Report on medicines use during COVID-19 pandemic

July 2020

Dear Readers,
this is a translation of the Report on Medicines use during COVID-19 pandemic released in July 2020.

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Please quote the Report as follows:

The Medicines Utilisation Monitoring Centre.
Report on Medicines use during COVID-19 pandemic, year 2020.
Rome: Italian Medicines Agency, 2020.

ISBN: 978-88-944943-9-6

The Report is available at the following website:
www.aifa.gov.it

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INTRODUCING THE REPORT ON MEDICINES USE DURING THE COVID-19 PANDEMIC

The COVID-19 health emergency that hit Italy last March and April and the impact it has had on health facilities at least in part of the country require a rigorous, lucid and rational assessment of what happened during those months, in order to draw the appropriate lessons and recommendations for the future.

In this context, the need to draw up a specific OsMed Report emerged to provide a comprehensive analysis of the use of medicines during the COVID-19 pandemic. The present report aims to analyse the type of medicines used to deal with COVID-19, both in an outpatient and inpatient setting, also in light of the regulatory decisions taken by the Agency.

The first section of the report focuses on medicines specifically used to treat COVID-19, including those evaluated by AIFA during the different phases and in different settings (compassionate use, off-label use, investigational studies, etc.), for the treatment of COVID-19 patients. In this context, a significant increase was registered in the consumption of hydroxychloroquine and azithromycin, of some antiviral agents and of interleukin 6 inhibitors. The time trend of purchases reflects the different phases of the pandemic and shows an initial extensive off-label use of medicines that was then channelled, thanks to the centralisation of approvals of COVID-19 clinical trials at AIFA, into clinical protocols showing a greater methodological rigour and ensuring ethical prescription for patients.

A chapter in the report is dedicated to the analysis of medicines for injection and oxygen, that are most likely to be used in intensive care units (ICUs). The most significant data in this regard relate to the positive and substantially homogeneous correlation across the national territory, with reduced regional variability, between the number of individuals tested positive for COVID-19 and the change in use between pre and post COVID-19 periods. This proves that hospital shortages were effectively dealt with and that the numerous measures implemented by AIFA, industry associations and regions were successful in minimising distribution distortions and avoiding the concentration of supplies in certain facilities.

As regards the inpatient use of medicines for treating chronic diseases, with the exception of antivirals, an overall stability of consumption of strategic therapeutic categories, such as cancer medicines, was recorded.

At territorial level, no significant differences emerged in the consumption of medicines for treating the main chronic diseases in the pre and post COVID-19 periods. This is also indicative of the successful strategies implemented to promote the continuity of care to the benefit of chronic and fragile patients.

Finally, the analysis of private purchases by citizens through local pharmacies (public and private) contributes to describe the use of certain medicines lacking solid evidence of effectiveness. This points out the need for independent, professional and authoritative information on the matter, in order to fight against the many false expectations and beliefs that have characterised the current pandemic.

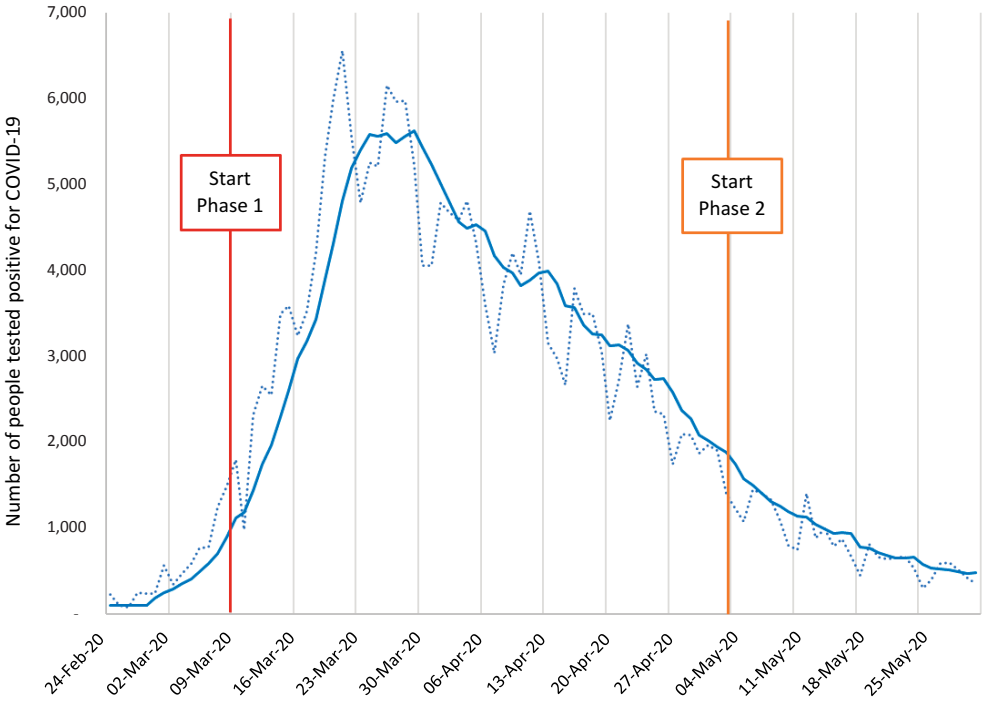
Similarly, it should be emphasised that the very act of performing a precise and rigorous monitoring of the pharmaceutical consumption in such a short time demonstrates the efficiency, even in emergency conditions, of the mapping of medicine movements updated and integrated using different information paths.

The Report seeks to optimise and integrate the information collected from different sources available and allows to timely capture the use of medicines in the national territory as well as to identify and plan interventions for promoting the rational use of medicines, also in emergencies.

RATIONALE

The present Report was prepared based on data from OsMed, which is the AIFA National Medicines Utilisation Monitoring Centre responsible for collecting and monitoring pharmaceutical trends in Italy, as well as on the information that AIFA receives on the use of medicines that have been mostly used during the COVID-19 pandemic. The aim is to analyse the type of medicines used for treating COVID-19, both in an inpatient and outpatient setting, in order to highlight the prevention and care activities that Italy has to manage during the pandemic. Figure 1 shows the trend in COVID-19 positive tests from February 2020 to the end of May 2020 (data from the Civil Protection website). A peak in mid-March 2020 can be observed (period between start of Phase 1 and Phase 2), where the number of individuals tested positive was over 6,000 per day. The graph shows two-time series: the dotted line represents the actual data of the Civil Protection, whereas the continuous line was calculated using the Kernel method that mitigates the real situation considering the average of the nearest observations.

Figure 1. Historic series relating to the number of COVID-19 positive individuals (February-May 2020)



This epidemiological overview was characterised by the emergence of new therapeutic needs, by a significant flexibility in the therapeutic schemes proposed (often off-label), as well as by specific organisational needs in the provision of care. Additionally, the lack of therapies of proven effectiveness, combined with the spread of a serious and substantially unknown disease, has led to a number of treatment protocols often based on very insufficient evidence and sometimes very heterogeneous among them. AIFA tried to manage this phenomenon from its outset, establishing which medicines could be made available to patients for off-label use, issuing precise recommendations on their utilisation and providing up-to-date information on the evidence available for the most widely employed medicines. Since knowledge on the efficacy and safety of potential treatments has improved progressively on the basis of the clinical experience and the acquisition of more solid and reliable evidence (going from few cases to small observational studies and then to controlled and randomised clinical trials), these recommendations were constantly updated, including to counter the dissemination of misleading information that sometimes created disproportionate expectations with consequent strong pressures on healthcare staff.

The aim of this document is to provide an overview of the different treatments used, by analysing the medicines purchased through the different channels described in paragraph 2 "Source of data and methodology". This analysis is essential for planning any preventive or corrective measure to manage a possible recurrence of the COVID-19 emergency.

DATA SOURCE AND METHODOLOGY

This document comprises three sections, which describe in detail the different modalities for dispensing medicines.

1) The first section focuses on medicines purchased by the health facilities belonging to the National Healthcare Service (NHS) and dispensed by hospital facilities (direct purchases).
2) The second section relates to medicines dispensed by local pharmacies (public and private) and reimbursed by the NHS and for which a prescription is necessary (medicines reimbursed by the NHS and *per conto* distribution).
3) Finally, the third section concerns purchases made by public and private local pharmacies for over-the-counter medicines (mainly class C medicines).

Sections 1 and 3 report data deriving from the Medicines Traceability flow (Ministerial Decree dated 15 July 2004 as amended), which registers the movements of medicines along the supply chain. In particular, section 1 focuses on movements of medicines supplied by companies and/or wholesalers to NHS facilities. Section 3 deals with movements of medicines supplied to local pharmacies, mainly representing private purchases by citizens. Traceability data are updated at 11 June 2020.

Data used in section 2 come from pharmaceutical prescriptions reimbursed by the NHS, which includes medicines dispensed through public and private pharmacies. Data from the health insurance card are updated at 23 May 2020.

Data relating to the purchase of medicines described above are analysed against the number of individuals who tested positive for COVID-19 in each region, as obtained from data published by the Civil Protection on 31 May 2020.

All tables report monthly data for the pre- and post-COVID-19 period. The pre-COVID-19 period is calculated as the average of December 2019, January and February 2020. The post COVID-19 period is calculated as the average of March, April and May 2020.

The absolute difference between the post- and pre-COVID-19 periods is defined as *"pre-post absolute delta"*. The relative difference between the two periods, i.e. the ratio between absolute difference and pre-COVID-19 mean, is defined as *"relative pre-post COVID-19 delta"*. Finally, for each pre-post COVID-19 absolute difference, Student's bidirectional T test was performed on the difference in mean values (the zero hypothesis is that the difference is equal to 0). Therefore, a p-value <0.001 should be attributed to a pre-post absolute delta significantly different from 0.

Consumption is indicated as packages per 10,000 inhabitants per day, standardised for the number of days in each month. To take account of the different demographic structure (age and gender) of the regions, the resident population according to the Italian Institute of

Statistics (ISTAT) data in each region was recalculated based on the weight system established by the Planning Department the Ministry of Health.

Weight system developed by the Planning Department of the Italian Ministry of Health

Age group	0	1-4	5-14	15-44 Men	15-44 Women	45-64	65-74	≥74
Weight	1	0.969	0.695	0.693	0.771	2.104	4.176	4.29

The procedure used for calculating the weighed population was as follows: the number of people by age and gender in each region was calculated (data source: http://demo.istat.it/). The number of people in each class was then multiplied by the corresponding weight. The sum of the values thus obtained at regional level was re-proportioned to the Italian population of the reference year (2019: 60,359,546 inhabitants).

This method for standardising the population implies that a region with a population older than the national average will have a more numerous weighed population than the resident population and vice versa. The table below reports the resident population according to ISTAT data and weighed population in 2019.

Table 1. Resident population according to ISTAT data and weighed population in 2018 and 2019

Region	Resident population at 1.1.2019	Weighed population 2019
Piedmont	4,356,406	4,582,727
Valle d'Aosta	125,666	128,939
Lombardy	10,060,574	10,024,134
A.P. of Bolzano	531,178	497,490
A.P. of Trento	541,098	532,711
Veneto	4,905,854	4,939,047
Friuli Venezia Giulia	1,215,220	1,294,259
Liguria	1,550,640	1,720,657
Emilia Romagna	4,459,477	4,558,718
Tuscany	3,729,641	3,909,954
Umbria	882,015	923,787
Marche	1,525,271	1,577,546
Lazio	5,879,082	5,787,806
Abruzzo	1,311,580	1,335,576
Molise	305,617	315,223
Campania	5,801,692	5,334,689
Puglia	4,029,053	3,948,443
Basilicata	562,869	564,566
Calabria	1,947,131	1,888,306
Sicily	4,999,891	4,809,687
Sardinia	1,639,591	1,685,282
Italy	**60,359,546**	**60,359,546**

The historical series in the graphs show the percentage change against a fixed base, set at January 2019. For ease of reading, the historical series was mitigated with a 3-month moving average filter.

1. SUPPLY OF MEDICINES IN THE FIRST 5 MONTHS OF 2020 WITH THE DIRECT PURCHASING METHOD (NHS STRUCTURES)

Section 1 is divided into three sub-analyses divided by type of medicines analysed:

- **medicines used for COVID-19**: includes medicines that have been evaluated by AIFA, at different stages and for various reasons (compassionate use, off-label use, experimental studies, etc.), for the treatment of patients with COVID-19;
- **injectable medicines and oxygen used in hospital care**: includes oxygen and injectable medicines for which, in consideration of their specific mechanism of action, it is believed that there may have been an increase in consumption such as to be investigated;
- **other medicines used in hospital care**: includes medicines used in hospitals for which, in consideration of their specific mechanism of action or the role they play in the treatment of chronic diseases, it is believed that an increase in consumption may have occurred.

It should be noted that the inclusion of medicines in the aforementioned subsections is mutually exclusive, so that the data relating to a specific medicine are considered only once.

1.1. Medicines used for COVID-19

Table 1.1. shows the pharmaceutical consumption for the medicines used for COVID-19 in the pre- and post-COVID-19 periods. The delta of the packages per 10,000 inhabitants per day between the two periods is reported in absolute and percentage values.

The greatest difference in absolute terms between the pre- and post-COVID period is found for hydroxychloroquine and azithromycin. A significant increase is also observed for the anti-HIV antiviral darunavir/cobicistat and for lopinavir/ritonavir (although not statistically significant) and for the interleukin 6 (IL-6) inhibitors tocilizumab and sarilumab. Please note that hydroxychloroquine, chloroquine, lopinavir/ritonavir (and in case of intolerance or lack of the latter, darunavir/ritonavir) have been made reimbursable by the NHS in their off-label use for COVID-19 from 17 March 2020, first also in combination and then only in monotherapy. On 26 March 2020 AIFA suspended the authorisation for the off-label use of hydroxychloroquine outside of clinical trials. The off-label use of azithromycin for COVID-19 has never been authorised by AIFA, either as monotherapy or in combination with hydroxychloroquine or antivirals. Finally, the use of tocilizumab, initially administered in an uncontrolled manner through requests for compassionate use, was made possible in clinical trials.

Table 1.1. Distribution of active ingredients by consumption variation (packages per 10,000 inhabitants per day) in the pre- and post- COVID-19 periods

Category	ATC	PRE COVID-19 Period				POST COVID-19 Period				Comparison		
		Packages x 10,000 inhab. per day			average pre	Packages x 10,000 inhab. per day			average post	absolute delta pre-post *(*)*	relative delta pre-post	p - value
		Dec-19	Jan-20	Feb-20		Mar-20	Apr-20	May-20				
azithromycin	J01FA10	0.24	0.46	0.46	0.39	1.93	1.36	0.15	1.15	0.76	195.40	***0.000***
hydroxyl-chloroquine	P01BA02	0.01	0.01	0.02	0.01	0.64	0.93	0.28	0.61	0.60	4,661.67	***0.000***
methyl-prednisolone	H02AB04	1.03	2.13	1.64	1.60	1.50	1.74	1.82	1.69	0.09	5.33	0.169
tocilizumab IV	L04AC07	0.03	0.05	0.04	0.04	0.11	0.04	0.03	0.06	0.02	54.80	***0.000***
darunavir/ cobicistat	J05AR14	0.03	0.05	0.04	0.04	0.10	0.04	0.02	0.05	0.01	29.42	***0.000***
anakinra	L04AC03	0.01	0.02	0.01	0.01	0.03	0.03	0.01	0.02	0.01	73.80	0.010
lopinavir/ ritonavir	J05AR10	0.00	0.00	0.01	0.00	0.02	0.00	0.00	0.01	0.00	97.64	0.003
baricitinib	L04AA37	0.01	0.03	0.02	0.02	0.03	0.02	0.01	0.02	0.00	17.46	0.003
sarilumab	L04AC14	0.00	0.01	0.00	0.00	0.01	0.01	0.00	0.01	0.00	60.10	0.001
colchicine	M04AC01	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	70.36	0.057
ruxolitinib	L01XE18	0.02	0.03	0.02	0.02	0.03	0.02	0.02	0.02	0.00	6.72	0.195
canakinumab	L04AC08	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	45.03	0.159
tofacitinib	L04AA29	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.00	8.44	0.954
heparins	B01AB12	3.45	6.06	5.21	4.90	5.93	5.14	2.78	4.62	-0.29	-5.90	0.329

(*) in decreasing order

The time series in Figure 1.1.a shows the trend of the delta percentage for the months from January 2019 to May 2020, in terms of packages per 10,000 inhabitants per day of the medicines used for COVID-19, considering January 2019 as the base month for comparison.

In the time series of hydroxychloroquine (in green) the values with reference to the secondary axis have been reported in order to reproduce the graph more clearly. The data of the time series show a more rapid increase for tocilizumab, antivirals and antibiotics, while the increase in the consumption of hydroxychloroquine, although more significant and sustained, appears slightly delayed, reaching a peak between April and May.

Figure 1.1.a. Categories of medicines used for COVID-19, time series of the pre-post COVID-19 delta percentage related to the period January 2019 - May 2020

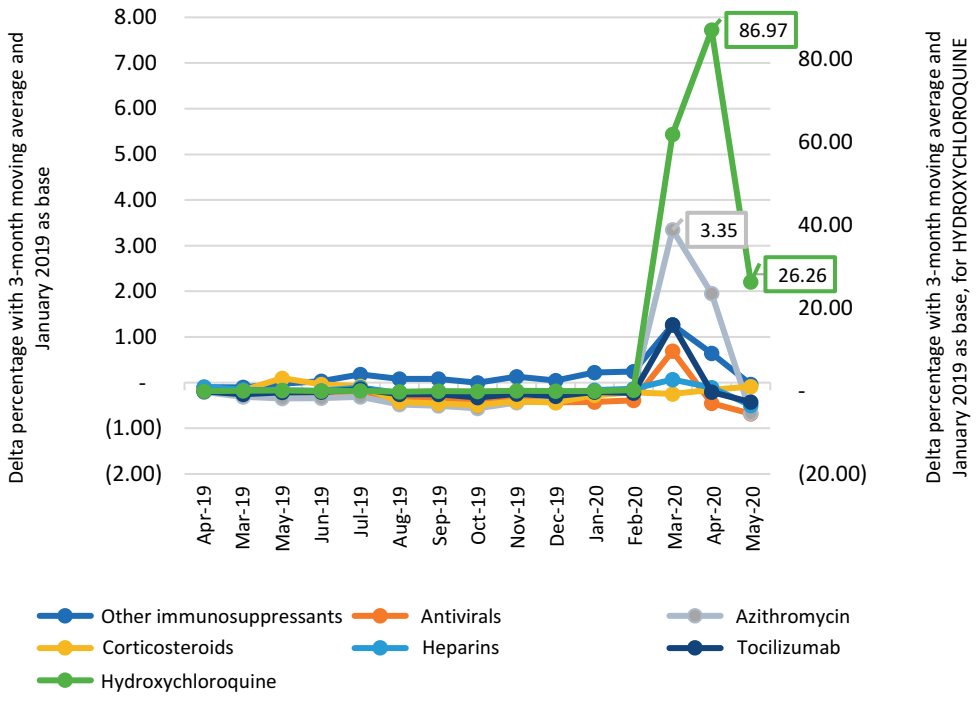


Figure 1.1.b shows the geographical distribution of the pre-post COVID-19 variation in consumption (packages per 10,000 inhabitants per day) for the different categories of medicines used for COVID-19, differentiating between the regions most affected by COVID-19 and the others.

The greatest increase in terms of percentage changes was found for hydroxychloroquine which recorded a variation equal to 4.662% (the data is not shown in the graph in order not to alter the readability of the reference scale for the other medicines and reported separately in Figure 1.1.c).

There were important changes for azithromycin (in particular in Emilia Romagna and Lombardy), followed by tocilizumab and immunosuppressants in general, which include other biological medicines that act on the different phases of the cytokine storm. The different extent of the variations in relation to the geographical areas probably depends on the application of different therapeutic protocols and the impact of the trials underway in the different regions.

Figure 1.1.b. Pre-post COVID-19 percentage change for the categories used for COVID-19. Comparison between the regions most affected by COVID-19 and the rest of Italy

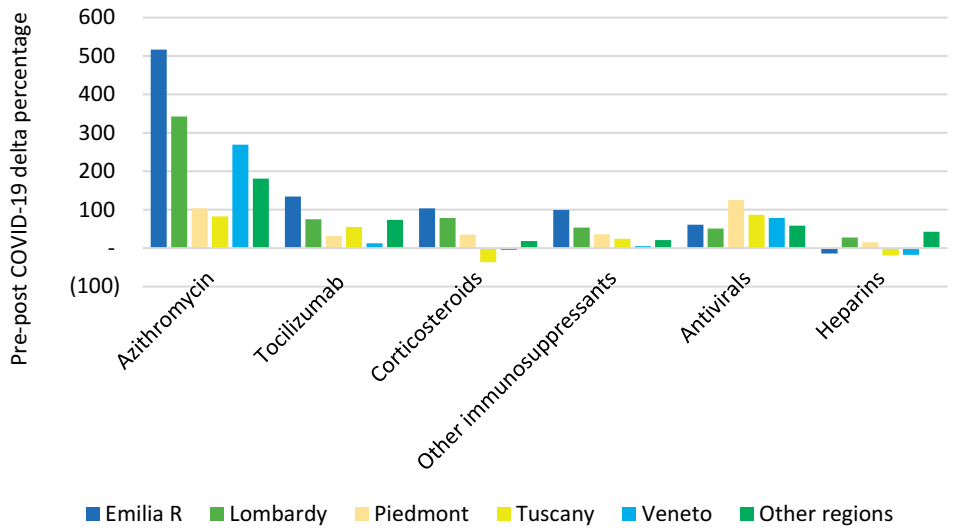
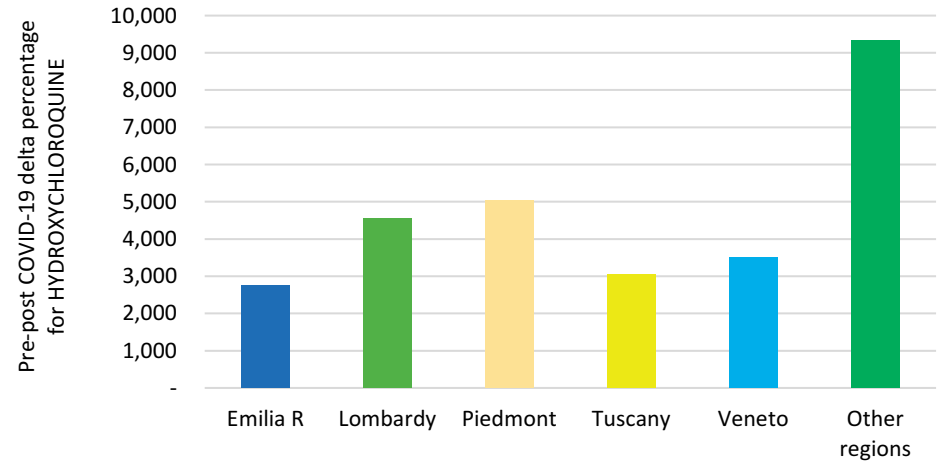


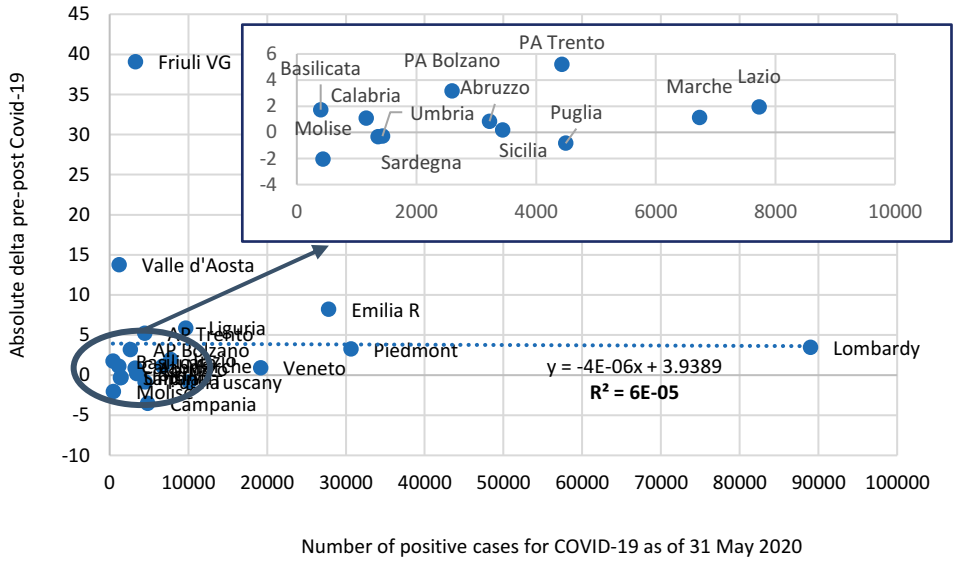
Figure 1.1.c shows the geographical distribution of the pre-post COVID-19 variation in the consumption (packages per 10,000 inhabitants per day) of hydroxychloroquine, differentiating the regions most affected by COVID-19 impact from the others. The analysis shows that over 50% of the variation can be attributed to the regions with the greatest epidemiological impact of the disease, with a substantially homogeneous distribution among them.

Figure 1.1.c. Regional distribution of the pre-post COVID-19 delta percentage for the active ingredient hydroxychloroquine



Analysing the relationship between the absolute delta pre-post COVID-19 of the medicines used for COVID-19 and the number of positive cases as of May 31, 2020 (Figure 1.1.d), it emerges, at least for the five regions with the greatest epidemiological impact, a substantially homogenous positive correlation, while other regions show anomalous trends, suggesting hoarding phenomena especially in regions bordering the areas with the highest prevalence of COVID-19. The value of the coefficient of determination is very close to zero, so the linear prediction line does not perfectly explain the data.

Figure 1.1.d. Categories of medicines used for COVID-19, correlation between number of positive cases by region and observed absolute delta pre-post COVID-19



1.2. Medicines used in hospital care: injectable medicines and oxygen

This section aims to assess the trend in the consumption of oxygen and injectable medicines likely to be mainly used in intensive care in order to estimate the prescribing trend during the period of the COVID-19 pandemic. Table 1.2 shows pharmaceutical consumption in terms of packages per 10,000 inhabitants per day. The variation between periods is calculated in absolute terms and relative percentages, as previously described.

The analysis of the movements shows a numerically important and statistically significant increase for the following therapeutic categories: oxygen, general anaesthetics, sedatives and injectable curare derivatives (with a muscle relaxant effect), as well as inotropic medicines. The consumption of injectable ascorbic acid and nonspecific injectable antidotes (including acetylcysteine and glutathione) also increased significantly.

Table 1.2. Distribution of categories of medicines (oxygen and injectable medicines) used in hospital care by consumption variation (packages per 10,000 inhabitants per day) in the pre- and post- COVID-19 periods

Category	ATC	PRE COVID-19 Period				POST COVID-19 Period				Comparison		
		Packages x 10,000 inhab. per day			average pre	Packages x 10,000 inhab. per day			average post	Absolute delta pre-post *(*)*	Relative delta pre-post	p -value
		Dec-19	Jan-20	Feb-20		Mar-20	Apr-20	May-20				
Oxygen	V03	51.58	55.01	53.78	53.46	94.99	83.11	38.37	72.16	18.70	34.98	***0.000***
Injectable general anaesthetics	N01	0.72	0.96	0.77	0.82	2.65	2.09	0.56	1.77	0.95	116.04	***0.000***
Injectable cardiac stimulants	C01	1.11	1.78	1.79	1.56	2.85	2.70	0.92	2.15	0.59	37.84	***0.000***
Injectable curare derivatives	M03	0.15	0.21	0.20	0.19	1.03	0.51	0.49	0.68	0.49	264.10	***0.000***
Injectable ascorbic acid	A11	0.20	0.28	0.20	0.22	0.67	1.14	0.24	0.68	0.46	204.53	***0.000***
Injectable hypnotics and sedatives	N05	0.15	0.37	0.42	0.31	1.43	0.57	0.32	0.77	0.46	145.78	***0.000***
Injectable antidotes	V03	0.19	0.21	0.18	0.19	0.26	0.56	0.16	0.33	0.13	69.67	***0.000***
Pain therapy - injectables	N02	1.13	1.42	1.16	1.24	2.20	1.28	0.51	1.33	0.09	7.61	0.082
Injectable anxiolytics	N05	0.05	0.17	0.16	0.13	0.23	0.13	0.13	0.17	0.04	30.31	0.145
Injectable xanthines	R03	0.03	0.07	0.07	0.06	0.15	0.09	0.03	0.09	0.03	59.12	0.072
Injectable thrombolytics	B01	0.10	0.12	0.10	0.11	0.18	0.17	0.06	0.14	0.03	27.60	0.007
Injectable antiemetics	A04	0.16	0.23	0.20	0.19	0.15	0.29	0.19	0.21	0.02	8.01	0.832
Injectable mucolytics	R05	0.01	0.01	0.01	0.01	0.01	0.01	0.00	0.01	-0.01	-52.79	0.161
Injectable antihemorragics	B02	0.40	0.57	0.46	0.48	0.49	0.42	0.14	0.35	-0.13	-27.43	0.611
Injectable antipyretics	N02	1.32	2.44	1.99	1.92	2.61	1.91	0.49	1.67	-0.24	-12.78	0.005
Injectable corticosteroids	H02	1.16	2.21	1.70	1.69	2.40	1.09	0.55	1.35	-0.35	-20.41	0.093
Injectable NSAIDs	M01	1.10	1.86	1.46	1.47	1.76	0.55	0.60	0.97	-0.50	-33.98	0.011
Injectable local anaesthetics	N01	1.22	1.35	1.59	1.39	1.57	0.56	0.41	0.84	- 0.54	- 39.16	0.035

(*) in decreasing order

The time series in Figure 1.2.a shows the trend of the percentage delta for the months from January 2019 to May 2020, in terms of packages per 10,000 inhabitants per day of injectable medicines and oxygen, considering January 2019 as the base month for comparison.

The evaluation of the time series shows the increased consumption of general anaesthetics, injectable sedatives and curare derivatives from February.

Figure 1.2.a. Categories of medicines (oxygen and injectable medicines) used in hospital care, time series of the pre-post COVID-19 delta percentage related to the period January 2019 - May 2020

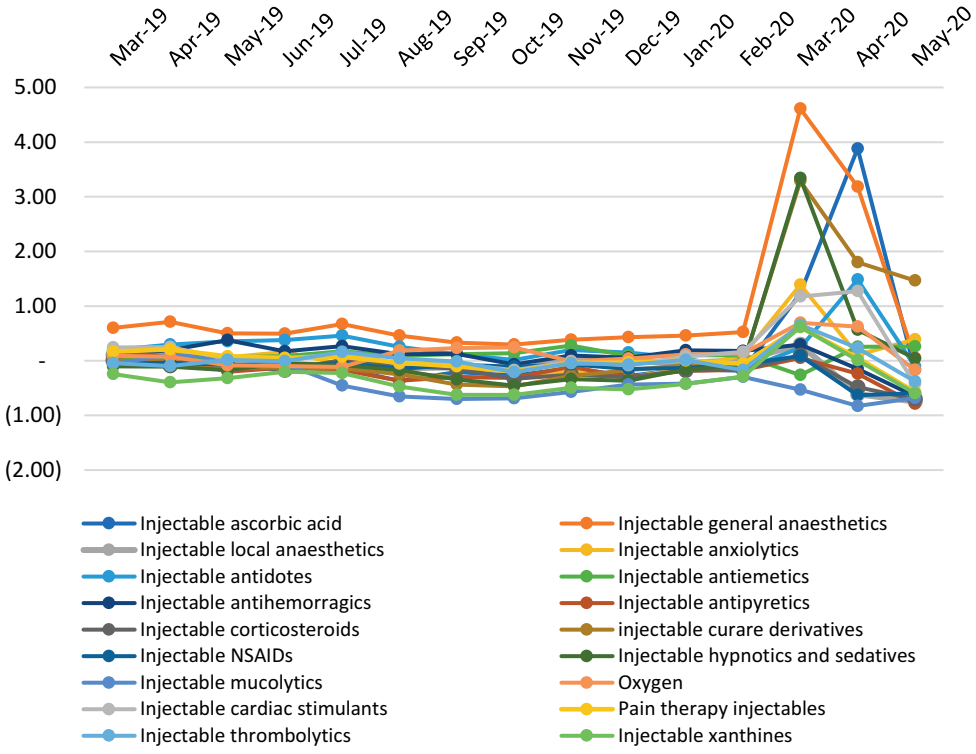
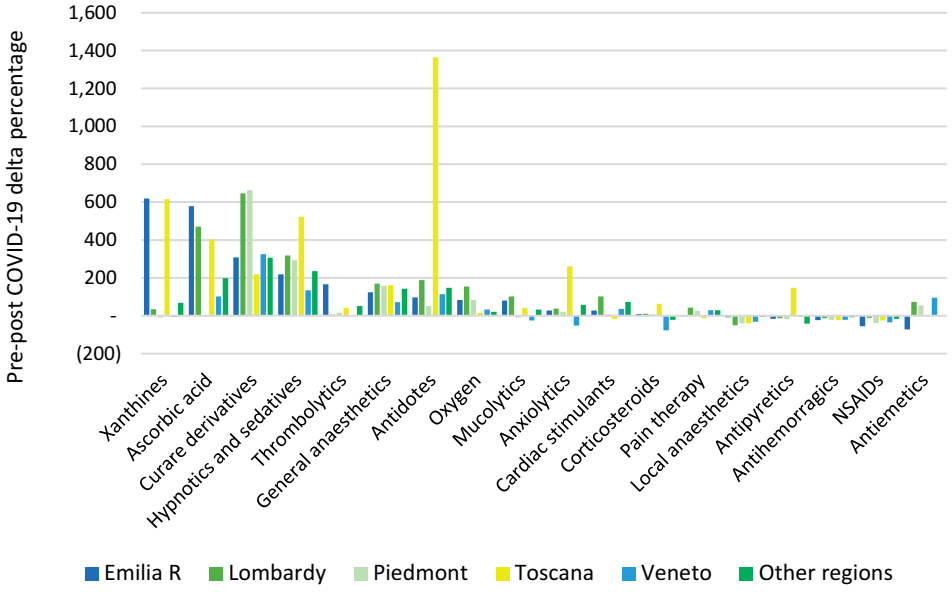


Figure 1.2.b shows the geographical distribution of the variation in consumption of the aforementioned categories, differentiating between the regions most affected by COVID-19 and the others.

The data show important regional differences in the use of the medicines under examination, which are likely to be linked to different protocols for the management of emergencies. The most important regional differences are found for xanthines (medicines with a bronchodilator effect), ascorbic acid, curare derivatives and antidotes.

Figure 1.2.b. Pre-post COVID-19 delta percentage for the categories of medicines (oxygen and injectable medicines) used in hospital care. Comparison between Italy and the regions most affected by COVID-19

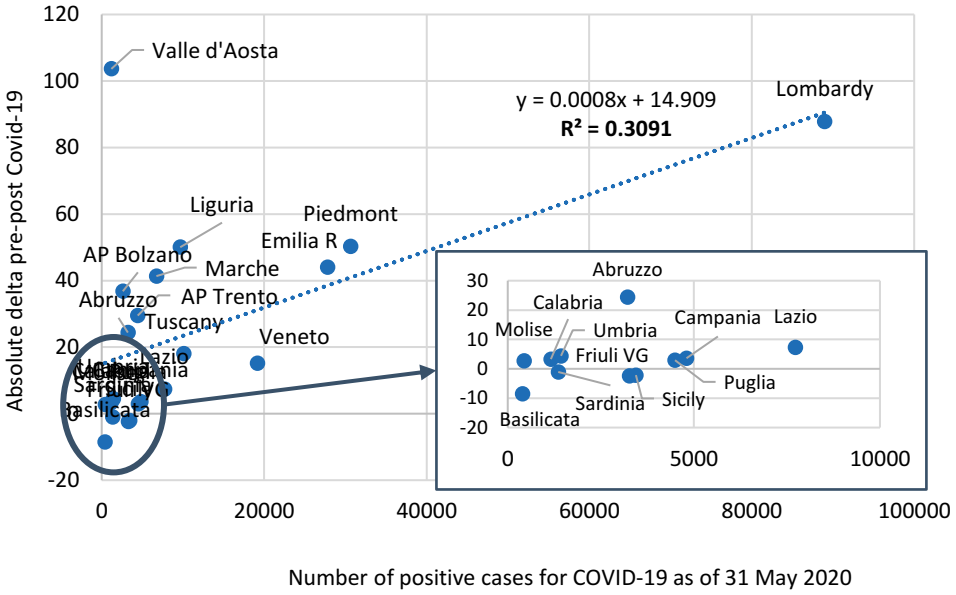


The scatter plot in Figure 1.2.c shows the regional correlation between the number of positive cases as of May 31, 2020 and the absolute delta values between the pre- and post-COVID-19 periods, in terms of packages per 10,000 inhabitants per day, for the medicines analysed.

From the graphic representation, a positive and substantially homogenous correlation emerges throughout the national territory with few regional anomalies, as can be seen in the positive coefficient of determination.

In the analysis of these data it is necessary to take into account the fact that, in the period under examination, there have been numerous interventions by AIFA, the sector categories and the regions to calm distributional distortions and avoid supply phenomena relating to the most used medicines in intensive care such as general injectable anaesthetics.

Figure 1.2.c. Categories of medicines (oxygen and injectable medicines) used in hospital care, correlation between number of positive cases by region and observed absolute delta pre-post COVID-19



1.3. Other medicines used in hospital care

The purpose of this section is to evaluate the trend of consumption in hospital care with regard to medicines for which, in consideration of their specific mechanism of action or the role they play in the treatment of chronic diseases, it is believed that they may have been subject to anomalous variations in consumption. This subsection, as specified above, excludes medicinal products already included in section 3.1 on special uses for COVID-19.

Table 1.3.a shows the pharmaceutical consumption in terms of packages per 10,000 inhabitants per day registered for medicines used in hospital care. The analysis shows a significant increase in the class of antiretroviral medicines for HIV and antivirals in general with a reduction, however, for the consumption of DAA medicines for HCV. The other therapeutic categories remain substantially unchanged. This finding may derive from the fact that the infectious disease facilities, primarily engaged in the management of the emergency, have guaranteed the continuity of chronic care, limiting access to therapies of a defined and extendable duration such as those for HCV on the basis of the current epidemiological scenario of hepatitis C in Italy. These data seem to suggest that there have been no particular critical issues in the supply of oncological therapies or chronic therapies for neurological diseases.

Table 1.3.a Categories used in hospital care, absolute delta, relative delta and p-value calculated on the absolute delta between the per capita consumptions per 10,000 inhabitants per day relating to the pre and post COVID-19 period

Category	PRE COVID-19 Period				POST COVID-19 Period				Comparison		
	Packages x 10,000 inhab. per day			Average pre	Packages x 10,000 inhab. per day			Average pre	Absolute delta pre-post (*)	Relative delta pre-post	p - value
	Dec-19	Jan-20	Feb-20		Mar-20	Apr-20	May-20				
Anti-HIV antivirals	0.73	1.22	1.00	0.98	1.55	0.93	0.82	1.10	0.12	11.96	***0.000***
Hypnotics and sedatives	0.24	0.40	0.37	0.33	0.45	0.50	0.23	0.39	0.06	17.44	0.067
Antifungals	0.25	0.38	0.30	0.31	0.47	0.35	0.24	0.35	0.04	13.44	***0.011***
Other antivirals	0.13	0.27	0.24	0.21	0.26	0.27	0.13	0.22	0.01	3.35	***0.000***
Multiple Sclerosis	0.26	0.43	0.35	0.35	0.46	0.32	0.28	0.35	0.01	1.73	0.002
Immunosuppressants and immunomodulators	1.54	2.81	2.14	2.16	2.89	1.91	1.70	2.17	0.01	0.25	0.061
Antineoplastics	2.56	4.23	3.37	3.38	4.15	3.22	2.80	3.39	0.00	0.14	0.002
Antiemetics	0.09	0.15	0.12	0.12	0.18	0.11	0.08	0.12	0.00	1.34	0.974
Anti-HCV antivirals	0.03	0.04	0.04	0.04	0.03	0.01	0.00	0.01	-0.02	-62.50	***0.000***
Pain therapy	1.05	1.93	1.52	1.50	1.85	1.26	0.72	1.28	-0.22	-14.89	0.737
Antibiotics	9.41	14.23	13.41	12.35	18.83	10.29	5.38	11.50	-0.85	-6.89	0.231

(*) in decreasing order

The time series in Figure 1.3.b shows the trend of the percentage delta for the months from January 2019 to May 2020, in terms of packages per 10,000 inhabitants per day of the medicines used in hospital care, considering January 2019 as the base month for comparison.

During March-April 2020 there is an increase in consumption of the main categories examined, with the exclusion of the medicines for the treatment of hepatitis C.

Figure 1.3.b. Categories of medicines used in hospital care, time series of pre-post COVID-19 delta percentage related to the period January 2019 -May 2020

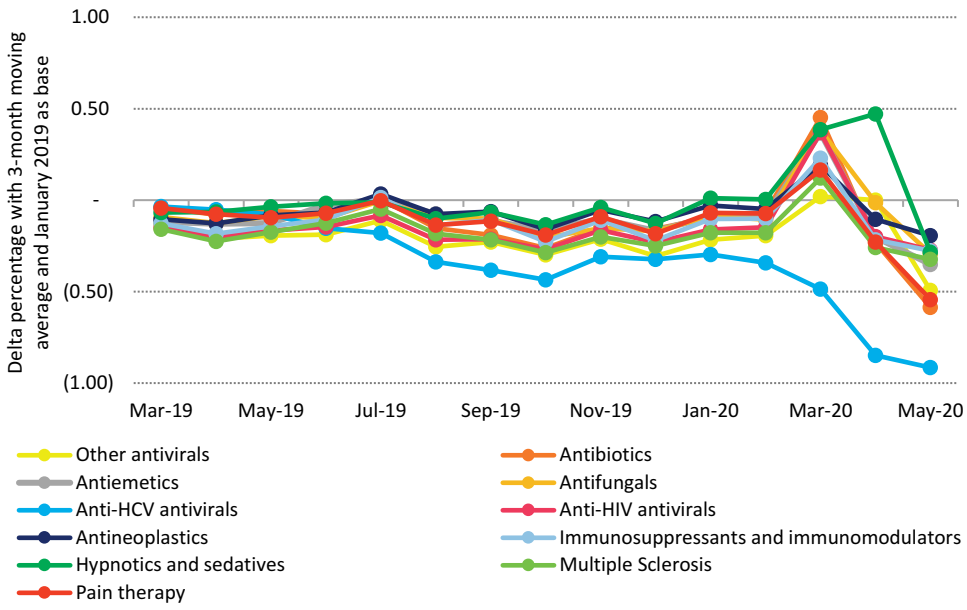
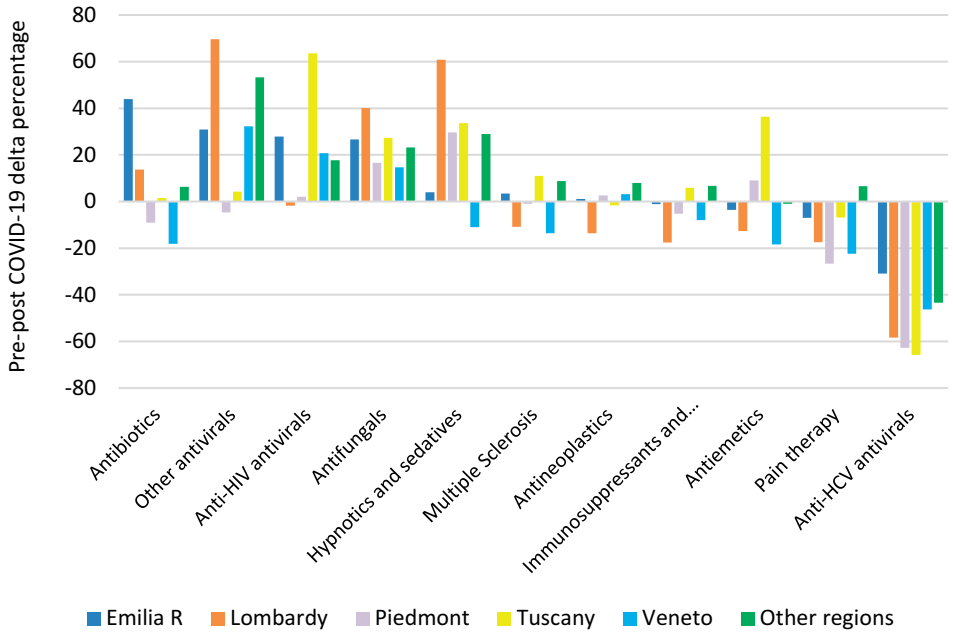


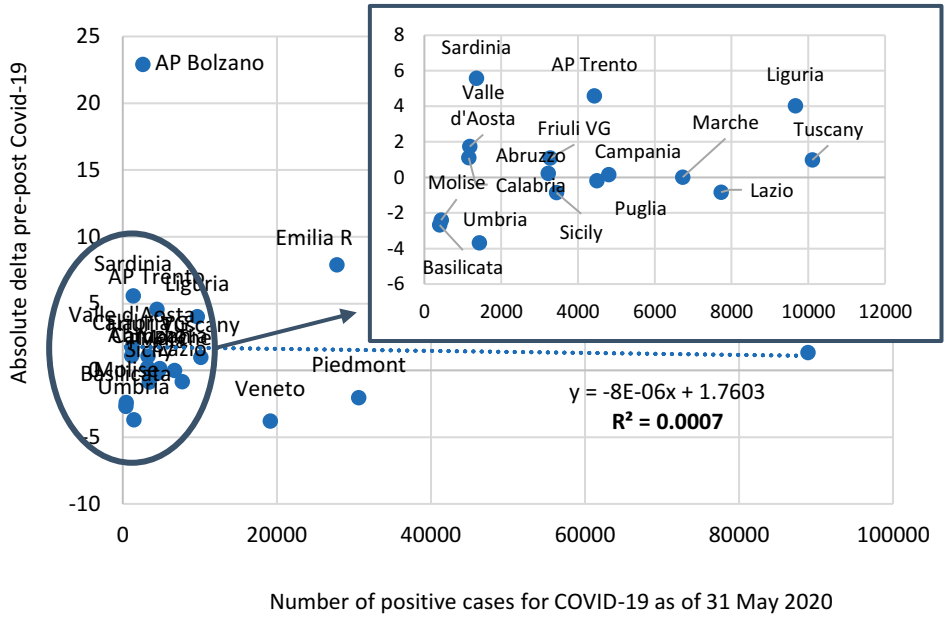
Figure 1.3.c shows the geographic distribution of the pre-post COVID-19 variation in consumption (packages per 10,000 inhabitants per day) for the different categories of medicines used in hospital care, differentiating between the regions most affected by COVID-19 and the others. The greatest regional differences are evident for antibiotics, for HIV antivirals and for hypnotics and sedatives, while greater increasing and decreasing homogeneity is observed for antifungals and anti-HCV antivirals.

Figure 1.3.c. Pre-post COVID-19 percentage change for the categories used in hospital care between the regions most affected by COVID-19 and the rest of Italy



The scatter plot in Figure 1.3.d shows the correlation between the number of positive cases as of May 31, 2020 and the absolute variation between the pre- and post-COVID-19 periods, in terms of packages per 10,000 inhabitants per day, for the medicines used in hospital care. The value of the coefficient of determination is very low and therefore does not summarize the data information.

Figure 1.3.d Categories used in hospital care, correlation between number of positive cases by region and observed absolute delta pre-post COVID-19



2. MEDICINES SUPPLYING IN THE OUTPATIENT SECTOR IN THE FIRST 4 MONTHS OF 2020

Section 2 concerns outpatient pharmaceuticals and presents consumption data, expressed in terms of packages x 10,000 inhabitants per day, of medicines purchased in approved care regime and *per conto* distribution by the NHS, through public and private pharmacies.

2.1. Medicines for chronic diseases

Patients with chronic diseases and multiple conditions are mostly exposed to risk of infection and SARS-CoV-2. Therefore, measures were taken during the pandemic in order to protect vulnerable patients. Among the initiatives implemented, the most important ones are the extension of validity of therapeutic plans, patient access to medication through electronic prescriptions and continuously updated information on institutional websites.

In this section consumption trend (packages x 10,000 inhabitants per day) of medicines indicated for the treatment of the main chronic diseases and purchased in approved care regime and *per conto* distribution by the NHS, through public and private pharmacies, is reported in order to assess if the lockdown influenced the prescribing habits of practitioners or the patient behaviour in terms of access to medicines.

The pharmaceutical categories taken into consideration are indicated for the treatment of:

- Diabetes
- Cardiovascular impairments and hypertension
- Dyslipidaemia
- Dementia
- Psychosis
- Anxiety and depression
- Epilepsy
- Parkinson
- Respiratory diseases (Asthma and Obstructive Pulmonary Disease)
- Osteoporosis
- Thyroid diseases (hypo-hyper thyroidism)

A reduction of consumption for the examined pharmaceutical categories is noted during February 2020 compared to the previous month (Table 2.1).

This reduction is followed by a significant increase in consumption during March 2020. The trend registered in March corresponds with the beginning of the lockdown during which prescribing physicians and patients procured medicines with a view to potential health problems. It was followed by a rebound, with average values, during the month of April.

At national level before and after the COVID-19 emergency, there are no significant differences in consumption expressed in packaged x 10,000 inhabitants per day for the examined pharmaceutical categories. This is indicative of the operation of the strategies put in place to guarantee the continuity of care for chronic and frail patients.

Anticoagulants, antipsychotics, antidiabetics and platelet inhibitors are overall the products registering a higher increase in consumption after the coronavirus emergency if compared to the period before the emergency. On the other hand, medicines to treat asthma, COPD and osteoporosis registered a reduction, though this is not a significant reduction.

As far as antihypertensives are concerned, there has been considerable debate over the correlation of this pharmaceutical category with the mechanism of onset of COVID-19. In the case of ACE inhibitors and sartans, the correlation with COVID was debated for the angiotensin-converting enzyme 2 (ACE2) used by the coronavirus to permeate the cell membrane. To date, only molecular hypotheses can be formulated and assessed by in vitro studies, but results of observational studies recently published did not prove a correlation between the use of these medicines and the onset of COVID-19. The consumption of antihypertensives has remained stable; therefore, only further studies may allow to assess any switch (borne by the NHS) to different categories of antihypertensives by prescribing physicians.

During pandemics there is a higher risk of developing anxiety disorders, depression and violent behaviours. According to psychologists, conditions of high emotional stress, such as the lockdown, may increase mental disorders at national level.

Though the use of pharmacological treatments prescribed by a physician may be assessed at long term during the year, consumption of some medicines acting on the central nervous system was specifically registered in the lockdown.

An increase in consumption of antipsychotics is mostly observed in March 2020. The use of this therapeutic category is for a wide range of indications, including the treatment of disorders in case of psychotic symptoms as in depression. Only a long term assessment and the study of individual subcategories may provide further details.

Also in this case, a not significant reduction in consumption is registered, except for an increase in March. A long term evaluation is needed also for this category if you consider its use in anxiety disorders as well as in anxious–depressive syndromes.

Table 2.1. Categories used for the main chronic conditions through inpatient pharmaceutical care (approved care regime + PCD), absolute delta, relative delta and p-value calculated on the absolute delta between the per capita consumptions per 10,000 inhabitants per day relating to the pre and post COVID-19 period

Category	PRE COVID-19 Period			POST COVID-19 Period			Comparison		
	Packages x 10,000 inhab. per day		average pre	Packages x 10,000 inhab. per day		average pre	Absolute delta pre-post (*)	Relative delta pre-post	p - value
	Jan-20	Feb-20		Mar-20	Apr-20				
Antidiabetics	26.90	25.85	26.37	29.98	23.79	26.88	0.51	1.93	0.686
Antiplatelets	25.07	23.28	24.18	27.41	21.80	24.60	0.43	1.77	0.714
Lipid-lowering factors	39.11	36.94	38.03	42.37	34.28	38.33	0.30	0.78	0.773
Anticoagulants	7.18	7.01	7.10	8.13	6.51	7.32	0.22	3.12	0.584
Antipsychotics	5.60	5.55	5.57	6.12	5.28	5.70	0.13	2.32	0.530
Anti-hypertensives	148.93	140.43	144.68	159.85	129.63	144.74	0.06	0.04	0.837
Antidementia	0.83	0.79	0.81	0.89	0.73	0.81	-0.00	-0.52	0.878
Anti-Parkinson	3.78	3.63	3.71	4.06	3.28	3.67	-0.04	-0.95	0.924
Antiepileptics	8.81	8.60	8.71	9.41	7.77	8.59	-0.11	-1.31	0.953
Medicines for thyroid	9.46	8.95	9.20	10.13	8.04	9.09	-0.12	-1.27	0.958
Antidepressants	18.00	16.92	17.46	18.78	15.70	17.24	-0.22	-1.27	0.957
Medicines for osteoporosis	17.54	17.30	17.42	17.23	15.44	16.34	-1.08	-6.21	0.388
Asthma and COPD	16.83	16.76	16.79	16.11	11.71	13.91	-2.88	-17.18	0.172

(*) in decreasing order

2.2. Medicines for the treatment of COVID-19 and/or tested in experimental studies

During the period examined, several active substances were tested in clinical trials and/or were used off label, on the basis of little scientific evidence and even though they were not indicated for the treatment of COVID-19. AIFA informed citizens through fact sheets, published on the website, on some medicines advising on the efficacy, safety evidence, interactions and recommended use in patients. Among the active substances supplied by pharmacies (public and private), the trend of consumption expressed in packages per 10,000 inhabitants per day (Table 2.2) of hydroxychloroquine and colchicine, heparins and azithromycin was principally studied.

Hydroxychloroquine is an active substance indicated for the treatment of some rheumatic disease, such as rheumatoid arthritis and lupus erythematosus. The off-label use of hydroxychloroquine was authorized exclusively within the national plan of COVID-19 pandemic management, therefore since 2 April 2020 AIFA has published specific fact sheets and their subsequent updates. It is the only active substance studied presenting a significant increase in consumption during the post COVID-19 period. The increase is particularly apparent from March 2020, compared to February 2020. This suggests there has been no interruption in the treatment of patients receiving chronic therapy and there has probably been an increase in consumption due to the treatment of COVID-19.

On 15 April 2020 AIFA authorized an Italian multicentric study to evaluate the efficacy and safety of colchicine, approved for the prophylactic treatment and acute attacks of gouty arthritis as well as for the treatment of pericarditis. National consumption of colchicine expressed in packages x 10,000 inhabitants per day has remained stable for the period examined.

Low molecular weight heparins (LMWH) are indicated for the prophylaxis of venous thromboembolism. They are also used in the treatment of deep vein thrombosis, pulmonary embolism and acute coronary syndrome. LMWHs are used for the treatment of COVID-19 in case of pneumonia and hypomobility of bedridden patients to prevent thrombotic events. A decrease in consumption of heparins has been apparent since February-March and it is confirmed during the post COVID-19 period, though not significantly. It may be due to a decrease in LMWH prescribing for the treatment of thromboembolism in surgical patients as a result of the reduction of surgical interventions during the pandemic period.

Since 9 April 2020 the fact sheet on azithromycin (later updated) has been made public by AIFA. The active substance belongs to the antibiotic class of macrolides authorized for the treatment of upper and lower respiratory infections, odontostomatological infections, skin and soft tissue infections, non-gonococcal urethritis, soft ulcers caused by sensitive bacterial strains. It is deemed to be a treatment for COVID-19 because in a French trial it has been added to the hydroxychloroquine treatment arm for the prevention of bacterial superinfections. In the period examined, the national trend of consumption did not reflect

the consumption trend of hydroxychloroquine, but a decrease, though not significant, was registered during the post COVID-19 period. This suggests that the use of azithromycin has maintained its indications with seasonal peaks that are typical of antimicrobial agents.

Table 2.2. Categories used for treatment of COVID-19 disease and/or associated with experimental studies through inpatient pharmaceutical care (approved care regime + PCD), absolute delta, relative delta and p-value calculated on the absolute delta between the per capita consumptions per 10,000 inhabitants per day relating to the pre and post COVID-19 period

Category	Categories/ Substances	PRE COVID-19 Period			POST COVID-19 Period			Comparison		
		Packages x 10,000 inhab. per day		average pre	**Packages x 10,000 inhab. per day**		average pre	Absolute delta pre-post *(*)*	Relative delta pre-post	p - value
		Jan-20	Feb-20		Mar-20	Apr-20				
hydroxyl-chloroquine	Antimalarials	0.72	0.69	0.70	0.93	0.97	0.95	0.25	35.15	***0.001***
colchicine	Other immune-suppressants	0.09	0.09	0.09	0.09	0.08	0.09	-0.00	-1.99	0.957
heparins	Anti-thrombotics	3.27	3.46	3.36	2.95	2.72	2.83	-0.53	-15.73	0.015
azithromycin	Antibiotics	3.53	3.54	3.54	3.08	2.27	2.67	-0.86	-24.39	0.057

(*) in decreasing order

3. SUPPLY OF MEDICINES IN THE FIRST 5 MONTHS OF 2020 IN THE CHANNEL OF PRIVATE PHARMACY PURCHASES

Section 3 is devoted to the analysis of medicines acquired by local (public and private) pharmacies for supply in private regimen, that is in charge of citizens. The categories listed include class-C medicines (non-reimbursed medicines) and the active substance hydroxychloroquine which, despite being a class-A medicine (reimbursed medicines), could be delivered directly to patients at their own expense.

As can be seen from the data set out in Table 3.1, the categories or active substances for which public or private pharmacies have made the most significant supply for direct dispensation to patients were: hydroxychloroquine, ascorbic acid (vitamin C), anxiolytics for non-parenteral use and products based on vitamin D and analogues, the latter however not being significant.

In contrast, the categories and active substances for which pharmacies have been less supplied are non-steroidal anti-inflammatory medicines and antipyretics.

It should be noted that the figure for hydroxychloroquine includes both the amount supplied with prescriptions for medicines under approved care regime (Table 2.2) and a surplus amount. From this correlation analysis it emerges that in the period January-February 2020 the supply was maintained at the expected levels through prescriptions under approved care regime; in the following period, pharmacies supplied themselves with larger amounts reaching a peak in April 2020, with a rise to more than double, compared to March 2020, of the number of packages compared to the three-month period pre COVID-19. Also in May the increase is confirmed: this trend suggests that supplies have actually been provided to citizens. Moreover, the comparison between April and May, comparing the data on hydroxychloroquine in Tables 2.2 and 3.1, suggests that the differential is ascribable to sales in private regime.

Medicines containing ascorbic acid authorised with indication for vitamin C deficiency are class-C OTC products and can therefore be supplied without prescription. Many reports released during the pandemic period have attributed healing and preventive properties with regard to COVID-19 disease to high dose ascorbic acid. These reports were related to parenteral administration of this vitamin as part of ongoing studies in China, and probably also explain this increase in the supply of products in the territorial pharmacies channel, which reached a peak in March 2020.

Anxiolytics and hypnoinductive benzodiazepines for oral use can be dispensed directly with a repeatable prescription charged to citizen (class-C). These represent the products majorly procured by pharmacies after products based on ascorbic acid. However, it should be noted that, also in this case, the largest procurement was recorded, as predictable, in the month of March 2020 (in correspondence with the lockdown period). Supplies have decreased in the months of April and May, bringing back the average to a value which is however

meaningful in terms of increase. As similarly reported in Section 2, also for anxiolytics, monitoring of long-term consumption may suggest the possible psychological impact of the pandemic period on the population.

Also for vitamin D products, during the pandemic, news has been disseminated on a possible role in reducing the risk of acute respiratory tract infections and for the treatment of two of the typical symptoms of COVID-19 disease, being anosmia and augesia, that is respectively, loss of smell and taste complained by multiple patients. Also in this case, the news stemmed from the possible benefits of vitamin D supplementation in combination with other medicines in patients with COVID-19. The largest increase, in terms of procurement by pharmacies, was observed in the period February-March 2020, and then bounced back in the following months, with values returning to average levels; these changes in supply are considered non-significant.

It should be remembered that, both in the case of vitamin C and vitamin D, the Ministry of Health specified through its site that there is no supporting evidence available.

With regard to phosphodiesterase inhibitors (e.g. sildenafil, tadalafil etc.), a marked reduction in purchases during the lockdown can be observed. This contraction is also confirmed in April and represents overall a significant reduction when comparing the pre and post COVID periods.

Given the main indication of the molecules belonging to this category, i.e. erectile dysfunction, this reduction could be attributed to a change in habitual behaviours with consequent reduction in the use of these medicines during quarantine.

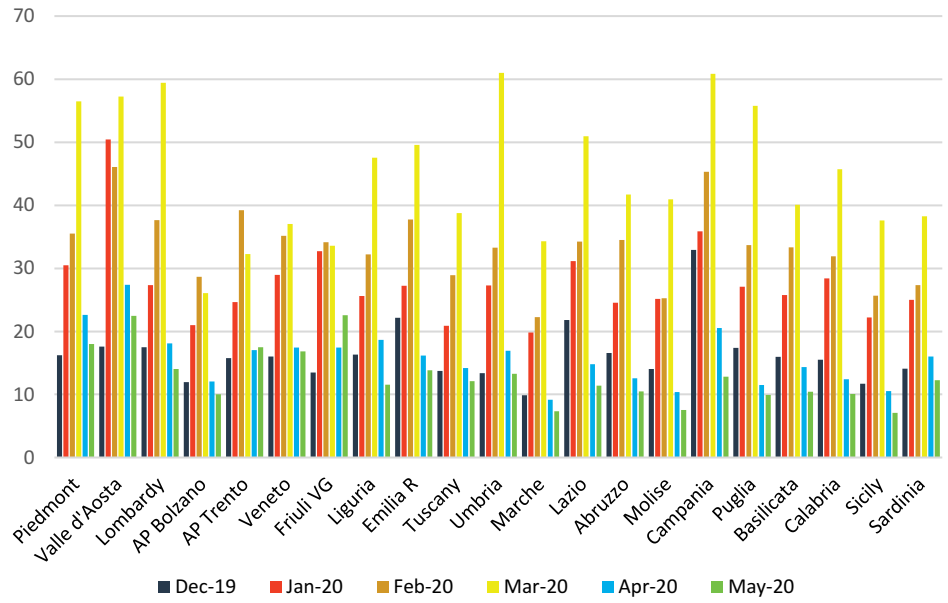
Table 3.1. Categories of medicines procured by public and private pharmacies for private purchase, absolute delta, relative delta and p-value calculated on the absolute delta between consumption per capita per 10,000 inhabitants per day between the pre and post COVID-19 period.

Category	PRE COVID-19 Period				POST COVID-19 Period				Comparison		
	Packages x 10,000 inhab. per day			average pre	Packages x 10,000 inhab. per day			average pre	Absolute delta pre-post *(*)*	Relative delta pre-post	p - value
	Dec-19	Jan-20	Feb-20		Mar-20	Apr-20	Mag-20				
Anxiolytics	19.74	25.81	24.10	23.22	27.50	23.06	21.75	24.11	0.89	3.83	***0.000***
Hydroxychloroquine	0.60	0.72	0.72	0.68	1.42	1.78	1.12	1.44	0.76	111.84	***0.000***
Vitamin D and analogues	13.04	17.41	17.68	16.05	18.27	16.02	15.26	16.51	0.47	2.91	0.003
Ascorbic acid	0.11	0.14	0.23	0.16	0.59	0.04	0.02	0.21	0.05	34.12	0.001
NSAIDs and antipyretics	0.10	0.15	0.16	0.14	0.13	0.05	0.05	0.08	-0.06	-42.67	***0.000***
Phosphodiesterase inhibitors	2.62	3.09	2.67	2.79	1.92	1.37	1.96	1.75	-1.04	-37.38	***0.000***
Antipyretics	26.17	37.12	44.84	36.04	59.40	20.10	15.31	31.61	-4.44	-12.31	***0.000***
NSAIDs	27.28	36.86	40.04	34.72	35.43	25.89	23.67	28.33	-6.39	-18.41	***0.000***

(*) in decreasing order of absolute delta

Figure 3.1 reports figures for purchases of the active substance paracetamol during the period of interest (December 2019 – May 2020), in terms of packages per 10,000 inhabitants per day purchased by public and private pharmacies. As also described in paragraph "2. Data source and methodology", the reference population used in relation to the regions shall be the one weighted for the population of the regions. In all Italian regions the highest purchase values are observed in March 2020 during the pandemic peak outbreak and the beginning of the lockdown period.

Figure 3.1. Paracetamol consumption handled by pharmacies purchased by public and private pharmacies, packages per 10,000 inhabitants per day



REFERENCES

- Wang T. et al. *Comorbidities and multi-organ injuries in the treatment of COVID-19*. Lancet 2020; 395: e52.
- Sorveglianza integrata COVID-19: i principali dati nazionali. Disponibili al link https://www.epicentro.iss.it/coronavirus/sars-cov-2-sorveglianza-dati.
- Misure transitorie relative alla proroga dei piani terapeutici AIFA in tema di contenimento e gestione dell'emergenza epidemiologica da COVID-19 - Comunicato dell'11 marzo 2020.
- Proroga della compilazione dei Registri di monitoraggio AIFA - Comunicato del 12 marzo 2020.
- Ordinanza del Capo della protezione civile del 19 marzo 2020 sulle modalità alternative al promemoria cartaceo per limitare gli accessi presso gli studi dei medici del SSN.
- Decreto Interministeriale del 25 marzo 2020 " *Estensione della dematerializzazione delle ricette e dei piani terapeutici e modalita' alternative al promemoria cartaceo della ricetta elettronica*".
- Nota MEF-MdS del 6 maggio 2020 "*Art. 50 della legge 326/2003 - attivazione ricetta dematerializzata ai sensi del decreto 2 novembre 2011 per i medici SASN*".
- Nota MEF-MdS del 14 maggio 2020 "*Prescrizioni di medicinali contenenti sostanze stupefacenti o psicotrope con ricetta de materializzata*".
- Hoffman et al. *SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor*. Cell Volume 181, Issue 2, 16 April 2020, Pages 271-280.e8.
- Precisazioni AIFA su Malattia da coronavirus COVID-19 ed utilizzo di ACE-INIBITORI E SARTANI. 17 marzo 2020
- Documento Informativo della Società Italiana di Farmacologia "Uso di Ace-Inibitori/Sartani ed infezione da COVID-19" pubblicato su sito SIF 13 marzo 2020.
- *Keep mental health in mind* Editorial_ Nat Med . 2020 May;26(5):631.
- Yao H. et al. *Patients with mental health disorders in the COVID-19 epidemic*. Lancet Psychiatry 2020;7:e21.
- Brooks SK et al. *The psychological impact of quarantine and how to reduce it: rapid review of the evidence*. Lancet 2020;395:912–20.
- *Multidisciplinary research priorities for the COVID-19 pandemic: a call for action for mental health science* Lancet Psychiatry. 2020 Jun; 7(6): 547–560.
- Elaine W Yu et al. *Osteoporosis Management in the Era of COVID-19* J Bone Miner Res. 2020 May 26: 10.1002/jbmr.4049.
- Schede Farmaci utilizzabili per il trattamento della malattia COVID-19 sito AIFA disponibile al link https://www.AIFA.gov.it/aggiornamento-sui-farmaci-utilizzabili-per-il-trattamento-della-malattia-COVID19.

- Sperimentazioni cliniche COVID- 19 AIFA disponibile al link https://www.AIFA.gov.it/sperimentazioni-cliniche-COVID-19.
- Banca Dati Stampati AIFA: Riassunto caratteristiche dei prodotti medicinali a base dei principi attivi presi in esame disponibile al link https://farmaci.AIFAfarmaco.gov.it/bancadatifarmaci/.
- Ministero della Salute su Vitamina C e D: ww.salute.gov.it/portale/nuovocoronavirus/dettaglioContenutiNuovoCoronavirus.jsp?lingua=italiano&id=5387&area=nuovoCoronavirus&menu=vuoto.
- Anitra C. Carr "*A new clinical trial to test high-dose vitamin C in patients with COVID-19*" Crit Care. 2020; 24: 133 _ 2020 Apr 7.
- Banca Dati dei Trial Clinici in corso disponibile al link Clinicaltrial.gov.

ANNEX: List of therapeutic categories used

Therapeutic categories	Active ingredients
Ascorbic acid	
Ascorbic acid	ascorbic acid
Other antivirals	
Other injectable antivirals	aciclovir, cidofovir, ganciclovir
Other antivirals, non-injectable	aciclovir, brivudine, famciclovir, oseltamivir, valaciclovir, valganciclovir, zanamivir
Other immunosuppressants	
anakinra	anakinra
baricitinib	baricitinib
canakinumab	canakinumab
colchicine	colchicine
ruxolitinib	ruxolitinib
tofacitinib	tofacitinib
General anaesthetics	
General anaesthetics, injectable	alfentanil, fentanyl, ketamine, propofol, remifentanil, sufentanil
General anaesthetics, non-injectable	desflurane, isoflurane, propofol, sevoflurane
Local anaesthetics	
Local anaesthetics, injectable	articaine/adrenaline, bupivacaine, bupivacaine/adrenaline, cetrimonium/lidocaine, levobupivacaine, lidocaine, mepivacaine, prilocaine, ropivacaine
Anxiolytics	
Injectable anxiolytics	delorazepam, diazepam, lorazepam
Non-injectable anxiolytics	alprazolam, bromazepam, clobazam, clorazepate, chlordiazepoxide, clotiazepam, delorazepam, diazepam, etizolam, ketazolam, lorazepam, nordazepam, oxazepam, pinazepam, prazepam
Antiplatelets	
Antiplatelets, excluding P2Y12 inhibitors	acetylsalicylic acid/magnesium hydroxide/algeldrate, cilostazol, dipyridamole, dipyridamole/ acetylsalicylic acid, epoprostenol, iloprost, indobufen, picotamide, selexipag, sulfinpyrazone, treprostinil
Inhibitors of platelet receptor P2Y12	cangrelor, clopidogrel, prasugrel, ticlopidine
Inhibitors of IIb/IIIa glycoprotein	abciximab, eptifibatide, tirofiban
Ticagrelor	ticagrelor
Antibiotics *(continued)*	
Other cephalosporins and penems	ceftaroline, ceftobiprole, ceftolozane/tazobactam
Other antimicrobials	clofoctol, daptomicyn, Fosfomycin, linezolid, tedizolid phosphate
Other quinolones	pipemidic acid
Amphenicoles	chloramphenicol, thiamphenicol
Aminoglycosides	amikacin, gentamycin, netilmicin, tobramycin
Penicillin combinations, including betalactamase inhibitors	amoxicillin/clavulanic acid, ampicillin/sulbactam, piperacillin/tazobactam
Azithromycin	azithromycin
Carbapenems	ertapenem, imipenem/cilastatin, meropenem
I generation cephalosporins	cefalexin, cefazoline
II generation cephalosporins	cefaclor, cefmetazole, cefoxitin, cefprozil, cefuroxime
III generation cephalosporins	avibactam/ceftazidime, cefditoren, cefixime, cefodizime, cefotaxime, cefpodoxime, ceftazidime, ceftibuten, ceftriaxone

Therapeutic categories	Active ingredients
Antibiotics *(continued)*	
IV generation cephalosporins	cefepime
Imidazole derivatives	metronidazole
Nitrofuran derivatives	nitrofurantoin
Fluoroquinolones	ciprofloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, pefloxacin, prulifloxacin, rufloxacin
Glycopeptides	dalbavancin, teicoplanin, vancomycin
Macrolides and lincosamides	azithromycin, clarithromycin, clindamycin, erythromycin, josamycin, lincomycin, miocamycin, roxithromycin, spiramycin, telithromycin
Monobactams	aztreonam
Broad spectrum penicillins	amoxicillin, ampicillin, bacampicillin, piperacillin
Penicillins resistant to beta lactamases	flucloxacillin, sodium oxacillin
Penicillins sensitive to beta lactamases	benzylpenicillin, benzathine benzylpenicillin
Polimixin	colistimethate
Sulfonamides plain and in combination	sulfadiazine, trimethoprim/sulfamethoxazole
Tetracyclines	doxycycline, limecycline (tetracycline-levo-methilenlysin), minocycline, tetracycline, tigecycline
Anticoagulants	
Vitamin K antagonists	acenocoumarol, warfarin
Antithrombotics	alteplase, argatroban, bivalirudin, defibrotide, human protein C, tenecteplase, urokinase
EBPM	Bemiparin sodium, dalteparin sodium, enoxaparin, nadroparin calcium, parnaparin
Heparina and heparinoids	antithrombin iii, dermatan sodium sulfate, heparin, sulodexide
Fondaparinux	fondaparinux
NAO	apixaban, dabigatran, edoxaban, rivaroxaban
Antidepressants	
Other antidepressants	mianserin, mirtazapine, oxitriptan, trazodone
SNRI antidepressants	duloxetine, venlafaxine
SSRI antidepressants	citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
Tricyclic antidepressants	amitriptyline, clomipramine, dosulepin, maprotiline, nortriptyline, trimipramine
Bupropion	bupropion
NaSSA (agomelatoninergics)	agomelatine
NaRi (norepinephrine reuptake inhibitors)	reboxetine
SMS (serotonin modulators and stimulators)	vortioxetine
Antidiabetics *(continued)*	
Acarbose	acarbose
GLP-1 (Glucagon-like one) analogues	dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide
Gliflozins (SGLT2 inhibitors), plain	canagliflozin, empagliflozin
Gliflozins/metformin, combinations	canagliflozin/metformin, dapagliflozin/metformin, empagliflozin/metformin

Therapeutic categories	Active ingredients
Antidiabetics *(continued)*	
Gliptins (DPP-4 inhibitors), plain	alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin
Gliptins (DPP-4 inhibitors), in combination	alogliptin/metformin, alogliptin/pioglitazone, dapagliflozin/saxagliptin, linagliptin/empagliflozin, linagliptin/metformin, saxagliptin/metformin, sitagliptin/metformin, vildagliptin/metformin
Insulins in combinations	insulin degludec/liraglutide, insulin glargine/lixisenatide
Insulins in combinations (long/intermediate with fast)	insulin aspart, insulin degludec, insulin detemir, insulin glargine, insulin lispro, recombinant DNA human insulin/recombinant DNA isophane human insulin
Insulin, fast acting	insulin aspart, insulin glulisine, insulin lispro, recombinant DNA human insulin
Insulin, intermediate acting	insulin lispro, recombinant DNA isophane human insulin
Metformin, plain and in combination	metformin, metformin/glibenclamide
Pioglitazone plain and in combination	pioglitazone, pioglitazone/glimepiride, pioglitazone/metformin
Repaglinide	repaglinide
Sulfonylureas, plain	glibenclamide, gliclazide, glimepiride, glipizide, gliquidone
Antidotes	
Injectable antidotes	acetylcysteine, edetic acid, methylene blue, flumazenil, glutathione, idarucizumab, hydroxycobalamin, naloxone, pralidoxime methyl-sulfate, protamine, sugammadex, thiosulfate
Non-injectable antidotes	ipecacuanha
Antiemetics	
Injectable antiemetics	aprepitant, granisetron, ondansetron, palonosetron, scopolamine, tropisetron
Non-injectable antiemetics	aprepitant, dimenhydrinate, granisetron, ondansetron, palonosetron/netupitant, prochlorperazine
Antihemorrhagics	
Injectable antihemorrhagics	tranexamic acid, alfa 1 human antitrypsin, fitomenadione, mesylated gabexate
Non-injectable antihemorrhagics	tranexamic acid, phyomenadione
Antiepileptics	
Other antiepileptics	brivaracetam, felbamate, lacosamide, lamotrigine, levetiracetam, perampanel, retigabine, stiripentol, sultiame, topiramate, zonisamide
Barbiturates and derivatives	phenobarbital, primidone
Benzodiazepine derivatives	clonazepam
Carboxamide derivatives	carbamazepine, eslicarbazepine, oxcarbazepine, rufinamide
Fatty acid derivatives – valproic acid and derivatives	valproic acid, valpromide
Fatty acid derivatives, plain and in combination	buxamine, buxamine/phenobarbital/phenytoin, tiagabine, vigabatrin
Suximide derivatives	ethosuximide
Phenytoin plain or in combination	Phenytoin sodium, phenytoin/methylphenobarbital
Antifungals	
Injectable antifungals	amphotericin b, anidulafungin, caspofungin, flucytosine, fluconazole, isavuconazole, micafungin, voriconazole
Non-injectable antifungals	fluconazole, isavuconazole, itraconazole, ketoconazole, miconazole, posaconazole, voriconazole
ACE inhibitors	benazepril, captopril, cilazapril, delapril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, trandolapril, zofenopril

Therapeutic categories	Active ingredients
Antihypertensives	
ACE inhibitors and diuretics (combinations)	benazepril/hydrochlorothiazide, captopril/hydrochlorothiazide, cilazapril/hydrochlorothiazide, delapril/indapamide, enalapril/hydrochlorothiazide, fosinopril/hydrochlorothiazide, lisinopril/hydrochlorothiazide, moexipril/hydrochlorothiazide, perindopril/indapamide, quinapril/hydrochlorothiazide, ramipril/hydrochlorothiazide, zofenopril/hydrochlorothiazide
ACE inhibitors, other combinations	bisoprolol/perindopril, perindopril/indapamide/amlodipine
ACE inhibitors and calcium channel blockers (combinations)	delapril/manidipine, enalapril/lercanidipine, perindopril/amlodipine, ramipril/amlodipine, ramipril/felodipine
Alpha-adrenoreceptor agonists	metildopa
Imidazoline receptor agonists	clonidine, moxonidine
Alfa blockers	doxazosin, terazosin, urapidil
Aliskiren plain or in combination	aliskiren, aliskiren/hydrochlorothiazide
Angiotensin II receptor blockers and diuretics (combinations)	candesartan/hydrochlorothiazide, eprosartan/hydrochlorothiazide, irbesartan/hydrochlorothiazide, losartan/hydrochlorothiazide, olmesartan medoxomil/hydrochlorothiazide, telmisartan/hydrochlorothiazide, valsartan/hydrochlorothiazide
Angiotensin II receptor blockers and diuretics (combinations)	sacubitril/valsartan
Angiotensin II receptor blockers (ARBs)	candesartan, eprosartan, irbesartan, losartan, olmesartan medoxomil, telmisartan, valsartan
Angiotensin II receptor blockers and calcium channel blockers (combinations)	candesartan/amlodipine, olmesartan medoxomil/amlodipine
Beta blockers	acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, cicloprolol, esmolol, labetalol, metoprolol, nadolol, nebivolol, pindolol, propranolol, sotalol, timolol
Beta blockers and diuretics (combinations)	atenolol/chlortalidone, bisoprolol/hydrochlorothiazide, nebivolol/hydrochlorothiazide
Calcium channel blockers (dihydropyridines)	amlodipine, barnidipine, clevidipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine
Calcium channel blockers (not dihydropyridines)	diltiazem, verapamil
High-ceiling diuretics, plain or in combination with potassium-sparing agents	etacrynic acid, furosemide, furosemide/triamterene, piretanide, torasemide
Potassium-sparing diuretics	canrenone, eplerenone, potassium canrenoate, spironolactone
Medicines acting on arteriolar muscle	minoxidil, nitroprusside
Thiazides and similars (including combinations)	chlortalidone, hydrochlorothiazide, indapamide, metolazone, potassium canrenoate/butizide, spironolactone/hydrochlorothiazide
Antipyretics *(continued)*	
Other analgesics and antipyretics	delta-9-tetrahydrocannabinol/cannabidiol, methoxyflurane, viminol, ziconotide
Other antipyretics – salicylic acid and derivatives	acetylsalicylic acid
Other antipyretics - anilides	paracetamol, paracetamol in combination
Other antipyretics - pyrazolones	metamizole, oxolamine/propyphenazone, propyphenazone/butalbital/caffeine

Therapeutic categories	Active ingredients
Antipyretics *(continued)*	
Injectable antipyretics	acetylsalicylic acid, delta-9-tetrahydrocannabinol/cannabidiol, metamizole, paracetamol, ziconotide
Non-injectable antipyretics	acetylsalicylic acid, metamizole, oxolamine/propyphenazone, paracetamol, paracetamol in combination, propyphenazone/butalbital/caffeine, viminol
Antipsychotics	
Atypical and other antipsychotics	amisulpride, aripiprazole, asenapine, cariprazine, clozapine, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone
Typical antipsychotics	haloperidol, bromperidol, chlorpromazine, clotiapine, droperidol, fluphenazine, levomepromazine, lithium, loxapine, perphenazine, periciazine, pimozide, promazine, sulpiride, tiapride, trifluoperazine, zuclopenthixol
Antivirals	
darunavir/cobicistat	darunavir/cobicistat
lopinavir/ritonavir	lopinavir/ritonavir
Anti-HCV antivirals	
Other HCV antivirals	dasabuvir, sofosbuvir
Anti-HCV antivirals in combination	elbasvir/grazoprevir, glecaprevir/pibrentasvir, ledipasvir/sofosbuvir, ombitasvir/ritonavir, sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir
Nucleosides and nucleotides excl. inhibitors of reverse transcriptase	ribavirin
Anti-HIV antivirals	
Other anti-HIV antivirals	enfuvirtide, maraviroc
Anti-HIV antivirals in coformulated regimens	abacavir/lamivudine, abacavir/lamivudine/zidovudine, bictegravir/emtricitabine/tenofovir alafenamide, cobicistat/darunavir/emtricitabine/tenofovir alafenamide, dolutegravir/abacavir/lamivudine, dolutegravir/rilpivirine, efavirenz/emtricitabine/tenofovir disoproxil, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, emtricitabine/rilpivirine/tenofovir alafenamide, emtricitabine/rilpivirine/tenofovir disoproxil, emtricitabine/tenofovir disoproxil, emtricitabine/tenofovir disoproxil/elvitegravir/cobicistat, lamivudine/zidovudine
Nucleosides and nucleotides inhibitors of reverse transcriptase	abacavir, adefovir dipivoxil, didanosine, emtricitabine, emtricitabine/tenofovir alafenamide, entecavir, lamivudine, stavudine, telbivudine, tenofovir alafenamide, tenofovir disoproxil, zidovudine
Integrase inhibitors	dolutegravir, raltegravir
Protease inhibitors plain or in combination	atazanavir, atazanavir/cobicistat, darunavir, darunavir/cobicistat, fosamprenavir, lopinavir/ritonavir, ritonavir, saquinavir, tipranavir
Non-nucleoside inhibitors of reverse transcriptase	doravirine, efavirenz, etravirine, nevirapine, rilpivirine
Asthma and COPD *(continued)*	
Monoclonal antibodies	benralizumab, mepolizumab, omalizumab
Antileukotrienes (LTRA)	montelukast
Bronchodilators - theophylline	ambroxol acefyllinate, aminophylline, bamifylline, diprofylline, doxofylline, theophylline
Chromones	Cromoglicic acid, nedocromil sodium

Therapeutic categories	Active ingredients
Asthma and COPD *(continued)*	
ICS	beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, mometasone
PDE-4 inhibitor	Roflumilast
LABA	clenbuterol, formoterol, olodaterol, salmeterol
LABA+ICS	beclomethasone/formoterol, budesonide/formoterol, fluticasone/formoterol, salmeterol/fluticasone
LABA+LAMA	aclidinium/formoterol, indacaterol/glycopyrronium, olodaterol/tiotropium, umeclidinium/vilanterol
LAMA	aclidinium, glycopyrronium, tiotropium, umeclidinium
LAMA+LABA+ICS	glycopyrronium/beclomethasone/formoterol, vilanterol/fluticasone/umeclidinium
SABA	fenoterol, salbutamol
SABA+ICS	beclomethasone/salbutamol, salbutamol/flunisolide
SABA+SAMA	fenoterol/ipratropium, salbutamol/ipratropium
SAMA	ipratropium, oxitropium
Ultra-LABA	indacaterol
Ultra-LABA+ICS	fluticasone furoate/vilanterol
Benzodiazepines	
Anxiolytics	alprazolam, bromazepam, clobazam, clorazepate, chlordiazepoxide, clotiazepam, delorazepam, diazepam, etizolam, ketazolam, lorazepam, nordazepam, oxazepam, pinazepam, prazepam
Hypnotics	brotizolam, estazolam, flunitrazepam, flurazepam, lormetazepam, midazolam, nitrazepam, triazolam
Sedatives	zaleplon, zolpidem, zopiclone
Emergency contraceptives	
Emergency contraceptives	ethinylestradiol/etonogestrel, levonorgestrel, ulipristal
Corticosteroids	
Injectable corticosteroids	betamethasone, hydrocortisone, methylprednisolone, triamcinolone
Non-injectable corticosteroids	dexamethasone
Curare derivatives	
Injectable curare derivatives	atracurium, cisatracurium, mivacurium chloride, rocuronium, suxametonium, vecuronium
Heparins	
heparins	antithrombin iii, bemiparin sodium, dalteparin sodium, enoxaparin, heparin, mesoglycan, nadroparin calcium, parnaparin, sulodexide
NSAIDs	
Injectable NSAIDs	diclofenac, ibuprofen, indomethacin, ketoprofen, ketorolac, meloxicam, parecoxib, piroxicam
Non-injectable NSAIDs	aceclofenac, niflumic acid, tiaprofenic acid, amtolmetin guacil, celecoxib, cinnoxicam, condroitin sulfate, dexibuprofen, dexketoprofen, diacerein, diclofenac, diclofenac/misoprostol, esomeprazole/naproxen, etoricoxib, flurbiprofen, glucosamine, ibuprofen, indomethacin, ketoprofen, ketoprofen/sucralfate, ketorolac, lornoxicam, meloxicam, morniflumate, nabumetone, naproxen, nimesulide, oxaprozin piroxicam, proglumetacin, tenoxicam

Therapeutic categories	Active ingredients
NSAIDs and antipyretics	
Injectable NSAIDs and antipyretics	diclofenac
Non-injectable NSAIDs and antipyretics	acetylsalicylic acid/ascorbic acid, diclofenac, glucosamine, ibuprofen, ketoprofen, morniflumate, naproxen, oxolamine/propyphenazone, paracetamol, paracetamol in combination
Antidementia medicines	
Other antidementia medicines	memantine
Anticholinesterase medicines	donepezil, galantamine, rivastigmine
Anti-Parkinson medicines	
Amantadine	amantadine
COMT inhibitors	entacapone, opicapone, tolcapone
DOPA-derivatives agonists	levodopa/benserazide, levodopa/carbidopa/entacapone, melevodopa/carbidopa
Dopamine-agonists	apomorphine, bromocriptine, cabergoline, pramipexole, ropinirole, rotigotine
MAO inhibitors	rasagiline, safinamide, selegiline
Antineoplastic medicines *(continued)*	
Monoclonal antibodies	bevacizumab, blinatumomab, brentuximab vedotin, cetuximab, daratumumab, elotuzumab, ipilimumab, nivolumab, obinutuzumab, ofatumumab, olaratumab, panitumumab, pembrolizumab, pertuzumab, ramucirumab, rituximab, trastuzumab, trastuzumab emtansine
Cytostatic antineoplastics - alkylating agents	bendamustine, busulfan, carmustine, cyclophosphamide, chlorambucil, dacarbazine, fotemustine, ifosfamide, melfalan, pipobroman, temozolomide, tiotepa
Cytostatic antineoplastics - antimetabolites	Acetylsalicylic acid/fluorouracil, azacytidine, capecitabine, cytarabine, cladribine, clofarabine, decitabine, fludarabine, fluorouracil, gemcitabine, mercaptopurine, methotrexate, nelarabine, pemetrexed, raltitrexed, tegafur/gimeracil/oteracil, tioguanine, trifluridine/tipiracil
Cytostatic antineoplastics - cytostatic - others	5-aminolevulinic acid, arsenous acid, aflibercept, anagrelide, bexarotene, bortezomib, carfilzomib, eribulin, estramustine, idelalisib, hydroxycarbamide, irinotecan, methylaminolevulinate chlorhydrate, mitotane, olaparib, pegaspargase, pentostatin, procarbazine, topotecan, tretinoin, venetoclax, vismodegib
Cytostatic antineoplastics - platinum compounds	carboplatin, cisplatin, oxaliplatin
Cytotoxic antineoplastics – cytotoxic antibiotics - anthracyclines and related substances	daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone, pixantrone
Cytotoxic antineoplastics - cytotoxic antibiotics -others	bleomycin, dactinomycin, mitomycin
Cytotoxic antineoplastics - products of natural derivation - others	etoposide, trabectedin, vinblastine, vincristine, vindesine, vinflunine, vinorelbine
Cytotoxic antineoplastics - products of natural derivation – taxanes	cabazitaxel, docetaxel, paclitaxel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