RISK-BASED PRIORITIZATION OF ACTIVE PHARMACEUTICAL INGREDIENTS IN DANISH SURFACE WATERS FOR FUTURE MONITORING

Scientific Report from DCE – Danish Centre for Environment and Energy No. 601 2024

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Data sheet

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Abstract: A comprehensive screening and prioritization of prescription Active Pharmaceutical Ingredients (APIs) used in Denmark in 2021 was conducted based on semi-quantitative risk ranking integrating hazard and exposure information. The study identifies 50 APIs of highest concern, including sex hormones, antibiotics, antineoplastics, and SSRIs. Notably, 70% of the top 50 APIs have not been previously detected in Danish surface water, suggesting a need for expanded monitoring encompassing wastewater. Six APIs are recommended for inclusion in monitoring campaigns due to their presence on the EU Commission's watch list. Data on aquatic antineoplastics remain limited, warranting prioritization in future surveillance. SSRIs and benzodiazepines are highlighted for their potency and hydrophobic nature, respectively, necessitating inclusion in monitoring efforts. While analytical methods exist, research is needed to identify human metabolites and transformation products. Moreover, efforts align with green chemistry principles and sustainability strategies, emphasizing safe and sustainable management of APIs. Prioritization of monitoring streams receiving wastewater is recommended, aligning with proposed directives on urban wastewater treatment. Overall, further research and enhanced toxicity analyses are essential for a comprehensive understanding of API risks and effective management strategies.

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Preface

This work was commissioned by the Danish Environmental Protection Agency (DK EPA) to develop a relative environmental risk ranking of pharmaceuticals used in Denmark. The aim of the report is to support the DK EPA in prioritizing active pharmaceutical ingredients (APIs) based on their relative environmental risks in Denmark for further API- and site specific-assessment and management, including monitoring needs.

Sammenfatning

Vi har screenet og prioriteret alle receptpligtige Active Pharmaceutical Ingredients (API'er) til human forbrug i brug i Danmark i 2021 baseret på en relativ semikvantitativ risiko-ranking. Denne metode omfatter fareoplysninger og eksponeringsoplysninger. Resultatet er, at alle API'ere er rangordnede og en liste på de højstprioriterede 50 API'er, der potentielt giver anledning til bekymring, herunder kønshormoner, antibiotika, antineoplast og antidepressiver, fx serotinin genoptag hæmmere (SSRI'er), er præsenteret. De vigtigste konklusioner af denne undersøgelse er følgende:

Femogtredive af de 50 højest scorende API'er (70 %) er ikke tidligere blevet målt for og dermed ikke påvist i overfladevand i Danmark. Det bør derfor overvejes, om der er behov for at udvikle en overvågningsplan, der ud over overfladevand, også bør omfatte spildevand. I den forbindelse, er der seks API'er (Metformin, Clindamycin, Miconazole, Fipronil, Clotrimazole og Imazalil) som bør overvejes inkluderet i fremtidige overvågningskampagner, da de er på EU-Kommissionens observationsliste.

Datakilder om antineoplast i vandmiljøet samt en vurdering af deres miljøtoksicitet er stadig relativt sparsomme. Ingen af de højt scorende anti-neoplaster (Methotrexat og Anastrozole), som er højtscorende pga. af deres giftighed, er tidligere rapporteret i Danmark. Methotrexat og Anastrozole bør således, sammen med andre antineoplastiske stoffer, prioriteres i fremtidige overvågningskampagner.

SSRI'er er potente forbindelser; stoffer som Citalopram og Sertralin bør derfor også prioriteres i fremtidige overvågningskampagner. Benzodiazepiner (BZD'er) er hydrofobe forbindelser, der kan findes i spildevand (bundet til partikler) samt sediment, fx Diazepam og Midazolam, og som derfor også bør prioriteres i fremtidige overvågningskampagner.

Mangel på overvågningsdata for flere af de i top-50 prioriterede forbindelser skyldes ikke primært mangel på analytiske metoder. For de fleste stoffer, kan de eksisterende metoder nå detektionsgrænser der er tilstrækkeligt lave i forhold til økotoksikologiske Predicted No Effect Concentrations (PNEC). Litteraturgennemgangen tyder også på, at det vil være muligt at optimere analysemetoderne yderligere for at øge følsomheden. Passiv prøveudtagning kan opkoncentrere stofferne, men er primært egnet til screeningundersøgelser, da måleresultaterne kun vil være semi-kvantitative "for hovedparten af APIer".

Med hensyn til overvågningsprogrammer, anbefales det at prioritere vandløb, der modtager vand fra rensningsanlæg, da spildevandsudledning forventes at være den mest betydelige kilde til API'er i miljøet. Overvågningen bør følge forslaget til Europa-Parlamentets direktiv om rensning af byspildevand og forslaget om at gennemføre kvaternær spildevandsrensning for anlæg over 100 000 PE/10 000 PE.

Der er behov for en forskningsindsats for at identificere og karakterisere humane metabolitter og omdannelsesprodukter fra rensningsprocessen, for at optimere overvågningskampagner. For begge disse, såvel som mange overordnede API'er, er der desuden en begrænset viden om pharmakodynamisk og receptordreven toksicitet. Disse data er nødvendige for at opnå en mere

nøjagtig vurdering af stoffernes toksicitet og dermed de potentielle risici de kunne repræsentere. Håndteringen af API'er bør fremadrettet foretages i overensstemmelse med principperne om grøn kemi for API'er og kemikaliestrategien for bæredygtighed (CSS), og principperne bag *safe and sustainable by design* (SSbD) kan overvejes.

Summary

We have screened and prioritised all prescription Active Pharmaceutical Ingredients (APIs) used to treat humans in use in Denmark in 2021 based on a relatively semi-quantitative risk ranking. This method includes hazard information and exposure information. The result is a list of all APIs as well as of the 50 APIs of potential highest concern, including sex hormones, antibiotics, antineoplastics and antidepressants such as SSRIs. The main conclusions of this study are as follows:

Thirtyfive of the 50 highest scoring APIs (70 %) have not previously been measured for and thus not detected in surface water in Denmark. Consideration should therefore be given to the need to develop a monitoring plan which should include wastewater in addition to surface waters. In this context, there are six APIs (Metformin, Clindamycin, Miconazole, Fipronil, Clotrimazole and Imazalil) that should be considered included in future monitoring campaigns as they are on the EU Commission's watch list.

Data sources on aquatic antineoplastics and an assessment of their environmental toxicity are still relatively sparse. None of the high-scoring antineoplasts (Methotrexate and Anastrozole) that scores high due to their toxicity, have previously been reported in Denmark. Methotrexate and Anastrozole should, along with other antineoplastic agents, be prioritised in future surveillance campaigns.

SSRIs are potent compounds, drugs such as Citalopram and Sertraline should therefore also be prioritized in future surveillance campaigns. Benzodiazepines (BZDs) are hydrophobic compounds that can be found in wastewater as well as sediment, e.g. Diazepam and Midazolam, should therefore also be prioritised in future monitoring campaigns.

The lack of monitoring data for several of the top 50 priority compounds is not due to a lack of analytical methods. For most substances, existing methods can reach detection limits (LODs) that are sufficiently low compared to ecotoxicological Predicted No Effect Concentrations (PNEC) values. The literature review also suggests that it will be possible to further optimise analytical methods to increase sensitivity. Passive sampling is primarily suitable for screening studies, as the measurement results will only be semi-quantitative for a large fraction of APIs.

With regard to monitoring programmes, it is recommended to give priority to streams receiving water from treatment plants, as wastewater discharge is expected to be the most significant source of APIs in the environment. Monitoring should be aligned with the proposal for a Directive of the European Parliament concerning urban wastewater treatment and the proposal to implement quaternary wastewater treatment for plants above 100 000 p.e./10 000 p.e.

Research efforts are needed to identify and characterise human metabolites and transformation products before these types of compounds can possibly be included in monitoring campaigns. For both of these, as well as many parent APIs, there is a limited knowledge and amount of pharmacodynamic and receptor-driven toxicity analyses and data. These are necessary to obtain a

more accurate assessment of the toxicity of the substances and thus the potential risks they could represent. The management of APIs going forward is done in accordance with the principles of green chemistry for APIs and the chemicals strategy for sustainability (CSS) and the principles behind safe and sustainable by design (SSbD) can be considered.

1 Introduction

Residues of active pharmaceutical ingredients (APIs) have been found in surface waters across the world. The introduction of APIs in the European Water Framework Directive (WFD)[1] through their inclusion in watch lists has been an important step towards the monitoring of APIs in the aquatic environment. The German Environment Agency (UBA) [2] has compiled a database of compounds and concentrations measured in the environment covering 771 APIs in total. The Danish Organisation for Water and Wastewater (DANVA) commissioned a report by COWI in 2021 to document the measured APIs in Danish surface waters and found that 136 APIs had been detected in Danish waters. Moreover, the DK EPA initiated a project at Aarhus University to screen Danish surface waters using novel non-target analytical methods, which confirmed the occurrence of 34 APIs[3]. The presence of APIs in the environment and in particular surface waters thus raises questions of potential environmental risks. The Organisation for Economic Cooperation and Development (OECD) has, moreover, pointed towards these environmental challenges and associated risk assessment and management need, as cited in the text box below. The presence of many APIs in the environment and primarily in surface waters causes the need to develop prioritization methods[4]. The OECD concluded in their report on pharmaceutical residues in surface waters:

OECD (2019): About 2 000 active pharmaceutical ingredients (APIs) are being administered worldwide in prescription medicines, non-prescription drugs and veterinary drugs, the residues of which are of increasing environmental concern as the number and density of humans and livestock requiring healthcare escalates. Active pharmaceutical ingredients are found in surface waters, groundwater, drinking water, soil, manure, biota, sediment, and the food chain. Although the contribution of each emission source varies across regions and types, the dominant sources of pharmaceuticals in the environment stem from untreated household wastewater and effluent from municipal wastewater treatment plants. Emissions from manufacturing plants and intensive agriculture and aquaculture can be important pollution hotspots locally. Because pharmaceuticals are intentionally designed to interact with living organisms at low doses, even low concentrations in the environment can have unintended, negative impacts on freshwater ecosystems. For example, active substances in oral contraceptives have caused the feminization of fish and amphibians; psychiatric drugs, such as fluoxetine, alter fish behavior making them less risk-averse and vulnerable to predators; and the over-use and discharge of antibiotics to water bodies exacerbates the problem of antimicrobial resistance – declared by the World Health Organization as an urgent, global health crisis that is projected to cause more deaths globally than cancer by 2050.

[1] Tiedeken, E.J., Tahar, A., McHugh, B. & Rowan, N.J. (2017). Monitoring, sources, receptors, and control measures for three European Union watch list substances of emerging concern in receiving waters – A 20 year systematic review. *Science of The Total Environment*, *574*, 1140–1163. https://doi.org/10.1016/J.SCITOTENV.2016.09.084

[2] https://www.umweltbundesamt.de/en/database-pharmaceuticals-in-the-environment-0

[3] Nanusha et al. (2022). Environmental Pollution 315 https://doi.org/10.1016/j.envpol.2022.120346.

[4] OECD (2019). Pharmaceutical Residues in Freshwater: Hazards and Policy Responses, OECD Studies on Water, OECD Publishing, Paris, https://doi.org/10.1787/c936f42d-en.

In 2019, the European Union adopted a strategic approach to pharmaceuticals in the environment[5] as part of the Green Deal and as required by Article 8c of Directive 2008/105/EC as amended by Directive 2013/39/EU. The EU points towards the following concerns behind the strategic approach:

EU strategic approach to pharmaceuticals in the environment (2019): There is overwhelming evidence that traces of pharmaceuticals in the environment, in particular in water and soil, could have an adverse impact on wildlife such as fish, birds, and insects and knock-on effects on wider ecosystems, including antimicrobial resistance. Pharmaceutical residues are now found across Europe's soils and surface waters and have even reached the drinking water, although not in quantities that cause immediate concern. Access to safe, qualitative, and effective pharmaceutical treatments must remain fully available to citizens and animals. This comes to light during the ongoing COVID-19 pandemic probably more than ever, including the need for sustainable supply chains and consumption patterns. At the same time, it must be avoided that there is an undue impact of pharmaceutical residues on the environment. Indeed, as highlighted by the pandemic, our health and well-being strongly depend on a healthy environment. The Zero Pollution ambition for a toxic-free environment, as expressed in the European Green Deal, aims to protect both public health and ecosystems through avoiding negative effects of chemical substances, including certain pharmaceutical residues, on air, soil, and water. The Pharmaceutical Strategy for Europe focuses on availability, affordability, sustainability, and security of supply of pharmaceuticals, as well as enabling innovation.

The Baltic Sea Action Plan 2021[6] moreover stresses the importance of identifying and prioritizing APIs for monitoring based on hazardous and risk properties in the Baltic Sea region under the points HL 22-27. Hence, APIs in surface waters are also a priority in Denmark, for the Ministry of the Environment as well as the Danish EPA.

The aim of this report is therefore to support the Danish EPA with a risk-based prioritization of prescription APIs for humans in Danish surface waters with a view to future monitoring efforts. The report is an overall relative risk ranking of all prescription APIs for humans (veterinary and not over-the-counter drugs are not included if they are not on the list of prescription APIs) that may be present in Danish waters. We have particularly focused on being as exhaustive as possible with regard to the APIs currently in use in Denmark and potentially emitted to surface waters. This information can then be used to guide further targeted and site-specific aquatic risk evaluations of APIs of concern e.g. APIs with high scores. However, it is important to note that the relative risk ranking developed here does not precisely reflect the compound or site-specific aquatic risk – it is a tool to help prioritize data and identify knowledge-gaps and recognize APIs of concern for further specific risk assessment.

As pointed out by the OECD and the EU above, the primary environmental concerns pertaining to APIs are their pharmacodynamic properties, and that the main source to the environment for APIs are via wastewater effluent. Hence, this report focusses on APIs used in Denmark which may reach the environment via wastewater. We are aware of potential additional sources, for example from agricultural uses, which are not considered here. In an international perspective, these are of less immediate concern as pointed out by the OECD. Denmark has a highly industrialized agricultural sector with a very high density of animals, primarily pigs, relative to mostly any other

[5] https://ec.europa.eu/environment/water/water-dangersub/pdf/strategic_approach_pharmaceuticals_env.PDF
[6] https://helcom.fi/baltic-sea-action-plan/

country on the planet. The manure and slurry from the pig production is generally digested, treated and applied to farmland. This contains residues of veterinary APIs (several also consumed by humans) and is expected to be higher and of more weighted potential concern relative to the general picture in EU and OECD. The major concern in this case is antibiotics and development of antimicrobial resistance (AMR). The diversity and complexity of veterinary APIs are obviously lower than used in humans and hence the pharmacodynamic driven sublethal effects of veterinary APIs are generally of lower concern than human APIs – as reflected in the EU and OECD assessments – but the picture might be a bit more complex in Denmark as mentioned above. The DANMAP[7] monitoring of AMR and use of medicines in animal production underscores the importance of the topic in Denmark. Due to the intense conventional animal production and application of manure on farmland it is a fair assumption that residues of veterinary APIs will via drainage end up in streams and surface waters in higher amounts than in many other OECD countries. This is however not assessed in this report which focus on human APIs. Despite the animal production – the assessment by OECD and EU to focus on human APIs is still highly relevant for Denmark in an overall risk context due to the volume, complexity, and pharmacodynamic nature of human APIs used.

The report moreover reviews the predicted-no-effect-concentrations (PNEC) values for selected high risk APIs; treatment technologies for the removal of the highest risk APIs; the use of passive sampling and other methods for the purpose of lowering the detection limit for low PNEC active ingredients, in particular for highly toxic or high risk APIs; and finally analytical possibilities in relation to the development of a monitoring programme for APIs in surface waters. New and emerging Environmental Quality Standards have been developed for APIs by the Danish EPA[8], European member states as well as novel prioritization projects such as the imi-premier project[9] which also ranks APIs in the EU. There are in other words ongoing efforts to focus and improve the aquatic risk assessment of APIs in line with the aims of this report aiming to support national and EU policies.

[7] https://www.danmap.org/about-danmap
[8] https://mst.dk/kemi/kemikalier/graensevaerdier-og-kvalitetskriterier/miljoekvalitetskriterier/
[9] https://imi-premier.eu/prioritization-and-selection-of-apis-using-a-risk-based-approach/

2 Methods

A semi-quantitative prioritisation approach was used in this report to all APIs that may potentially enter the aquatic environment in Denmark. The approach is similar to the methodology recently published in a scientific report by Sanderson et al. (2021)[10] , using tiers that allow compounds with certain qualities passing through to the next tier. However, the approach has been adapted to the specific challenges posed by medicines in comparison to industrial chemical pollutants. First, the compounds were scored (from 0 to 3 as maximum) according to a defined quantitative approach based on the assessed severity of a particular property, e.g. hazard classification (see section 2.3). Second, this score was weighted (from 0 to 10 as maximum) to evaluate the parameter according to origin and quality of the data. The different weighting also represents the use and number of times the compound has been measured in environmental samples in Denmark and Europe. Details are given in the appendices of the report. Importantly, no APIs are screened out of the assessment – all APIs are scored – see Appendixes.

The focus of the study has been on investigating and prioritising the parent drug, or the API, in contrast to transformation products as also reported for medicines in environmental samples. Including transformation products in the prioritization would be too extensive and time-consuming as part of this study, but a useful extension in future studies.

2.1 Establishment of a curated list of APIs sold in Denmark

A list of all approved APIs in Denmark was downloaded from the Danish Medicines Agency's (DMA) webpage[11]. In total, 2 574 unique APIs were approved for sale on the Danish market in September 2022 (see Figure 1). September 2022 is therefore the latest date for inclusion of any compounds and results pertaining to presences in the environment and toxicity and property data. The number of APIs was reduced based on their availability according to the list medicinpriser.dk[12], a database administered by the DMA. This list contains prices for all available medicines in Denmark and thus reflects which APIs are available for sale and in actual use in Denmark. This database is updated every fortnight. Applying the information from medicinpriser.dk, the number of entries was reduced from the original 2 574 approved and available APIs to 1 506 individual APIs in actual use in Denmark. The justification for this step is that we consider it unlikely that a medicine not routinely available on the Danish market is used in such quantities that it would have an adverse effect on the environment. This list also includes those used in hospitals.

The prioritisation scheme does not include the private import of medicines from the EU and third countries. Since this import is illegal and there is currently no official statistics of the prevalence of importing medicines or

[10] Sanderson, H., Fauser, P. & Vorkamp, K. 2021. Prioritization of emerging contaminants for a Nordic screening study. Aarhus University, DCE – Danish Centre for Environment and Energy, 32 pp. Scientific Report No. 446. http://dce2.au.dk/pub/SR446.pdf

[11] https://laegemiddelstyrelsen.dk/da/godkendelse/godkendelse-af-medicin/lister-over-godkendte-og-afregistrerede-laegemidler/saadan-bruger-du-listen-over-godkendte-laegemidler/ - downloaded on 20220912

[12] https://www.medicinpriser.dk/

amounts of APIs, it was assumed for the purpose of this study that this occurrence is so low that it would not significantly impact the results from this study.

This initial list of 1506 APIs currently available on the Danish market was further curated by removing vaccines, inorganic salts and plant and animal extracts, here considered Chemical Substances of Unknown or Variable Composition, Complex Reaction Products and Biological Materials (UVCBs). For instance, plant and animal extracts are complex biological matrices with an undefined chemical composition, and we are therefore unable to evaluate them according to the steps in this prioritisation scheme. These omissions further reduced the initial list from 1506 APIs to 1024 APIs.

In an environmental and analytical chemical context the main identifier is the CAS number, a unique identification number assigned by the Chemical Abstracts Service (CAS). We performed searches for the chemical name[13] to retrieve these CAS numbers for the APIs in the different databases.

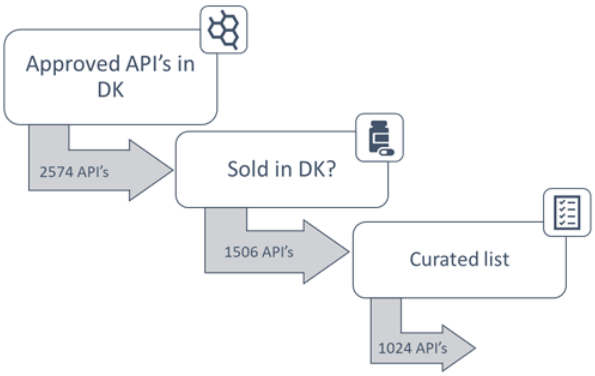

Figure 1. Schematic over the initial steps for establishing a list over approved APIs in use in Denmark and the selection of these APIs.

2.2 Prioritisation tiers

The ranking process applied in this study consists of a series of tiers where APIs qualify for subsequent prioritisation steps based on scores. We applied three semi-quantitative and progressive prioritisation rankings in a tiered approach to develop a ranked list of all compounds based on both hazard and risk (see Figure 2), which will be described in detail below.

[13] Sanderson, H., Fauser, P. & Vorkamp, K. 2021. Prioritization of emerging contaminants for a Nordic screening study. Aarhus University, DCE – Danish Centre for Environment and Energy, 32 pp. Scientific Report No. 446. http://dce2.au.dk/pub/SR446.pdf & https://comptox.epa.gov/dashboard/batch-search

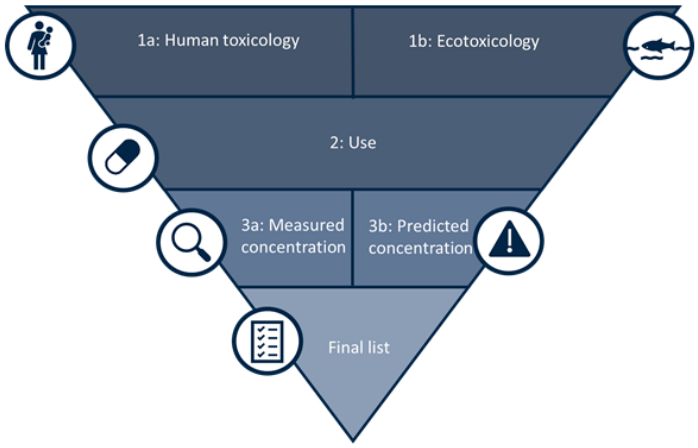

Figure 2. Tiers used in this tiered prioritisation scheme.

The complete curated list of APIs is presented in Appendix 1. The first tier (1a and b) is hazard-based, addressing human health hazards as well as environmental hazards in terms of persistence, bioaccumulation (e.g. Log K_{ow}), toxicity (PBT) and other ecotoxicologically relevant parameters. Tier 2 and tiers 3a and b are linked to exposure, either by use or monitored/predicted environmental concentration. Lastly, the final step of the prioritisation scheme is the summarization of the overall risk score resulting in the final list. All APIs in use in Denmark are included – no APIs are left out all are scores and ranked.

2.3 Scoring system and weighting of databases

The compounds are scored from 0 to 3 as maximum based on the assessed severity of a particular property, e.g. hazard classification in tiers 1a and 1b. Moreover, depending on the origin and quality of the data, e.g. presence on lists and uncertainty of the parameter, this score was weighted from 0 to 10 as maximum (see Table 1). Such weighting considers the severity and relevance to human health and environmental impact as well as, in certain cases, monitoring data from countries that are geographically close to Denmark, mainly Germany and Sweden. The only exception to the maximum of 10 in weighting was for compounds on the European Commission's 2022/1307[14] watch list (as part of the European Water Framework Directive). Compounds appearing on this list were given a weighting score of 100, to ensure that these compounds progressed to the final list as they are highly prioritized in the EU. As mentioned above this ranking does not include over the counter drugs (OTC) as the databases over these are less robust than those for prescription APIs. We recognize that a large volume of OTC drugs is consumed, in particular painkillers such as paracetamol – where close to one billion tables are sold in 2022 in Denmark[15]. And hence these in particular, as well as other OTC drugs should be considered in further evaluations, but they are outside this analysis in the same way as veterinary APIs.

[14] COMMISSION IMPLEMENTING DECISION (EU) 2022/1307 of 22 July 2022 establishing a watch list of substances for Union-wide monitoring in the field of water policy pursuant to Directive 2008/105/EC of the European Parliament and of the Council. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32022D1307

[15] nyhedsbrevsanalyse-om-medicinforbrug-og--udgifter-i-2022.pdf (apotekerforeningen.dk)

Table 1. Overview of the prioritization scheme: Original lists of compounds and data sources for scoring parameters; Number of entries in the lists; Scoring.

Data sources for the tiers	Total number of compounds	Tier 1 a Scoring parameter	Tier 1b Scoring parameter	Tier 2 Scoring parameter	Tier 3a Scoring parameter	Tier 3b Scoring parameter	Weighting factor	Source
REACH Article 59 Candidate list	194	See section 2.2.4	Hazard statement code(s)-Environmental hazard				10	https://echa.europa.eu/en/candidate-list-table
		Hazard statement code(s)						
REACH Annex XIV Authorisation list	55	See section 2.2.4					1	https://echa.europa.eu/da/authorisation-list
REACH Annex XVII Restriction list	125	See section 2.2.4					10	https://echa.europa.eu/da/substances-restricted-under-reach
Community Rolling Action Plan (CoRAP) list of the European Chemical Agency (ECHA)	307	Hazard statement code(s)	Hazard statement code(s)-Environmental hazard				5	https://echa.europa.eu/da/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table
Substitute It Now! (SIN) list	761	See section 2.2.4	See section 2.2.5				7	https://chemsec.org/buisness-tool/sin-list
		Hazard class and category code(s)					10	
List of possible endocrine disrupting compounds (EDC)	430	Category					3	https://edlists.org
Authorised medicinal products and new medicinal products in Denmark	2574	ATC code (first three characters)					5	https://laegemiddelstyrelsen.dk/en/licensing/licensing-of-medicines/lists-of-authorised-and-deregistered-medicines/how-to-use-the-list-of-authorised-medicinal-products/
Roos et al. (2012)	582	Pregnancy cat.1					8	https://www.sciencedirect.com/science/article/pii/S0048969712000824?via%3Dihub
			$LogK_{ow}$				1	
						PEC/PNEC	5	
EU Commission's watch list of substances for Union-wide monitoring in the field of water policy	26		Included				100	https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32022D1307
Measured API toxicity (Sanderson et al. 2012)	194		LD_{50}/LC_{50}				2	https://link.springer.com/article/10.1007/s00128-012-0921-3
			$LogK_{ow}$				1	
ECOSAR (Sanderson et al. 2003)	2842		$LogK_{ow}$				1	https://www.sciencedirect.com/science/article/pii/S0273230004000029?via%3Dihub#TBL1
							3	

Annual sale in Danish pharmacies				Number of patients using API annually			6	https://www.esundhed.dk/Emner/Laegemidler/Apotekernes-salg-af-laegemidler
Umweltbundesamt (UBA) Database - Pharmaceuticals in the environment	276,895				All countries		1	https://www.umweltbundesamt.de/en/database-pharmaceuticals-in-the-environment-0
NORMAN Ecotoxicology Database	757				Lowest PNEC that is based on experimental data		2	https://www.norman-network.com/nds/ecotox/lowestPnecsIndex.php?checkSelect=2
COWI report (2021)	136				Maximum MEC/PNEC		10	Personal correspondence and data delivery by COWI and DANVA
					Average MEC/PNEC			
					In hospital effluent?		2	
NORMAN Ecotoxicology Database	31,148					Lowest PNEC that is based on predicted data	1	https://www.norman-network.com/nds/ecotox/lowestPnecsIndex.php?checkSelect=2
Calculated PEC	84						3	See section 2.8.1

2.4 Tier 1a: Hazard - Human toxicity tier

The initial prioritisation step was based on existing hazard identifications of chemicals, for example established under REACH, as presented in Table 1. This initial tier applied to the APIs in the curated list is a combined score from studies in human toxicology as well ecotoxicology in accordance with procedures previously described in Sanderson et al. (2021)[4] , here adapted to pharmaceuticals.

The lists and databases in Table 1 address several different hazard properties such as the potential for endocrine disruption or carcinogenicity, mutagenicity, and reprotoxicity (CMR). The human toxicology tier also scored compounds according to hazard statements such as H350 - May cause cancer (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard) and H301- Toxic if swallowed.

In pharmacology, the use of Anatomical Therapeutic Chemical (ATC) Classification or ATC codes is used to identify the various APIs and medicines since these compounds can have several generic names. The ATC code also provides information on the therapeutic use for the API. The APIs on the curated list were scored according to the ATC classification, where for instance antibacterial use, sex hormones and other compounds with effects on the endocrine system, APIs with antifungal and/or antiparasitic effects as well as antineoplastic and immunomodulating agents were prioritised due to their mode of action and thus scored high, see Table 2. Some compounds were ranked with a slightly lower priority, however still of relevance for the prioritisation scheme, such as compounds with psychoactive effects.

[4] Sanderson, H., Fauser, P. & Vorkamp, K. 2021. Prioritization of emerging contaminants for a Nordic screening study. Aarhus University, DCE – Danish Centre for Environment and Energy, 32 pp. Scientific Report No. 446.
http://dce2.au.dk/pub/SR446.pdf

Table 2. Overview of the ATC codes and their ATC scoring. Entries with scores above zero are marked red.

ATC code	Specification	Weighted score	Score
A01	Stomatological Preparations	0	0
A02	Drugs For Acid Related Disorders	0	0
A03	Drugs For Functional Gastrointestinal Disorders	0	0
A04	Antiemetics And Antinauseants	0	0
A05	Bile And Liver Therapy	0	0
A06	Drugs For Constipation	0	0
A08	Antiobesity Preparations, Excl. Diet Products	0	0
A09	Digestives, Incl. Enzymes	0	0
A10	Drugs Used In Diabetes	0	0
A11	Vitamins	0	0
A12	Mineral Supplements	0	0
A13	Tonics	0	0
A14	Anabolic Agents For Systemic Use	0	0
A15	Appetite Stimulants	0	0
A16	Other Alimentary Tract And Metabolism Products	0	0
B01	Anticoagulant (Blood Thinner)	0	0
B02	Antihemorrhagics	0	0
B05	Blood Substitutes And Perfusion Solutions	0	0
B06	Other Hematological Agents	0	0
C01	Cardiac Therapy	0	0
C02	Antihypertensives	0	0
C03	Diuretics	0	0
C04	Peripheral Vasodilators	0	0
C05	Vasoprotectives	0	0
C07	Beta Blocking Agents	0	0
C08	Calcium Channel Blockers	0	0
C09	Treat High Blood Pressure (Hypertension)	0	0
C10	Lipid Modifying Agents	0	0
D01	Antifungals For Dermatological Use	5	1
D02	Emollients And Protectives	0	0
D03	Preparations For Treatment of Wounds And Ulcers	0	0
D04	Antipruritics, Incl. Antihistamines, Anesthetics, Etc.	0	0
D05	Antipsoriatics	0	0
D06	Antibiotics And Chemotherapeutics For Dermatological Use	5	1
D07	Corticosteroids, Dermatological Preparations	5	1
D08	Antiseptics And Disinfectants	0	0
D09	Medicated Dressings	0	0
D10	Anti-Acne Preparations	0	0
D11	Other Dermatological Preparations	0	0
G01	Gynecological Antiinfectives And Antiseptics	5	1
G02	Other Gynecologicals	5	1
G03	Sex Hormones And Modulators Of The Genital System	5	1
G04	Urologicals	0	0
H01	Pituitary And Hypothalamic Hormones And Analogues	5	1
H02	Corticosteroids For Systemic Use	5	1
H03	Thyroid Therapy	5	1
H04	Pancreatic Hormones	5	1

Continued			
H05	Calcium Homeostasis	5	1
J01	Antibacterials For Systemic Use	5	1
J02	Antimycotics For Systemic Use	5	1
J04	Antimycobacterials	5	1
J05	Antivirals For Systemic Use	5	1
J06	Immune Sera And Immunoglobulins	0	0
J07	Vaccines	0	0
L01	Antineoplastic Agents	5	1
L02	Endocrine Therapy	5	1
L03	Immunostimulants	5	1
L04	Immunosuppressants	5	1
M01	Benzodiazepine (Anxiolytic)	0	0
M02	Topical Products For Joint And Muscular Pain	0	0
M03	Muscle Relaxants	0	0
M04	Antigout Preparations	0	0
M05	Drugs For Treatment Of Bone Diseases	0	0
M09	Other Drugs For Disorders Of The Musculo-Skeletal System	0	0
N01	Anesthetics	2.5	0.5
N02	Analgesics	2.5	0.5
N03	Anti-Convulsion	2.5	0.5
N04	Anti-Parkinson Drugs	2.5	0.5
N05	Psycholeptics	2.5	0.5
N06	Anti-Depressants	2.5	0.5
N07	Other Nervous System Drugs	2.5	0.5
P01	Antiprotozoals	5	1
P02	Anthelmintics	5	1
P03	Ectoparasiticides, Incl. Scabicides, Insecticides And Repellents	5	1
R01	Nasal Preparations	0	0
R02	Throat Preparations	0	0
R03	Drugs For Obstructive Airway Diseases	0	0
R05	Cough And Cold Preparations	0	0
R06	Antihistamines For Systemic Use	0	0
R07	Other Respiratory System Products	0	0
S01	Ophthalmologicals	0	0
S02	Otologicals	0	0
S03	Ophthalmological And Otological Preparations	0	0
V01	Allergens	0	0
V03	All Other Therapeutic Products	0	0
V04	Diagnostic Agents	0	0
V06	General Nutrients	0	0
V07	All Other Non-Therapeutic Products	0	0
V08	Contrast Media	0	0
V09	Diagnostic Radiopharmaceuticals	0	0
V10	Therapeutic Radiopharmaceuticals	0	0
V20	Surgical Dressings	0	0

2.5 Tier 1 b: Hazard - Ecotoxicology screening

Due to the extensive use of APIs and their incomplete removal in wastewater treatment plants, APIs are introduced into the receiving waters continuously. Most APIs have a comparatively high polarity and relatively low volatility, causing them to remain mostly in the water phase. The toxicity of the APIs for aquatic organisms is determined by several factors such as API concentration and potency, exposure time, type and developmental stage of the organism, water temperature and pH, as well as the physico-chemical properties of the API.

Besides scoring for environmental hazard classifications such as H410 - Very toxic to aquatic life with long lasting effects, the score for the ecotoxicological tier was obtained from available data on physico-chemical properties of the APIs, such as their n-Octanol/Water Partition Coefficients (Log K_{ow}) as well as toxicity measured (LD_{50} and LC_{50}) in living organisms such as rats, fish, and algae. Log K_{ow} has an ecotoxicological significance since it can be used as a relative indicator of the tendency of an organic compound to be absorbed by living organisms.

The toxicity parameters LD_{50} and LC_{50} are defined as the lethal dose for 50 % of a test population and the lethal concentration (in an environmental matrix such as water) for 50 % of a test population respectively. In the case of LD50, data obtained from rats (*R. norvegicus*) were chosen as a well-established model organism to represent mammals. As for LC_{50}, fish and algae species were chosen as model organisms for determining toxicity in an aquatic environment.

The initial scoring step was based on the data found in the lists presented in Table 1 for both human and environmental hazards. All APIs were scored and ranked – see the complete database for individual endpoints.

2.6 Tier 2: Use of medicine in DK

The use amount is a parameter for understanding and quantifying potential exposure concentrations in the environment, and it was therefore selected as the second tier. The database used for this tier was the official Danish database for sales of medicines in registered pharmacies in 2021 operated by The Danish Health Data Authority[16]. We used statistics from 2021 as we considered that these data most accurately reflected the use of medicines in Denmark in 2022. However, there is no official statistic for 2021 for the sale of over the counter ("håndkøb") medicines by establishments that are not registered pharmacies. Another important factor for the tier is the measurement of amount or use of medicines in Denmark. The two most suitable options for calculations of the use were defined daily dose (DDD) or the number of persons using the medicine. DDD is the assumed average maintenance dose for a drug used by an adult person[17]. However, some groups of medications, such as antineoplastic agents, anaesthetics, and dermatological products, do not have DDDs. As some of the subcategories for the medications (D0, L01 and N01) were considered prioritised ATC groups (see Table 2), the use of DDDs

[16] https://www.esundhed.dk/Emner/Laegemidler/Apotekernes-salg-af-laegemidler
[17] https://www.who.int/tools/atc-ddd-toolkit/about-ddd

was therefore considered unsuitable for evaluating the use of medicines in Denmark.

Instead, the number of persons reportedly using a medicine on a quarterly basis, which were tallied together to constitute a year, was used to establish which medicines were consumed in Denmark in which amounts. The scores for use in Denmark are presented in Table 3.

Table 3. The scores for use in Denmark (persons/year) used in this study.

Use (persons/year)	Score
>200,000	3
100,000-199,999	2.5
50000-99999	2
20000-49999	1.5
10000-19999	1
5000-9999	0.5
1000-5000	0.3
<1000	0.1

2.7 Tier 3a Measured values - including risk

For Tier 3a, all APIs are investigated with a screening consisting of risk ratios constituting the ratio between measured concentrations and measured toxicity values in COWI (2021). Monitoring data are limited for APIs in the Danish environment. There are no systematic datasets for neither wastewater nor surface water in Denmark, however there is a multitude of data generated in various different contexts, mostly research projects. Examples of such datasets are the COWI report (2021) and the CWPharma 2 project[18].

To overcome this lack of data from Denmark, the third prioritisation step was based on the data sources for measured API exposure concentrations presented in Table 1.

Monitoring data were used to calculate risk characterisation ratios (RCR) between measured environmental concentration (MEC) and the predicted no-effect concentration (PNEC), taken from the ECOSAR list (Sanderson et al. 2003), according to Equation 1:

$$RCR = \frac{Measured\ Environmental\ Concentration\ (MEC)}{Predicted\ No{-}effect\ Concentration\ (PNEC)} \quad \text{Eq. 1}$$

In this analysis, we used the database from UBA where exposure was assessed based on the number of occurrences combined for all countries in the database. In total, the UBA database consists of 2,062 publications and contains 992 unique pharmaceutical substances in 61 matrices, of which 749 have been detected in Europe. In total, 242 of the entries registered in the UBA database as parent drugs were found on the curated list of 1024 APIs we worked with.

Moreover, the NORMAN Ecotoxicology Database for measured environmental concentrations contains 815 entries that NORMAN experts have agreed to

[18] https://projects.au.dk/waterpurification/cwpharma-2

use for prioritisation purposes. Most of the data represents freshwater concentrations. However, the database also contains measured data from sediments as well as biota including fish and molluscs. In total, 48 of the entries registered in the NORMAN Ecotoxicology Database[19] were found to be in our curated list of 1024 APIs. The scoring from 0-30 reflects the severity of the endpoint to the aquatic environmental impacts and risks.

The scores for risk of APIs with RCR based on measured environmental concentrations are shown in Table 4.

Table 4. The weighted scores for risk using measured environmental concentration (MEC/PNEC).

MEC/PNEC	Score
>1	30
0.8-0.999	10
<0.8	0

2.8 Tier 3b: Predicted values – including risk

Tier 3b addresses a scoring of a combined assessment of predicted toxicity values and risk ratios based on predicted environmental concentrations for all APIs when possible. The NORMAN Ecotoxicology Database lists the lowest predicted PNECs based on Quantitative Structure–Activity Relationship (QSAR) models (ECOSAR) that have been evaluated by experts. All the weighted scores for risk of APIs with PECs calculated from Eq. 2 are shown in Table 5. These aquatic toxicity data are also deemed more specifically relevant for the aquatic environment and is hence scored from 0-9.

$$RCR = \frac{Predicted\ Environmental\ Concentration\ (PEC)}{Predicted\ No{-}effect\ Concentration\ (PNEC)} \quad \text{Eq. 2}$$

Table 5. The weighted scores for risk using predicted environmental concentrations (PEC/PNEC).

PEC/PNEC	Score
>1	9
0.8-0.999	1.5
<0.8	0

2.9 Review of analytical methods

For the review of analytical methodologies, a systematic approach was followed to determine i) the availability of analytical methods for the prioritized APIs, ii) which type of instrumentation was used, iii) how the sample was injected (directly, after extraction or pre-concentration steps) and iv) which limits of detection (LODs) were achieved. First, we included the information from our own laboratory methods when available. Second, for the systematic approach the database Scopus was used in the week 49 and 50 of 2022, and week 9 of 2024, using the search details: TITLE-ABS-KEY (API AND "surface water") and TITLE-ABS-KEY (API AND "wastewater"), where API was substituted for the different prioritised compounds (both using name and CAS

[19] https://www.norman-network.com/nds/ecotox/

number). When no method was found with this search criteria, the search detail was expanded to TITLE-ABS-KEY (API AND "analytical method") and/or TITLE-ABS-KEY (API AND "LC-MS").

2.10 API removal in Wastewater Treatment Plants (WWTPs)

A brief overview of the effectiveness of current WWTP technology, as well as mature advanced treatment solutions for API removal is provided in the present report, based on the outcomes of the Project CW Pharma 2 [20].

[20] https://projects.au.dk/waterpurification/cwpharma-2

3 Results

By applying the three tiers (Figure 2), we can split the database in different ways. Of the 1024 APIs on the initial list and in the complete database, 733 could be considered hazardous for humans and/or the environment. Of these 733 APIs, 347 were in use by Danish patients in 2021. Of these 112 had measured aquatic environmental data and 210 had predicted environmental data. However, 25 APIs of the 347 compounds did not have any monitored or predicted environmental data. These were given a penalty score corresponding to 25 % (6.75) of the total possible score for Tier 3b.

The 347 APIs on the final list were divided into seven generic prioritisation groups based on their total score (see Table 6) to make the reference to relative score easier to distinguish. The APIs in the first groups are the ones with the highest priority for future monitoring campaigns. We further recommend that in particular the APIs where there currently are no Danish monitoring data are further prioritised, to obtain concentrations in effluent waters and surface waters for a better assessment of potential adverse effects.

Table 6. Grouping of APIs according to their total score, where group 1 is the most highly prioritized group.

Group	Total score
1	>100
2	>75
3	>60
4	>50
5	>20
6	>10
7	<10

3.1 Top-50 ranked APIs in Denmark

Table 7 displays the top-50 highest ranked APIs in Denmark for future prioritisation for monitoring in Danish surface waters. See Appendix 3 for all APIs from the initial list and their scoring.

The top-50 highest ranked APIs in Denmark have various therapeutical uses, such as antibiotics, treatment for high blood pressure, anticonvulsant agents, hormones, as well as several different types of antidepressant and anxiolytic medicines. Of the 50 top-scoring APIs, 64 % (n=35) have not previously been measured in Denmark.

The APIs metformin, clindamycin, miconazole, fipronil, clotrimazole and imazalil also appear on the EU Commission's fourth watch list of substances for EU-wide monitoring in the field of water policy (2022). The compounds on this watch list are selected because they are considered to pose a potential risk to the aquatic environment[21]. From Table 7, it can further be concluded that the most prevalent groups of APIs amongst the 50 top-scorers from the

[21] Commission Implementing Decision (EU) 2020/1161 of 4 August 2020 establishing a watch list of substances for Union-wide monitoring in the field of water policy pursuant to Directive 2008/105/EC of the European Parliament and of the Council.

prioritisation scheme are drugs to treat hypertension (high blood pressure) (16 %, n=8) and anticonvulsant medication (8 %, n=4).

3.1.1 Metformin

Metformin is usually recommended as the first-line choice of pharmaceutical to be used to treat type II diabetes by lowering the blood glucose levels. After ingestion, metformin is transported to the liver, where it inhibits mitochondrial metabolism and causes activation of an enzyme involved in the regulation of glucose metabolism[22]. More recent studies have also indicated that metformin affects intestinal cells and causes a reduced net glucose uptake[23]. Metformin does not undergo any metabolism in the liver and is excreted via the urine as an unchanged API. Metformin is one of the most commonly found drugs in aquatic environments[24]. It also affects the steroid production, and although the API does not have a hormone-like structure, it can affect the endocrine system in vertebrates, such as fish and other animals.

3.1.2 Clindamycin

Clindamycin is an antibiotic effective against anaerobic bacteria (either gram-positive or gram-negative). It affects bacterial protein biosynthesis by interaction with the bacterial ribosome[25]. The API is used to treat acne as well as bacterial vaginosis in non-pregnant women, and roughly 15 % of the API is excreted in its unchanged form. The remainder of the ingested clindamycin is excreted as inactive metabolites[26]. One of the major issues associated with antibiotics in the environment is antibiotics resistance, where the environmental exposure of antibiotics ultimately causes a reduction of the therapeutic effect in humans and animals by promoting the spread of bacterial antibiotic resistance genes[27].

3.1.3 Miconazole

Miconazole is used as an antifungal medication to treat diseases caused by dermatomyces (fungi naturally occurring on human skin). One of the main effects of miconazole is the inhibitory effect on the production of ergosterol, and thus it targets fungi-specific cell wall synthesis. The API is metabolised in

[22] Misra P, Chakrabarti R. The role of AMP kinase in diabetes. Indian J Med Res. 2007 Mar;125(3):389-98. PMID: 17496363.
[23] Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. Diabetologia. 2017 Sep;60(9):1577-1585. doi: 10.1007/s00125-017-4342-z. Epub 2017 Aug 3. PMID: 28776086; PMCID: PMC5552828.
[24] Eliane Papa Ambrosio-Albuquerque, Luis Fernando Cusioli, Rosângela Bergamasco, Adriana Aparecida Sinópolis Gigliolli, Luara Lupepsa, Brennda Ribeiro Paupitz, Pablo Américo Barbieri, Luciana Andreia Borin-Carvalho, Ana Luiza de Brito Portela-Castro, Metformin environmental exposure: A systematic review, Environmental Toxicology and Pharmacology,Volume 83, 2021, https://doi.org/10.1016/j.etap.2021.103588
[25] Spížek J, Řezanka T. Lincosamides: Chemical structure, biosynthesis, mechanism of action, resistance, and applications. Biochem Pharmacol. 2017 Jun 1;133:20-28. doi: 10.1016/j.bcp.2016.12.001. Epub 2016 Dec 7. PMID: 27940264.
[26] https://go.drugbank.com/drugs/DB01190
[27] Danner, M.-C., Robertson, A., Behrends, V., & Reiss, J. (2019). Antibiotic pollution in surface fresh waters: Occurrence and effects. Science of the Total Environment, 793-804.

the liver and does not result in any pharmaceutically active metabolites. Less than 1 % of the unchanged API is recovered in urine[28].

3.1.4 Treatment of hypertension (high blood pressure)

Medication for treatment of hypertension is highly prescribed and thus, these APIs are expected to be present in wastewater. There are several different mechanisms of actions, such as diuretics, angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blocker (ARB) and so-called beta-blockers. The use of pharmaceuticals to treat hypertension has nearly doubled in Western countries in the last two decades[29], and these APIs have been detected in hospital effluent as well as municipal wastewaters[30]. There is currently a large knowledge gap regarding the ecotoxicological effect of most pharmaceuticals used to treat hypertension, with the exception of beta-blockers. Beta-blockers such as the sartans losartan and irbesartan (see Table 7), interact with β-adrenergic receptors, and have been implicated to affect various physiological functions in animals, such as cardiovascular regulation, metabolism, and growth.

Bumetanide (see Table 7) is an example of a diuretic used to treat hypertension by decreasing the re-adsorption of sodium by the kidneys. Roughly half of the bumetanide is excreted through the urine as an unchanged pharmaceutical[31]. Examples of ACEI pharmaceuticals are lisinopril, enalapril and trandolapril that inhibit the enzyme angiotensin from increasing vascular resistance. A majority of the dose administered for these ACEI APIs are either excreted via urine as unchanged pharmaceuticals or active metabolites[32].

3.1.5 Anticonvulsant medication

Anticonvulsants are a diverse group of pharmaceuticals used to treat epileptic seizures. They are used increasingly in the treatment of mental disorders such as bipolar disorder and neuropathic pain. In recent years, the consumption of these APIs has increased globally[33]. These APIs are usually used to treat the symptoms of epilepsy and not the actual reason for the condition. Although the mechanism of action for carbamazepine, an important anticonvulsant (see Table 7), is not fully elucidated, the major hypothesis is that this API inhibits sodium channel activity in the post-synaptic neurons, causing a stabilization of neuron membranes and thus inhibit neuron signalling[34]. Carbamazepine is only partially metabolised in the liver, and over 70 % of the unchanged drug

[28] https://go.drugbank.com/drugs/DB01110
[29] OECD Health Statistics 2019, https//www.oecd-ilibrary.org/social-issues-migration- health/data/oecd-health–statistics health-data-en
[30] Kun Zhang, Yanbin Zhao, Karl Fent, Cardiovascular drugs and lipid regulating agents in surface waters at global scale: Occurrence, ecotoxicity and risk assessment, Science of The Total Environment. Volume 729,2020, https://doi.org/10.1016/j.scitotenv.2020.138770.
[31] https://go.drugbank.com/drugs/DB00887
[32] https://go.drugbank.com/drugs/DB00722
[33] Jesús Daniel Cardoso-Vera, Gustavo Axel Elizalde-Velázquez, Hariz Islas-Flores, Alejandro Mejía-García, José Mario Ortega-Olvera, Leobardo Manuel Gómez-Oliván, A review of antiepileptic drugs: Part 1 occurrence, fate in aquatic environments and removal during different treatment technologies, Science of The Total Environment, Volume 768, 2021, https://doi.org/10.1016/j.scitotenv.2021.145487.
[34] Ambrósio, A.F., Soares-da-Silva, P., Carvalho, C.M. *et al*. Mechanisms of Action of Carbamazepine and Its Derivatives, Oxcarbazepine, BIA 2-093, and BIA 2-024. *Neurochem Res* **27**, 121–130 (2002). https://doi.org/10.1023/A:1014814924965

can be recovered in urine[35]. It has been shown that conventional WWTPs are inefficient in their removal of carbamazepine[36]. Like carbamazepine, the mechanism of action for lamotrigine (see Table 7) is hypothesised to involve the inhibition of the sodium channel activity and the release of presynaptic excitatory neurotransmitters. Lamotrigine is excreted mainly via the urine, approximately as 10 % unchanged API and the rest as metabolites[37]. Conversely, pregabalin (see Table 7) is structurally similar to the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and is hypothesised to inhibit voltage-gated calcium channels. Pregabalin is almost exclusively excreted in the urine as an unchanged drug[38].

3.1.6 Fipronil

Is primarily used as an insecticide. Fipronil or, 5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(trifluoromethyl)sulfinyl]-1H-pyrazole-3-carbonitrile, is a member of the class of pyrazoles that is 1H-pyrazole that is substituted at positions 1, 3, 4, and 5 by 2,6-dichloro-4-(trifluoromethyl)phenyl, cyano, (trifluoromethyl)sulfinyl, and amino groups, respectively. It is a nitrile, a dichlorobenzene, a primary amino compound, a member of pyrazoles, a sulfoxide and a member of (trifluoromethyl)benzenes. Fipronil blocks the passage of chloride ions through the GABA-regulated chloride channel, disrupting CNS activity. (T10) Organic nitriles decompose into cyanide ions both in vivo and in vitro. Consequently the primary mechanism of toxicity for organic nitriles is their production of toxic cyanide ions or hydrogen cyanide. Cyanide is an inhibitor of cytochrome c oxidase in the fourth complex of the electron transport chain (found in the membrane of the mitochondria of eukaryotic cells)[39].

3.1.7 Clotrimazole

Clotrimazole is a member of the class of imidazoles that is 1H-imidazole in which the hydrogen attached to a nitrogen is replaced by a monochlorotrityl group. It has a role as an antiinfective agent. It is as mentioned a member of imidazoles, a member of monochlorobenzenes, a conazole antifungal drug and an imidazole antifungal drug. This drug is a broad spectrum antimycotic or antifungal agent. Clotrimazole's antimycotic properties were discovered in the late 1960s. Clotrimazole falls under the *imidazole* category of *azole* antifungals, possessing broad-spectrum antimycotic activity. The minimal side effect profile of this drug and its uncomplicated metabolic profile have led it to gain widespread acceptance for the treatment of mycotic outbreaks such as vaginal yeast infections as well as athlete's foot. It is a known environmental contaminant and a xenobiotic in part due to the high use[40].

[35] https://go.drugbank.com/drugs/DB00564
[36] Cristiano S. Leal, Daniela P. Mesquita, António Luís Amaral, Almerinda M. Amaral & Eugénio C. Ferreira (2020) Environmental impact and biological removal processes of pharmaceutically active compounds: The particular case of sulfonamides, anticonvulsants and steroid estrogens, Critical Reviews in Environmental Science and Technology, 50:7, 698-742, DOI: 10.1080/10643389.2019.1642831
[37] https://go.drugbank.com/drugs/DB00555
[38] https://go.drugbank.com/drugs/DB00230
[39] https://pubchem.ncbi.nlm.nih.gov/compound/Fipronil#section=FIFRA-Requirements
[40] https://pubchem.ncbi.nlm.nih.gov/compound/2812

3.1.8 Imazalil

Imazalil is a slightly yellow to brown solidified oil and is used as a fungicide. Imazalil is also known as Enilconazole (1-[2-(allyloxy)-2-(2,4-dichlorophenyl)ethyl]imidazole) and is a member of the class of imidazoles – and thus shares some of the properties as mentioned above for Clotrimazole. There is relatively sparse toxicological information about Imazalil[41].

[41] https://pubchem.ncbi.nlm.nih.gov/compound/37175

Table 7. Top 50 APIs in Denmark according to the prioritization in this project. APIs previously analysed in Denmark are indicated with blue background.

Preferred name	CAS Number	Therapeutic use	Comment – Therapeutic use	Total score	Prioritisation group	Previously analysed in DK?	On the 4. EU watch list
Metformin	657-24-9	Drugs used in diabetes	Antihyperglycemic (lowers blood sugar levels)	162,3	1	No	Yes
Estradiol	50-28-2	Sex hormones and modulators of the the genital system	Female steroid hormone	150,0	1	Yes	No
Trimethoprim	738-70-5	Antibacterials for systemic use	Antibiotic	144,6	1	Yes	Yes
Carbamazepine	298-46-4	Antiepileptics	Anticonvulsant medication	144,2	1	Yes	No
17-alpha-estradiol	57-63-6	Sex hormones and modulators of the the genital system	Female steroid hormone	132	1	Yes	No
Fipronil	12006837-3	Psycholeptics	CNS GABA-A inhibitor	130,5	1	No	Yes
Clindamycin	18323-44-9	Antibacterials for systemic use	Antibiotic	125,4	1	No	Yes
Miconazole	22916-47-8	Stomatological preparations	Antifungal	124,3	1	No	Yes
Imazalil	35554-44-0	Radiopharmaceuticals	Contrast	122,4	1	No	Yes
Citalopram	59729-33-8	Psychoanaleptics	Antidepressant	121,6	1	Yes	No
Clotrimazole	23593-75-1	Gynecological antiinfectives and antiseptics	Antifungal	114,8	1	No	Yes
Diclofenac	15307-86-5	Other dermatological preparations	Nonsteroidal anti-inflammatory drug (NSAID)	91,6	2	Yes	No
Amoxicillin	26787-78-0	Antibacterials for systemic use	Antibiotic	90,2	2	Yes	No
Warfarin	81-81-2	Antithrombotic agents	Anticoagulant (blood thinner)	81,4	2	Yes	No
Tiotropium bromide	136310-93-5	Drugs for obstructive airway diseases	Anti-asthmatic	80,6	2	No	No
Metoprolol	51384-51-1	Beta blocking agents	Treat high blood pressure (hypertension)	80,0	2	Yes	No
Diazepam	439-14-5	Psycholeptics	Benzodiazepine (anxiolytic)	79,6	2	No	No
Sertraline	79617-96-2	Psychoanaleptics	Anti-depressant (Selective serotonin reuptake inhibitor (SSRI))	79,4	2	Yes	No
Midazolam	59467-70-8	Psycholeptics	Benzodiazepine (anxiolytic)	78,0	2	No	No
Lisinopril	76547-98-3	Agents acting on the Renin-Angiotensin system	Treat high blood pressure (hypertension)	75,8	3	No	No
Propylthiouracil	51-52-5	Thyroid therapy	Tretment of hyperthyroidism	75,1	3	No	No

Carbidopa	28860-95-9	Antiepileptics	Used in treatment for Parkinson disease	74,0	3	No	No
Etoricoxib	202409-33-4	Psychoanaleptics	COX-2 selective inhibitor for treatment of pain	74,0	3	No	No
Moxonidine	75438-57-2	Antihypertensives	Treat high blood pressure (hypertension)	73,5	3	No	No
Risperidone	106266-06-2	Psycholeptics	Anti-psyhcotic	73,0	3	No	No
Oxycodone	76-42-6	Analgesics	Opiod	72,3	3	No	No
Misoprostol	59122-46-2	Drugs for acid related disorders	Also used to terminate pregnancies	72,1	3	No	No
Pregabalin	128013-69-4	Antiepileptics	Anticonvulsant medication	72,0	3	No	No
Lamotrigine	84057-84-1	Antiepileptics	Anticonvulsant medication	71,6	3	Yes	No
Bumetanide	28395-03-1	Diuretics	Treat high blood pressure (hypertension)	71,0	3	No	No
Zonisamide	68291-97-4	Antiepileptics	Anticonvulsant medication	70,6	3	No	No
Olsalazine	15722-48-2	Antidiarrheals	Used to treat inflammatory bowel disease (IBS)	70,1	3	No	No
Ibandronic acid	114084-78-5	Antithrombotic agents	Treatment of osteoporosis	70,1	3	No	No
Naproxen	22204-53-1	Gynaecological antiinfectives and antiseptics	Antifungal	69,9	3	Yes	No
Enalapril	75847-73-3	Agents acting on the Renin-Angiotensin system	Treat high blood pressure (hypertension)	68,8	3	Yes	No
Felodipine	72509-76-3	Calcium channel blockers	Treat high blood pressure (hypertension)	68,5	3	No	No
Desogestrel	54024-22-5	Sex hormones and modulators of the genital system	Female steroid hormone (synthetic)	68,1	3	No	No
Trandolapril	87679-37-6	Agents acting on the Renin-Angiotensin system	Treat high blood pressure (hypertension)	67,8	3	No	No
Anastrozole	120511-73-1	Endocrine therapy	Used to decrease estrogen levels (breast cancer)	67,6	3	No	No
Losartan	114798-26-4	Agents acting on the Renin-Angiotensin system	Treat high blood pressure (hypertension)	66,9	3	Yes	No
Atorvastatin	134523-00-5	Lipid modifying agents	Useed to lower lipid levels	66,5	3	No	No
Clioquinol	130-26-7	Antibacterials for systemic use	Antifungal	66,25	3	No	No
Budesonide	51333-22-3	Antidiarrheals	Anti-asthmatic	65,5	3	No	No
Mirtazapine	61337-67-5	Psychoanaleptics	Anti-depressant	65,1	3	No	No

Mycophenolate mofetil	128794-94-5	Immunosuppressants	Immunosuppressant (prevent the rejection of organs)	65,1	3	No	No
Levocabastine	79516-68-0	Calcium channel blockers	Antihistamine	63,8	3	No	No
Risedronic acid	105462-24-6	Drugs for treatment of bone diseases	Treatment of osteoporosis	63,8	3	No	No
Droperidol	548-73-2	Anti-depressants	Anti-psyhcotic	63,8	3	No	No
Salicylicacid	69-72-7	Painkiller	Nonsteroidal anti-inflammatory drug (NSAID)	63,4	3	Yes	No
Conestat alfa	80295-38-1	Blood forming organs	Hemotological agent	61,8	3	No	No

3.2 Total score for groups of APIs

In Figure 4, the total scores for the APIs within each ATC code group are presented. The ATC code group with the highest total score is the group of pharmaceuticals directed at the "Nervous system" including both anti-depressants such as the selective serotonin reuptake inhibitor (SSRI) citalopram, pharmaceuticals in the benzodiazepines (BZD) class, such as diazepam, and medicines for pain relief such as several different opioids (oxycodone, morphine and codeine). The second highest scoring group of APIs are pharmaceuticals used to treat illnesses regarding the cardiovascular system, such as the aforementioned pharmaceuticals used to treat hypertension. The ATC code with the highest combined score is also the one with the highest number of entries. In general, these total scores are strongly influenced by the number of entries for each ATC code.

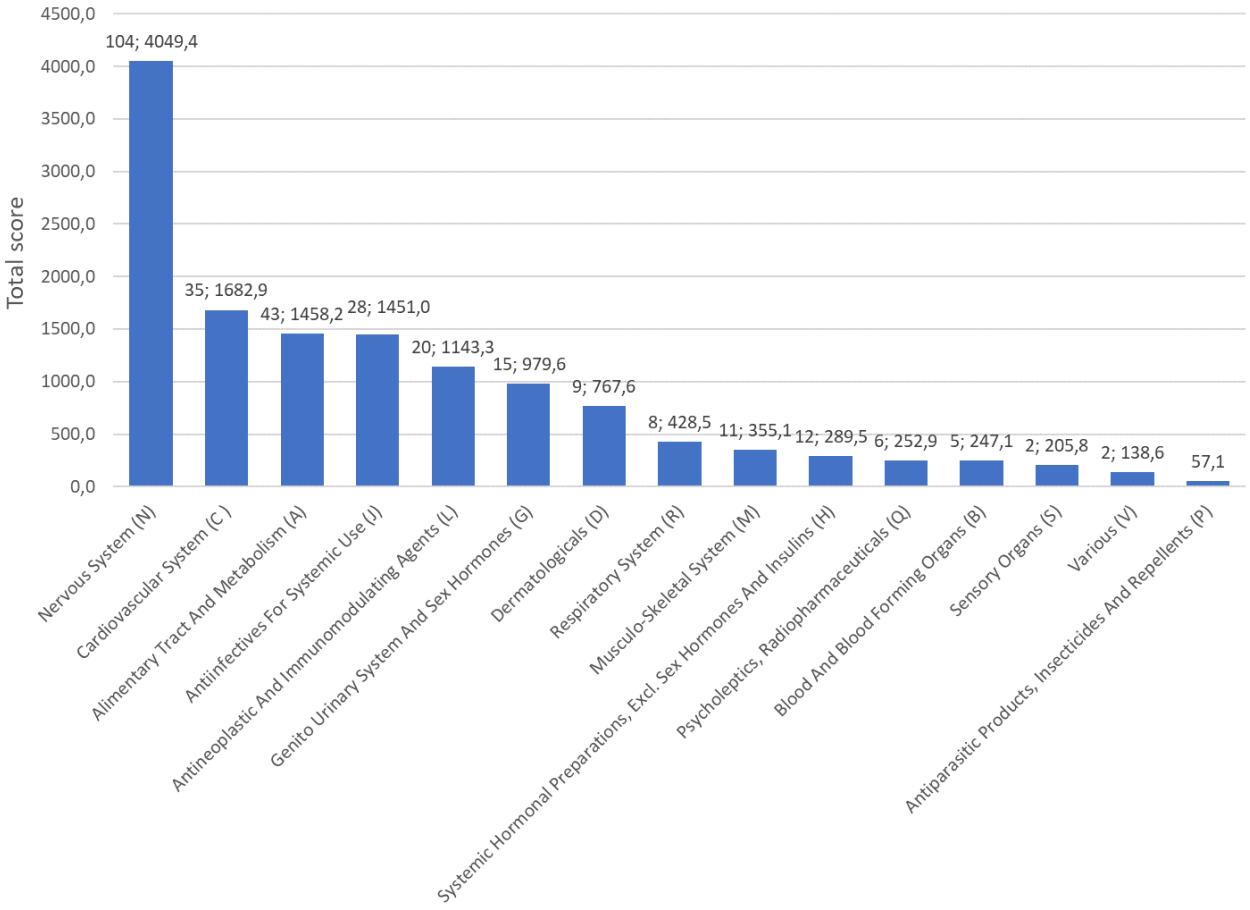

Figure 4. Total API group risk score – the number above the group is the number and APIs within each ATC group.

3.2.1 Nervous system -Selective serotonin reuptake inhibitors (SSRIs)

One of the groups of pharmaceuticals belonging to the "Nervous system" ATC code is the group of SSRIs. The primary mechanism of SSRI pharmaceuticals such as citalopram and sertraline (see Table 7) is to inhibit the presynaptic reuptake by the neurotransmitter serotonin at the serotonin transporter in the synaptic cleft between two neurons[42]. By inhibiting this reuptake, the

[42] Edinoff AN, Akuly HA, Hanna TA, Ochoa CO, Patti SJ, Ghaffar YA, Kaye AD, Viswanath O, Urits I, Boyer AG, Cornett EM, Kaye AM. Selective Serotonin Reuptake Inhibitors and Adverse Effects: A Narrative Review. Neurol Int. 2021 Aug 5;13(3):387-401. doi: 10.3390/neurolint13030038. PMID: 34449705; PMCID: PMC8395812

concentration of serotonin increases in the synaptic cleft. Serotonin is involved in various processes in the body, affecting mood, appetite, sleep, and cognitive actions such as memory and learning. These antidepressants are amongst the most prescribed pharmaceuticals globally and have previously been detected in various environmental media such as wastewater, surface water, groundwater and drinking water – see the UBA database. Moreover, SSRIs have been found in sediment and biota. In Denmark, citalopram and sertraline have previously been measured in water samples, see below in section on detections.

Due to the same mode of action for all these chemical compounds, a concentration addition model has been demonstrated for mixtures of SSRIs. SSRIs are potent compounds, and even low environmental concentrations have shown effects, indirectly affecting survival in non-target organisms such as algae and plants. SSRIs also bioaccumulated in fish. The effects on fish, molluscs, and other aquatic invertebrates after exposure to SSRIs include delays in physiological development, a decrease in aggressiveness, and inhibition of feeding responses[43,44].

3.2.2 Nervous system - Benzodiazepines (BZDs)

The BZDs such as diazepam and midazolam are also assigned to the "Nervous system" ATC code. These APIs act as central nervous system (CNS) depressants and are primarily used to treat anxiety but can also be used to treat other types of disorders such as seizures and alcohol withdrawal syndromes. BZDs as a pharmaceutical group act to increase signalling from the GABA-A receptor in the CNS. The GABA neurotransmitter is one of the most common neurotransmitters in the CNS and functions as an inhibitor to reduce the signal strength of CNS stimulants[45]. Furthermore, BZDs are hydrophobic compounds and can persist in organic carbon-rich environmental media such as sludge and sediment for prolonged periods of times. It has been shown that exposure to high aquatic concentrations of BZDs alters critical behaviours in wild fish, such as prolonging the appropriate response to predator attacking[46]. Neither diazepam nor midazolam have previously been analysed in Danish environmental monitoring campaigns.

3.2.3 Nervous system - Opioids

Another large group of pharmaceuticals assigned to the "Nervous system" ATC code are the opioids oxycodone (see Table 7), morphine, and codeine,

[43] Peter P. Fong, Alex T. Ford, The biological effects of antidepressants on the molluscs and crustaceans: A review,
Aquatic Toxicology, Volume 151, 2014, Pages 4-13, https://doi.org/10.1016/j.aquatox.2013.12.003.

[44] Demeestere, K., Petrović, M., Gros, M. *et al.* Trace analysis of antidepressants in environmental waters by molecularly imprinted polymer-based solid-phase extraction followed by ultra-performance liquid chromatography coupled to triple quadrupole mass spectrometry. *Anal Bioanal Chem* **396**, 825–837 (2010). https://doi.org/10.1007/s00216-009-3270-2

[45] Griffin CE 3rd, Kaye AM, Bueno FR, Kaye AD. Benzodiazepine pharmacology and central nervous system-mediated effects. Ochsner J. 2013 Summer;13(2):214-23. PMID: 23789008; PMCID: PMC3684331.

[46] Brodin, T., Nordling, J., Lagesson, A., Klaminder, J., Hellström, G., Christensen, B. & Fick, J. (2017) Environmental relevant levels of a benzodiazepine (oxazepam) alters important behavioral traits in a common planktivorous fish, (*Rutilus rutilus*), Journal of Toxicology and Environmental Health, Part A, 80:16-18, 963-970, DOI: 10.1080/15287394.2017.1352214

used for the treatment of acute and chronic pain. Moreover, there is also a non-negligible illicit use of opioids for recreational purposes in most countries. There are different types of opioids, naturally derived, semi-synthetic, and synthetic ones[47]. Opioids bind to opioid receptors, mainly located in the CNS, the peripheral nervous system as well as the gastro-intestinal tract. Several different opioids have been measured in treated wastewater due to incomplete removal, however it has been pointed out that the current monitoring methods are not covering metabolites and transformation products, which limits the understanding of the environmental fate and possible transformation of these compounds[37]. Neither oxycodone, morphine nor codeine have previously been included in Danish environmental monitoring campaigns.

3.2.4 Cardiovascular system

Cardiovascular system APIs are highly prescribed and used in Denmark compounds with lipid-lowering APIs such as statins. Statins have been shown to being able to interact with chlorophyll development pathways in the duckweed (*Lemna gibba*) and have herbicidal effects in plants as the synthesis pathways in the initial phases are shared with the synthesis of cholostrol in humans as intended with the API (Brain et al. 2006)[48]. Carbamazapine is another important and persistent API in this category which has been found frequently in surface waters across the world for decades (Clara et al 2004)[49] and also found in Danish waters[50] (see Figure 7).

3.2.5 Anti-infectives for systemic use

Figure 4 also shows that the third highest scoring group of APIs is "Anti-infectives for systemic use", or antibiotics. One of the major problems associated with the release of antibiotics in the environment is antibiotics resistance, meaning that the environmental exposure of antibiotics ultimately causes a reduction of the therapeutic effect in humans and animals by promoting the spread of bacterial antibiotic resistance genes[51].

This group contains pharmaceuticals such as clindamycin, trimethoprim and amoxicillin. Compounds in this group represent a range of mechanisms of action such as inhibiting the bacterial DNA synthesis (trimethroprim) or the

[47] Campos-Mañas, M.C., Ferrer, I., Thurman, E.M. & Agüera, A. (2018). Opioid occurrence in environmental water samples—A review, Trends in Environmental Analytical Chemistry, Volume 20, 2018. https://doi.org/10.1016/j.teac.2018.e00059

[48] Richard A. Brain, Tamara S. Reitsma, Linda I. Lissemore, Ketut (Jim) Bestari, Paul K. Sibley, and Keith R. Solomon. Herbicidal Effects of Statin Pharmaceuticals in *Lemna gibba*. *Environmental Science & Technology* 2006 *40* (16), 5116-5123 DOI: 10.1021/es0600274

[49] Clara M, Strenn B, Kreuzinger N. Carbamazepine as a possible anthropogenic marker in the aquatic environment: investigations on the behaviour of Carbamazepine in wastewater treatment and during groundwater infiltration. Water Res. 2004 Feb;38(4):947-54. doi: 10.1016/j.watres.2003.10.058. PMID: 14769414.

[50] Kilpinen K, Devers J, Castro M, Tisler S, Jørgensen MB, Mortensen P, Christensen JH. Catchment area, fate, and environmental risks investigation of micropollutants in Danish wastewater. Environ Sci Pollut Res Int. 2023 Dec;30(57):121107-121123. doi: 10.1007/s11356-023-30331-z. Epub 2023 Nov 10. PMID: 37950122; PMCID: PMC10698095.

[51] Danner, M.-C., Robertson, A., Behrends, V. & Reiss, J. (2019). Antibiotic pollution in surface fresh waters: Occurrence and effects. Science of the Total Environment, 793-804.

cell wall synthesis (amoxicillin), whereas others, such as clarithromycin, inhibit the bacterial protein synthesis. Trimethroprim is mainly used to treat urinary and respiratory tract infections and is primarily metabolised in the liver. Roughly half of an ingested dose of trimethroprim is excreted via the urine as an unchanged API[52]. Amoxicillin has been used as medicine since the early 1970s and is a well-established treatment against pneumonia, skin infections, streptococcal sore throat, and urinary tract infections. In particular, this antibiotic is effective against infections caused by gram-negative bacteria. Furthermore, the mode of action for amoxicillin is the inhibition of enzymes (penicillin-binding protein 1 and other high molecular weight penicillin binding proteins) involved in the cell wall synthesis via glycosyltransferase and transpeptidase reactions[53].

3.2.6 Antineoplastic and immunomodulating agents

There are several different types of drugs used in chemotherapy with various modes of action. These APIs have in common that they are cytotoxic, meaning that at cellular level, they induce cell death (apoptosis) and/or inhibit cellular growth[54]. Due to this cytotoxic property, as well as an increased use due to a rising cancer incidence, antineoplastic pharmaceuticals have been predicted over the last decade to become one of the emerging chemical classes in ecotoxicology[55]. Yet, even after more than a decade, data on the occurrence of antineoplastics in the aquatic environment and their toxicity to aquatic wildlife are still relatively sparse in comparison with other pharmaceuticals such as antidepressants like SSRIs[56]

The alkylators and alkylator-related agents will bind to macromolecular structures within the cell, typically DNA, and inhibit normal functions during cell division which will trigger apoptosis. Moreover, there are a few drugs on the market that affect cells from the outside, by either breaking down amino acids necessary for tumour growth or by increasing disruptions of the cell membrane. One of the largest groups of antineoplastic pharmaceuticals is the group of antimetabolites. These are structurally similar to essential components for the cell, and by replacing these key molecules in critical processes such as DNA replication or RNA synthesis, they trigger apoptosis. For instance, methotrexate is one of these antimetabolites. Approximately 80 % of the methotrexate administered is excreted unchanged via the urine[57]. Other antineoplastic pharmaceuticals, such as anastrozole used for the treatment of certain types of breast cancer, will inhibit cell signalling. Approximately one tenth of the anastrosole administered is excreted unchanged via the urine. Methotrexate and anastrozole have not previously been analysed in environmental samples in Denmark.

[52] https://go.drugbank.com/drugs/DB00440
[53] https://go.drugbank.com/drugs/DB01060
[54] Peter Nygren (2001) What is cancer chemotherapy?, Acta Oncologica, 40:2-3, 166-174, DOI: 10.1080/02841860151116204
[55] Johnson, A.C., Jürgens, M.D., Williams, R.J., Kümmerer, K., Kortenkamp, A. & Sumpter, J.P. 2008. Do cytotoxic chemotherapy drugs discharged into rivers pose a risk to the environment and human health? An overview and UK case study. J Hydrol 348:167–175.
[56] Wormington, A.M., De María, M., Kurita, H.G., Bisesi, J.H., Jr, Denslow, N.D. and Martyniuk, C.J. (2020), Antineoplastic Agents: Environmental Prevalence and Adverse Outcomes in Aquatic Organisms. Environ Toxicol Chem, 39: 967-985. https://doi.org/10.1002/etc.4687
[57] https://go.drugbank.com/drugs/DB00563

3.2.7 Genito urinary system and sex hormones - Female sex hormones

In general, hormones are biologically very potent compounds, and exposure to even minute environmental concentration might be sufficient to trigger adverse effects such as disruptions in hormone synthesis in aquatic animals. In particular, research interest in the environmental fate as well as the effect on ecosystems of steroid estrogens (SE) has been increasing steadily in recent years[58]. The second highest scoring API in the prioritisation scheme is estradiol (E2), and 17-alpha-estradiol is the fifth highest, both are naturally occurring estrogen steroid hormone (estrogen receptor agonist), classified as the major female sex hormone. The main pharmaceutical use of E2 is to treat symptoms associated with the female menopause, such as decreased muscle mass, osteoporosis and vaginal atrophy and dryness.

Other APIs in this ATC group include misoprostol (see Table 7), mainly used to terminate pregnancies, and the synthetic progestin desogestrel, used together with E2 in combination birth control pills. Roughly 70 % of the administered misoprostol is recovered unchanged in the urine[59]. Desogestrel, however, is exclusively eliminated through its metabolites[60].

3.3 Average scores for ATC groups and top-five APIs within each ATC group

There are different ways to analyse the data to focus on the categories and individual APIs of elevated concern. Figure 5 shows the average risk scores for APIs within each ATC group, the error bars indicate the standard deviation.

[58] Xiaomin Zhao, Kassandra L. Grimes, Lisa M. Colosi, Wu-Seng Lung, Attenuation, transport, and management of estrogens: A review, Chemosphere, Volume 230, 2019, Pages 462-478, https://doi.org/10.1016/j.chemosphere.2019.05.086.
[59] https://go.drugbank.com/drugs/DB00929
[60] https://go.drugbank.com/drugs/DB00304

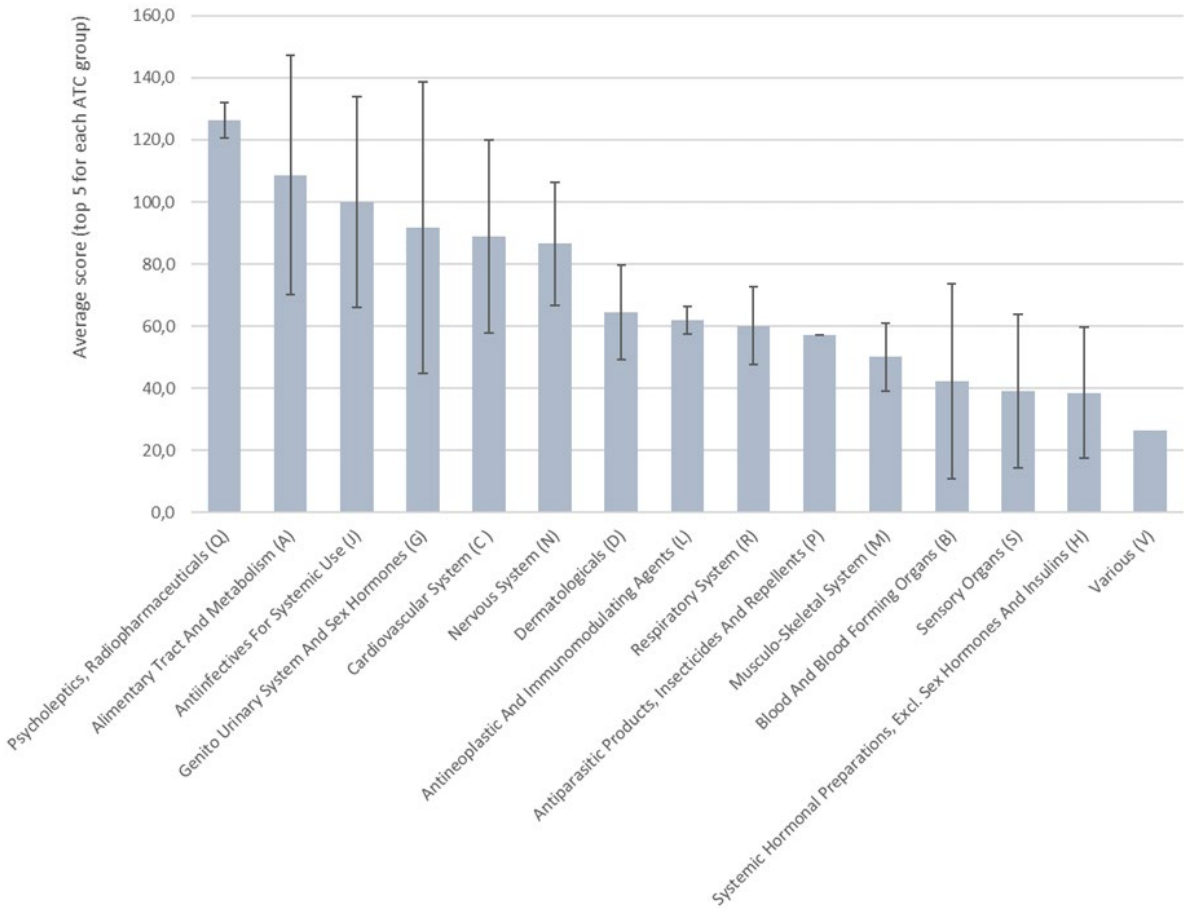

Figure 5. Average risk scores within each ATC group (+/- SD).

Figure 6 shows the risk score of the top five APIs within the top five ATC groups from Figure 5.

"Psycholeptics, radiopharmaceuticals", "Alimentary tract and metabolism", "Antiinfectants for systemic use", "Genito urinary system and sex hormones", "Cardiovacsular system", "Nervous system". "Psycholeptics, radiopharmaceuticals" consists of fipronil and imazalil, and Figure 6 shows the risk score of the top five APIs within the other five ATC classes.

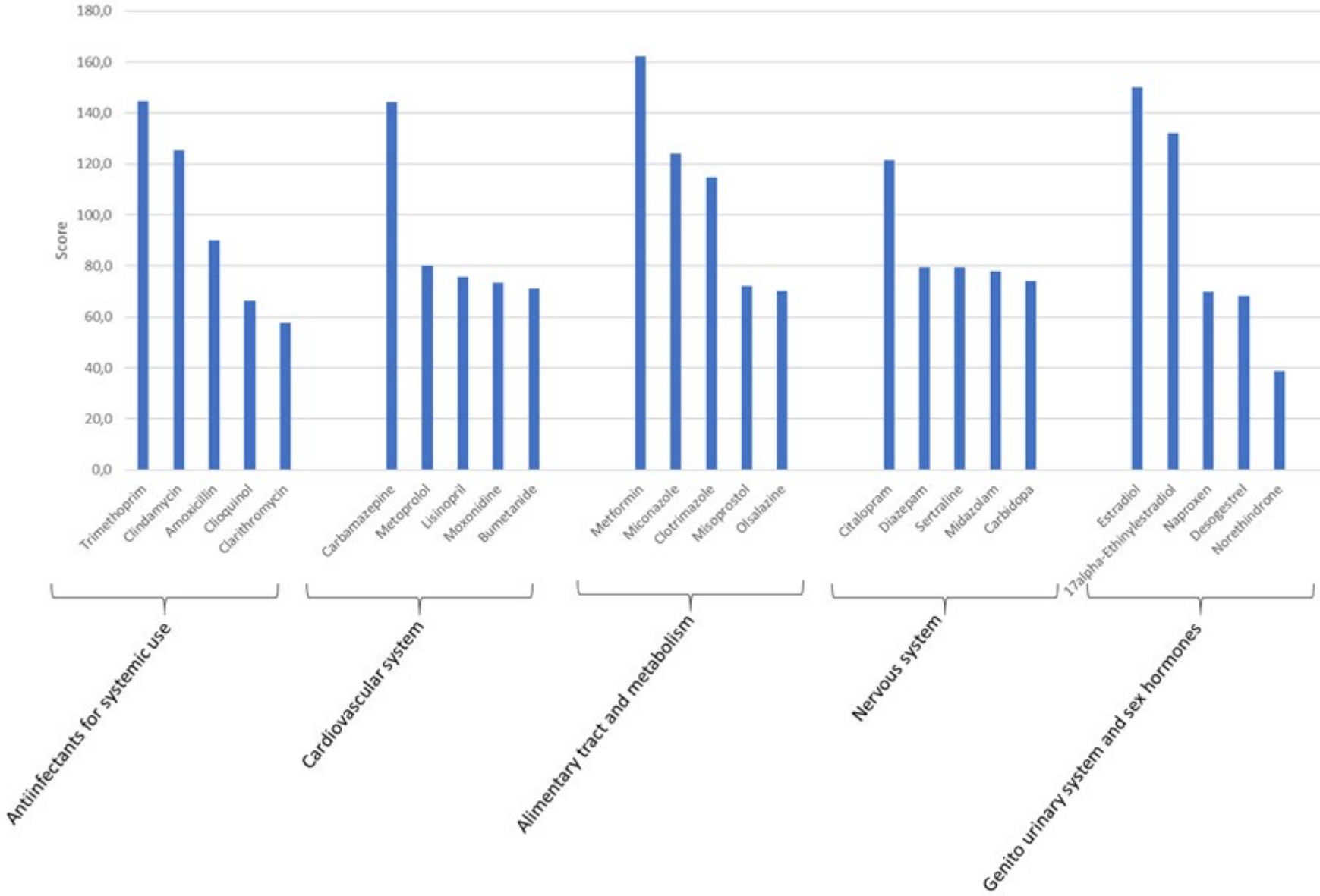

Figure 6. Scores for the top five highest scoring APIs within each ATC code.

Monitoring data are critically scarce for Danish surface waters, as also shown in the COWI report of 2021[61]. The COWI report of surface waters mainly includes data from a Norwegian screening campaign and a wide assessment of pharmaceuticals in the aquatic environment of the Baltic Sea region, where a few sampling points seem to be in Danish Waters. Data in Danish reports or databases[62],[63],[64] for APIs is scarce. A few more data are available for Danish wastewater effluents. The most concise dataset on Danish effluents was created in the project "CW Pharma 2"[65] containing data on 36 APIs (Figure 7). A few (7) of these APIs overlap with the 50 priority APIs identified in this study (Table 7), but it still denotes the lack of broader monitoring data for Danish waters.

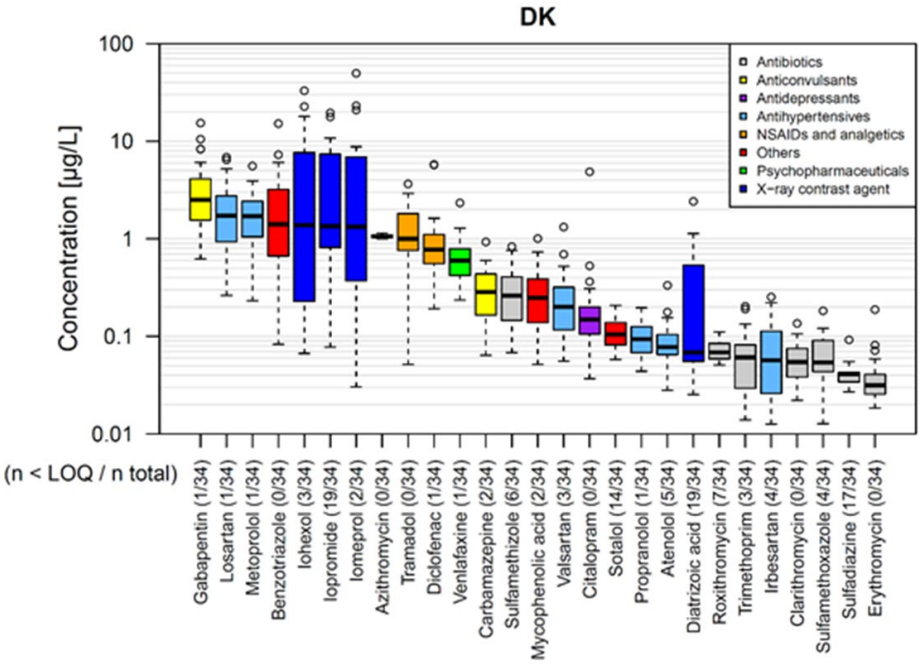

Figure 7. Pharmaceutical (plus benzotriazole) concentrations in wastewater effluent from 34 Danish WWTPs. Pharmaceuticals that were below LOQ in all samples are not shown (Data from CWPharma 2 as published in Stapf et al., 2021)[66].

The lack of monitoring data raised the question whether the problem could be a lack of analytical tools. To verify this, a literature review on available analytical methods was performed covering the prioritised APIs listed in Table 7. The outcomes are presented in the following section.

[61] COWI, 2021: Medicinrester i spildevand og vandmiljø. COWI, Maj 2021 – A212451
[62] Naturstyrelsen. 2015. Punktkilder 2014. Miljø- og Fødevareministeriet, Naturstyrelsen.
[63] Naturstyrelsen, 2015. NOVANA-screeningsundersøgelse for humane lægemidler i vandmiljøet. Miljøministeriet, Naturstyrelsen.
[64] Mogensen, B., Bossi, R., Kjær, J., Juhler, R. & Boutrup, S. 2007. Lægemidler og triclosan i punktkilder og vandmiljøet. Faglig rapport fra DMU nr. 638, 2007.
[65] https://projects.au.dk/waterpurification/cwpharma-2
[66] Stapf, M., Zhiteneva, V., Saoudi, R., Miehe, U., Kharel, S., Bester, K., Kuokkanen, A., Bogusz, A., Trzcińska, M., Lember, E., Muulmann, M., Putna-Nīmane, I., Liepina, I., Thisgaard, P., Melchiorsen, L.R. & Brauner, T. 2021: WWTP fitness check for API removal technology – CW Pharma 2, summary report, 2021.

3.4 Analytical chemical methods

Measuring pharmaceuticals in the environment usually includes extraction, clean-up and pre-concentration steps prior to the determination by high-performance liquid chromatography (HPLC) or gas chromatography (GC), typically combined with mass spectrometry (MS). Due to the polar nature of pharmaceuticals, HPLC has been the preferred technique. In terms of detectors, tandem mass spectrometry (MS/MS) is commonly used due to the higher specificity and sensitivity compared to single quadrupole MS. The following sections describe how pharmaceuticals and specific APIs are typically analysed, and discusses the advantages and disadvantages of using passive sampling, suspect screening and non-target screening approaches for these types of compounds.

3.4.1 General remarks

For most pharmaceuticals the concentrations in the wastewater-related environment (e.g. primary recipients) are relatively high (10 to 1000 ng/L) and pharmaceuticals, including those prioritised in Table 7, can be measured relatively easily using HPLC-MS/MS with a moderate or no preconcentration step. One example is diclofenac (EU Environmental Quality Standard EQS 100 ng/L) for which current analytical instruments achieve the sensitivity required to detect this compound at the concentrations required for reporting under the European Water Framework Directive (WFD)[67]. However, some APIs are currently connected with very low PNECs (<< 1 ng/L) which will require method optimization before relevant environmental monitoring is possible for these compounds. Typically, the partitioning of pharmaceuticals to organic materials (K_{ow}) is very low to moderate ($\log K_{ow}$ ranges from –1 to 4) which makes it difficult to pre-concentrate a larger fraction of the pharmaceuticals. This requires dedicated solid phase extraction (SPE) methods. For specific methods on specific families of compounds or prioritised APIs see below.

3.4.2 Estrogenic compounds such as ethinyl estradiol

PEC values for estrogenic compounds such as ethinyl estradiol (EE) are extremely low (pg/L) while current instrumental limits of quantifications for these compounds are in the range of µg/L in either GC-MS or HPLC-MS/MS approaches. As PNECs are also in the pg/L range extreme sensitivity is needed to monitor these compounds at effect levels. Thus, pre-concentration of up to a factor of 1000000 is needed to monitor EE in surface waters[68]. Passive sampling can concentrate these compounds by a factor of up to 1000 or 10000, but it thus cannot solve the problem entirely. Moreover, the obstacle to use passive sampling for the monitoring of estrogens is that these analytes are known to be adsorbed to particles ($\log K_{ow}$ 3 to 4), while passive sampling

[67] Tiedeken, E.J., Tahar, A., McHugh, B. & Rowan, N.J. 2017: Monitoring, sources, receptors, and control measures for three European Union watch list substances of emerging concern in receiving waters – A 20 year systematic review. *Science of The Total Environment*, *574*, 1140–1163. https://doi.org/10.1016/J.SCITOTENV.2016.09.084

[68] Tiedeken, E.J., Tahar, A., McHugh, B., & Rowan, N.J. 2017: Monitoring, sources, receptors, and control measures for three European Union watch list substances of emerging concern in receiving waters – A 20 year systematic review. *Science of The Total Environment*, *574*, 1140–1163. https://doi.org/10.1016/J.SCITOTENV.2016.09.084

measures the freely dissolved fraction only[69]. As discussed with several European agencies the only way to monitor ethinyl estradiol in surface waters is to mount a centrifuge and a high-volume solid phase extraction device on a truck to extract 1-10 m^3 of water[70]. This solid phase needs then to be extracted with, e.g., 100 mL solvent that can successively undergo a dedicated clean-up and condensation procedure for final analysis by HPLC-MS/MS. Such approaches are established for the monitoring of organic pollutants in the marine environment[71], but less common for surface waters. Bioassays can measure hormonal activity, but do not provide information on the identity of the compound. However, this approach also requires vigorous pre-concentration, by a factor of up to 10000 - 100000[72]. Overall, although methods are available for estrogenic compounds, there is a need to optimize sensitivity to enable monitoring at PNEC level.

3.4.3 Transformation products (metabolites)

Even though many transformation products from human metabolism are known, the bacterial metabolism occurring in the WWTPs is less well known. Therefore, knowledge of transformation products and metabolites is needed to be able to monitor environmental pollution due to pharmaceuticals. If the identity of these compounds is not known, methods cannot be optimized to include them. Transformation products can be predicted in-silico, but often reactions in the environment do not follow the models. Therefore, dedicated laboratory experiments for assessing the formation of transformation products are needed, usually involving high-resolution mass spectrometry (HRMS), followed by dedicated mass balance experiments in WWTPs as demonstrated by Li et al. (2023)[73]. There is a need for elucidating the environmentally relevant transformation products for every given API, as each compound can generate several transformation products, some of which might also retain the activity/effect of the API. Furthermore, there is a need to ecotoxicologically assess the transformation products – their concentrations are often in the same range as the respective parent compounds.

3.4.4 Prioritised APIs

The prioritised APIs in Table 7 include compounds which are commonly analysed and several which are analysed less frequently. The literature review of state-of-the-art methods to measure APIs in water matrices is summarized in Table 8. Where methods for analysis in water were not available, other matrices, e.g., human samples or biota, were included. For elucidating how useful the existing methods are, published LODs were also collected together with existing PNECs for freshwater.

[69] Caban, M., Lis, H. & Stepnowski, P. 2021: Limitations of Integrative Passive Samplers as a Tool for the Quantification of Pharmaceuticals in the Environment – A Critical Review with the Latest Innovations.
Https://Doi.Org/10.1080/10408347.2021.1881755, *52*(6), 1386–1407.
https://doi.org/10.1080/10408347.2021.1881755
[70] Bester, K. & Schluesener, M., Personal communication, 2021.
[71] https://doi.org/10.1016/S0021-9673(01)00529-5
[72] DOI: 10.1002/etc.11 https://doi.org/10.1016/j.ecoenv.2020.111574
[73] https://doi.org/10.1016/j.watres.2022.119352

Table 8. Overview of current state-of-the-art methods to measure the 50 prioritized APIs in water samples in alphabetical order, n.f. = Not found, n.r. = Not reported, DI stands for direct injection.

Name of API	CAS Number	Known analytical methods for (surface) water samples	Lowest PNEC Freshwater (ng/L)	Published LODs (ng/L)	Other known methods	References
Metformin	657-24-9	DI-HPLC-MS/MS	10000	9		(1)
Estradiol	50-28-2	SPE-GC-MS (4), SPE-UHPLC-MS/MS (5)	0.1	0.01 (2), 0.8 (3)		(2, 3)
Trimethoprim	738-70-5	DI-HPLC-MS/MS	91.4	0.9 (1), 3 (4),		(1, 4)
Carbamazepine	298-46-4	DI-HPLC-MS/MS	50	0.7 (1), 8 (4),		(1, 4)
17-alpha-estradiol	57-63-6	SPE-GC-MS (2), SPE-UHPLC-MS/MS (3)	0.035	0.01 ng/L (2), 1.4 ng/L (3)		(2, 3)
Fipronil	12006837-3	SPE-LC-MS/MS	19	0.1		(5)
Clindamycin	18323-44-9	DI-HPLC-MS/MS, SPE-UHPLC-qToF-MS/MS	44	4 (4), 12.7 (6		(1,6)
Miconazole	22916-47-8	DI-HPLC-MS/MS	200	4		(1)
Imazalil	35554-44-0	SPE-LC-MS/MS	870	0.5		(7)
Citalopram	59729-33-8	DI-HPLC-MS/MS	16000	0.8 (1), 17 (4),		(1, 4)
Clotrimazole	23593-75-1	SPE-UHPLC-MS-MS	30	1		(8)
Diclofenac	15307-86-5	DI-HPLC-MS/MS	50	7		(4)
Amoxicillin	26787-78-0	DI-HPLC-MS/MS	78	9		(9)
Warfarin	81-81-2	SPE-UHPLC-MS/MS	500	1.1		(10)
Tiotropium bromide	136310-93-5	SPE-HPLC-MS/MS	2620	30		(11)
Metoprolol	51384-51-1	DI-HPLC-MS/MS, SPE-UHPLC-MS/MS	7300	7 (1), 0.4 (10)		(1, 10)
Diazepam	439-14-5	DI-HPLC-MS/MS	291	0.8		(1)
Sertraline	79617-96-2	DI-HPLC-MS/MS	91.4	13		(1)
Midazolam	59467-70-8	SPE-UHPLC-qToF-MS/MS	200	10		(6)
Lisinopril	76547-98-3	SPE-UHPLC-MS/MS	100000	12		(10)
Propylthiouracil	51-52-5		3400		LC-MS/MS method for milk samples	(12)
Carbidopa	28860-95-9		19500		LC-MS/MS methods for human samples	(13)
Etoricoxib	202409-33-4	SPE-UHPLC-MS/MS	75000	5		(14)
Moxonidine	75438-57-2	SPE- UHPLC-qToF-MS/MS	1790	n.r.		(15)
Risperidone	106266-06-2	SPE-HPLC-MS/MS	380	5		(16)

Oxycodone	76-42-6	SPE-UHPLC-qToF-MS/MS	8040	310		(6)
Misoprostol	59122-46-2		1280		LC-MS/MS meth-ods for human samples	(17)
Pregabalin	128013-69-4	DI-HPLC-MS/MS	n.f.	11		(1)
Lamotrigine	84057-84-1	SPE-UHPLC-qToF-MS/MS	5450	125		(6)
Bumetanide	28395-03-1	SPE-UPLC-MS/MS	57700	0.1		(18)
Zonisamide	68291-97-4		1000000		LC-MS/MS method for human plasma	(19)
Olsalazine	15722-48-2		600		LC-UV method for human samples	(20)
Ibandronic acid	114084-78-5		14400		LC-MS/MS method for urine and plasma with derivatization	(21)
Naproxen	22204-53-1	DI-HPLC-MS/MS (5), SPE-LC-MS/MS (9)	1700	18 (1), 0.08 (12)		(1, 22)
Enalapril	75847-73-3	SPE-UHPLC-MS/MS	1580	0.3 (6), 1 (7)		(10, 11)
Felodipine	72509-76-3	SPE-HPLC-MS/MS	2000	50		(23)
Desogestrel	54024-22-5	SPE-HPLC-MS/MS	1840	23.9		(24)
Trandolapril	87679-37-6		240		LC-MS/MS method for rat plasma	(25)
Anastrozole	120511-73-1	SPE- LC-(HR)MS/MS	1000	150		(26)
Losartan	114798-26-4	DI-HPLC-MS/MS	1.5	13		(4)
Atorvastatin	134523-00-5	SPE-LC-MS/MS	130	0.6		(22)
Clioquinol	130-26-7		360	n.f.	n.f.	
Budesonide	51333-22-3	SPE-UHPLC-MS/MS	56000	0.17		(27)
Mirtazapine	61337-67-5	SPE-UHPLC-qToF-MS/MS	1000	2.36		(6)
Mycophenolate mofetil	128794-94-5	SPE-LC-MS/MS	2230	0.13		(28)
Levocabastine	79516-68-0		170		LC-MS/MS method for fresh-water invertebrate	(29)
Risedronic acid	105462-24-6		17800		LC-MS/MS method for urine and plasma with derivatization	(21)
Droperidol	548-73-2		67		LC-HRMS method for plasma	(30)
Salicylic acid	69-72-7	SPE-UHPLC-qToF-MS/MS, SPE-LC-MS/MS	8	131 (6), 4 (12)		(6, 12)
Conestat alfa	80295-38-1		n.f.	n.f.	n.f.	

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Table 8 shows that 38 of the 50 prioritized APIs has been measured in waters, 10 APIs have not been analysed in waters but methods are available for other matrices, while no methodological reference was found for 2 APIs. The majority of the existing methods for the prioritized APIs used LC-MS/MS technology. A GC-MS based method was identified for estradiol and other hormones. The most recent publications also used LC-HRMS instrumentation for both non-target analysis and quantification of selected compounds. For several compounds, direct injection (DI) can achieve LODs in the range of ng/L compatible with current PNECs. For the majority of the other compounds, SPE (mostly offline, but online-SPE is common as well and can be fully automatized with the LC-MS analysis) has been the pre-concentration step of choice. Only losartan has a reported LOD above the PNEC for a direct injection method, but the difference is a factor of 10. This means that the use of SPE instead of direct injection can overcome it. For the 10 componds for which no methods for waters were found, all can be analysed by LC-MS/MS in complex human sample matrices. Thus, it is expected that they can be easly analysed in water by LC-MS/MS. The exception will be ibandronic acid and risedronic acid, for which existing LC-MS/MS methods require derivatization.

3.4.5 Accredited analysis of APIs in water

In Denmark, accredited methods are only available for two compounds in water, estradiol (E2) and salicylic acid. For approximately half of the identified APIs, accredited laboratories exist in Denmark, but these are forensic and food/veterinary laboratories, and they are not accredited for analysis of APIs in water. It is, however, expected that environmental laboratories will have non-accredited methods for some of the compounds but not all.

3.4.6 Passive sampling and other sampling methods for monitoring APIs

Passive sampling allows for integrating sampling over time and pre-concentrations on site and without pumps. The passive sampling devices are in contact with the water for a defined time and absorb the compounds through diffusion processes. The sorbing phase is extracted with organic solvents, which can be analysed, by e.g., HPLC-MS/MS or GC-MS. The advantage of this approach is that time integrated sampling is possible without costly 24 h composite sampling equipment (active pumps and control units) and that it can work without power supply in the field. Further, as the compounds accumulate in the passive sampler, low water concentrations can be elevated. However, to achieve quantitative data, compound-specific uptake rates and partition coefficients need to be known, which are further influenced by environmental factors. The respective combination of sorption materials and geometry of sampler needs to be calibrated under representative environmental conditions, including a relevant water phase (as partitioning from wastewater with a high fraction of organic material will be different to partitioning from pure water). The sorption material should match the physical-chemical properties of the compounds to ensure efficient uptake. Great progress has been made over the past few decades in the field of passive sampling of nonpolar

organic compounds (log K_{ow} > 4) in the aquatic environment[74]. However, passive sampling measures the dissolved phase concentration of a contaminant (and not the whole water concentration, as required by the EU WFD). Thus, passive sampling cannot be used currently to assess compliance with EQS for the organic contaminants under the WFD, but only for moderately polar to polar organic compounds (with log Log Kow < 5) where the concentration in the water column is not dominated by the fraction adsorbed to colloids and particles in water[75]. Nevertheless, passive sampling is recommended in the European Commission Guidance Document on surface water chemical monitoring and in the Directive 2013/39/EU as a complementary method to improve the quality of the assessment and as a resource saving measure. Passive sampling of very polar compounds, including some pharmaceuticals, is a field of ongoing research[76] and currently only allows semi-quantitative measurements.

In conclusion, passive samplers can be used to detect pharmaceuticals present at quite low concentrations, but it will not be suitable for precise quantification. Another possibility for high volume sampling of water is *in situ* SPE by which a large amount of water is pumped through an SPE column at the sampling location, which might be attractive for determining natural and synthetic hormones, as described above. The challenge of this sampling method is that particulate organic material will be collected at the inlet of the SPE column, which can clog the column. A pre-filter will therefore be necessary. Further, the use of a pump can also be a challenge in the field. It will be necessary to use different types of SPE columns in order to cover the range of compounds. There are several commercial SPE solutions that can handle up to 3-5 litres. The sampling method is more costly and complex than direct injection but can lower the limits of quantification.

3.4.7 Suspect screening and non-target analysis

Applying targeted analytical methods will only detect the targeted substances. Hence, other APIs or transformation products potentially present in the sample are not discovered. Holistic non-target analysis (NTA) uses advanced HRMS to identify unknown chemicals in a sample without a predefined list of molecular targets (Gravert 2021 & Nanusha 2022, https://doi.org/10.1021/acs.est.7b02184). In suspect screening studies, the generated HRMS data are searched against a predefined list of chemical substances. There is a clear difference between NTA and suspect screening studies, however the term NTA is generally used for both approaches (Sobus

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2018). NTA is in its infancy and learning from e.g. metabolomic disciplines, and is now gaining traction across disciplines such as in food safety evaluations. It has a large potential for effective evaluation of water quality (Hollender 2019). Today, HRMS platforms hyphenated with e.g. liquid or ion chromatography (LC-HRMS or IC-HRMS), typically capture tens of thousands of molecular entities from a broad chemical space (log D -10 to 10) most relevant for the aquatic environment using NTA workflows (Hansen 2021, Frøkjær 2021, Hansen 2022, Nanusha 2022). We recently validated a novel NTA concept for water samples and demonstrated that Danish groundwater, drinking water, river water and rainwater contained thousands of chemical entities — many of these APIs (Frøkjær 2021). Most recent developments have been directed at increasing sensitivity of NTA platforms and using computational methods for semi-quantification of unknown substances with reasonable uncertainties (Liigand, 2020, Nanusha, 2022, Hansen, 2023). The concept was recently applied to 32 surface water samples in Denmark and confirmed the presence of 34 APIs in the aquatic environment (Figure 8).

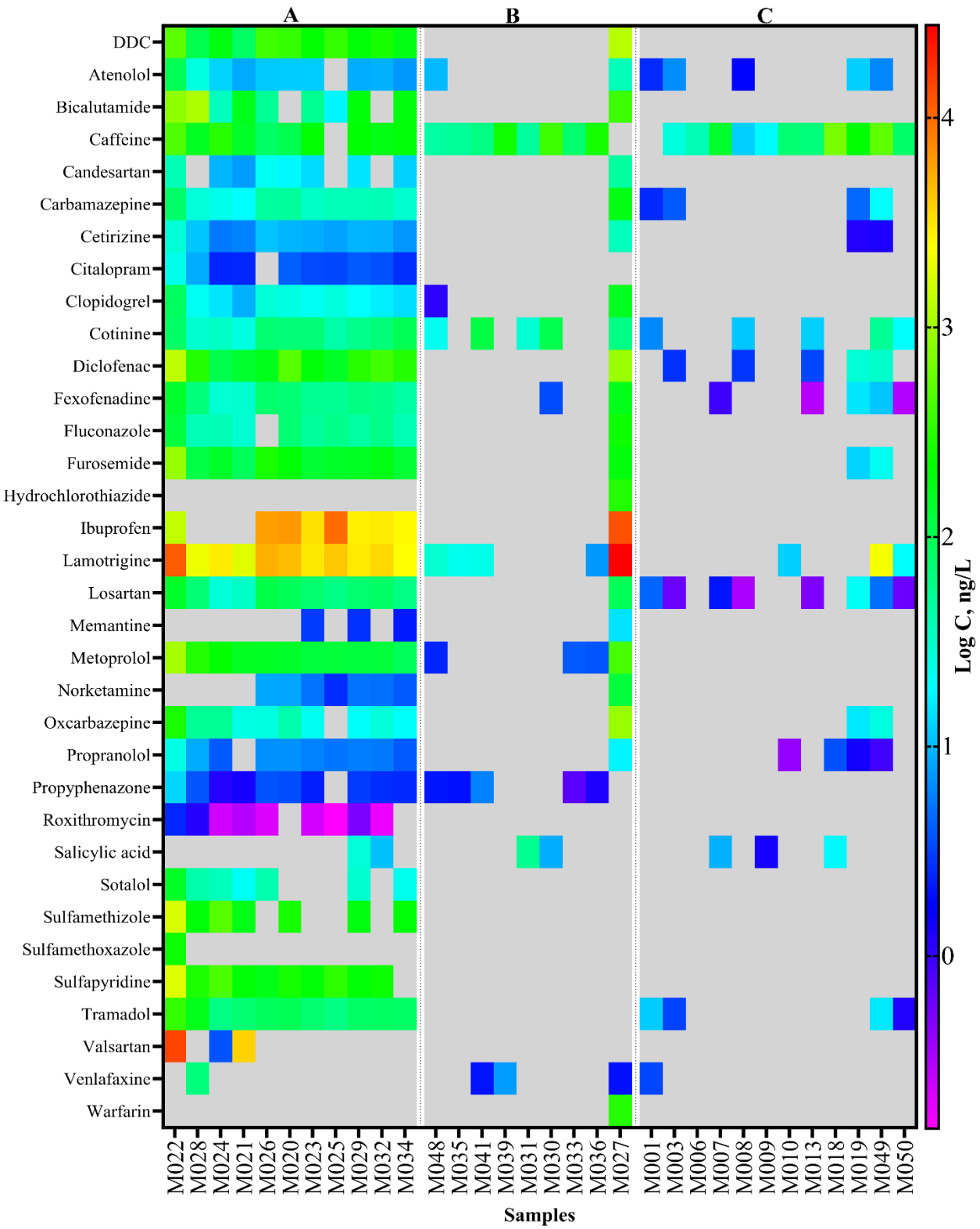

Figure 8. Heatmap (modified from Nanusha et al. 2022) displaying the concentration (Log C, ng/L) of pharmaceuticals in surface water from three locations in Denmark; Faxe (A), Ringsted (B), and Jutland (C). (Abbreviation: DDC – 10,11-Dihydro-10,11-dihydroxycarbamazepine).

NTA also provides the means for retrospective analysis to discover previously uncharacterized molecular entities in the data. We recently demonstrated opportunities for retrospective analysis by reanalysing NTA data from Danish surface waters for per- and polyfluoroalkyl substances (PFAS) and chemical

components used in car tyre production and discovered substances such as 6-PPD-quinone and 6:2 fluorinated telomer sulfonate (Hansen 2023).

Collectively, NTA will be able to capture a snapshot of the presence of environmentally relevant compounds potentially affecting water quality status, including APIs. Based on ongoing developments of semi-quantitative approaches, NTA may also provide measured environmental concentrations (MECs) of known and unknown chemicals, including APIs, in the future, while target analyses currently provide the most accurate and precise data. NTA, in particular suspect screening, will be a suitable approach to study the presence of the 50 prioritized APIs in the Danish environment. However, it needs to be mentioned, that NTA tends to have higher limits of detection than target/quantitative methods, mostly due to the differences in the type of mass spectrometer being used.

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Hollender et al. High resolution mass spectrometry-based Non-target screening can support regulatory environmental monitoring and chemicals management. Environ. Sci. Eur. 31, (2019).

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3.5 Screening program

The APIs in the present report are in general expected to come from point sources, in particular WWTPs, and not from diffuse sources. However, these exist as well e.g. in areas with poor coverage of wastewater infrastructure. In some cases, hospitals might have higher concentrations of pharmaceuticals and their metabolites in their effluent compared to urban sources in general. However, most pharmaceuticals used in Denmark are consumed in private

homes. Hospital loads have been found to contribute up to 10 %[77,78], a small contribution to the overall pharmaceutical load of wastewater treatment plants. However, this varies from country to country and from substance to substance and is not the case when a drug's use is primarily hospital based. As there are no or only few diffuse sources of the present APIs, only streams which receive water from WWTPs are expected to be at risk of being affected by pharmaceuticals and their metabolites.

The following parameters should be considered in relation to designing a screening program for the selected APIs for freshwater, for example under the NOVANA monitoring program.

Relevant sampling sites could be:

- Wastewater treatment plants that receive effluent from a hospital (inlet and outlet)
- Wastewater treatment plant in a larger city (inlet and outlet)
- Freshwater streams that receive treated wastewater in dense population areas (larger city), upstream and downstream of WWTP
- Freshwater streams that receive treated wastewater in smaller population areas (small city), upstream and downstream of WWTP
- Streams which do not receive wastewater, neither treated nor untreated (background data)

Some of the sampling sites could be combined in the sampling design.

Most larger cities in Denmark are placed close to the sea or fjords so the majority of the larger wastewater treatment plants lead the treated wastewater to the sea instead of local streams. The area around Silkeborg could be a possibility as a case for a larger city with a hospital based on previous findings. However, if possible, sampling sites should be distributed in Jutland, Funen and Zealand to include the geographical perspective.

It is expected, that the consumed amounts of pharmaceuticals are relatively constant during the year, possibly with a slightly higher consumption during the winter season. As rain will dilute contaminants in the water for combined sewer systems, both for fresh water and wastewater, it could be relevant to have both a sampling campaign in the summer (dry season) and in the winter/autumn (wet season).

These suggestions only focus on human APIs. There is no doubt that veterinarian drugs from agricultural activities can also affect fresh waters and likely from more diverse sources. Screening for veterinarian drugs might require a different sampling strategy. However, this is outside the scope of the present study.

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[78] Ulvi, A., Aydın, S. & Aydın, M.E. 2022: Fate of selected pharmaceuticals in hospital and municipal wastewater effluent: occurrence, removal, and environmental risk assessment. Environ Sci Pollut Res Int. 2022 Oct; 29(50):75609-75625. doi: 10.1007/s11356-022-21131-y. Epub 2022 Jun 3. PMID: 35655023; PMCID: PMC9162898.

3.6 Behaviour of APIs in wastewater treatment plants

Conventional WWTPs have never been designed to treat/remove APIs. In the Danish context, their function by design is to control the emission of organic carbon and nutrients. This means that research in the field of wastewater and APIs has addressed 1) how current conventional WWTP cope with the APIs and 2) the development of dedicated advanced treatment processes to specifically remove APIs.

Conventional wastewater treatment: Even though specific APIs such as ibuprofen can be removed quantitatively in conventional activated sludge (by forming metabolites), usually near to no removal is observed for several other APIs (e.g. carbamazine). Some are actually (re-)formed especially those that are excreted by humans as conjugates (e.g. acetylation of sulfonamide antibiotics), which are usually not determined. Thus, it is quite common, that, e.g. higher quantities of sulfonamides are found in the effluents of WWTPs than in the influents.

Advanced wastewater treatment with ozone: Generally speaking, ozone can remove more than 80 % of the pharmaceuticals in the wastewater. However, removal by ozone is a reaction, which leads to transformation products (e.g. Kharel et al., 2020[79], 2021[80] and 2022[81]). This is a promising procedure for compounds where the (adverse) effect is closely related to structure (such as estrogenic compounds) but less effective for compounds where this is not given. Our group at AU has conducted several projects in this field[82].

Advanced wastewater treatment with granulated activated carbon (GAC): Generally speaking, GAC can remove more than 80 % of the pharmaceuticals in wastewater. However, the capacities of GAC depend on the water quality, and if not carefully checked for each compound, single compounds might break through rapidly[83].

Combined ozone-GAC: The scientific literature agrees that the combination of ozonation and GAC is able to remove all tested compounds very efficiently. However, although this approach is currently the only effective one that is readily available, it demands significant energy usage and will in the long run (>20 years) not be the most sustainable possible way.

[79] https://doi.org/10.1016/j.scitotenv.2020.139064
[80] https://doi.org/10.1016/j.scitotenv.2020.143989
[81] https://doi.org/10.1016/j.scitotenv.2022.157259
[82] https://projects.au.dk/fileadmin/www.waterpurification.au.dk/CWPharma_2/CWPharma2_FitnessCheckSummary_final_accepted.pdf
[83] https://projects.au.dk/fileadmin/www.waterpurification.au.dk/20220704_O2_3_post_clarifications_final.pdf

This is in line with the current proposal for the Directive of the European Parliament and of the Council concerning urban wastewater treatment (recast), proposing a minimum of 80 % removal for a list of indicator substances of organic micropollutants including APIs. The list of indicator substances in this proposal contains 12 compounds, including carbamazepine, diclofenac, metoprolol and irbesartan which are among the top scored APIs in the current study. However, one of the key issues to be discussed in the future might be how many other compounds/APIs should be included. In summary, mature technology exists to reach the proposed targets. However, the long-term sustainability of the proposed advanced treatment systems as well as the concerns with transformation products will need further research.

4 Conclusions

The aim of this report was to provide a semi-quantitative relative risk ranking of all prescription APIs to humans in use in Denmark – this is provided in the figures and the appendices of the report. The report is not only a ranking of APIs relative to specific aquatic risk expressed as ecotoxicty evaluation in PEC/PNEC assessments – but also includes other aspects such as ATC class and human toxicity, e.g. carcinogenicity. The compound-specific aquatic risk evaluation should use e.g. the EQS or PNEC value of the API and the measured or predicted environmental concentration – however, for many APIs the data coverage is limited (e.g. the highest ranked metformin on the EU watch list has not been measured in Danish waters yet). Five other compounds on the EU watch list (clindamycin, miconazole, fipronil, clotrimazole and imazalil) have also not yet been measured in Danish waters – hence these might be of concern in Danish waters and should be included in future monitoring.

The results of this study agree with the overall conclusions of the COWI report that pointed towards 13 APIs of potential aquatic concern including sex hormones, antibiotics, antineoplastics and SSRIs. The imi-premier[84] EU project prioritized 15 APIs (diflunisal, disulfiram, dosulepin, eprosartan, felbinac, flecainide, melperone, mesalazine, nevirapine, orphenadrine, prazosin, repaglinide, sulfasalazine, sulpiride and trimebutine). The present report expands the analysis to include also compounds that had not been widely considered previously. The major conclusions of the present work, considering both the prioritization exercise, and the review of analytical tools and wastewater treatment technology entail the following 13 recommendations:

1. A data gap that needs to be further explored to properly assess the exposure of APIs which are known environmental contaminants such as diclofenac is the quantity of medicines bought over the counter. We assume that the sale of medicines containing this API is severely understated by using only data from sale at pharmacies. We used the Danish Medicines Agency databases as the primary data source to assess the use and occurrence in Denmark. However, the Danish National Health Authority also has a database on sales and use[85], which is based on data from Statistics Denmark[86]. One would think that Statistics Denmark retrieve their data from the Medicines Agency – however, we found that compounds such as Iopromide and Sulfamethoxazole – which have been found in Danish waters but are not reported in the Medicines Agency database in 2021 and they are hence not prioritized in this report. Some APIs may be sold in combination with another API, e.g. Sulfamethoxazole with Trimetoprim (SAD) – this combination does however also not appear in the database Medicinpriser.dk. Hence, assurance of the use of Sulfamethoxazole is important in evaluation of APIs in Denmark. Assurance of the complete databases also including over the counter drugs sales and veterinary APIs is needed to improve the prioritization.

[84] https://imi-premier.eu/prioritization-and-selection-of-apis-using-a-risk-based-approach/
[85] https://medstat.dk/en
[86] https://www.dst.dk/en/

2. Of the 50 top-scoring APIs, 32 (64 %) have not previously been measured in Danish waters, at least not included in reports. There are five ATC classes of potential higher concern than others: "Antiinfectants for systemic use", "Alimentary tract and metabolism", "Cardiovascular system", "Nervous system", "Genito urinary system and sex hormones". Several of the top scorers in these classes have not been included in Danish monitoring campaigns. There is hence a need for a monitoring plan that should include surface waters and WWTP effluents to characterize the releases of potentially problematic APIs. Specifically, our recommendation is that metformin, miconazole, clindamycin, fipronil, clotrimazole and imazalil (Section 3.1) are considered in future monitoring campaigns as they have been included in the EU Commission's watch list. These APIs are used in Denmark and can thus be potentially released to the environment. Another factor that needs further consideration is the excretion of the unchanged drug or potentially ecotoxic metabolites. Moreover, some of the top-scoring pharmaceuticals, such as treatments for hypertension and anticonvulsant medicines, are used to treat chronic diseases or symptoms meaning that any increase in use could cause an increase in environmental concentrations as patients will use these pharmaceuticals for an extended time period.
3. One group of pharmaceuticals with an increased use over the last decades and with large knowledge gaps in terms of ecotoxicity, are APIs used to treat hypertension (elevated blood pressure). A significant portion of these compounds is usually eliminated in their unchanged form via the urine, and it is therefore recommended that these compounds are included in future studies regarding their toxicity in aquatic environments. Like pharmaceuticals used to treat hypertension, the use of anticonvulsion medication is increasing and there are currently very few studies regarding the ecotoxicity of the APIs carbamazepine, lamotrigine and pregabalin. For several of these pharmaceuticals, a large proportion is excreted unchanged via the urine, and in the case of carbamazepine, WWTPs are inefficient in their removal of this pharmaceutical.
4. Occurrence data of highly toxic antineoplastics in the aquatic environment as well as knowledge of their environmental toxicity[87] are still relatively sparse in comparison with other pharmaceuticals such as the antidepressants SSRIs[88]. We know that these compounds are highly pharmacodynamic and thus also often toxic, based on their use and mode of action. As there is an increase of antineoplastic use globally, their potential adverse effects on the environment need further investigation. Since neither of the highly scoring and highly toxic antineoplastics (methotrexate and anastrozole) has previously been analysed in Denmark, these should be prioritized in future monitoring campaigns.
5. SSRIs are potent compounds, and even low environmental concentrations have been shown to indirectly affect survival in non-target organisms such as algae and plants. SSRIs, such as citalopram and sertraline, should therefore also be prioritized in considering future monitoring campaigns.

[87] Sanderson, H., Brain, R.A., Johnson, D.J., Wilson, C.J. & Solomon, K.R. 2004: Toxicity classification and evaluation of four pharmaceuticals classes: antibiotics, antineoplastics, cardiovascular, and sex hormones, Toxicology, Volume 203, Issues 1–3, 2004, Pages 27-40, ISSN 0300-483X, https://doi.org/10.1016/j.tox.2004.05.015

[88] Wormington, A.M., De María, M., Kurita, H.G., Bisesi, J.H., Jr, Denslow, N.D. & Martyniuk, C.J. 2020: Antineoplastic Agents: Environmental Prevalence and Adverse Outcomes in Aquatic Organisms. Environ Toxicol Chem, 39: 967-985. https://doi.org/10.1002/etc.4687

6. Benzodiazepines (BZDs) are hydrophobic compounds that can persist in wastewater effluents, as well as sediment for prolonged times. It has been shown that exposure to high aquatic concentrations of BZDs alters critical behaviours in wild fish, such as prolonging the appropriate response to predators. BZDs, such as diazepam and midazolam, should be considered prioritized in future monitoring campaigns.
7. Furthermore, some of the opioid metabolites or transformation products may have pronounced ecotoxicity. None of the opioids listed in this report have previously been reported as included in previous Danish monitoring campaigns, thus e.g. opioids could be considered in future monitoring campaigns.
8. The lack of monitoring data for the top 50 prioritized compounds is not due to a lack of analytical methods. The available methods to monitor most of the API classes in surface waters (and WWTPs) can, for the majority, deliver LODs in line with the respective PNECs. There are a few compounds, such as estrogenic compounds, for which improvements in terms of pre-concentration steps specifically targeting surface waters are needed.
9. Passive sampling could be useful for screening purposes, but currently only allows semi-quantitative concentrations of APIs.
10. It is recommended to prioritise monitoring in streams which receive water from wastewater treatment plants, as diffuse sources of APIs are expected to play a minor role in terms of loadings to the environment. Relevant sampling sites could be WWTPs (with or without hospital input), freshwater streams (with or without input or WWTPs and streams which do not receive wastewater (background data). Here, WWTP dimensions should include small and large cities and be aligned with the proposal for the Directive of the European Parliament and of the Council concerning urban wastewater treatment and the proposal to implement quaternary wastewater treatment for plants over 100,000 PE/10,000 PE.
11. Removal of APIs in wastewater treatment has only been studied for a limited number of APIs. Nevertheless, the current EU proposal for the new directive to include quaternary treatment specifically focused on organic micropollutants includes 12 of the APIs currently prioritized as indicator compounds. Research efforts should be placed in assessing the indicator list to ensure that those with the highest human and environmental risk are included. Some APIs have EQS values that should be used to assess the specific risk they may represent as well as evaluating the feasibility of the analytical method applied. Among the top-10 APIs identified in this report #2 estradiol has an EQS = 0.1 ng/L and #7 diclofenac EQS = 0.04 µg/L.
12. The lack of information on API metabolites in wastewater influent and effluent is a major obstacle in more comprehensive monitoring efforts. Research efforts are needed to identify and characterise human metabolites and transformation products. In addition, receptor driven toxicity data are limited for many parent APIs and nearly all transformation products.
13. Future work could also involve medical professionals, such as pharmacists and doctors, to investigate safe substitutions for some of the APIs with the highest score, with the same mode of action but with a lower environmental risk, to follow the principles of green chemistry for APIs[89] and the Chemicals Strategy of Sustainability.

This report is a semi-quantitative risk ranking of all prescription APIs to humans in Denmark, with the aim to support the prioritization of APIs to focus

[89] Kar, S., Sanderson, H., Roy, K., Benfenati, E. & Leszczynski, J. 2022: Green Chemistry in the Synthesis of Pharmaceuticals. *Chemical Reviews* 2022 *122* (3), 3637-3710 DOI: 10.1021/acs.chemrev.1c00631

further analysis and assessment. Given the many data gaps, additional data may need to be collected to assess aquatic risks, and existing PEC/MEC as well as PNEC values may have to be qualified and substantiated. The work focussed on the human APIs – it does not include veterinary APIs, over-the-counter (OTC) pharmaceuticals, pharmaceutical additives, vitamins, metals, herbal medicines, mixtures (UVCBs) or metabolites of APIs. Inclusion of these materials would strengthen the overall assessment, but it would require additional research efforts. It would be relevant to include these in subsequent assessments in particular highly used OTC drugs such as Paracetamol as well as veterinary APIs.

Appendixes

Appendix 1 Curated list of all prescription human APIs sold in Denmark (2021)

Preferred name	CAS registration number	ATC code
Metformin	657-24-9	A10BA02, A10BD23, A10BD02 ,A10BD18 ,A10BD11 ,A10BD25 ,A10BD22 ,A10BD14 ,A10BD16 ,A10BD17 ,A10BD05 ,A10BD15 ,A10BD07 ,A10BD10 ,A10BD13 ,A10BD20 ,A10BD08 ,A10BD03 ,
Estradiol	50-28-2	G03CA03
Trimethoprim	738-70-5	J01EA01, QJ51EA01
Carbamazepine	298-46-4	C09AA01
Fipronil	120068-37-3	QP53AX15
17alpha-Ethinylestradiol	57-63-6	G03CA01, L02AA03
Clindamycin	18323-44-9	J01FA09
Miconazole	22916-47-8	A01AB09, A07AC01, D01AC02 ,G01AF04 ,J02AB01 ,S02AA13
Imazalil	35554-44-0	QD01AC90
Citalopram	59729-33-8	N07CA02
Clotrimazole	23593-75-1	A01AB18
Diclofenac	15307-86-5	D11AX18
Amoxicillin	26787-78-0	J01CA04, QG51AA03 ,
Warfarin	81-81-2	B01AA03, QB01AA03
Tiotropiumbromide	136310-93-5	R03BB04
Metoprolol	51384-51-1	C07AB02
Diazepam	439-14-5	N05BA01
Sertraline	79617-96-2	N06AB06
Midazolam	59467-70-8	N05CD08
Carbidopa	28860-95-9	N03AF01
Etoricoxib	202409-33-4	N06AB10
Moxonidine	75438-57-2	C02AC05
Ketoconazole	65277-42-1	J02AB02
Risperidone	106266-06-2	N05AX08
Oxycodone	76-42-6	N02AA05, N02AA55, N02AJ18 ,N02AJ19 ,N02AA56 ,N02AJ17
Misoprostol	59122-46-2	A02BB01, G02AD06
Pregabalin	128013-69-4	N03AX16
Lamotrigine	84057-84-1	N03AX09
Bumetanide	28395-03-1	C03CA02
Zonisamide	68291-97-4	N03AX15
Lisinopril	76547-98-3	C09AA03, C09BA03 ,C10BX07 ,C09BB03 ,
Olsalazine	15722-48-2	A07EC03
Ibandronicacid	114084-78-5	B01AB01, C05BA03, S01XA14 ,
Naproxen	22204-53-1	G02CC02, M01AE02 ,M02AA12 ,M01AE56 ,M01AE52
Propylthiouracil	51-52-5	H03BA02
Enalapril	75847-73-3	C09AA02
Desogestrel	54024-22-5	G03XX01
Trandolapril	87679-37-6	C09AA10

Anastrozole	120511-73-1	L02BG03
Losartan	114798-26-4	C09CA01
Atorvastatin	134523-00-5	C10AA05
Budesonide	51333-22-3	A07EA06
Mirtazapine	61337-67-5	N06AX11
Mycophenolatemofetil	128794-94-5	L04AA06
Levocabastine	79516-68-0	C08CA09
Risedronicacid	105462-24-6	M05BA07
Salicylicacid	69-72-7	A01AD05, B01AC06, D01AE12 ,N02BA01 ,S01BC08
Acitretin	55079-83-9	D05BB02
Atenolol	29122-68-7	C07AB03
Busulfan	55-98-1	L01AB01
Clioquinol	130-26-7	J01FA09
Felodipine	72509-76-3	C08CA02
Methylphenidate	113-45-1	N06BA04
Latanoprost	130209-82-4	D11AX22, P02CF01, QP54AA01 ,QS02QA03 ,
Irbesartan	138402-11-6	C09CA04, C09DA04,
Oxcarbazepine	28721-07-5	N03AF02
Riluzole	1744-22-5	N07XX02
Baclofen	1134-47-0	M03BX01
Fulvestrant	129453-61-8	LO2BA03
Omeprazole	73590-58-6	A02BC01
Droperidol	548-73-2	N06DA02
Sumatriptan	103628-46-2	N02CC01
Buprenorphine	52485-79-7	N01BB01
Clarithromycin	81103-11-9	J01FA09
Travoprost	157283-68-6	S01EE04
Montelukast	158966-92-8	R03DC03
Tetrabenazine	58-46-8	N07XX06
Mebendazole	31431-39-7	P02CA01, QP52AC09
Mometasone	105102-22-5	D07AC13, R01AD09 ,R03BA07
Sirolimus	53123-88-9	L04AA10, S01XA23
Conestat alfa	80295-38-1	R05DA04, Combinations: N02AA59 , N02AA79 , N02AJ08 , N02AJ06 , N02AJ07
Nepafenac	78281-72-8	S01BC10
Morphine	57-27-2	N02AA01
Methotrexate	59-05-2	L01BA01, L04AX03
Rotigotine	99755-59-6	N04BC09
Rotigotine	92206-54-7	N04BC09
Ziprasidone	146939-27-7	N05AE04
Pilocarpine	92-13-7	N07AX01, S01EB01
Clonazepam	1622-61-3	D04AA14, R06AA04,
Rufinamide	106308-44-5	N03AF03
Valsartan	137862-53-4	C09CA03, C09DX05 ,C09DA03 ,C09DX02 ,C09DX01 ,C09DB08, C09DB01 ,C09DX04 ,C10BX10
Theophylline	58-55-9	R03DA04
Nitrazepam	146-22-5	N05CD02

Captopril	62571-86-2	C09AA01
Oxazepam	604-75-1	N05BA04
Ciprofloxacin	85721-33-1	J01MA02, S01AE03, S02AA15, S03AA07, J01RA10, J01RA11, J01RA12
Levetiracetam	102767-28-2	C07AG01
Pregabalin	148553-50-8	N03AX16
Etoposide	33419-42-0	LO1CB01
Tafluprost	209860-87-7	S01EE05
Dacarbazine	4342-03-4	L01AX04
Aripiprazole	129722-12-9	N05AX12
Codeine	76-57-3	N02AA59
Ifosfamide	3778-73-2	N05BB01
Fludarabine	21679-14-1	N01AH01, N02AB03
Furosemide	54-31-9	N06AB08
Mianserin	24219-97-4	N06AX03
Nortriptyline	72-69-5	N06AA10
Salmeterol	89365-50-4	R03AC12
Rivastigmine	123441-03-2	N06DA03
Alprazolam	28981-97-7	N05BA12
Mesalazine	89-57-6	A07EC02
Metolazone	17560-51-9	C03BA08
Spironolactone	52-01-7	C03DA01
Deferoxamine	70-51-9	V03AC01
Haloperidol	52-86-8	A10BB09
Nifedipine	21829-25-4	C08CA05
Ceftazidimepentahydrate	78439-06-2	J01DD02
Bexarotene	153559-49-0	L01XF03
Fentanyl	437-38-7	M01AH05
Tacrolimus	104987-11-3	D11AH01, L04AD02
Metoclopramide	364-62-5	A03FA01
Dopamine	51-61-6	A06AD16, B05BC01, B05CX04, R05CB16, V04CX04
Phenobarbital	50-06-6	N03AA02
Azithromycin	83905-01-5	J01FA10, S01AA26, J01RA07
Etonogestrel	54048-10-1	D10AF02, J01FA01, S01AA17, QJ51FA01,
Dexamethasone	50-02-2	M05BX04
Naloxone	465-65-6	A06AH04, V03AB15
Ampicillin	69-53-4	J01CA01, S01AA19, QJ51CA01, J01CR50, J01CA51
Chlorprothixene	113-59-7	N05BA02
Lorazepam	846-49-1	N05BA06
Acyclovir	59277-89-3	J05AB01, D06BB03, S01AD03, D06BB53
Naltrexone	16590-41-3	N07BB04
CJ023423	415903-37-6	J01MA02, S01AE03, S02AA15, S03AA07, J01RA10, J01RA11, J01RA12
Erythromycin	114-07-8	J01FA01
Docetaxel	114977-28-5	D04AA32, D04AA33, R06AA02
Levothyroxine	51-48-9	N03AX09
Norethindrone	68-22-4	G03AC01, G03DC02

Alendronatesodium	121268-17-5	M05BA04
Naratriptan	121679-13-8	N02CC02
Desloratadine	100643-71-8	V03AC01
Tibolone	5630-53-5	G03CX01
Methylprednisolone	83-43-2	D07AA01, D07AC14, D10AA02, H02AB04, D07CA02, S01CA08, H02BX01
Cytarabine	147-94-4	L01AA01
Perphenazine	58-39-9	N05AB03
Mifepristone	84371-65-3	G03XB01
Cimicoxib	265114-23-6	D01AE14, G01AX12 ,
Pivampicillin	33817-20-8	J01CA02
Moxifloxacin	151096-09-2	J01MA14, S01AE07
Exemestane	107868-30-4	N01AX14, N06AX27,
Bisacodyl	603-50-9	N04AA02
Diltiazemhydrochloride	33286-22-5	N05BA01
Nortriptylinehydrochloride	894-71-3	N06AA10
Dienogest	65928-58-7	R05DA09
Nitrofurantoin	67-20-9	J01XE01
Phenylephrine	59-42-7	C01CA06, R01AA04, R01AB01,(combinations), R01BA03 ,S01FB01 ,S01GA05
Triptorelin	57773-63-4	L02AE04, QH01CA97
Teriparatide	52232-67-4	H05AA02
Cabotegravir	1229006-15-8	G02CB03, N04BC06 ,
Domperidone	57808-66-9	A11GA01, G01AD03, S01XA15 ,
Procyclidine	77-37-2	N04AA04
Pimozide	2062-78-4	N05AG02
Timolol	26839-75-8	C07AA06, S01ED01, C07BA06 ,C07DA06
Vortioxetinehydrobromide	960203-27-4	N06AX26
Midazolam maleate	65607-69-4	N05CD08
Paroxetinehydrochlo-ridehemihydrate	110429-35-1	N06AB05
Cholestyramineresin	11041-12-6	N05AF03
Testosteroneenanthate	315-37-7	G03BA03
Prednisolone	50-24-8	A07EA01, C05AA04, D07AA03 ,D07XA02 ,H02AB06 ,H02AB06 ,R01AD02 ,S01BA04 ,S01CB02 ,S02BA03 ,S03BA02 ,D07CA03 ,S01CA02 ,S02CA01 ,S03CA02 ,D07BA01 ,S01BB02 ,V03AB05 ,A01AC54 ,R01AD52
Atropine	51-55-8	A03BA01, S01FA01,
Stiripentol	137767-55-6	N03AX17
Testosteroneundecylate	5949-44-0	G03BA03
Caplacizumab	915810-67-2	L01BC06
Octreotide	83150-76-9	H01CB02
Ustekinumab	815610-63-0	L04AC05
Rifabutin	72559-06-9	J04AB04
Nintedanib	656247-17-5	L01EX09
Bilastine	202189-78-4	L02BB03
Fremanezumab	1655501-53-3	N05AF01
Oxytocin	50-56-6	G02AC, H01BB02

Zuclopenthixolacetate	85721-05-7	N05AF05
Lisdexamfetaminedimesyl-ate	608137-33-3	N06BA12
Colchicine	64-86-8	N05AH02
Verapamilhydrochloride	152-11-4	C08DA01
Idelalisib	870281-82-6	H02AB09
Aspirin	50-78-2	A01AD05, B01AC06, N02BA01
Apremilast	608141-41-9	L04AA32
Roxithromycin	80214-83-1	J01FA06
Zuclopenthixoldecanoate	64053-00-5	N05AF05
Asenapine	65576-45-6	N05AH05
Ganirelix	124904-93-4	N02CC07
Sertindole	106516-24-9	N05AE03
Dextromethorphanhydro-bromidemonohydrate	6700-34-1	R05DA09
Fostamatinib	901119-35-5	L01BC02
Zuclopenthixoldihydrochlo-ride	58045-23-1	N05AF05
Bupivacainehydrochloride	18010-40-7	C03CA02
Triptorelin Acetate	140194-24-7	L02AE04, QH01CA97
Tramadolhydrochloride	36282-47-0	N02AX02, N02AJ13
Tenoxicam	59804-37-4	M01AC02
Gentamicin	1403-66-3	D06AX01, D09AA02, (dressing) J01XC01, S01AA13
Buspironehydrochloride	33386-08-2	L02AE01, QH01CA90,
Raloxifenehydrochloride	82640-04-8	G03XC01
Tadalafil	171596-29-5	G04BE08
Pramipexole	104632-26-0	N04BC05
6_Mercaptopurine	50-44-2	L01BB02
Elotuzumab	915296-00-3	G03AC10, G03AA12, G03FA17
HyaluronateSodium	9067-32-7	L02AE03
Gelatin	9000-70-8	L02BA03
Carboxymethylcellulose	9000-11-7	L01XA02
Aztreonam lysine	827611-49-4	J01DF01
Luproliteacetate	34973-08-5	L02AE02
Enflicoxib	251442-94-1	D11AX16, P01CX03
Tenofovir disoproxil succin-ate	1637632-97-3	J05AF07
Lutropinalfa	152923-57-4	G03GA07
Tenofovir disoproxil phos-phate	1453166-76-1	J05AF07
Idursulfase beta	1271734-34-9	L01XX05
Fosfomycin	23155-02-4	C05AA11, D07AC08
Pivmecillinam	32886-97-8	J01CA08
Fostemsavir tromethamine	864953-39-9	N05AF01
Ipratropiumbromidehydrate	66985-17-9	N06AA02
Bisoprololfumarate	104344-23-2	N04AA02
Cloxacillin	61-72-3	B01AC04
Ichthammol	8029-68-3	G03G

Cannabidiol	13956-29-1	N03AX24
Lactulose	4618-18-2	N06AF01
Glycopyrronium	13283-82-4	D06AX07, J01GB03, S01AA11, S02AA14, S03AA06, QA07AA91, QG01AA91, QG51AA04, QJ51GB03 (WHO)
Aprepitant	170729-80-3	A04AD12
Gadopentetatedimeglumine	86050-77-3	G03GA09, G03GA05, G03GA06, G03GA10, G03GA04
Selegilinehydrochloride	14611-52-0	N04BD01, QN06AX90
Gadoteridol	120066-54-8	J01XX01
Folinicacidcalciumsalt	1492-18-8	N07CA03
Oxytetracycline	79-57-2	D06AA03, G01AA07, J01AA06, S01AA04, QG51AA01, QJ51AA06
Nalmefene	55096-26-9	N07BB05
Methadonehydrochloride	1095-90-5	N02AC52, N07BC02, QN02AC90
Safinamidemesylate	202825-46-5	N04BD03
Solriamfetolhydrochloride	178429-65-7	N06BA14
Calcipotriene	112965-21-6	N06BC01, D11AX26, V04CG30
Melatonin	73-31-4	N05CH01
Nicorandil	65141-46-0	C01DX16
Midodrine	42794-76-3	C01CA17
Propafenone Hydrochloride	34183-22-7	C01BC03
Terbinafine	91161-71-6	D01AE15, D01BA02
Diphenhydramine	58-73-1	D04AA32, D04AA33, R06AA02
Lithium citrate	919-16-4	N05AN
Benethaminepenicillin	751-84-8	C03AA01
Metyrapone	54-36-4	V04CD01
Isoproterenol	7683-59-2	A10A
Metronidazolebenzoate	13182-89-3	A01AB17, D06BX01, G01AF01, J01XD01, P01AB01, QP51AA01
Venlafaxinehydrochloride	99300-78-4	N06AX16
Efavirenz	154598-52-4	J01AA02, A01AB22
VitaminB12	68-19-9	B03B
Mepivacaine	96-88-8	N01BB03
Sumatriptansuccinate	103628-48-4	N02CC01
Sulfasalazine	599-79-1	A07EC01
Epinephrine	51-43-4	A10BK03, A10BD19, A10BD20
Zolmitriptan	139264-17-8	N02CC03
Rabeprazole	117976-89-3	A02BC04, A02BC54, A02BD12 ,A02BD13
Bupropionhydrochloride	31677-93-7	N02AE01, N07BC01
Dronedarone	141626-36-0	N06DA02
Sodiumfluoride	7681-49-4	A01AA01, A12CD01, V09IX06
Medroxyprogesteroneace-tate	71-58-9	G03AC06, G03DA02, L02AB02
Ulipristalacetate	126784-99-4	G03AD02, G03XB02
Methimazole	60-56-0	H03BB02
Propranololhydrochloride	318-98-9	C07AA05
Valacyclovir hydrochloride monohydrate	521915-75-3	J05AB11
Methylaminolevulinate	33320-16-0	L01XD03
Rifampicin	13292-46-1	J04AB02, QJ54AB02

Primidone	125-33-7	N03AA03
Lymecycline	992-21-2	J01AA04
Chlorohexidine	55-56-1	H01CC02
Flupenthixol	2709-56-0	J01CF05
Clorsulon	60200-06-8	J01FF01, D10AF01, G01AA10, D10AF51
Rizatriptanbenzoate	145202-66-0	N02CC04
Econazole	27220-47-9	S01EC03
Fenbendazole	43210-67-9	M01AB08
Glucagon	9007-92-5	H01CC01
Mupirocin	12650-69-0	D06AX09, R01AX06
Dextroamphetamine	51-64-9	H01BA02
Baricitinib	1187594-09-7	L04AA37
Apomorphinehydrochloride	314-19-2	G04BE07, N04BC07, QV03AB95
Ritonavir	155213-67-5	J05AE03
Dipyrone	68-89-3	G03DB08, G03AB08, G03FA15
Tolfenamicacid	13710-19-5	M01AG02
Linezolid	165800-03-3	J01XX08
Tenofovirdisoproxil	201341-05-1	J05AF07
Idarubicin	58957-92-9	C03AA03, C03AB03, C03AX01, C03EA01, C09BX03, C09DX01, C09DX03, C09DX06, C09DX07, C09XA52, C09XA54
Nonanedioicacid	123-99-9	D10AX03
Doxycycline	564-25-0	A03FA03, QP51AX24
Sodiumvalproate	1069-66-5	N03AG01
Agomelatine	138112-76-2	N06AX22
Hydroxyurea	127-07-1	N05AD01
Pentoxifylline	6493-05-6	C04AD03
Famciclovir	104227-87-4	N03AF04
Pipamperone	1893-33-0	N05AD05
Sulfamethizole	144-82-1	B05CA04, D06BA04, J01EB02, S01AB01, QJ01EQ02
Cephalexin	15686-71-2	L01XX33, M01AH01
Ceftriaxone	73384-59-5	J01DD02
Hesperidin	520-26-3	H04AA01
Acetazolamide	59-66-5	S01EC01
Ciclopirox	29342-05-0	C10AC01
Cobimetinib	934660-93-2	J01CF02, QJ51CF02, QS01AA90
Scopolamine	51-34-3	A04AD01, N05CM05, S01FA02
Vancomycin	1404-90-6	A07AA09, J01XA01, S01AA28
Cenobamate	913088-80-9	J01DC02, S01AA27, QJ51DC02
Fenfluramine	458-24-2	G03AC08
Fluticasonefuroate	397864-44-7	H02AA02
Nafarelinacetate	76932-60-0	H01CA02
Ceftolozanesulfate	936111-69-2	J01DD02
Mebeverinehydrochloride	2753-45-9	A03AA04
Pimecrolimus	137071-32-0	D11AH02
Acipimox	51037-30-0	C10AD06
Icodextrin	337376-15-5	H01A

Modafinil	68693-11-8	N06BA07
Phenylbutazone	50-33-9	M01AA01, M02AA01
Adalimumab	331731-18-1	L04AB04
Ceftobiprolemedocaril	252188-71-9	J01DD02
Cemiplimab	1801342-60-8	J01DD04
Certolizumabpegol	428863-50-7	J01DB01, QJ51DB01 ,
Dabrafenib	1195765-45-7	L04AD01, S01XA18 ,
Febuxostat	144060-53-7	J04AK02
Fexofenadinehydrochloride	153439-40-8	L02BG06
FG-4592	808118-40-3	J05AB09, S01AD07 ,
Quininehydrochloride	130-89-2	G02CB
Lurasidone	367514-87-2	N05AE05
Quinagolidehydrochloride	94424-50-7	G02CB
Tobramycinsulfate	49842-07-1	J01GB01, S01AA12
Cilastatin	82009-34-5	R01AD13, R03BA08 ,
Fluoresceinsodium	518-47-8	C01BC04
Nystatin	1400-61-9	A07AA02, D01AA01, G01AA01
Vildagliptin	274901-16-5	A10BH02, A10BD08
Burosumab	1610833-03-8	N06AX12
Gleptoferron	57680-55-4	N06DA04
Perampanel	380917-97-5	N03AX22
Amikacinsulfate	39831-55-5	D06AX12, J01GB06, S01AA21, J01RA06, QD06AX12, QJ01GB06, QS01AA21, QJ01RA06
Pizotifen Malate	24359-22-6	N02CX01
Amlodipinebesylate	111470-99-6	C08CA01
Stiripentol	49763-96-4	N03AX17
Frunevetmab	1708936-80-4	R01AD12, R03BA09, R03AK10, R03AL08
Gemtuzumabozogamicin	220578-59-6	C03CA01
Metoprololsuccinate	98418-47-4	C07AB02
Sildenafilcitrate	171599-83-0	G04BE03
Gadotericacid	72573-82-1	R03AC13, R03AC13, R03CC15
Semaglutide	910463-68-2	A10BJ06
Blinatumomab	853426-35-4	C07AB07
Beclomethasonedipropio-natemonohydrate	77011-63-3	A07EA07, D07AC15, R01AD01, R03BA01
Heparin	9005-49-6	A10BB12
TolterodineL-tartrate	124937-52-6	G04BD07
DL-Dobutamine	34368-04-2	C05AE03, C08DB01 (WHO
Ixazomibcitrate	1239908-20-3	R01AX03, R03BB01
Ixekizumab	1143503-69-8	R01AX03, R03BB01
Adapalene	106685-40-9	D10AD03
Canakinumab	914613-48-2	A10BK02
Isatuximab	1461640-62-9	R03AC18
Leuprorelin	53714-56-0	M01AB15, S01BC05
VitaminD3	67-97-0	A11CC05
Bivalirudin	128270-60-0	A06AB02, A06AG02
Calcium(6S)-folinate	80433-71-2	D05AX02

DiroximelFumarate	1577222-14-0	A08AA03
Emedastinedifumarate	87233-62-3	A10BJ05
Pulmozyme	143831-71-4	R05CB13
Terazosinhydrochloride	63074-08-8	G04CA03
Avanafil	330784-47-9	G04BE10
Balsalazide disodium	82101-18-6	A07EC04
Benralizumab	1044511-01-4	D04AB03, S01HA02
Bezlotoxumab	1246264-45-8	C07AB05, S01ED02
Fluticasonepropionate	80474-14-2	V03AB25
Heparinsodium	9041-08-1	A10BB07
Humanchorionicgonadotro-pin	9002-61-3	A16AX09
Ibritumomab	206181-63-7	B01AB01, C05BA03, S01XA14
Icosapentethyl	86227-47-6	D03AX05, M09AX01, R01AX09, S01KA01
Imlifidase	1947415-68-0	C10AX06
Lexiscan	313348-27-5	V03AE03
Naloxegoloxalate	1354744-91-4	A06AH03
Naloxonehydrochloride	357-08-4	A06AH04, V03AB15
Opium	8008-60-4	A07DA02, N02AA02
Palivizumab	188039-54-5	J06BD01
Phytonadione	84-80-0	B02BA01
Roflumilast	162401-32-3	R03DX07
Sapropterindihydrochloride	69056-38-8	A16AX07
Sevelamercarbonate	845273-93-0	V03AE02
Vancomycinhydrochloride	1404-93-9	A07AA09, J01XA01, S01AA28
Zinc(II)acetatedihydrate	5970-45-6	A16AX05
Zoledronate	118072-93-8	M05BA08
Zoledronicacidmonohydrate	165800-06-6	M05BA08
Diatrizoatesodium	737-31-5	A01AC02, C05AA09, D07AB19, D10AA03, H02AB02, R01AD03, S01BA01, S02BA06, S03BA01
Cysteaminehydrochloride	156-57-0	L01AA01
Prasugrel	150322-43-3	B01AC22
Nitrogenmustardhydrochlo-ride	55-86-7	L01AA
Carminicacid	1260-17-9	N05AX15
Cerliponase alfa	151662-36-1	N03AX25
Edoxabantosylate	480449-71-6	N06AA16
Felypressin	56-59-7	N03AD01
Mepivicainehydrochloride	1722-62-9	N01BB03
Phenprocoumon	435-97-2	B01AA04
Probenecid	57-66-9	M04AB01
Tropicamide	1508-75-4	S01FA06
Pitolisant	362665-56-3	N07XX11
Apraclonidinehydrochloride	73218-79-8	S01EA03
Promethazinehydrochloride	58-33-3	D04AA10, R06AD02
Alprostadil	745-65-3	C01EA01, G04BE01
Etodolac	41340-25-4	A10BK04

Tetracyclinehydrochloride	64-75-5	A01AB13, D06AA04, J01AA07, S01AA09, S02AA08, S03AA02, QG01AA90, QG51AA02, QJ51AA07
Timololmaleatesalt	26921-17-5	C07AA06, S01ED01, C07BA06, C07DA06
Trimetazidinedihydrochloride	13171-25-0	C01EB15
SodiumOxybate	502-85-2	N07XX04
Eptifibatide	188627-80-7	M01AX01
AmphotericinB	1397-89-3	A01AB04, A07AA07, G01AA03, J02AA01
Sotalolhydrochloride	959-24-0	C07AA07
Naphthylmethyl-2-imidazolinenitrate	5144-52-5	S01GA
Orphenadrinehydrochloride	341-69-5	M03BC01, N04AB02
Ticagrelor	274693-27-5	B01AC24
Mirabegron	223673-61-8	G04BD12
Salmeterolxinafoate	94749-08-3	R03AC12
Doravirine	1338225-97-0	A06AD16, B05BC01, B05CX04, R05CB16, V04CX04
Entrectinib	1108743-60-7	S01GX06
Olodaterol	868049-49-4	R03AC19
Epoprostenol	35121-78-9	C09AA02
Formoterolhemifumarate	43229-80-7	C05AA10 , D07AC04, S01BA15, S02BA08
Cysteaminebitartrate	27761-19-9	S01FA04
Ketobemidonehydrochloride	5965-49-1	C09CA04, C09DA04
Diethylpropion	90-84-6	
Milrinone	78415-72-2	C01CE02
Cladribine	4291-63-8	L01XA01
Bortezomib	179324-69-7	S02AA03, D08AD
Carboplatin	41575-94-4	
Ketorolac	74103-06-3	V03AE08
Letrozole	112809-51-5	M01AE03, M01AE17, M02AA10
Glimepiride	93479-97-1	QJ01FA95
Sunitinib	557795-19-4	L01EX01
Capecitabine	154361-50-9	
Biperiden	514-65-8	L04AC21
Xylometazoline	526-36-3	R01AA07, S01GA03
Clozapine	5786-21-0	
Prilocaine	721-50-6	N01BB04
Paclitaxel	33069-62-4	L01,L01CD03
Hydrocortisone	50-23-7	L04AC16
Lidocaine	137-58-6	L01EH01
Levonorgestrel	797-63-7	J05AF05
Ketoprofen	22071-15-4	L01CE02
Betamethasone	378-44-9	B06AC06
Celecoxib	169590-42-5	J01DI54
Deferasirox	201530-41-8	L01FC01
Donepezil	120014-06-4	C01CA07
Clopidogrel	113665-84-2	R03AC14 ,R03CC13 ,QG02CA91 ,
Bicalutamide	113299-38-0	L01XF03

Bicalutamide	90357-06-5	J06BC03
Levodopa	59-92-7	N04BA01
Loratadine	79794-75-5	R06AX13
Atovaquone	95233-18-4	P01AX06
2_4-Dichlorobenzylalcohol	1777-82-8	R02AA03
21_Hydroxyprogesterone	64-85-7	G03DA03
Abacavir	136470-78-5	J05AF06
Abatacept	332348-12-6	L04AA24
Abemaciclib	1231929-97-7	L01EF03
Abrocitinib	1622902-68-4	D11AH08
ABT-199	1257044-40-8	L01XX52
Acalabrutinib	1420477-60-6	L01EL02
Acetylpromazine	61-00-7	N05AA04
Aclidiniumbromide	320345-99-1	R03BB05
Acrivastine	87848-99-5	R06AX18
Adefovir	106941-25-7	J05AF08
Adenosine	58-61-7	C01EB10
Aflibercept	862111-32-8	L01XX44, S01LA05
Aglepristone	124478-60-0	G03XB90
Alanylglutamine	39537-23-0	
Albuterolsulfate	51022-70-9	
Alectinib	1256580-46-7	L01ED03
Alemtuzumab	216503-57-0	L04AA34
Alginicacid	9005-32-7	A02BX13
alpha1-Antitrypsin	9041-92-3	B02AB02
Alteplase	105857-23-6	B01AD02, S01XA13
Altrenogest	850-52-2	QG03DX90
Amantadine	768-94-5	C02KX02
Ambrisentan	177036-94-1	C02KX02
Amdinocillin	32887-01-7	J01CA11
Amorolfine	67467-83-8	D01AE16
Amorolfine	78613-35-1	D01AE16
Amprolium	13082-85-4	QP51AX09
Amsacrine	51264-14-3	L01XX01
Andexanet alfa	1262449-58-0	V03AB38
AngiotensinIIacetate	68521-88-0	C01CX09
Anifrolumab	1326232-46-5	L04AA51
Antazoline Hemisulfate	84803-70-3	
Antithrombin,III	90170-80-2	
Apramycinsulfate	65710-07-8	QA07AA92, QJ01GB90, QJ51GB90
Argatroban	74863-84-6	B01AE03
ARN-509	956104-40-8	L02BB05
Arsenite	15502-74-6	
Articaine	23964-58-1	N01BB08
Asfotase alfa	1174277-80-5	A16AB13
Ataluren	775304-57-9	M09AX03

Atezolizumab	1380723-44-3	L01FF05
Atosiban	90779-69-4	G02CX01
Avalglucosidase alfa	1802558-87-7	A16AB22
Avapritinib	1703793-34-3	L01EX18
Avatrombopag	570406-98-3	B02BX08
Avelumab	1537032-82-8	L01FF04
Axitinib	319460-85-0	L01EK01
Azacitidine	320-67-2	L01BC07
Azelastinehydrochloride	79307-93-0	R01AC03, R06AX19, S01GX07
Bariumsulfate	7727-43-7	V08BA01
Beclomethasone Dipropio-nate	08-09-5534	B06AC01
Bedaquilinefumarate	845533-86-0	A07EA07, D07AC15, R01AD01, R03BA01
Bedinvetmab	2171034-69-6	J04AK05
Belatacept	706808-37-9	QN02BG91
Benazeprilhydrochloride	86541-74-4	L04AA28
Bendamustinehydrochloride	3543-75-7	C09AA07
Bendroflumethiazide	73-48-3	L01AA09
Benoxinate	99-43-4	J01CE08
Benserazidehydrochloride	14919-77-8	R03DX10
Benzenesulfonicacid,4-eth-enyl-,homopolymer	28210-41-5	QN04AC01
Benzocaine	94-09-7	
Benzoylperoxide	94-36-0	
Benzydamine	642-72-8	C05AD03,D04AB04, QN01AX92, N01BA05, R02AD01
Berotralstathydrochloride	1809010-52-3	D10AE01, D10AE51
beta-Galactosidase	9031-11-2	A01AD02, G02CC03, M01AX07, M02AA05, R02AX03
Betaxolol Hydrochloride	63659-19-8	
Bimekizumab	1418205-77-2	
Binimetinib	606143-89-9	R06AX29, S01GX13
Biperidenlactate	7085-45-2	L01EE03
Blood-coagulationfactorIX	9001-28-9	B01AE06
Boricacid	10043-35-3	L01FX07
Boricacid_crudenatural	11113-50-1	
Bosentan	147536-97-8	L01XG01
Bosutinib	380843-75-4	C02KX01
Brodalumab	1174395-19-7	L01EA04
Bromocriptine	25614-03-3	L04AC12
Buserelin	57982-77-1	M05BX05
Butorphanol	42408-82-2	L01AB01
Cabergoline	81409-90-7	N02AF01, QR05DA90
Cabozantinib	849217-68-1	J05AJ04
Caffeine	58-08-2	L01EX07
CalciumD-gluconate	299-28-5	V03AF03
Calciumdichloridedihydrate	10035-04-8	A12AA03, D11AX03
Canagliflozin	842133-18-0	A12AA20
Candesartan	139481-59-7	L04AC08

CangrelorTetrasodium	163706-36-3	C09CA06
Cannabidiol	74219-29-7	B01AC25
Capsaicin	404-86-4	B01AX07
Carbomer	9007-20-9	N04BA05
Carfilzomib	868540-17-4	
Cariprazine	839712-12-8	L01XG02
Carprofen	53716-49-7	V04
Catridecacog	606138-08-3	QM01AE91
Cefadroxil	50370-12-2	B02BD11
Cefazolin	25953-19-9	J01DB05
Cefepimechloridehydrochloridehydrate	123171-59-5	J01DB04, QJ51DB04
Cefotaxime	63527-52-6	J01DE01
Cefovecin	234096-34-5	J01DD01
Ceftaroline	189345-04-8	QJ01DD91
Ceftazidime	72558-82-8	J01DI02
Cefuroxime	55268-75-2	J01DI01
Ceritinib	1032900-25-6	L01FF06
Cetirizine	83881-51-0	L01ED02
Cetrorelixacetate	145672-81-7	A16AB17
Cetuximab	205923-56-4	L04AB05
Chlordiazepoxide	58-25-3	R06AE07, S01GX12
Chloroprocaine	133-16-4	L01FE01
Chlortetracyclinehydrochloride	64-72-2	A01AB03, B05CA02, D08AC02, D09AA12, (dressing), R02AA05, S01AX09, S02AA09, S03AA04
Chlorzoxazone	95-25-0	N01BA04
Chondroitinsulfatase	9025-60-9	A01AB21, D06AA02, J01AA03, S01AA02, QG51AA08, QJ51AA03
Ciclesonide	141845-82-1	M03BB03
Cidofovir	113852-37-2	M01AX25
Cinnarizine	16699-20-0	J05AB12
Cinnarizine	298-57-7	J01DH51
Cisplatin	15663-27-1	N07CA02
Clemastine	15686-51-8	
Clenbuterol	37148-27-9	L04AA40, L01BB04
Closantel	57808-65-8	D08AH30, D09AA10, (dressing) G01AC02, P01AA02, S02AA05
Cloxacillinbenzathine	23736-58-5	
Cobicistat	1004316-88-4	A01AB18, D01AC01, G01AF02, QJ02AB90
Colesevelamhydrochloride	182815-44-7	V03AX03
Colistimethatesodium	8068-28-8	L01EE02
Cosyntropin	16960-16-0	M04AC01
Crizanlizumab	1690318-25-2	C10AC04
Crizotinib	877399-52-5	A07AA10, J01XB01, QA07AA10, QA07AA98, QG51AG07, QJ01XB01, QJ51XB01
Cromolynsodium	15826-37-6	B06AC01
Cyclizine	82-92-8	H01AA02
Cyclopentolatehydrochloride	5870-29-1	B06AX01

Cyclophosphamide	50-18-0	L01ED01
Cyclophosphamidemonohy-drate	6055-19-2	A07EB01, D11AH03, R01AC01, R03BC01, S01GX01
CyclosporinA	59865-13-3	
Cyproteroneacetate	427-51-0	R06AE03
Dacomitinib	1110813-31-4	A16AA04, S01XA21
Dalbavancin	171500-79-1	A16AA04, S01XA21
Damoctocog alfa pegol	1363853-26-2	L01BC01
Daptomycin	103060-53-3	L01BC01
Daratumumab	945721-28-8	L01EC02
Darifenacin	133099-04-4	L01AX04
Darolutamide	1297538-32-9	L01EB07
D-Ascorbicacid	10504-35-5	J01XA04
Daunorubicin	20830-81-3	B02BD02
Decitabine	2353-33-5	J01XX09
Defibrotidesodium	83712-60-1	L02BB06
Degarelix	214766-78-6	A11GA01, G01AD03, S01XA15
Dehydroepiandrosterone	53-43-0	L01DB02
Deltamethrin	52918-63-5	L01DB02
Denosumab	615258-40-7	L01BC08
Desflurane	57041-67-5	V03AC03
Deslorelinacetate	82318-06-7	B01AX01
Desmopressin	16679-58-6	L02BX02
Detomidine	76631-46-4	P03BA03, QP53AC11
Dexibuprofen	51146-56-6	N01AB07
Dexmedetomidine	113775-47-6	R06AX27
Dexrazone	24584-09-6	QH01CA93
D-Glucose	50-99-7	QN05CM90
Dibotermin alfa	246539-15-1	N05CM18, QN05CM18
Diclazuril	101831-37-2	V03AF02
Digoxin	20830-75-5	V08AA01
Dinoprostone	363-24-6	
Dinutuximab	1363687-32-4	QP51AJ03
DL-Ascorbicacid	62624-30-0	C01AA05
DL-Mannitol	87-78-5	G02AD02
D-Mannitol	69-65-8	L01FX06
Docusatehydrogen	10041-19-7	N02BB02
Dolutegravir	1051375-16-6	L04AX09
Dorzolamidehydrochloride	130693-82-2	L01CD02
Dostarlimab	2022215-59-2	A06AA02
Dothiepinhydrochloride	897-15-4	J05AJ03, J05AR13, J05AR21, J05AR27
Drospirenone	67392-87-4	C01CA04
Dulaglutide	923950-08-7	J05AG06
Durvalumab	1428935-60-7	J05AG06
Eculizumab	219685-50-4	L01FF07
Eflornithine	70052-12-9	C01BD07

Eliglustat	491833-29-5	N05AD08
Emicizumab	1610943-06-0	L01FF03
Empagliflozin	864070-44-0	D01AC03, G01AF05
Emtricitabine	143491-57-0	L04AA25
Encorafenib	1269440-17-6	J05AG03
Enfortumab	1346452-25-2	A16AX10
Enrofloxacin	93106-60-6	
Enzalutamide	915087-33-1	B02BX06
Epirubicin	56420-45-2	J05AF09
Epoetin beta	122312-54-3	J05AF09
Epoetin zeta	604802-70-2	J05AF09
Eprinomectin	123997-26-2	L01EC03
Eptinezumab	1644539-04-7	L01FX13
Eribulin Mesylate	441045-17-6	QJ01MA90
Ertapenem	153832-46-3	L01EX14
Ertugliflozin	1210344-83-4	L02BB04
Escitalopram	128196-01-0	L01DB03
Escitalopramoxalate	219861-08-2	B03XA01
Esketamine	33643-46-8	B03XA
Eslicarbazepineacetate	236395-14-5	B01AC09
Esmolol	81147-92-4	QP54AA04
Ethambutoldihydrochloride	1070-11-7	B01AC16
Ethamsylate	2624-44-4	N02CD05
Ethosuximide	77-67-8	J01DH03
Febantel	58306-30-2	C07AB09
Fedratinibhydrochloride	1374744-69-0	B02BX01
Fenoterolhydrobromide	1944-12-3	L01CB01
Fibrinogens	9001-32-5	P02CA06, QP52AC13
Fidaxomicin	873857-62-6	M04AA03
Filgrastim	121181-53-1	L01EJ02
Finerenone	1050477-31-0	C08CA02
Flecainide	54143-55-4	P02CA06, QP52AC13
Florfenicol	73231-34-2	A08AA02, N03AX26
Floxacillin	5250-39-5	R03AC04, G02CA03
Fludrocortisone	127-31-1	R06AX26
Flumazenil	78755-81-4	B03XA05
Flumethrin	69770-45-2	B02BB01
Flunarizine	52468-60-7	A07AA12
Flunixinmeglumine	42461-84-7	L03AA02
Fluocinoloneacetonide	67-73-2	C03DA05
Fluocinonide	356-12-7	QP53AX15
Fluorouracil	51-21-8	QJ01BA90 ,QJ51BA90
Fluralaner	864731-61-3	L01BB05
Fluvoxaminemaleate	61718-82-9	QP53AC05
Folicacid	59-30-3	QP53AC05
Follitropin	146479-72-3	QM01AG90

Fosphenytoin	93390-81-9	S01JA01
FrovatriptanSuccinatemon-ohydrate	158930-17-7	QP53BE02
Fusidicacid	6990-06-3	B03BB01, V04CX02, B03AE02, B03AE01, B03BB51
Gadobenatedimeglumine	127000-20-8	B03BB01, V04CX02, B03AE02, B03AE01, B03BB51
Galantaminehydrobromide	1953-04-4	N03AB05
Galsulfase	552858-79-4	B02BX09
Gamithromycin	145435-72-9	J05AX29
Ganciclovir	82410-32-0	N02CD03
Gefitinib	184475-35-2	QN02BG90
Gilteritinibfumarate	1254053-84-3	V08CA08
Givosiran	1639325-43-1	V08CA01
Glatirameracetate	147245-92-9	V08CA02
Glecaprevir	1365970-03-1	V08CA04
Gliclazide	21187-98-4	A16AB08
Glipizide	29094-61-9	J05AB06, S01AD09
Glucosamine	3416-24-8	L01EB01
Glycerol	56-81-5	B05AA06
Glycerolphenylbutyrate	611168-24-2	L01FX02
Goserelin	65807-02-5	L01EX13
Guaifenesin	93-14-1	A16AX16
Guselkumab	1350289-85-8	L03AX13
Halofuginone	55837-20-2	J05AP57
Halofuginone lactate	82186-71-8	
Hexaminolevulinatehydro-chloride	140898-91-5	M01AX05
Histamine	51-45-6	A06AG04, A06AX01
Humangrowthhormone	12629-01-5	A03AB02, D11AA01, R03BB06 (WHO
Hydrochlorothiazide	58-93-5	R05CA03, QM03BX90
Hydrocortisoneacetate	50-03-3	QP51AX08
Hydroxypropylmethylcellu-lose	9004-65-3	
Hydroxyzinehydrochloride	1244-76-4	B01AB01, C05BA03, S01XA14
Ibrutinib	936563-96-1	
Ibuprofen	15687-27-1	V04CX06
Icatibant	130308-48-4	L03AX14, V04CG03
Idarucizumab	1362509-93-0	A01AC03, A07EA02, C05AA01, D07AA02, H02AB09, S01BA02, S02BA01
Idebenone	58186-27-9	A01AC03, A07EA02, C05AA01, D07AA02, H02AB09, S01BA02, S02BA01
Iloprosttromethamine	697225-02-8	M05BA06
Imatinib	152459-95-5	V10XX02
Imepitoin	188116-07-6	C01EB16, G02CC01, M01AE01, M02AA13, R02AX02
Imidacloprid	138261-41-3	B06AC02
Imipraminehydrochloride	113-52-0	D10BX01, D05AA
Imiquimod	99011-02-6	B05DA
Inclisiran	1639324-58-5	L01DB06
Indacaterolacetate	1000160-96-2	V03AB37

Indapamide	26807-65-8	N06BX13
Infliximab	170277-31-3	L01EM01
Inotersen	1492984-65-2	A16AB10
Inotuzumab_ozogamicin	635715-01-4	L01AA06
Insulin	9004-10-8	B01AC11
Iodixanol	92339-11-2	L01EA01
Iohexol	66108-95-0	QD01AC90
Iomeprol	78649-41-9	QN03AX90
Ipilimumab	477202-00-9	QP53AX17
Ipratropiumbromide	22254-24-6	QP53AX17
Irinotecan	97682-44-5	L04AA41
Iron(III)citrate	3522-50-7	C10AX16
Isavuconazonium	742049-41-8	C03BA11
Isocarboxazid	59-63-2	L04AB02
Isoflurane	26675-46-7	N07XX15
Isoniazid	54-85-3	L01FB01
Isosorbide	652-67-5	V08AB09
Isosorbide5-mononitrate	16051-77-7	V08AB02
Ivacaftor	873054-44-5	V08AB10
Ivermectin	70288-86-7	L01FX04
Labetalol	36894-69-6	L01FC02
Lacidipine	103890-78-4	J02AC05
Lamivudine	134678-17-4	N01AB06
Lanthanumcarbonate	54451-24-0	C01CA02, R03AB02, R03CB01
Lapatinib	231277-92	C01D
Laronidase	210589-09-6	A16AB05
Larotrectinib	1223403-58-4	C01D
L-Ascorbicacid	50-81-7	R07AX02, R07AX30, R07AX31, R07AX32
Ledipasvir	1256388-51-8	D11AX22, P02CF01, QP54AA01, QS02QA03
Lenalidomide	191732-72-6	L01XG03
Lenograstim	135968-09-1	L04AC13
Lenvatinib	417716-92-8	N02AB01
Letermovir	917389-32-3	J02AB02, D01AC08, G01AF11, H02CA03
Levocetirizine	130018-77-8	A06AD11
Levofloxacin	100986-85-4	J05AF05
Lidocaine Hydrochloride	73-78-9	L01EX12
Linaclotide	851199-59-2	A06AX04
Linagliptin	668270-12-0	A10BH05
Lincomycin	154-21-2	J01FF02, QJ51FF02
Liraglutide	204656-20-2	A10BJ02
Lisinoprildihydrate	83915-83-7	C09AA03, C09BA03, C10BX07, C09BB03
Lokivetmab	1533403-95-0	QD11AH91
Lomitapide	182431-12-5	C10AX12
Lomustine	13010-47-4	L01AD02
Lonoctocog alfa	1388129-63-2	B02BD02
Loperamide	53179-11-6	A07DA03, A07DA05

Lorlatinib	1454846-35-5	L01ED05
Lotilaner	1369852-71-0	QP53BE04
Lumacaftor	936727-05-8	
Luspatercept	1373715-00-4	B03XA06
Macimorelin	381231-18-1	V04CD06
Magnesium citrate	7779-25-1	A06AD19, A12CC04, B05CB03
Magnesiumhydrogencitrate	144-23-0	A06AD19, A12CC04, B05CB03
Magnesiumhydroxide	1309-42-8	A02AA04, G04BX01
Magnesiumsufateheptahydrate	10034-99-8	A06AD04
Maraviroc	376348-65-1	J05AX09
Maropitant	147116-67-4	QA04AD90
Maropitant citrate	359875-09-5	QA04AD90
Mecasermin	68562-41-4	H01AC03
Meclizine	569-65-3	R06AE05
Medetomidine	86347-14-0	QN05CM91
Megestrol	3562-63-8	G03AC05
Melphalan	148-82-3	L01AA03
Menbutone	3562-99-0	A05BA01
Mepolizumab	196078-29-2	R03DX09
Mercaptoethanesulfonicacid	3375-50-6	
Methenamine hippurate	5714-73-8	
Methoprene	65733-16-6	QP53AX28
Methoxy polyethylene glycol-epoetin beta	677324-53-7	B03XA03
Methoxyflurane	76-38-0	N02BG09
Methylnaltrexone	83387-25-1	A06AH01
metreleptin	186018-45-1	A16AA07
Midostaurin	120685-11-2	L01EX10
Mifamurtide	83461-56-7	L03AX15
Migalastathydrochloride	75172-81-5	A16AX14
Miglustat	72599-27-0	
Milbemycin oxime	129496-10-2	QP54AB01
Minoxidil	38304-91-5	C02DC01, D11AX01
Mitomycin	1404-00-8	L01DC03
MitomycinC	50-07-7	L01DC03
Mitotane	53-19-0	L01XX23
Mitoxantrone	65271-80-9	L01DB07
Mivacuriumchloride	106861-44-3	M03AC10
Mogamulizumab	1159266-37-1	L01FX09
Moxidectin	113507-06-5	P02CX03, QP54AB02
Nandrolone	434-22-0	A14AB01, S01XA11
Natalizumab	189261-10-7	L04AA23
Nelarabine	121032-29-9	L01BB07
Neomycin	1404-04-2	A01AB08, A07AA01, B05CA09, D06AX04, J01GB05, R02AB01, S01AA03, S02AA07, S03AA01

NeomycinBsulfate	25389-98-4	A01AB08, A07AA01, B05CA09, D06AX04, J01GB05, R02AB01, S01AA03, S02AA07, S03AA01
Neomycinsulfate	1405-10-3	A01AB08, A07AA01, B05CA09, D06AX04, J01GB05, R02AB01, S01AA03, S02AA07, S03AA01
Neostigmine	59-99-4	N07AA01, S01EB06 ,QA03AB93
Neratinibmaleate	915942-22-2	L01EH02
Netupitant	290297-26-6	
Nevirapine	129618-40-2	J05AG01
Nicotine	54-11-5	N07BA01, QP53AX13
Nilotinibhydrochloridemono-hydrate	923288-90-8	L01EA03
Nitenpyram	120738-89-8	QP53BX02
Nitenpyram	150824-47-8	QP53BX02
Nitisinone	104206-65-7	A16AX04
Nivolumab	946414-94-4	L01FF01
Nonacog beta pegol	1175512-71-6	B02BD04
Norepinephrine	51-41-2	C01CA03
Nusinersensodium	1258984-36-9	M09AX07
Obeticholicacid	459789-99-2	A05AA04
Obinutuzumab	949142-50-1	L01FA03
Oclacitinib	1208319-26-9	QD11AH90
Ocrelizumab	637334-45-3	L04AA36
Octocogalfa	139076-62-3	B02BD02
Odevixibat	501692-44-0	A05AX05
Olaparib	763113-22-0	L01XK01
Olodaterolhydrochloride	869477-96-3	R03AC19
Omalizumab	242138-07-4	R03DX05
Onasemnogene abepar-vovec	1922968-73-7	M09AX09
Osateroneacetate	105149-00-6	
Osilodrostatphosphate	1315449-72-9	H02CA02
Osimertinibmesylate	1421373-66-1	L01EB04
Oxaliplatin	61825-94-3	L01XA03
Oxfendazole	53716-50-0	QP52AC02
Oxyclozanide	2277-92-1	QP52AG06
Ozanimod	1306760-87-1	L04AA38
Ozanimodhydrochloride	1618636-37-5	L04AA38
Palbociclib	571190-30-2	L01EF01
Palonosetronhydrochloride	135729-62-3	A04AA05
Pamidronicacid	40391-99-9	M05BA03
p-Aminosalicylicacid	65-49-6	J04AA01
Pancreatictrypsininhibitor	9087-70-1	B02AB01
Panitumumab	339177-26-3	L01FE02
Panobinostat	404950-80-7	L01XH03
Parecoxib	198470-84-7	M01AH04
Paromomycinsulfate	1263-89-4	A07AA06, QJ01GB92
Patisiransodium	1386913-72-9	N07XX12

Pazopanibhydrochloride	635702-64-6	L01EX03
Pegcetacoplan	2019171-69-6	L04AA54
Peginterferonalfa-2a	198153-51-4	L03AB11, L03AB61
Pegvaliase	1585984-95-7	A16AB19
Pegvisomant	218620-50-9	H01AX01
Pembrolizumab	1374853-91-4	L01FF02
Pemetrexed	137281-23-3	L01BA04
Pemigatinib	1513857-77-6	L01EN02
Penethamatehydriodide	808-71-9	QJ01CE90
Pentosanpolysulfatesodium	140207-93-8	C05BA04
Pergolidemethanesulfonate	66104-23-2	N04BC02
PerindoprilL-arginine	612548-45-5	C09AA04 ,
Permethrin	52645-53-1	P03AC04 ,QP53AC04
Pertuzumab	380610-27-5	L01FD02
Phenylpropanolamine	14838-15-4	R01BA01
Phoxim	14816-18-3	QP53AE03
Pibrentasvir	1353900-92-1	J05AP57
Pimobendan	74150-27-9	QC01CE90
Piperacillin	61477-96-1	J01CA12
Pirfenidone	53179-13-8	L04AX05
Piroxicam	36322-90-4	M01AC01 ,M02AA07 ,S01BC06
Pixantrone Dimaleate	144675-97-8	L01DB11
Plerixafor	110078-46-1	L03AX16
Podofilox	518-28-5	D07BB04
Polatuzumabvedotin	1313206-42-6	L01FX14
Polyacrylicacid	9003-01-4	
Polyoxyethylenedodecylmo-noether	9002-92-0	
Polyvinylpyrrolidone	9003-39-8	
Pomalidomide	19171-19-8	L04AX06
Ponatinibhydrochloride	1114544-31-8	L01EA05
Pralsetinib	2097132-94-8	L01EX23
Praziquantel	55268-74-1	P02BA01, QP52AA01
Prednisolone21-trime-thylacetate	1107-99-9	S02BA03
Prednisoloneacetate	52-21-1	S02BA03
Prednisone	53-03-2	S02BA03
Prilocainehydrochloride	1786-81-8	N01BB04
Procainehydrochloride	51-05-8	N01BA02, C05AD05, S01HA05
Proguanilhydrochloride	637-32-1	P01BB01
Protamines,sulfates	9009-65-8	V03AB14
Puromycindihydrochloride	58-58-2	
Pyrantel	15686-83-6	P02CC01, QP52AF02
Pyrantelpamoate	22204-24-6	P02CC01, QP52AF02
Pyriproxyfen	95737-68-1	QP53AX23
Raltegravir	518048-05-0	J05AJ01
Ramucirumab	947687-13-0	L01FG02

Rasburicase	134774-45-1	V03AF07
Ravulizumab	1803171-55-2	L04AA43
Regorafenib	755037-03-7	L01EX05
Remimazolam Tosilate	308242-62-8	N05CD14
Reslizumab	241473-69-8	R03DX08
Ribociclib	1211441-98-3	L01EF02
Rilpivirinehydrochloride	700361-47-3	J05AG05 ,
Riociguat	625115-55-1	C02KX05
Risankizumab	1612838-76-2	L04AC18
Risdiplam	1825352-65-5	M09AX10
Robenacoxib	220991-32-2	QM01AH91
Rocuroniumbromide	119302-91-9	M03AC09
Romifidine	65896-16-4	QN05CM93
Romiplostim	267639-76-9	B02BX04
Ropeginterferon ALFA-2B	1335098-50-4	L03AB15
Rurioctocog alfa pegol	1417412-83-9	B02BD02
Ruxolitinib Phosphate	1092939-17-7	L01EJ01
Sacituzumabgovitecan	1491917-83-9	L01FX17
Sacubitril	149709-62-6	C09DX04
Salmoncalcitonin	47931-85-1	
Satralizumab	1535963-91-7	L04AC19
Saxagliptinhydrochloride	709031-78-7	A10BH03
Sebelipase alfa	1276027-63-4	A16AB14
Selamectin	220119-17-5	QP54AA05, QP53BX55
Selexipag	475086-01-2	B01AC27
Selpercatinib	2152628-33-4	L01EX22
Siltuximab	541502-14-1	L04AC11
Simethicone	8050-81-5	A03AX13
Simoctocog alfa	1219013-68-9	B02BD02
Siponimod fumarate	1234627-85-0	L04AA42
Sitagliptinphosphatemono-hydrate	654671-77-9	A10BH01
Sodium citrate tribasic dihy-drate	6123-04-3	B05CB02
Sodium2-mercap-toethanesulfonate	19767-45-4	R05CB05, V03AF01
Sodium4-phenylbutyrate	1716-12-7	A16AX03
Sodiumglycerophos-phateanhydrous	1334-74-3	B05XA14
Sodiumnitroprussidedihy-drate	13755-38-9	C02DD01, QC02DD01
Sodiumpicosulfatemonohy-drate	1307301-38-7	A06AB08
Sodiumsalicylate	54-21-7	N02BA04
Sodiumzirconiumcyclosili-cate	17141-74-1	
Sofosbuvir	1190307-88-0	J05AP08, J05AP51, J05AP55, J05AP56
Solifenacin succinate	242478-38-2	G04BD08

Somapacitan	1338578-34-9	H01AC07
Sonidegib	956697-53-3	L01XJ02
Sorafenibtosylate	475207-59-1	L01EX02
Sotorasib	2252403-56-6	L01XX73
Streptozotocin	18883-66-4	L01AD04
Succinylcholine	306-40-1	M03AB01
Sucroseoctasulfate-aluminumcomplex	54182-58-0	
Sugammadexsodium	343306-79-6	V03AB35
Sulfadiazine	68-35-9	J01EC02, QJ01EQ10
Sulfadoxine	2447-57-6	QJ01EQ13
Sulfurfluoride	2551-62-4	
Sunitinibmalate	341031-54-7	L01EX01
Tafamidis Meglumine	951395-08-7	N07XX08
Tafasitamab	1422527-84-1	L01FX12
Talazoparibtosylate	1373431-65-2	L01XK04
Tamsulosinhydrochloride	106463-17-6	G04CA02
Tazobactam	89786-04-9	J01CG02
Tazobactamsodium	89785-84-2	J01CG02
Teduglutide	197922-42-2	A16AX08
Tegafur	37076-68-9	L01BC03
Tegafur	17902-23-7	L01BC03
Teicoplanin	61036-62-2	J01XA02
Telotristatetiprate	1137608-69-5	A16AX15
tenecteplase	191588-94-0	B01AD11
Tenofoviralafenamide	379270-37-8	J05AF13
Teriflunomide	163451-81-8	L04AA31
Terlipressin	14636-12-5	H01BA04
Tetracosactidehexaacetate	22633-88-1	H01AA02
Tetraethyleneglycolmonododecylether	5274-68-0	
Tetraethylthiuramdisulfide	97-77-8	P03AA05
Tezacaftor	1152311-62-0	R07AX31
Thiopental	76-75-5	N01AF03 ,N05CA19
Thiotepa	52-24-4	L01AC01
thyrotropin alfa	194100-83-9	H01AB01
Tiamulin	55297-95-5	QJ01XQ01
Tigilanoltiglate	943001-56-7	QL01XX91
Tildipirosin	328898-40-4	QJ01FA99
Tildrakizumab	1326244-10-3	L04AC17
Tiletaminehydrochloride	14176-50-2	
Tilmicosin	108050-54-0	QJ01FA91
Tiotropiumbromidemonohydrate	139404-48-1	R03BB04
Tipiracilhydrochloride	183204-72-0	L01BC59
Tirbanibulin	897016-82-9	D06BX03
Tisagenlecleucel	1823078-37-0	L01XX71

Tivozanib monohydrochloride monohydrate	682745-41-1	L01EK03
Tizanidinehydrochloride	64461-82-1	M03BX02
Tocilizumab	375823-41-9	L04AC07
Tofacitinibcitrate	540737-29-9	L04AA29
Toltrazuril	69004-03-1	QP51AJ01
Topotecanhydrochloride	119413-54-6	L01CE01
Torsemide	56211-40-6	C03CA04
Tralokinumab	1044515-88-9	D11AH07
Trametinib	871700-17-3	L01EE01
Trastuzumab	180288-69-1	L01FD01
Trastuzumab deruxtecan	1826843-81-5	L01FD04
Trastuzumabemtansine	1018448-65-1	L01FD03
Treosulfan	299-75-2	L01AB02
Treprostinil	81846-19-7	B01AC21
Triamcinoloneacetonide	76-25-5	A01AC01, D07AB09, H02AB08
Trichloroethylene	79-01-6	N01AB05
Trientinehydrochloride	38260-01-4	A16AX12
Trifarotene	895542-09-3	D10AD06
Trifluridine	70-00-8	S01AD02
Trilostane	13647-35-3	H02CA01
Trimagnesiumdicitrate	3344-18-1	
Trinitroglycerin	55-63-0	C01DA02
Troxerutin	7085-55-4	C05CA04
Tucatinib	937263-43-9	L01EH03
Turoctocog alfa	1192451-26-5	B02BD02
Tylosinphosphateandbentonitedrugcombination	1405-53-4	QJ01FA90, QJ51FA90
Tylosintartrate	74610-55-2	QJ01FA90, QJ51FA90
Tylvalosin tartrate	63428-13-7	QJ01FA92
Umeclidiniumbromide	869113-09-7	R03BB07, R03AL03
Upadacitinib Hydrate	2050057-56-0	L04AA44
Vandetanib	443913-73-3	L01EX04
Vasopressintannate	113-79-1	H01BA01
Vedolizumab	943609-66-3	L04AA33
Velaglucerase alfa	884604-91-5	A16AB10
VelcalcetideHydrochloride	1334237-71-6	H05BX04
Velmanase alfa	1492823-75-2	A16AB15
Velpatasvir	1377049-84-7	J05AP55
Veltassa	1415477-49-4	V03AE09
Vemurafenib	918504-65-1	L01EC01
Vericiguat	1350653-20-1	C01DX22
Vernakalant Hydrochloride	748810-28-8	C01BG11
Vilanterol	503068-34-6	R03AK10
Vildagliptin	1217546-82-1	A10BH02, A10BD08
Vinblastinesulfate	143-67-9	L01CA01
Vincristine	57-22-7	L01CA02

Vincristinesulfate	2068-78-2	L01CA02
Vinflunine Tartrate	1201898-17-0	L01CA04
Vinorelbinetartrate	125317-39-7	L01CA04
Vismodegib	879085-55-9	L01XJ01
Volanesorsen sodium	1573402-50-2	C10AX18
Vonicog alfa	109319-16-6	B02BD10
Voretigene neparvovec	1646819-03-5	S01XA27
Xylazine	7361-61-7	QN05CM92
Zanamivir	139110-80-8	J05AH01
Zanubrutinib	1691249-45-2	L01EL03
Ziconotide	107452-89-1	N02BG08
Zidovudine	30516-87-1	J05AF01
Zolazepam hydrochloride	33754-49-3	
α-Galactosidase	9025-35-8	A16AB03

Appendix 2 List of prescription human APIs with hazard score zero

Preferred name	CASRN	ATC code
Cilastatin	82009-34-5	R01AD13, R03BA08
Nystatin	1400-61-9	A07AA02, D01AA01, G01AA01
Vildagliptin	274901-16-5	A10BH02, A10BD08
Amlodipinebesylate	111470-99-6	C08CA01
Frunevetmab	1708936-80-4	R01AD12, R03BA09, R03AK10, R03AL08
Gemtuzumabozogamicin	220578-59-6	C03CA01
Metoprololsuccinate	98418-47-4	C07AB02
Sildenafilcitrate	171599-83-0	G04BE03
Gadotericacid	72573-82-1	R03AC13, R03AC13, R03CC15
Semaglutide	910463-68-2	A10BJ06
Blinatumomab	853426-35-4	C07AB07
Beclomethasonedipropionatemonohy-drate	77011-63-3	A07EA07, D07AC15, R01AD01, R03BA01
Heparin	9005-49-6	A10BB12
TolterodineL-tartrate	124937-52-6	G04BD07
DL-Dobutamine	34368-04-2	C05AE03, C08DB01 (WHO
Ixazomibcitrate	1239908-20-3	R01AX03, R03BB01
Ixekizumab	1143503-69-8	R01AX03, R03BB01
Adapalene	106685-40-9	D10AD03
Canakinumab	914613-48-2	A10BK02
Isatuximab	1461640-62-9	R03AC18
Leuprorelin	53714-56-0	M01AB15, S01BC05
VitaminD3	67-97-0	A11CC05
Bivalirudin	128270-60-0	A06AB02, A06AG02,
Calcium(6S)-folinate	80433-71-2	D05AX02
DiroximelFumarate	1577222-14-0	A08AA03
Emedastinedifumarate	87233-62-3	A10BJ05
Pulmozyme	143831-71-4	R05CB13
Terazosinhydrochloride	63074-08-8	G04CA03
Avanafil	330784-47-9	G04BE10
Balsalazide disodium	82101-18-6	A07EC04
Benralizumab	1044511-01-4	D04AB03,S01HA02
Bezlotoxumab	1246264-45-8	C07AB05, S01ED02
Fluticasonepropionate	80474-14-2	V03AB25
Heparinsodium	9041-08-1	A10BB07
Humanchorionicgonadotropin	9002-61-3	A16AX09
Ibritumomab	206181-63-7	B01AB01, C05BA03, S01XA14
Icosapentethyl	86227-47-6	D03AX05, M09AX01, R01AX09, S01KA01
Imlifidase	1947415-68-0	C10AX06
Lexiscan	313348-27-5	V03AE03
Naloxegoloxalate	1354744-91-4	A06AH03
Naloxonehydrochloride	357-08-4	A06AH04, V03AB15
Opium	8008-60-4	A07DA02, N02AA02
Palivizumab	188039-54-5	J06BD01
Phytonadione	84-80-0	B02BA01
Roflumilast	162401-32-3	R03DX07
Sapropterindihydrochloride	69056-38-8	A16AX07
Sevelamercarbonate	845273-93-0	V03AE02

Vancomycinhydrochloride	1404-93-9	A07AA09, J01XA01, S01AA28
Zinc(II)acetatedihydrate	5970-45-6	A16AX05
Zoledronate	118072-93-8	M05BA08
Zoledronicacidmonohydrate	165800-06-6	M05BA08
Apraclonidinehydrochloride	73218-79-8	S01EA03
Ticagrelor	274693-27-5	B01AC24
Mirabegron	223673-61-8	G04BD12
Salmeterolxinafoate	94749-08-3	R03AC12
Doravirine	1338225-97-0	A06AD16, B05BC01, B05CX04, R05CB16, V04CX04
Entrectinib	1108743-60-7	S01GX06
Olodaterol	868049-49-4	R03AC19
Epoprostenol	35121-78-9	C09AA02
Formoterolhemifumarate	43229-80-7	C05AA10, D07AC04, S01BA15, S02BA08
Cysteaminebitartrate	27761-19-9	S01FA04
Ketobemidonehydrochloride	5965-49-1	C09CA04, C09DA04
Diethylpropion	90-84-6	B05CX01, V04CA02, V06DC01
Abrocitinib	1622902-68-4	D11AH08
Aclidiniumbromide	320345-99-1	R03BB05
Alanylglutamine	39537-23-0	
Alginicacid	9005-32-7	A02BX13
alpha1-Antitrypsin	9041-92-3	B02AB02
Alteplase	105857-23-6	B01AD02, S01XA13
Amantadine	768-94-5	C02KX02
Amprolium	13082-85-4	QP51AX09
Andexanet alfa	1262449-58-0	V03AB38
AngiotensinIIacetate	68521-88-0	C01CX09
Antazoline Hemisulfate	84803-70-3	
Antithrombin,III	90170-80-2	
Apramycinsulfate	65710-07-8	QA07AA92, QJ01GB90, QJ51GB90
Argatroban	74863-84-6	B01AE03
Arsenite	15502-74-6	
Asfotase alfa	1174277-80-5	A16AB13
Ataluren	775304-57-9	M09AX03
Avalglucosidase alfa	1802558-87-7	A16AB22
Avatrombopag	570406-98-3	B02BX08
Azelastinehydrochloride	79307-93-0	R01AC03, R06AX19, S01GX07
Beclomethasone Dipropionate	08-09-5534	B06AC01
Bedaquilinefumarate	845533-86-0	A07EA07, D07AC15, R01AD01, R03BA01
Belatacept	706808-37-9	QN02BG91
Bendamustinehydrochloride	3543-75-7	C09AA07
Benzenesulfonicacid,4-ethenyl-,homopolymer	28210-41-5	QN04AC01
Berotralstathydrochloride	1809010-52-3	D10AE01, D10AE51
beta-Galactosidase	9031-11-2	A01AD02, G02CC03, M01AX07, M02AA05, R02AX03
Betaxolol Hydrochloride	63659-19-8	
Bimekizumab	1418205-77-2	
Binimetinib	606143-89-9	R06AX29, S01GX13
Blood-coagulationfactorIX	9001-28-9	B01AE06
Bosutinib	380843-75-4	C02KX01

Buserelin	57982-77-1	M05BX05
Calciumdichloridedihydrate	10035-04-8	A12AA03, D11AX03
Canagliflozin	842133-18-0	A12AA20
CangrelorTetrasodium	163706-36-3	C09CA06
Cannabidiol	74219-29-7	B01AC25
Carfilzomib	868540-17-4	
Catridecacog	606138-08-3	QM01AE91
Ceftaroline	189345-04-8	QJ01DD91
Cetrorelixacetate	145672-81-7	A16AB17
Chondroitinsulfatase	9025-60-9	A01AB21, D06AA02, J01AA03, S01AA02, QG51AA08, QJ51AA03
Ciclesonide	141845-82-1	M03BB03
Cidofovir	113852-37-2	M01AX25
Closantel	57808-65-8	D08AH30, D09AA10, (dressing) G01AC02, P01AA02, S02AA05
Cobicistat	1004316-88-4	A01AB18, D01AC01, G01AF02, QJ02AB90
Colesevelamhydrochloride	182815-44-7	V03AX03
Cosyntropin	16960-16-0	M04AC01
Crizanlizumab	1690318-25-2	C10AC04
Crizotinib	877399-52-5	A07AA10, J01XB01, QA07AA10, QA07AA98, QG51AG07, QJ01XB01, QJ51XB01
Cyclophosphamidemonohydrate	6055-19-2	A07EB01, D11AH03, R01AC01, R03BC01, S01GX01
Dacomitinib	1110813-31-4	A16AA04, S01XA21
Dalbavancin	171500-79-1	A16AA04, S01XA21
Degarelix	214766-78-6	A11GA01, G01AD03, S01XA15
Deslorelinacetate	82318-06-7	B01AX01
Dexmedetomidine	113775-47-6	R06AX27
Dexrazone	24584-09-6	QH01CA93
Diclazuril	101831-37-2	V03AF02
Dinutuximab	1363687-32-4	QP51AJ03
DL-Ascorbicacid	62624-30-0	C01AA05
Dostarlimab	2022215-59-2	A06AA02
Drospirenone	67392-87-4	C01CA04
Eflornithine	70052-12-9	C01BD07
Enfortumab	1346452-25-2	A16AX10
Enzalutamide	915087-33-1	B02BX06
Eribulin Mesylate	441045-17-6	QJ01MA90
Escitalopramoxalate	219861-08-2	B03XA01
Esketamine	33643-46-8	B03XA
Eslicarbazepineacetate	236395-14-5	B01AC09
Fedratinibhydrochloride	1374744-69-0	B02BX01
Fidaxomicin	873857-62-6	M04AA03
Finerenone	1050477-31-0	C08CA02
Florfenicol	73231-34-2	A08AA02, N03AX26
Flumethrin	69770-45-2	B02BB01
Fluvoxaminemaleate	61718-82-9	QP53AC05
Follitropin	146479-72-3	QM01AG90
FrovatriptanSuccinatemonohydrate	158930-17-7	QP53BE02
Fusidicacid	6990-06-3	B03BB01, V04CX02, B03AE02, B03AE01, B03BB51

Gadobenatedimeglumine	127000-20-8	B03BB01, V04CX02, B03AE02, B03AE01, B03BB51
Galsulfase	552858-79-4	B02BX09
Gilteritinibfumarate	1254053-84-3	V08CA08
Givosiran	1639325-43-1	V08CA01
Glatirameracetate	147245-92-9	V08CA02
Glecaprevir	1365970-03-1	V08CA04
Halofuginone lactate	82186-71-8	
Hexaminolevulinatehydrochloride	140898-91-5	M01AX05
Humangrowthhormone	12629-01-5	A03AB02, D11AA01, R03BB06 (WHO
Hydroxypropylmethylcellulose	9004-65-3	
Hydroxyzinehydrochloride	1244-76-4	B01AB01, C05BA03, S01XA14
Ibrutinib	936563-96-1	
Idarucizumab	1362509-93-0	A01AC03, A07EA02, C05AA01, D07AA02, H02AB09, S01BA02, S02BA01
Idebenone	58186-27-9	A01AC03, A07EA02, C05AA01, D07AA02, H02AB09, S01BA02, S02BA01
Iloprosttromethamine	697225-02-8	M05BA06
Imepitoin	188116-07-6	C01EB16, G02CC01, M01AE01, M02AA13, R02AX02
Imiquimod	99011-02-6	B05DA
Indacaterolacetate	1000160-96-2	V03AB37
Inotersen	1492984-65-2	A16AB10
Insulin	9004-10-8	B01AC11
Iomeprol	78649-41-9	QN03AX90
Ipilimumab	477202-00-9	QP53AX17
Iron(III)citrate	3522-50-7	C10AX16
Isavuconazonium	742049-41-8	C03BA11
Ivacaftor	873054-44-5	V08AB10
Laronidase	210589-09-6	A16AB05
Larotrectinib	1223403-58-4	C01D
Ledipasvir	1256388-51-8	D11AX22, P02CF01, QP54AA01, QS02QA03
Levocetirizine	130018-77-8	A06AD11
Linaclotide	851199-59-2	A06AX04
Linagliptin	668270-12-0	A10BH05
Liraglutide	204656-20-2	A10BJ02
Lisinoprildihydrate	83915-83-7	C09AA03, C09BA03, C10BX07, C09BB03
Lokivetmab	1533403-95-0	QD11AH91
Lomitapide	182431-12-5	C10AX12
Lonoctocog alfa	1388129-63-2	B02BD02
Lotilaner	1369852-71-0	QP53BE04
Lumacaftor	936727-05-8	R07AX30
Luspatercept	1373715-00-4	B03XA06
Macimorelin	381231-18-1	V04CD06
Magnesium citrate	7779-25-1	A06AD19, A12CC04, B05CB03
Magnesiumhydrogencitrate	144-23-0	A06AD19, A12CC04, B05CB03
Magnesiumsufateheptahydrate	10034-99-8	A06AD04
Maropitant	147116-67-4	QA04AD90

Maropitant citrate	359875-09-5	QA04AD90
Meclizine	569-65-3	R06AE05
Medetomidine	86347-14-0	QN05CM91
Mepolizumab	196078-29-2	R03DX09
Mercaptoethanesulfonicacid	3375-50-6	
Methenamine hippurate	5714-73-8	
Methoprene	65733-16-6	QP53AX28
Methoxy polyethylene glycol-epoetin beta	677324-53-7	B03XA03
Methylnaltrexone	83387-25-1	A06AH01
metreleptin	186018-45-1	A16AA07
Migalastathydrochloride	75172-81-5	A16AX14
Milbemycin oxime	129496-10-2	QP54AB01
Mivacuriumchloride	106861-44-3	M03AC10
NeomycinBsulfate	25389-98-4	A01AB08, A07AA01, B05CA09, D06AX04, J01GB05, R02AB01, S01AA03, S02AA07, S03AA01
Neomycinsulfate	1405-10-3	A01AB08, A07AA01, B05CA09, D06AX04, J01GB05, R02AB01, S01AA03, S02AA07, S03AA01
Netupitant	290297-26-6	
Nitenpyram	120738-89-8	QP53BX02
Nitenpyram	150824-47-8	QP53BX02
Nonacog beta pegol	1175512-71-6	B02BD04
Nusinersensodium	1258984-36-9	M09AX07
Obeticholicacid	459789-99-2	A05AA04
Oclacitinib	1208319-26-9	QD11AH90
Octocogalfa	139076-62-3	B02BD02
Odevixibat	501692-44-0	A05AX05
Olodaterolhydrochloride	869477-96-3	R03AC19
Omalizumab	242138-07-4	R03DX05
Onasemnogene abeparvovec	1922968-73-7	M09AX09
Osateroneacetate	105149-00-6	
Oxyclozanide	2277-92-1	QP52AG06
Palonosetronhydrochloride	135729-62-3	A04AA05
Pancreatictrypsininhibitor	9087-70-1	B02AB01
Paromomycinsulfate	1263-89-4	A07AA06, QJ01GB92
Pegvaliase	1585984-95-7	A16AB19
Pentosanpolysulfatesodium	140207-93-8	C05BA04
PerindoprilL-arginine	612548-45-5	C09AA04 ,
Pimobendan	74150-27-9	QC01CE90
Polyacrylicacid	9003-01-4	
Polyoxyethylenedodecylmonoether	9002-92-0	
Polyvinylpyrrolidone	9003-39-8	
Protamines,sulfates	9009-65-8	V03AB14
Puromycindihydrochloride	58-58-2	
Rasburicase	134774-45-1	V03AF07
Reslizumab	241473-69-8	R03DX08
Riociguat	625115-55-1	C02KX05
Risdiplam	1825352-65-5	M09AX10
Robenacoxib	220991-32-2	QM01AH91
Romifidine	65896-16-4	QN05CM93
Romiplostim	267639-76-9	B02BX04
Rurioctocog alfa pegol	1417412-83-9	B02BD02

Sacubitril	149709-62-6	C09DX04
Salmoncalcitonin	47931-85-1	
Saxagliptinhydrochloride	709031-78-7	A10BH03
Sebelipase alfa	1276027-63-4	A16AB14
Selamectin	220119-17-5	QP54AA05, QP53BX55
Selexipag	475086-01-2	B01AC27
Simethicone	8050-81-5	A03AX13
Simoctocog alfa	1219013-68-9	B02BD02
Sitagliptinphosphatemonohydrate	654671-77-9	A10BH01
Sodium citrate tribasic dihydrate	6123-04-3	B05CB02
Sodium2-mercaptoethanesulfonate	19767-45-4	R05CB05, V03AF01
Sodium4-phenylbutyrate	1716-12-7	A16AX03
Sodiumglycerophosphateanhydrous	1334-74-3	B05XA14
Sodiumnitroprussidedihydrate	13755-38-9	C02DD01, QC02DD01
Sodiumpicosulfatemonohydrate	1307301-38-7	A06AB08
Sodiumzirconiumcyclosilicate	17141-74-1	
Solifenacin succinate	242478-38-2	G04BD08
Succinylcholine	306-40-1	M03AB01
Sucroseoctasulfate-aluminumcomplex	54182-58-0	
Sugammadexsodium	343306-79-6	V03AB35
Sulfurfluoride	2551-62-4	
Tamsulosinhydrochloride	106463-17-6	G04CA02
Teduglutide	197922-42-2	A16AX08
Telotristatetiprate	1137608-69-5	A16AX15
tenecteplase	191588-94-0	B01AD11
Tetraethyleneglycolmonododecylether	5274-68-0	
Tezacaftor	1152311-62-0	R07AX31
Tiamulin	55297-95-5	QJ01XQ01
Tigilanoltiglate	943001-56-7	QL01XX91
Tildipirosin	328898-40-4	QJ01FA99
Tiletaminehydrochloride	14176-50-2	
Tiotropiumbromidemonohydrate	139404-48-1	R03BB04
Tizanidinehydrochloride	64461-82-1	M03BX02
Toltrazuril	69004-03-1	QP51AJ01
Tralokinumab	1044515-88-9	D11AH07
Triamcinoloneacetonide	76-25-5	A01AC01, D07AB09, H02AB08
Trientinehydrochloride	38260-01-4	A16AX12
Trifarotene	895542-09-3	D10AD06
Trimagnesiumdicitrate	3344-18-1	
Troxerutin	7085-55-4	C05CA04
Turoctocog alfa	1192451-26-5	B02BD02
Tylosinphosphateandbentonitedrugcombination	1405-53-4	QJ01FA90, QJ51FA90
Tylosintartrate	74610-55-2	QJ01FA90, QJ51FA90
Tylvalosin tartrate	63428-13-7	QJ01FA92
Umeclidiniumbromide	869113-09-7	R03BB07, R03AL03
Velaglucerase alfa	884604-91-5	A16AB10
Velmanase alfa	1492823-75-2	A16AB15
Veltassa	1415477-49-4	V03AE09
Vericiguat	1350653-20-1	C01DX22
Vernakalant Hydrochloride	748810-28-8	C01BG11
Vilanterol	503068-34-6	R03AK10
Vildagliptin	1217546-82-1	A10BH02, A10BD08

Volanesorsen sodium	1573402-50-2	C10AX18
Vonicog alfa	109319-16-6	B02BD10
Voretigene neparvovec	1646819-03-5	S01XA27
Zolazepam hydrochloride	33754-49-3	
α-Galactosidase	9025-35-8	A16AB03

Appendix 3 Full list of ranked prescription human APIs – highest to lowest

Preferred name	CASRN	Total score
Metformin	657-24-9	162,30
Estradiol	50-28-2	150,00
Trimethoprim	738-70-5	144,60
Carbamazepine	298-46-4	144,20
17alpha-Ethinylestradiol	57-63-6	132,00
Fipronil	120068-37-3	130,50
Clindamycin	18323-44-9	125,35
Miconazole	22916-47-8	124,25
Imazalil	35554-44-0	122,40
Citalopram	59729-33-8	121,60
Clotrimazole	23593-75-1	114,75
Diclofenac	15307-86-5	91,60
Amoxicillin	26787-78-0	90,20
Warfarin	81-81-2	81,40
Tiotropiumbromide	136310-93-5	80,60
Metoprolol	51384-51-1	80,00
Diazepam	439-14-5	79,60
Sertraline	79617-96-2	79,40
Midazolam	59467-70-8	78,00
Lisinopril	76547-98-3	75,75
Propylthiouracil	51-52-5	75,05
Carbidopa	28860-95-9	74,00
Etoricoxib	202409-33-4	74,00
Moxonidine	75438-57-2	73,50
Ketoconazole	65277-42-1	73,10
Risperidone	106266-06-2	73,00
Oxycodone	76-42-6	72,25
Misoprostol	59122-46-2	72,10
Pregabalin	128013-69-4	72,00
Lamotrigine	84057-84-1	71,60
Bumetanide	28395-03-1	71,00
Zonisamide	68291-97-4	70,55
Olsalazine	15722-48-2	70,10
Ibandronicacid	114084-78-5	70,10
Naproxen	22204-53-1	69,90
Enalapril	75847-73-3	68,75
Desogestrel	54024-22-5	68,10
Trandolapril	87679-37-6	67,75
Anastrozole	120511-73-1	67,60
Losartan	114798-26-4	66,90
Atorvastatin	134523-00-5	66,50
Clioquinol	130-26-7	66,25
Budesonide	51333-22-3	65,50
Mirtazapine	61337-67-5	65,10
Mycophenolatemofetil	128794-94-5	65,10
Levocabastine	79516-68-0	63,80
Risedronicacid	105462-24-6	63,80
Droperidol	548-73-2	63,75
Salicylicacid	69-72-7	63,40
Conestat alfa	80295-38-1	61,75

Atenolol	29122-68-7	61,30
Busulfan	55-98-1	61,05
Felodipine	72509-76-3	61,00
Methylphenidate	113-45-1	60,50
Latanoprost	130209-82-4	60,25
Irbesartan	138402-11-6	59,70
Oxcarbazepine	28721-07-5	59,50
Riluzole	1744-22-5	59,35
Baclofen	1134-47-0	59,30
Acitretin	55079-83-9	59,25
Fulvestrant	129453-61-8	59,00
Omeprazole	73590-58-6	59,00
Sumatriptan	103628-46-2	58,50
Buprenorphine	52485-79-7	57,60
Clarithromycin	81103-11-9	57,50
Travoprost	157283-68-6	57,50
Montelukast	158966-92-8	57,50
Tafluprost	209860-87-7	57,25
Mebendazole	31431-39-7	57,05
Sirolimus	53123-88-9	56,85
Mometasone	105102-22-5	56,85
Dacarbazine	4342-03-4	56,75
Nepafenac	78281-72-8	56,30
Morphine	57-27-2	56,25
Methotrexate	59-05-2	56,10
Rotigotine	99755-59-6	55,55
Rotigotine	92206-54-7	55,55
Ziprasidone	146939-27-7	55,55
Tetrabenazine	58-46-8	54,85
Fludarabine	21679-14-1	54,85
Pilocarpine	92-13-7	54,60
Clonazepam	1622-61-3	54,50
Rufinamide	106308-44-5	54,35
Valsartan	137862-53-4	54,30
Nitrazepam	146-22-5	53,75
Captopril	62571-86-2	53,65
Oxazepam	604-75-1	53,25
Ciprofloxacin	85721-33-1	53,20
Levetiracetam	102767-28-2	53,05
Pregabalin	148553-50-8	53,00
Etoposide	33419-42-0	52,80
Metolazone	17560-51-9	52,35
Theophylline	58-55-9	52,05
Deferoxamine	70-51-9	51,85
Codeine	76-57-3	51,35
Aripiprazole	129722-12-9	51,30
Bexarotene	153559-49-0	51,25
Dopamine	51-61-6	51,25
Ifosfamide	3778-73-2	50,75
Furosemide	54-31-9	49,60
Mianserin	24219-97-4	48,75
Nortriptyline	72-69-5	48,75
Salmeterol	89365-50-4	48,60

Rivastigmine	123441-03-2	48,10
Alprazolam	28981-97-7	47,75
Mesalazine	89-57-6	47,60
Spironolactone	52-01-7	47,05
Haloperidol	52-86-8	46,50
Nifedipine	21829-25-4	46,25
Ceftazidimepentahydrate	78439-06-2	46,10
Fentanyl	437-38-7	45,60
Tacrolimus	104987-11-3	45,55
Metoclopramide	364-62-5	45,25
Phenobarbital	50-06-6	44,15
Azithromycin	83905-01-5	43,20
Etonogestrel	54048-10-1	42,80
Dexamethasone	50-02-2	42,75
Naloxone	465-65-6	42,35
Ampicillin	69-53-4	42,10
Chlorprothixene	113-59-7	41,50
Lorazepam	846-49-1	41,25
Acyclovir	59277-89-3	40,75
Naltrexone	16590-41-3	40,55
CJ023423	415903-37-6	40,10
Erythromycin	114-07-8	39,90
Docetaxel	114977-28-5	39,80
Levothyroxine	51-48-9	39,70
Norethindrone	68-22-4	38,75
Alendronatesodium	121268-17-5	38,70
Naratriptan	121679-13-8	38,60
Desloratadine	100643-71-8	38,60
Tibolone	5630-53-5	38,35
Vortioxetinehydrobromide	960203-27-4	38,25
Midazolam maleate	65607-69-4	38,25
Paroxetinehydrochloridehemihydrate	110429-35-1	38,25
Cholestyramineresin	11041-12-6	38,25
Nitrofurantoin	67-20-9	37,75
Testosteroneundecylate	5949-44-0	37,75
Methylprednisolone	83-43-2	37,75
Cytarabine	147-94-4	37,65
Perphenazine	58-39-9	37,55
Oxytocin	50-56-6	37,25
Zuclopenthixolacetate	85721-05-7	37,25
Mifepristone	84371-65-3	37,15
Zuclopenthixoldecanoate	64053-00-5	35,25
Cimicoxib	265114-23-6	35,20
Pivampicillin	33817-20-8	34,75
Moxifloxacin	151096-09-2	34,75
Dextromethorphanhydrobromidemono-hydrate	6700-34-1	34,75
Fostamatinib	901119-35-5	34,75
Exemestane	107868-30-4	34,65
Bisacodyl	603-50-9	34,50
Diltiazemhydrochloride	33286-22-5	34,20
Nortriptylinehydrochloride	894-71-3	34,20
Dienogest	65928-58-7	34,10

Phenylephrine	59-42-7	33,80
Bupivacainehydrochloride	18010-40-7	33,75
Triptorelin	57773-63-4	33,55
Teriparatide	52232-67-4	33,55
Cabotegravir	1229006-15-8	33,55
Triptorelin Acetate	140194-24-7	33,55
Domperidone	57808-66-9	33,35
Timolol	26839-75-8	33,25
Testosteroneenanthate	315-37-7	33,00
Prednisolone	50-24-8	32,95
6_Mercaptopurine	50-44-2	32,85
Atropine	51-55-8	32,85
Caplacizumab	915810-67-2	32,35
Octreotide	83150-76-9	32,35
Ustekinumab	815610-63-0	32,35
Rifabutin	72559-06-9	32,35
Nintedanib	656247-17-5	32,35
Bilastine	202189-78-4	32,35
Elotuzumab	915296-00-3	32,35
HyaluronateSodium	9067-32-7	32,35
Gelatin	9000-70-8	32,35
Carboxymethylcellulose	9000-11-7	32,35
Aztreonam lysine	827611-49-4	32,35
Luproliteacetate	34973-08-5	32,35
Enflicoxib	251442-94-1	32,35
Tenofovir disoproxil succinate	1637632-97-3	32,35
Lutropinalfa	152923-57-4	32,35
Tenofovir disoproxil phosphate	1453166-76-1	32,35
Idursulfase beta	1271734-34-9	32,35
Fremanezumab	1655501-53-3	32,25
Fosfomycin	23155-02-4	32,25
Fostemsavir tromethamine	864953-39-9	32,25
Ipratropiumbromidehydrate	66985-17-9	32,25
Bisoprololfumarate	104344-23-2	32,25
Lisdexamfetaminedimesylate	608137-33-3	31,90
Ichthammol	8029-68-3	31,75
Lactulose	4618-18-2	31,55
Procyclidine	77-37-2	31,05
Pimozide	2062-78-4	31,05
Selegilinehydrochloride	14611-52-0	31,05
Colchicine	64-86-8	31,05
Verapamilhydrochloride	152-11-4	31,00
Idelalisib	870281-82-6	30,80
Pivmecillinam	32886-97-8	30,75
Aspirin	50-78-2	30,75
Apremilast	608141-41-9	30,60
Stiripentol	137767-55-6	30,35
Roxithromycin	80214-83-1	30,25
Asenapine	65576-45-6	29,85
Ganirelix	124904-93-4	29,85
Sertindole	106516-24-9	29,85
Safinamidemesylate	202825-46-5	29,85
Solriamfetolhydrochloride	178429-65-7	29,85

Calcipotriene	112965-21-6	29,85
Nicorandil	65141-46-0	29,05
Midodrine	42794-76-3	29,05
Zuclopenthixoldihydrochloride	58045-23-1	28,70
Melatonin	73-31-4	28,25
Tramadolhydrochloride	36282-47-0	28,25
Tenoxicam	59804-37-4	27,90
Benethaminepenicillin	751-84-8	27,85
Metyrapone	54-36-4	27,85
Gentamicin	1403-66-3	27,85
Buspironehydrochloride	33386-08-2	27,80
Raloxifenehydrochloride	82640-04-8	27,80
Tadalafil	171596-29-5	27,75
Pramipexole	104632-26-0	27,60
Isoproterenol	7683-59-2	27,25
Metronidazolebenzoate	13182-89-3	27,25
Cloxacillin	61-72-3	26,75
Cannabidiol	13956-29-1	26,50
Glycopyrronium	13283-82-4	26,10
Aprepitant	170729-80-3	26,10
Gadopentetatedimeglumine	86050-77-3	26,00
Gadoteridol	120066-54-8	25,80
Folinicacidcalciumsalt	1492-18-8	25,60
Oxytetracycline	79-57-2	25,40
Nalmefene	55096-26-9	25,30
Methadonehydrochloride	1095-90-5	25,20
Sumatriptansuccinate	103628-48-4	24,25
Propafenone Hydrochloride	34183-22-7	23,60
Terbinafine	91161-71-6	23,25
Epinephrine	51-43-4	22,75
Zolmitriptan	139264-17-8	22,75
Diphenhydramine	58-73-1	22,70
Lithium citrate	919-16-4	22,70
Sodiumfluoride	7681-49-4	22,25
Venlafaxinehydrochloride	99300-78-4	21,60
Methimazole	60-56-0	21,25
Efavirenz	154598-52-4	21,25
VitaminB12	68-19-9	21,20
Mepivacaine	96-88-8	20,85
Valacyclovir hydrochloride monohydrate	521915-75-3	20,75
Methylaminolevulinate	33320-16-0	20,35
Sulfasalazine	599-79-1	19,25
Rabeprazole	117976-89-3	18,90
Bupropionhydrochloride	31677-93-7	18,85
Dronedarone	141626-36-0	18,55
Clorsulon	60200-06-8	18,25
Rizatriptanbenzoate	145202-66-0	18,25
Glucagon	9007-92-5	17,75
Mupirocin	12650-69-0	17,75
Medroxyprogesteroneacetate	71-58-9	17,75
Ulipristalacetate	126784-99-4	17,65
Propranololhydrochloride	318-98-9	17,50
Idarubicin	58957-92-9	16,25

Nonanedioicacid	123-99-9	16,25
Rifampicin	13292-46-1	15,85
Agomelatine	138112-76-2	15,75
Hydroxyurea	127-07-1	15,75
Primidone	125-33-7	15,55
Lymecycline	992-21-2	15,50
Chlorohexidine	55-56-1	14,65
Flupenthixol	2709-56-0	14,55
Econazole	27220-47-9	14,25
Fenbendazole	43210-67-9	14,25
Hesperidin	520-26-3	14,05
Dextroamphetamine	51-64-9	13,90
Ciclopirox	29342-05-0	13,75
Baricitinib	1187594-09-7	13,60
Cenobamate	913088-80-9	13,55
Fenfluramine	458-24-2	13,55
Fluticasonefuroate	397864-44-7	13,55
Nafarelinacetate	76932-60-0	13,55
Ritonavir	155213-67-5	13,35
Pimecrolimus	137071-32-0	13,25
Dipyrone	68-89-3	13,15
Tolfenamicacid	13710-19-5	13,05
Linezolid	165800-03-3	12,95
Modafinil	68693-11-8	12,75
Tenofovirdisoproxil	201341-05-1	12,65
Doxycycline	564-25-0	12,50
Sodiumvalproate	1069-66-5	12,40
Adalimumab	331731-18-1	12,35
Ceftobiprolemedocaril	252188-71-9	12,35
Cemiplimab	1801342-60-8	12,35
Certolizumabpegol	428863-50-7	12,35
Dabrafenib	1195765-45-7	12,35
Febuxostat	144060-53-7	12,35
Fexofenadinehydrochloride	153439-40-8	12,35
FG-4592	808118-40-3	12,35
Quininehydrochloride	130-89-2	12,25
Pentoxifylline	6493-05-6	11,85
Quinagolidehydrochloride	94424-50-7	11,75
Famciclovir	104227-87-4	11,35
Pipamperone	1893-33-0	11,35
Sulfamethizole	144-82-1	11,25
Cephalexin	15686-71-2	11,10
Burosumab	1610833-03-8	11,05
Gleptoferron	57680-55-4	11,05
Perampanel	380917-97-5	11,05
Ceftriaxone	73384-59-5	10,60
Apomorphinehydrochloride	314-19-2	10,50
Prasugrel	150322-43-3	10,25
Acetazolamide	59-66-5	10,05
Cobimetinib	934660-93-2	10,00
Carminicacid	1260-17-9	9,85
Cerliponase alfa	151662-36-1	9,85
Edoxabantosylate	480449-71-6	9,85

Felypressin	56-59-7	9,85
Scopolamine	51-34-3	9,85
Vancomycin	1404-90-6	9,85
Ceftolozanesulfate	936111-69-2	9,60
Phenprocoumon	435-97-2	9,55
Probenecid	57-66-9	9,55
Tropicamide	1508-75-4	9,55
Mebeverinehydrochloride	2753-45-9	9,50
Acipimox	51037-30-0	9,35
Icodextrin	337376-15-5	9,00
Phenylbutazone	50-33-9	8,85
Etodolac	41340-25-4	8,35
Lurasidone	367514-87-2	8,30
Eptifibatide	188627-80-7	7,85
Tobramycinsulfate	49842-07-1	7,80
Cilastatin	82009-34-5	7,65
Fluoresceinsodium	518-47-8	7,50
Nystatin	1400-61-9	7,35
Vildagliptin	274901-16-5	7,35
AmphotericinB	1397-89-3	7,25
Amikacinsulfate	39831-55-5	7,20
Pizotifen Malate	24359-22-6	7,10
Amlodipinebesylate	111470-99-6	7,05
Stiripentol	49763-96-4	6,80
Frunevetmab	1708936-80-4	6,75
Gemtuzumabozogamicin	220578-59-6	6,75
Metoprololsuccinate	98418-47-4	6,75
Sildenafilcitrate	171599-83-0	6,75
Gadotericacid	72573-82-1	6,75
Semaglutide	910463-68-2	6,75
Blinatumomab	853426-35-4	6,75
Beclomethasonedipropionatemonohy-drate	77011-63-3	6,75
Heparin	9005-49-6	6,75
TolterodineL-tartrate	124937-52-6	6,75
DL-Dobutamine	34368-04-2	6,75
Ixazomibcitrate	1239908-20-3	6,75
Ixekizumab	1143503-69-8	6,75
Adapalene	106685-40-9	6,75
Canakinumab	914613-48-2	6,75
Isatuximab	1461640-62-9	6,75
Leuprorelin	53714-56-0	6,75
VitaminD3	67-97-0	6,75
Bivalirudin	128270-60-0	6,75
Calcium(6S)-folinate	80433-71-2	6,75
DiroximelFumarate	1577222-14-0	6,75
Emedastinedifumarate	87233-62-3	6,75
Pulmozyme	143831-71-4	6,75
Terazosinhydrochloride	63074-08-8	6,75
Avanafil	330784-47-9	6,75
Balsalazide disodium	82101-18-6	6,75
Benralizumab	1044511-01-4	6,75
Bezlotoxumab	1246264-45-8	6,75

Fluticasonepropionate	80474-14-2	6,75
Heparinsodium	9041-08-1	6,75
Humanchorionicgonadotropin	9002-61-3	6,75
Ibritumomab	206181-63-7	6,75
Icosapentethyl	86227-47-6	6,75
Imlifidase	1947415-68-0	6,75
Lexiscan	313348-27-5	6,75
Naloxegoloxalate	1354744-91-4	6,75
Naloxonehydrochloride	357-08-4	6,75
Opium	8008-60-4	6,75
Palivizumab	188039-54-5	6,75
Phytonadione	84-80-0	6,75
Roflumilast	162401-32-3	6,75
Sapropterindihydrochloride	69056-38-8	6,75
Sevelamercarbonate	845273-93-0	6,75
Vancomycinhydrochloride	1404-93-9	6,75
Zinc(II)acetatedihydrate	5970-45-6	6,75
Zoledronate	118072-93-8	6,75
Zoledronicacidmonohydrate	165800-06-6	6,75
Diatrizoatesodium	737-31-5	6,70
Cysteaminehydrochloride	156-57-0	6,50
Nitrogenmustardhydrochloride	55-86-7	6,30
Mepivicainehydrochloride	1722-62-9	5,80
Pitolisant	362665-56-3	5,70
Apraclonidinehydrochloride	73218-79-8	5,00
Promethazinehydrochloride	58-33-3	4,90
Alprostadil	745-65-3	4,70
Tetracyclinehydrochloride	64-75-5	4,50
Timololmaleatesalt	26921-17-5	4,50
Trimetazidinedihydrochloride	13171-25-0	4,50
SodiumOxybate	502-85-2	4,40
Sotalolhydrochloride	959-24-0	3,30
Naphthylmethyl-2-imidazolinenitrate	5144-52-5	3,20
Orphenadrinehydrochloride	341-69-5	3,20
Ticagrelor	274693-27-5	3,10
Mirabegron	223673-61-8	2,20
Salmeterolxinafoate	94749-08-3	2,20
Doravirine	1338225-97-0	2,20
Entrectinib	1108743-60-7	2,00
Olodaterol	868049-49-4	2,00
Epoprostenol	35121-78-9	1,10
Formoterolhemifumarate	43229-80-7	0,40
Cysteaminebitartrate	27761-19-9	0,20
Ketobemidonehydrochloride	5965-49-1	0,20
Diethylpropion	90-84-6	0,20
Milrinone	78415-72-2	0
Cladribine	4291-63-8	0
Bortezomib	179324-69-7	0
Carboplatin	41575-94-4	0
Ketorolac	74103-06-3	0
Letrozole	112809-51-5	0
Glimepiride	93479-97-1	0
Sunitinib	557795-19-4	0

Capecitabine	154361-50-9	0
Biperiden	514-65-8	0
Xylometazoline	526-36-3	0
Clozapine	5786-21-0	0
Prilocaine	721-50-6	0
Paclitaxel	33069-62-4	0
Hydrocortisone	50-23-7	0
Lidocaine	137-58-6	0
Levonorgestrel	797-63-7	0
Ketoprofen	22071-15-4	0
Betamethasone	378-44-9	0
Celecoxib	169590-42-5	0
Deferasirox	201530-41-8	0
Donepezil	120014-06-4	0
Clopidogrel	113665-84-2	0
Bicalutamide	113299-38-0	0
Bicalutamide	90357-06-5	0
Levodopa	59-92-7	0
Loratadine	79794-75-5	0
Atovaquone	95233-18-4	0
2_4-Dichlorobenzylalcohol	1777-82-8	0
21_Hydroxyprogesterone	64-85-7	0
Abacavir	136470-78-5	0
Abatacept	332348-12-6	0
Abemaciclib	1231929-97-7	0
Abrocitinib	1622902-68-4	0
ABT-199	1257044-40-8	0
Acalabrutinib	1420477-60-6	0
Acetylpromazine	61-00-7	0
Aclidiniumbromide	320345-99-1	0
Acrivastine	87848-99-5	0
Adefovir	106941-25-7	0
Adenosine	58-61-7	0
Aflibercept	862111-32-8	0
Aglepristone	124478-60-0	0
Alanylglutamine	39537-23-0	0
Albuterolsulfate	51022-70-9	0
Alectinib	1256580-46-7	0
Alemtuzumab	216503-57-0	0
Alginicacid	9005-32-7	0
alpha1-Antitrypsin	9041-92-3	0
Alteplase	105857-23-6	0
Altrenogest	850-52-2	0
Amantadine	768-94-5	0
Ambrisentan	177036-94-1	0
Amdinocillin	32887-01-7	0
Amorolfine	67467-83-8	0
Amorolfine	78613-35-1	0
Amprolium	13082-85-4	0
Amsacrine	51264-14-3	0
Andexanet alfa	1262449-58-0	0
AngiotensinIIacetate	68521-88-0	0
Anifrolumab	1326232-46-5	0

Antazoline Hemisulfate	84803-70-3	0
Antithrombin,III	90170-80-2	0
Apramycinsulfate	65710-07-8	0
Argatroban	74863-84-6	0
ARN-509	956104-40-8	0
Arsenite	15502-74-6	0
Articaine	23964-58-1	0
Asfotase alfa	1174277-80-5	0
Ataluren	775304-57-9	0
Atezolizumab	1380723-44-3	0
Atosiban	90779-69-4	0
Avalglucosidase alfa	1802558-87-7	0
Avapritinib	1703793-34-3	0
Avatrombopag	570406-98-3	0
Avelumab	1537032-82-8	0
Axitinib	319460-85-0	0
Azacitidine	320-67-2	0
Azelastinehydrochloride	79307-93-0	0
Bariumsulfate	7727-43-7	0
Beclomethasone Dipropionate	08-09-5534	0
Bedaquilinefumarate	845533-86-0	0
Bedinvetmab	2171034-69-6	0
Belatacept	706808-37-9	0
Benazeprilhydrochloride	86541-74-4	0
Bendamustinehydrochloride	3543-75-7	0
Bendroflumethiazide	73-48-3	0
Benoxinate	99-43-4	0
Benserazidehydrochloride	14919-77-8	0
Benzenesulfonicacid,4-ethenyl-,homo-polymer	28210-41-5	0
Benzocaine	94-09-7	0
Benzoylperoxide	94-36-0	0
Benzydamine	642-72-8	0
Berotralstathydrochloride	1809010-52-3	0
beta-Galactosidase	9031-11-2	0
Betaxolol Hydrochloride	63659-19-8	0
Bimekizumab	1418205-77-2	0
Binimetinib	606143-89-9	0
Biperidenlactate	7085-45-2	0
Blood-coagulationfactorIX	9001-28-9	0
Boricacid	10043-35-3	0
Boricacid_crudenatural	11113-50-1	0
Bosentan	147536-97-8	0
Bosutinib	380843-75-4	0
Brodalumab	1174395-19-7	0
Bromocriptine	25614-03-3	0
Buserelin	57982-77-1	0
Butorphanol	42408-82-2	0
Cabergoline	81409-90-7	0
Cabozantinib	849217-68-1	0
Caffeine	58-08-2	0
CalciumD-gluconate	299-28-5	0
Calciumdichloridedihydrate	10035-04-8	0

Canagliflozin	842133-18-0	0
Candesartan	139481-59-7	0
CangrelorTetrasodium	163706-36-3	0
Cannabidiol	74219-29-7	0
Capsaicin	404-86-4	0
Carbomer	9007-20-9	0
Carfilzomib	868540-17-4	0
Cariprazine	839712-12-8	0
Carprofen	53716-49-7	0
Catridecacog	606138-08-3	0
Cefadroxil	50370-12-2	0
Cefazolin	25953-19-9	0
Cefepimechloridehydrochloridehydrate	123171-59-5	0
Cefotaxime	63527-52-6	0
Cefovecin	234096-34-5	0
Ceftaroline	189345-04-8	0
Ceftazidime	72558-82-8	0
Cefuroxime	55268-75-2	0
Ceritinib	1032900-25-6	0
Cetirizine	83881-51-0	0
Cetrorelixacetate	145672-81-7	0
Cetuximab	205923-56-4	0
Chlordiazepoxide	58-25-3	0
Chloroprocaine	133-16-4	0
Chlortetracyclinehydrochloride	64-72-2	0
Chlorzoxazone	95-25-0	0
Chondroitinsulfatase	9025-60-9	0
Ciclesonide	141845-82-1	0
Cidofovir	113852-37-2	0
Cinnarizine	16699-20-0	0
Cinnarizine	298-57-7	0
Cisplatin	15663-27-1	0
Clemastine	15686-51-8	0
Clenbuterol	37148-27-9	0
Closantel	57808-65-8	0
Cloxacillinbenzathine	23736-58-5	0
Cobicistat	1004316-88-4	0
Colesevelamhydrochloride	182815-44-7	0
Colistimethatesodium	8068-28-8	0
Cosyntropin	16960-16-0	0
Crizanlizumab	1690318-25-2	0
Crizotinib	877399-52-5	0
Cromolynsodium	15826-37-6	0
Cyclizine	82-92-8	0
Cyclopentolatehydrochloride	5870-29-1	0
Cyclophosphamide	50-18-0	0
Cyclophosphamidemonohydrate	6055-19-2	0
CyclosporinA	59865-13-3	0
Cyproteroneacetate	427-51-0	0
Dacomitinib	1110813-31-4	0
Dalbavancin	171500-79-1	0
Damoctocog alfa pegol	1363853-26-2	0
Daptomycin	103060-53-3	0

Daratumumab	945721-28-8	0
Darifenacin	133099-04-4	0
Darolutamide	1297538-32-9	0
D-Ascorbicacid	10504-35-5	0
Daunorubicin	20830-81-3	0
Decitabine	2353-33-5	0
Defibrotidesodium	83712-60-1	0
Degarelix	214766-78-6	0
Dehydroepiandrosterone	53-43-0	0
Deltamethrin	52918-63-5	0
Denosumab	615258-40-7	0
Desflurane	57041-67-5	0
Deslorelinacetate	82318-06-7	0
Desmopressin	16679-58-6	0
Detomidine	76631-46-4	0
Dexibuprofen	51146-56-6	0
Dexmedetomidine	113775-47-6	0
Dexrazone	24584-09-6	0
D-Glucose	50-99-7	0
Dibotermin alfa	246539-15-1	0
Diclazuril	101831-37-2	0
Digoxin	20830-75-5	0
Dinoprostone	363-24-6	0
Dinutuximab	1363687-32-4	0
DL-Ascorbicacid	62624-30-0	0
DL-Mannitol	87-78-5	0
D-Mannitol	69-65-8	0
Docusatehydrogen	10041-19-7	0
Dolutegravir	1051375-16-6	0
Dorzolamidehydrochloride	130693-82-2	0
Dostarlimab	2022215-59-2	0
Dothiepinhydrochloride	897-15-4	0
Drospirenone	67392-87-4	0
Dulaglutide	923950-08-7	0
Durvalumab	1428935-60-7	0
Eculizumab	219685-50-4	0
Eflornithine	70052-12-9	0
Eliglustat	491833-29-5	0
Emicizumab	1610943-06-0	0
Empagliflozin	864070-44-0	0
Emtricitabine	143491-57-0	0
Encorafenib	1269440-17-6	0
Enfortumab	1346452-25-2	0
Enrofloxacin	93106-60-6	0
Enzalutamide	915087-33-1	0
Epirubicin	56420-45-2	0
Epoetin beta	122312-54-3	0
Epoetin zeta	604802-70-2	0
Eprinomectin	123997-26-2	0
Eptinezumab	1644539-04-7	0
Eribulin Mesylate	441045-17-6	0
Ertapenem	153832-46-3	0
Ertugliflozin	1210344-83-4	0

Escitalopram	128196-01-0	0
Escitalopramoxalate	219861-08-2	0
Esketamine	33643-46-8	0
Eslicarbazepineacetate	236395-14-5	0
Esmolol	81147-92-4	0
Ethambutoldihydrochloride	1070-11-7	0
Ethamsylate	2624-44-4	0
Ethosuximide	77-67-8	0
Febantel	58306-30-2	0
Fedratinibhydrochloride	1374744-69-0	0
Fenoterolhydrobromide	1944-12-3	0
Fibrinogens	9001-32-5	0
Fidaxomicin	873857-62-6	0
Filgrastim	121181-53-1	0
Finerenone	1050477-31-0	0
Flecainide	54143-55-4	0
Florfenicol	73231-34-2	0
Floxacillin	5250-39-5	0
Fludrocortisone	127-31-1	0
Flumazenil	78755-81-4	0
Flumethrin	69770-45-2	0
Flunarizine	52468-60-7	0
Flunixinmeglumine	42461-84-7	0
Fluocinoloneacetonide	67-73-2	0
Fluocinonide	356-12-7	0
Fluorouracil	51-21-8	0
Fluralaner	864731-61-3	0
Fluvoxaminemaleate	61718-82-9	0
Folicacid	59-30-3	0
Follitropin	146479-72-3	0
Fosphenytoin	93390-81-9	0
FrovatriptanSuccinatemonohydrate	158930-17-7	0
Fusidicacid	6990-06-3	0
Gadobenatedimeglumine	127000-20-8	0
Galantaminehydrobromide	1953-04-4	0
Galsulfase	552858-79-4	0
Gamithromycin	145435-72-9	0
Ganciclovir	82410-32-0	0
Gefitinib	184475-35-2	0
Gilteritinibfumarate	1254053-84-3	0
Givosiran	1639325-43-1	0
Glatirameracetate	147245-92-9	0
Glecaprevir	1365970-03-1	0
Gliclazide	21187-98-4	0
Glipizide	29094-61-9	0
Glucosamine	3416-24-8	0
Glycerol	56-81-5	0
Glycerolphenylbutyrate	611168-24-2	0
Goserelin	65807-02-5	0
Guaifenesin	93-14-1	0
Guselkumab	1350289-85-8	0
Halofuginone	55837-20-2	0
Halofuginone lactate	82186-71-8	0

Hexaminolevulinatehydrochloride	140898-91-5	0
Histamine	51-45-6	0
Humangrowthhormone	12629-01-5	0
Hydrochlorothiazide	58-93-5	0
Hydrocortisoneacetate	50-03-3	0
Hydroxypropylmethylcellulose	9004-65-3	0
Hydroxyzinehydrochloride	1244-76-4	0
Ibrutinib	936563-96-1	0
Ibuprofen	15687-27-1	0
Icatibant	130308-48-4	0
Idarucizumab	1362509-93-0	0
Idebenone	58186-27-9	0
Iloprosttromethamine	697225-02-8	0
Imatinib	152459-95-5	0
Imepitoin	188116-07-6	0
Imidacloprid	138261-41-3	0
Imipraminehydrochloride	113-52-0	0
Imiquimod	99011-02-6	0
Inclisiran	1639324-58-5	0
Indacaterolacetate	1000160-96-2	0
Indapamide	26807-65-8	0
Infliximab	170277-31-3	0
Inotersen	1492984-65-2	0
Inotuzumab_ozogamicin	635715-01-4	0
Insulin	9004-10-8	0
Iodixanol	92339-11-2	0
Iohexol	66108-95-0	0
Iomeprol	78649-41-9	0
Ipilimumab	477202-00-9	0
Ipratropiumbromide	22254-24-6	0
Irinotecan	97682-44-5	0
Iron(III)citrate	3522-50-7	0
Isavuconazonium	742049-41-8	0
Isocarboxazid	59-63-2	0
Isoflurane	26675-46-7	0
Isoniazid	54-85-3	0
Isosorbide	652-67-5	0
Isosorbide5-mononitrate	16051-77-7	0
Ivacaftor	873054-44-5	0
Ivermectin	70288-86-7	0
Labetalol	36894-69-6	0
Lacidipine	103890-78-4	0
Lamivudine	134678-17-4	0
Lanthanumcarbonate	54451-24-0	0
Lapatinib	231277-92	0
Laronidase	210589-09-6	0
Larotrectinib	1223403-58-4	0
L-Ascorbicacid	50-81-7	0
Ledipasvir	1256388-51-8	0
Lenalidomide	191732-72-6	0
Lenograstim	135968-09-1	0
Lenvatinib	417716-92-8	0
Letermovir	917389-32-3	0

Levocetirizine	130018-77-8	0
Levofloxacin	100986-85-4	0
Lidocaine Hydrochloride	73-78-9	0
Linaclotide	851199-59-2	0
Linagliptin	668270-12-0	0
Lincomycin	154-21-2	0
Liraglutide	204656-20-2	0
Lisinoprildihydrate	83915-83-7	0
Lokivetmab	1533403-95-0	0
Lomitapide	182431-12-5	0
Lomustine	13010-47-4	0
Lonoctocog alfa	1388129-63-2	0
Loperamide	53179-11-6	0
Lorlatinib	1454846-35-5	0
Lotilaner	1369852-71-0	0
Lumacaftor	936727-05-8	0
Luspatercept	1373715-00-4	0
Macimorelin	381231-18-1	0
Magnesium citrate	7779-25-1	0
Magnesiumhydrogencitrate	144-23-0	0
Magnesiumhydroxide	1309-42-8	0
Magnesiumsufateheptahydrate	10034-99-8	0
Maraviroc	376348-65-1	0
Maropitant	147116-67-4	0
Maropitant citrate	359875-09-5	0
Mecasermin	68562-41-4	0
Meclizine	569-65-3	0
Medetomidine	86347-14-0	0
Megestrol	3562-63-8	0
Melphalan	148-82-3	0
Menbutone	3562-99-0	0
Mepolizumab	196078-29-2	0
Mercaptoethanesulfonicacid	3375-50-6	0
Methenamine hippurate	5714-73-8	0
Methoprene	65733-16-6	0
Methoxy polyethylene glycol-epoetin beta	677324-53-7	0
Methoxyflurane	76-38-0	0
Methylnaltrexone	83387-25-1	0
metreleptin	186018-45-1	0
Midostaurin	120685-11-2	0
Mifamurtide	83461-56-7	0
Migalastathydrochloride	75172-81-5	0
Miglustat	72599-27-0	0
Milbemycin oxime	129496-10-2	0
Minoxidil	38304-91-5	0
Mitomycin	1404-00-8	0
MitomycinC	50-07-7	0
Mitotane	53-19-0	0
Mitoxantrone	65271-80-9	0
Mivacuriumchloride	106861-44-3	0
Mogamulizumab	1159266-37-1	0
Moxidectin	113507-06-5	0

Nandrolone	434-22-0	0
Natalizumab	189261-10-7	0
Nelarabine	121032-29-9	0
Neomycin	1404-04-2	0
NeomycinBsulfate	25389-98-4	0
Neomycinsulfate	1405-10-3	0
Neostigmine	59-99-4	0
Neratinibmaleate	915942-22-2	0
Netupitant	290297-26-6	0
Nevirapine	129618-40-2	0
Nicotine	54-11-5	0
Nilotinibhydrochloridemonohydrate	923288-90-8	0
Nitenpyram	120738-89-8	0
Nitenpyram	150824-47-8	0
Nitisinone	104206-65-7	0
Nivolumab	946414-94-4	0
Nonacog beta pegol	1175512-71-6	0
Norepinephrine	51-41-2	0
Nusinersensodium	1258984-36-9	0
Obeticholicacid	459789-99-2	0
Obinutuzumab	949142-50-1	0
Oclacitinib	1208319-26-9	0
Ocrelizumab	637334-45-3	0
Octocogalfa	139076-62-3	0
Odevixibat	501692-44-0	0
Olaparib	763113-22-0	0
Olodaterolhydrochloride	869477-96-3	0
Omalizumab	242138-07-4	0
Onasemnogene abeparvovec	1922968-73-7	0
Osateroneacetate	105149-00-6	0
Osilodrostatphosphate	1315449-72-9	0
Osimertinibmesylate	1421373-66-1	0
Oxaliplatin	61825-94-3	0
Oxfendazole	53716-50-0	0
Oxyclozanide	2277-92-1	0
Ozanimod	1306760-87-1	0
Ozanimodhydrochloride	1618636-37-5	0
Palbociclib	571190-30-2	0
Palonosetronhydrochloride	135729-62-3	0
Pamidronicacid	40391-99-9	0
p-Aminosalicylicacid	65-49-6	0
Pancreatictrypsininhibitor	9087-70-1	0
Panitumumab	339177-26-3	0
Panobinostat	404950-80-7	0
Parecoxib	198470-84-7	0
Paromomycinsulfate	1263-89-4	0
Patisiransodium	1386913-72-9	0
Pazopanibhydrochloride	635702-64-6	0
Pegcetacoplan	2019171-69-6	0
Peginterferonalfa-2a	198153-51-4	0
Pegvaliase	1585984-95-7	0
Pegvisomant	218620-50-9	0
Pembrolizumab	1374853-91-4	0

Pemetrexed	137281-23-3	0
Pemigatinib	1513857-77-6	0
Penethamatehydriodide	808-71-9	0
Pentosanpolysulfatesodium	140207-93-8	0
Pergolidemethanesulfonate	66104-23-2	0
PerindoprilL-arginine	612548-45-5	0
Permethrin	52645-53-1	0
Pertuzumab	380610-27-5	0
Phenylpropanolamine	14838-15-4	0
Phoxim	14816-18-3	0
Pibrentasvir	1353900-92-1	0
Pimobendan	74150-27-9	0
Piperacillin	61477-96-1	0
Pirfenidone	53179-13-8	0
Piroxicam	36322-90-4	0
Pixantrone Dimaleate	144675-97-8	0
Plerixafor	110078-46-1	0
Podofilox	518-28-5	0
Polatuzumabvedotin	1313206-42-6	0
Polyacrylicacid	9003-01-4	0
Polyoxyethylenedodecylmonoether	9002-92-0	0
Polyvinylpyrrolidone	9003-39-8	0
Pomalidomide	19171-19-8	0
Ponatinibhydrochloride	1114544-31-8	0
Pralsetinib	2097132-94-8	0
Praziquantel	55268-74-1	0
Prednisolone21-trimethylacetate	1107-99-9	0
Prednisoloneacetate	52-21-1	0
Prednisone	53-03-2	0
Prilocainehydrochloride	1786-81-8	0
Procainehydrochloride	51-05-8	0
Proguanilhydrochloride	637-32-1	0
Protamines,sulfates	9009-65-8	0
Puromycindihydrochloride	58-58-2	0
Pyrantel	15686-83-6	0
Pyrantelpamoate	22204-24-6	0
Pyriproxyfen	95737-68-1	0
Raltegravir	518048-05-0	0
Ramucirumab	947687-13-0	0
Rasburicase	134774-45-1	0
Ravulizumab	1803171-55-2	0
Regorafenib	755037-03-7	0
Remimazolam Tosilate	308242-62-8	0
Reslizumab	241473-69-8	0
Ribociclib	1211441-98-3	0
Rilpivirinehydrochloride	700361-47-3	0
Riociguat	625115-55-1	0
Risankizumab	1612838-76-2	0
Risdiplam	1825352-65-5	0
Robenacoxib	220991-32-2	0
Rocuroniumbromide	119302-91-9	0
Romifidine	65896-16-4	0
Romiplostim	267639-76-9	0

Ropeginterferon ALFA-2B	1335098-50-4	0
Rurioctocog alfa pegol	1417412-83-9	0
Ruxolitinib Phosphate	1092939-17-7	0
Sacituzumabgovitecan	1491917-83-9	0
Sacubitril	149709-62-6	0
Salmoncalcitonin	47931-85-1	0
Satralizumab	1535963-91-7	0
Saxagliptinhydrochloride	709031-78-7	0
Sebelipase alfa	1276027-63-4	0
Selamectin	220119-17-5	0
Selexipag	475086-01-2	0
Selpercatinib	2152628-33-4	0
Siltuximab	541502-14-1	0
Simethicone	8050-81-5	0
Simoctocog alfa	1219013-68-9	0
Siponimod fumarate	1234627-85-0	0
Sitagliptinphosphatemonohydrate	654671-77-9	0
Sodium citrate tribasic dihydrate	6123-04-3	0
Sodium2-mercaptoethanesulfonate	19767-45-4	0
Sodium4-phenylbutyrate	1716-12-7	0
Sodiumglycerophosphateanhydrous	1334-74-3	0
Sodiumnitroprussidedihydrate	13755-38-9	0
Sodiumpicosulfatemonohydrate	1307301-38-7	0
Sodiumsalicylate	54-21-7	0
Sodiumzirconiumcyclosilicate	17141-74-1	0
Sofosbuvir	1190307-88-0	0
Solifenacin succinate	242478-38-2	0
Somapacitan	1338578-34-9	0
Sonidegib	956697-53-3	0
Sorafenibtosylate	475207-59-1	0
Sotorasib	2252403-56-6	0
Streptozotocin	18883-66-4	0
Succinylcholine	306-40-1	0
Sucroseoctasulfate-aluminumcomplex	54182-58-0	0
Sugammadexsodium	343306-79-6	0
Sulfadiazine	68-35-9	0
Sulfadoxine	2447-57-6	0
Sulfurfluoride	2551-62-4	0
Sunitinibmalate	341031-54-7	0
Tafamidis Meglumine	951395-08-7	0
Tafasitamab	1422527-84-1	0
Talazoparibtosylate	1373431-65-2	0
Tamsulosinhydrochloride	106463-17-6	0
Tazobactam	89786-04-9	0
Tazobactamsodium	89785-84-2	0
Teduglutide	197922-42-2	0
Tegafur	37076-68-9	0
Tegafur	17902-23-7	0
Teicoplanin	61036-62-2	0
Telotristatetiprate	1137608-69-5	0
tenecteplase	191588-94-0	0
Tenofoviralafenamide	379270-37-8	0
Teriflunomide	163451-81-8	0

Terlipressin	14636-12-5	0
Tetracosactidehexaacetate	22633-88-1	0
Tetraethyleneglycolmonododecylether	5274-68-0	0
Tetraethylthiuramdisulfide	97-77-8	0
Tezacaftor	1152311-62-0	0
Thiopental	76-75-5	0
Thiotepa	52-24-4	0
thyrotropin alfa	194100-83-9	0
Tiamulin	55297-95-5	0
Tigilanoltiglate	943001-56-7	0
Tildipirosin	328898-40-4	0
Tildrakizumab	1326244-10-3	0
Tiletaminehydrochloride	14176-50-2	0
Tilmicosin	108050-54-0	0
Tiotropiumbromidemonohydrate	139404-48-1	0
Tipiracilhydrochloride	183204-72-0	0
Tirbanibulin	897016-82-9	0
Tisagenlecleucel	1823078-37-0	0
Tivozanib monohydrochloride monohydrate	682745-41-1	0
Tizanidinehydrochloride	64461-82-1	0
Tocilizumab	375823-41-9	0
Tofacitinibcitrate	540737-29-9	0
Toltrazuril	69004-03-1	0
Topotecanhydrochloride	119413-54-6	0
Torsemide	56211-40-6	0
Tralokinumab	1044515-88-9	0
Trametinib	871700-17-3	0
Trastuzumab	180288-69-1	0
Trastuzumab deruxtecan	1826843-81-5	0
Trastuzumabemtansine	1018448-65-1	0
Treosulfan	299-75-2	0
Treprostinil	81846-19-7	0
Triamcinoloneacetonide	76-25-5	0
Trichloroethylene	79-01-6	0
Trientinehydrochloride	38260-01-4	0
Trifarotene	895542-09-3	0
Trifluridine	70-00-8	0
Trilostane	13647-35-3	0
Trimagnesiumdicitrate	3344-18-1	0
Trinitroglycerin	55-63-0	0
Troxerutin	7085-55-4	0
Tucatinib	937263-43-9	0
Turoctocog alfa	1192451-26-5	0
Tylosinphosphateandbentonitedrugcombination	1405-53-4	0
Tylosintartrate	74610-55-2	0
Tylvalosin tartrate	63428-13-7	0
Umeclidiniumbromide	869113-09-7	0
Upadacitinib Hydrate	2050057-56-0	0
Vandetanib	443913-73-3	0
Vasopressintannate	113-79-1	0
Vedolizumab	943609-66-3	0

Velaglucerase alfa	884604-91-5	0
VelcalcetideHydrochloride	1334237-71-6	0
Velmanase alfa	1492823-75-2	0
Velpatasvir	1377049-84-7	0
Veltassa	1415477-49-4	0
Vemurafenib	918504-65-1	0
Vericiguat	1350653-20-1	0
Vernakalant Hydrochloride	748810-28-8	0
Vilanterol	503068-34-6	0
Vildagliptin	1217546-82-1	0
Vinblastinesulfate	143-67-9	0
Vincristine	57-22-7	0
Vincristinesulfate	2068-78-2	0
Vinflunine Tartrate	1201898-17-0	0
Vinorelbinetartrate	125317-39-7	0
Vismodegib	879085-55-9	0
Volanesorsen sodium	1573402-50-2	0
Vonicog alfa	109319-16-6	0
Voretigene neparvovec	1646819-03-5	0
Xylazine	7361-61-7	0
Zanamivir	139110-80-8	0
Zanubrutinib	1691249-45-2	0
Ziconotide	107452-89-1	0
Zidovudine	30516-87-1	0
Zolazepam hydrochloride	33754-49-3	0
α-Galactosidase	9025-35-8	0

Appendix 4 List of prescription human APIs with no reported use in Denmark 2021

Preferred name	CASRN	ATC code
Ketoconazole	65277-42-1	J02AB02
Salicylicacid	69-72-7	A01AD05 ,B01AC06 ,D01AE12 ,N02BA01 ,S01BC08
Busulfan	55-98-1	L01AB01
Fulvestrant	129453-61-8	LO2BA03
Pilocarpine	92-13-7	N07AX01 ,S01EB01
Clonazepam	1622-61-3	D04AA14 ,R06AA04 ,
Etoposide	33419-42-0	LO1CB01
Dacarbazine	4342-03-4	L01AX04
Bexarotene	153559-49-0	L01XF03
Dopamine	51-61-6	A06AD16 ,B05BC01 ,B05CX04 ,R05CB16 ,V04CX04 ,
Etonogestrel	54048-10-1	D10AF02 ,J01FA01 ,S01AA17 ,QJ51FA01 ,
Naloxone	465-65-6	A06AH04, V03AB15
Docetaxel	114977-28-5	D04AA32 ,D04AA33 ,R06AA02 ,
Methylprednisolone	83-43-2	D07AA01 ,D07AC14 ,D10AA02 ,H02AB04 ,D07CA02 ,S01CA08 ,H02BX01
Timolol	26839-75-8	C07AA06 ,S01ED01 ,C07BA06 ,C07DA06
Oxytocin	50-56-6	G02AC, H01BB02
Aspirin	50-78-2	A01AD05, B01AC06, N02BA01
Fosfomycin	23155-02-4	C05AA11, D07AC08
Ichthammol	8029-68-3	G03G
Glycopyrronium	13283-82-4	D06AX07, J01GB03, S01AA11, S02AA14, S03AA06, QA07AA91, QG01AA91, QG51AA04, QJ51GB03 (WHO
Methadonehydrochloride	1095-90-5	N02AC52, N07BC02, QN02AC90
Terbinafine	91161-71-6	D01AE15 ,D01BA02
Diphenhydramine	58-73-1	D04AA32, D04AA33, R06AA02
Lithium citrate	919-16-4	N05AN
Isoproterenol	7683-59-2	A10A
Metronidazolebenzoate	13182-89-3	A01AB17, D06BX01, G01AF01, J01XD01, P01AB01, QP51AA01
VitaminB12	68-19-9	B03B
Apomorphinehydrochloride	314-19-2	G04BE07, N04BC07, QV03AB95
Sulfamethizole	144-82-1	B05CA04, D06BA04, J01EB02, S01AB01, QJ01EQ02
Cephalexin	15686-71-2	L01XX33, M01AH01
Icodextrin	337376-15-5	H01A
Quininehydrochloride	130-89-2	G02CB
Quinagolidehydrochloride	94424-50-7	G02CB
Amikacinsulfate	39831-55-5	D06AX12, J01GB06, S01AA21, J01RA06, QD06AX12, QJ01GB06, QS01AA21, QJ01RA06
Diatrizoatesodium	737-31-5	A01AC02, C05AA09, D07AB19, D10AA03, H02AB02, R01AD03, S01BA01, S02BA06, S03BA01
Nitrogenmustardhydrochloride	55-86-7	L01AA
Promethazinehydrochloride	58-33-3	D04AA10, R06AD02

Tetracyclinehydrochloride	64-75-5	A01AB13, D06AA04, J01AA07, S01AA09, S02AA08, S03AA02, QG01AA90, QG51AA02, QJ51AA07
Timololmaleatesalt	26921-17-5	C07AA06, S01ED01, C07BA06, C07DA06
AmphotericinB	1397-89-3	A01AB04, A07AA07, G01AA03, J02AA01
Naphthylmethyl-2-imidaz-olinenitrate	5144-52-5	S01GA
Orphenadrinehydrochloride	341-69-5	M03BC01, N04AB02
Milrinone	78415-72-2	C01CE02
Cladribine	4291-63-8	L01XA01
Bortezomib	179324-69-7	S02AA03, D08AD
Carboplatin	41575-94-4	
Ketorolac	74103-06-3	V03AE08
Letrozole	112809-51-5	M01AE03, M01AE17, M02AA10
Glimepiride	93479-97-1	QJ01FA95
Sunitinib	557795-19-4	L01EX01
Capecitabine	154361-50-9	
Biperiden	514-65-8	L04AC21
Xylometazoline	526-36-3	R01AA07, S01GA03
Clozapine	5786-21-0	
Prilocaine	721-50-6	N01BB04
Paclitaxel	33069-62-4	L01,L01CD03
Hydrocortisone	50-23-7	L04AC16
Lidocaine	137-58-6	L01EH01
Levonorgestrel	797-63-7	J05AF05
Ketoprofen	22071-15-4	L01CE02
Betamethasone	378-44-9	B06AC06
Celecoxib	169590-42-5	J01DI54
Deferasirox	201530-41-8	L01FC01
Donepezil	120014-06-4	C01CA07
Clopidogrel	113665-84-2	R03AC14, R03CC13, QG02CA91
Bicalutamide	113299-38-0	L01XF03
Bicalutamide	90357-06-5	J06BC03
Levodopa	59-92-7	N04BA01
Loratadine	79794-75-5	R06AX13
Atovaquone	95233-18-4	P01AX06
2_4-Dichlorobenzylalcohol	1777-82-8	R02AA03
21_Hydroxyprogesterone	64-85-7	G03DA03
Abacavir	136470-78-5	J05AF06
Abatacept	332348-12-6	L04AA24
Abemaciclib	1231929-97-7	L01EF03
ABT-199	1257044-40-8	L01XX52
Acalabrutinib	1420477-60-6	L01EL02
Acetylpromazine	61-00-7	N05AA04
Acrivastine	87848-99-5	R06AX18
Adefovir	106941-25-7	J05AF08
Adenosine	58-61-7	C01EB10
Aflibercept	862111-32-8	L01XX44, S01LA05
Aglepristone	124478-60-0	G03XB90
Albuterolsulfate	51022-70-9	
Alectinib	1256580-46-7	L01ED03
Alemtuzumab	216503-57-0	L04AA34
Altrenogest	850-52-2	QG03DX90

Ambrisentan	177036-94-1	C02KX02
Amdinocillin	32887-01-7	J01CA11
Amorolfine	67467-83-8	D01AE16
Amorolfine	78613-35-1	D01AE16
Amsacrine	51264-14-3	L01XX01
Anifrolumab	1326232-46-5	L04AA51
ARN-509	956104-40-8	L02BB05
Articaine	23964-58-1	N01BB08
Atezolizumab	1380723-44-3	L01FF05
Atosiban	90779-69-4	G02CX01
Avapritinib	1703793-34-3	L01EX18
Avelumab	1537032-82-8	L01FF04
Axitinib	319460-85-0	L01EK01
Azacitidine	320-67-2	L01BC07
Bariumsulfate	7727-43-7	V08BA01
Bedinvetmab	2171034-69-6	J04AK05
Benazeprilhydrochloride	86541-74-4	L04AA28
Bendroflumethiazide	73-48-3	L01AA09
Benoxinate	99-43-4	J01CE08
Benserazidehydrochloride	14919-77-8	R03DX10
Benzocaine	94-09-7	
Benzoylperoxide	94-36-0	
Benzydamine	642-72-8	C05AD03, D04AB04, QN01AX92, N01BA05, R02AD01
Biperidenlactate	7085-45-2	L01EE03
Boricacid	10043-35-3	L01FX07
Boricacid_crudenatural	11113-50-1	
Bosentan	147536-97-8	L01XG01
Brodalumab	1174395-19-7	L01EA04
Bromocriptine	25614-03-3	L04AC12
Butorphanol	42408-82-2	L01AB01
Cabergoline	81409-90-7	N02AF01, QR05DA90
Cabozantinib	849217-68-1	J05AJ04
Caffeine	58-08-2	L01EX07
CalciumD-gluconate	299-28-5	V03AF03
Candesartan	139481-59-7	L04AC08
Capsaicin	404-86-4	B01AX07
Carbomer	9007-20-9	N04BA05
Cariprazine	839712-12-8	L01XG02
Carprofen	53716-49-7	V04
Cefadroxil	50370-12-2	B02BD11
Cefazolin	25953-19-9	J01DB05
Cefepimechloridehydrochlo-ridehydrate	123171-59-5	J01DB04, QJ51DB04
Cefotaxime	63527-52-6	J01DE01
Cefovecin	234096-34-5	J01DD01
Ceftazidime	72558-82-8	J01DI02
Cefuroxime	55268-75-2	J01DI01
Ceritinib	1032900-25-6	L01FF06 ,
Cetirizine	83881-51-0	L01ED02
Cetuximab	205923-56-4	L04AB05
Chlordiazepoxide	58-25-3	R06AE07, S01GX12
Chloroprocaine	133-16-4	L01FE01

Chlortetracyclinehydrochloride	64-72-2	A01AB03, B05CA02, D08AC02, D09AA12, (dressing), R02AA05, S01AX09, S02AA09, S03AA04
Chlorzoxazone	95-25-0	N01BA04
Cinnarizine	16699-20-0	J05AB12
Cinnarizine	298-57-7	J01DH51
Cisplatin	15663-27-1	N07CA02
Clemastine	15686-51-8	
Clenbuterol	37148-27-9	L04AA40, L01BB04
Cloxacillinbenzathine	23736-58-5	
Colistimethatesodium	8068-28-8	L01EE02
Cromolynsodium	15826-37-6	B06AC01
Cyclizine	82-92-8	H01AA02
Cyclopentolatehydrochloride	5870-29-1	B06AX01
Cyclophosphamide	50-18-0	L01ED01
CyclosporinA	59865-13-3	
Cyproteroneacetate	427-51-0	R06AE03
Damoctocog alfa pegol	1363853-26-2	L01BC01
Daptomycin	103060-53-3	L01BC01
Daratumumab	945721-28-8	L01EC02
Darifenacin	133099-04-4	L01AX04
Darolutamide	1297538-32-9	L01EB07
D-Ascorbicacid	10504-35-5	J01XA04
Daunorubicin	20830-81-3	B02BD02
Decitabine	2353-33-5	J01XX09
Defibrotidesodium	83712-60-1	L02BB06
Dehydroepiandrosterone	53-43-0	L01DB02
Deltamethrin	52918-63-5	L01DB02
Denosumab	615258-40-7	L01BC08
Desflurane	57041-67-5	V03AC03
Desmopressin	16679-58-6	L02BX02
Detomidine	76631-46-4	P03BA03, QP53AC11
Dexibuprofen	51146-56-6	N01AB07
D-Glucose	50-99-7	QN05CM90
Dibotermin alfa	246539-15-1	N05CM18, QN05CM18
Digoxin	20830-75-5	V08AA01
Dinoprostone	363-24-6	
DL-Mannitol	87-78-5	G02AD02
D-Mannitol	69-65-8	L01FX06
Docusatehydrogen	10041-19-7	N02BB02
Dolutegravir	1051375-16-6	L04AX09
Dorzolamidehydrochloride	130693-82-2	L01CD02
Dothiepinhydrochloride	897-15-4	J05AJ03, J05AR13, J05AR21, J05AR27
Dulaglutide	923950-08-7	J05AG06
Durvalumab	1428935-60-7	J05AG06
Eculizumab	219685-50-4	L01FF07
Eliglustat	491833-29-5	N05AD08
Emicizumab	1610943-06-0	L01FF03
Empagliflozin	864070-44-0	D01AC03, G01AF05
Emtricitabine	143491-57-0	L04AA25
Encorafenib	1269440-17-6	J05AG03
Enrofloxacin	93106-60-6	L01FX08
Epirubicin	56420-45-2	J05AF09

Epoetin beta	122312-54-3	J05AF09
Epoetin zeta	604802-70-2	J05AF09
Eprinomectin	123997-26-2	L01EC03
Eptinezumab	1644539-04-7	L01FX13
Ertapenem	153832-46-3	L01EX14
Ertugliflozin	1210344-83-4	L02BB04
Escitalopram	128196-01-0	L01DB03
Esmolol	81147-92-4	QP54AA04
Ethambutoldihydrochloride	1070-11-7	B01AC16
Ethamsylate	2624-44-4	N02CD05
Ethosuximide	77-67-8	J01DH03
Febantel	58306-30-2	C07AB09
Fenoterolhydrobromide	1944-12-3	L01CB01
Fibrinogens	9001-32-5	P02CA06, QP52AC13
Filgrastim	121181-53-1	L01EJ02
Flecainide	54143-55-4	P02CA06, QP52AC13
Floxacillin	5250-39-5	R03AC04, G02CA03
Fludrocortisone	127-31-1	R06AX26
Flumazenil	78755-81-4	B03XA05
Flunarizine	52468-60-7	A07AA12
Flunixinmeglumine	42461-84-7	L03AA02
Fluocinoloneacetonide	67-73-2	C03DA05
Fluocinonide	356-12-7	QP53AX15
Fluorouracil	51-21-8	QJ01BA90, QJ51BA90
Fluralaner	864731-61-3	L01BB05
Folicacid	59-30-3	QP53AC05
Fosphenytoin	93390-81-9	S01JA01
Galantaminehydrobromide	1953-04-4	N03AB05
Gamithromycin	145435-72-9	J05AX29
Ganciclovir	82410-32-0	N02CD03
Gefitinib	184475-35-2	QN02BG90
Gliclazide	21187-98-4	A16AB08
Glipizide	29094-61-9	J05AB06, S01AD09
Glucosamine	3416-24-8	L01EB01
Glycerol	56-81-5	B05AA06
Glycerolphenylbutyrate	611168-24-2	L01FX02
Goserelin	65807-02-5	L01EX13
Guaifenesin	93-14-1	A16AX16
Guselkumab	1350289-85-8	L03AX13
Halofuginone	55837-20-2	J05AP57
Histamine	51-45-6	A06AG04, A06AX01
Hydrochlorothiazide	58-93-5	R05CA03, QM03BX90
Hydrocortisoneacetate	50-03-3	QP51AX08
Ibuprofen	15687-27-1	V04CX06
Icatibant	130308-48-4	L03AX14, V04CG03
Imatinib	152459-95-5	V10XX02
Imidacloprid	138261-41-3	B06AC02
Imipraminehydrochloride	113-52-0	D10BX01, D05AA
Inclisiran	1639324-58-5	L01DB06
Indapamide	26807-65-8	N06BX13
Infliximab	170277-31-3	L01EM01
Inotuzumab_ozogamicin	635715-01-4	L01AA06
Iodixanol	92339-11-2	L01EA01

Iohexol	66108-95-0	QD01AC90
Ipratropiumbromide	22254-24-6	QP53AX17
Irinotecan	97682-44-5	L04AA41
Isocarboxazid	59-63-2	L04AB02
Isoflurane	26675-46-7	N07XX15
Isoniazid	54-85-3	L01FB01
Isosorbide	652-67-5	V08AB09
Isosorbide5-mononitrate	16051-77-7	V08AB02
Ivermectin	70288-86-7	L01FX04
Labetalol	36894-69-6	L01FC02
Lacidipine	103890-78-4	J02AC05
Lamivudine	134678-17-4	N01AB06
Lanthanumcarbonate	54451-24-0	C01CA02, R03AB02, R03CB01
Lapatinib	231277-92	C01D
L-Ascorbicacid	50-81-7	R07AX02, R07AX30, R07AX31, R07AX32
Lenalidomide	191732-72-6	L01XG03
Lenograstim	135968-09-1	L04AC13
Lenvatinib	417716-92-8	N02AB01
Letermovir	917389-32-3	J02AB02, D01AC08, G01AF11, H02CA03
Levofloxacin	100986-85-4	J05AF05
Lidocaine Hydrochloride	73-78-9	L01EX12
Lincomycin	154-21-2	J01FF02, QJ51FF02
Lomustine	13010-47-4	L01AD02
Loperamide	53179-11-6	A07DA03, A07DA05
Lorlatinib	1454846-35-5	L01ED05
Magnesiumhydroxide	1309-42-8	A02AA04, G04BX01
Maraviroc	376348-65-1	J05AX09
Mecasermin	68562-41-4	H01AC03
Megestrol	3562-63-8	G03AC05
Melphalan	148-82-3	L01AA03
Menbutone	3562-99-0	A05BA01
Methoxyflurane	76-38-0	N02BG09
Midostaurin	120685-11-2	L01EX10
Mifamurtide	83461-56-7	L03AX15
Miglustat	72599-27-0	A16AX06
Minoxidil	38304-91-5	C02DC01, D11AX01
Mitomycin	1404-00-8	L01DC03
MitomycinC	50-07-7	L01DC03
Mitotane	53-19-0	L01XX23
Mitoxantrone	65271-80-9	L01DB07
Mogamulizumab	1159266-37-1	L01FX09
Moxidectin	113507-06-5	P02CX03, QP54AB02
Nandrolone	434-22-0	A14AB01, S01XA11
Natalizumab	189261-10-7	L04AA23
Nelarabine	121032-29-9	L01BB07
Neomycin	1404-04-2	A01AB08, A07AA01, B05CA09 D06AX04 J01GB05, R02AB01, S01AA03, S02AA07, S03AA01
Neostigmine	59-99-4	N07AA01, S01EB06, QA03AB93
Neratinibmaleate	915942-22-2	L01EH02
Nevirapine	129618-40-2	J05AG01
Nicotine	54-11-5	N07BA01, QP53AX13

Nilotinibhydrochloridemonohy-drate	923288-90-8	L01EA03
Nitisinone	104206-65-7	A16AX04
Nivolumab	946414-94-4	L01FF01
Norepinephrine	51-41-2	C01CA03
Obinutuzumab	949142-50-1	L01FA03
Ocrelizumab	637334-45-3	L04AA36
Olaparib	763113-22-0	L01XK01
Osilodrostatphosphate	1315449-72-9	H02CA02
Osimertinibmesylate	1421373-66-1	L01EB04
Oxaliplatin	61825-94-3	L01XA03
Oxfendazole	53716-50-0	QP52AC02
Ozanimod	1306760-87-1	L04AA38
Ozanimodhydrochloride	1618636-37-5	L04AA38
Palbociclib	571190-30-2	L01EF01
Pamidronicacid	40391-99-9	M05BA03
p-Aminosalicylicacid	65-49-6	J04AA01
Panitumumab	339177-26-3	L01FE02
Panobinostat	404950-80-7	L01XH03
Parecoxib	198470-84-7	M01AH04
Patisiransodium	1386913-72-9	N07XX12
Pazopanibhydrochloride	635702-64-6	L01EX03
Pegcetacoplan	2019171-69-6	L04AA54
Peginterferonalfa-2a	198153-51-4	L03AB11, L03AB61
Pegvisomant	218620-50-9	H01AX01
Pembrolizumab	1374853-91-4	L01FF02
Pemetrexed	137281-23-3	L01BA04
Pemigatinib	1513857-77-6	L01EN02
Penethamatehydriodide	808-71-9	QJ01CE90
Pergolidemethanesulfonate	66104-23-2	N04BC02
Permethrin	52645-53-1	P03AC04, QP53AC04
Pertuzumab	380610-27-5	L01FD02
Phenylpropanolamine	14838-15-4	R01BA01
Phoxim	14816-18-3	QP53AE03
Pibrentasvir	1353900-92-1	J05AP57
Piperacillin	61477-96-1	J01CA12
Pirfenidone	53179-13-8	L04AX05
Piroxicam	36322-90-4	M01AC01, M02AA07, S01BC06
Pixantrone Dimaleate	144675-97-8	L01DB11
Plerixafor	110078-46-1	L03AX16
Podofilox	518-28-5	D07BB04
Polatuzumabvedotin	1313206-42-6	L01FX14
Pomalidomide	19171-19-8	L04AX06
Ponatinibhydrochloride	1114544-31-8	L01EA05
Pralsetinib	2097132-94-8	L01EX23
Praziquantel	55268-74-1	P02BA01, QP52AA01
Prednisolone21-trime-thylacetate	1107-99-9	S02BA03
Prednisoloneacetate	52-21-1	S02BA03
Prednisone	53-03-2	S02BA03
Prilocainehydrochloride	1786-81-8	N01BB04
Procainehydrochloride	51-05-8	N01BA02, C05AD05, S01HA05
Proguanilhydrochloride	637-32-1	P01BB01

Pyrantel	15686-83-6	P02CC01, QP52AF02
Pyrantelpamoate	22204-24-6	P02CC01, QP52AF02
Pyriproxyfen	95737-68-1	QP53AX23
Raltegravir	518048-05-0	J05AJ01
Ramucirumab	947687-13-0	L01FG02
Ravulizumab	1803171-55-2	L04AA43
Regorafenib	755037-03-7	L01EX05
Remimazolam Tosilate	308242-62-8	N05CD14
Ribociclib	1211441-98-3	L01EF02
Rilpivirinehydrochloride	700361-47-3	J05AG05 ,
Risankizumab	1612838-76-2	L04AC18
Rocuroniumbromide	119302-91-9	M03AC09
Ropeginterferon ALFA-2B	1335098-50-4	L03AB15
Ruxolitinib Phosphate	1092939-17-7	L01EJ01
Sacituzumabgovitecan	1491917-83-9	L01FX17
Satralizumab	1535963-91-7	L04AC19
Selpercatinib	2152628-33-4	L01EX22
Siltuximab	541502-14-1	L04AC11
Siponimod fumarate	1234627-85-0	L04AA42
Sodiumsalicylate	54-21-7	N02BA04
Sofosbuvir	1190307-88-0	J05AP08, J05AP51, J05AP55, J05AP56
Somapacitan	1338578-34-9	H01AC07
Sonidegib	956697-53-3	L01XJ02
Sorafenibtosylate	475207-59-1	L01EX02
Sotorasib	2252403-56-6	L01XX73
Streptozotocin	18883-66-4	L01AD04
Sulfadiazine	68-35-9	J01EC02, QJ01EQ10
Sulfadoxine	2447-57-6	QJ01EQ13
Sunitinibmalate	341031-54-7	L01EX01
Tafamidis Meglumine	951395-08-7	N07XX08
Tafasitamab	1422527-84-1	L01FX12
Talazoparibtosylate	1373431-65-2	L01XK04
Tazobactam	89786-04-9	J01CG02
Tazobactamsodium	89785-84-2	J01CG02
Tegafur	37076-68-9	L01BC03
Tegafur	17902-23-7	L01BC03
Teicoplanin	61036-62-2	J01XA02
Tenofoviralafenamide	379270-37-8	J05AF13
Teriflunomide	163451-81-8	L04AA31
Terlipressin	14636-12-5	H01BA04
Tetracosactidehexaacetate	22633-88-1	H01AA02
Tetraethylthiuramdisulfide	97-77-8	P03AA05
Thiopental	76-75-5	N01AF03, N05CA19
Thiotepa	52-24-4	L01AC01
thyrotropin alfa	194100-83-9	H01AB01
Tildrakizumab	1326244-10-3	L04AC17
Tilmicosin	108050-54-0	QJ01FA91
Tipiracilhydrochloride	183204-72-0	L01BC59
Tirbanibulin	897016-82-9	D06BX03
Tisagenlecleucel	1823078-37-0	L01XX71
Tivozanib monohydrochloride monohydrate	682745-41-1	L01EK03
Tocilizumab	375823-41-9	L04AC07

Tofacitinibcitrate	540737-29-9	L04AA29
Topotecanhydrochloride	119413-54-6	L01CE01
Torsemide	56211-40-6	C03CA04
Trametinib	871700-17-3	L01EE01
Trastuzumab	180288-69-1	L01FD01
Trastuzumab deruxtecan	1826843-81-5	L01FD04
Trastuzumabemtansine	1018448-65-1	L01FD03
Treosulfan	299-75-2	L01AB02
Treprostinil	81846-19-7	B01AC21
Trichloroethylene	79-01-6	N01AB05
Trifluridine	70-00-8	S01AD02
Trilostane	13647-35-3	H02CA01
Trinitroglycerin	55-63-0	C01DA02
Tucatinib	937263-43-9	L01EH03
Upadacitinib Hydrate	2050057-56-0	L04AA44
Vandetanib	443913-73-3	L01EX04
Vasopressintannate	113-79-1	H01BA01
Vedolizumab	943609-66-3	L04AA33
VelcalcetideHydrochloride	1334237-71-6	H05BX04
Velpatasvir	1377049-84-7	J05AP55
Vemurafenib	918504-65-1	L01EC01
Vinblastinesulfate	143-67-9	L01CA01
Vincristine	57-22-7	L01CA02
Vincristinesulfate	2068-78-2	L01CA02
Vinflunine Tartrate	1201898-17-0	L01CA04
Vinorelbinetartrate	125317-39-7	L01CA04
Vismodegib	879085-55-9	L01XJ01
Xylazine	7361-61-7	QN05CM92
Zanamivir	139110-80-8	J05AH01
Zanubrutinib	1691249-45-2	L01EL03
Ziconotide	107452-89-1	N02BG08
Zidovudine	30516-87-1	J05AF01

Appendix 5 List of prescription human APIs without monitoring or hazard data

Preferred name	CASRN	ATC code
Zonisamide	68291-97-4	N03AX15
Trandolapril	87679-37-6	C09AA10
Latanoprost	130209-82-4	D11AX22, P02CF01, QP54AA01, QS02QA03
Riluzole	1744-22-5	N07XX02
Sirolimus	53123-88-9	L04AA10, S01XA23
Rotigotine	99755-59-6	N04BC09
Rotigotine	92206-54-7	N04BC09
Ziprasidone	146939-27-7	N05AE04
Rufinamide	106308-44-5	N03AF03
Levetiracetam	102767-28-2	C07AG01
Pivampicillin	33817-20-8	J01CA02
Moxifloxacin	151096-09-2	J01MA14, S01AE07
Triptorelin	57773-63-4	L02AE04, QH01CA97
Teriparatide	52232-67-4	H05AA02
Cabotegravir	1229006-15-8	G02CB03, N04BC06
Caplacizumab	915810-67-2	L01BC06
Octreotide	83150-76-9	H01CB02
Ustekinumab	815610-63-0	L04AC05
Rifabutin	72559-06-9	J04AB04
Nintedanib	656247-17-5	L01EX09
Bilastine	202189-78-4	L02BB03
Fremanezumab	1655501-53-3	N05AF01
Asenapine	65576-45-6	N05AH05
Ganirelix	124904-93-4	N02CC07
Sertindole	106516-24-9	N05AE03

RISK-BASED PRIORITIZATION OF ACTIVE PHARMACEUTICAL INGREDIENTS IN DANISH SURFACE WATERS FOR FUTURE MONITORING

A comprehensive screening and prioritization of prescription Active Pharmaceutical Ingredients (APIs) used in Denmark in 2021 was conducted based on semi-quantitative risk ranking integrating hazard and exposure information. The study identifies 50 APIs of highest concern, including sex hormones, antibiotics, antineoplastics, and SSRIs. Notably, 70% of the top 50 APIs have not been previously detected in Danish surface water, suggesting a need for expanded monitoring encompassing wastewater. Six APIs are recommended for inclusion in monitoring campaigns due to their presence on the EU Commission's watch list. Data on aquatic antineoplastics remain limited, warranting prioritization in future surveillance. SSRIs and benzodiazepines are highlighted for their potency and hydrophobic nature, respectively, necessitating inclusion in monitoring efforts. While analytical methods exist, research is needed to identify human metabolites and transformation products. Moreover, efforts align with green chemistry principles and sustainability strategies, emphasizing safe and sustainable management of APIs. Prioritization of monitoring streams receiving wastewater is recommended, aligning with proposed directives on urban wastewater treatment. Overall, further research and enhanced toxicity analyses are essential for a comprehensive understanding of API risks and effective management strategies.

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