

Supplementary Materials

Supplementary File S1.

Medicines (listed by active substance) recommended in clinical guidelines as of March 2020 to treat COVID-19 symptoms.

Name	Active substance	Guideline				
		ATC-5	PAHO	Austria	Italy	Spain
ranitidine		A02BA02	✓			
omeprazole		A02BC01	✓			
atropine		A03BA01	✓			
metoclopramide		A03FA01	✓			
ondansetron		A04AA01	✓			
heparin		B01AB01	✓			
enoxaparin		B01AB05	✓			
sodium chloride ¹		B05XA0	✓		✓	
potassium lactate		B05XA15	✓			
norepinephrine		C01CA03	✓		✓	
dobutamine		C01CA07	✓		✓	
epinephrine		C01CA24	✓			
milrinone		C01CE02			✓	
levosimendan		C01CX08			✓	
chlorhexidine		D08AC02	✓			
povidone-iodine		D08AG02	✓			
ethanol		D08AX08	✓			
dexamethasone		H02AB02			✓	
methylprednisolone		H02AB04				✓
hydrocortisone		H02AB09	✓		✓	✓
amoxicillin / clavulanic acid		J01CR02	✓			✓
piperacillin / tazobactam		J01CR05	✓			
ceftazidime		J01DD02	✓			✓
ceftriaxone		J01DD04	✓			✓
cefditoren		J01DD16				✓
meropenem		J01DH02	✓			
ceftaroline		J01DI02				✓
clarithromycin		J01FA09				✓
azithromycin		J01FA10	✓			✓
amikacin		J01GB06	✓			
levofloxacin		J01MA12				✓
moxifloxacin		J01MA14				✓
vancomycin		J01XA01	✓			
amphotericin B		J02AA01	✓			
remdesivir		J05AB16		✓	✓	✓
oseltamivir		J05AH02	✓			
Lopinavir / ritonavir		J05AR10		✓	✓	✓
favipiravir		J05AX27		✓		
interferon beta-1b		L03AB08				✓
anakinra		L04AC03				✓
tocilizumab		L04AC07		✓		✓
suxamethonium		M03AB01	✓			
atracurium		M03AC04	✓			
propofol		N01AX10	✓			

Active substance		Guideline			
Name	ATC-5	PAHO	Austria	Italy	Spain
morphine	N02AA01	✓			
fentanyl	N02AB03	✓			
paracetamol	N02BE01	✓			
haloperidol	N05AD01	✓			
lorazepam	N05BA06	✓			
midazolam	N05CD08	✓			
hydroxychloroquine	P01BA02		✓	✓	✓
ipratropium bromide	R01AX03	✓			
salbutamol	R03AC02	✓			
oxygen	V03AN01	✓	✓	✓	✓

¹ In the PAHO recommendations and the Austrian guideline “saline solution” was indicated which can also include salt solutions (B05CB) such as sodium citrate, magnesium citrate, sodium bicarbonate and combinations.

Supplementary File S2:

Medicines (listed per ATC-5) recommended for the treatment of COVID-19 symptoms in guidelines as of March 2020 and further active substances of the same chemical group (ATC-4 group)

Active substance recommended for treatment of COVID-19 symptoms		ATC-4 code	Further substances in this ATC-4 group
Name	ATC-5		
ranitidine (EM)	A02BA02	A02BA	cimetidine famotidine nizatidine niperotidine roxatidine ranitidine bismuth citrate lafutidine cimetidine, combinations famotidine, combinations
omeprazole (EM)	A02BC01	A02BC	pantoprazole rabeprazole esomeprazole dexlansoprazole dexrabeprazole vonoprazan tegoprazan lansoprazole, combinations rabeprazole, combinations
atropine (EM)	A03BA01	A03BA	hyoscyamine belladonna total alkaloids
metoclopramide (EM)	A03FA01	A03FA	cisapride domperidone bromopride alizapride clebopride itopride cinitapride mosapride
ondansetron (EM)	A04AA01	A04AA	gransetron (EM) tropisetron (EM) dolasetron (EM) palonosetron (EM) palonosetron, combinations
heparin (EM)	B01AB01	B01AB	antithrombin III dalteparin (EM) nadroparin (EM) parnaparin reviparin danaparoid tinzaparin sulodexide bemiparin heparin, combinations
enoxaparin (EM)	B01AB05		
sodium chloride (EM) ¹	B05XA03	B05XA	potassium chloride (EM)

Active substance recommended for treatment of COVID-19 symptoms		ATC-4 code	Further substances in this ATC-4 group
Name	ATC-5		
potassium lactate	B05XA15		sodium bicarbonate ammonium chloride magnesium sulfate (EM) potassium phosphate, incl. combinations with other potassium salts calcium chloride sodium acetate sodium phosphate magnesium phosphate magnesium chloride zinc chloride hydrochloric acid sodium glycerophosphate cardioplegia solutions potassium acetate zinc sulfate (EM) combinations of electrolytes (EM) electrolytes in combination with other drugs
norepinephrine	C01CA03	C01CA	etilefrine isoprenaline norepinephrine dopamine (EM) phenylephrine oxedrine metaraminol methoxamine mephentermine dimetofrine prenalterol dopexamine gepefrine ibopamine midodrine octopamine fenoldopam cafedrine arbutamine theodrenaline amezinium metilsulfate ephedrine (EM) droxidopa combinations etilefrine, combinations
dobutamine	C01CA07		
epinephrine (EM)	C01CA24		
milrinone	C01CE02	C01CE	amrinone enoximone bucladesine
levosimendan	C01CX08	C01CX	angiotensinamide xamoterol angiotensin II

Active substance recommended for treatment of COVID-19 symptoms		ATC-4 code	Further substances in this ATC-4 group	
Name	ATC-5			
chlorhexidine (EM)	D08AC02	D08AC	dibrompropamidine propamidine hexamidine polihexanide chlorhexidine, combinations	
povidone-iodine (EM)	D08AG02	D08AG	iodine/octylphenoxypropolyglycoether iodine (EM) diiodohydroxypropane	
ethanol (EM)	D08AX08	D08AX	hydrogen peroxide eosin propanol (EM) tosylchloramide sodium isopropanol potassium permanganate (EM) sodium hypochlorite propanol, combinations	
dexamethasone (EM)	H02AB02	H02AB	betamethasone (EM) fluocortolone paramethasone prednisolone (EM) prednisone (EM) triamcinolone cortisone prednylidene rimexolone deflazacort cloprednol meprednisone cortivazol	
methylprednisolone (EM)	H02AB04			
hydrocortisone (EM)	H02AB09			
amoxicillin / clavulanic acid (EM)	J01CR02	J01CR	ampicillin and beta-lactamase inhibitor amoxicillin and beta-lactamase inhibitor (other than clavulanic acid) ticarcillin and beta-lactamase inhibitor sultamicillin piperacillin and beta-lactamase inhibitor other than tazobactam) combinations of penicillins	
piperacillin / tazobactam (EM)	J01CR05			

Active substance recommended for treatment of COVID-19 symptoms		ATC-4 code	Further substances in this ATC-4 group
Name	ATC-5		
ceftazidime (EM)	J01DD02	J01DD	cefotaxime (EM) cefsulodin cefmenoxime latamoxef ceftizoxime cefixime (EM) cefodizime cefetamet cefpiramide cefoperazone cefpodoxime ceftibuten cefdinir cefcapene cefteram cefotaxime and beta-lactamase inhibitor ceftazidime and beta-lactamase inhibitor (EM) ceftriaxone, combinations cefoperazone and beta-lactamase inhibitor ceftriaxone and beta-lactamase inhibitor cefpodoxime and beta-lactamase inhibitor
cefditoren	J01DD16		
meropenem (EM)	J01DH02	J01DH	ertapenem doripenem biapenem tebipenem pivoxil imipenem and cilastatin meropenem and vaborbactam panipenem and betamipron imipenem, cilastatin and relebactam
ceftaroline	J01DI02	J01DI	ceftobiprole medocaril faropenem cefiderocol (EM) ceftolozane and beta-lactamase inhibitor
clarithromycin (EM)	J01FA09	J01FA	erythromycin (EM) spiramycin midecamycin oleandomycin roxithromycin josamycin troleandomycin miocamycin rokitamycin dirithromycin flurithromycin telithromycin solithromycin
azithromycin (EM)	J01FA10		

Active substance recommended for treatment of COVID-19 symptoms		ATC-4 code	Further substances in this ATC-4 group
Name	ATC-5		
amikacin (EM)	J01GB06	J01GB	tobramycin (EM) gentamicin (EM) kanamycin (EM) neomycin netilmicin (EM) sisomicin dibekacin ribostamycin isepamicin arbekacin bekanamycin plazomicin (EM)
levofloxacin (EM)	J01MA12	J01MA	ofloxacin (EM) ciprofloxacin (EM) pefloxacin enoxacin temafloxacin norfloxacin lomefloxacin fleroxacin sparfloxacin rufloxacin grepafloxacin trovafloxacin gemifloxacin gatifloxacin prulifloxacin pazuflroxacin garenoxacin sitaflroxacin tosuflroxacin delafloxacin levonadifloxacin lascuflroxacin
moxifloxacin (EM)	J01MA14		
vancomycin (EM)	J01XA01	J01XA	teicoplanin telavancin dalbavancin oritavancin
amphotericin B (EM)	J02AA01	J02AA	hachimycin
remdesivir	J05AB16	J05AB	aciclovir (EM) idoxuridine vidarabine ganciclovir famciclovir valaciclovir (EM) cidofovir penciclovir valganciclovir (EM) brivudine brincidofovir

Active substance recommended for treatment of COVID-19 symptoms		ATC-4 code	Further substances in this ATC-4 group
Name	ATC-5		
oseltamivir (EM)	J05AH02	J05AH	zanamivir peramivir laninamivir
lopinavir / ritonavir (EM)	J05AR10	J05AR	zidovudine and lamivudine lamivudine and abacavir (EM) tenofovir disoproxil and emtricitabine zidovudine, lamivudine and abacavir zidovudine, lamivudine and nevirapine emtricitabine, tenofovir disoproxil and efavirenz stavudine, lamivudine and nevirapine emtricitabine, tenofovir disoproxil and rilpivirine emtricitabine, tenofovir disoproxil, elvitegravir and cobicistat lamivudine, tenofovir disoproxil and efavirenz lamivudine and tenofovir disoproxil lamivudine, abacavir and dolutegravir darunavir and cobicistat atazanavir and cobicistat lamivudine and raltegravir emtricitabine and tenofovir alafenamide emtricitabine, tenofovir alafenamide, elvitegravir and cobicistat emtricitabine, tenofovir alafenamide and rilpivirine emtricitabine, tenofovir alafenamide and bictegravir dolutegravir and rilpivirine emtricitabine, tenofovir alafenamide, darunavir and cobicistat atazanavir and ritonavir (EM) lamivudine, tenofovir disoproxil and doravirine lamivudine and dolutegravir darunavir and ritonavir lamivudine, tenofovir disoproxil and dolutegravir
favipiravir	J05AX27	J05AX	moroxydine lysozyme inosine pranobex pleconaril enfuvirtide maraviroc maribavir umifenovir enisamium iodide letermovir tilorone pentanedioic acid imidazolyl ethanamide ibalizumab tecovirimat baloxavir marboxil amenamevir bulevirtide fostemsavir lenacapavir

Active substance recommended for treatment of COVID-19 symptoms		ATC-4 code	Further substances in this ATC-4 group
Name	ATC-5		
interferon beta-1b	L03AB08	L03AB	interferon alfa natural interferon beta natural interferon gamma interferon alfa-2a interferon alfa-2b interferon alfa-n1 interferon beta-1a interferon alfacon-1 peginterferon alfa-2b (EM) peginterferon alfa-2a (EM) albinterferon alfa-2b peginterferon beta-1a cepeginterferon alfa-2b ropoginterferon alfa-2b peginterferon alfacon-2 peginterferon alfa-2b, combinations peginterferon alfa-2a, combinations
anakinra	L04AC03	L04AC	daclizumab basiliximab rilonacept ustekinumab canakinumab briakinumab secukinumab siltuximab brodalumab ixekizumab sarilumab sirukumab guselkumab tildrakizumab risankizumab satralizumab netakimab bimekizumab spesolimab
tocilizumab	L04AC07		
suxamethonium (EM)	M03AB01	M03AB	<i>no further active substances</i>
atracurium (EM)	M03AC04	M03AC	pancuronium gallamine vecuronium (EM) hexafluronium pipecuronium bromide doxacurium chloride fazadinium bromide rocuronium bromide mivacurium chloride cisatracurium

Active substance recommended for treatment of COVID-19 symptoms		ATC-4 code	Further substances in this ATC-4 group
Name	ATC-5		
propofol (EM)	N01AX10	N01AX	ketamine (EM) propanidid alfaxalone etomidate sodium oxybate nitrous oxide (EM) esketamine xenon nitrous oxide, combinations
morphine (EM)	N02AA01	N02AA	opium hydromorphone (EM) nicomorphine oxycodone (EM) dihydrocodeine papaveretum oxymorphone morphine, combinations hydromorphone and naloxone oxycodone and naloxone oxycodone and naltrexone dihydrocodeine, combinations codeine, combinations excl. psycholeptics codeine, combinations with psycholeptics
fentanyl (EM)	N02AB03	N02AB	ketobemidone pethidine pethidine, combinations excl. psycholeptics pethidine, combinations with psycholeptics
paracetamol (EM)	N02BE01	N02BE	phenacetin bucetin propacetamol paracetamol, combinations excl. psycholeptics phenacetin, combinations excl. psycholeptics bucetin, combinations excl. psycholeptics paracetamol, combinations with psycholeptics phenacetin, combinations with psycholeptics bucetin, combinations with psycholeptics
haloperidol (EM)	N05AD01	N05AD	trifluperidol melperone moperone pipamperone bromperidol benperidol droperidol fluanisone lumateperone

Active substance recommended for treatment of COVID-19 symptoms		ATC-4 code	Further substances in this ATC-4 group	
Name	ATC-5			
lorazepam (EM)	N05BA06	N05BA	diazepam (EM) chlordiazepoxide medazepam oxazepam potassium clorazepate adinazolam bromazepam clobazam ketazolam prazepam alprazolam halazepam pinazepam camazepam nordazepam fludiazepam ethyl loflazepate etizolam clotiazepam cloxazolam tofisopam bentazepam mexazolam lorazepam, combinations	
midazolam (EM)	N05CD08	N05CD	flurazepam nitrazepam flunitrazepam estazolam triazolam lormetazepam temazepam brotizolam quazepam loprazolam doxefazepam cinolazepam remimazolam nimetazepam	
ipratropium bromide (EM)	R01AX03	R01AX	calcium hexamine thiocyanate retinol (EM) ritiometan mupirocin (EM) hexamidine framycetin hyaluronic acid various combinations	

Active substance recommended for treatment of COVID-19 symptoms		ATC-4 code	Further substances in this ATC-4 group
Name	ATC-5		
salbutamol (EM)	R03AC02	R03AC	fenoterol rimiterol hexoprenaline isoetarin pirbuterol tretoquinol carbuterol tulobuterol salmeterol (EM) formoterol (EM) clenbuterol reprotoerol procaterol bitolterol indacaterol olodaterol
oxygen (EM)	V03AN01	V03AN	carbon dioxide helium nitrogen medical air

EM = classified as essential medicine by the World Health Organization (<https://apps.who.int/iris/rest/bitstreams/1145259/retrieve>)

Supplementary File S3:

Shortage notifications for medicines to treat COVID-19 symptoms and further active substances of the same chemical group (ATC-4 group)

Medicine		Included in		Country	Shortage notifications			
Active substance	ATC-5	EML	GL		02 / 2020	03 / 2020	04 / 2020	11 / 2021
famotidine	A02BA03	N	N	AT	-	-	2	-
				IT	-	-	-	-
				ES	-	-	-	-
omeprazole	A02BC01	Y	Y	AT	-	-	-	2
				IT	-	-	-	-
				ES	1	3	2	-
pantoprazole	A02BC02	N	N	AT	-	1	1	-
				IT	2	1	1	1
				ES	1	-	-	-
lansoprazole	A02BC03	N	N	AT	-	-	-	-
				IT	-	-	-	1
				ES	-	-	-	-
rabeprazole	A02BC04	N	N	AT	-	-	1	-
				IT	-	-	-	-
				ES	-	-	-	-
esomeprazole	A02BC05	N	N	AT	-	-	1	-
				IT	1	-	1	-
				ES	-	-	-	-
ondansetron	A04AA01	Y	Y	AT	-	-	-	-
				IT	-	-	1	-
				ES	1	2	2	-
granisetron	A04AA02	Y	N	AT	-	-	1	-
				IT	-	-	-	-
				ES	2	-	-	-
heparin	B01AB01	Y	Y	AT	-	-	-	-
				IT	-	-	-	1
				ES	-	-	-	-
enoxaparin	B01AB05	N	N	AT	-	-	-	-
				IT	-	-	-	-
				ES	-	-	5	-
sodium bicarbonate	B05XA02	N	N	AT	-	-	-	-
				IT	-	-	-	-
				ES	-	-	1	-
sodium chloride	B05XA03	Y	Y	AT	-	-	1	-
				IT	-	-	-	-
				ES	-	-	-	1
chlorhexidine, combinations	D08AC52	N	N	AT	-	-	-	-
				IT	-	-	-	-
				ES	-	1	3	-
ethanol	D08AX08	Y	Y	AT	-	-	-	-
				IT	-	-	-	-
				ES	-	-	2	-
dexamethasone	H02AB02	Y	Y	AT	-	-	1	-
				IT	-	-	-	-
				ES	-	-	-	-

Medicine		Included in		Country	Shortage notifications			
Active substance	ATC-5	EML	GL		02 / 2020	03 / 2020	04 / 2020	11 / 2021
methylpredni-solone	H02AB04	Y	Y	AT	-	-	-	1
				IT	-	2	-	-
				ES	-	-	1	-
prednisone	H02AB07	Y	N	AT	-	-	-	-
				IT	-	-	-	-
				ES	-	-	2	-
hydrocortisone	H02AB09	Y	N	AT	-	-	-	-
				IT	-	-	-	-
				ES	-	1	1	-
amoxicillin / clavulanic acid	J01CR02	Y	N	AT	1	2	1	-
				IT	-	-	-	-
				ES	-	-	1	-
piperacillin / tazobactam	J01CR05	Y	Y	AT	-	-	-	-
				IT	-	-	-	-
				ES	-	2	1	-
combinations of penicillins	J01CR50	Y	N	AT	-	-	4	-
				IT	-	-	-	-
				ES	-	-	-	-
cefotaxime	J01DD01	Y	N	AT	-	-	-	-
				IT	-	-	-	3
				ES	-	-	-	-
ceftazidime	J01DD02	Y	Y	AT	-	-	-	-
				IT	-	-	-	-
				ES	-	1	-	-
cefixime	J01DD08	Y	N	AT	-	-	-	-
				IT	-	-	-	-
				ES	-	-	1	-
cefditoren	J01DD16	N	Y	AT	-	-	-	-
				IT	-	-	-	-
				ES	-	-	1	-
roxithromycin	J01FA06	N	N	AT	-	-	-	-
				IT	1	1	-	-
				ES	-	-	-	-
clarithromycin	J01FA09	Y	Y	AT	-	-	-	-
				IT	-	-	2	4
				ES	-	2	-	-
azithromycin	J01FA10	Y	Y	AT	-	-	-	-
				IT	-	-	-	2
				ES	-	3	2	-
ciprofloxacin	J01MA02	Y	N	AT	-	-	1	1
				IT	-	1	-	1
				ES	-	-	-	-
levofloxacin	J01MA12	Y	Y	AT	-	-	-	-
				IT	-	-	-	-
				ES	-	2	1	-
moxifloxacin	J01MA14	Y	Y	AT	-	-	-	-
				IT	-	-	-	-
				ES	-	1	-	1

Medicine		Included in		Country	Shortage notifications			
Active substance	ATC-5	EML	GL		02 / 2020	03 / 2020	04 / 2020	11 / 2021
vancomycin	J01XA01	Y	Y	AT	-	-	-	-
				IT	-	-	-	-
				ES	-	-	-	1
oseltamivir	J05AH02	Y	Y	AT	-	1	-	-
				IT	-	-	-	-
				ES	-	-	-	-
lamivudine / abacavir	J05AR02	N	N	AT	-	-	1	-
				IT	-	-	1	1
				ES	-	-	-	-
lopinavir / ritonavir	J05AR10	Y	Y	AT	-	-	-	-
				IT	-	5	-	1
				ES	-	-	-	-
darunavir / cobicistat	J05AR14	N	N	AT	-	-	-	-
				IT	-	1	-	-
				ES	-	-	-	-
tocilizumab	L04AC07	N	Y	AT	-	-	-	-
				IT	-	-	1	-
				ES	-	-	-	-
suxamethonium	M03AB01	Y	Y	AT	-	-	-	-
				IT	-	-	-	-
				ES	-	-	1	-
atracurium	M03AC04	Y	Y	AT	-	-	-	-
				IT	-	4	-	-
				ES	-	1	-	-
rocuronium bromide	M03AC09	N	N	AT	-	-	1	-
				IT	-	5	1	1
				ES	-	-	1	-
mivacurium chloride	M03AC10	N	N	AT	-	-	-	-
				IT	-	1	1	-
				ES	-	-	-	-
cisatracurium	M03AC11	N	N	AT	-	1	-	-
				IT	-	3	5	-
				ES	-	4	-	-
propofol	N01AX10	Y	Y	AT	-	-	-	-
				IT	-	9	2	2
				ES	1	4	4	-
morphine	N02AA01	Y	Y	AT	-	-	-	-
				IT	-	-	2	-
				ES	-	1	-	-
fentanyl	N02AB03	Y	Y	AT	-	-	-	-
				IT	-	5	4	1
				ES	-	6	-	-
paracetamol	N02BE01	Y	Y	AT	-	-	7	-
				IT	-	2	9	-
				ES	3	10	35	3
haloperidol	N05AD01	Y	Y	AT	-	-	-	-
				IT	-	-	-	-
				ES	-	2	-	-

Medicine		Included in		Country	Shortage notifications			
Active substance	ATC-5	EML	GL		02 / 2020	03 / 2020	04 / 2020	11 / 2021
midazolam	N05CD08	Y	Y	AT	-	-	4	-
				IT	-	-	5	-
				ES	-	-	-	-

AT = Austria, EML = WHO Model Essential Medicines List (information on whether, or not, a medicine has been in the WHO EML), ES = Spain, GL = guideline (information on whether, or not, a medicine has been included in at least one of the four reviewed guidelines), IT = Italy, N = no, Y = yes

Note: A notification is counted in the month in which the shortage was notified to start.

Supplementary File S4:
Background information retrieved from the shortage registers

Information on expected end dates as share of shortages notifications

End dates	Country	1 st wave (02-04/2020)	4 th wave (11/2021)	Total
No expected end date indicated	Austria	52%	75%	54%
	Italy	36%	32%	35%
	Spain	25%	17%	24%

Austria: 33 shortages notifications – 1st wave, 4 – 4th wave, 37 – total

Italy: 80 – 1st wave, 19 – 4th wave, 99 – total

Spain: 122 – 1st wave, 6 – 4th wave, 128 – total

Data do not sum up to 100% as further options (e.g. shortages resolved in later months) are possible.

Information on causes

Austria Causes for Austria	1st wave		4th wave	
	Total (n = 33)		Total (n = 4)	
Capacity constraints at the manufacturing site	24%		No specific cause was provided for the 4 th wave;	
Delays in manufacturing	21%		all included active substances	
Increased demand	33%		targeted by a shortage notification indicated the reason	
Other	9%		“out of stock”	
Prioritisation of supply to other countries	3%			
Regulatory changes	3%			
Shortage of the active substance	6%			

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Italy - 1st wave		Italy - 4th wave	
Causes	n = 80	Causes	n = 19
High demand: quota distribution	1%	High demand: discontinuous supplies	5%
Permanent marketing ceased	14%	Permanent marketing ceased	11%
Increased demand	60%	Increased demand	37%
Production problems	21%	Production problems	32%
Reduced availability: contingent distribution	4%	Temporary marketing ceased	16%

Italy: slightly different categories indicated for the 1st wave and 4th wave

Spain: Information not included in the register

Recommendation for alternatives

Austria: Information not included in the register

Italy:

Existence of generic alternatives for 76% (n = 80) in the 1st wave, 84% (n = 19) in the 4th wave, 78% (n=99) in total

Spain:

Existence of generic alternatives for 88% (n = 122); no such information available for the 4th wave