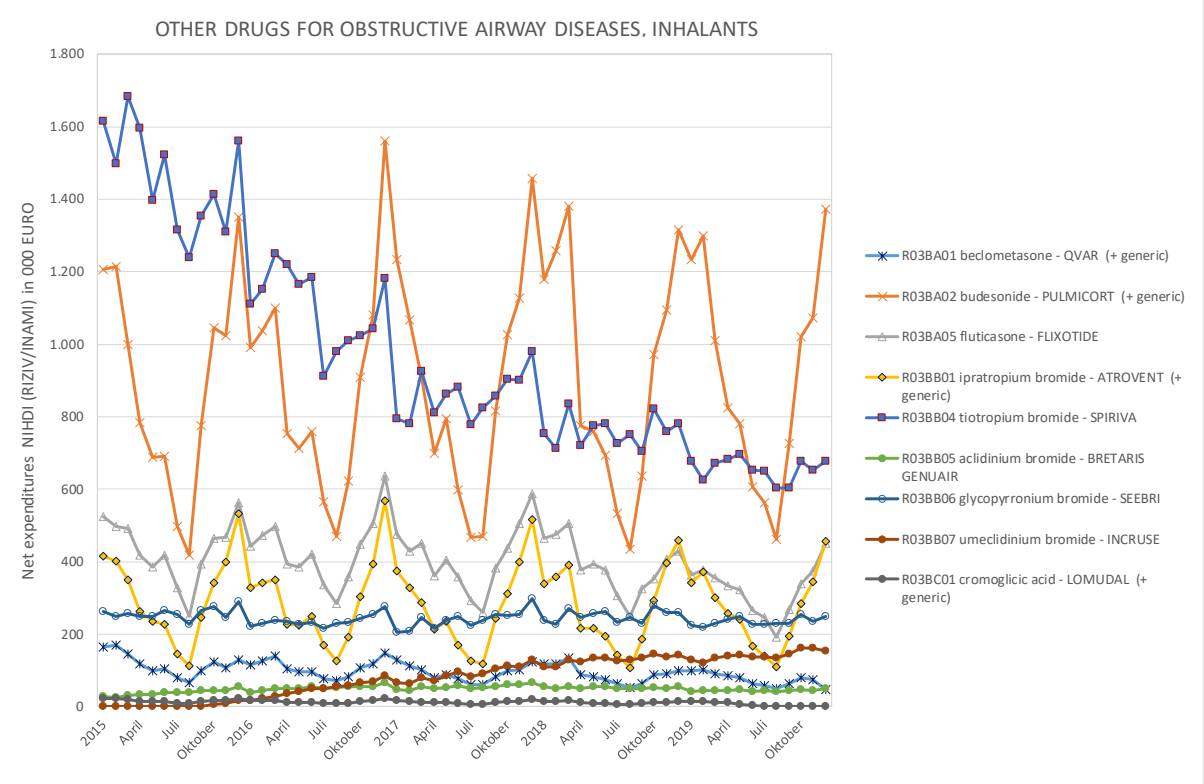
Figure 51: evolution of NIHDI net annual expenditure and number of DDDs (public pharmacies 2010 – 2019) for ATC class R03B, other drugs for obstructive airway diseases, inhalants



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: 455,000 in 2019. 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).

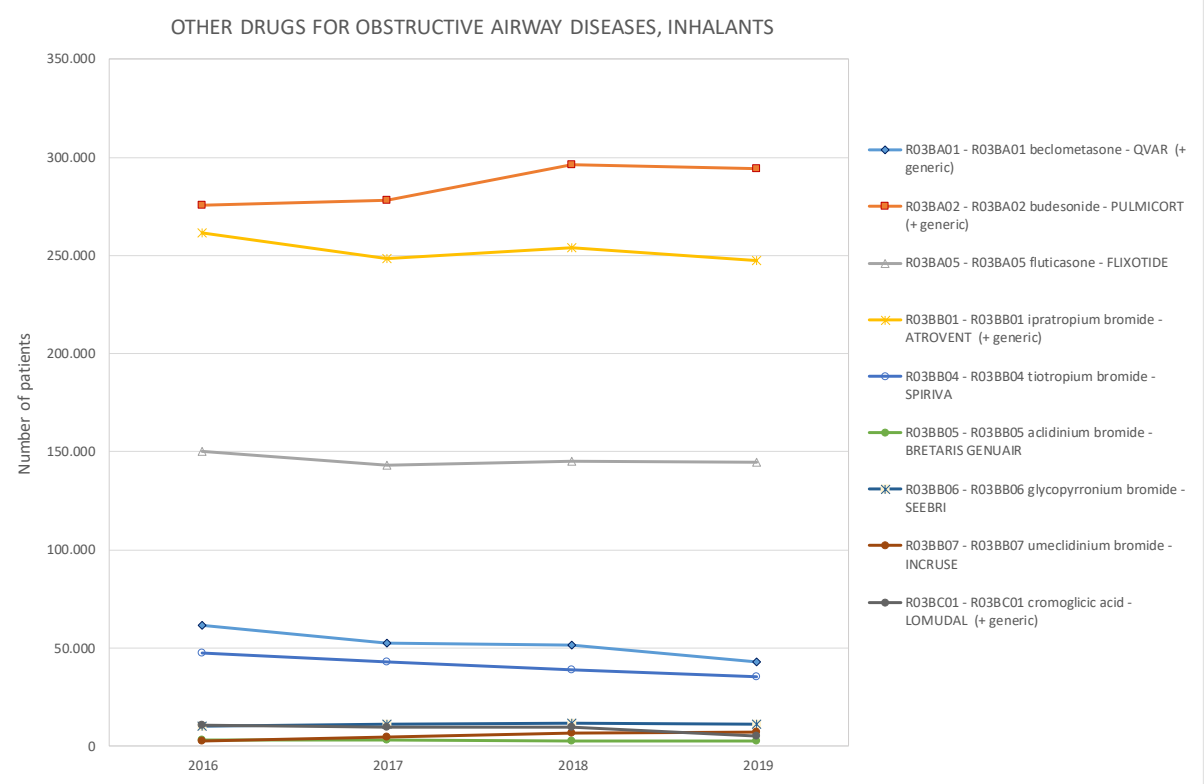
Figure 52: evolution of NIHDI net monthly expenditure (public pharmacies 2015 – 2019) for ATC class R03B other drugs for obstructive airway diseases, inhalants



This figure shows the seasonal trend (with winter peaks) for the most-used drugs.

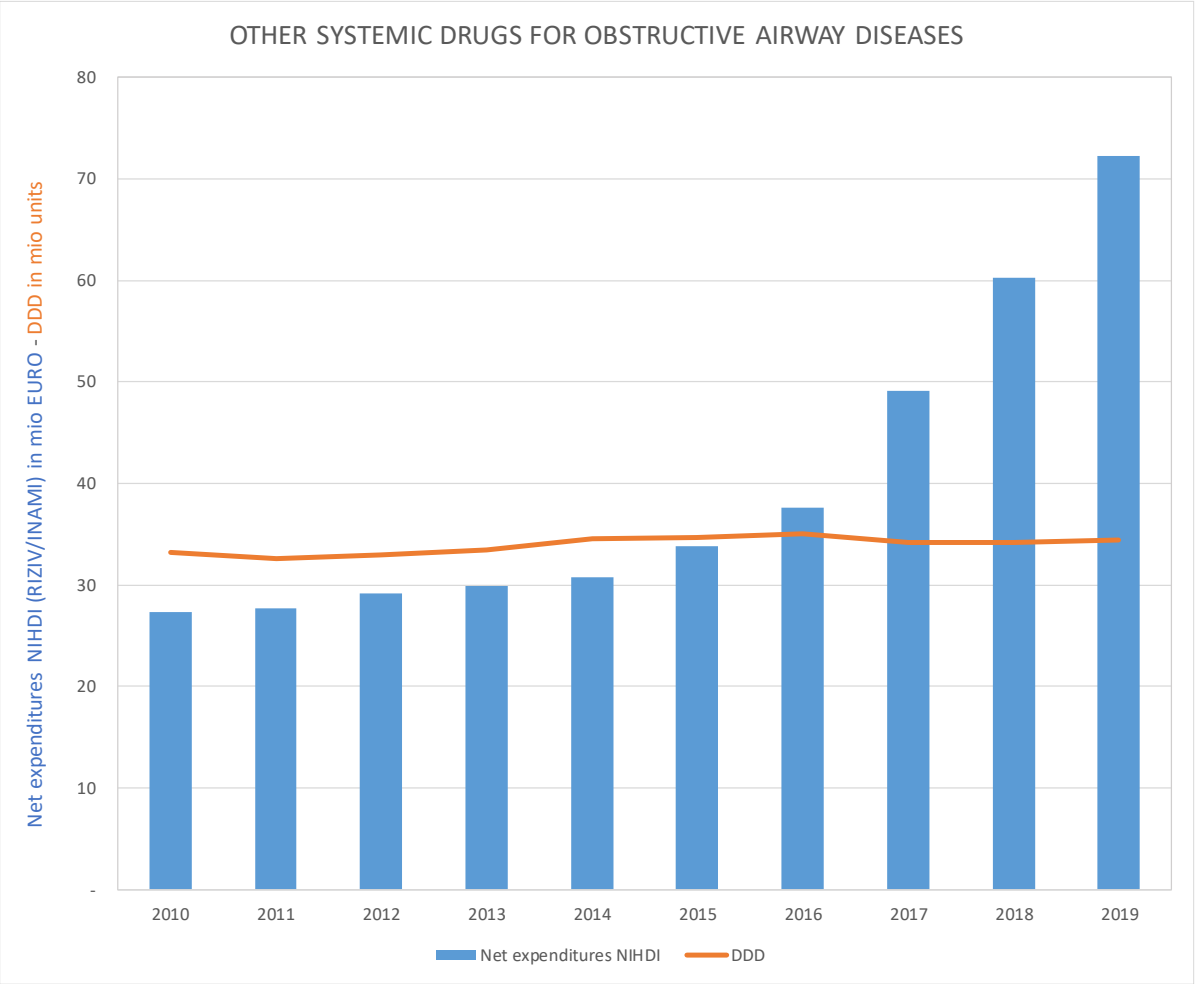
Cromoglycate (Lomudal ®) was taken off the Belgian market in 2019.

Figure 53: evolution of number of patients per year (public pharmacies 2016 – 2019) 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).

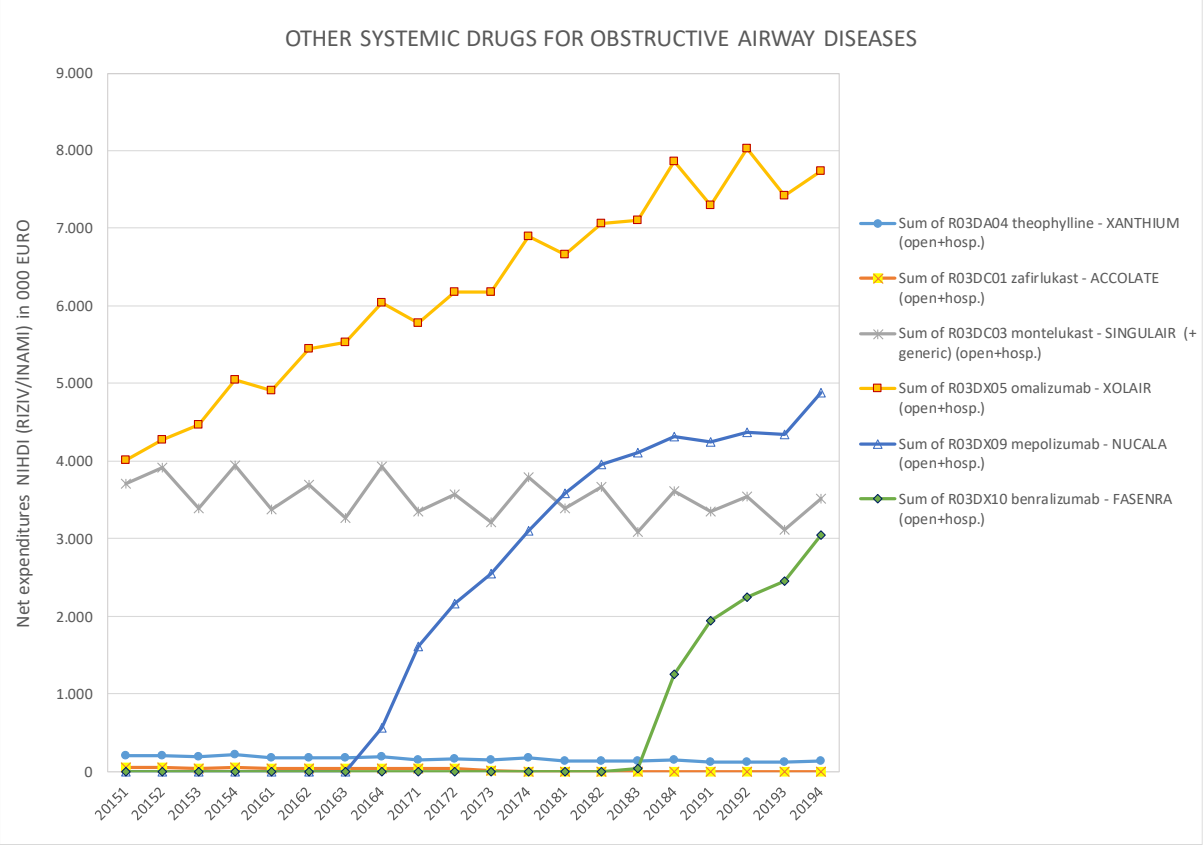
*Figure 54: evolution of NIHDI net annual expenditure and number of DDDs (public pharmacies **and hospitals** (all patients) 2010 - 2019) for ATC class R03D other systemic drugs for obstructive airway diseases*



The drugs in the ATC class R03D include theophylline (R03DA), the leukotriene antagonists (R03DC) and the monoclonal antibodies (R03DX); exclusively as a last resort for serious asthma. The increase in expenditure is related to this latter class of drugs. Until 2016, only 1 molecule was available (omalizumab, Xolair®); since then, mepolizumab (Nucala®, 2017), reslizumab (Cinquaero®, 2018) and benralizumab (Fasenra®, 2018) have become reimbursable. Omalizumab is also used for the treatment of urticaria.

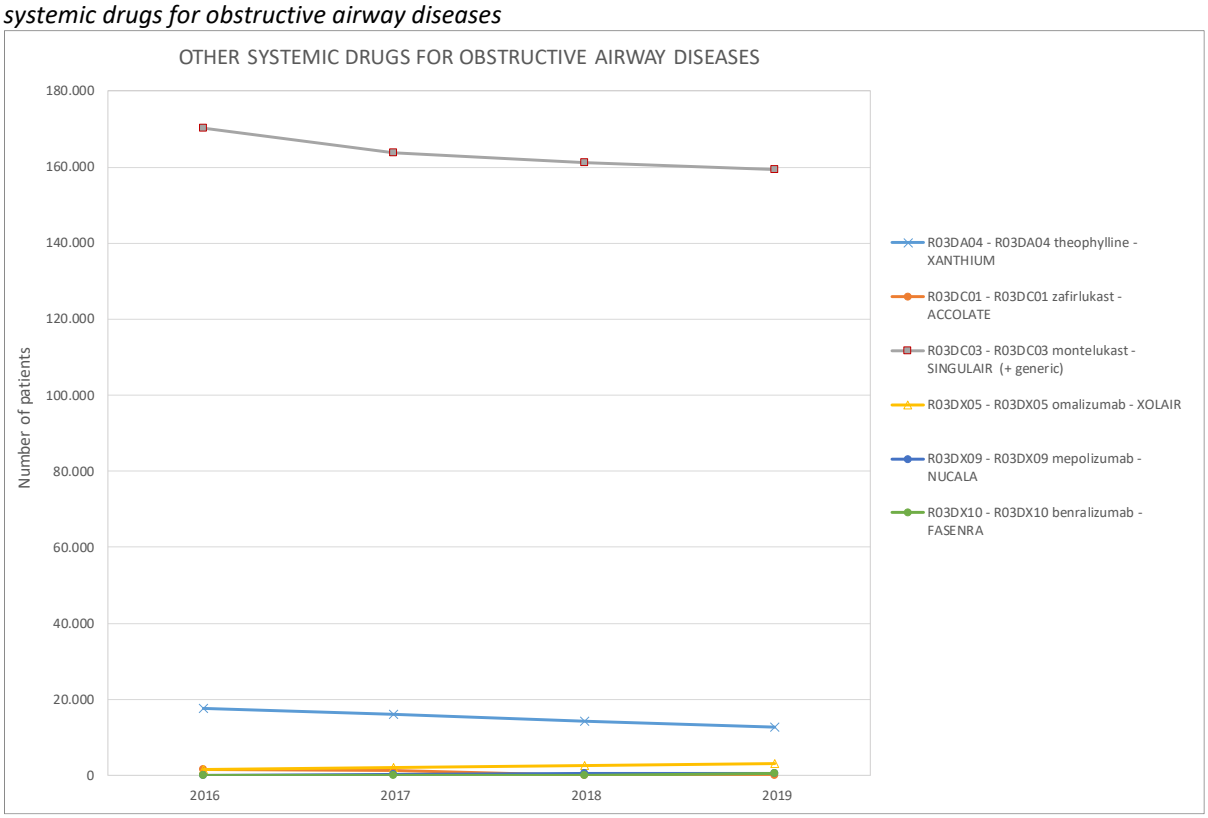
These very expensive drugs can be used on only a relatively small number of patients – which is why the number of DDDs is only increasing slightly.

*Figure 55: evolution of NIHDI net quarterly expenditure (public pharmacies **and hospitals** (all patients) 2010 - 2019) for ATC class R03D other systemic drugs for obstructive airway diseases*



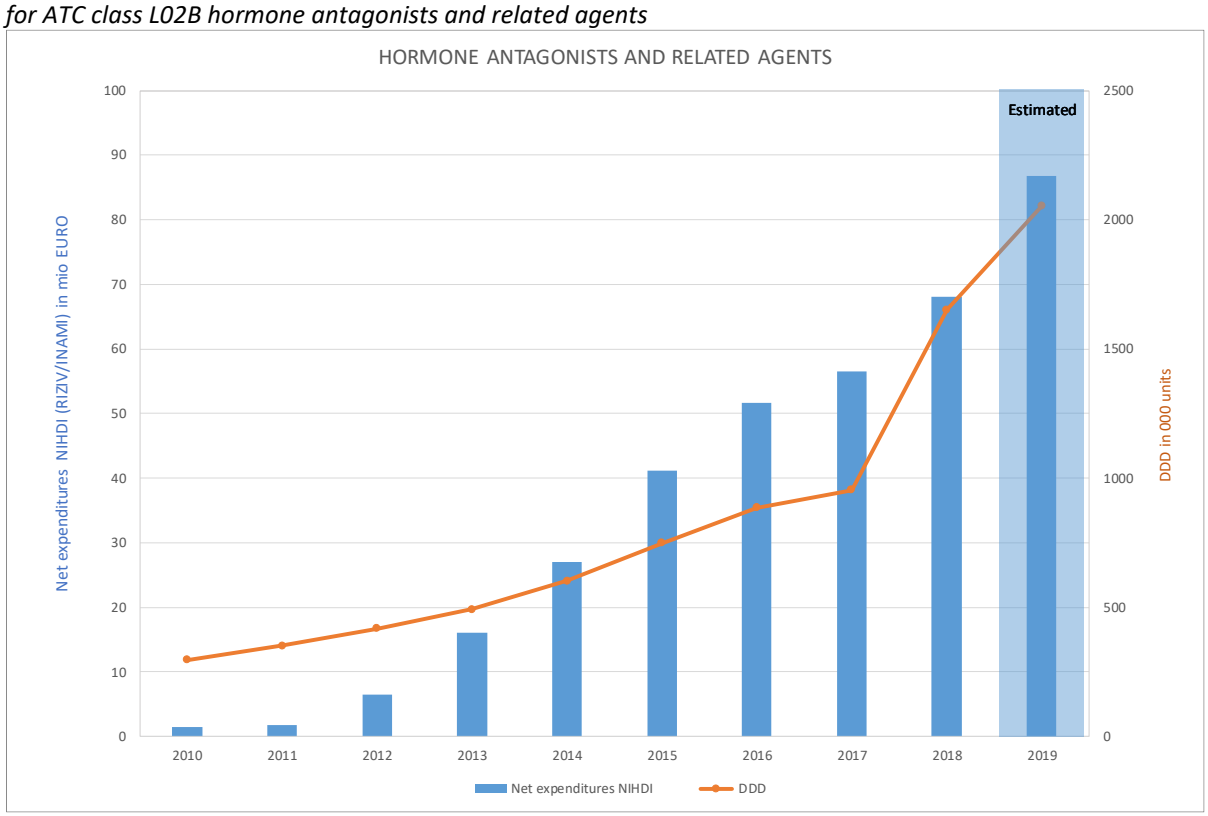
This graph illustrates the increase in expenditure related to monoclonal antibodies, and new molecules becoming eligible for reimbursement (mepolizumab in 2016, benralizumab in 2018).
NB: omalizumab is also used for the treatment of urticaria.

Figure 56: evolution of number of patients per year (public pharmacies 2016 – 2019) for ATC class R03D other systemic drugs for obstructive airway diseases



This graph shows that monoclonal antibodies, in theory used as a last resort for serious asthma, are only applicable to a minority of patients.

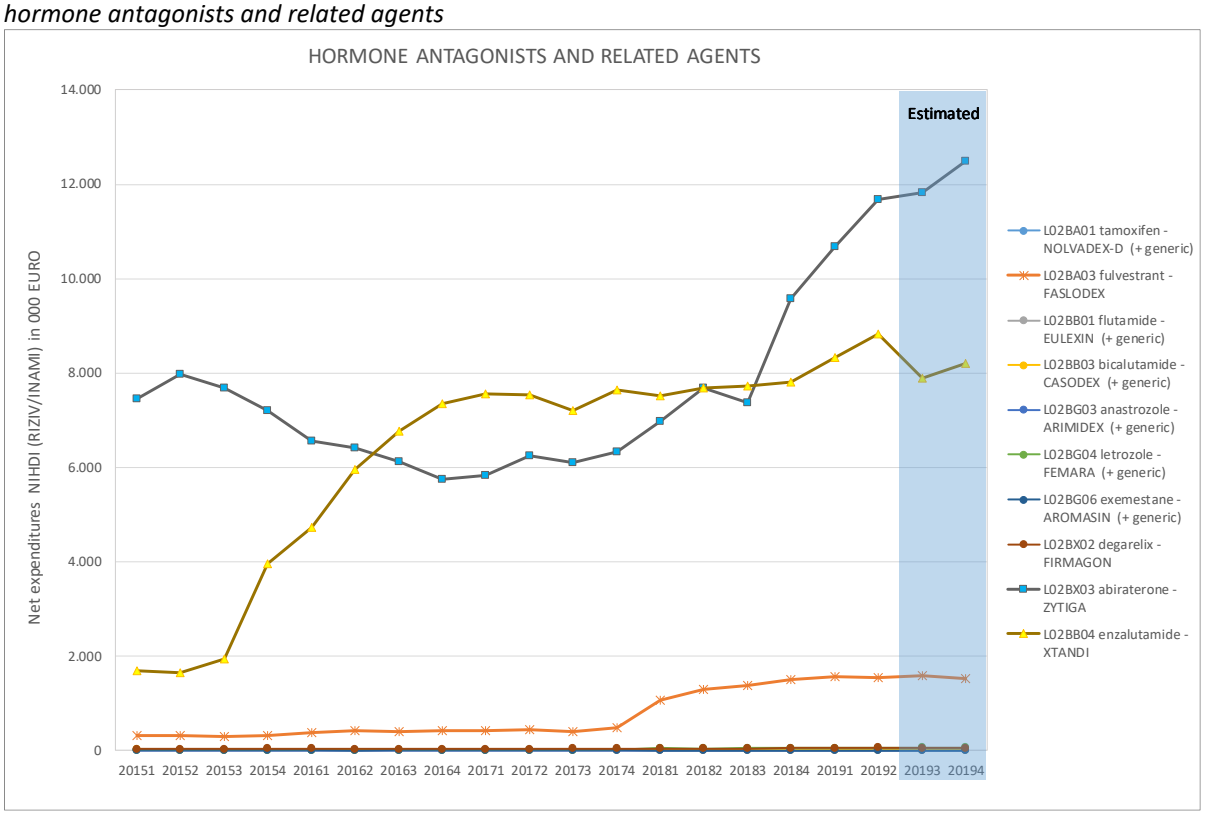
Figure 57: evolution of NIHDI net annual expenditure and number of DDDs (hospitals (all patients) 2010 – 2019) for ATC class L02B hormone antagonists and related agents



In recent years, expenditure on this class of medicines has increased sharply.

Most of the NIHDI net expenditure in hospitals is accounted for by Xtandi® and Zytiga®, and, to a lesser extent, by tamoxifen, fulvestrant and the aromatase inhibitors. The sudden increase in the use (DDDs) of hormone antagonists and related agents since 2017 is largely due to an increase in the use of the active substances letrozole and fulvestrant.

Figure 58: evolution of NIHDI net quarterly expenditure (hospitals (all patients) 2015-2019) for ATC class L02B hormone antagonists and related agents



The above graph on ATC class L02B hormone antagonists and related agents shows that NIHDI net expenditure in hospitals is very limited for tamoxifen, fulvestrant and the aromatase inhibitors. Farmanet data show that, apart from fulvestrant, which is administered via an intramuscular injection, most expenditure is incurred in public pharmacies. For pharmaceutical specialties based on letrozole and degarelix, the net expenditure in public pharmacies is around twenty times higher than in hospitals – and expenditure on tamoxifen is even 300 times higher. For the other aromatase inhibitors, the net cost in public pharmacies is between 55 and 105 times higher than in hospitals.

Most of the net expenditure on this ATC class is generated by the pharmaceutical specialties Zytiga® and Xtandi®; the reimbursable indications have been extended for both these products.

Since 1 August 2012, the pharmaceutical specialty Zytiga® is eligible for reimbursement for the post-docetaxel treatment of metastatic castration-resistant prostate cancer (mCRPC) in adult men. In February 2014 reimbursement was extended to the indication metastatic castration-resistant prostate cancer (mCRPC) pre-docetaxel.

When the pharmaceutical specialty Xtandi® became available and eligible for reimbursement, in December 2014, the use of Zytiga® fell, as can be seen in the figures as of the second half of 2015. Since 1 December 2014, Xtandi® is also reimbursed for mCRPC post-docetaxel, and also for mCRPC pre-docetaxel since 1 October 2015.

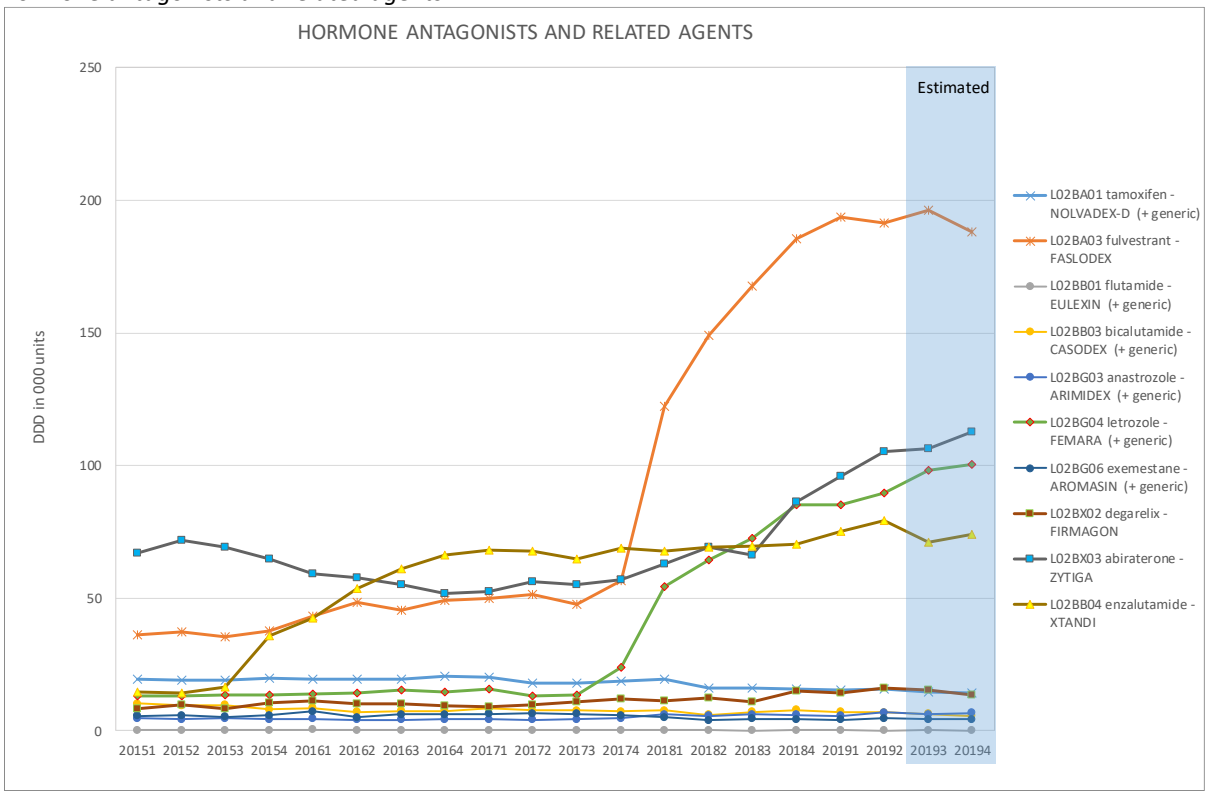
In the last quarter of 2018, there was a striking increase in expenditure on Zytiga®. This is due to the extension, from 1 October 2018, of reimbursement to the indication 'treatment of newly diagnosed high-risk metastatic hormone-sensitive prostate cancer (mHSPC) in adult men, in combination with androgen deprivation therapy (ADT)'. The extension to this new indication meant a significant increase in the number of patients eligible for treatment. The above graph clearly illustrates the scale of this increase.

Since 1 October 2019, Xtandi® too is reimbursed for a third indication (non-metastatic castration resistant prostate cancer). The increase in the number of patients eligible for treatment with Xtandi® for this indication will probably be far smaller.

Finally, it is worth mentioning that both specialties (Zytiga® and Xtandi®) are reimbursed under a convention, so the actual expenditure is lower.

The increase in net expenditure on fulvestrant in the fourth quarter of 2017 can be explained by an increase in the use of fulvestrant in first-line treatment (see **Error! Reference source not found.** 59)

Figure 59: evolution of number of DDDs per quarter (hospitals (all patients) 2015 – 2019) for ATC class L02B hormone antagonists and related agents



The most striking increase in use (in number of DDDs) is for the active ingredient fulvestrant. This is probably due to the publication of the results of the FALCON clinical study in 2017. The extension of reimbursement to first-line treatment (with a corresponding 6.53% drop in price) only, however, came into force on 1 August 2018.

The rise in the number of DDDs of letrozole is due to the first CDK4/6 inhibitor becoming eligible for reimbursement in December 2017, in combination with letrozole/anastrozole.

OTHER CLASSES OF MEDICINES (PUBLIC PHARMACIES) (without a detailed analysis)

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. In 2019, we can see a slight increase in expenditure on this class. Compared with 2018, we can see that in 2019, combinations based on angiotensin II receptor blockers (C09D) and (to a lesser extent) combinations based on ACE inhibitors (C09B) are mainly responsible for this increase.

With regard to the number of DDDs and the number of patients, we can also see, after a relatively stable period, an increase in 2019 compared to previous years.

Figure 60: evolution of NIHDI net annual expenditure (public pharmacies 2010 - 2019) for ATC class C09 agents acting on the renin-angiotensin system

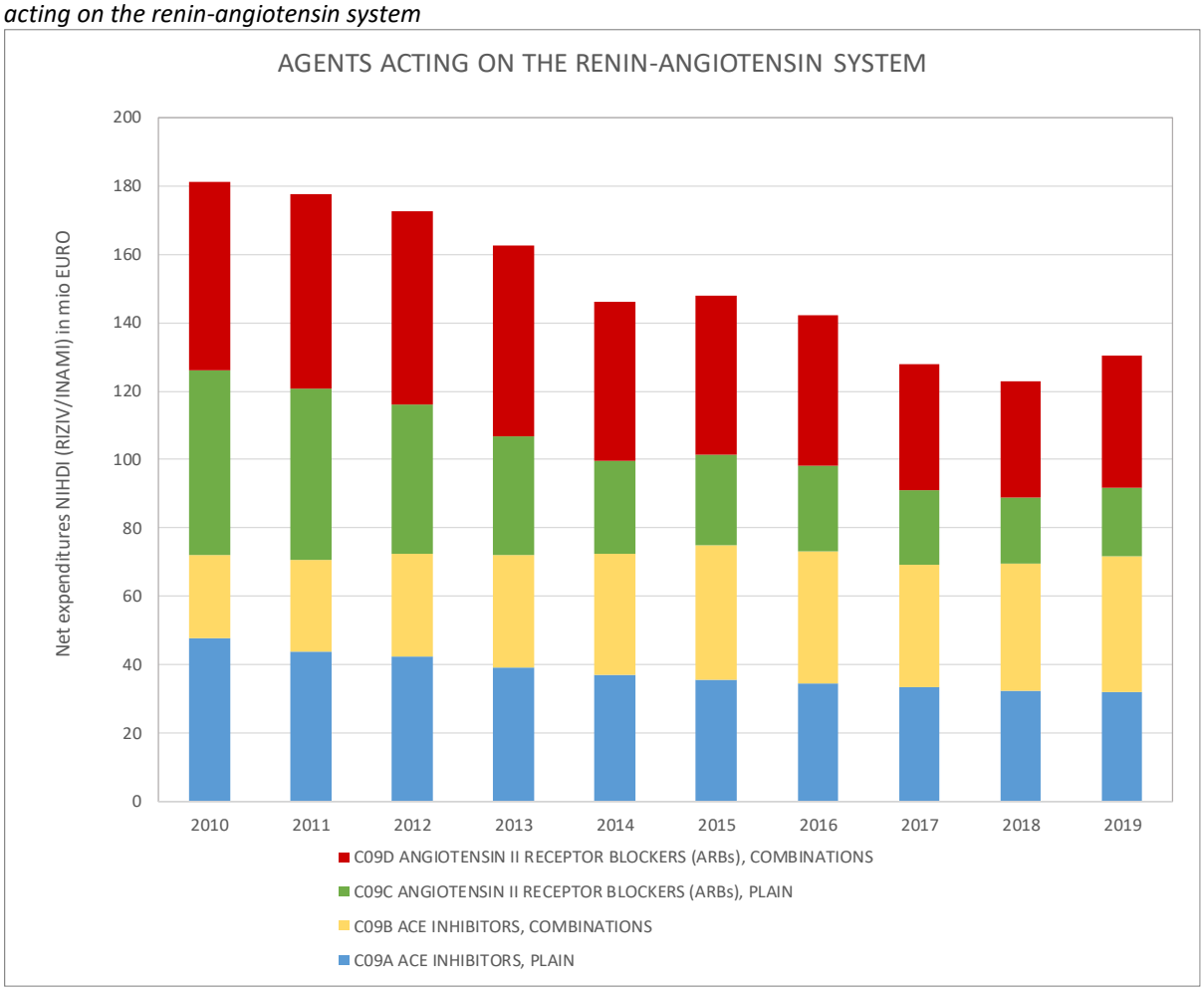
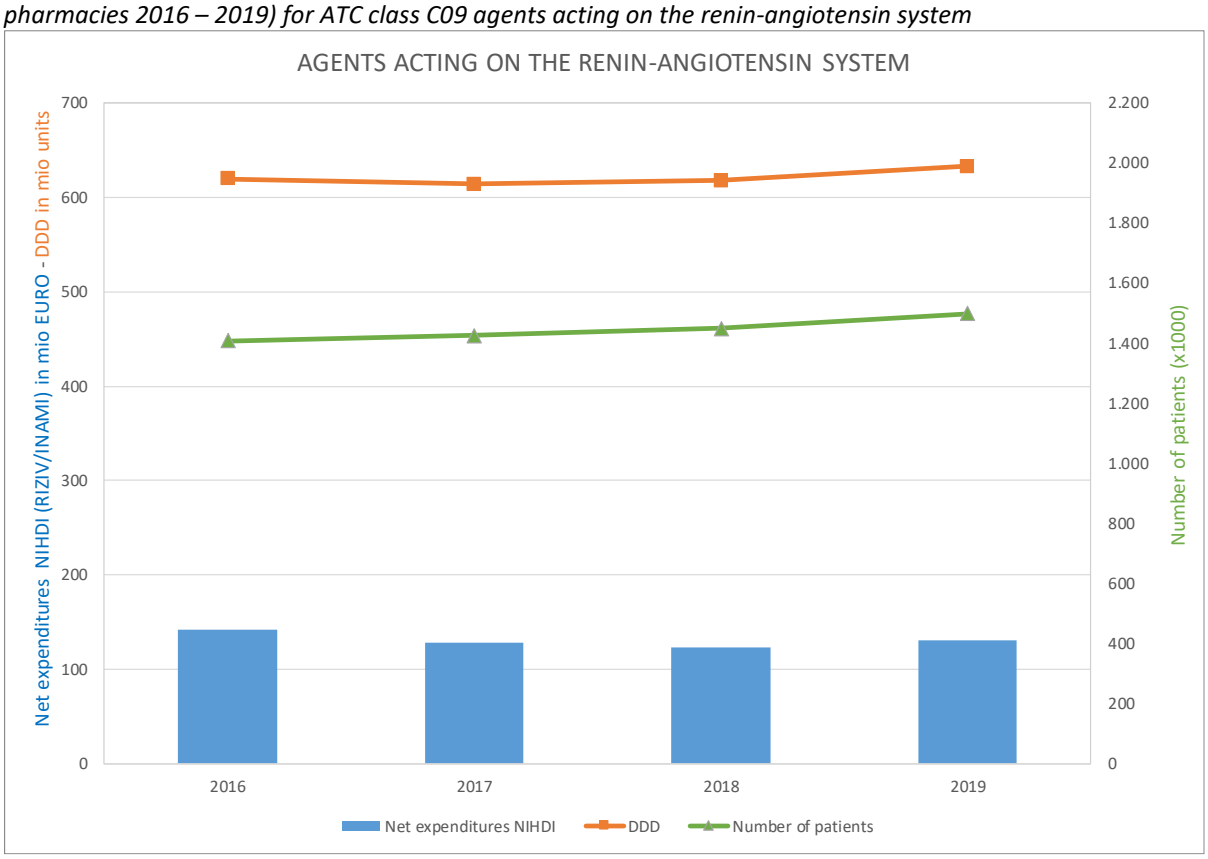


Figure 61: evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2016 – 2019) for ATC class C09 agents acting on the renin-angiotensin system



ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACE INHIBITORS), COMBINATIONS

In recent years, we have seen a constant increase in DDDs of combinations based on ACE inhibitors, and this trend has continued in the period between 2017 and 2019 inclusive. Expenditure on this class then fell sharply in 2017, when the combi-cliff was applied to specialties based on perindopril + amlodipine (Coveram® + generics).

In 2018 and 2019 a gradual increase in net annual expenditure can again be observed. As well as this gradual increase in expenditure on Coveram® (+ generics) and Coversyl® (+ generics), we can also see a clear upward trend in expenditure on the specialties Triplixam® and Bipressil®. We can see the same trend with regard to the number of DDDs per month and the number of patients.

Figure 62: evolution of NIHDI net annual expenditure and number of DDDs (public pharmacies 2010 – 2019) for ATC class C09B ACE inhibitors, combinations

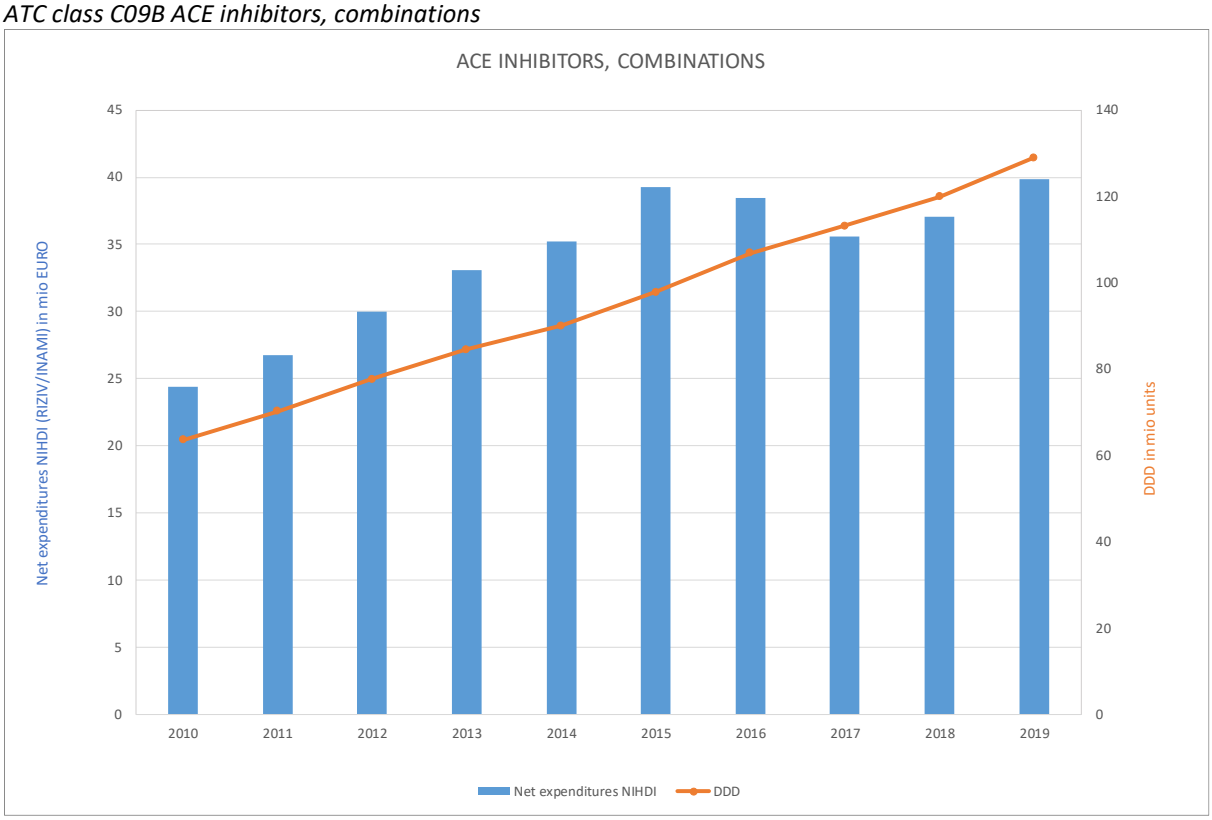


Figure 63: evolution of NIHDI net monthly expenditure (public pharmacies 2015 – 2019) for ATC class C09B ACE inhibitors, combinations

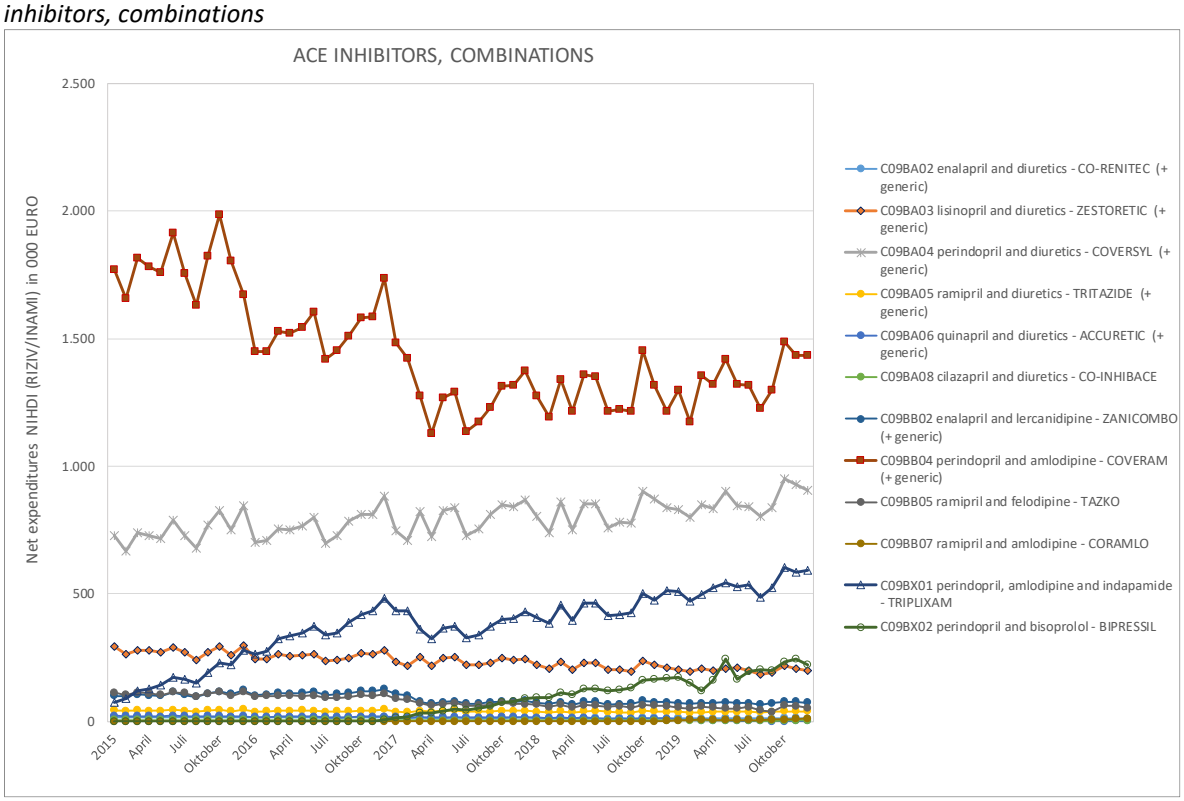


Figure 64: evolution of number of DDDs per month (public pharmacies 2015 – 2019) for ATC class C09B ACE inhibitors, combinations

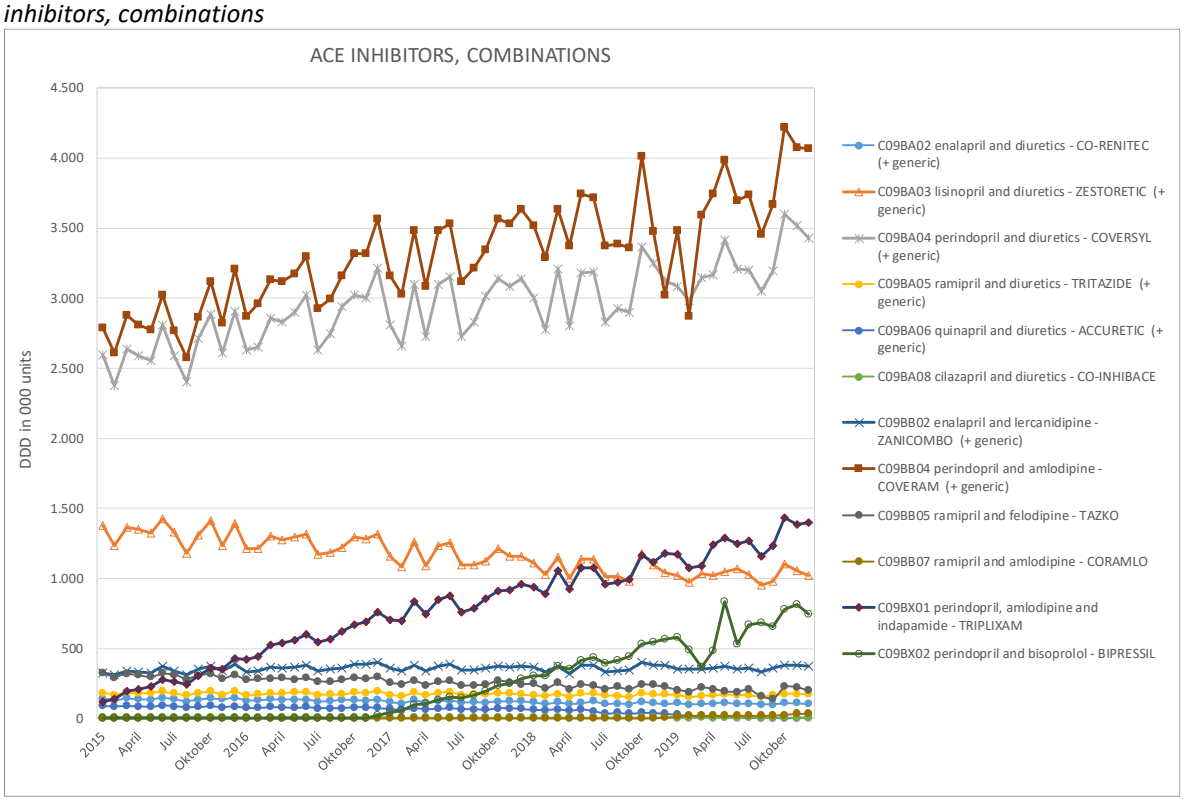


Figure 65: evolution of number of patients per year (public pharmacies 2016 – 2019) for ATC class C09B ACE inhibitors, combinations

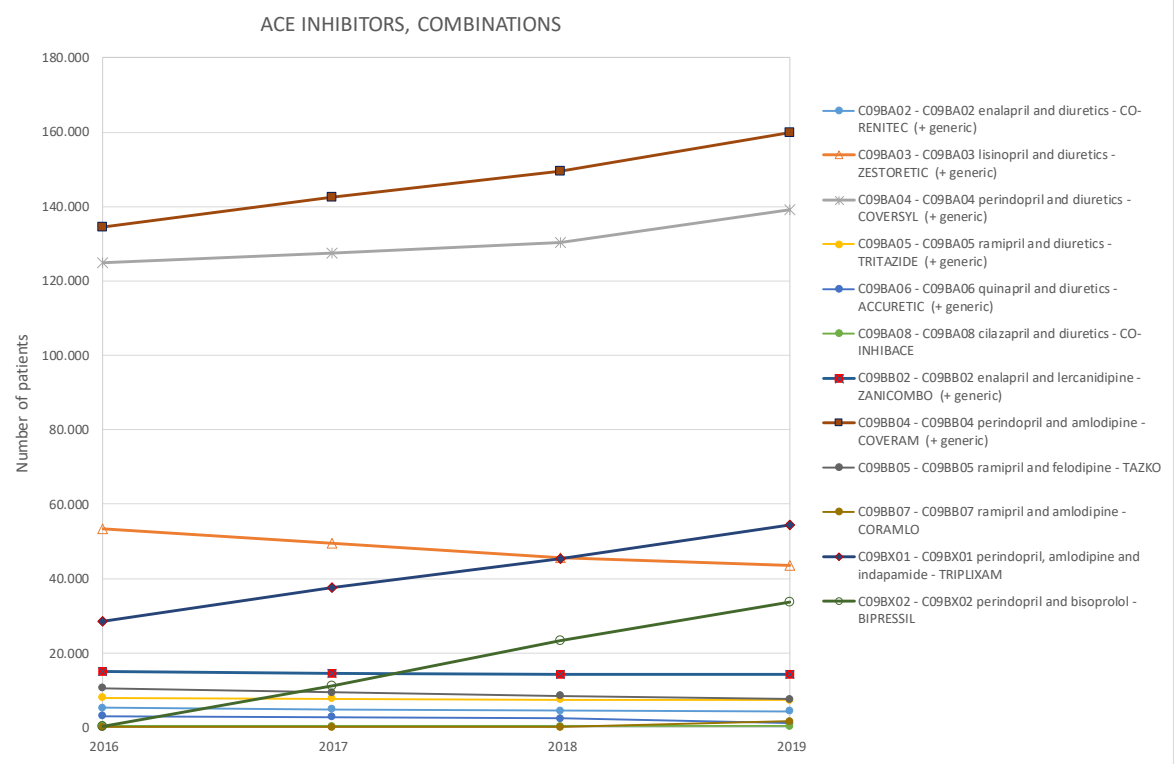
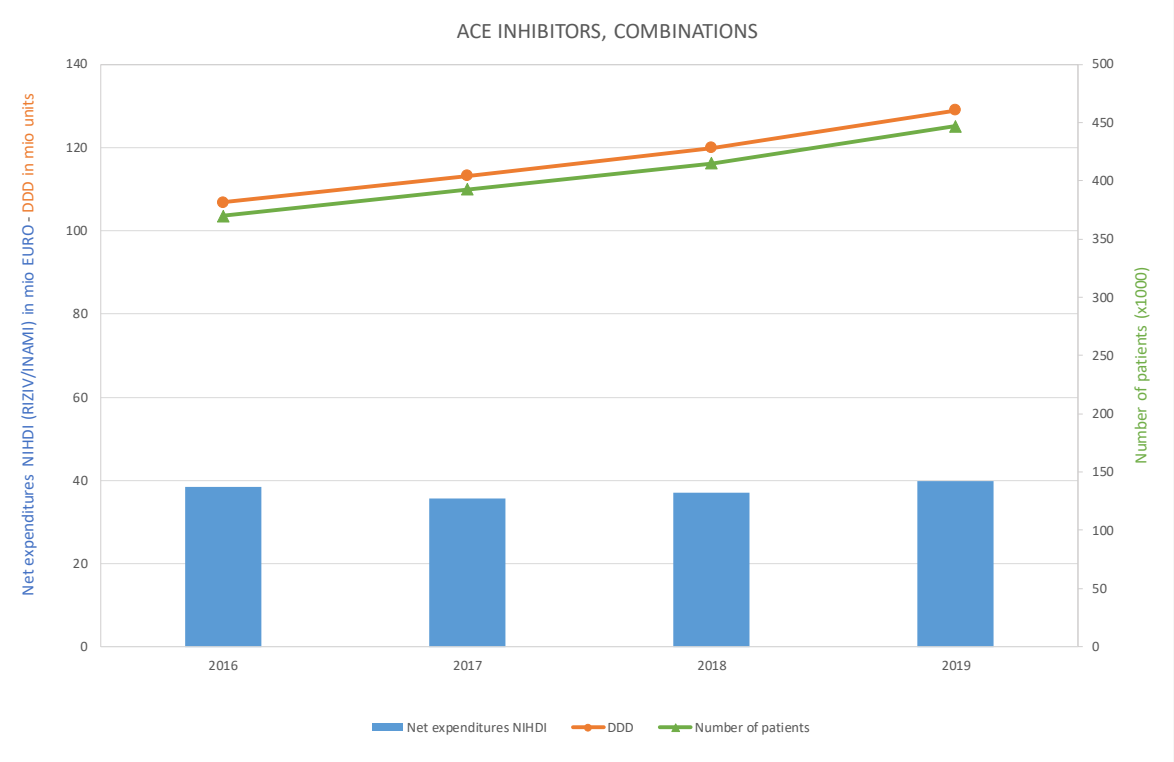


Figure 66: evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2016 – 2019) for ATC class C09B ACE inhibitors, combinations



ANGIOTENSIN II RECEPTOR BLOCKERS (SARTANS), COMBINATIONS

Following a period of stable numbers of DDDs per month from 2014 up to and including 2017, we can see a clear increase in 2018 and 2019. This is largely due to the following specialties, 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.

As well as the increase in these 'old faithfuls', the specialty Entresto®, eligible for reimbursement since 1 November 2016, is also clearly on the rise.

With regard to expenditure on this class, the most striking element is the steep fall in spending in 2017. This is due to:

- the group review of the sartans, leading to transfer of all olmesartan-based specialties 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 specialty Entresto®, which in previous years was partially reimbursed under a convention, but which has been eligible for full reimbursement since 1 June 2020.

Figure 67: evolution of NIHDI net annual expenditure and number of DDDs (public pharmacies 2010 – 2019) for ATC class C09D angiotensin II receptor blockers, combinations

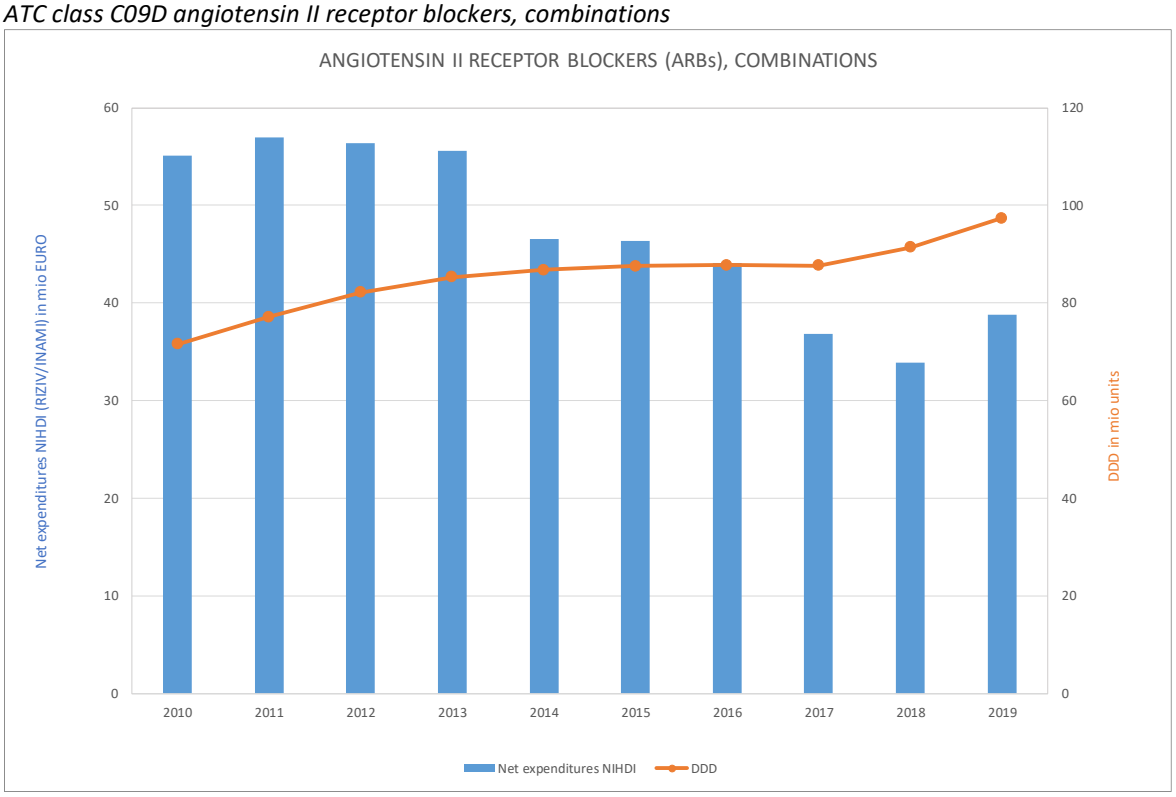


Figure 68: evolution of NIHDI net monthly expenditure (public pharmacies 2015 – 2019) for ATC class C09D angiotensin II receptor blockers, combinations

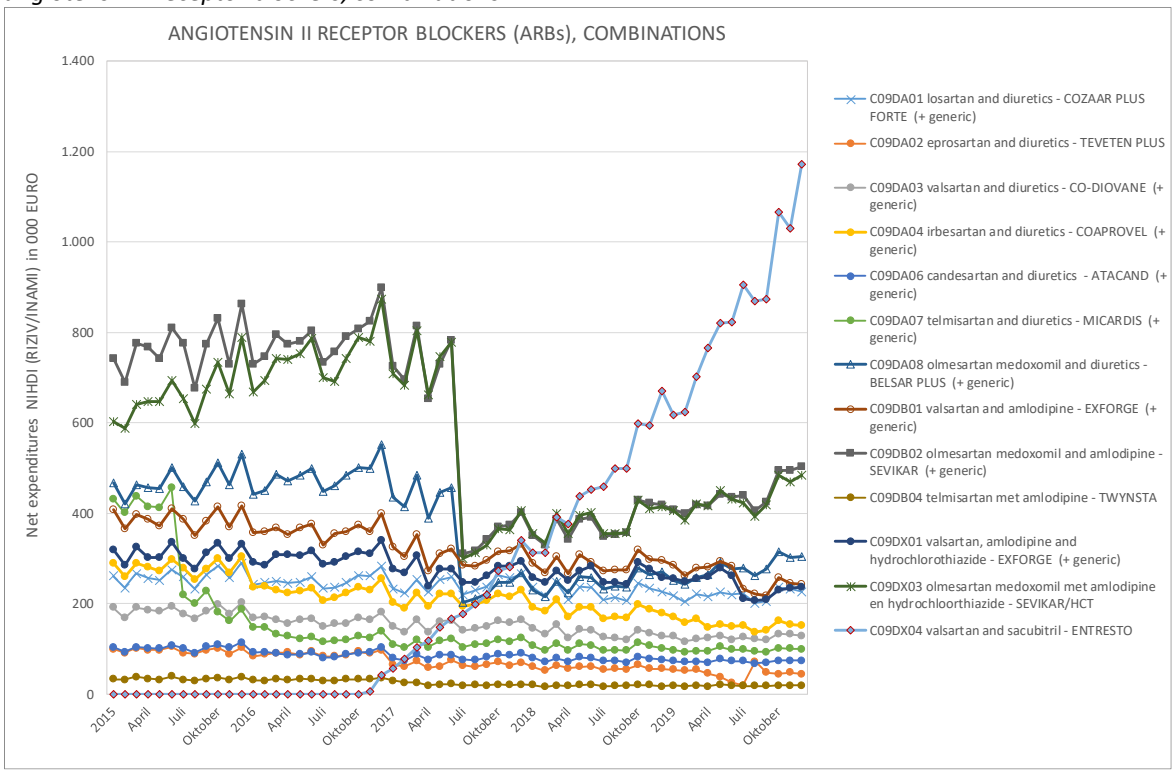


Figure 69: evolution of number of DDDs per month (public pharmacies 2015 – 2019) for ATC class C09D angiotensin II receptor blockers, combinations

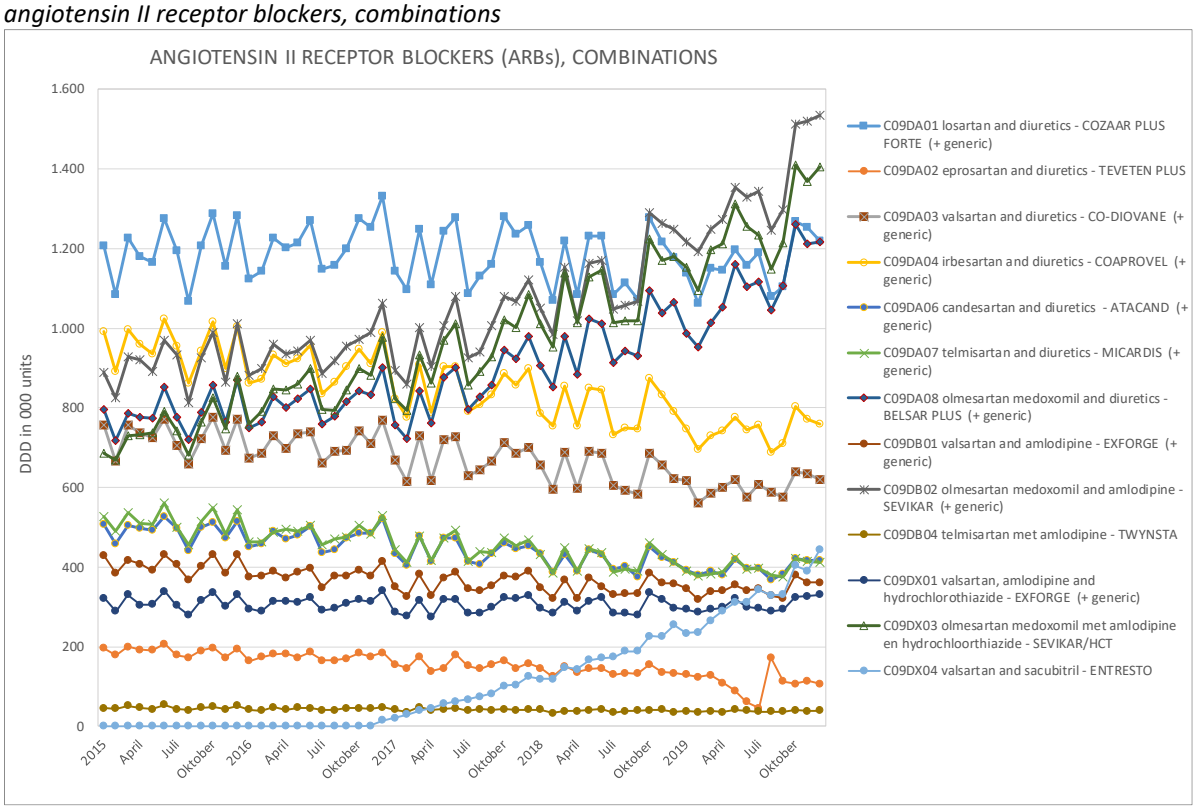


Figure 70: evolution of number of patients per year (public pharmacies 2016 – 2019) for ATC class C09D angiotensin II receptor blockers, combinations

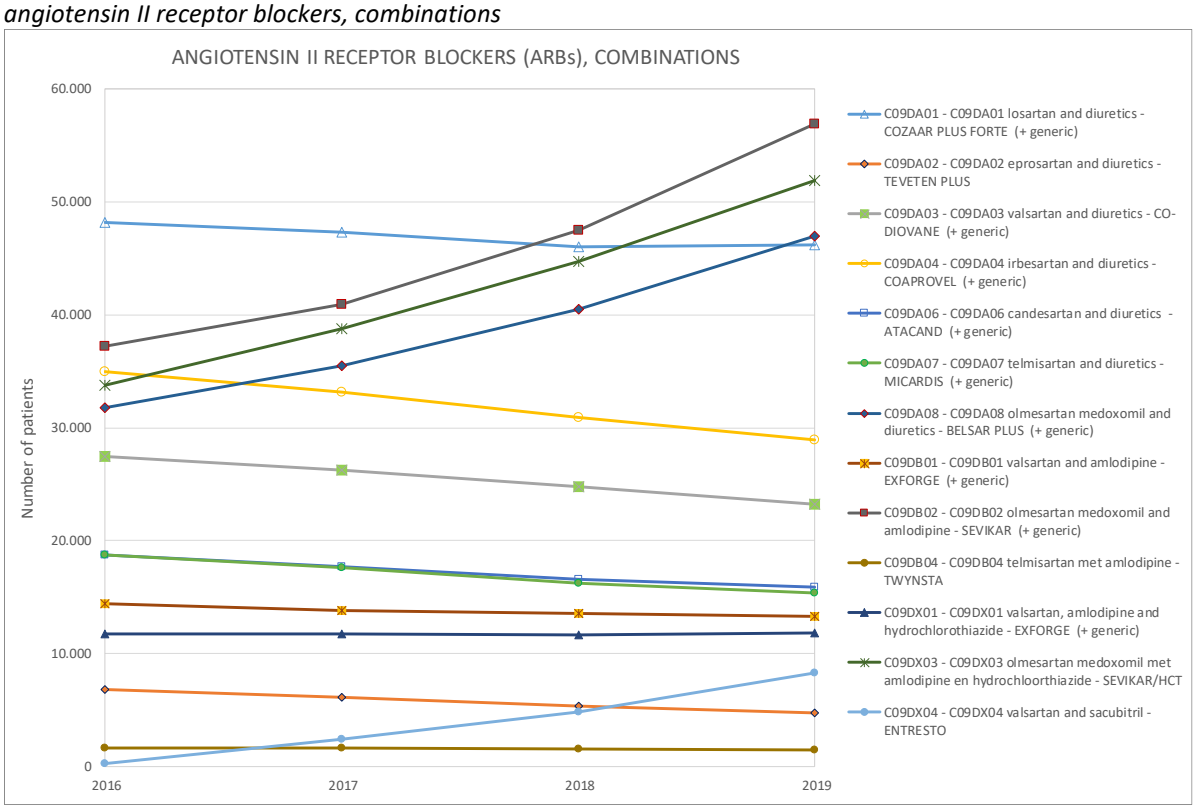
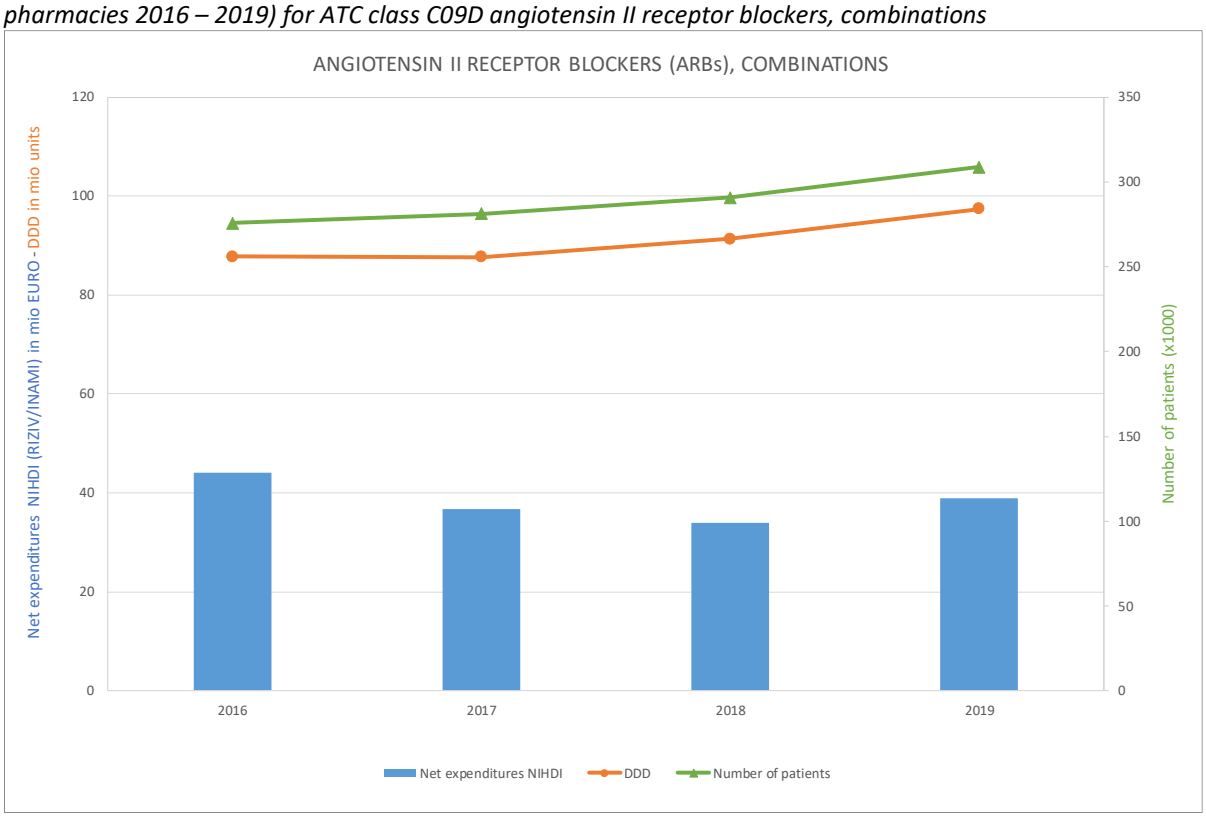


Figure 71: evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2016 – 2019) for ATC class C09D angiotensin II receptor blockers, combinations



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 specialties having omeprazole, lansoprazole, pantoprazole or rabeprazole as their active ingredients, 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 specialties. The aim of this measure was to regulate the price of generic specialties for which the *patent cliff* was not applied on 1 January 2017, since the reference specialty was not available.

Figure 72: evolution of NIHDI net expenditure and number of DDDs (public pharmacies 2010 – 2019) for ATC class A02B drugs for peptic ulcer and reflux disease

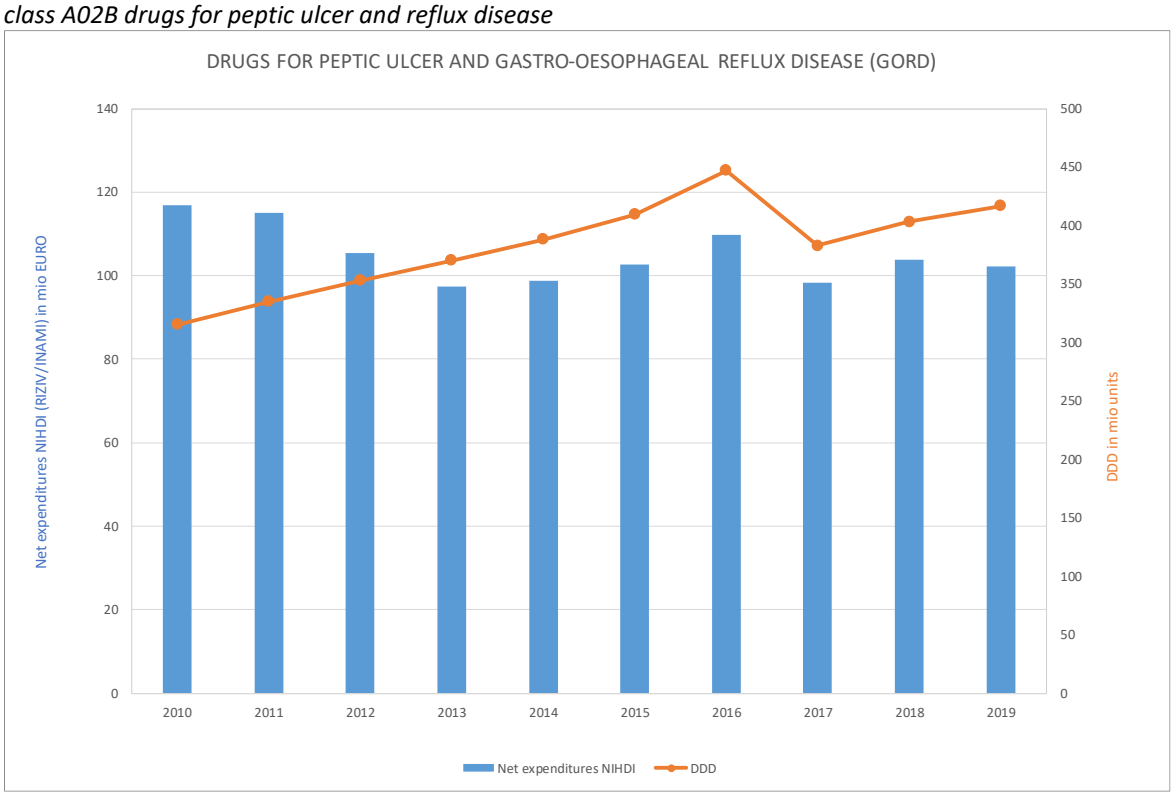


Figure 73: evolution of NIHDI net monthly expenditure (public pharmacies 2015 – 2019) for ATC class A02B drugs for peptic ulcer and reflux disease

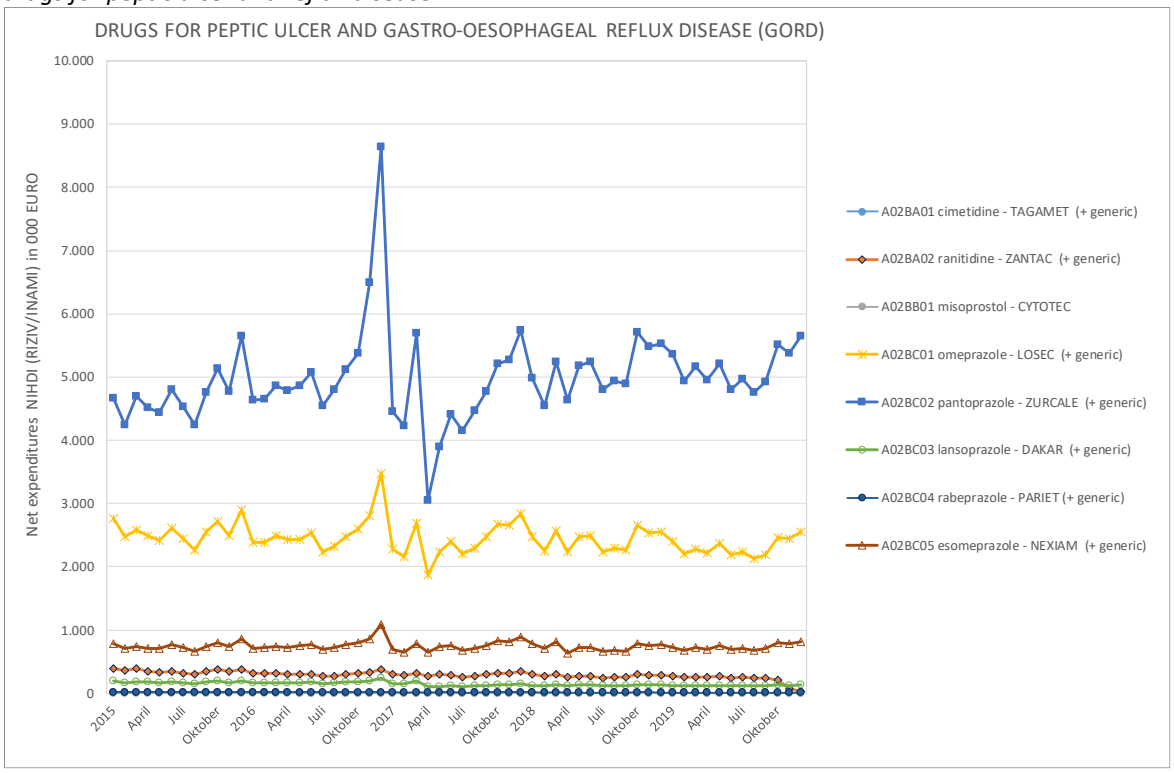


Figure 74: evolution of number of DDDs per month (public pharmacies 2015 – 2019) for ATC class A02B drugs for peptic ulcer and reflux disease

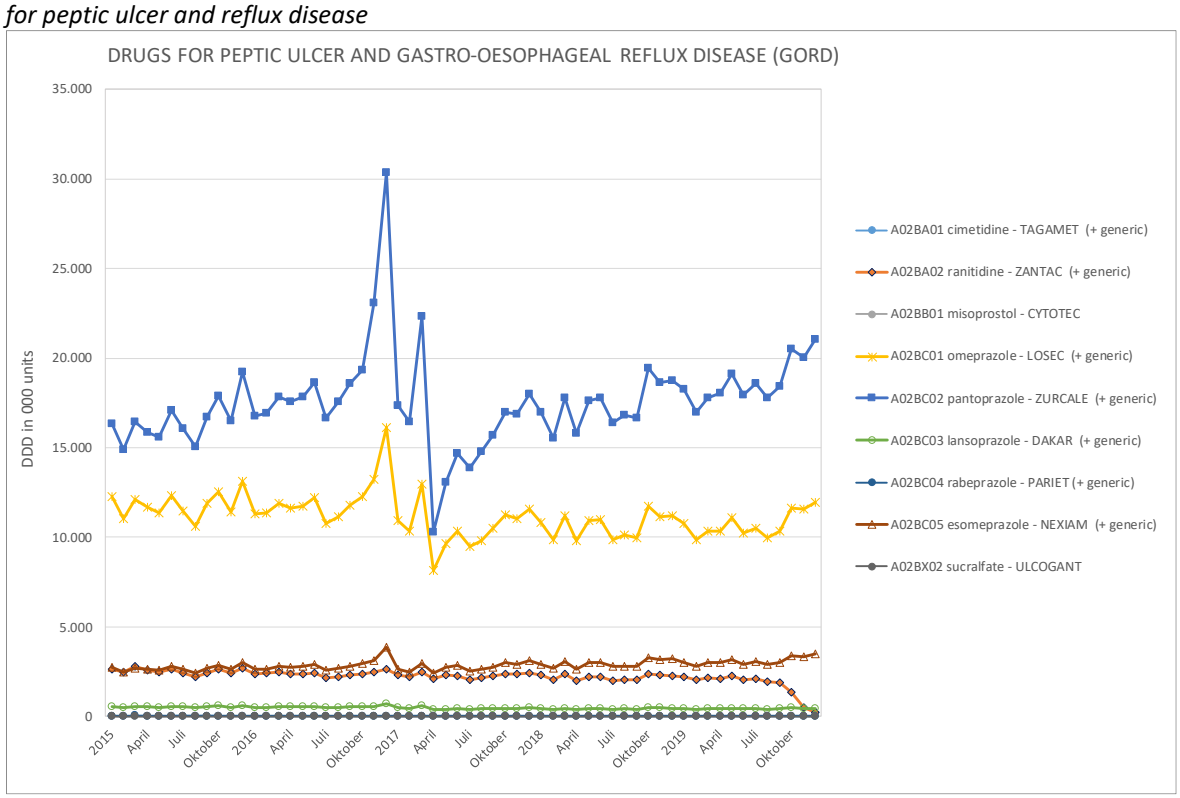


Figure 75: evolution of number of patients per year (public pharmacies 2016 – 2019) for ATC class A02B drugs for peptic ulcer and reflux disease

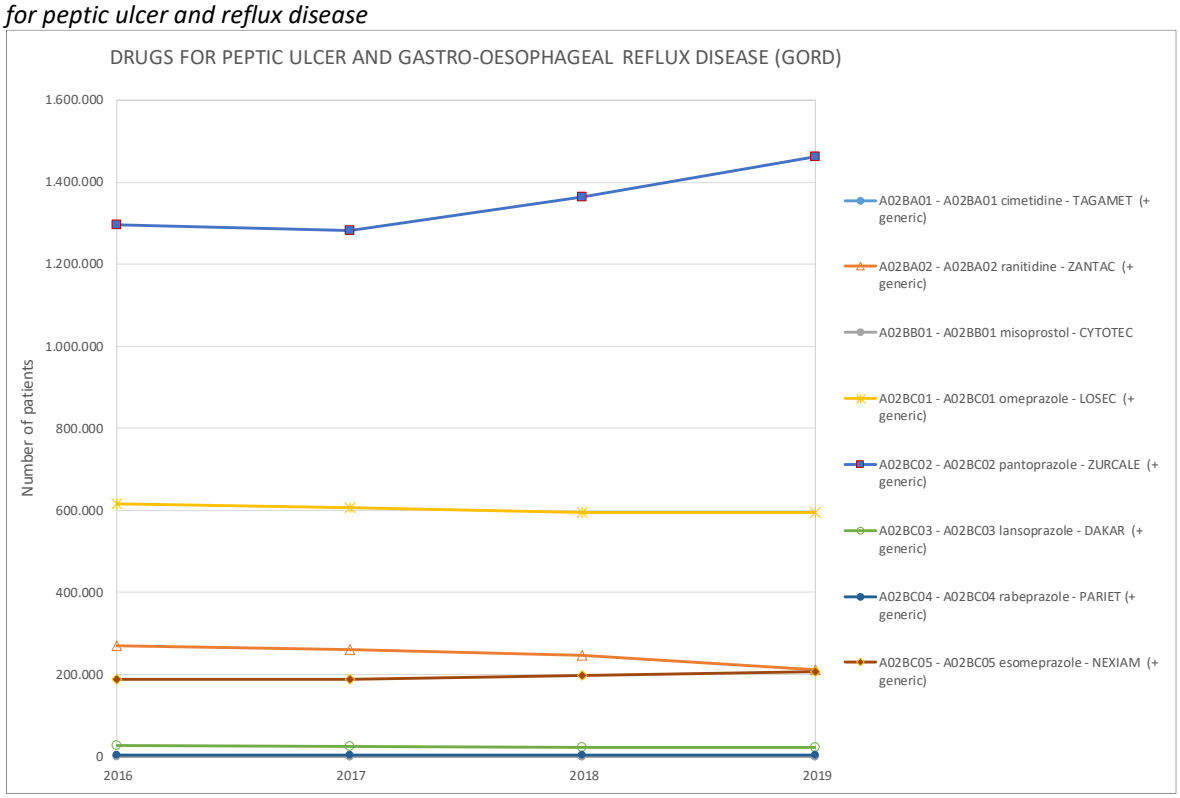


Figure 76: evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2016 – 2019) for ATC class A02B drugs for peptic ulcer and reflux disease

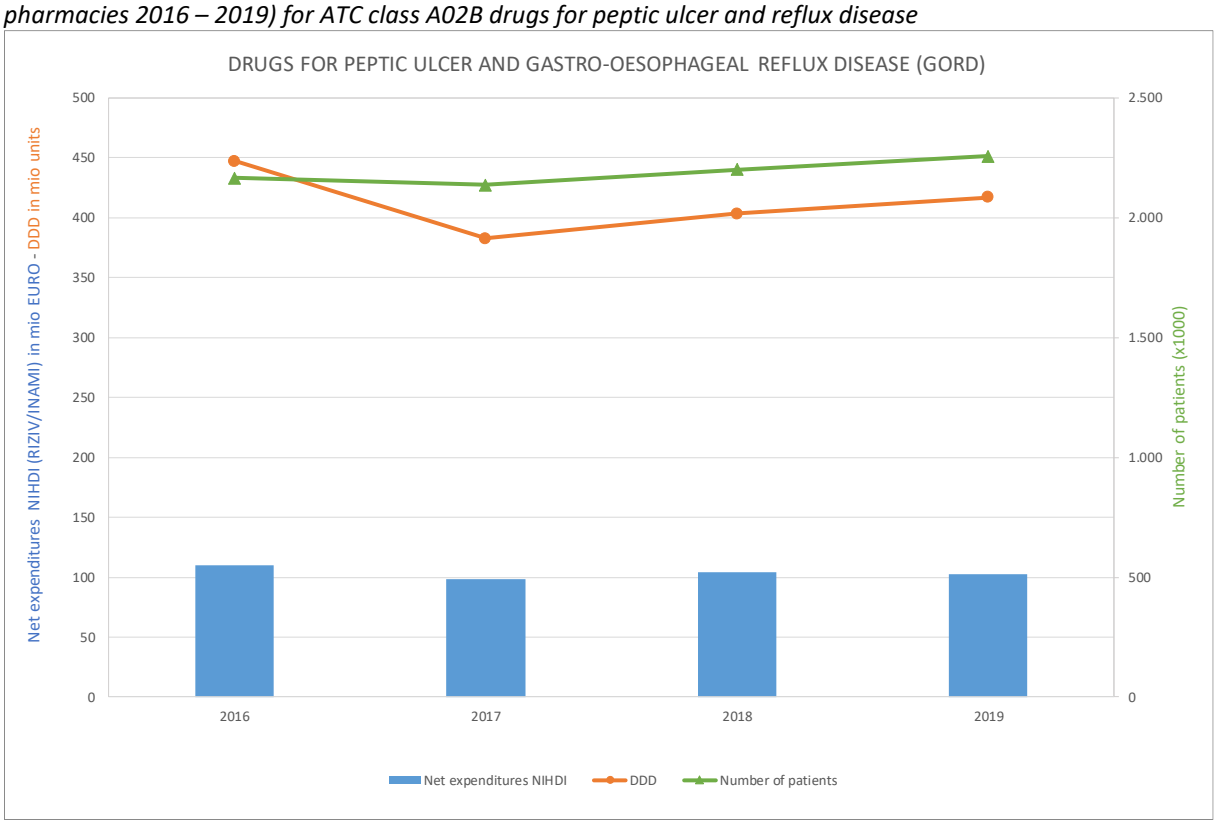
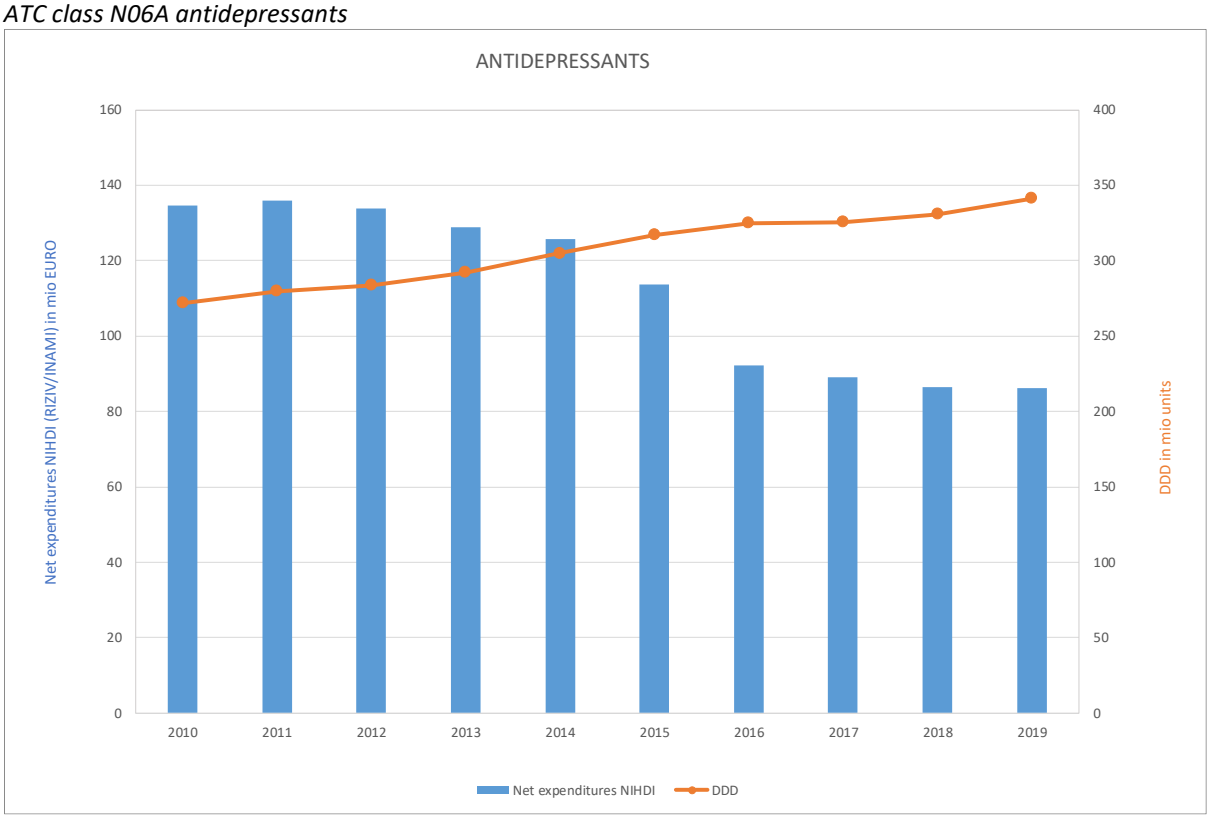


Figure 77: evolution of NIHDI net annual expenditure and number of DDDs (public pharmacies 2010 – 2019) for ATC class N06A antidepressants



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. Nevertheless, there was still a slight reduction in expenditure in 2018 and 2019, despite the steady increase in DDDs.

Figure 78: evolution of NIHDI net monthly expenditure (public pharmacies 2015 – 2019) for ATC class N06A antidepressants

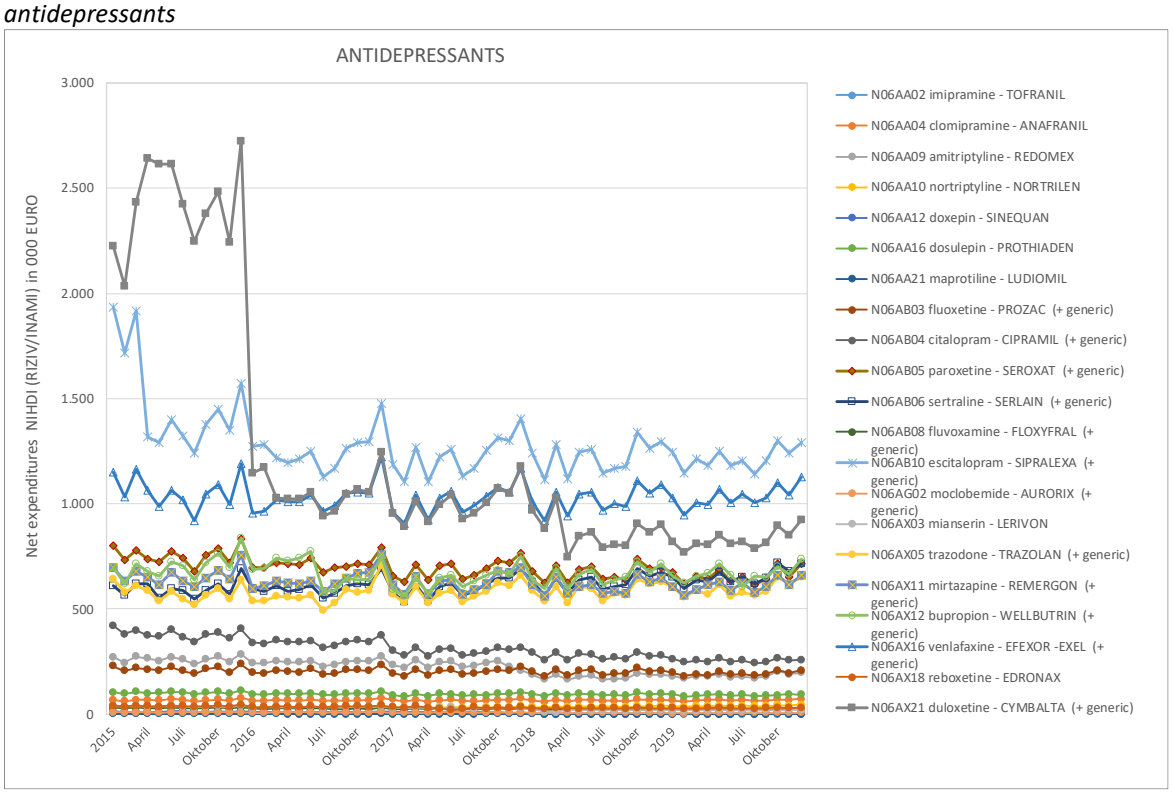


Figure 79: evolution of number of DDDs per month (public pharmacies 2015 – 2019) for ATC class N06A antidepressants

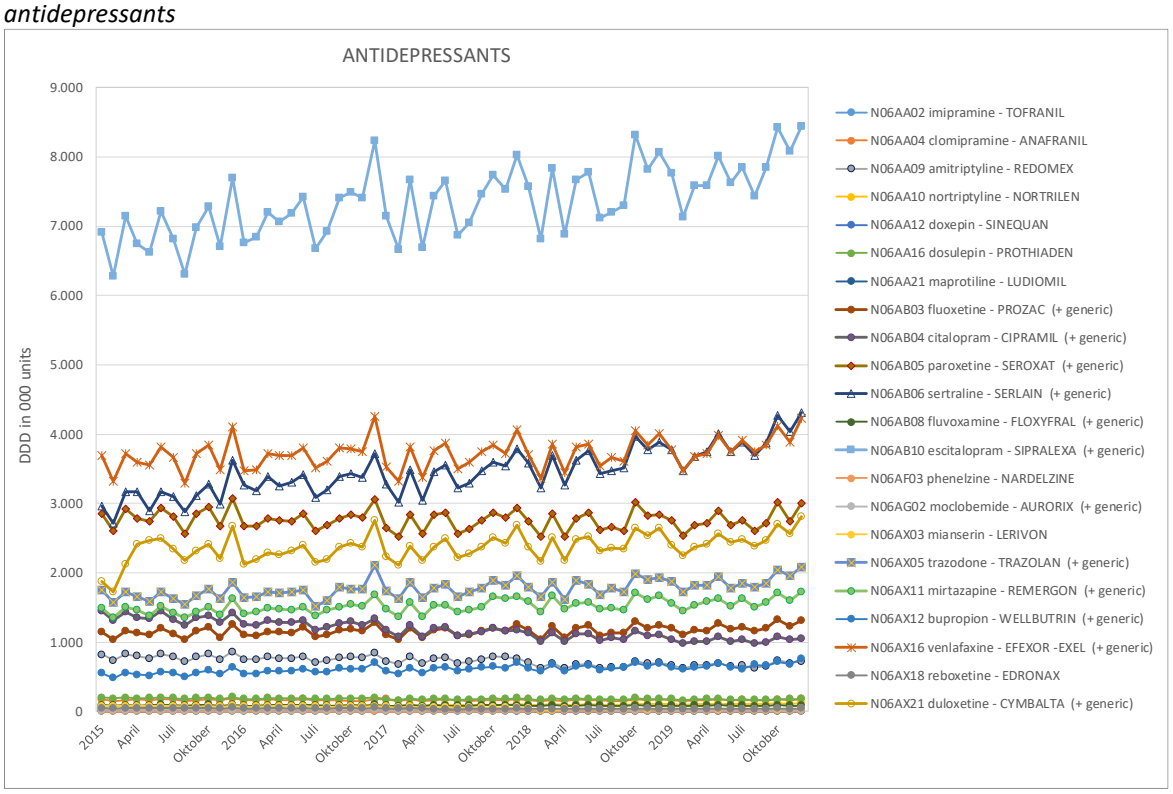
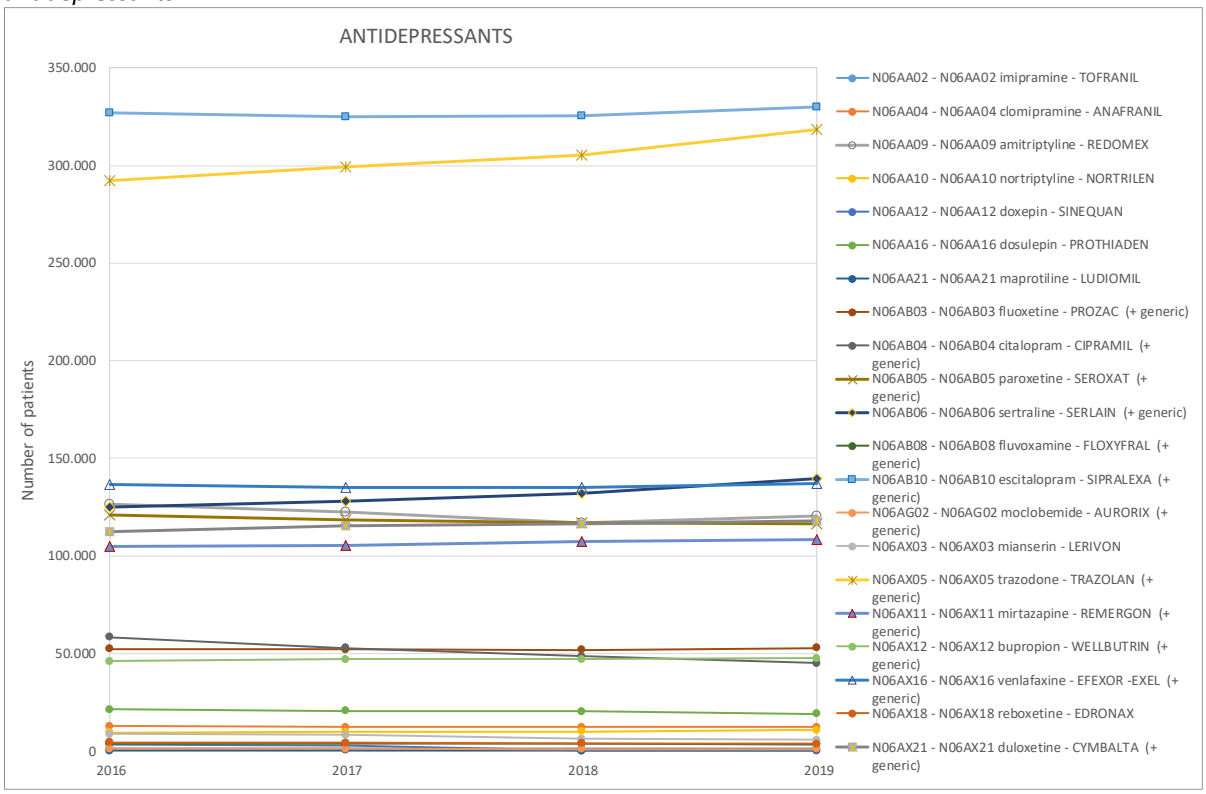


Figure 80: evolution of number of patients per year (public pharmacies 2016 – 2019) for ATC class N06A antidepressants

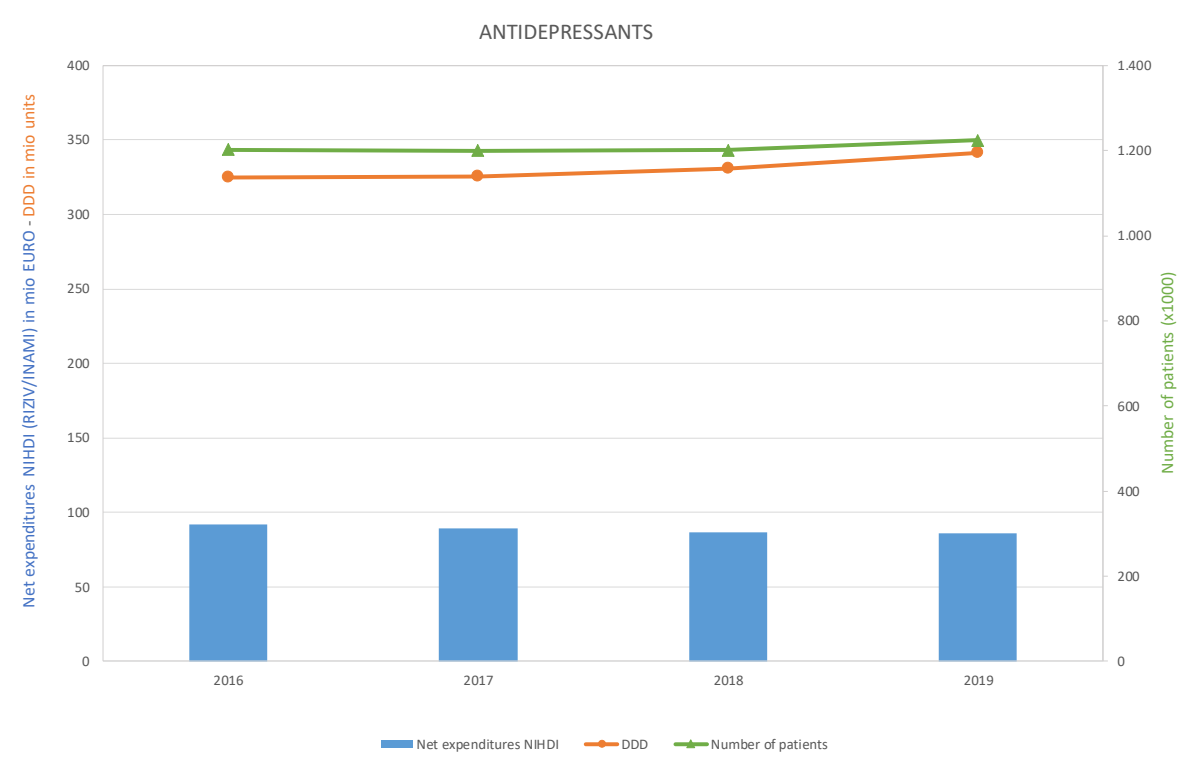


Expenditure on antidepressants is on a slight downward trend. The steep fall seen in previous years (2015 and 2016), and largely due to the arrival of various generics and the opening up of some reference clusters, has continued, less steeply, since 2017. A downward trend in expenditure is particularly noticeable for medicines based on duloxetine. Given that the number of DDDs of this molecule is fairly stable, the drop in expenditure can be explained by a further fall in prices.

The most used antidepressants, both in terms of numbers of patients and in number of DDDs, are antidepressants based on escitalopram (Sipralexa and generics). Since 2016, this molecule has accounted for most of the expenditure on antidepressants.

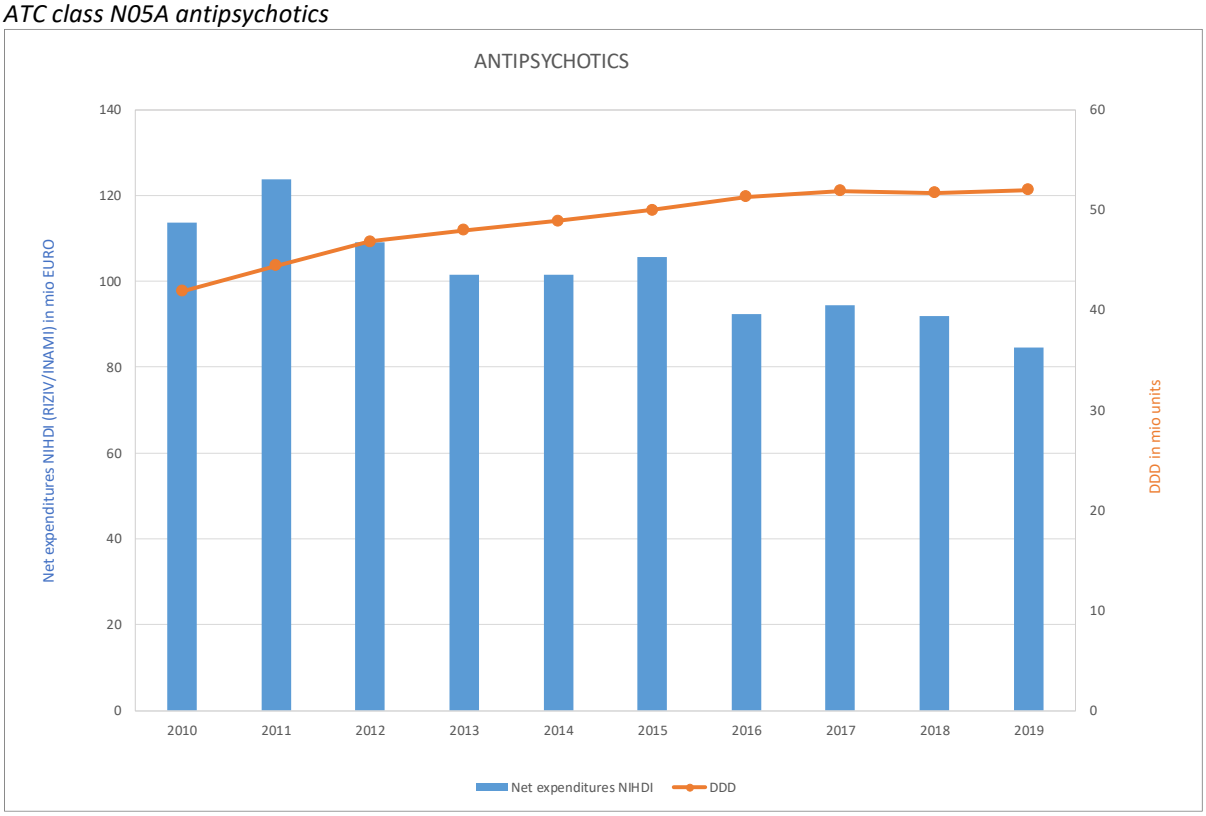
The number of patients remains relatively stable for most antidepressants. Only the molecule trazodone stands out as an antidepressant used by an increasing number of patients. This increase, however, is not reflected in the number of DDDs, nor in the expenditure figures. The total number of patients using antidepressants has not changed noticeably. In 2019, there was a slight increase compared to 2018 (a rise of 1.4%).

Figure 81: evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2016 – 2019) for ATC class N06A antidepressants



Conclusion: The recent evolution in antidepressants is relatively limited. For three years in a row, the number of patients has remained quite stable, with a slight increase in 2019. This increase is reflected in the number of DDDs, which has grown somewhat more strongly in 2019 than in previous years. Expenditure, however, has been on a slight downward trend in the last four years.

Figure 82: evolution of NIHDI net annual expenditure and number of DDDs (public pharmacies 2010 – 2019) for ATC class N05A antipsychotics



The upward trend in the number of DDDs, observable for some time now, has levelled off since 2017. Expenditure is generally on a downward trend, which, after a slight rise in 2017, has continued in 2018 and 2019.

Figure 83: evolution of NIHDI net monthly expenditure (public pharmacies 2015 – 2019) for ATC class N05A antipsychotics

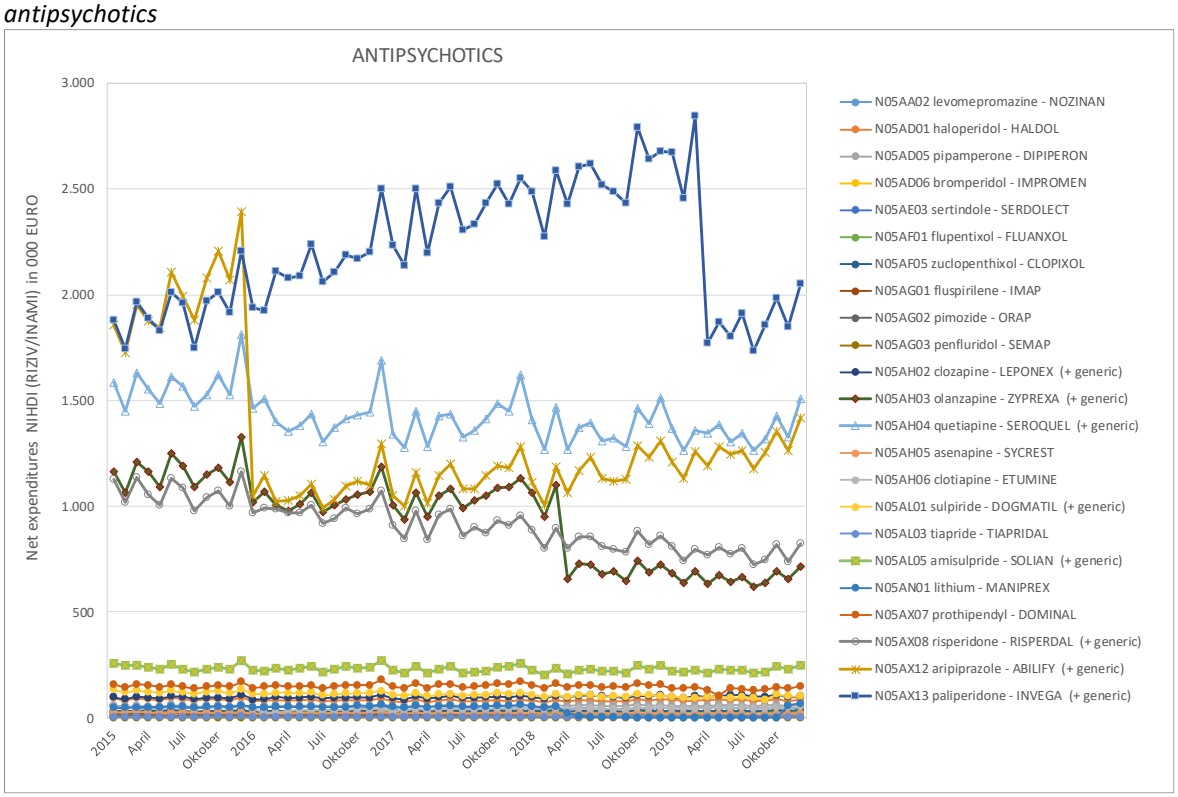


Figure 84: evolution of number of DDDs per month (public pharmacies 2015 – 2019) for ATC class N05A antipsychotics

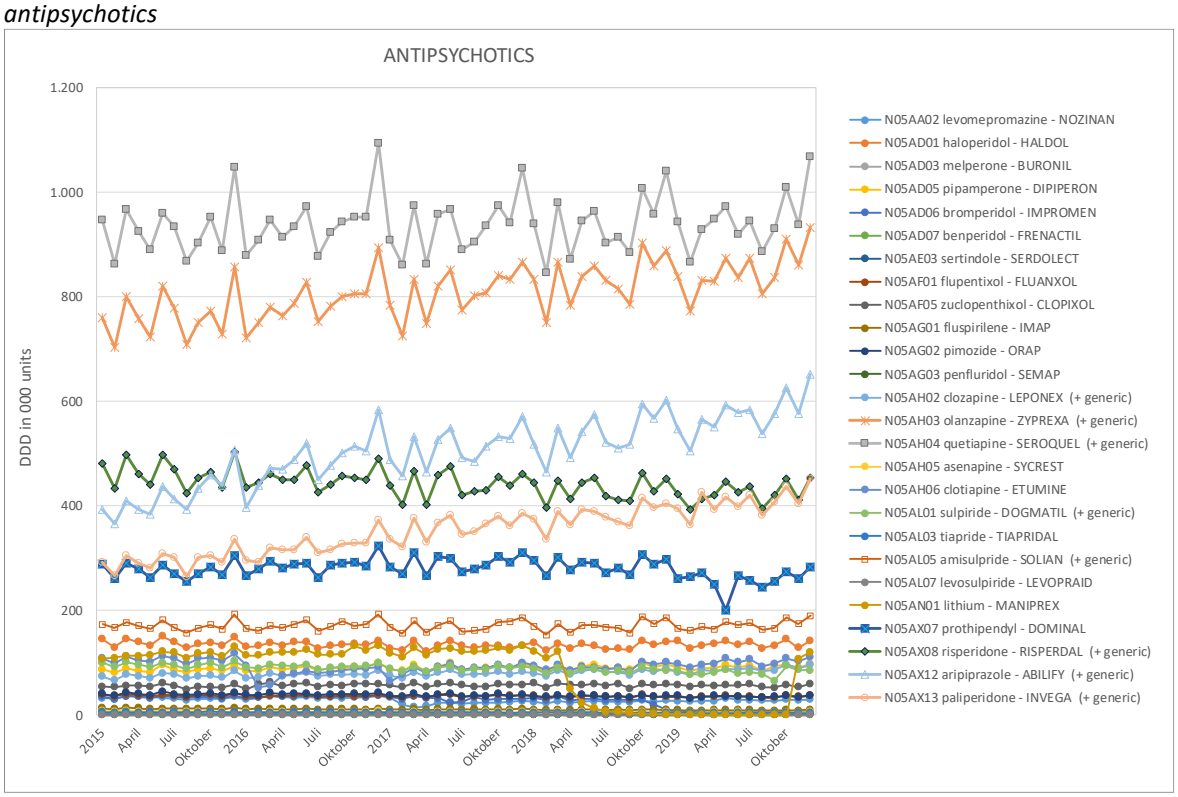
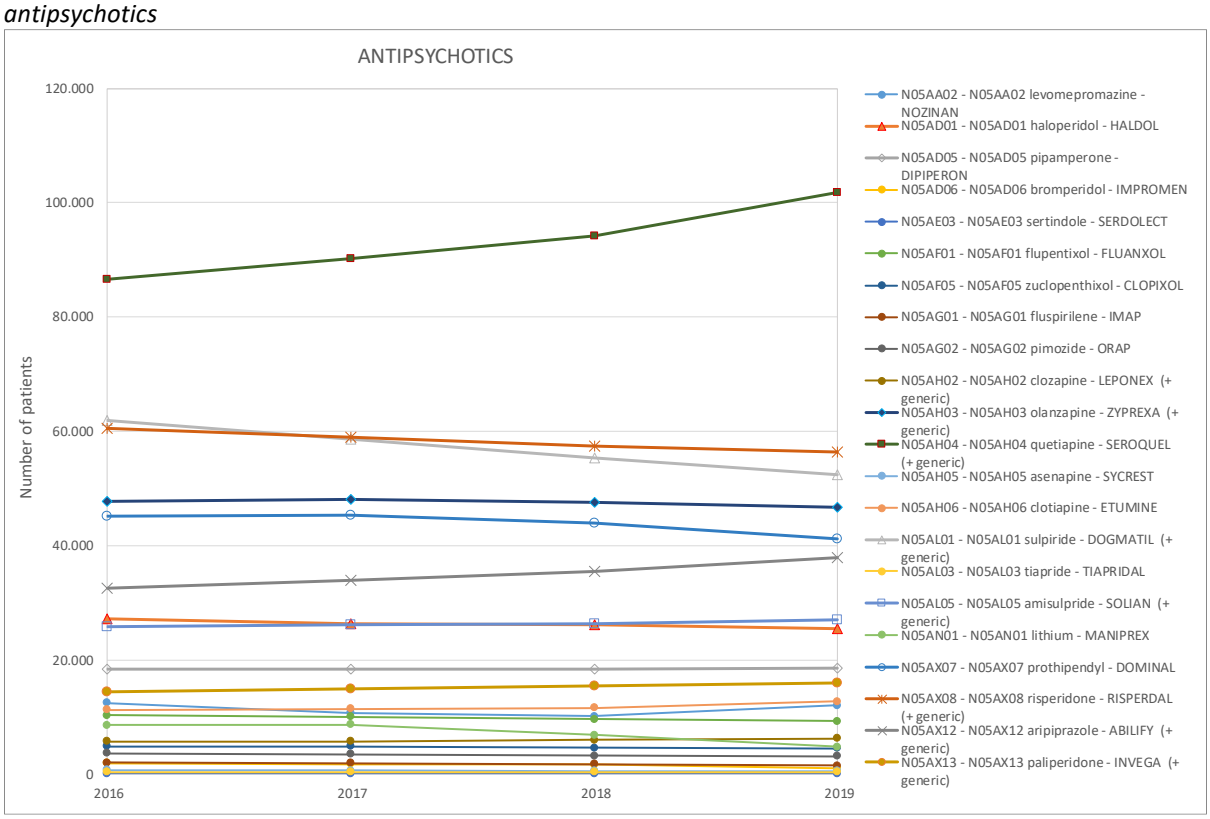


Figure 85: evolution of number of patients per year (public pharmacies 2016 – 2019) for ATC class N05A antipsychotics



In 2018 and 2019, 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).

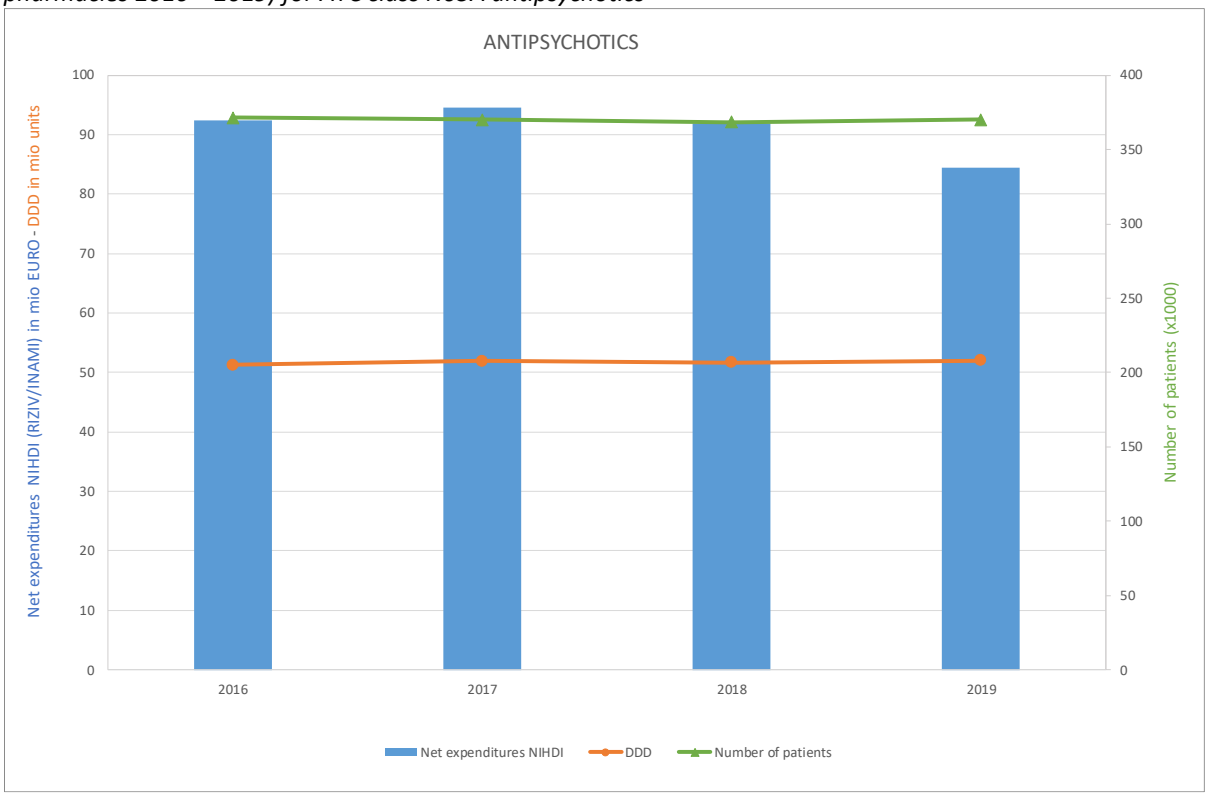
Spending on olanzapine fell noticeably in April 2018. At that time, the company reduced the price of various olanzapine-based specialties. This price reduction followed the introduction of the so-called 'ceiling prices', with a risk that more expensive packs of drugs would no longer be reimbursed.

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. Yet paliperidone still accounts for most of the expenditure on antipsychotics (29% of the expenditure in 2019) . Moreover, expenditure on this molecule is still on an upward trend, even after application of the reference reimbursement system. Spending on Abilify® and generics (aripiprazole) 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 three years, apart from some seasonal peaks and the spending on lithium (see below).

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. The reduction for the remaining antipsychotics masks the increase for Seroquel ® and generics: the total number of patients treated with antipsychotics is stable.
There has also been little change in the number of DDDs in recent years. This is true for all the antipsychotics, except for lithium-based drugs (see below).

It is worth paying particular attention to lithium. The impact of spending on this molecule is quite limited in terms of spending on antipsychotics as a whole. The number of patients and the number of DDDs is also relatively low, compared to the whole group. Nevertheless, there is a striking kink in all three curves (expenditure, number of patients, number of DDDs) from the beginning of 2018. This clear drop is due to the long-time unavailability of Maniprex®. Since 1 November 2019, Camcolit® (also based on lithium) is reimbursed as an alternative treatment for bipolar disorders, as is reflected in a rise in the relevant curves.

Figure 86: evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2016 – 2019) for ATC class N05A antipsychotics



Conclusion: There have been no striking changes in the last three years in the use of antipsychotics. Both the number of patients and the number of DDDs have remained stable. Expenditure fell slightly in 2018 and 2019, due to, respectively, the ceiling price for olanzapine and application of the reference reimbursement system for paliperidone.

N03A – ANTI-EPILEPTICS

Figure 87: evolution of NIHDI net annual expenditure and number of DDDs (public pharmacies 2010 – 2019) for ATC class N03A anti-epileptics

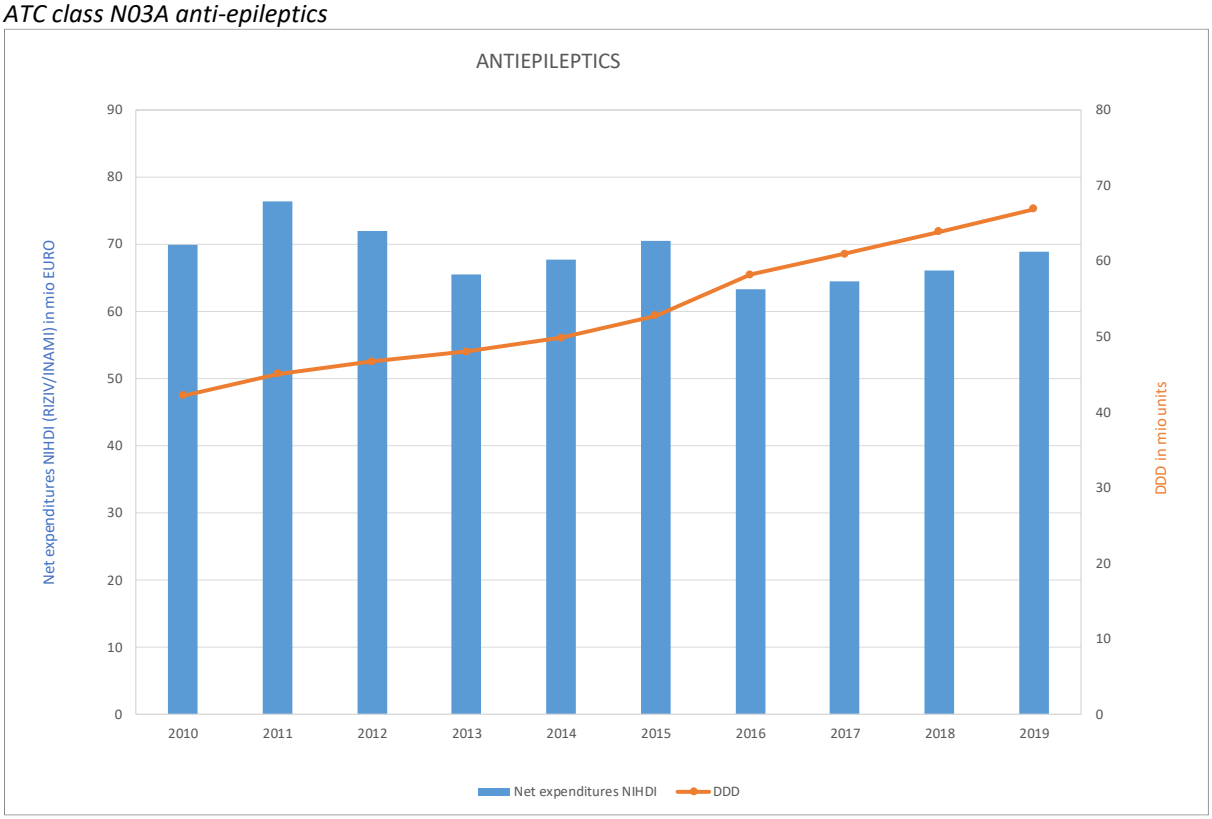


Figure 88: evolution of NIHDI net monthly expenditure (public pharmacies 2015 – 2019) for ATC class N03A anti-epileptics

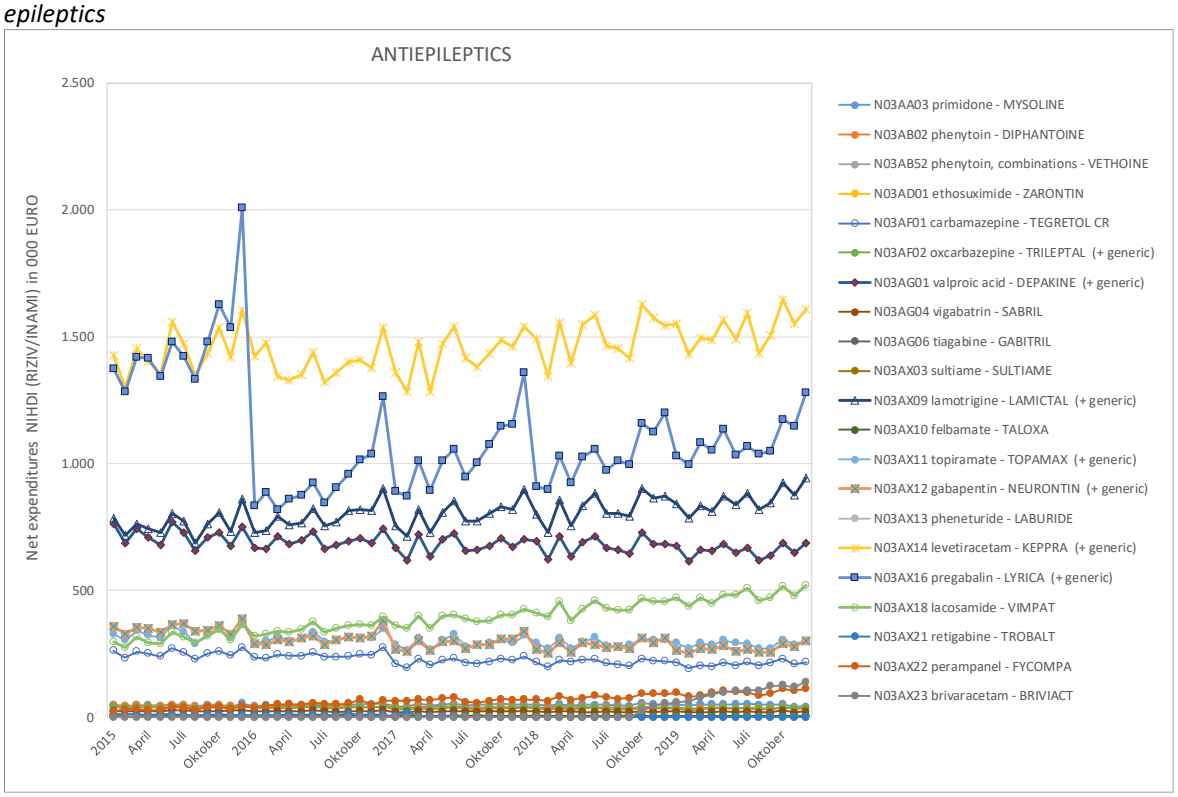


Figure 89: evolution of number of DDDs per month (public pharmacies 2015 – 2019) for ATC class N03A anti-epileptics

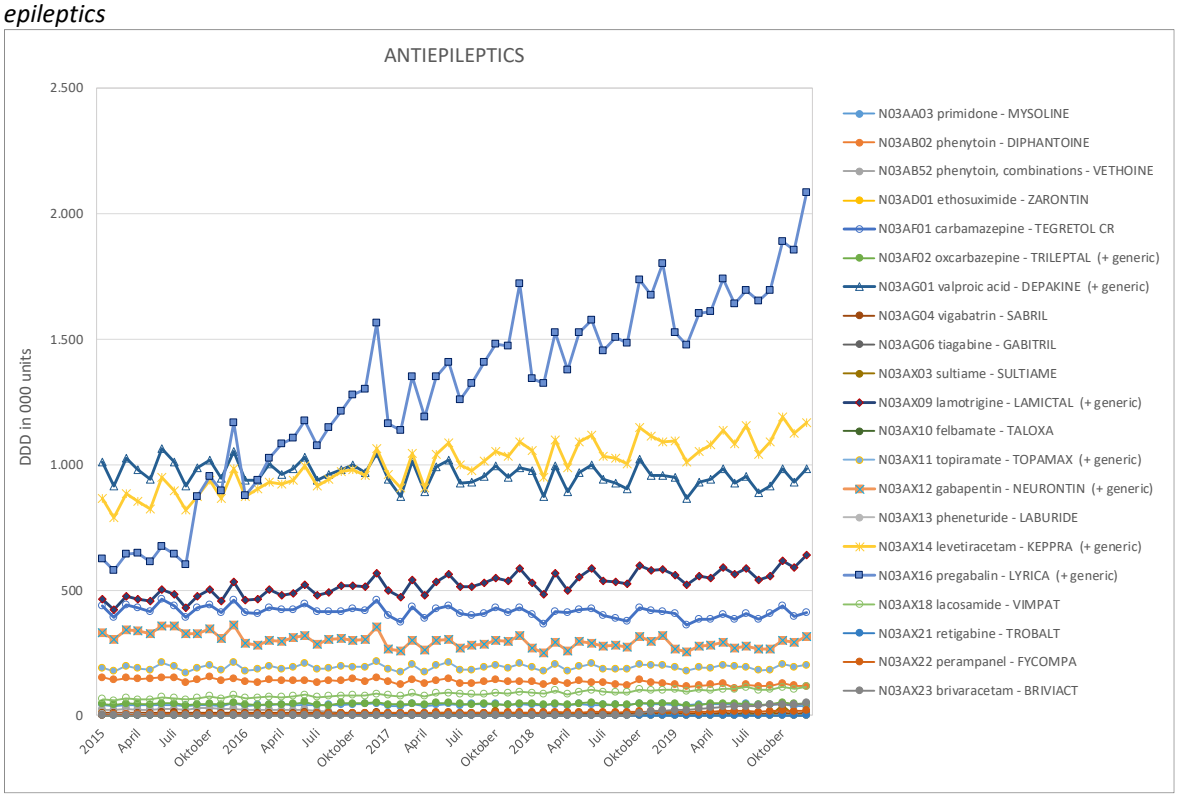
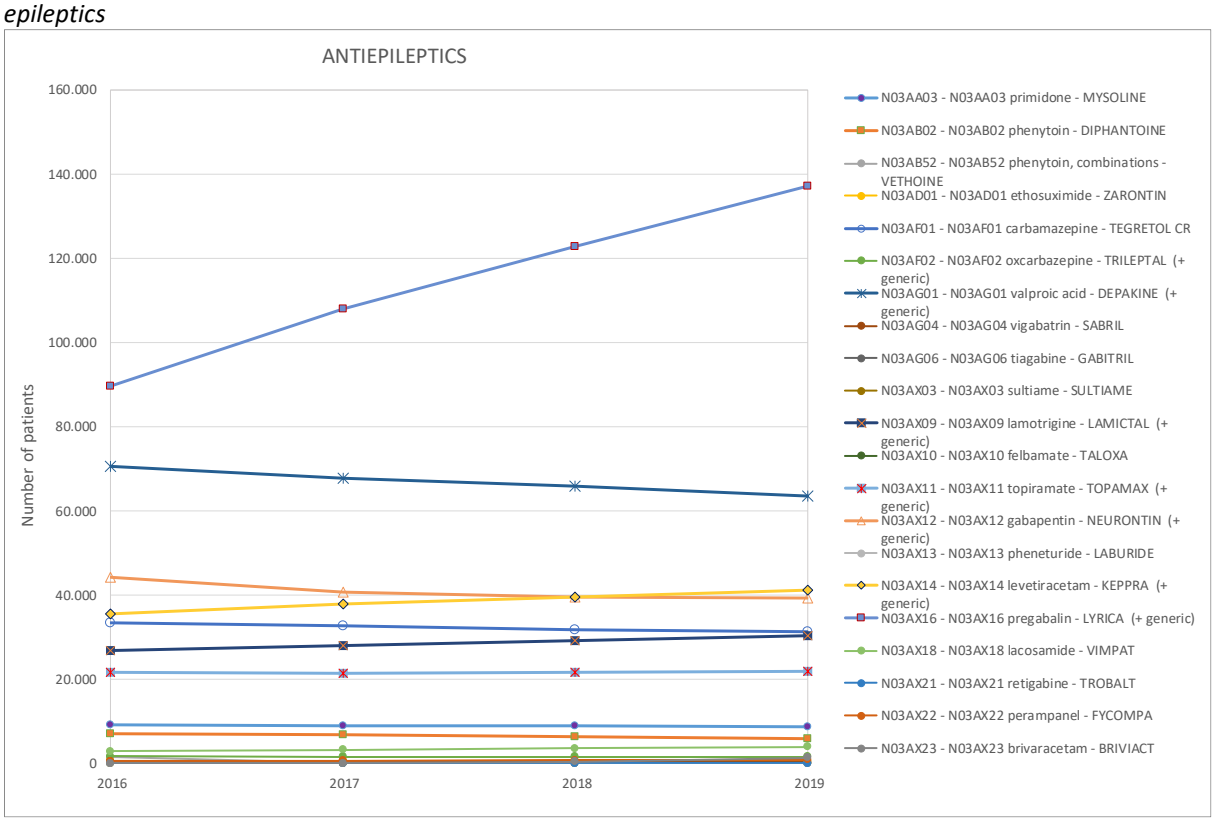


Figure 90: evolution of number of patients per year (public pharmacies 2016 – 2019) for ATC class N03A anti-epileptics



Expenditure on anti-epileptics has experienced a slight upward trend over the last three 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 for pregabalin is due to the opening of the reference reimbursement system for this molecule.

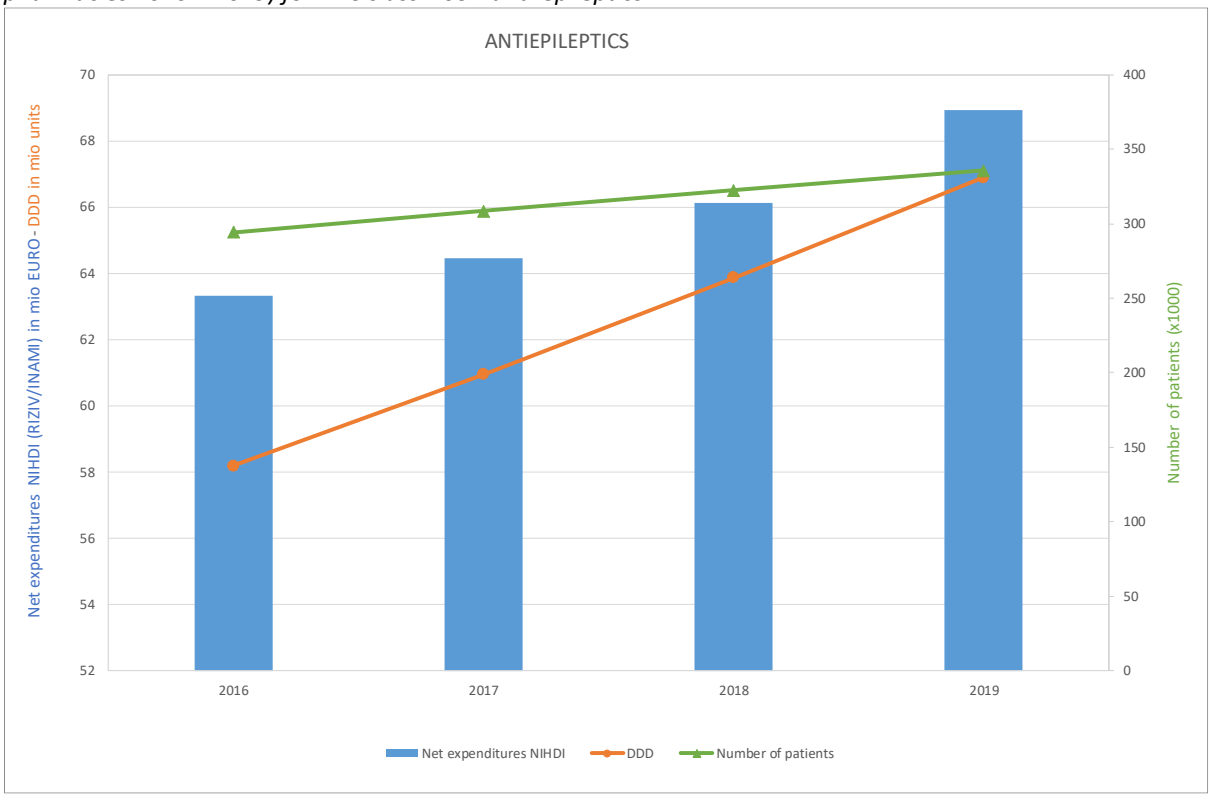
With regard to the number of patients, a very steep increase may be seen for Lyrica ® and its generics. Here, we should note that pregabalin is also indicated for other indications (anxiety disorders and neuropathic pain) and that Lyrica® has been reimbursed in chapter I since 1 September 2015. In 2019, only 1.5% 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), 98.5% 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, or even slightly decreasing. The fact that the increase in expenditure is less pronounced than the increasing number of patients can be explained by the reduction in the price of pregabalin at the beginning of 2016 as a result of the opening of the reference cluster.

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 specialties 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 91: evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2016 – 2019) for ATC class N03A anti-epileptics



Conclusion: The expenditure, the number of patients and the use in DDDs have all experienced a marked upward trend in recent years. 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.

B02B – VITAMIN K AND OTHER HAEMOSTATICS

Figure 92: evolution of NIHDI net annual expenditure and number of DDDs (public pharmacies 2010 – 2019) for ATC class B02B vitamin K and other haemostatics

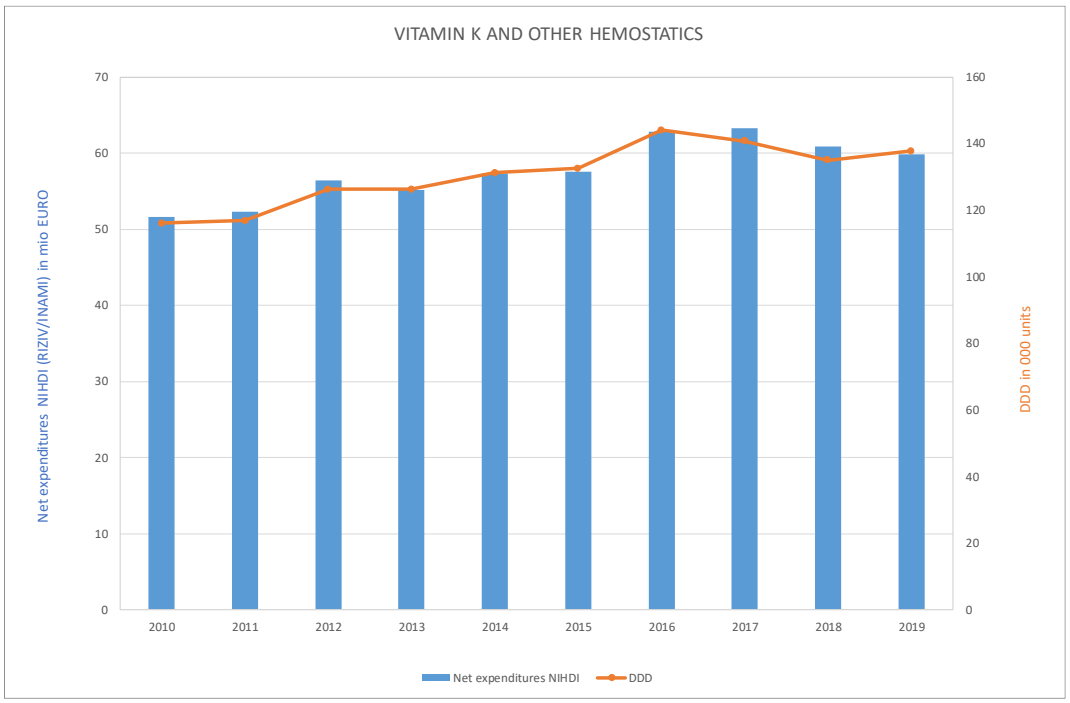
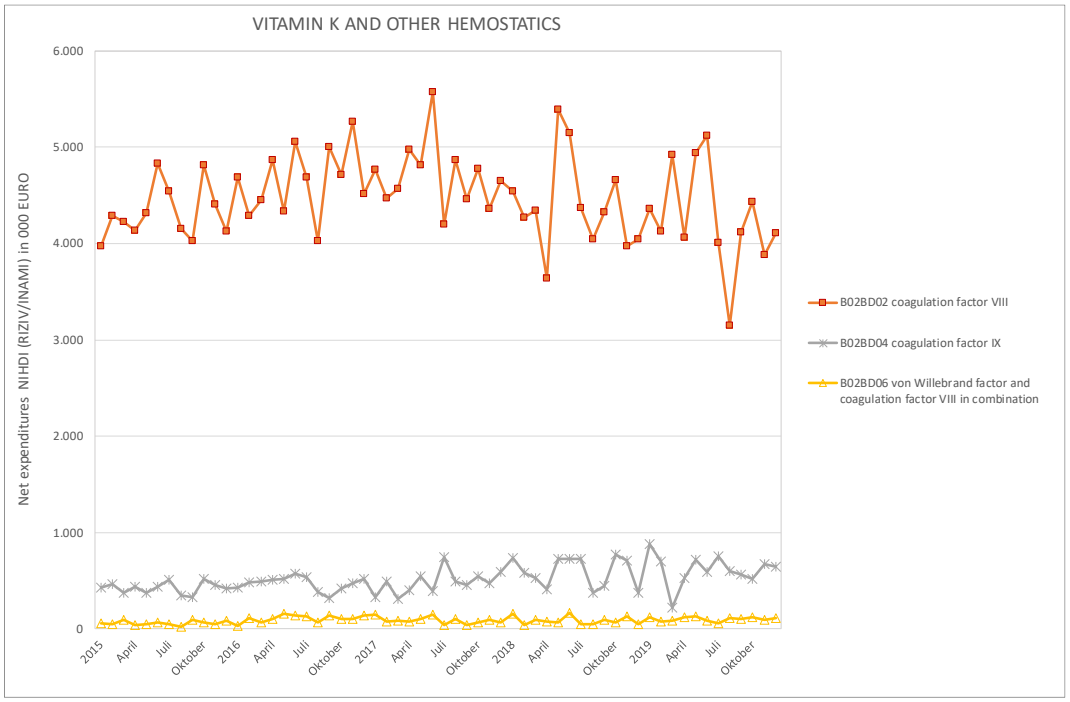
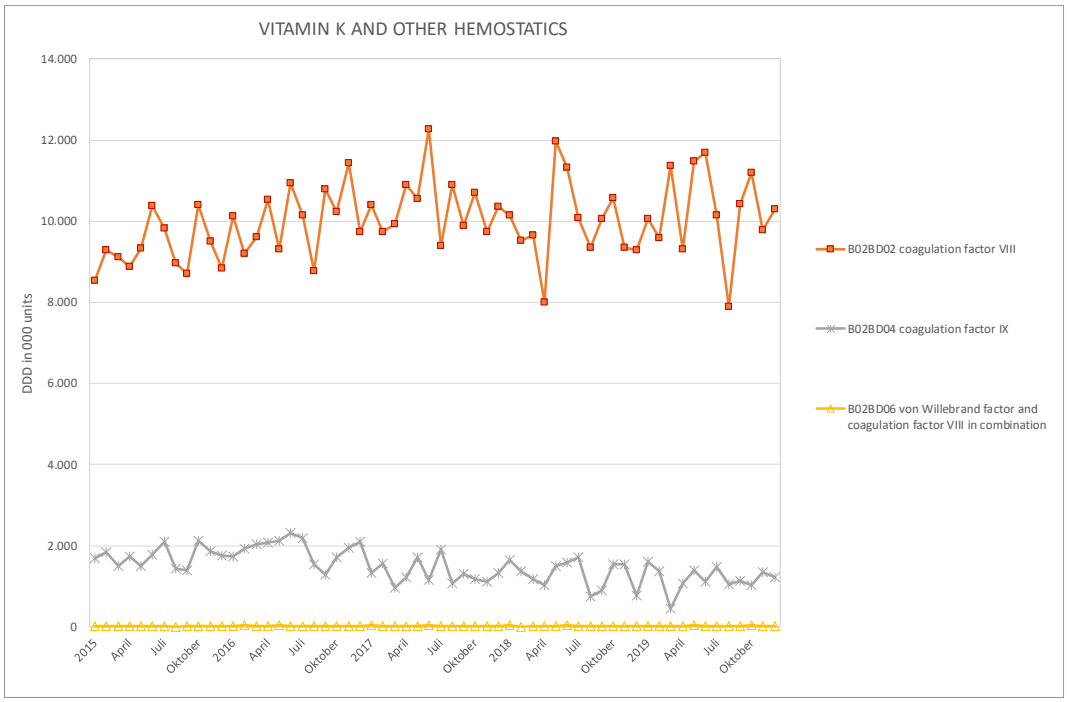


Figure 93: evolution of NIHDI net monthly expenditure (public pharmacies 2015 – 2019) for ATC class B02B vitamin K and other haemostatics



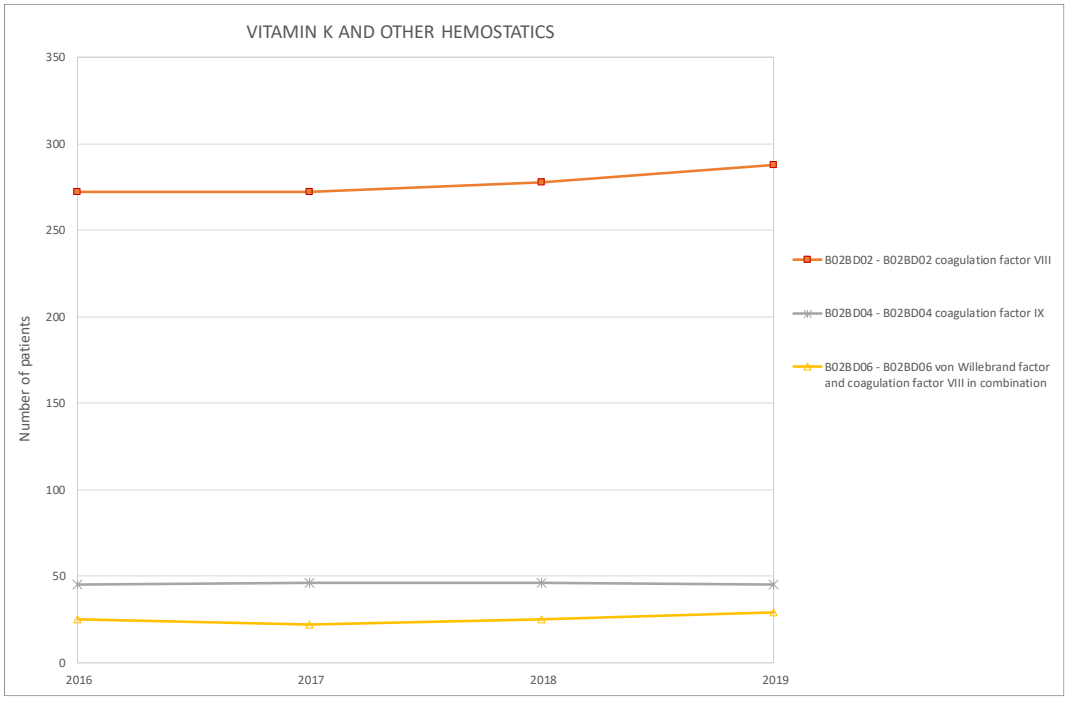
B02BD02: ADVATE, ADYNOVI, AFSTYLA, ELOCTA, FACTANE, HELIXATE NEXGEN, JIVI, KOGENATE, KOVALTRY, NUWIQ, OCTANATE, REFACTO
B02BD04: ALPROLIX, BENEFIX, IDELVION, NONAFACT
B02BD06: HAEMATE P, WILATE

Figure 94: evolution of number of DDDs per month (public pharmacies 2015 – 2019) for ATC class B02B vitamin K and other haemostatics



B02BD02: ADVATE, ADYNOVI, AFSTYLA, ELOCTA, FACTANE, HELIXATE NEXGEN, JIVI, KOGENATE, KOVALTRY, NUWIQ, OCTANATE, REFACTO
B02BD04: ALPROLIX, BENEFIX, IDELVION, NONAFACT
B02BD06: HAEMATE P, WILATE

Figure 95: evolution of number of patients per year (public pharmacies 2016 – 2019) for ATC class B02B vitamin K and other haemostatics



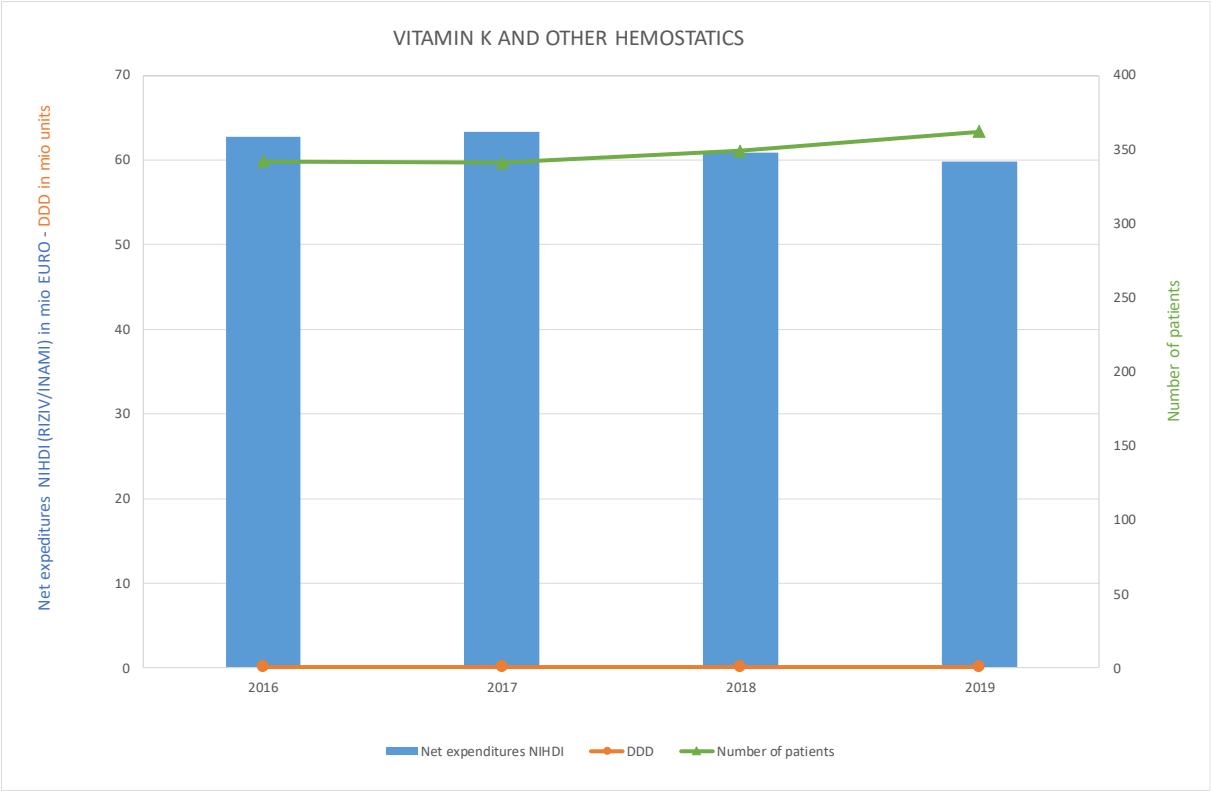
B02BD02: ADVATE, ADYNOVI, AFSTYLA, ELOCTA, FACTANE, HELIXATE NEXGEN, JIVI, KOGENATE, KOVALTRY, NUWIQ, OCTANATE, REFACTO
B02BD04: ALPROLIX, BENEFIX, IDELVION, NONAFACT
B02BD06: HAEMATE P, WILATE

On 1 July 2017, the price of Kogenate® and Helixate Nexgen® was reduced because the molecule coagulation factor VIII had been on the market for 18 years. This has resulted in a decreasing trend in expenditure on this molecule since 2017. Expenditure on coagulation factor IX (Alprolix®, Benefix®, Idelvion® and Nonafact®) is increasing slightly. Given that coagulation factor VIII is responsible for the lion's share of expenditure within the group shown, the fall in expenditure on this molecule is reflected in the expenditure on the whole group: this has also been on a decreasing trend since 2017.

The number of patients being treated remains relatively stable. In 2019, there was a slight increase. It should be noted that these are rare disorders, which means that a small increase in the absolute number of patients leads to a visible increase.

The use in DDDs fluctuates slightly: after a decrease in 2017 and 2018, a limited increase can be observed again in 2019.

Figure 96: evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2016 – 2019) for ATC class B02B vitamin K and other haemostatics



The number of DDDs used cannot be seen from the graph above. In 2016, 2017, 2018 and 2019 respectively, these amounted to: 144,083, 140,803, 135,043 and 137,752.

M05B – DRUGS AFFECTING BONE STRUCTURE AND MINERALIZATION

Figure 97: evolution of NIHDI net annual expenditure and number of DDDs (public pharmacies 2010 – 2019) for ATC class M05B drugs affecting bone structure and mineralization

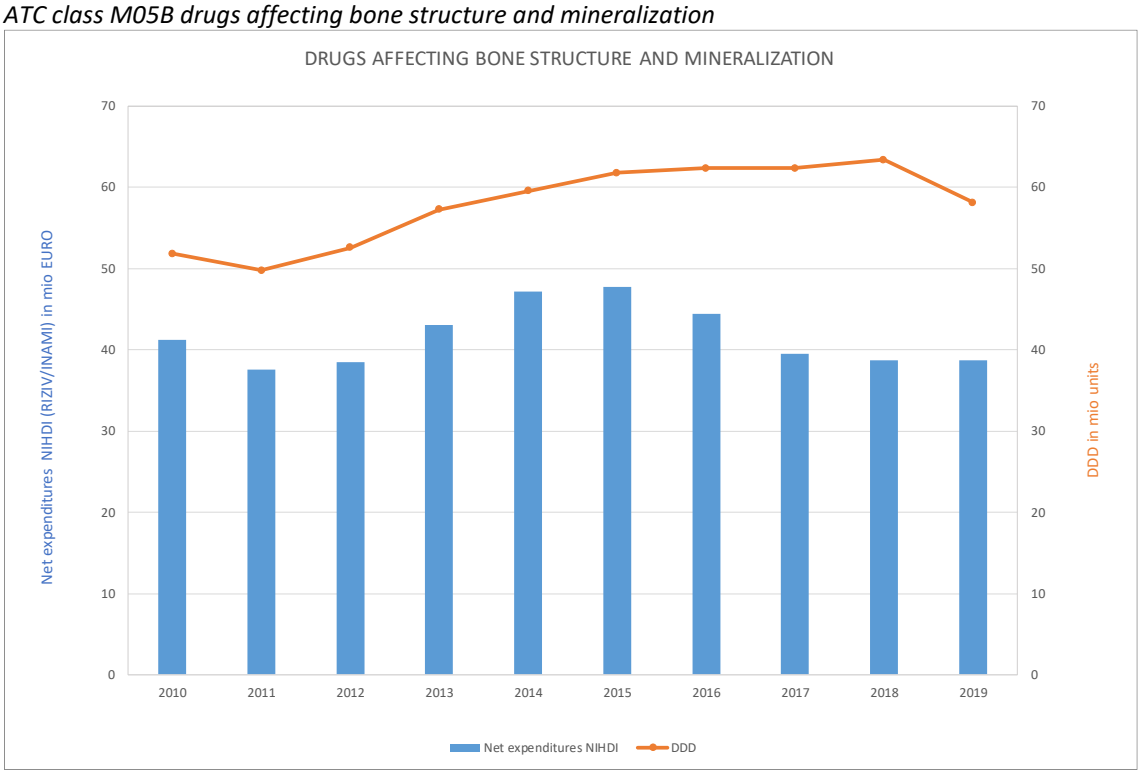
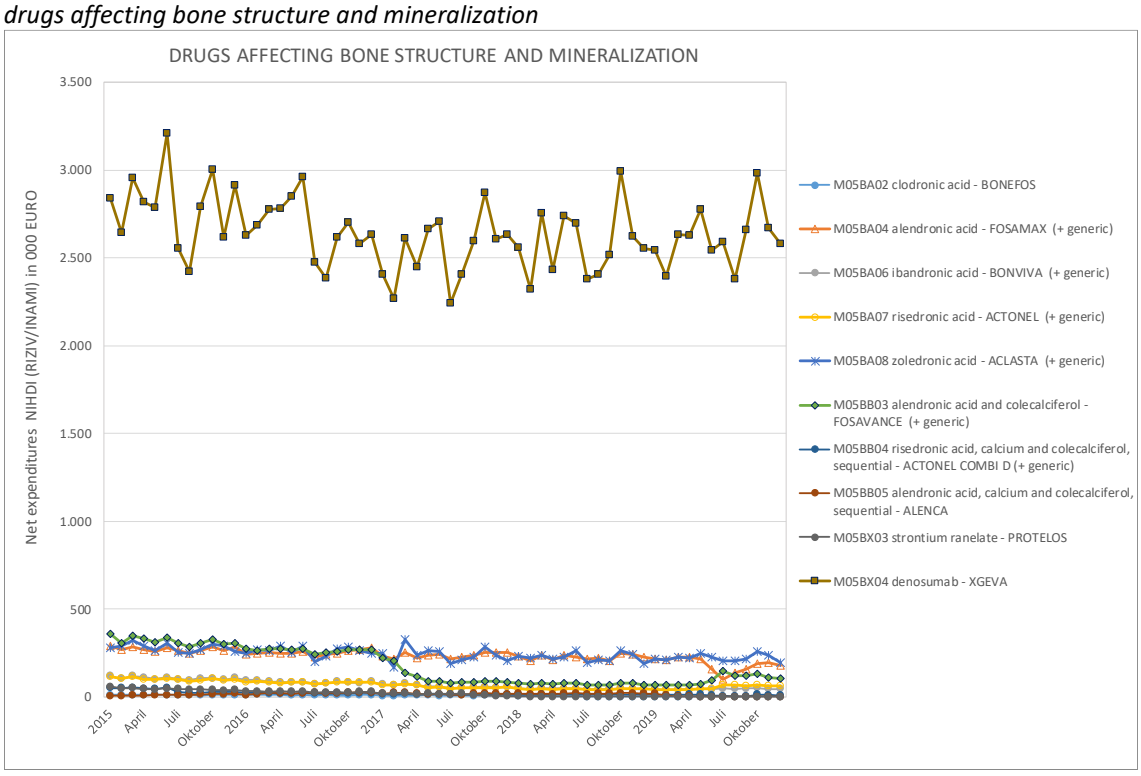


Figure 98: evolution of NIHDI net monthly expenditure (public pharmacies 2015 – 2019) for ATC class M05B drugs affecting bone structure and mineralization



The fall in expenditure on drugs affecting bone structure and mineralization, which was clearly noticeable from 2015, has stabilised since 2017. This stabilisation of expenditure on the class can also be seen for the 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, 81% of the expenditure on ATC-class M05B was due to denosumab (where Prolia ® and Xgeva ® account for 37% and 44% respectively of the expenditure on the M05B class). On 1 March 2017 the combi-cliff was applied to Fosavance® and its generics, resulting in a fall in expenditure for these molecules. In 2019, a temporary kink is seen in spending on Fosamax® (decrease) and Fosavance® (increase), which is due to the temporary lack of availability of Fosamax® (see below).

Whereas specialties based on denosumab (Prolia ®/ Xgeva®) are the biggest players in terms of expenditure (in 2019, the proportion Prolia ® / Xgeva ® was 46% / 56%), Fosamax® (and its generics) is at the top in terms of number of patients. In mid-2019, however, there was a clear decline in the number of patients being treated with Fosamax®. This sudden fall was due to a temporary lack of availability. At the same time, an increase can be seen in the number of patients using Fosavance®. This increase can be explained by a switch from Fosamax® to alternatives as a result of the lack of availability 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.

When we look at use in terms of DDDs, we see that specialties based on denosumab (Prolia ®/ Xgeva®) are used most (in 2019, the proportion Prolia ® / Xgeva ® was 42% / 58%) and that this use is showing an increasing trend. For the other drugs, we see a reflection of the data on number of patients: a clear decrease for Fosamax® (and its generics), (partly) offset by an increase for Fosavance® and to a lesser extent for Actonel®. The disappearance of Alenca® at the beginning of 2019 can also be seen on the DDD graph.

Figure 99: evolution of number DDDs per month (public pharmacies 2015 – 2019) for ATC class M05B drugs affecting bone structure and mineralization

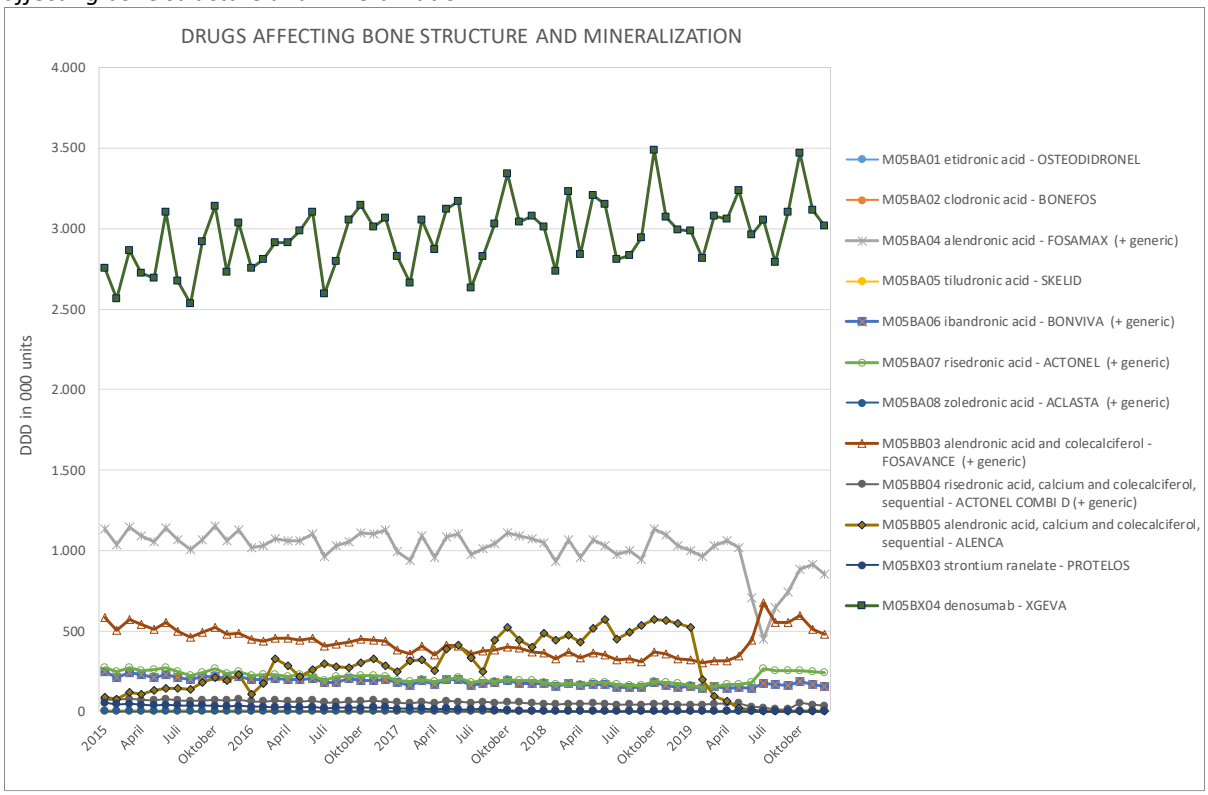


Figure 100: evolution of number of patients per month (public pharmacies 2016 – 2019) for ATC class M05B drugs affecting bone structure and mineralization

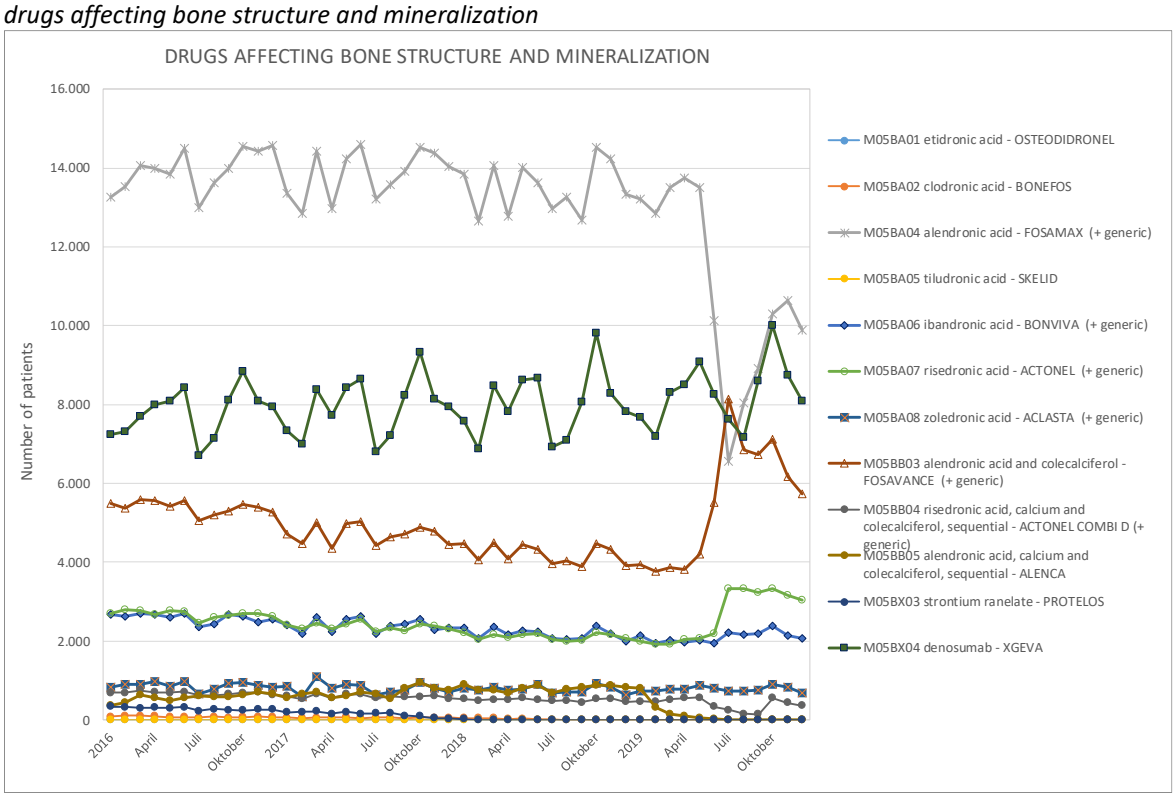
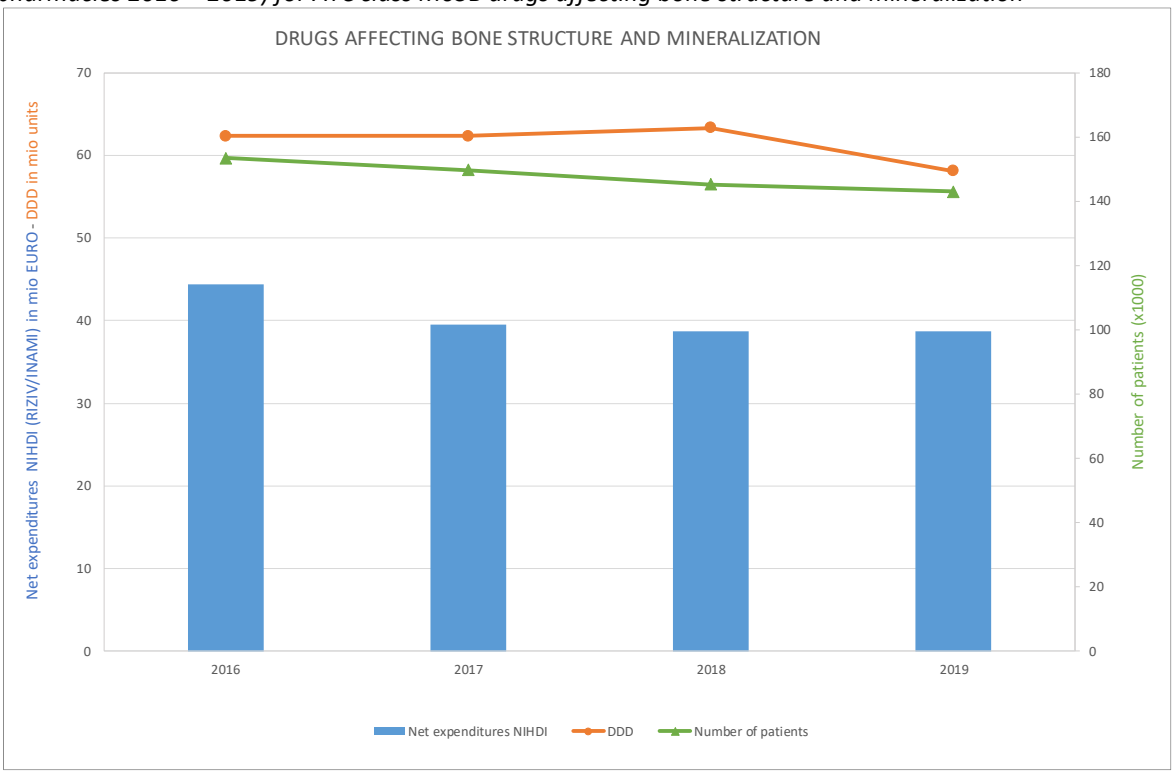


Figure 101: evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2016 – 2019) for ATC class M05B drugs affecting bone structure and mineralization



Conclusion: Expenditure on this class is stabilising. The number of patients shows a slight downward trend, whereas the DDDs show a slight upward trend. Only in 2019, for the first time since 2011, can we see a fall in the number of DDDs.

L03A – IMMUNOSTIMULANTS

Since 2014, we can see a clear fall in net expenditure, the number of patients treated, as well as the number of DDDs for ATC class L03A, immunostimulants. The most striking change is the decline in the use of Avonex®, the specialty based on interferon beta-1a.

Avonex® is used for the treatment of multiple sclerosis. The sharp fall in the use of this specialty is probably due to the reimbursement of new first-line drugs for multiple sclerosis, such as Aubagio® (L04AA31), Tecfidera® (L04AX07), Plegridy® (peginterferon beta-1a), etc.

Furthermore, a number of price reductions have also been implemented in this class, which are one of the causes of the fall in net annual expenditure:

- Interferon beta-1a:
  - 01/01/2019: 'old medicines' measure (18 years)

- Interferon beta-1b:
  - 01/03/2017: regularization of 'biologicals': For those biological specialties whose price was already reduced by 7.5% between 1 January 2014 and 1 January 2017 under the 'biologicals' measure, an additional price reduction of 2.7% was implemented, to reach a total price reduction of 10%.
  - 01/04/2018: regulation of 'biologicals': For those biological specialties whose price was already reduced by 10% before 1 April 2018 under the 'biologicals' measure, an additional price reduction of 5.56% was implemented, to reach a total price reduction of 15%.

- Peginterferon:
  - 01/07/2017: 'old medicines' measure (12 years)

- Filgrastim:
  - 01/03/2017: regulation of 'biologicals': For those biological specialties whose price was already reduced by 7.5% between 1 January 2014 and 1 January 2017 under the 'biologicals' measure, an additional price reduction of 2.7% was implemented, to reach a total price reduction of 10%.
  - 01/04/2018: regulation of 'biologicals': For those biological specialties whose price was already reduced by 10% before 1 April 2018 under the 'biologicals' measure, an additional price reduction of 5.56% was implemented, to reach a total price reduction of 15%.

- Pegfilgrastim:
  - 01/01/2018: 'old medicines' measure (12 years)
  - 01/10/2019: application of 'bio-cliff'

- Glatirameer:
  - 01/07/2018: 'old medicines' measure (15 years)

Figure 102: evolution of NIHDI annual expenditure and number of DDDs (public pharmacies 2010 – 2019) for ATC class L03A immunostimulants

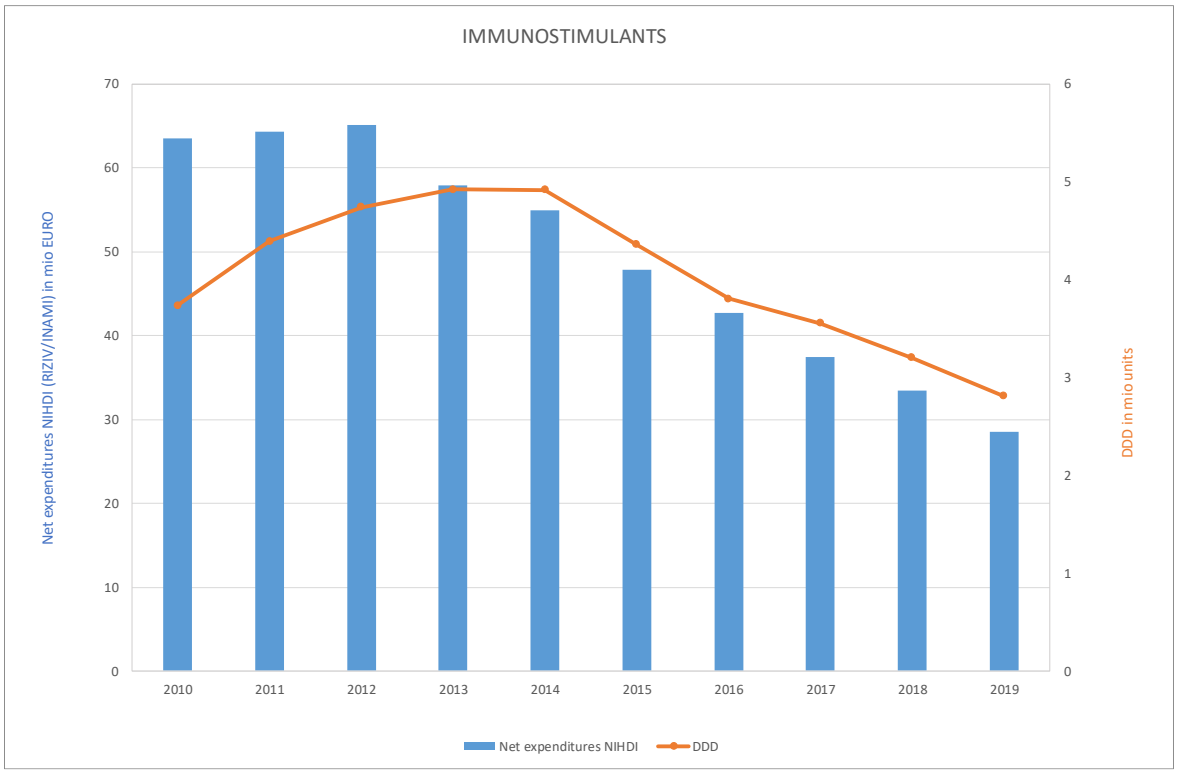


Figure 103: evolution of NIHDI net monthly expenditure (public pharmacies 2015 – 2019) for ATC class L03A immunostimulants

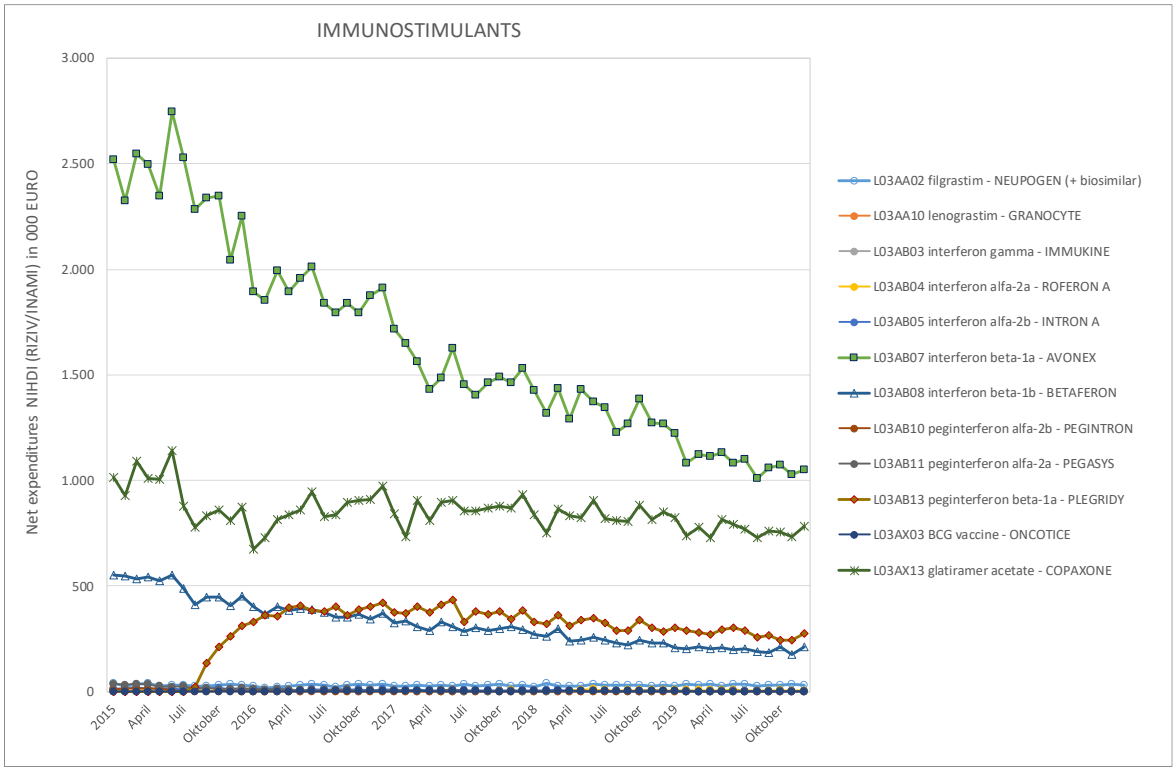


Figure 104: evolution of number of DDDs per month (public pharmacies 2015 – 2019) for ATC class L03A immunostimulants

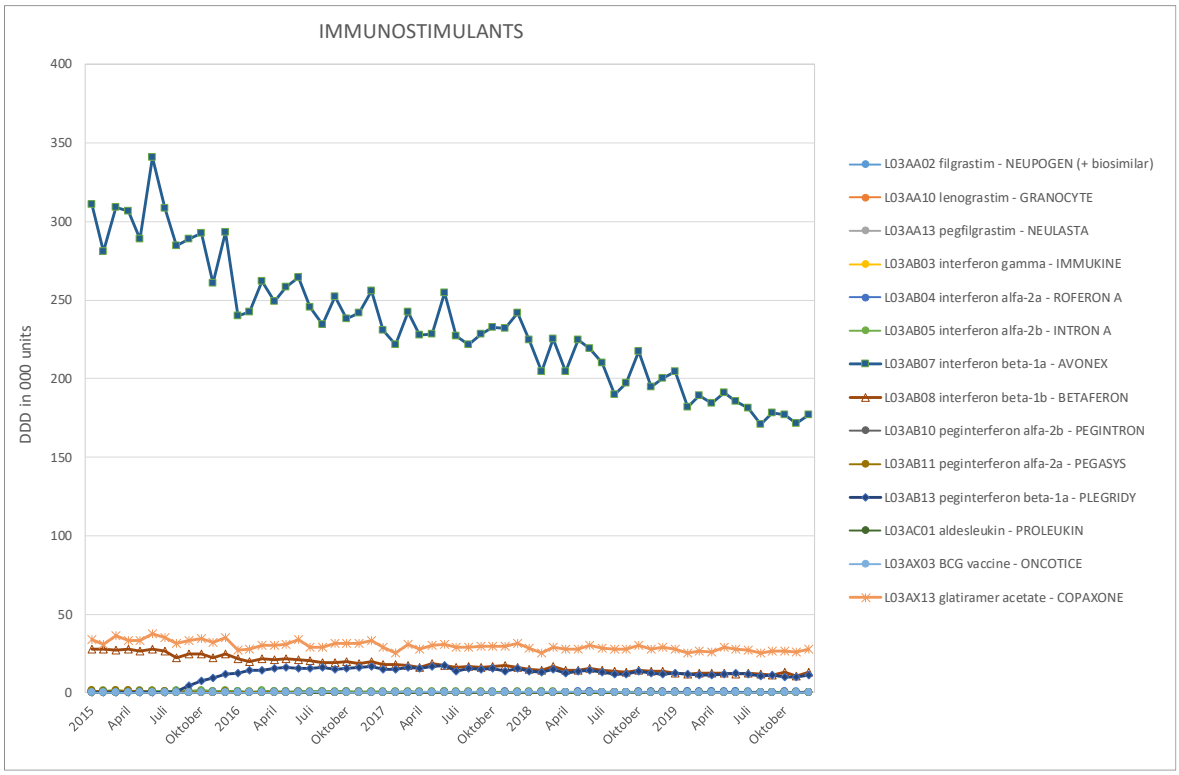


Figure 105: evolution of number of patients per year (public pharmacies 2016 – 2019) for ATC class L03A immunostimulants

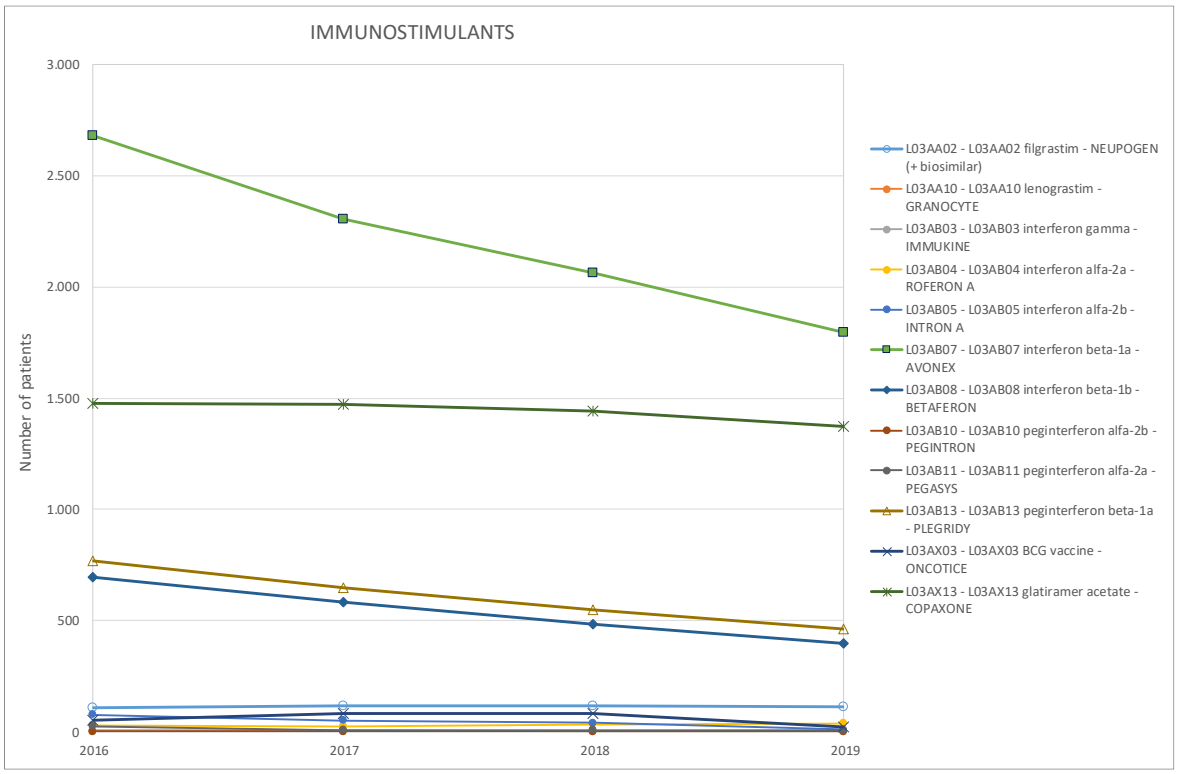
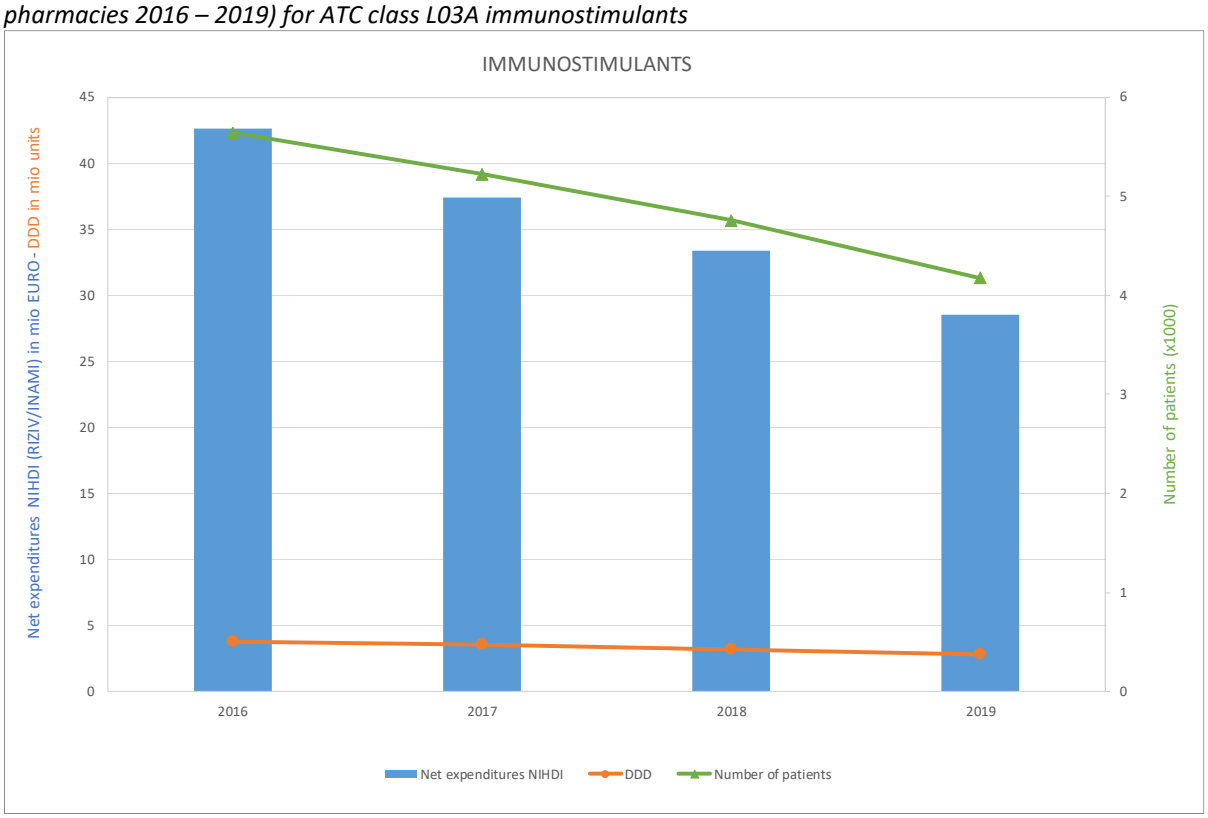


Figure 106: evolution of NIHDI net annual expenditure, number of patients and number of DDDs (public pharmacies 2016 – 2019) for ATC class L03A immunostimulants



DOSSIERS

At this point in time (October 2020), seven Immune Checkpoint Inhibitors have been registered by the European Medicines Agency (EMA):
ipilimumab, pembrolizumab, nivolumab, cemiplimab, durvalumab, atezolizumab and avelumab.

Anti-CTLA-4

Ipilimumab is, to date, the only anti-CTLA-4 antibody registered.

Ipilimumab (Yervoy®) is eligible for reimbursement as a monotherapy or in combination with nivolumab for the treatment of advanced (inoperable or metastatic) melanoma in adults aged at least 18, with an Eastern Cooperative Oncology Group (ECOG) performance of 0 or 1.

Yervoy® was initially reimbursed on the basis of a randomised, double-blind, multi-centre phase 3 study comparing ipilimumab as a monotherapy, ipilimumab in combination with a peptide vaccine (gp100) and gp100 as a monotherapy, in patients with previously treated advanced melanoma.
The median overall survival was 10 months with ipilimumab +/- gp100 versus 6.4 months with gp100 (hazard ratio 0.68).

Yervoy® was reimbursed in first line treatment on the basis of a study which allocated patients randomly to chemotherapy plus either ipilimumab or a placebo. The median survival was 11.2 months with chemotherapy plus ipilimumab and 9.1 months with chemotherapy plus a placebo (hazard ratio 0.69).
Later, both Keytruda® and Opdivo® seemed to result in a better survival time when compared directly with ipilimumab, with a hazard ratio of, respectively, 0.61 and 0.65.
In Checkmate-067, Opdivo® alone or in combination with Yervoy® was compared with Yervoy® alone.
Both nivolumab alone and nivolumab in combination with ipilimumab resulted in significantly better progression-free survival and overall survival. The study was not designed to compare nivolumab alone with nivolumab + ipilimumab.

Figure 107: evolution of NIHDI net annual expenditure for the anti-CTLA-4 drugs: ipilimumab

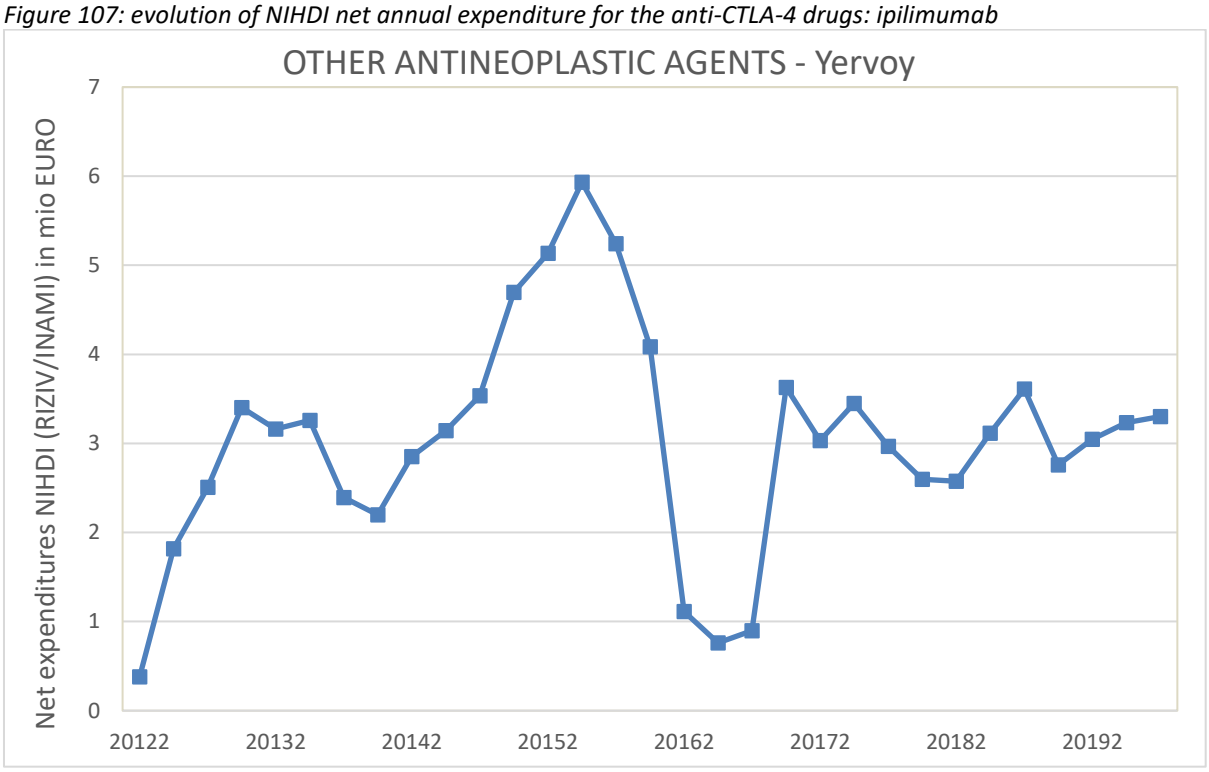
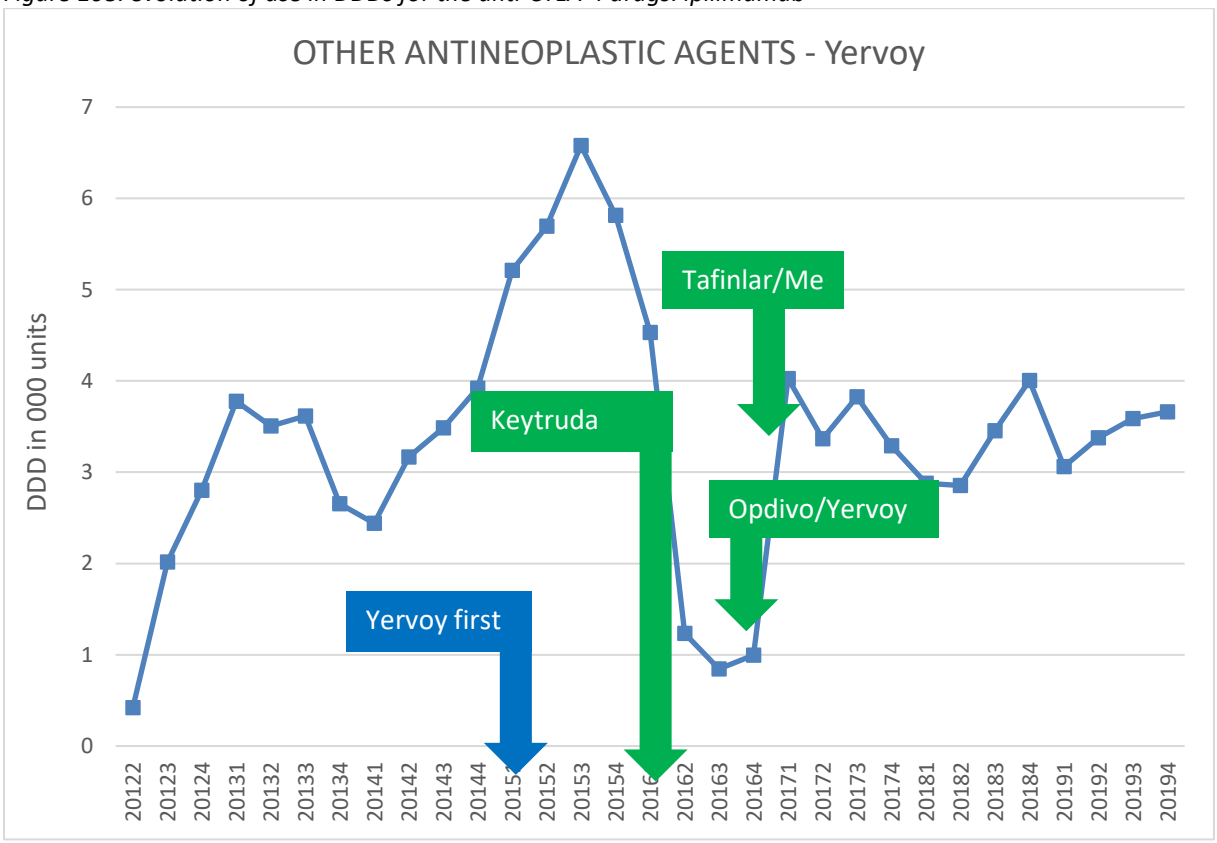


Figure 108: evolution of use in DDDs for the anti-CTLA-4 drugs: ipilimumab



Yervoy® has been eligible for reimbursement since 1 June 2012. Expenditure (and use, expressed in DDDs) has gone up and down over time. Its evolution has been influenced by increased reimbursability for ipilimumab, and by the new eligibility for reimbursement of other treatment options for melanoma, as well as increased reimbursability for these alternatives.

- Since 1 June 2015, Yervoy® has also been eligible for reimbursement as a first-line treatment. This extension of the indication has resulted in an increase in expenditure and use.

- Since 1 April 2016 and 1 May 2016, respectively, Opdivo® (nivolumab) and Keytruda® (pembrolizumab) are eligible for reimbursement for advanced (inoperable or metastatic) melanoma in adults as a monotherapy. A drop in the expenditure on/use of Yervoy® can be observed.

- Since 1 January 2017, Yervoy® is reimbursed for treatment of advanced (inoperable or metastatic) melanoma in adults in combination with Opdivo®.

- Since 1 February 2017, Mekenist®/Tafinlar® are also reimbursed for advanced BRAF mutated melanoma.

- Since 1 January 2019 and 1 February 2019, reimbursability has been extended for, respectively, Keytruda® and Opdivo® (melanoma adjuvant therapy)

- Since 1/8/2019, Tafinlar® /Mekinist® have been reimbursed for stage III BRAF mutated melanoma after complete resection.

Anti-PD-(L)1

According to the current conventions concluded under Article 112 and following of the Royal Decree of 1 February 2018 concerning the procedures, terms and conditions for reimbursement by the compulsory insurance for medical care and benefits towards costs of pharmaceutical specialties, anti-PD-(L)1 drugs are only assessed by the CRM at the time of the initial registration. After that, the anti-PD-(L)1 drugs can be reimbursed without a prior assessment by the Commission for Reimbursement of Medicines (CRM) for all EMA-registered indications, from the first day of the month following notification by the company of registration of a new indication by the EMA.

Indications, reimbursability date, CRM evaluation, studies

Anti-PD-1

Pembrolizumab (Keytruda®)

Indication	Date of reimbursability	CRM evaluation	Study phase	Endpoint reached
Advanced (inoperable or metastatic) melanoma in adults (monotherapy).	1 May 2016	yes	3	yes
First-line treatment of metastatic non-small cell lung cancer (NSCLC) in adults with tumours which show PD-L1 expression with a tumour proportion score (TPS) > or = 50 % without EGFR- or ALK-positive tumour mutations (monotherapy).	1 May 2017	yes	3	yes
Treatment of locally advanced or metastatic NSCLC in adults with tumours showing PD-L1-expression with a TPS > or = 1 % and who have undergone at least one previous lot of chemotherapy (monotherapy).	1 May 2017	yes	3	yes
Patients with relapsed or refractory classical Hodgkin Lymphoma (cHL), where autologous stem cell transplant (ASCT) and brentuximab vedotin (BV) have failed, or who are not eligible for a transplant and where BV has failed (monotherapy).	1 June 2017	no	2	NCS[4]
Locally advanced or metastatic urothelial cancer in adults who have previously undergone platinum-based chemotherapy (monotherapy).	1 October 2017	no	3	yes

[4] Non-comparative study, primary endpoint was response rate

Locally advanced or metastatic urothelial cancer in adults who are not eligible for cisplatin chemotherapy and whose tumours show PD-L1-expression with a combined positive score (CPS) > or = 10 (monotherapy).	1 October 2018	no	2	NCS[5]
Metastatic non-squamous cell-NSCLC in adults with tumours without EGFR- or ALK-positive mutations, in combination with pemetrexed and platinum chemotherapy.	1 October 2018	no	3	yes
Adjuvant treatment for adults with stage III melanoma affecting the lymph nodes and where complete resection has taken place (monotherapy).	1 January 2019	no	3	yes
First-line treatment of metastatic squamous cell NSCLC in adults in combination with carboplatin and either paclitaxel or nab-paclitaxel (nab-paclitaxel is not eligible for reimbursement in this indication).	1 April 2019	no	3	yes
First-line treatment of advanced renal cell carcinoma (RCC) in adults in combination with axitinib.	1 October 2019	no	3	yes
First-line treatment of metastatic or inoperable recurrent head neck squamous cell carcinoma (HNSCC) in adults where the tumours show PD-L1-expression with a CPS ≥ 1 (monotherapy or in combination with platinum- and 5-fluoro-uracil (5 FU)-chemotherapy).	1 December 2019	no	3	yes

N.B. Keytruda® as a monotherapy has also been approved by the EMA for the treatment of recurrent or metastatic head neck squamous cell carcinoma in adults, where the tumours show PD-L1-expression with a TPS ≥ 50 % and where there is progression during or after platinum chemotherapy. The NIHDI, however, has not received notification of this registration from the EMA, and this indication is not therefore eligible for reimbursement.

Nivolumab (Opdivo®)

Indication	Date of reimbursability	CRM evaluation	Study phase	Endpoint reached
Advanced (inoperable or metastatic) melanoma in adults (monotherapy).	1 April 2016	yes	3	yes
Advanced (inoperable or metastatic) melanoma in adults (in combination with ipilimumab).	1 January 2017	yes [6]	3	yes
Locally advanced or metastatic non-small cell lung cancer (NSCLC), after prior chemotherapy treatment in adults.	1 January 2017	yes	3	yes

[5] Non-comparative study: primary endpoint was response rate

[6] In connection with the Yervoy dossier

Relapsed or refractory classical Hodgkin Lymphoma (cHL) after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.	1 January 2017	no	2	NCS[7]
Advanced renal cell carcinoma after prior treatment (monotherapy).	1 January 2017	yes	3	yes
Recurrent or metastatic squamous cell cancer of the head-neck area in adults who show progression during or after treatment with platinum-based therapy (monotherapy).	1 June 2017	no	3	yes
Locally advanced inoperable or metastatic urothelial cancer in adults after failed platinum-based therapy (monotherapy).	1 July 2017	no	2	NCS[8]
The adjuvant treatment of melanoma in adults whose lymph nodes are affected or in the case of metastatic disease following complete resection (monotherapy).	1 February 2019	no	3	yes
First-line treatment in combination with ipilimumab, of advanced renal cell cancer with with intermediate/poor-risk in adults.	1 February 2019	yes [9]	3	yes

Cemiplimab (Libtayo®)

The request to add cemiplimab (Libtayo®) to the list of reimbursable specialties is currently (October 2020) being investigated by the CRM. Cemiplimab is indicated for the treatment of metastatic or locally advanced cutaneous squamous cell cancer (CSCC) for cases not eligible for curative surgery or curative radiotherapy.

[7] Non-comparative study: the primary endpoint was the response rate

[8] Non-comparative study: the primary endpoint was the response rate

[9] In connection with the Yervoy dossier

Anti-PD-L1

Durvalumab (Imfinzi®)

Indication	Date of reimbursability	CRM evaluation	Study phase	Endpoint reached
Locally advanced, unresectable non-small cell lung cancer (NSCLC), with tumours expressing PD-L1 in >=1% of the tumour cells and where the disease showed no progression following platinum-based chemotherapy with radiotherapy (monotherapy).	1 May 2019	yes	3	yes

Atezolizumab (Tecentriq®)

Indication	Date of reimbursability	CRM evaluation	Study phase	Endpoint reached
Locally advanced or metastatic non-small cell lung cancer (NSCLC), following earlier chemotherapy treatment for adults (monotherapy)	1 March 2018	yes	3	yes
Locally advanced or metastatic urothelial carcinoma (UC) following earlier treatment with platinum-based chemotherapy, for adults (monotherapy)	1 March 2018	no	3	no
Treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) for whom cisplatin is not suitable and whose tumours have a PD-L1-expression of > or = 5% (monotherapy) (NB: for patients whose treatment began before 01.08.2018, the additional restriction concerning PD-L1-expression does not apply).	1 March 2018	no	2	no
In combination with bevacizumab, paclitaxel and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous cell non-small cell lung cancer (NSCLC); for patients with EGFR-mutated or ALK-positive NSCLC, the specialty, combined with bevacizumab, paclitaxel and carboplatin, is only indicated after the failure of suitable targeted treatments.	1 April 2019	Yes [10]	3	yes
In combination with nab-paclitaxel and carboplatin for first-line treatment of adult patients with metastatic non-squamous cell	1 October 2019	no	3	yes

[10] In connection with the Avastin dossier

NSCLC, and with no EGFR-mutated or ALK-positive NSCLC (nab-Paclitaxel is not reimbursed for this indication).				
In combination with carboplatin and etoposide, it is indicated for first-line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC).	1 October 2019	no	3	yes

Avelumab (Bavencio®)

Indication	Date of reimbursability	CRM evaluation	Phase study	Endpoint reached
Metastatic merkel cell carcinoma (MCC) (monotherapy).	1 August 2018	yes	2	NCS[11]
First line treatment for advanced renal cell carcinoma (RCC) in adults in combination with axitinib	1 December 2019	yes [12]	3	Partial Immature

[11] Non comparative study: the primary endpoint was the response rate

[12] In connection with the Inlyta dossier

Clinical evidence

For most of the reimbursable indications, there is sound level 1 evidence of efficacy. There are some exceptions, where products were registered and reimbursed on the basis of a lower level of evidence, and, in a couple of cases, even with negative studies.

Anti-PD-1

Pembrolizumab (Keytruda®)

Positive studies: primary endpoint(s) reached

- *Phase 3 studies*
  - advanced (inoperable or metastatic) melanoma in adults (monotherapy): primary endpoint reached in randomised phase 3 study in which Keytruda 10 mg/kg was compared every 2 or every 3 weeks with ipilimumab (KEYNOTE-006):
    - better overall survival (median 32.7 months versus 15.9 months; hazard ratio 0.73)
    - better progression-free survival (median: Keytruda every 2 weeks: 4.1 months; Keytruda every 3 weeks: 5.6 months; ipilimumab 2.8 months; hazard ratio 0.61).
  - first-line treatment of metastatic non-small cell lung cancer (NSCLC) in adults with tumours showing PD-L1-expression with a tumour proportion score (TPS) > or = 50 % without EGFR- or ALK-positive tumour mutations (monotherapy): primary endpoint reached in randomised study versus chemotherapy (KEYNOTE-024):
    - better progression-free survival (median 7.6 months versus 5.6 months; hazard ratio 0.53).
  - treatment of locally advanced or metastatic NSCLC in adults with tumours showing PD-L1-expression with a TPS > or = 1 % and who have undergone at least one previous lot of chemotherapy (monotherapy): most important primary endpoint (overall survival) reached in randomised phase 3 study, comparing two doses of Keytruda (2 mg/kg and 10 mg/kg) with docetaxel (KEYNOTE-010):
    - better overall survival (median Keytruda 2 mg/kg: 10.4 months [hazard ratio 0.77]; Keytruda 10 mg/kg: 13.2 months [hazard ratio 0.61]; docetaxel 8.4 months).
    - no difference in progression-free survival (median 3.9 and 4 months with Keytruda versus 4.1 months with docetaxel)
  - locally advanced or metastatic urothelial carcinoma in adults who have previously undergone platinum-based chemotherapy (monotherapy): most important primary endpoint (overall survival) reached in randomised phase 3 study compared with chemotherapy (KEYNOTE-045):
    - better overall survival (median 10.1 months versus 7.2 months; hazard ratio 0.72)
    - no difference in progression-free survival (median 2.1 months versus 3.3 months; hazard ratio 0.96)
  - metastatic non-squamous cell-NSCLC in adults with tumours without EGFR- or ALK-positive mutations, in combination with pemetrexed and platinum-based chemotherapy: primary endpoints reached in randomised phase 3 study compared with placebo (KEYNOTE-189):
    - better overall survival (median 22 months versus 10.6 months; hazard ratio 0.56).
    - better progression-free survival (median 9 months versus 4.9 months; hazard ratio 0.49).
  - adjuvant treatment in adults with stage III melanoma affecting the lymph nodes and who have undergone complete resection (monotherapy): primary endpoint reached in randomised phase 3 study versus placebo (KEYNOTE 054):
    - better relapse-free survival (relapse-free after 3 years 63.7 % versus 44.1 %; hazard ratio 0.56)
  - first-line treatment of metastatic squamous cell-NSCLC in adults in combination with carboplatin and/or paclitaxel or nab-paclitaxel (nab-paclitaxel is not eligible for reimbursement in this indication): primary endpoints reached in randomised phase 3 study versus placebo (KEYNOTE-407):

- better overall survival (median 17.1 months versus 11.6 months; hazard ratio 0.71)
- better progression-free survival (median 8 months versus 5.1 months; hazard ratio 0.57).

- first-line treatment of advanced renal cell carcinoma (RCC) in adults in combination with axitinib. Primary endpoints reached in randomised phase 3 study comparing Keytruda + axitinib with sunitinib in monotherapy
  - better overall survival (survival after 18 months 82.3% versus 72.1%; hazard ratio 0.53)
  - better progression-free survival (median 15.1 months versus 11.1 months; hazard ratio 0.69)
- first-line treatment of metastatic or inoperable recurring head-neck squamous cell cancer (HNSCC) in adults with tumours showing PD-L1-expression with a CPS ≥ 1 (monotherapy or in combination with platinum- and 5-fluoro-uracil (5 FU)-chemotherapy): most important primary endpoints (overall survival) reached in randomised phase 3 study comparing pembrolizumab monotherapy and pembrolizumab + chemotherapy with standard chemotherapy + cetuximab:
  - better overall survival with Keytruda monotherapy in the PD-L1 positive population (median 12.3 months versus 10.3 months; hazard ratio 0.74)
  - better overall survival with Keytruda + chemotherapy in de PD-L1 positive population (median 13.6 months versus 10.4 months; hazard ratio 0.65)
  - no difference in progression-free survival with Keytruda monotherapy in the PD-L1 positive population (median 3.2 months versus 5.0 months; hazard ratio 1.13).
  - no difference in progression-free survival with Keytruda + chemotherapy in the PD-L1 positive population (median 5.1 months versus 5.0 months; hazard ratio 0.84).

No level 1 evidence

- *Phase 2 studies*

  - Locally advanced or metastatic urothelial carcinoma in adults not eligible for cisplatin-based chemotherapy and whose tumours show PD-L1-expression with a combined positive score (CPS) > or = 10 (monotherapy): primary endpoint in non-randomised study (KEYNOTE-052) was response rate: 29.2%
  - relapsed or refractory classical Hodgkin Lymphoma (cHL) in patients where autologous stem cell transplant (ASCT) and brentuximab vedotin (BV) have failed or who are not eligible for transplants and where BV has failed (monotherapy): primary endpoint in non-randomised study (KEYNOTE-087) was response rate: 71.4%.

Nivolumab (Opdivo®)

Positive studies: primary endpoint(s) reached

- *Phase 3 studies*

  - advanced (inoperable or metastatic) melanoma in adults (monotherapy). Primary endpoints reached in randomised phase 3 study versus ipilimumab (CheckMate-067)
    - better overall survival (median 36.9 months versus 19.9 months; hazard ratio 0.63)
    - better progression-free survival (median 6.9 months versus 2.9 months; hazard ratio 0.53)
  - advanced (inoperable or metastatic) melanoma in adults (in combination with ipilimumab). Primary endpoints reached in randomised phase 3 study versus ipilimumab (CheckMate-067).
    - better overall survival (median not reached versus 19.9 months; hazard ratio 0.52)
    - better progression-free survival (median 11.5 months versus 2.9 months; hazard ratio 0.42)
  - locally advanced or metastatic non-small cell lung cancer (NSCLC), after previous treatment with chemotherapy, adults. Primary endpoint reached in 2 randomised phase 3 studies versus docetaxel:
    - squamous cell carcinoma (CheckMate 017): better overall survival (median 9.2 months versus 6.0 months; hazard ratio 0.59)

- non squamous cell carcinoma: better overall survival (median 12.2 months versus 9.4 months; hazard ratio 0.73)

- indicated as a monotherapy for the treatment of advanced renal cell carcinoma after previous treatment. Primary endpoint reached in randomised phase 3 study versus everolimus (Checkmate-025).
  - better overall survival (median 25.8 months versus 19.7 months; hazard ratio 0.72).
- recurrent or metastatic squamous cell carcinoma of the head-neck area in adults showing progression during or after treatment with platinum-based therapy (monotherapy). Primary endpoint reached in randomised phase 3 study versus standard chemotherapy or cetuximab (CheckMate 141).
  - better overall survival (median 7.5 months versus 5.1 months; hazard ratio 0.70).
- adjuvant treatment of melanoma in adults whose lymph nodes are affected or in the case of metastatic disease where complete resection has been carried out (monotherapy). Primary endpoint reached in randomised phase 3 study versus ipilimumab (CheckMate-238)
  - better relapse-free survival (median not reached versus 24.9 months; hazard ratio 0.68)
- first-line treatment, in combination with ipilimumab, of advanced renal cell carcinoma with intermediate/poor risk profile in adults. Primary endpoint reached in randomised phase 3 study (Checkmate-214**)**
  - better overall survival (median not reached versus 26.6 months; hazard ratio 0.66)
  - better progression-free survival (median 8.2 versus 8.3 months; hazard ratio 0.77)
  - higher better response rate (42 % versus 29%)

No level 1 evidence

- *Phase 2 studies*

  - locally advanced inoperable or metastatic urothelial carcinoma in adults after failure of prior platinum-based therapy (monotherapy). Primary endpoint in non-randomised phase 2 study (CheckMate 275) was response rate: 19.6%.
  - relapsing or refractory classical Hodgkin Lymphoma (cHL) following autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin. Primary endpoint in non-randomised phase 2 study (CheckMate-205) was response rate: 71%.

Anti-PD-L1

Durvalumab (Imfinzi®)

Positive study: primary endpoint reached

- *Phase 3 study*
  - locally advanced unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 in >=1% of the tumour cells and in whom the disease has not shown any progression following platinum-based chemotherapy with radiotherapy (monotherapy): primary endpoints reached in a randomised phase 3 study versus placebo (PACIFIC):
    - better progression-free survival (median 16.8 months versus 5.6 months; hazard ratio 0.52).
    - better overall survival (median not reached versus 29.1 months; hazard ratio 0.69).

Atezolizumab (Tecentriq®)

Positive studies: primary endpoint(s) reached

- *Phase 3 studies*
  - locally advanced or metastatic non-small cell lung cancer (NSCLC), after prior treatment with chemotherapy in adults (monotherapy): primary endpoint reached in randomised phase 3 study versus docetaxel (OAK):
    - better overall survival (median 13.3 months versus 9.8 months; hazard ratio 0.80).
  - in combination with carboplatin and etoposide, for first-line treatment of patients with extensive-stage small cell lung carcinoma (ES-SCLC). Primary endpoints reached in randomised phase 3 study versus placebo (IMpower 133):
    - better progression-free survival (median 5.2 months versus 4.3 months; hazard ratio 0.77).
    - better overall survival (median 12.3 months versus 10.3 months; hazard ratio 0.755)
  - in combination with nab-paclitaxel and carboplatin for first-line treatment of adult patients with metastatic non squamous cell NSCLC with no EGFR-mutated or ALK-positive NSCLC (nab-Paclitaxel is not eligible for reimbursement in this indication): primary endpoint reached in randomised phase 3 study versus placebo (IMpower 130)
    - better overall survival (median 18.6 months versus 13.9 months; hazard ratio 0.79)
    - better progression-free survival (median 7.0 months versus 5.5 months; hazard ratio 0.64)
  - in combination with bevacizumab, paclitaxel and carboplatin, for first-line treatment of metastatic non-squamous cell non-small cell lung carcinoma (NSCLC); for patients with EGFR-mutated or ALK-positive NSCLC, this specialty, in combination with bevacizumab, paclitaxel and carboplatin, is only indicated if suitable targeted treatments have failed: primary endpoint reached in randomised phase 3 study versus bevacizumab, paclitaxel and carboplatin alone (IMpower150).
    - better progression-free survival (median 8.4 months versus 6.8 months; hazard ratio 0.59)
    - better overall survival (median 19.2 months versus 14.7 months; hazard ratio 0.78)

Negative studies: primary endpoint(s) **NOT** reached

- *Phase 3 study*
  - Locally advanced or metastatic urothelial carcinoma (UC) after previous treatment with platinum-based chemotherapy in adults (monotherapy): primary endpoint NOT reached in randomised phase 3 study versus chemotherapy (IMvigor211).
    - no difference in overall survival (median 11.1 months versus 10.6 months; hazard ratio 0.87).

- *Phase 2 studies*

  - treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) for patients for whom cisplatin is not suited, and whose tumours have PD-L1 expression of > or = 5% (monotherapy) (NB: for patients whose treatment began before 01.08.2018, the additional restriction on PD-L1 expression does not apply). Predetermined primary endpoint (response rate ≥ 40 %) not reached in non randomised phase 2 study (IMvigor210); response rate in study was 15.1%.

Avelumab (Bavencio®)

- *Phase 3 study*

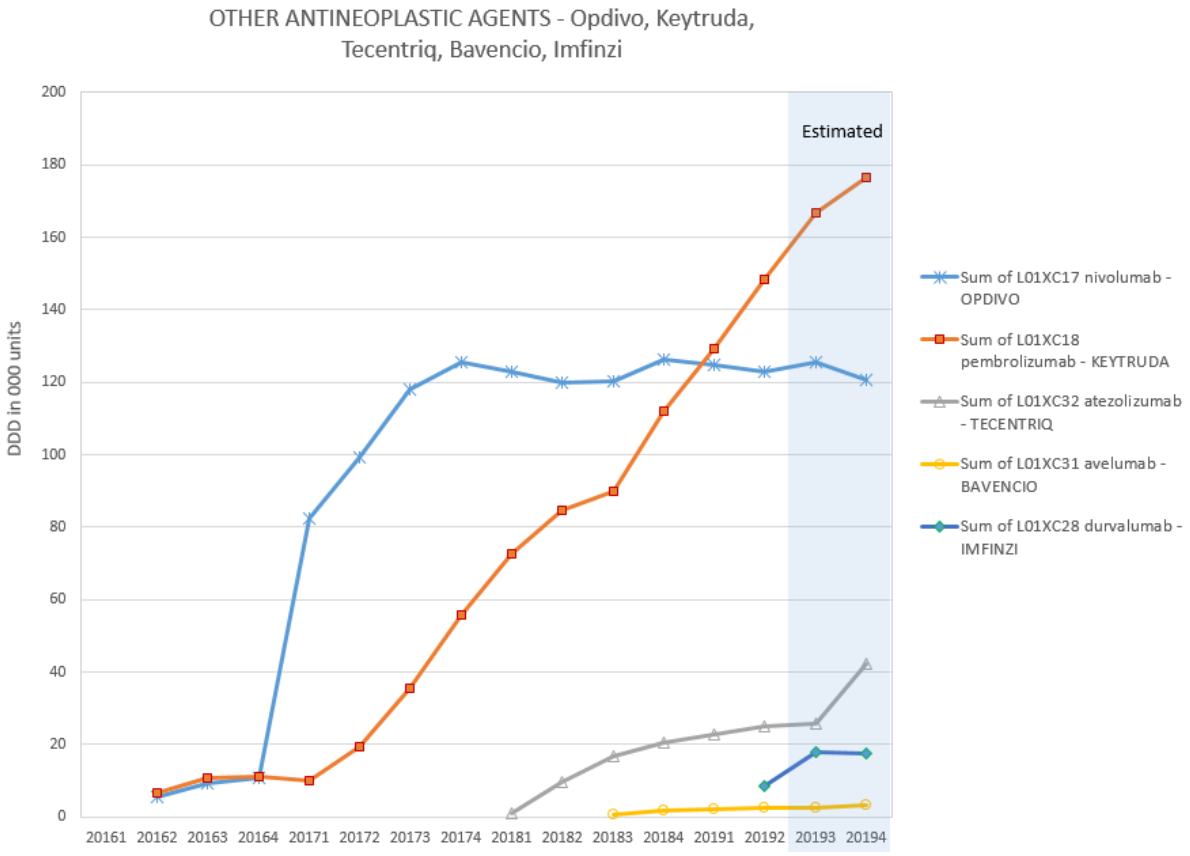
  - first-line treatment of advanced renal cell carcinoma (RCC) in adults in combination with axitinib. Results immature for most important primary endpoint (overall survival) in randomised phase 3 study (JAVELIN Renal 101), in which Bavencio + Inlyta were compared with sunitinib. The second primary endpoint was reached
    - better progression-free survival (median 13.3 versus 8.0 months; hazard ratio 0.69)
    - overall survival: results immature (hazard ratio 0.8, not significant)

- *Phase 2 study*

  - metastatic merkel cell carcinoma (MCC) (monotherapy). Response rate in non-randomised phase 2 study (JAVELIN Merkel 200) was 33 % in pre-treated patients and 62.1 % in those who had received no prior treatment.

Evolution of use (DDDs)

Figure 109: evolution of use in DDDs for the anti-PD-(L)1 drugs: pembrolizumab, nivolumab, durvalumab, atezolizumab and avelumab



Evolution of expenditure and reimbursement data

Figure 110: evolution of net expenditure on anti-PD-(L)1 drugs: pembrolizumab, nivolumab, durvalumab, atezolizumab and avelumab

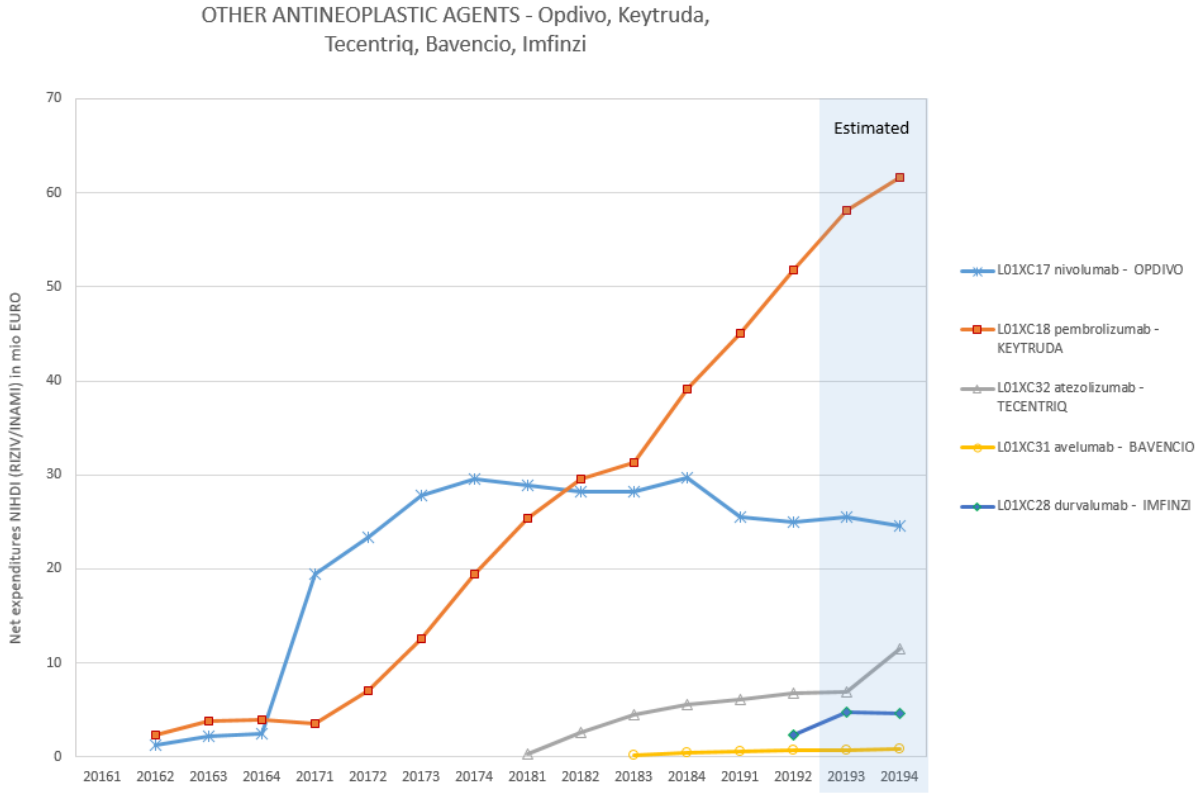


Figure 111: evolution of net expenditure on pembrolizumab against the timeline for reimbursement of additional indications

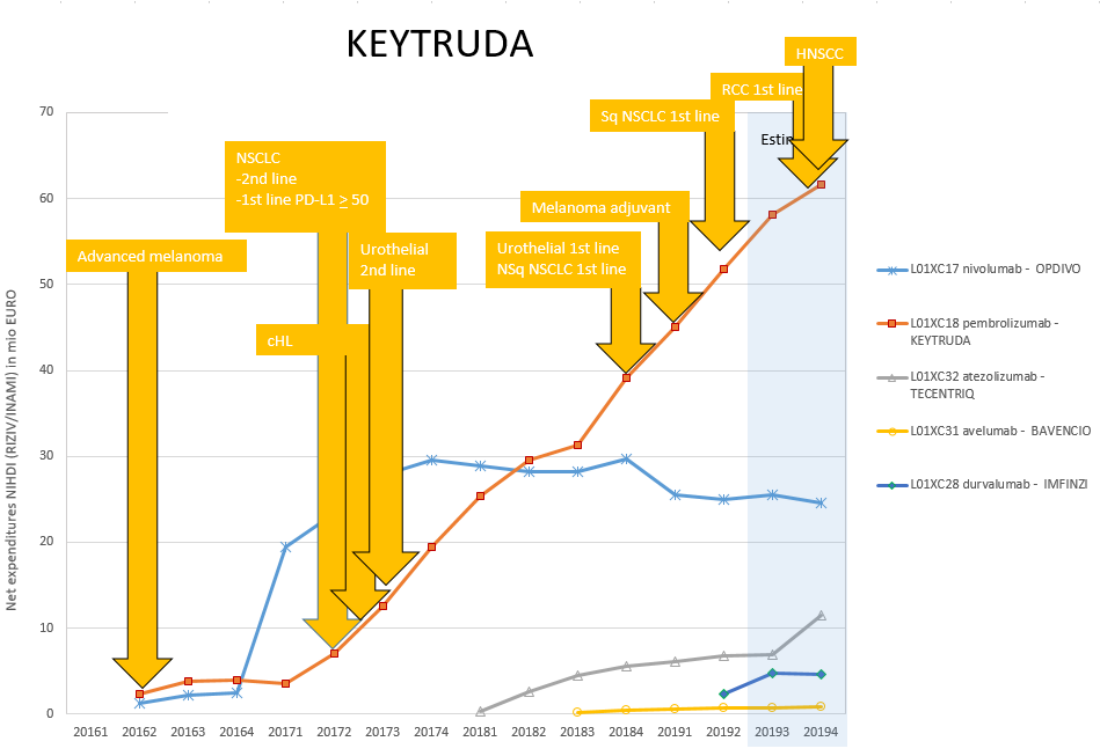


Figure 112: evolution of net expenditure on nivolumab against the timeline for reimbursement of additional indications

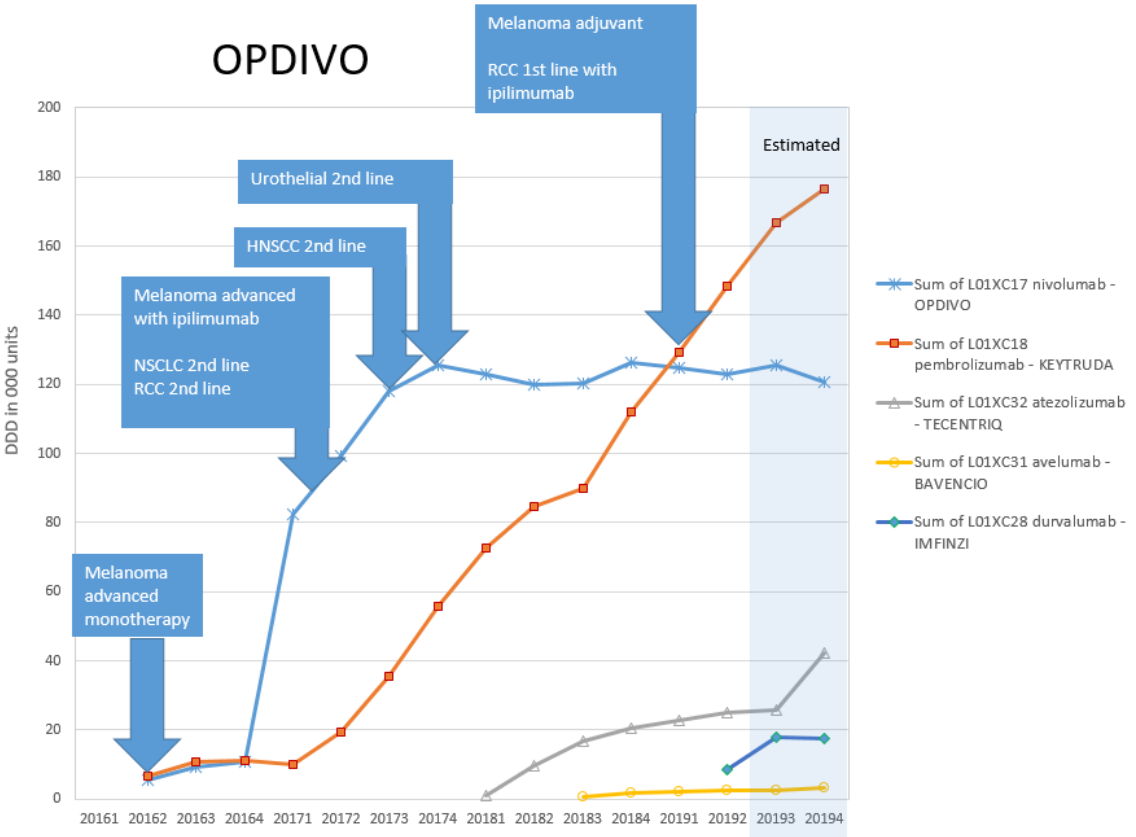


Figure 113: evolution of net expenditure on atezolizumab against the timeline for reimbursement of additional indications

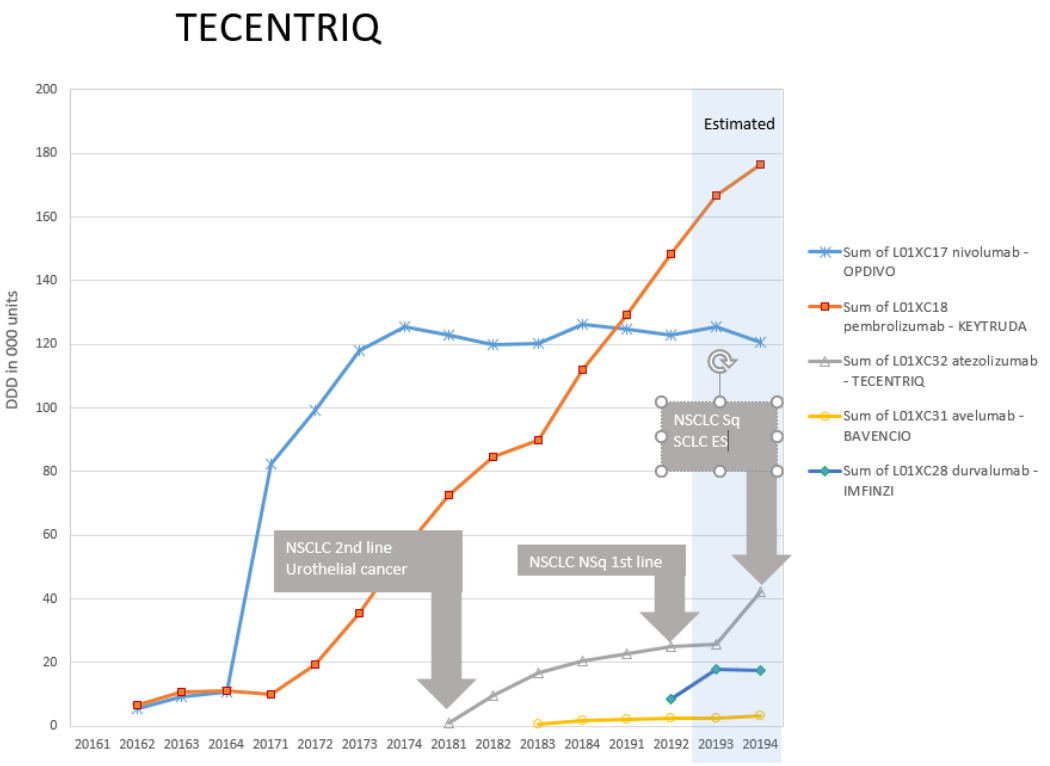
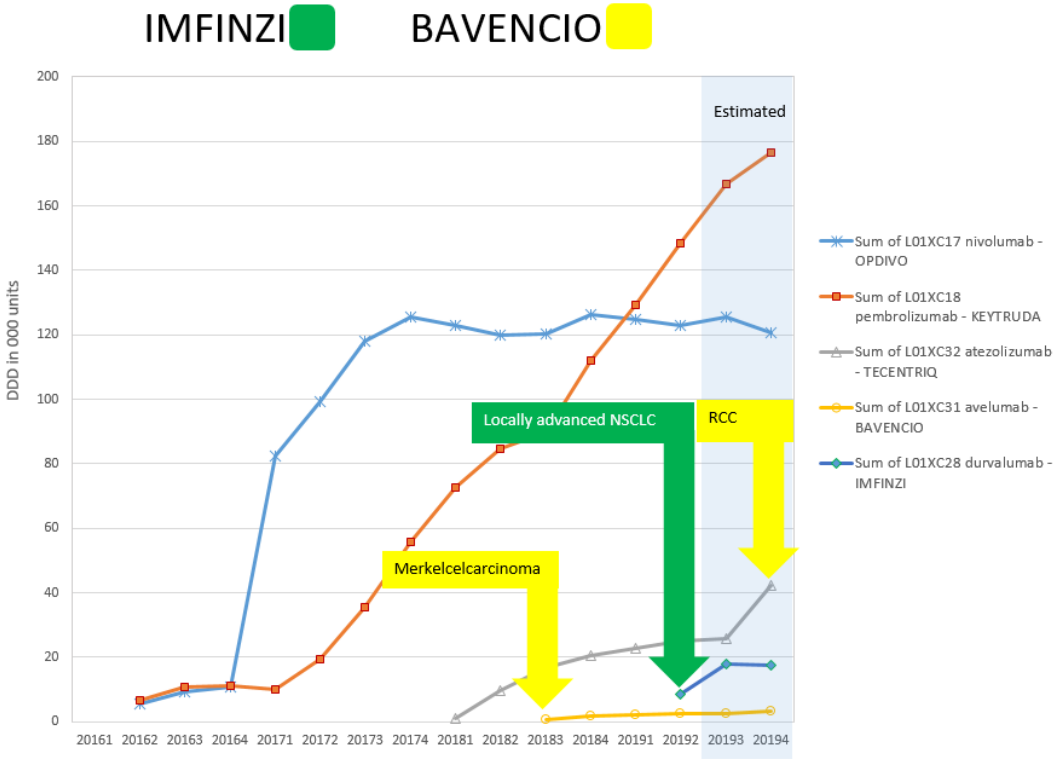


Figure 114: evolution of net expenditure on avelumab and durvalumab against the timeline for reimbursement of additional indications



Weekly cost per product (patient 80 kg)

Keytruda	Opdivo	Tecentriq	Imfinzi	Bavencio
2,306.84 €	1,529.83 €	1,871.10 €	2,139.42 €	1,816.00 €

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. 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 Minister responsible 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 01.02.2018 concerning the procedures, terms and conditions for reimbursement by the compulsory insurance for medical care and benefits towards costs of pharmaceutical specialties. 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 21.12.2001 concerning the procedures, terms and conditions for reimbursement by the compulsory insurance for medical care and benefits towards costs of pharmaceutical specialties. 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 specialty 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 specialty on the positive list and highlighted with the letter 'T'; including, then, for generics, biosimilars, specialties 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 insurance for medical care and benefits towards costs of pharmaceutical specialties – Articles 111 to 117 inclusive.

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 specialty 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 R.D. of 01.02.2018;
- Repayment of an amount corresponding to all or part of the difference between the expenditure foreseen and the actual expenditure on the specialty in question;
- A reduction in the reimbursement basis of (an)other pharmaceutical specialty/ies marketed by the applicant, resulting in reduced expenditure for the health insurance on a medicine other than the specialty 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 specialty ('outcomes-based agreement'), or maybe the costs are only reimbursed when the specialty is administered for a treatment which has been shown, with sufficient scientific proof, to be effective and safe.

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, the expenditure figures for pharmaceutical specialties reported in this MORSE report do not take account of the compensation received by the NIHDI by virtue of Article 81/111 conventions.

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 pharmaceutical specialties, often negotiations are the only way to ensure that a patient has access to certain medicines.

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 specialties, 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/nl/gezondheidsonderwerpen.

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.

SOME FIGURES

The option of Article 81/111 conventions was introduced in 2010 (see also 'Principle').
The information given refers to reimbursement dossiers for which a request was submitted by the company to the Minister for Social Affairs for the launch of a negotiation procedure, in the period 2010-2019. 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 2010-2019, a total of 340 requests for the launch of Article 81/111 negotiations were received by the Minister for Social Affairs.
In 20 cases (6%) the request was part of a CRM parallel distribution procedure. None of these cases ended in a convention and they are not included in the table below.

Table 17 shows the status of the requests received.

Table 17: Evolution of number of requests to conclude an Article 81/111 convention

year of submission of request for conclusion of a convention	*2010*	*2011*	*2012*	*2013*	*2014*	*2015*	*2016*	*2017*	*2018*	*2019*	*total*
request refused	*0*	*3*	*2*	*1*	*2*	*0*	*1*	*1*	*0*	*3*	***13***
request accepted	*14*	*14*	*16*	*16*	*25*	*37*	*47*	*34*	*42*	*62*	***307***
currently being processed											0
no convention concluded	8	6	4	3	6	4	5	6	7	9	58
convention expired	6	8	12	13	18	27	16	5	3	0	108
convention in force	0	0	0	0	1	6	26	23	32	53	141
total	**14**	**17**	**18**	**17**	**27**	**37**	**48**	**35**	**42**	**65**	***320***

Table 18 shows in more detail that the increase observed is not just a rise in requests to conclude a convention 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 18: Evolution of number of requests to conclude an Article 81/111 convention – details on outcomes

year of submission of request for conclusion of a convention	*2010*	*2011*	*2012*	*2013*	*2014*	*2015*	*2016*	*2017*	*2018*	*2019*	*total*
being processed											***0***
no convention concluded	8	9	6	4	8	4	6	7	7	12	***71***
new convention (first convention for a molecule)	6	8	10	12	15	21	25	13	10	15	***135***
convention following previous convention and reassessment by the CRM	0	0	0	0	0	4	3	4	12	17	***40***
additional convention (additional indication)	0	0	1	1	3	4	2	0	4	4	***19***
amendment to an existing convention (new indication/change of indication)	0	0	0	0	1	2	9	7	5	13	***37***
amendment to an existing convention (new packaging/new dosage)	0	0	1	0	0	2	3	4	4	4	***18***
total	**14**	**17**	**18**	**17**	**27**	**37**	**48**	**35**	**42**	**65**	***320***

The negotiators have 120 days to reach an agreement; during the CRM reimbursement procedure the applicant may twice request a 90-day suspension; and the CRM reimbursement procedure can also be suspended if some information is missing at submission or if the FPS Economy has not assigned a price.

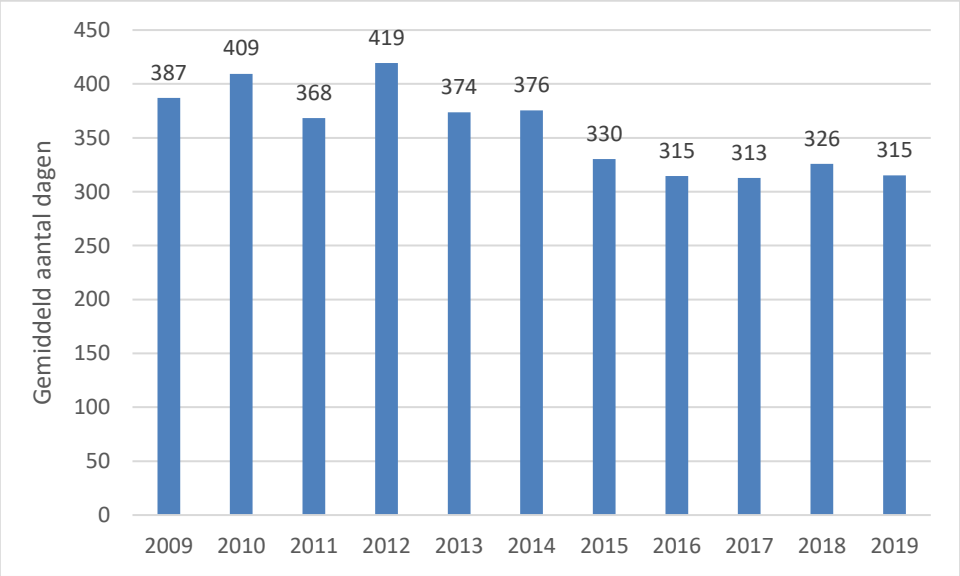
Possible suspensions are included in the number of days given in the following analysis.

Since the possibility of concluding a convention was introduced, the average number of days between submission of a request for reimbursement and the entry into force of that reimbursement is 338 days. This is the average of all cases with the exception of one outlier where the procedure took 1,443 days.

In the case of 68% 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 135 days. The longest-but-one period between submission and entry into force of the reimbursement was 581 days (i.e. ± 1.5 years), due to suspensions during the procedure.

Over the years, the time between submission of the reimbursement request and the entry into force of the reimbursement has remained relatively stable (around 10 months). Given that conventions are largely concluded for medicines deemed by the pharmaceutical company to have therapeutic added value or for orphan drugs, the two-to-three-month acceleration compared to ten years ago means that patients have quicker access to innovative medicines.

Figure 115: Evolution of time between submission of the reimbursement dossier and entry into force of reimbursement



Of the 108 conventions which have expired, no new CRM procedure seems to have been launched for 5 of them (4.63%).

For 34.26% (37/108) of the expired conventions, a new CRM procedure was launched and the specialty/indication was definitively included in the list of reimbursable specialties.

For 56.48% (61/108) of the expired conventions, a new CRM procedure was launched and the specialty/indication was temporarily included in the list of reimbursable specialties, via a new convention.

In the case of 4.63% (5/108) of the expired conventions, a new CRM procedure was launched, but the (temporary or definitive) reimbursability was not retained. As a result, the specialty/indication is no longer reimbursed.

Figure 116: Expired conventions – current situation

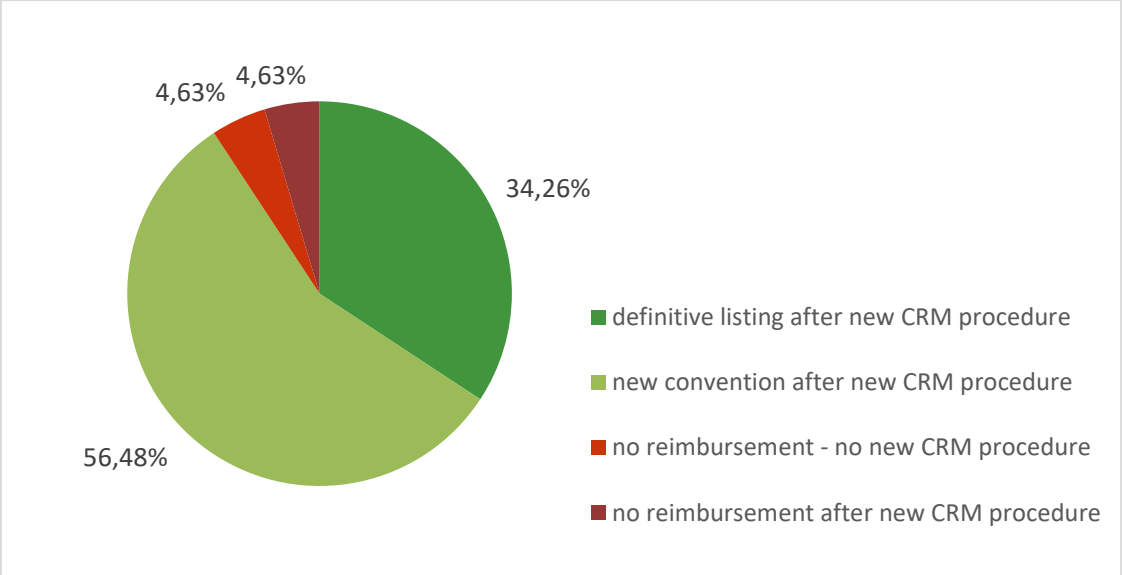
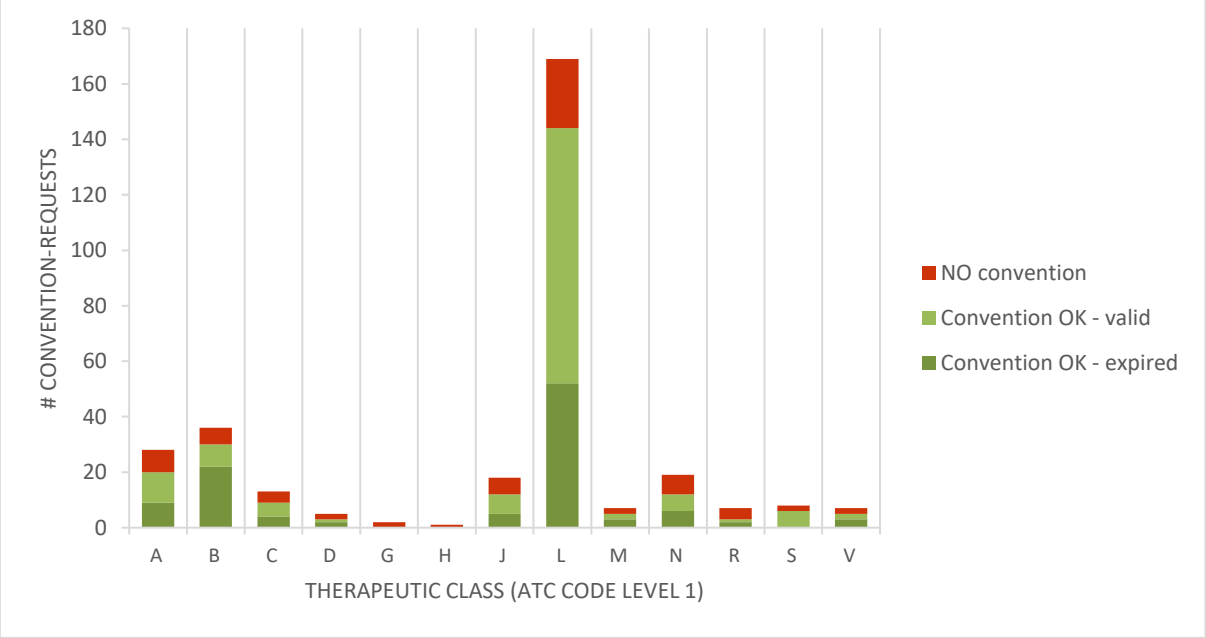


Figure 117 gives an overview per ATC class (level 1) of the number of requests leading to negotiations since the introduction of this procedure.

Figure 117: Overview of requests for Article 81/111 conventions per ATC class

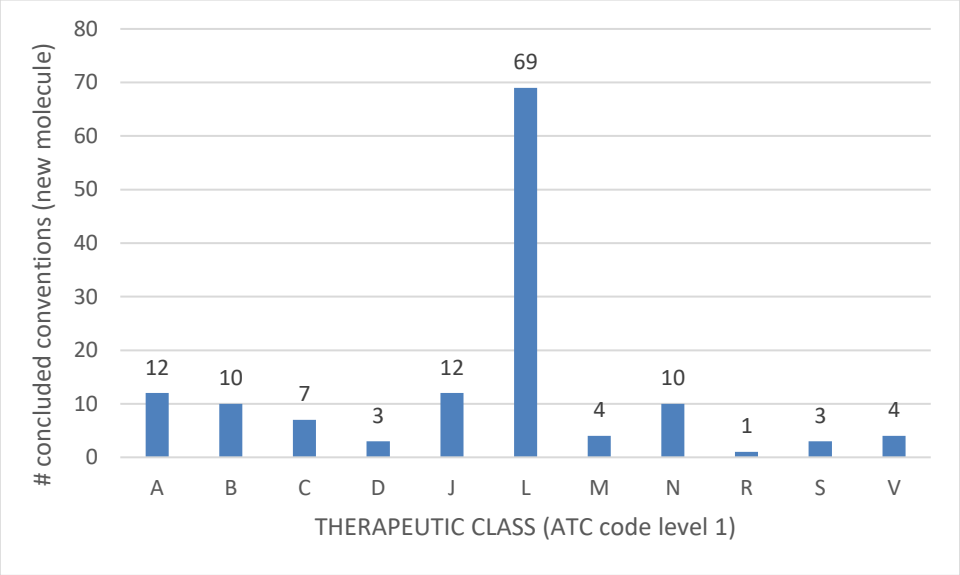


For some pharmaceutical specialties, more than one indication is reimbursed by means of a convention, so for some specialties, more than one convention may be concluded.

Most conventions (58%) were concluded for medicines in ATC class L, 'Antineoplastic and immunomodulating agents'. Next were medicines from ATC class B 'Blood and blood forming organs' (12%).

In terms of molecules, one or more conventions were concluded in the period 2010-2019 for 135 molecules (unique ATC code).

Figure 118: Overview of number of Article 81/111 conventions concluded per ATC class



Conventions per status of CRM opinion

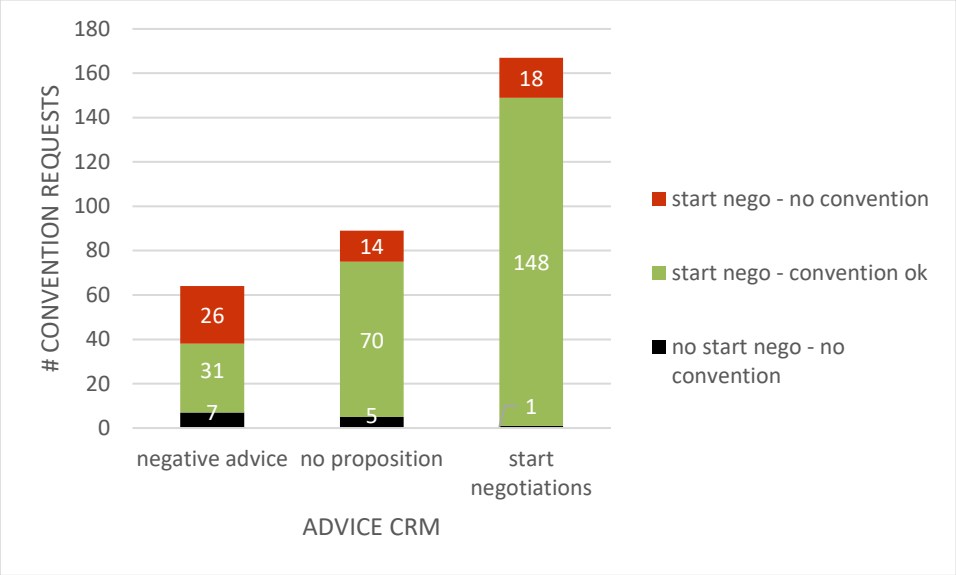
Until 01.07.2014, a company which had received a negative opinion from the CRM could submit a request to enter into negotiations. Since 01.02.2018, this has again become possible, although only after an explicit demand from the Minister for Social Affairs, asking for a company which has received a negative opinion from the CRM to be permitted to lodge a request to launch negotiations.

In 7 of the 64 dossiers (10.9%) on which the CRM gave a negative opinion, the minister in question refused to launch a negotiating procedure. In 31 of the 64 dossiers (48.4%) on which the CRM issued a negative opinion, a convention was finally concluded.

A convention was concluded in 148 of the 167 cases (88.6%) where the CRM had issued a proposal to negotiate, and in 70 of the 89 cases (78.7%) on which the CRM did not issue an opinion.

There have also been a limited number of CRM procedures where the Commission proposed the launch of negotiations, but where the company did not submit a request to the Minister for Social Affairs. In these cases, the medicine was listed definitively – but at a reduced price.

Figure 119: 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

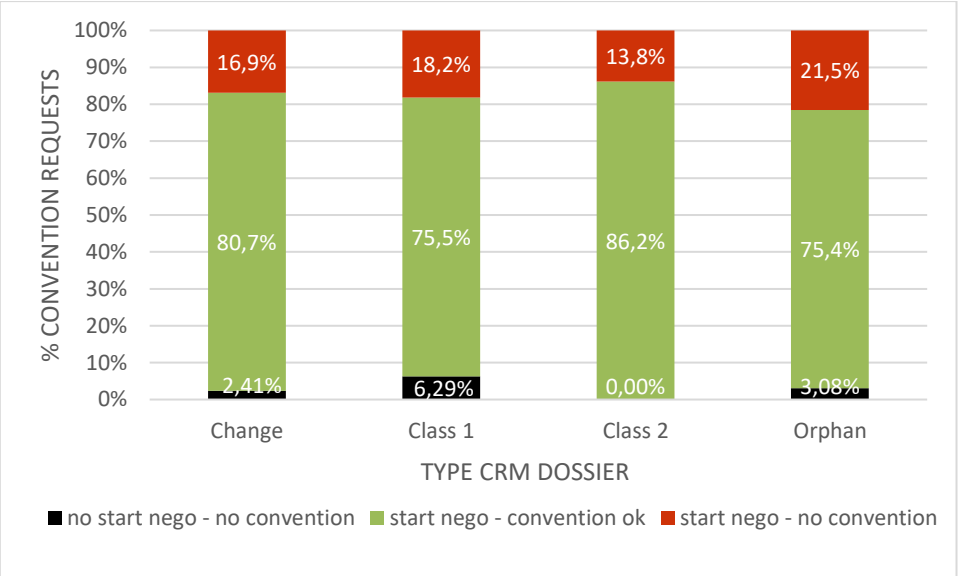
In the case of 75.5% (108/143) of reimbursement requests for which the pharmaceutical company claims therapeutic added value ('Class 1'), a convention is concluded and temporary reimbursement takes place. For 75.4% (49/65) of requests regarding an orphan drug, a convention is concluded.

In requests for negotiations where no claim of therapeutic added value is made, the specialty is listed temporarily in 86.2% (25/29) of the cases. In such cases, the reference specialty is also 'under contract', which probably makes it more likely that agreement will be reached.

80.7% (67/83) 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 limited number of cases, the request to launch negotiations is rejected by the Minister for Social Affairs.

Figure 120: Overview of Article 81/111 convention requests, by type of reimbursement request submitted by the pharmaceutical company



No convention

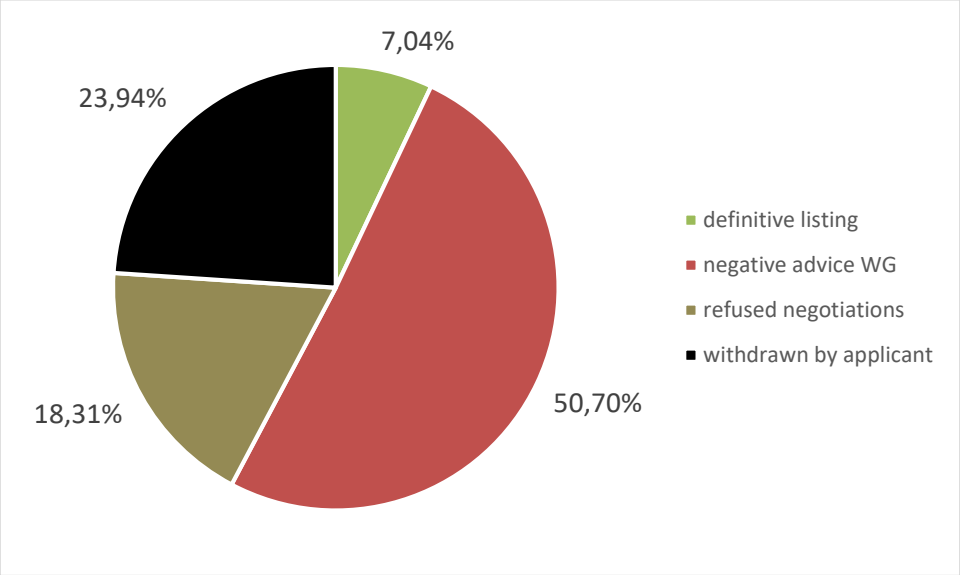
Even when the pharmaceutical company has made a request for negotiations to the Minister of Social Affairs, the procedure does not always result in a convention.

In 7% of such cases, the specialty is included definitively in the list of reimbursable pharmaceutical specialties without a convention. Often, the list price is directly reduced.

In 18% 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.

In around half of cases, the working group carrying out the negotiations decides that no agreement can be reached, and informs the Minister of this. In around a quarter of the cases, the pharmaceutical company withdraws from the negotiations in mid-procedure.

Figure 121: Overview of reasons why no convention is concluded

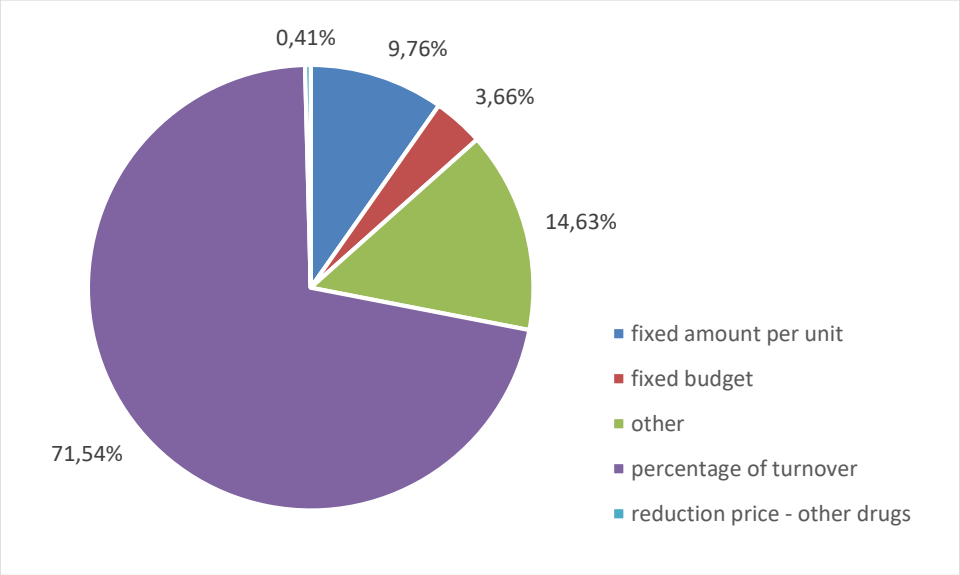


Budgetary compensation mechanism

85% of the conventions concluded have included only one budgetary compensation mechanism.

- In most of them (71.54%), 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 9.76% of the conventions concluded, the applicant is required to repay a set amount per unit sold.
- In 6.66% 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 specialty. 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 (0.41%). This shows that this is not the preferred compensation mechanism, possibly because of its uncertain outcome.

Figure 122: Overview of Article 81/111 convention requests, by budgetary compensation mechanism



The remaining 14.63% 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 specialty 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.

As previously reported, there is no separate budget for pharmaceutical specialties 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 01.02.2018).

The following points should be borne in mind when interpreting the table:

- 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, 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 specialties, is not accounted for (the compensation figures are therefore underestimated).

- With regard to the turnover figures, in some cases the full turnover for the specialty is used, including the turnover for that specialty for 'non-contracted' indications. This is currently only the case for medicines in ATC class L (ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS).
  (The turnover figures are therefore overestimated, and the average refund percentages are underestimated).

- 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 pharmaceutical specialties within the health insurance system. Application of the 'prepayment' system should provide a more accurate picture of the actual net expenditure per calendar year.

- 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 'system of prepayments' that aims to approximate the actual net expenditure on pharmaceutical specialities 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. Table 19 shows these figures.

- 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 specialties.

- The data refer to the situation on 27.08.2020, source Pharmaceutical Policy directorate (database on follow-up of Article 81/111 conventions)

Table 19: Overview, per year, of turnover figures, compensation and net expenditure (ex factory prices, expressed in 000 EUROS).

	2010	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
Gross turnover	**2.349**	**8.680**	**53.411**	**131.470**	**225.160**	**466.079**	**652.716**	**1.070.151**	**1.316.037**	**1.570.255**
Prepayments	-	-	-	-	-	-	-	100.491	195.504	387.036
Balance	-	1.249	2.630	23.729	41.428	56.629	121.316	172.656	162.078	218.136
Net expenditure	**2.349**	**7.432**	**50.780**	**107.741**	**183.731**	**409.450**	**531.400**	**797.003**	**958.455**	**965.083**
Percentage of compensation	0,0%	14,4%	4,9%	18,0%	18,4%	12,2%	18,6%	25,5%	27,2%	38,5%

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 SPECIALTIES

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

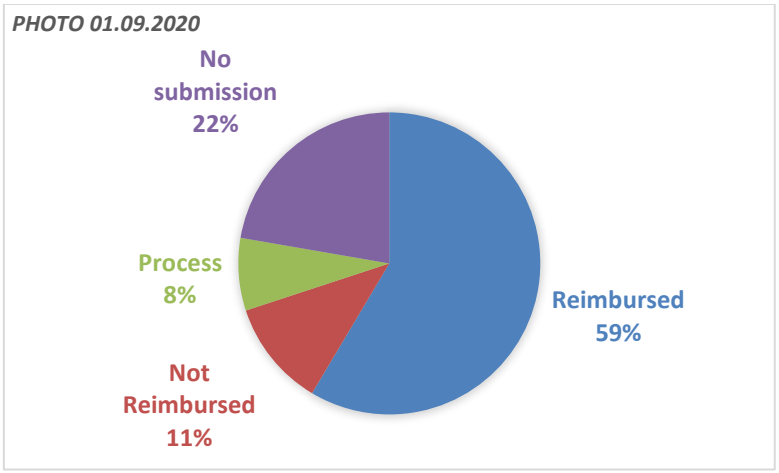
- be withdrawn by the company, particularly in order to extend the indications;
- be lost when, for example, the ten-year exclusivity expires or
- not be obtained if the company has not gone through the designation process.

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

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 September 2020, at the time of the reimbursement evaluation, there were 193 registered medicines considered as orphan drugs, or previously regarded as orphan drugs. Of these almost 200 specialties, only 2/3 were eligible for reimbursement (113 on 1 September 2020).

Figure 123: Reimbursement status of pharmaceutical specialties which have, or have had, the status of orphan drugs



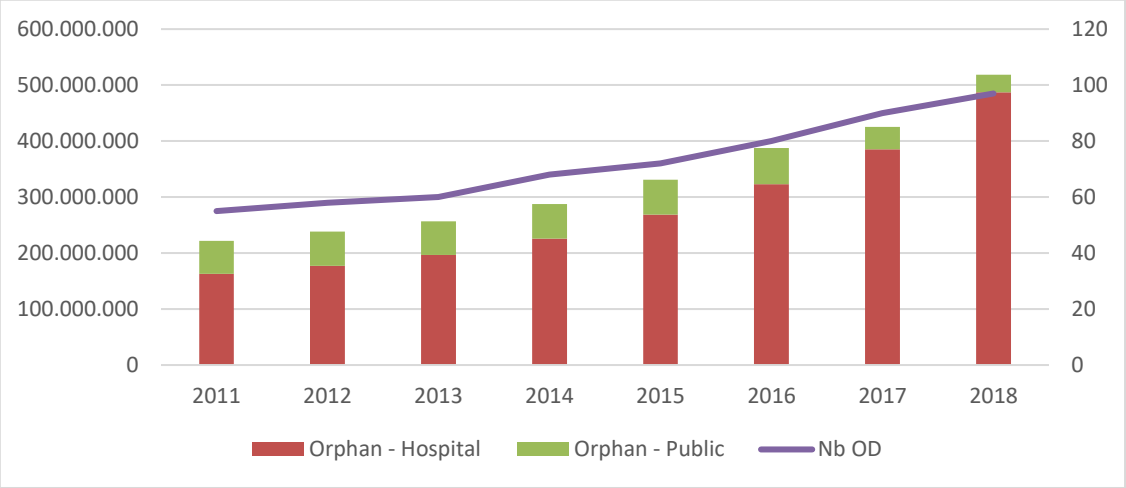
A follow-up of the reimbursement requests to the Commission for Reimbursement of Medicines confirms that this trend has existed for some years, since the percentages have remained very similar compared to the previous report: almost 60% of the medicines classified as orphan drugs are eligible for reimbursement. For just over 10%, reimbursement was refused, not just for budgetary reasons, but also often because cheaper alternatives exist or because some information, required for the procedure, was lacking. Just over 5% are part-way through the process in the CRM, but for slightly below 25% of these drugs, the authorisation holder did not apply for reimbursement in Belgium.

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.

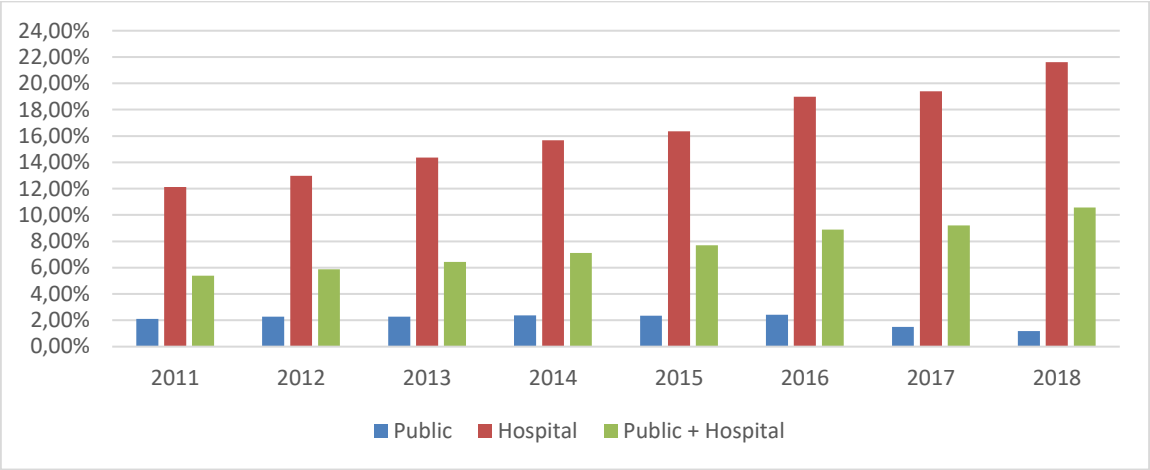
The two figures below (Figure 124 and Figure 125) show firstly the intrinsic evolution of NIHDI expenditure on orphan drugs and, secondly, the percentage which they represent in the total expenditure on reimbursable medicines.

Figure 124: evolution of NIHDI net annual expenditure (public pharmacies and hospitals) and number of orphan drugs eligible for reimbursement, 2011 - 2018



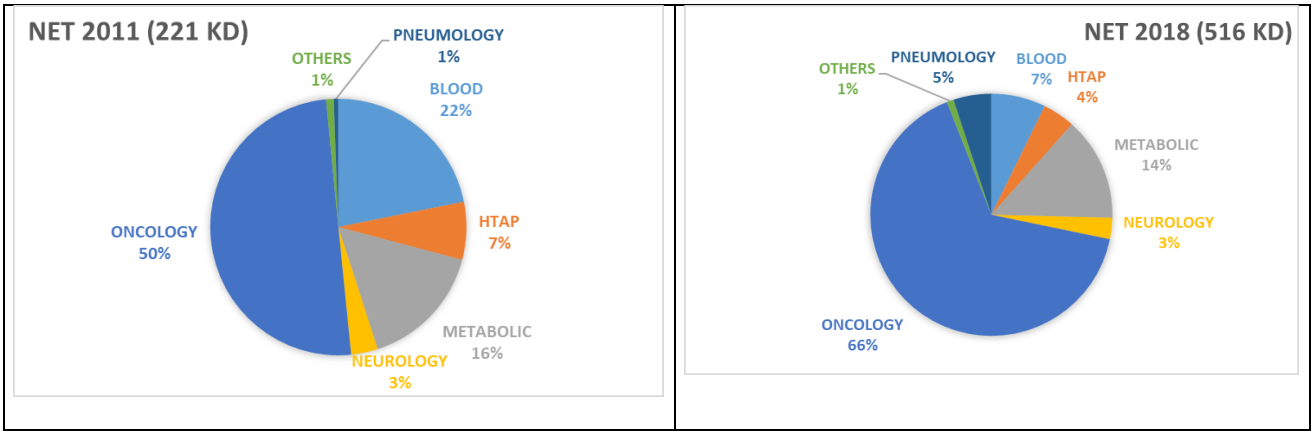
Between 2011 and 2018, expenditure has evolved by a factor of 2.34, while the number of orphan drugs becoming eligible for reimbursement between these two years increased by a multiplication factor of 1.75.

Figure 125: orphan drugs as a percentage of NIHDI net annual expenditure, by place of delivery (public pharmacies and hospitals), 2011 - 2018



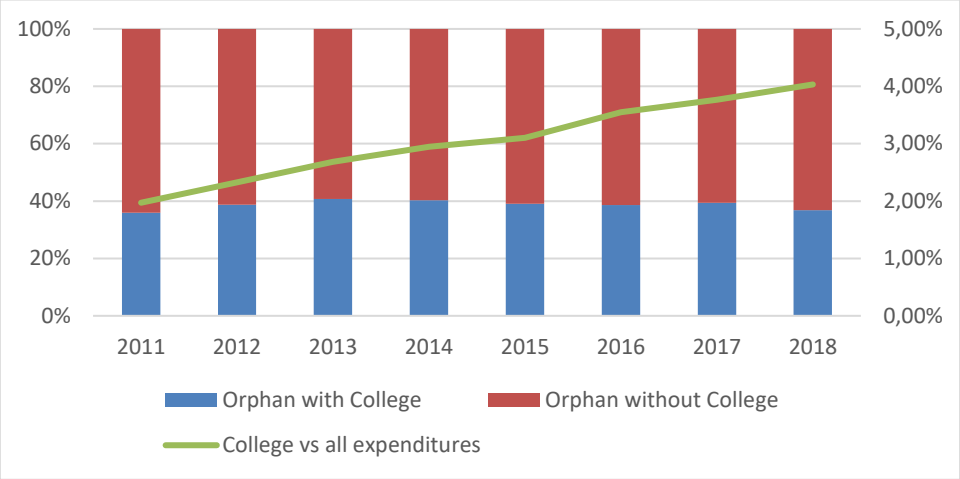
Based on Figure 125, we can roughly estimate that expenditure on specialties with, or which previously had, the status of orphan drugs, makes up 10% of total net expenditure on reimbursable pharmaceutical specialties, varying according to place of delivery, from 1% of net expenditure in public pharmacies to 20% of hospital expenditure.

Figure 126: Breakdown of orphan drugs by area of medicine, and a comparative overview of expenditure on these areas



This comparison shows the shift towards greater specification in the treatment of cancer, and more targeted indications; this means that cancer medicines can obtain designation as orphan drugs, while for blood-related diseases, use of the designation has become less frequent.

Figure 127: Orphan drugs which have, or have had, a College, as a percentage of reimbursable expenditure



This diagram shows the proportion of expenditure linked to a prior opinion from a College, as a percentage of all expenditure on specialties which have, or have had, orphan drug status. The green line shows the expenditure on 'orphan drugs with a College' as a proportion of the total net expenditure on reimbursable pharmaceutical specialties.

GENERAL COMMENTS

The comments made in the previous 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 evolution increase of expenditure on metabolic diseases is partly due to the emergence of new drugs, but also to the evolution increase in genetic screenings and a posology which usually depends on the weight of the patient. Based on data from the Colleges, the average annual cost per patient for this sort of molecule is 215,000 euros, with a range between 50,000 and 400,000 euros.

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 pharmaceutical specialties and important for the speed of reimbursement of sometimes innovative new medicines.
- For orphan drugs 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 2012 and 2019, 9.85% of class 1 requests and requests for reimbursability for orphan drugs 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 (6 requests in 2015, 6 requests in 2016, 8 requests in 2017, 6 requests in 2018 and 1 request in 2019).
- 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 pharmaceutical specialties, 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 pharmaceutical specialties. 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 specialties 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 specialties 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 specialty 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 specialties on which the CRM has given a negative opinion - solely on the basis of a reasoned proposal from the Minister of Social Affairs;

  …

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 2019.
- 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 specialties, the dossiers are taken together if the company responsible, the type of dossier, the day '0' (day of the request), active ingredient, 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 2018 and 2019 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 pharmaceutical specialties 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 pharmaceutical specialties) is lower than the average number of dossiers submitted every year during the last 10 years, with considerable differences between the types of request (see Figure 128). 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).

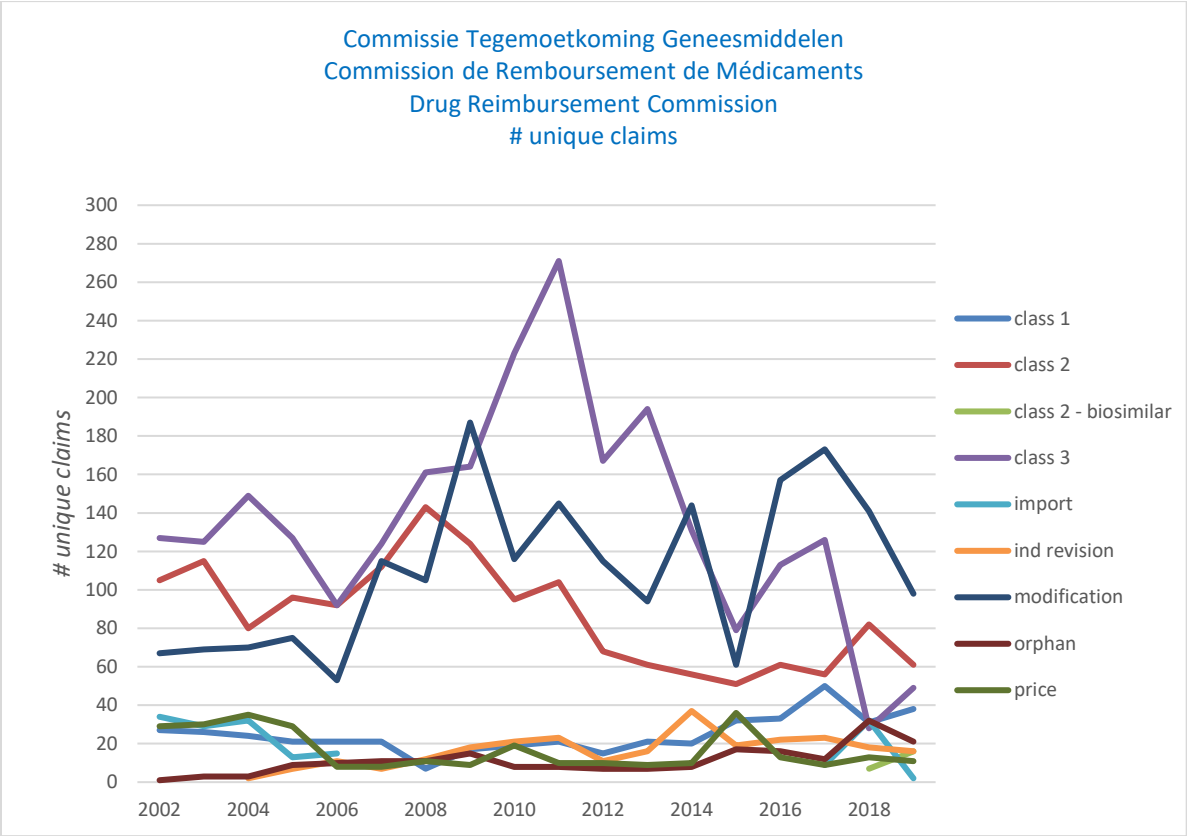
It should be noted that:

- After reaching a low point in 2008, the number of class 1 requests has grown since 2009 to 50 requests in 2017, 31 in 2018 and 38 in 2019.
- The number of orphan drug requests is considerably higher in 2018 and 2019 than the numbers observed since 2010: between 2010 and 2014 there were 7 or 8 orphan drug requests per year, while in 2015, 2016 and 2017, there were 17,16 and 12 respectively, then 32 in 2018 and 21 in 2019.
- In past years, the number of class 2 requests has remained relatively stable (51 requests in 2015, 61 in 2016, 56 in 2017, 82 in 2018 and 61 in 2019).
- The number of class 3 requests – non-administrative procedure – has reached 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 pharmaceutical specialties (79 requests in 2015, 113 in 2016, 126 in 2017, 28 in 2018 and 49 in 2019).
- The high number of requests to amend the reimbursement arrangements is striking in certain years, particularly in 2007, 2009, 2011, 2014, 2016 and 2017; 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, specialties based on paclitaxel, etc.), and also in 2014 (docetaxel-based specialties, oxaliplatin, anastrozole, etc.), in 2016 (specialties based on gemcitabine, irinotecan, growth hormones, etc.), and in 2017 (specialties based on COX-2 selective nonsteroidal anti-inflammatory drugs, piroxicam-based specialties, aliskiren-based specialties, 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, 186 completed 'class 3 – administrative procedure' dossiers, 22 completed 'parallel import - administrative procedure' dossiers nor 518 'Article 97 procedures - administrative proposals for amendments/corrections to the list';

Figure 128: 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 insurance for medical care and benefits towards costs of pharmaceutical specialties, states that the minister's decisions on the requests for reimbursement of new pharmaceutical specialties 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 insurance for medical care and benefits towards costs of pharmaceutical specialties.

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
- 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 specialty on the list of reimbursable pharmaceutical specialties (or for temporary listing of a new therapeutic indication of a specialty already on the list of reimbursable pharmaceutical specialties). 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.

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 20 shows the frequency, in 2015-2019, 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. The annexes to this report contain detailed data on the various years.

We can see clearly that for the class 1 dossiers submitted, it is less usual to reach a two thirds majority on a proposal (in 21% of the cases, there is no proposal from the Commission).

Table 20: number of unique requests for inclusion in the list of reimbursable pharmaceutical specialties versus proposals by the Commission for Reimbursement of Medicines (2015-2019)

2015 – 2019									
	positive		art.81 bis/art. 112		negative		no proposal		total
	number	%	number	%	number	%	number	%	number
class 1	20	17	55	47	17	15	25	21	117
class 2	141	71	9	5	30	15	19	10	199
class 2 – biosim	20	100	-	-	-	-	-	-	20
class 3	152	66	-	-	60	26	20	9	232
modification	290	72	47	12	44	11	21	5	402
Orphan	9	16	31	56	10	18	5	9	55
Total	632	62	142	14	161	16	90	9	1025

Table 21 shows, for the period 2015-2019, 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 postive or negative decisions. The annexes to this report also contain detailed data on the individual years.

Table 21: Ministerial decisions based on the CRM proposal (unique dossiers 2015-2019)

	positive decision Min		negative decision Min		no decision Min (pos)		total
CTG CRM proposal	#	%	#	%	#	%	**#**
class 1	**84**	**60.9**	**54**	**39.1**	**-**	**-**	**138**
positive prop	22	100.0	-	-	-	-	**20**
negative prop	4	20.0	16	80.0	-	-	**29**
no prop	13	44.8	16	55.2	-	-	**22**
art. 81bis	45	67.2	22	32.8	-	-	**67**
class 2	**216**	**89.6**	**24**	**10.0**	**1**	**0.4**	**241**
positive prop	168	100.0	-	-	-	-	**168**
negative prop	22	59.5	14	37.8	1	2.7	**37**
no prop	25	92.6	2	7.4	-	-	**27**
art. 81bis	1	11.1	8	88.9			**9**
class 2 - biosim	**20**	**100**	**-**	**-**	**-**	**-**	**20**
positive prop	20	100	-	-	-	-	**20**
negative prop	-	-	-	-	-	-	**-**
no prop	-	-	-	-	-	-	**-**
class 3	**265**	**88.9**	**25**	**8.4**	**8**	**2.7**	**298**
positive prop	193	99.5	-	-	1	0.5	**194**
negative prop	54	66.7	24	29.6	3	3.7	**81**
no prop	18	78.3	1	4.3	4	17.4	**23**

modification	**377**	**83.4**	**67**	**14.8**	**8**	**1.8**	**452**
positive prop	317	99.1	1	0.3	2	0.6	**320**
negative prop	9	18.0	38	76.0	3	6.0	**50**
no prop	17	63.0	8	29.6	2	7.4	**27**
art. 81bis	34	61.8	20	36.4	1	1.8	**55**
orphan	**38**	**56.7**	**29**	**43.3**	**-**	**-**	**67**
positive prop	12	100.0	-	-	-	-	**12**
negative prop	2	18.2	9	81.8	-	-	**11**
no prop	4	66.7	2	33.3	-	-	**6**
art. 81bis	20	52.6	18	47.4	-	-	**38**
total	**1000**	**82.2**	**199**	**16.4**	**17**	**1.4**	**1216**

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 6.3% 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 20% of class 1 dossiers on which a negative proposal was formulated).

For requests regarding the listing of an orphan drug, in 2 cases the Minister overruled a negative proposal from the Commission (i.e. in 18.2% of cases where a negative proposal was made regarding the listing of an orphan drug).

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 pharmaceutical specialties 2015-2019

CRM PROPOSALS PER TYPE OF REQUEST

Table 22: number of unique requests for inclusion in the list of reimbursable pharmaceutical specialties versus proposals of the Commission for Reimbursement of Medicines (2015)

2015									
	positive		negative		no proposal		Art. 81bis		total
	number	%	number	%	number	%	number	%	number
class 1	2	9 %	3	13 %	4	17 %	14	61 %	23
class 2	27	61 %	7	16 %	10	23 %	-	-	44
class 3	42	64 %	21	32 %	3	5 %	-	-	66
modification	32	63 %	4	8 %	6	12 %	9	18 %	51
orphan	3	23 %	1	8 %	2	15 %	7	54 %	13
Total	106	54 %	36	18 %	25	13 %	30	15 %	197

Table 23: number of unique requests for inclusion in the list of reimbursable pharmaceutical specialties versus proposals of the Commission for Reimbursement of Medicines (2016)

2016									
	positive		negative		no proposal		Art. 81bis		total
	number	%	number	%	number	%	number	%	number
class 1	8	27 %	1	3 %	6	20 %	1	50 %	30
class 2	33	73 %	5	11 %	7	16 %	-	-	45
class 3	68	65 %	21	20 %	15	14 %	-	-	104
modification	71	70 %	9	9 %	7	7 %	15	15 %	102
orphan	3	21 %	3	21 %	2	14 %	6	36 %	14
class 2 - biosim	1	100 %	-	-	-	-	-	-	1
Total	184	62 %	39	13 %	37	13 %	36	12 %	296

Table 24: number of unique requests for inclusion on the list of reimbursable pharmaceutical specialties versus proposals of the Commission for Reimbursement of Medicines (2017)

2017									
	positive		negative		no proposal		Art. 81bis		total
	number	%	number	%	number	%	number	%	number
class 1	8	20 %	10	24 %	5	12 %	18	44 %	41
class 2	31	67 %	8	17 %	7	15 %	-	-	46
class 3	55	63 %	29	33 %	3	3 %	-	-	87
modification	63	66 %	19	20 %	5	5 %	8	8 %	95
orphan	2	20 %	1	10 %	1	10 %	6	60 %	10
class 2 - biosim	-	-	-	-	-	-	-	-	-
Total	159	57 %	67	24 %	21	8 %	32	11 %	279

Table 25: number of unique requests for inclusion in the list of reimbursable pharmaceutical specialties versus proposals of the Commission for Reimbursement of Medicines (2018)

2018									
	positive		negative		no proposal		Art. 81bis		total
	number	%	number	%	number	%	number	%	number
class 1	1	5 %	5	23 %	7	32 %	9	41 %	22
class 2	44	72 %	8	13 %	4	7 %	5	8 %	61
class 3	13	68 %	6	32 %	-	-	-	-	19
modification	93	73 %	13	10 %	4	3 %	18	14 %	128
orphan	2	9 %	5	22 %	2	9 %	14	61 %	23
class 2 - biosim	6	100%	-	-	-	-	-	-	6
Total	159	61 %	37	14 %	17	7 %	46	18 %	259

Table 26: number of unique requests for inclusion in the list of reimbursable pharmaceutical specialties versus proposals of the Commission for Reimbursement of Medicines (2019)

2019									
	positive		negative		no proposal		Art. 81bis		total
	number	%	number	%	number	%	number	%	number
class 1	3	13 %	1	4 %	7	29 %	13	54 %	24
class 2	33	70 %	9	19 %	1	2 %	4	98 %	47
class 3	16	73 %	4	18 %	2	9 %	-	-	22
modification	61	79 %	5	6 %	5	6 %	5	6 %	76
orphan	2	25 %	1	13 %	-	-	6	75 %	9
class 2 - biosim	13	100%	-	-	-	-	-	-	13
Total	128	67 %	20	10 %	15	8 %	28	15 %	191

DECISIONS OF THE MINISTER based on the CRM PROPOSAL

Table 27: Ministerial decisions based on the CRM proposal (unique dossiers 2015)

2015											
	positive decision Min		negative decision Min		no decision Min (pos)		no data		withdrawn (company)		**total**
CTG CRM proposal	number	%	number	%	number	%	number	%	number	%	**number**
class 1	**18**	**69.2 %**	**6**	**23.1 %**	**-**	**-**	**-**	**-**	**2**	**7.7 %**	**26**
positive prop	2	100 %	-	-	-	-	-	-	-	-	**2**
Art. 81bis	14	100 %	-	-	-	-	-	-	-	-	**14**
negative prop	-	-	4	66.7 %	-	-	-	-	2	33.3 %	**6**
no prop	2	50 %	2	50 %	-	-	-	-	-	-	**4**
class 2	**41**	**89.1 %**	**3**	**6.5%**	**-**	**-**	**-**	**-**	**2**	**4.3 %**	**46**
positive prop	27	100 %	-	-	-	-	-	-	-	-	**27**
negative prop	4	44.4 %	3	33.3 %	-	-	-	-	2	22.2 %	**9**
no prop	10	100%	-	-	-	-	-	-	-	-	**10**
class 3	**59**	**84.3 %**	**7**	**10.0 %**	**1**	**1.4 %**	**-**	**-**	**3**	**4.3 %**	**70**
positive prop	43	93.5 %	-	-	-	-	-	-	3	6.5 %	**46**
negative prop	15	71.4 %	6	28.6 %	-	-	-	-	-	-	**21**
no prop	1	33.3 %	1	33.3 %	1	33.3 %	-	-	-	-	**3**
modification	**46**	**88.5 %**	**5**	**9.6%**	**-**	**-**	**-**	**-**	**1**	**1.9 %**	**52**
positive prop	32	100 %	-	-	-	-	-	-	-	-	**32**
Art. 81bis	7	77.8 %	2	22.2 %	-	-	-	-	-	-	**9**
negative prop	1	20.0 %	3	60.0 %	-	-	-	-	1	20.0 %	**5**
no prop	6	100 %	-	-	-	-	-	-	-	-	**6**
orphan	**10**	**62.5 %**	**4**	**25.0 %**	**-**	**-**	**-**	**-**	**2**	**12.5 %**	**16**
positive prop	3	100 %	-	-	-	-	-	-	-	-	**3**

Art. 81bis	5	71.4 %	2	28.6 %	-	-	-	-	-	-	**7**
negative prop	-	-	2	50 %	-	-	-	-	2	50 %	**4**
no prop	2	100 %	-	-	-	-	-	-	-	-	**2**
total	**174**	**82.9 %**	**25**	**11.9 %**	**1**	**0.5 %**	**-**	**-**	**10**	**4.8%**	**210**

Table 28: Ministerial decisions based on the CRM proposal (unique dossiers 2016)

2016											
	positive decision Min		negative decision Min		no decision Min (pos)		no data		withdrawn (company)		**total**
CTG CRM proposal	number	%	number	%	number	%	number	%	number	%	**number**
class 1	**24**	**82.8 %**	**4**	**13.8 %**	**-**	**-**	**-**	**-**	**1**	**3.4 %**	**29**
positive prop	8	100 %	-	-	-	-	-	-	-	-	**8**
Art. 81bis	12	92.3 %	1	7.7 %	-	-	-	-	-	-	**13**
negative prop	-	-	2	66.7 %	-	-	-	-	1	33.3 %	**3**
no prop	4	80 %	1	20 %	-	-	-	-	-	-	**5**
class 2	**41**	**82 %**	**5**	**10 %**	**-**	**-**	**-**	**-**	**4**	**8 %**	**50**
positive prop	32	97 %	-	-	-	-	-	-	1	3 %	**33**
negative prop	2	25 %	5	50 %	-	-	-	-	2	25 %	**9**
no prop	7	77.8 %	1	11.1 %	-	-	-	-	1	11.1 %	**9**
class 2 - biosim	**1**	**100%**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**1**
positive prop	1	100%	-	-	-	-	-	-	-	-	**1**
negative prop	-	-	-	-	-	-	-	-	-	-	**-**
no prop	-	-	-	-	-	-	-	-	-	-	**-**
class 3	**103**	**92%**	**5**	**4.5%**	**1**	**0.9 %**	**-**	**-**	**3**	**2.7 %**	**112**
positive prop	69	100%	-	-	-	-	-	-	-	-	**69**
negative prop	17	70.8 %	5	20.8 %	-	-	-	-	2	8.3 %	**24**
no prop	17	89.5 %	-	-	1	5.3 %	-	-	1	5.3 %	**19**
modification	**96**	**90.6 %**	**7**	**6.6%**	**2**	**1.9 %**	**-**	**-**	**1**	**0.9 %**	**106**
positive prop	73	98.6 **%**	-	-	1	1,4%	-	-	-	-	**74**
Art. 81bis	16	100 %	-	-	-	-	-	-	-	-	**16**
negative prop	2	22.2 %	7	77.8 %	-	-	-	-	-	-	**9**
no prop	5	71.4 %	-	-	1	14.3 %	-	-	1	14.3 %	**7**
orphan	**8**	**72.7 %**	**3**	**27.3 %**	**-**	**-**	**-**	**-**	**-**	**-**	**11**
positive prop	3	100 %	-	-	-	-	-	-	-	-	**3**
Art. 81bis	3	75%	1	25%	-	-	-	-	-	-	**4**

negative prop	1	33.3 %	2	66.7 %	-	-	-	-	-	-	**3**
no prop	1	100 %	-	-	-	-	-	-	-	-	**1**
total	**273**	**88.3 %**	**24**	**7.8%**	**3**	**1,0%**	**-**	**-**	**9**	**2.9%**	**309**

Table 29: Ministerial decisions based on the CRM proposal (unique dossiers 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**	**-**	**-**	**41**
positive prop	8	100.0	-	-	-	-	**8**
negative prop	4	40.0	6	60.0	-	-	**10**
no prop	1	20.0	4	80.0	-	-	**5**
Art. 81bis	14	77.8	4	22.2	-	-	**18**
class 2	**41**	**89.1**	**4**	**8.7**	**1**	**2.2**	**46**
positive prop	31	100.0	**-**	-	**-**	-	31
negative prop	4	50.0	3	37.5	1	12.5	8
no prop	6	85.7	1	14.3	-	-	7
class 3	**77**	**88.5**	**6**	**6.9**	**4**	**4.6**	**87**
positive prop	55	100.0	**-**	-	**-**	-	55
negative prop	20	69.0	6	20.7	3	10.3	29
no prop	2	66.7	-	-	1	33.3	3
modification	**72**	**75.8**	**19**	**20.0**	**4**	**4.2**	**95**
positive prop	61	96.8	1	1.6	1	1.6	63
no prop	4	80.0	1	20	-	-	5
negative prop	1	5.3	16	84.2	2	10.5	19
Art. 81bis	6	75.0	1	12.5	1	12.5	8
orphan	**9**	**90.0**	**1**	**10.0**	**-**	**-**	**10**
positive prop	2	100.0	**-**	-	-	-	2
No prop	1	100.0	-	-	-	-	1
negative prop			1	100.0	-	-	1
Art. 81bis	6	100.0	-	-	-	-	6
total	**226**	**81.0**	**44**	**15.8**	**9**	**3.2**	**279**

Table 30: Ministerial decisions based on the CRM proposal (unique dossiers 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**	**-**	**-**	**22**
positive prop	1	100.0			-	-	**1**
negative prop		0.0	5	100.0	-	-	**5**
no prop	3	42.9	4	57.1	-	-	**7**
Art. 81bis	3	33.3	6	66.7	-	-	**9**
class 2	**55**	**90.2**	**6**	**9.8**	**-**	**-**	**61**
positive prop	44	100.0	**-**	-	**-**	-	**44**
negative prop	6	75.0	2	25.0	-	-	**8**
no prop	4	100.0	-	-	-	-	**4**
Art. 81bis/art. 112	1	20.0	4	80.0			**5**
class 3	**14**	**73.7**	**4**	**21.1**	**1**	**20.0**	**19**
positive prop	12	92.3	**-**	-	1	7.7	**13**
negative prop	2	33.3	4	66.7	-	-	**6**
no prop	**-**	-	**-**	-	**-**	-	**0**
modification	**99**	**77.3**	**28**	**21.9**	**1**	**0.8**	**128**
positive prop	93	100.0	-	-	-	-	**93**
negative prop	2	15.4	11	84.6	-	-	**13**
no prop	-	0.0	3	75.0	1	25.0	**4**
Art. 81bis	4	22.2	14	77.8	-	-	**18**
orphan	**7**	**30.4**	**16**	**69.6**	**-**	**-**	**23**
positive prop	2	100.0	**-**	-	**-**	-	**2**
no prop	1	50.0	1	50.0	-	-	**2**
negative prop	-	-	5	100.0	-	-	**5**
Art. 81bis	4	28.6	10	71.4	-	-	**14**
total	**182**	**71.9**	**69**	**27.3**	**2**	**0.8**	**253**

Table 31: Ministerial decisions based on the CRM proposal (unique dossiers 2019)

	positive decision Min		negative decision Min		no decision Min (pos)		**total**
CTG CRM proposal	number	%	number	%	number	%	**number**
class 1	**7**	**29.2**	**17**	**70.8**	**-**	**-**	**24**
positive prop	3	100.0	-	-	-	-	**3**
negative prop		0.0	1	100.0	-	-	**1**
no prop	2	28.6	5	71.4	-	-	**7**
Art. 81bis	2	15.4	11	84.6	-	-	**13**
class 2	**41**	**87.2**	**6**	**12.8**	**-**	**-**	**47**
positive prop	33	100.0	-	-	-	-	**33**
negative prop	7	77.8	2	22.2	-	-	**9**
no prop	1	100.0	-	-	-	-	**1**
Art. 81bis/art. 112		0.0	4	100.0			**4**
class 3	**19**	**86.4**	**3**	**13.6**	**-**	**-**	**22**
positive prop	16	100.0		0.0	-	-	**16**
negative prop	1	25.0	3	75.0		-	**4**
no prop	2	100.0			-	-	**2**
modification	**68**	**88.3**	**8**	**10.4**	**1**	**1.3**	**77**
positive prop	61	100.0	-	-	-	-	**61**
negative prop	3	60.0	1	20.0	1	20.0	**5**
no prop	1	20.0	4	80.0	-	-	**5**
Art. 81bis	3	50.0	3	50.0	-	-	**6**
orphan	**4**	**50.0**	**4**	**50.0**	**-**	**-**	**8**
positive prop	2	100.0	-	-	-	-	**2**
negative prop	1	100.0	-	-	-	-	**1**
no prop	-	-	-	-	-	-	**0**
Art. 81bis	1	20.0	4	80.0	-	-	**5**
total	**139**	**78.1**	**38**	**21.3**	**1**	**0.6**	**178**

ANNEX 2

SAVINGS MEASURES 2017-2019

Savings measures 2017

Indexation of the basic fee for pharmacists and of the limit values for the patient co-payment: 1.1.2017

The basic fee for pharmacists was indexed on 1 January 2017. The fee increased from 4.16 euros to 4.20 euros (excl. VAT).
The limit values for the patient co-payment were also indexed. The new amounts are as follows:

Reimbursement categories	Patients with preferential entitlement. Not hospitalised	Normal entitlement Not hospitalised
category B	Co-payment: maximum 7.90 euros	Co-payment: maximum 11.90 euros
category B - large model	Co-payment: maximum 9.80 euros	Co-payment: maximum 14.80 euros
category C	Co-payment: maximum 9.80 euros	Co-payment: maximum 14.80 euros

Regularisation of the prices of some generic medicines in the reference reimbursement system: 1.1.2017

The aim of the savings measures is to regularise the price of generic specialties to which the 'patent cliff' was not applied on 1 March 2016, due to the absence of reference specialties in some clusters. These clusters contain:

- generic medicines with an active ingredient which has been reimbursable for less than 2 years, 16.50% reduction
- generic medicines with an active ingredient which has been reimbursable for more than 2 years but less than 4 years, 11.17% reduction
- generic medicines with an active ingredient which has been reimbursable for more than 4 years but less than 6 years, 6% reduction.

The clusters affected are:

- Cimetidine
- Flutamide
- Mitoxantrone
- Norfloxacin (no reduction)
- Paclitaxel
- Pantoprazole
- Pantoprazole (inj.)
- Vancomycin
- Vincristine (no reduction)

Simultaneous application of the 'combi-cliff' and the three-monthly reference reimbursement: 1.3.2017

The reimbursement basis of specialties with more than one active ingredient, which are not or are no longer protected by a patent or supplementary protection certificate, and to which the reference reimbursement system was applied before 1 March 2017 for at least one of its active ingredients, is reduced by operation of law so that the combination's reimbursement basis is not higher than the sum of the highest reimbursement bases of the cheapest available 'mono-specialties'.

The clusters affected are:

- Dexamethasone + Tobramycin
- Altizide + Spironolactone
- Fenoterol + Ipratropium
- Dipyridamole + Acetylsalicylic acid
- Diclofenac + Misoprostol
- Timolol + Brinzolamide

The reference reimbursement is deemed to be applied to the following clusters (even if generic medicines are not reimbursable or not available):

- Acebutolol + Hydrochlorothiazide
- Amiloride + Furosemide
- Metoprolol + Chlorthalidone
- Metoprolol + Felodipine
- Atenolol + Nifedipine
- Hydrochlorothiazide + Triamterene
- Felodipine + Ramipril
- Alendronate + Colecalciferol
- Timolol + Travoprost
- Enalapril + Lercanidipine
- Perindopril + Amlodipine
- Nebivolol + Hydrochlorothiazide
- Telmisartan + Amlodipine
- Pravastatin + Fenofibrate
- Alendronic acid + Calcium + Colecalciferol
- Perindopril, - arginine + Indapamide + Amlodipine, - besylate

Increased rate of reduction applied under the 'biologicals' measure: 1.3.2017

Biological specialties already subject to a 7.5% reduction between 1 January 2014 and 1 January 2017 under the 'biologicals' measures, were reduced by a further 2.7% to bring them to a reduction of - 10 %.

The clusters affected are:

- Filgrastim
- Heparin

- Infliximab
- Interferon beta-1b, human recombinant
- Nadroparin
- Recombinant growth hormone (somatropin)
- Coagulation factor VIII, recombinant (octocog alfa)
- Tinzaparin

Group review Immunoglobulins: 1.4.2017

Reimbursement kept for all reimbursable indications, with the exception of the indication 'acquired immunodeficiency syndrome', given the lack of scientific evidence for this indication.

Group review Sartans: 1.4.2017

- Transfer of all olmesartan-based specialties to chapter I, with a 10% price reduction.
- Other sartans: no changes

Group review proton pump inhibitors (PPI): 1.4.2017

Application of the following three measures:

1. Some package sizes no longer reimbursable for the following active ingredients:

molecules	dosage	Package size
omeprazole	40 mg	98x – 100x
lansoprazole	15 mg	84x – 98x – 100x
pantoprazole	40 mg	84x – 98x – 100x – 112x
rabeprazole	10 mg & 20 mg	98x – 100x
esomeprazole		

2. 33% price reduction for packs of 84, 98 and 100 based on lansoprazole 30 mg.

3. Transfer of all high dosage PPIs from chapter II to chapter IV.

Group review corticosteroids: 1.4.2017

Transfer of all corticosteroids in spray form from Category B to Category Cx (with no price reduction).

Group review antibiotics: 1.5.2017

Transfer of all orally administered antibiotics to Category C (with no price reduction).

Group review of urinary antispasmodics: 1.5.2017

No price reductions as part of this group review.

Oxybutynin

- Current reimbursement conditions maintained, but with a harmonisation of the reimbursement conditions in chapter IV, § 1950000.

Other active ingredients

- For the specialty Urispas®: scrapping of reimbursability in chapter I and listing in chapter IV, § 2680000
- For the other specialties: current reimbursement conditions maintained but with a harmonisation of the reimbursement conditions in chapter IV, § 2680000.

Group review bisphosphonates: 1.5.2017

- Transfer of all bisphosphonates to chapter I with a price reduction.
- Scrapping of reimbursability for specialties for which the price reduction was not accepted.

Group review of platelet aggregation inhibitors: 1.6.2017

Clopidogrel-based specialties:

- **Clopidogrel 75 mg:**
  - Transfer of all specialties with clopidogrel 75 mg to chapter I, with a price reduction.
  - Scrapping of reimbursability for specialties for which the price reduction was not accepted.
- **Plavix ® 300 mg**

Specialties based on ticloplidine and prasugrel:

No changes

Group review of nitrates and molsidomine: 1.8.2017

- No changes to the reimbursement conditions for specialties based on nitroglycerin (patches) or on isosorbide (Cedocard®).

- Specialties Coruno® and Corvaton®: Listing in chapter IV (restricted to patients already treated before the entry into force of the new reimbursement conditions) and (slight) price reduction for the 2 Coruno® specialties.

Savings measures 2018

Indexation of the basic fee for pharmacists: 1.1.2018

The basic fee for pharmacists was indexed on 1 January 2018. The fee increased from 4.20 euros to 4.27 euros (excl. VAT).
The limit values for the patient co-payment remained the same.

Group review infliximab: 1.1.2018

Transfer of infliximab-based specialties from category B to category Fb.
15% reduction in ex factory reimbursement basis (ex factory price remains unchanged).

'Ceiling prices' measure: 1.4.2018

From 1 April 2018, reimbursable pharmaceutical specialties which are not among the 'cheapest' for two successive three-monthly periods will no longer be reimbursed.

Increased reduction applied under the 'biologicals' measure: 1.4.2018

Biological specialties already subject to a 10% cut before 1 April 2018 under the biologicals measure have been reduced again, by 5.56%, to make a total reduction of - 15 %.

The clusters affected are:

- Etanercept
- Filgrastim
- Interferon beta-1b, human recombinant
- Nadroparin (Fradoxi® Pi-Pharma)
- Recombinant growth hormone (somatropin) (except Omnitrope®)
- Coagulation factor VIII, recombinant (octocog alfa) (Helixate Nexgen®)

Group review rosuvastatin: 1.4.2018

Transfer of Crestor® specialties from chapter II to chapter I, with alignment of prices to those of the generic drugs.
This measure is applied at the same time as the reference reimbursement (in total: price reduction for Crestor® between 66 and 88 % depending on packaging).

Group review for quinolones: 4.5.2018

Transfer of specialties containing a quinolone, with no price change, from chapter I to chapter IV (§ 9210000) for reimbursement in public pharmacies.
This measure is designed to limit the use of this class of antibiotics.

Group review gadolinium: 1.7.2018

1. Suspension of reimbursability for the specialties Magnevist®, Omniscan® and Multihance® from §710000, §3920000 and §1280300 where applicable

2. Restricted reimbursability for the specialty Multihance® to MRI-scanning of the liver to visualise primary and secondary tumours, and adjustment of the reimbursement criteria of §1280200 concerning this restriction.

3. Addition of a recommendation on the macrocyclic contrast agents in §71000, § 7290100, §7290200, §7290300, §7290400, §3930000, §3600100, §3600200, §3600300, §6610000, §6620000 and §179000 for the specialties Prohance®, Dotarem®, Dotagraph® and Gadovist®: where applicable, service providers should use the lowest possible dose needed to generate a clear MRI image.

No change in price.

Savings measures 2019

Indexation of pharmacists' economic margin and of the limit values for the patient co-payment: 1.1.2019

Pharmacists' economic margin was indexed on 1 January 2019.
The limit values for the patient co-payment were also indexed. The new amounts are the following:

Reimbursement category	Patients with privileged entitlement Not hospitalised	Normal entitlement Not hospitalised
Category B	Co-payment: maximum 8.00 euros	Co-payment: maximum 12.10 euros
Category B - large model	Co-payment: maximum 9.90 euros	Co-payment: maximum 15.00 euros
Category C	Co-payment: maximum 9.90 euros	Co-payment: maximum 15.00 euros

Group review corticosteroids in spray form: 1.3.2019

Transfer of corticosteroids in spray form from chapter I in category Cx to chapter IV (§ 9630000) in category C.
No change in price.

Application of the 'volume cliff': 1.4.2019

Prices/reimbursement bases of specialties containing an active ingredient (or a combination of active ingredients) which have been eligible for reimbursement for more than 15 years are henceforth subject to a percentage reduction which varies depending on turnover, rather than the 2.41% reduction which has been applied up to now.

Specialties subject to a 2.41% reduction before 1 April 2019, are, from this date, subject to the following adjustments:

- 2.47 % if their active ingredient (or combination of active ingredients) has generated an annual turnover above 1.5 million euros but below 10 million euros in 2017,

- 3.09 % if their active ingredient (or combination of active ingredients) has generated an annual turnover of above 10 million euros but below 20 million euros in 2017,
- 3.70 % if their active ingredient (or combination of active ingredients) has generated an annual turnover of more than 20 million euros but less than 30 million euros in 2017,
- 4.94 % if their active ingredient (or combination of active ingredients) has generated an annual turnover of more than 30 million euros but less than 40 million euros in 2017,
- 6.17 % if their active ingredient (or combination of active ingredients) has generated an annual turnover of more than 40 million euros but less than 50 million euros in 2017,
- 7.41 % if their active ingredient (or combination of active ingredients) has generated an annual turnover of more than 50 million euros but less than 60 million euros in 2017,
- 8.64 % if their active ingredient (or combination of active ingredients) has generated an annual turnover of more than 60 million euros but less than 70 million euros in 2017,
- 9.88 % if their active ingredient (or combination of active ingredients) has generated an annual turnover of more than 70 million euros in 2017.

Group review diabetes: 1.7.2019

Scrapping of the specialties Daonil® and Repaglinide Accord®, adjustments to the reimbursement conditions in chapter IV and price reduction as follows:

- NPH Insulins (ATC: A10AC): reimbursement bases reduced by 2.2%
- Long acting insulins (ATC: A10AE) except for A10AE54 and A10AE56: reimbursement bases reduced by 2.2 %
- Other insulins: reimbursement bases reduced by 2.2 %
- Metformin, Sulfamides & Glinides: reimbursement bases reduced by 0.5 %
- Glitazones & Gliptins: reimbursement bases reduced by 2.2 %
- Gliflozins: No change in the reimbursement basis.
- Incretins: reimbursement bases reduced by 10 %
- Suliqua® (A10AE54): reimbursement bases reduced by 10 %
- Xultophy® (A10AE56): reimbursement bases reduced by 2.2 %

Group review coagulation factors: 1.7.2019

Change to the reimbursement conditions and price reduction.

Creation of chapter VIII - Personalised Medicines: 1.7.2019

Group review HIV: 1.9.2019

- Listing of the following specialties in §6790200 (STSS):

- Iqymune® 10 %, Octagam® 5 %, Multigam® 5 % and Privigen® 10 %
- Nanogam® 5%: only the packs Nanogam® 50mg/ml, 100ml, Nanogam® 50mg/ml, 200ml and Nanogam® 50mg/ml, 400ml.

- Listing of the following specialties in §6790300 (MMN):

  - Privigen® 10%
  - Nanogam® 5%: only the packs Nanogam® 50mg/ml, 100ml, Nanogam® 50mg/ml, 200ml and Nanogam® 50mg/ml, 400ml.

- Listing of the following specialties in §6790400 (CIDP):

  - Iqymune® 10%
  - Nanogam® 5%: only the packs Nanogam® 50mg/ml, 100ml, Nanogam 50mg/ml, 200ml and Nanogam® 50mg/ml, 400ml.

No changes in price.

Group review kidney cancer: 1.9.2019

Adjustment of the reimbursement conditions for the relevant specialties to the therapeutic landscape and therapeutic recommendations (including cabozantinib and the combination ipilimumab + nivolumab as the new standard first-line treatment for patients with intermediate to high risk advanced renal cell carcinoma (mRCC)). No price changes.

Group review HIV: 1.10.2019

Pricereductions.
Specialties Truvada®, Atripla® and Descovy® no longer eligible for reimbursement.

Group review HIV: 1.12.2019

Pricereductions.

ANNEX 3

IMMUNOTHERAPY: OVERVIEW OF REGISTERED AND REIMBURSABLE INDICATIONS FOR THE PD(L)-1 INHIBITORS (situation October 2020)

	REGISTERED INDICATIONS				
TYPE TUMOUR	**OPDIVO**	**KEYTRUDA**	**TECENTRIQ**	**BAVENCIO**	**IMFINZI**
1. Melanoma	OPDIVO as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults	KEYTRUDA as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.			
	OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.	KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection.			
2. Non small cell lung cancer (NSCLC)	OPDIVO as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults	KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.	Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR mutant or ALK-positive NSCLC should also have received targeted therapies before receiving Tecentriq.		IMFINZI as monotherapy is indicated for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.
		KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous non-small cell lung carcinoma in adults whose tumours have no EGFR or ALK positive mutations.			
		KEYTRUDA, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for			

		the first-line treatment of metastatic squamous non-small cell lung carcinoma in adults.			
		KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA.			
3. Renal cell carcinoma (RCC)	OPDIVO as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults.	KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults.		Bavencio in combination with axitinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).	
	OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma.				

4. Classical Hodgkin lymphoma (cHL)	OPDIVO as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.	KEYTRUDA as a monotherapy is indicated for the treatment of adults with recurrent or refractory classical Hodgkin lymphoma (cHL), when autologous stem cell transplant (ASCT) and brentuximab vedotin (BV) have failed or who are not being considered for a transplant and for whom BV has not worked.			
5. Squamous cell cancer of the head and neck (SCCHN)	OPDIVO as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy.	KEYTRUDA, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.			
		KEYTRUDA as monotherapy is indicated for the treatment of recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy.			

6. Urothelial carcinoma	OPDIVO as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.	KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.	TECENTRIQ as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC): • after prior platinum-containing chemotherapy, or • who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5%		
		KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10.			
7. Breast carcinoma			Tecentriq in combination with nab-paclitaxel is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease.		

8. Merkel cell carcinoma				Bavencio is indicated as monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (MCC).	

ANNEX 4

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