Review of the square box symbol uses in the 2019 WHO Model List of Essential Medicines: including proposed revisions to terminology, listings and integration in the electronic EML (*e*-EML)

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31 August 2020

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Executive summary

The heterogeneity of the uses of the square box symbol (SqB) in the EML to indicate that therapeutic equivalents could be selected at the national level was highlighted in a recent article.[1] The present analysis was conducted in order to characterize the extent of that heterogeneity and propose a change in the uses and nomenclature of the SqB, with the focus on the new *e*-EML and its expected added value and performance.

This analysis identified three main problems in the current use of the SqB symbol in the 2019 WHO-EML:

(1) **Heterogeneity**. In some entries, an '*' symbol is used to name therapeutic equivalents instead of the SqB. Also, the '*' symbol is used to specify that biosimilars can be used.
(2) **Inconsistencies**. Many entries appear as unrestricted SqB, although the descriptive text in the list or the recommendation in the full technical report of the meeting specifies therapeutic alternatives (thus, these are qualified or restricted SqB).
(3) **Undefinition.** If the ATC therapeutic group (ATC4 level) is considered as suitable therapeutic equivalents in the case of an unrestricted SqB, different problems have been identified: (i) products with ATC but not DDD; (ii) the available ATC4 alternatives cannot be administered by the same routes as the listed medicine, (iii) the ATC4 group includes medicines withdrawn due to severe adverse drug reactions or with safety warnings; (iv) some fixed-dose combinations include a double SqB symbol which could be misleading, and (v) some ATC4 groups include a mixture of medicines (e.g., different antimicrobial classes, antifungals and corticosteroids for ocular use, among others).

In order to reduce potential confusions during the selection process of a therapeutic alternative at the country level, **the recommendation is to gradually restrict all SqB listings to specific alternatives, according to the available evidence.** Additionally, to **avoid use of the asterisk symbols proposing alternative medicines**.

A new nomenclature can be promoted, such as the one implicit (and already in use in the *e*-EML) "*therapeutic equivalent*". But, as this name can have other interpretations in some countries, other expressions could be found, to avoid its confusion with "generic substitutes" or "biosimilar substitutes". For example: *Suitable therapeutic alternatives, therapeutic alternatives, akin therapeutics*, etc.

It is important that these modifications are communicated to the countries. A way to ensure that the messages reaches the members of the local expert committees is to prepare **short courses to strengthen the specific skills needed for the selection of suitable therapeutic alternatives.** This can be done under the umbrella of the WHO Academy initiative.

The new *e*-EML is a versatile tool. Its use will certainly grow once widely promoted. **This is an opportunity to improve the readability of the *Summary of evidence*** and the *Expert Committee recommendations* by presenting them more visually and **trying to homogenize how the therapeutic equivalent medicines are presented and linked between them**. This would enrich the tool and prepare it for an eventual link to an EML Formulary.

Finally, it would be interesting to study in detail which therapeutic equivalents have been selected by different countries. This information is be the basis to identify cases in which the selection could be revised or improved by the countries to ensure a more prudent or smart prescription, reduce avoidable risks and improve medicines expenditure.

[1] Cappello B, Moja L, Figueras A, Magrini N. The "Square Box": Therapeutic Equivalence as a Foundation of the WHO Model List of Essential Medicines. Front Pharmacol. 2020;11:578000

A. Background

The Square Box (SqB) symbol appeared in the early editions of the WHO Model List of Essential Medicines (EML). More than 40 years after the first edition of the EML in 1977, the uses of this symbol show heterogeneity, as highlighted by a recently published article.[2] In summary:

- When more than one therapeutic option is available for a given indication, the EML often includes a single medicine as representative of a group of equivalent and interchangeable medicines. The representative medicine of that group is listed with an accompanying 'square box' symbol.

- The intended purpose of the SqB is to highlight pharmacological classes or groups of medicines for which countries, institutions and health professionals can assume homogeneous therapeutic efficacy and safety and select the most appropriate single medicine based on price, local availability, and acceptability.

- The SqB concept is applied in the context of a comprehensive list: therapeutic equivalence or interchangeability cannot always be easily established. Different interpretations have been applied to different groups of medicines over the 40+ year history of the EML.

- The EML continues to evolve with time, with new medicines regularly considered for inclusion to meet changing public health needs. In 1983, quality information about medicines was scarce and its access very limited; four decades later, prescribers face an overflow of information which mixes biased and low-quality studies with relevant evidence.

- Additionally, a plethora of me-too medicines have been licensed entered the market, many of them without showing clear differences in efficacy or safety over the competitors, yet often at higher costs.

- Finally, the appearance of biologic products and their biosimilars has changed some paradigms of the chemical medicines and worsened the affordability of essential medicines at the country level.

The article concludes: "Therefore, it is time to perform an updated review of the SqB concept, definition and listings at the next update of the Model List in 2021".

In the 2003 meeting of the Expert Committee on Selection and Use of Essential Medicines, a review of SqB prepared by Dr Sue Hill and Dr Leo Offerhaus was presented, and several entries with SqB were reviewed after that meeting. The main recommendations made by the reviewers appear in the following Box.

[2] Cappello B, Moja L, Figueras A, Magrini N. The "Square Box": Therapeutic Equivalence as a Foundation of the WHO Model List of Essential Medicines. Front Pharmacol. 2020;11:578000.).

- It is recommended that for the Model EML, **square boxes should not be used to indicate substances for which there are known to be multiple suppliers of acceptable generic products**. Whilst this may be useful information, a different 'tagging' system should be used to avoid confusion.
- It is recommended that for the Model List, **the 'square box' symbol should be used primarily to indicate equivalence based on pharmacological class. The listed medicine should be the example of the class for which there is the best evidence for effectiveness and safety**. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price (based on international drug price information sources).
- It is recommended that the Model List **use the 'square box' to suggest therapeutic equivalence and interchangeability but only where this recommendation is made based on reviews of efficacy and safety and is consistent with standard treatment guidelines for the indication** (e.g. hypertension).

Ref: Hill S and Offerhaus L. Agenda Item 8: Review of 'square boxes'. WHO-EML, 2003.

The present review was conducted in 2020, taking into account these previous documents, with the following **purposes**:

(1) To analyse the entries of the 2019 EML to know the different uses of the SqB symbol, reviewing the medicines included under the SqB symbol in these entries, and identifying potential problems for countries during the adoption and adaptation process to prepare their own National Essential Medicines List (NEML).
(2) To present a proposal for a new and homogeneous way to suggest therapeutic equivalents of a given WHO-EML entry for the adaptation of the list at the country level.

The **methods** used for the present analysis consisted of:

i. Identification of differences in the 'therapeutic equivalent' concept, to consider if its use in the EML could be misleading and if the Expert Committee should propose a clear definition.
ii. The identification of all entries of the 2019 EML with either and SqB symbol or an asterisk (*) symbol suggesting alternative medicines to that included in the entry.
iii. Classification of the selected entries in three categories: (1) '*' symbol to suggest alternative medicines; (2) restricted SqB symbol, and (3) unrestricted SqB symbol.
iv. Analysis of the entries with an unrestricted SqB symbol to identify: (1) examples of entries for which specific alternatives are given in the listing recommendation in the text of the technical report at which the recommendation was made; (2) examples in which using the "therapeutic class" as equivalent (4th level of the ATC classification, ATC4) could be misleading; and (3) examples of entries for which the non-restriction could lead to less appropriate choices or wrong choices at the national level.

B. Therapeutic equivalents – Important international semantic differences

An evidence-based approach to clinical practice can aid rational prescribing. Still, that evidence-based approach requires relevant clinical information and time for clinicians to identify, review and interpret the evidence, as well as to translate it into clinical practice.[3] As the adjective "rational" has different connotations, other qualificatives with the same fundamental meaning are being used, such as balanced, prudent, smart or wise prescription process.

In summary, one of the components of the wise prescription process consists in the selection of the best medicine for a given patient based on the best evidence available, taking into account the efficacy, safety, convenience and cost of each potential active ingredient marketed for a given indication or condition.[4,5]

Usually, there is more than one therapeutic option available for a single indication, which can show minimal or wider differences in either its efficacy, safety or both, significant at the clinical level. In these cases, to facilitate an evidence-based selection, therapeutic guidelines, medicine formularies or the national EML become helpful tools by showing similar medicines which could be prescribed indistinctly.

The "comparability" or "equivalence" among these alternative medicines is based on the evaluation of the available scientific evidence, mainly randomised clinical trials and metanalysis if available, as well as large post-marketing observational and pharmacovigilance studies. These pieces of evidence allow stating that omeprazole and lansoprazole, or simvastatin and atorvastatin could be prescribed interchangeably. Regarding NEMLs, it is possible to list any of these alternatives, taking into account their availability in the country.

Different names are given to these comparable alternative medicines. One of the most common is "therapeutic equivalent".

Therapeutic equivalent. It is a medicine differing in its chemical structure from the original, but with an expected therapeutic effect and safety profile similar when it is taken at equivalent dosages.

But it should be noted that these names can have different meanings in different countries. In the US, for example, a position statement of the American College of Clinical Pharmacy in 1993 defined therapeutic equivalent medicines "as those chemically dissimilar but produce essentially the same therapeutic outcome and have similar toxicity profiles".[6] Notwithstanding, the 2020 edition of the US FDA 'Orange Book' has the following definitions:[7]

[3] Starkey ES, *et al*. Evidence-based prescribing. In: C Baker, *et al*. (Eds.) Prescribing medicines for children. From drug development to practical administration. Pharmaceutical Press. London, 2019.
[4] De Vries TPGM, *et al*. Guide to good prescribing : a practical manual WHO, 1994. https://apps.who.int/iris/handle/10665/59001
[5] British Pharmacological Society. Ten Principles of Good Prescribing. https://www.bps.ac.uk/education-engagement/teaching-pharmacology/ten-principles-of-good-prescribing
[6] American College of Clinical Pharmacy. Guidelines for Therapeutic Interchange. *Pharmacotherapy* 1993; 13: 252-256.
[7] US FDA. Approved drug products with therapeutic equivalence evaluations ('The Orange Book'). 40th Ed. 2020. https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book

Pharmaceutical equivalents. Drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient (…); do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standards of identity, strength, quality, and purity (…). They may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colours, flavours, preservatives), expiration date/time, and, within certain limits, labelling.

Pharmaceutical alternatives. Drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form, or the same salt or ester (e.g., tetracycline hydrochloride, 250mg capsules vs tetracycline phosphate complex, 250mg capsules; quinidine sulfate, 200mg tablets vs quinidine sulfate, 200mg capsules).

Therapeutic equivalents. Approved drug products are considered to be therapeutic equivalents if they are pharmaceutical equivalents for which bioequivalence has been demonstrated, and they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labelling.

FDA classifies as therapeutically equivalent those drug products that meet the following general criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the identical active drug ingredient in the identical dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent in that (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable in vitro standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labelled; and (5) they are manufactured in compliance with Current Good Manufacturing Practice regulations.

The concept of therapeutic equivalence applies only to drug products containing the identical active ingredient(s). It does not encompass a comparison of different therapeutic agents used for the same condition (e.g., meperidine hydrochloride vs morphine sulfate for the treatment of pain).

Ref.: https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book

Thus, according to the US FDA, the expression "therapeutically equivalent" is seen from a manufacturer point of view. It refers to what is known as "generic" in other countries, a product containing the same ingredient and strength than the brand-name but marketed under the DCI name or a different fantasy name. It is crucial to take into account these semantic differences to avoid confusions.

In the present report, a **'therapeutic equivalent' refers to a different chemical structure from the original, but with a similar expected therapeutic effect and safety profile**.

Other expressions are being used to describe 'therapeutic equivalents', such as **reference group** (or **similar**) which is defined as: **"**A cluster of therapeutically equivalent drugs. These reference groups may or may not be identical to drug classes identified by other classification systems".[8] The expression **'therapeutic group'** has also been used with the same meaning. According to de Vries, "all drugs with the same working mechanism (dynamics) and a similar molecular structure belong to one group. As the active substances in a drug group have the same working mechanism, their effects, side effects, contraindications and interactions are also similar.[9] '**Therapeutic substitute**' has also been used.

[8] Schneeweiss S. Reference drug programs: effectiveness and policy implications. Health Policy. 2007;81(1):17-28. doi:10.1016/j.healthpol.2006.05.001
[9] De Vries TPGM, et al. Guide to good prescribing : a practical manual WHO, 1994. https://apps.who.int/iris/handle/10665/59001

Whatever the name, the following conditions are required to be able to consider a therapeutic equivalent:[10] [11]

(1) Approved for the same indications of use.
(2) Have similar pharmacological effects - similar chemical structure, same pharmacologic group, or same biochemical or therapeutic activity.
(3) Have equivalent therapeutic efficacy and safety shown in clinical trials.
(4) In addition to the previous three requirements, pharmacokinetics, dosage, administration patterns, starting and ending conditions for the treatment, are considered to establish a safe interchange.

C. Analysis of the 2019 WHO Model List of Essential Medicines

Taking into account the previous considerations, the 2019 edition of the EML was analysed to identify all entries with an SqB symbol or an '*' symbol suggesting alternative medicines. The results will be grouped in three subchapters: (1) SqB with qualification; (2) SqB without qualification (unrestricted), and (3) potential problems related with the entry, its indication of use and possible alternatives.

1. Square Box with qualification

When specific names of medicines are given, SqB could be named simply "alternatives" or "therapeutic alternatives".

There include two main situations: entries with "*" but without the SqB symbol, and entries with a qualified SqB.

1.1 Listings with an asterisk (*) symbol without Square Box indication

The table below describes the entries including an asterisk "*" to indicate one or more alternative active ingredients. In some cases, the alternative belongs to the same therapeutic subgroup (ATC4 level), while in others, the proposed alternative belongs to the same therapeutic group (ATC3 level).

In other cases, the "*" is used to specify that biosimilars can be used instead of the original compound.

Section	Medicine	ATC5	Symbol	Alternative	ATC5	ATC level	Reason
1.1.2	Propofol	N01AX10	*	thiopental	N01AF03	ATC3	ALTERNATIVE (availability / cost)
6.1.3	Oxamniquine	P02BA02	*	praziquantel	P02BA01	ATC4	ALTERNATIVE (if praziquantel fails)
6.2.1	SMTX-TMP	J01EE01	*	single agent trimethoprim	J01EA01	ATC3	ALTERNATIVE (for UTI)
6.2.2	Clarithromycin	J01FA09	*	erythromycin	J01FA01	ATC4	ALTERNATIVE
	Meropenem	J01DH02	* [a]	imipenem+cilastatin	J01DH51	ATC4	ALTERNATIVE (infection site for acute bacterial meningitis where meropenem is preferred)
6.2.5	Meropenem	J01DH02	*	imipenem+cilastatin	J01DH51	ATC4	ALTERNATIVE

[10] Johnston A, Asmar R, Dahlöf B, et al. Generic and therapeutic substitution: a viewpoint on achieving best practice in Europe. *Br J Clin Pharmacol* 2011;72:727-730. doi:10.1111/j.1365-2125.2011.03987.x
[11] American College of Clinical Pharmacy. Guidelines for Therapeutic Interchange. *Pharmacotherapy* 1993; 13: 252-256.

6.4.2.4	efavirenz+emtricitabine*+tenofovir	J05AR06	*	lamivudine (3TC)	J05AF05	ATC3	ALTERNATIVE (based on resistance pattern, clinical trials and pharmacology)
	emtricitabine*+tenofovir	J05AR17	*†	lamivudine (3TC)	J05AF05	ATC3	ALTERNATIVE (based on resistance pattern, clinical trials and pharmacology) † Combination also indicated for pre-exposure prophylaxis
8.2.2	Rituximab	L01XC02	*	biosimilars	L01XC02	ATC5	ALTERNATIVE (biosimilars)
8.2.2	Trastuzumab	L01XC03	*	biosimilars	L01XC03	ATC5	ALTERNATIVE (biosimilars)
10.3	Deferoxamine	V03AC01	*	deferasirox oral form	V03AC03	ATC4	ALTERNATIVE (availability / cost)
17.5	oral rehydration salts	A07CA	*	trisodium citrate dihydrate may be replaced by sodium hydrogen carbonate (sodium bicarbonate) 2.5 g/L. However, as the stability of this latter formulation is very poor under tropical conditions, it is recommended only when manufactured for immediate use			ALTERNATIVE (tropical conditions)
19.2	anti-venom Ig	J06AA03	*	exact type to be defined locally			ALTERNATIVE (depending on local reality)
21.5	Atropine	S01FA01	* [a] [c]	homatropine or cyclopentolate	S01FA05 S01FA04	ATC4	ALTERNATIVE

Recommendation

Up to 14 entries include an asterisk (*) symbol to suggest one or more alternative compounds, but an SqB symbol is not used.

A few entries use the "*****" symbol to explain that biosimilars can be used instead of the original compounds. This suggests that the general use of biosimilars (situations, conditions, characteristics, evidence, etc.) could be clearly defined by the EC-WHO-EML, with statements valid for any biological product and its biosimilars.

1.2 Qualified Square Box listings

The 2019 EML includes the following qualified Square Box symbols in 15 entries.

Section	Medicine	ATC5	RoA	Alternative	ATC5	ATC level	Reason
2.2	Morphine	N02AA01	O, P	hydromorphone	N02AA03	ATC4	ALTERNATIVE
				oxycodone	N02AA05		
8.1	*Adalimumab*	*L04AB04*	*P*	*certolizumab pegol*	L04AB05	ATC4 / ATC5	*including quality-assured biosimilars*
				etanercept	L04AB01		
				golimumab	L04AB06		
				infliximab	L04AB02		
8.2.2	*Erlotinib*	*L01XE03*	*O*	*gefitinib*	L01XE02	ATC4	
				afatinib	L01XE13		
8.2.3	*Nivolumab*	*L01XC17*	*P*	*pembrolizumab*	L01XC18	ATC5	

10.1	*erythropoiesis-stimulating agents*	--	*Inj*	*epoetin alfa, beta and theta darbepoetin alfa methoxy - polyethylene glycol epoetin beta*	*B03XA01 B03XA02 B03XA03*	ATC4	*and their respective biosimilars*
10.2	Dabigatran	B01AE07	O	apixaban	*B01AF02*	ATC3	B01AE Direct thrombin inhibitors B01AF Direct factor Xa inhibitors
				edoxaban	*B01AF03*		
10.2	Enoxaparin	B01AB05	Inj	nadroparin	B01AB06	ATC4	
				dalteparin	B01AB04		
11.3	dextran 70	B05AA05	Inj	* Polygeline	B05AA06	ATC4	*polymer of urea and polypeptides derived from gelatin
12.1	Bisoprolol	C07AB07	O	metoprolol	C07AB02	ATC4	C01AB Beta blocking agents, selective
				carvedilol	C07AG02 Alpha and beta blocking agents	ATC3	
12.2	bisoprolol*	C07AB07	O	id	id	id	id
12.3	bisoprolol*	C07AB07	O	atenolol	C07AB03	ATC4	Note: atenolol should not be used as a first-line agent in uncomplicated hypertension in patients >60 years.
				metoprolol	C07AB02	ATC4	
				carvedilol	C07AG02	ATC3	
12.5	bisoprolol*	C07AB07	O	metoprolol carvedilol	id	ATC4	
18.5.2	gliclazide*	A10BB09	O[1]	glibenclamide	A10BB01	ATC4	* glibenclamide not suitable above 60 years
18.7	Methimazole *(= thiamazole)*	H03BB02	O	*carbimazole	H03BB01	ATC4	an alternative depending on local availability
24.5	*methadone**	*N07BC02*	*O*	buprenorphine	N07BC01	ATC4	*The square box is added to include buprenorphine Buprenorphine is administered SL*

[1] controlled release

Notes:
In most cases, the entry is one medicine of the therapeutic subgroup, and other medicines for the same therapeutic subgroup are proposed as alternatives. But, in a few cases, the entry is the name of the group. Alternatives are proposed (for example erythropoiesis-stimulating agents)
In *italics*, entries classified as "complementary list".

Recommendation:

Fifteen entries (12 medicines) included a qualified SqB symbol. In these cases, alternatives belonging to the same therapeutic subgroup (ATC4 level) or therapeutic group (ATC3 level) are given.

In some cases, the symbol includes reference to the biosimilars of the listed or alternative medicines. *Cf*. The previous comment on biosimilars.

Restricted alternatives help the work of selection committees at the national level. Restricted alternatives ensure an evidence-based homogeneity and, at the same time, allow the necessary heterogeneity according to national needs, availability or preferences.

2. Square Box without qualification (unrestricted)

When specific no specific names of medicines are given, SqB could be named “ATC4 alternatives”, “Therapeutic class alternatives” or “Therapeutic class equivalents”.

The complete list of ingredients potentially considered as part of the unrestricted SqB for each entry with this symbol appears in **Appendix 1**.

A careful analysis of the different entries and the displayed alternatives according to the therapeutic class (ATC4 level), shows a heterogeneity which could lead to suboptimal selections when building up the national EML.

Different situations are discussed in the examples below.

2.1 Therapeutic class alternatives without DDD

The therapeutic subgroup includes entries with a defined daily dose (DDD) and **without DDD**. However, the DDD does not necessarily coincide with the equipotent dose, but at least to have a DDD ensures that a panel of experts has revised the active ingredient and assigned a mean daily dose.

Examples:

Section	Medicine (RoA)	ATC5	ATC4	Active ingredients [a]	Nr in ATC4**	Nr in ATC4 (with DDD)
1.2	bupivacaine (I, ISpA)	N01BB01	N01BB Amides	**mepivacaine?, prilocaine?, butanilicaine?, cinchocaine?, etidocaine?, articaine?, ropivacaine?, levobupivacaine?**	10	0 (no DDD)
	lidocaine (I, ISpA, T)	N01BB02			10	0 (no DDD)
10.2	warfarin (O)	B01AA03	B01AA Vitamin K antagonists	dicoumarol (O), phenindione (O), phenprocoumon (O), acenocoumarol (O), ethyl biscoumacetate (O), **clorindione ?, diphenadione ?, tioclomarol ?, fluindione ?**	9	5
17.1	omeprazole (O,P)	A02BC01	A02BC Proton pump inhibitors	pantoprazole (O, P), lansoprazole (O), rabeprazole (O), esomeprazole (O, P), dexlansoprazole (O), **dexrabeprazole?, vonoprazan ?**	7	5
	ranitidine (O, P)	A02BA02	A02BA H2-receptor antagonists	cimetidine (O, P), famotidine (O, P), nizatidine (O, P), **niperotidine?,** roxatidine (O), ranitidine bismuth citrate (O), lafutidine (O)	7	6

? = without defined daily dose (DDD)

Recommendations:

None of the listed examples have a restriction of alternatives in the EML. So, in theory, any of the ingredients listed in each ATC4 could be selected.

Medicines without a defined daily dose value assigned by the WHO-CC in Oslo are either recently marketed or marketed in few countries. Then, the experience of use of these medicines is probably scarce, and the available published evidences is probably rare**. It could be recommended that medicines without a DDD are not considered as suitable therapeutic equivalents**.

2.2 Available routes of administration

Not all medicines listed in the same therapeutic class can be administered by the **same routes (RoA)**

Some examples:

Section	Medicine (RoA)	ATC5	ATC4	Active ingredients [a]	Nr in ATC4 **	Nr in ATC4 (=RoA)
1.3	Midazolam (O, P)	N05CD08	N05CD BZD derivatives	Flurazepam (O), nitrazepam (O), **flunitrazepam (O,P)**, estazolam (O), triazolam (O, SL), lormetazepam (O), temazepam (O), brotizolam (O), quazepam (O), loprazolam (O), doxefazepam?, cinolazepam?, remimazolam?	14	1
12.1	isosorbide dinitrate (O sl)	C01DA08	C01DA Organic nitrates	**glyceryl trinitrate (O, oral aerosol SL, TD)**, methylpropylpropanediol dinitrate ?, pentaerithrityl tetranitrate (O), propatylnitrate (O), trolnitrate (O), eritrityl tetranitrate (O), isosorbide mononitrate (O), tenitramine ?	8	1
17.1	omeprazole (O,P)	A02BC01	A02BC Proton pump inhibitors	**pantoprazole (O, P),** lansoprazole (O), rabeprazole (O), **esomeprazole (O, P),** dexlansoprazole (O), dexrabeprazole ?, vonoprazan ?	7	2
	ranitidine (O, P)	A02BA02	A02BA H2-receptor antagonists	**cimetidine (O, P), famotidine (O, P), nizatidine (O, P),** niperotidine ?, roxatidine (O), ranitidine bismuth citrate (O), lafutidine (O	7	3
18.4	medroxyprogesterone acetate (O)	G03DA02	G03DA Pregnen (4) derivatives	gestonorone (P), hydroxyprogesterone (P), **progesterone (O, P, R, V)**	3	1

? = no DDD.

Recommendation:
There can be a problem when the EML lists an entry with two or more possible RoA, and the potential alternatives listed in the same ATC4 level cannot be administered by the same routes. Thus, according to the medicine selected by the national selection committee, some RoAs cannot be covered.

2.3 Discontinued medicines and safety warnings

The WHO Collaborating Centre in Oslo maintains the ATC classification system. According to the ATC principles, "The WHO Collaborating Centre in Oslo establishes new entries in the ATC classification on requests from the users of the system". Also, it should be noted that "a major reason why a substance is not included is that no request has been received". And, last but not least: "***Obsolete drugs or drugs withdrawn from the market are kept in the ATC system, since the exclusion of substances from the ATC system may create difficulties for the users of the system when considering historical data***".

This last point is particularly important. If the therapeutic subgroup is used as a reference to select a therapeutic equivalent for any medicine listed in the EML with an unrestricted SqB symbol, it should be taken into account that a given country could select **a medicine with an ATC code, which has been withdrawn or is not recommended for use by medicines agencies**.

Some examples are:

Section	Medicine (RoA)	ATC5	ATC4	Active ingredients withdrawn by at least one country or with an alert for severe safety issues	ADR / References
1.3	midazolam (O, P)	N05CD08	N05CD	**flunitrazepam (O,P)**,	Abuse, Fr, 1991
				triazolam (O, SL),	Psychiatric adverse drug reactions, amnesia, Fr, Neth, Fin, Arg, 1991
				temazepam (O),	Diversion, abuse, and a relatively high rate of overdose deaths in comparison to other drugs of its group. This drug continues to be available in most of the world, including the US, but under strict controls. Swe, Nw, 1999
				brotizolam (O),	Animal carcinogenicity UK, 1989
3	loratadine (O)	R06AX13	R06AX	thenalidine (?)	Neutropenia, Canada, UK, US, 1963
				cyproheptadine (O)	Drug abuse@
				astemizole (O)	Fatal arrhythmia
				terfenadine (O)	Drug interactions/ventricular arrhythmias
5	lorazepam (P)	N05BA06 **b**	N05BA	camazepam (O),	Immunologic@
12.1	isosorbide dinitrate (O sl)	C01DA08	C01DA	erityrityl tetranitrate (O),	Insufficient evidence: skin@
12.6	simvastatin (O)	C10AA01	C10AA	**cerivastatin[12] (O)**	Risk of rhabdomyolysis
13.1	miconazole (T)	D01AC02	D01AC	ketoconazole?	Hepatotoxicity (Oral admin)@
15.2	chloroxylenol (T)	D08AE05	D08AE	hexachlorophene	Encephalopathy, mutagenicity, teratogenicity@
				phenol	
17.1	ranitidine (O, P)	A02BA02	A02BA	niperotidine ?	Safer alternatives (Dom. Rep., Lithuania)@
17.4	senna (O)	A06AB06	A06AB	**oxyphenisatine (O),**	Hepatotoxicity, Austr, France, Germany, US, UK
				dantron (O),	Mutagenic.[13] withdrawn from general use in the UK but permitted in terminal patients
				phenolphthalein (O),	Possible carcinogen, US, 1997
21.1	gentamicin Oc	S01AA11	S01AA	dihydrostreptomycin	Neuropsychiatric reaction. Ototoxicity
	tetracycline Oc oin	S01AA09			
	ofloxacin Oc **$**	S01AE03	S01AE	gatifloxacin	Increased risk of dysglycemia, US, 2006
21.4	timolol Oc	S01ED01	S01ED	metipranolol,	Uveitis, UK, others, 1990
22.1.1	ethinylestradiol + levonorgestrel (O)	G03AA07	G03AA	chlormadinone + ethinylestradiol	Animal Carcinogenicity (chlorm.). Mammary tumours in dogs
	ethinylestradiol + norethisterone (O)	G03AA05		lynestrenol + ethinylestradiol	Tumorigenicity (Australia) @ *First withdrawal based on evidence from animal research
				megestrol + ethinylestradiol	Tumorigenicity (Australia) @ *First withdrawal based on evidence from animal research
24.1	haloperidol (O,P)	N05AD01	N05AD	droperidol (P),	Cardiovascular; deaths @ UK
24.2.1	amitriptyline (O)	N06AA09	N06AA	amineptine,	risk of agranulocytosis and severe acne
	fluoxetine (O)	N06AB03	N06AB	**zimeldine (O),**	Risk of Guillain-Barré syndrome
24.3	diazepam (O)	N05BA01	N05BA	**camazepam (O) £**	Immunologic @
25.1	salbutamol (Inh)	R03AC02	R03AC	**fenoterol (Inh)**	Asthma mortality, NZ, 1990
	budesonide + formoterol Inh **€**	R03AK07	R03AK	isoprenaline and other drugs for obstructive airway diseases	Cardiovascular @
28	ciprofloxacin T ot	S02AA15	S02AA	clioquinol	Neurotoxicity, Fr, Ger, UK, US, 1973
				nitrofural,	Mutagenicity, Japan, US @
				gentamicin (topical)	Resistance, Netherlands, UAE @

	xylometazoline Inh	R01AA07	R01AA	**phenylephrine (N),**	Eye ADR, UK @

[1] Withdrawal of cerivastatin from the world market https://www.ncbi.nlm.nih.gov/pmc/articles/PMC59524/

@Onakpoya IJ, Heneghan CJ, Aronson JK. Worldwide withdrawal of medicinal products because of adverse drug reactions: a systematic review and analysis. *Crit Rev Toxicol*. 2016;46(6):477-489. doi:10.3109/10408444.2016.1149452

Bold means that the medicine has the same routes of administration than that listed in the EML.

In red, the component of a fixed-dose combination for which an alert has been issued.

$ The Expert Committee recommended that ofloxacin ophthalmic solution should be added to the EML and the EMLc with a square box symbol" (https://list.essentialmeds.org/recommendations/289), noting that other fluoroquinolones may be wide available and equally affordable in different settings. Thus, it should be interpreted that the possible alternatives are limited to the other fluoroquinolones within S01AE and not the entire ATC4 group.

£ The Expert Committee specified that alternatives are benzodiazepines with a plasma half-life > 12 hours. Canazepam has an active metabolite (temazepam); thus, its plasma half-life is longer than 12 hours.

€ The Expert Committee recommended listing with a square box symbol, representing alternative combination formulations containing an inhaled corticosteroid and a beta-2 agonist bronchodilator" (https://list.essentialmeds.org/recommendations/323); then, isoprenaline (a non-selective beta agonist) should not be considered a suitable alternative.

Recommendation: So, if any medicine listed under the same ATC4 therapeutic subgroup can be chosen according to the national availability or preferences, special attention should be paid to the active ingredients which have been withdrawn of the market by other countries or which alerts for the risk of severe adverse drug reactions have been described.
A restrictive list of alternatives could help to avoid medicines with a less favourable risk/benefit or even medicines discontinued or withdrawn from the market in some countries due to safety concerns.

3. Potential problems related to the entry, its indication of use and possible alternatives

In addition to the potential problems listed before and strictly related with the ATC/DDD classification system as a way to find alternative medicines listed with an unrestricted SqB symbol, looking for therapeutic equivalents suitable to be listed as alternatives by countries during the adaptation of the EML to their NEMLs can be difficult or misleading in some cases. In this chapter, some illustrative examples are detailed.

3.1 Lorazepam in epileptic seizures

Lorazepam (Parenteral route) is listed as an anticonvulsant/antiepileptic with an unrestricted SqB symbol.

The Expert Committee recommended the inclusion of parenteral lorazepam with a square box to replace diazepam on the Model List based on its comparative effectiveness and safety with respect to other medicines for the management of prolonged convulsive seizures and status epilepticus in adults and children.

According to the ATC classification, the pharmacological class of lorazepam (a benzodiazepine) is N05BA. This subgroup includes 22 compounds. Seven of them do not have a DDD value assigned. It also includes camazepam (a product with some safety warning, skin and immunologic reactions). Taking into account the listed route of administration for lorazepam (i.e., parenteral), only two alternatives are possible: diazepam and chlordiazepoxide.

It should be noted that in some countries "clonazepam" is promoted for epilepsy, and this product can be administered orally or parenterally. So, its listing to manage status epilepticus could be selected. Notwithstanding this, it is classified as N03AE01 (thus, therapeutic class N03AE "Benzodiazepine derivatives" for epilepsy).

Additionally, clonazepam could be mistaken with clobazam, cloxazolam or cloxazolam.

On the other hand, some reference books (as the BNF), suggest “midazolam” (N05CD08) as a potential treatment for the status epilepticus. Still, it is listed under the N05CD subgroup (includes benzodiazepines as hypnotic and sedatives).

Section	Medicine (RoA)	ATC5	ATC4	Active ingredients [a]
5	**Lorazepam (P)**	**N05BA06**	**N05BA BZD derivatives**	**diazepam (O, P, R), chlordiazepoxide (O, P), medazepam (O), oxazepam (O), potassium clorazepate (O), adinazolam (?), bromazepam (O), clobazam (O), ketazolam (?), prazepam (O), alprazolam (O), halazepam (O), pinazepam (?), camazepam (O), nordazepam (O), fludiazepam (O), ethyl loflazepate (O), etizolam (?), clotiazepam (?), cloxazolam (?), tobenoxaebrbuforfisopam (?), bentazepam (O)**

3.2 Aciclovir for herpes virus infections

Aciclovir (J05AB01) is listed as an antiherpes medicine, indicated for *Herpes simplex*, *Herpes zoster* and varicella. This entry has an SqB symbol in the paper list, but no alternatives are specified..

In the case of *Herpes simplex, zoster* and varicella, the Expert Committee recommended valaciclovir (ATC codes: J05AB11) as a therapeutic alternative. Thus, **this recommendation makes this a restricted SqB.**

Taking into account the ATC4 and the route of administration, “ganciclovir” (J05AB06) could also be selected. Notwithstanding, reference books such as the BNF include ganciclovir for the treatment of Cytomegalovirus, but not Herpes virus infections. Alternatively, the BNF also suggests famciclovir and valaciclovir as an oral treatment for *Herpes zoster*; both medicines can be administered orally.

Section	Medicine (RoA)	ATC5	ATC4	Active ingredients [a]
6.4.1	aciclovir (O, P)	J05AB01	J05AB Nucleos. nucleot. excl. rev. transcr. inhibitors	idoxuridine (?) vidarabine (P) **ganciclovir** (O, P) famciclovir (O) valaciclovir (O) cidofovir (P) penciclovir ? valganciclovir (O) brivudine (O)

3.3 Metronidazole as antiamoebic and antigiardiasis

Metronidazole is listed with an SqB symbol as antiamoebic and antigiardiasis to be administered orally or parenterally.

According to the ATC/DDD classification, oral and rectal metronidazole are listed as antiprotozoal (P01AB01), and parenteral metronidazole is listed as an antimicrobial (J01XD01). Thus, taking into account the selected ATC therapeutic subgroup, different potential alternatives could be selected. None has both routes of administration (oral and parenteral).

According to the BNF, tinidazole is proposed as an alternative both for amoebiasis and giardiasis. Both medicines appear listed as P01AB and J01XD. Data on the comparative efficacy, safety and cost of nimorazole and secnidazole should be obtained before deciding if they could be a suitable alternative for a NEML. **This example can be applied to other entries with unrestricted SqB symbols**.

Section	Medicine (RoA)	ATC5	ATC4	Active ingredients [a]
6.5.1	metronidazole (O, P)	P01AB01	P01AB Nitroimidazole derivatives	tinidazole (O, R), ornidazole (O), azanidazole ?, propenidazole ?, nimorazole (O), secnidazole (O)
			J01XD Imidazole derivatives	J01XD02 tinidazole (P) J01XD03 ornidazole (P)

3.4 Propranolol for migraine prophylaxis

Propranolol has been approved for the prophylaxis of migraine and is listed in the EML with a SqB symbol. However, the square box does not apply to the listing of propranolol on the EMLc for this indication for children.

Section	Medicine (RoA)	ATC5	ATC4	Active ingredients [a]
7.2.	Propranolol (O)	C07AA05	C07AA Beta blocking agents, non-selective	**alprenolol (O,P) oxprenolol (O,P) pindolol (O,P) timolol (O,P) sotalol (O,P) nadolol (O), mepindolol (O), carteolol (O), tertatolol (O)** bopindolol ? bupranolol ? **penbutolol (O)** cloranolol ?

According to the ATC classification, there are 13 non-selective beta-blocking agents listed, in addition to propranolol. Ten of them had a DDD assigned (all can be administered orally). In these cases, available evidence supporting the use of these ten potential alternatives for the prophylaxis of migraine is perhaps scarce. Thus, selecting one or another for a NEML could have an impact on the effects obtained by patients.

For example:

- A Japanese 2009 review (Shimizu T. Brain Nerve. 2009;61(10):1125-1130) concluded: “In contrast, several beta-blockers with intrinsic sympathetic activity (ISA), such as **alprenolol**, **oxprenolol**, **pindolol** and acebutolol, have not been demonstrated to be effective in migraine prophylaxis”.
- **Tertatolol**: a Pubmed search (tertatolol AND migraine) retrieved two animal studies. One of them (1992) concluded: “It is therefore suggested that tertatolol may prove effective in the treatment of migraine”.
- **Alprenolol**: a PubMed search retrieved six studies where both words were cited.
    - A 1988 review (DOI: 10.1002/ana.410230512) says alprenolol, among other medicines “display affinities of approximately 100 nM for this receptor (5-HT1A sites labelled by 3H-8-hydroxy-2-(N,N-dipropylamino)-tetralin).
- No references were found in PubMed for “Migraine” AND “**mepindolol”.**

These examples highlight the importance of limiting the use of the unrestricted SqB symbol, as a careful selection process is needed beyond belonging to the same therapeutic class. That review process requires an analysis of the availability and quality of the evidence about the efficacy and safety of the use of the medicine in that condition.

3.5 Levodopa + carbidopa for Parkinson disease

The combination levodopa + carbidopa is listed under Antiparkinson Medicines. Carbidopa is a peripheral decarboxylase inhibitor, and the EML includes an SqB symbol only for the carbidopa component of the combination.

The ATC classification does not have any specific code for "carbidopa". Carbidopa appears under "N04BA Dopa and dopa derivatives", and it is listed as: "levodopa + decarboxylase inhibitor". So, no alternative medicines can be identified according to the ATC list.

The use of the fixed-dose combination was established in the 1970s (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1612227/pdf/brmedj02003-0016.pdf), and the only available combination was that of levodopa + carbidopa. At present, other inhibitors are available (benserazide, methyldopa, alpha-Difluoromethyl-DOPA (DFMD) and 3',4',5,7-Tetrahydroxy-8-methoxyisoflavone). Benserazide does not have an ATC code. Methyldopa is used as antihypertensive and is classified as C02AB. Alpha-Difluoromethyl-DOPA is an irreversible inhibitor; there were only seven references in PubMed since 1974. Tetrahydroxy-8-methoxyisoflavone has not been marketed, and there is no reference in PubMed.

The BNF lists levodopa + carbidopa (co-careldopa) and levodopa + benserazide (co-beneldopa). But methyldopa is listed only for use as an antihypertensive medication.

Section	Medicine (RoA)	ATC5	ATC4	Active ingredients [a]
9	levodopa + **carbidopa** (T)	N04BA02 levodopa + decarboxylase inhibitor	N04BA Dopa and dopa derivatives	No ATC for carbidopa. No decarboxylase inhibitors specified

This is an example which shows that perhaps giving specific alternatives (benserazide, in this case) could be much more helpful for the professionals involved in the selection of medicines for the NEMLs.

3.6 Sublingual isosorbide dinitrate in patients with angina

Sublingual tablets of isosorbide dinitrate are listed with a square box for use in patients with angina pectoris.

Isosorbide dinitrate is listed as part of the C01DA therapeutic subgroup (organic nitrates). C01DA includes eight additional active ingredients; only six of them have a DDD assigned, and only one is listed as sublingual administration (glyceryl trinitrate). So, theoretically, this should be only alternative because the efficacy of isosorbide dinitrate is linked to the route of administration which is easy and provides quick absorption. But this medicine is just one in eight listed in the same therapeutic class (which includes erythrityl tetranitrate, a molecule with some safety concerns).

Section	Medicine (RoA)	ATC5	ATC4	Active ingredients [a]
12.1	isosorbide dinitrate (O sl)	C01DA08	C01DA Organic nitrates	glyceryl trinitrate (O, oral aerosol **SL**, TD), methylpropylpropanediol dinitrate ?, pentaerithrityl tetranitrate (O), propatylnitrate (O), trolnitrate (O), **erithrityl tetranitrate** (O), isosorbide mononitrate (O), tenitramine ?

3.7 Fixed-dose combination antihypertensive medicines

For the treatment of hypertension, some fixed-dose combinations of antihypertensive medicines have shown efficacy and safety.

One of these combinations includes angiotensin-converting enzyme inhibitors (ACEIs) and a diuretic or an angiotensin II receptor antagonist (ARA-II) and a diuretic. According to the BNF, the listed combinations (BNF #79, 2020) are:

		Diuretic
ACEI	Enalapril	Hydrochlorothiazide
	Lisinopril	
	Quinapril	
	Perindopril	Indapamide
ARA-II	Irbesartan	Hydrochlorothiazide
	Losartan	
	Olmesartan	
	Telmisartan	
	Valsartan	

Section	**Medicine (RoA)**	**ATC5**	**ATC4**	**Active ingredients** [a]
12.3	lisinopril + hydrochlorothiazide (O)	C09BA03[c]	C09BA ACE inhibitors and diuretics	captopril and diuretics, enalapril and diuretics, perindopril and diuretics, ramipril and diuretics, quinapril and diuretics, benazepril and diuretics, cilazapril and diuretics, fosinopril and diuretics, delapril and diuretics, moexipril and diuretics, zofenopril and diuretics
	telmisartan + hydrochlorothiazide (O)	C09DA07[c]	C09DA ARBs and diuretics	losartan and diuretics?, eprosartan and diuretics?, valsartan and diuretics?, irbesartan and diuretics?, candesartan and diuretics?, olmesartan medoxomil and diuretics?, azilsartan medoxomil and diuretics?, fimasartan and diuretics?

The EML includes a double SqB symbol for the two listed combinations including a diuretic. So, the spectrum of possibilities is broad, even if only C09BA products are considered. The "diuretic" used in the combination can vary a lot from one country to another, even beyond the thiazide or thiazide-like group.

The Expert Committee recommendation for antihypertensive FDCs in the meeting report states:

"***Square box listings of the components of the FDCs should be interpreted by countries as limited to****:*

- *– Lisinopril > any ACE inhibitor (ATC code C09AA--)*
- *– Telmisartan > any angiotensin receptor blocker (ATC code C09CA--)*
- *– Amlodipine > any once-daily dihydropyridine calcium channel blocker (intrinsically long-acting, e.g. amlodipine, lercanidipine, lacidipine; or modified-release, e.g. nifedipine, felodipine)*
- *– HCTZ > chlortalidone or indapamide*."

This explanation clarifies the meaning of the SqB in these entries. So, **this SqB is restricted** because suitable alternatives are given.

Note that this paragraph under the heading "Implementation considerations" describes possible combinations including diuretics and combinations including calcium channel blockers (the latter are part of another entry; see below).

A similar case is the fixed-dose combinations of lisinopril + amlodipine and telmisartan + amlodipine. Both entries have a double SqB symbol, for each component of the combination. And the options included in the same ATC4 therapeutic subgroup are variations of both components.

As it happens with many fixed-dose combinations, it is not sure that there is the same evidence regarding the benefits and safety of each combination in patients with hypertension.

Section	Medicine (RoA)	ATC5	ATC4	Active ingredients [a]
12.3	lisinopril + amlodipine (O)	C09BB03[c]	C09BB ACE inhibitors and calcium channel blockers	enalapril and lercanidipine?, lisinopril and amlodipine?, perindopril and amlodipine?, ramipril and felodipine?, enalapril and nitrendipine?, ramipril and amlodipine?, trandolapril and verapamil?, delapril and manidipine?
	telmisartan + amlodipine (O)	C09DB04[c]	C09DB ARBs and calcium channel blockers	valsartan and amlodipine?, olmesartan medoxomil and amlodipine?, irbesartan and amlodipine?, losartan and amlodipine?, candesartan and amlodipine?, valsartan and lercanidipine?, fimasartan and amlodipine?

Again, the Expert Committee recommendation for antihypertensive FDCs in the meeting report states:

*"**Square box listings of the components of the FDCs should be interpreted by countries as limited to**:*

- *Lisinopril > any ACE inhibitor (ATC code C09AA--)*
- *Telmisartan > any angiotensin receptor blocker (ATC code C09CA--)*
- *Amlodipine > any once-daily dihydropyridine calcium channel blocker (intrinsically long-acting, e.g. amlodipine, lercanidipine, lacidipine; or modified-release, e.g. nifedipine, felodipine)*
- *HCTZ > chlortalidone or indapamide."*

This example of an SqB symbol unrestricted is, in fact, a restricted SqB because different alternatives are given. The same comment applies to this example, as it should be ensured that there is published evidence of comparable efficacy and safety for all the possible combinations.

3.8 Statins for high-risk patients

Simvastatin is listed for high-risk patients. The entry includes an SqB symbol, and the ATC4 therapeutic subgroup is all HMG-CoA reductase inhibitors (7 listed). The BNF (#79, 2020) includes atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin. It should be noted that cerivastatin (listed in the ATC classification) was withdrawn from the market due to deaths associated with severe rhabdomyolysis in 2001.

Section	Medicine (RoA)	ATC5	ATC4	Active ingredients [a]
12.6	simvastatin (O)	C10AA01	C10AA HMG CoA reductase inhibitors	lovastatin (O) pravastatin (O) fluvastatin (O) atorvastatin (O) cerivastatin[13] (O) rosuvastatin[14] (O) pitavastatin (O)

The Expert Committee recommendation however, specifies that therapeutic equivalents are: **atorvastatin**, **pravastatin**, **fluvastatin** and **lovastatin**. "

It should be highlighted that no dosage recommendations are given for these alternative medicines. All these entries have a defined daily dose (DDD) value, but the DDD is "*the assumed average maintenance dose per day for a drug used for its main indication in adults. The DDD is a unit of measurement and does not necessarily reflect the recommended or Prescribed Daily Dose*".

This is important because many review articles are referencing the equivalent dosages of each statin. This is also important for interchangeability programs, which are common for these medicines in some countries.

This is another example of a restricted SqB symbol, as specific alternatives are given.

3.9 Ophthalmologic gentamicin

Eye drops of gentamicin are listed with a square box symbol for other specified conjunctivitis and also infectious blepharitis.

Ophthalmologic gentamicin is classified as part of the S01AA therapeutic subgroup, which includes 24 antimicrobials of different classes. Although the AWaRe classification has not included antibiotics for local administration, it should be noted that the S01AA therapeutic subgroup includes many Access antibiotics, but also some Watch antimicrobials (e.g., azithromycin, cefuroxime or vancomycin), and one Reserve (polymyxin b).

Section	Medicine (RoA)	ATC5	ATC4	Active ingredients [a]
21.1	Gentamicin	S01AA11	S01AA Antibiotics	chloramphenicol, chlortetracycline, neomycin, oxytetracycline, tyrothricin, framycetin, tetracycline, natamycin, gentamicin, tobramycin, fusidic acid, benzylpenicillin, dihydrostreptomycin, rifamycin, erythromycin, polymyxin B, ampicillin, amikacin, micronomicin, netilmicin, kanamycin, azidamfenicol, azithromycin, cefuroxime, vancomycin

For bacterial conjunctivitis, the Antibiotic Handbook suggests gentamicin 0.3% (eye drops), ofloxacin 0.3% (eye drops) or tetracycline 1% (eye ointment). Note that ofloxacin is listed in the S01AE therapeutic subgroup.

So, in this case, the unrestricted SqB symbol includes many options if guided only by the ATC4. At the same time, using the ATC4 does not allow the listing of at least one antibiotic recommended in the AB handbook because it belongs to another ATC4.

[13] Withdrawal of cerivastatin from the world market https://www.ncbi.nlm.nih.gov/pmc/articles/PMC59524/

3.10 Oral contraceptives

Two fixed-dose combinations of oral contraceptives are listed in the EML: ethinylestradiol + levonorgestrel and ethinylestradiol + norethisterone; both have a double SqB symbol (one for each component of the combination).

Thus, if the ATC4 is considered, 16 fixed-dose combinations of progestogens and estrogens are listed.

Section	Medicine (RoA)	ATC5	ATC4	Active ingredients [a]
22.1.1	ethinylestradiol + levonorgestrel (O)	G03AA07	G03AA Progestogens and estrogens, fixed combinations	etynodiol + ethinylestradiol, quingestanol + ethinylestradiol, **lynestrenol** + ethinylestradiol, **megestrol** + ethinylestradiol, norethisterone + ethinylestradiol, norgestrel + ethinylestradiol, levonorgestrel + ethinylestradiol, medroxyprogesterone + ethinylestradiol, **desogestrel + ethinylestradiol**, **gestodene + ethinylestradiol**, norgestimate + ethinylestradiol, **drospirenone + ethinylestradiol**, norelgestromin + ethinylestradiol, nomegestrol + estradiol, **chlormadinone + ethinylestradiol**, dienogest + ethinylestradiol, medroxyprogesterone + estradiol
	ethinylestradiol + norethisterone (O)	G03AA05		

It should be noted that some toxicity warnings have been raised for some active ingredients listed in this ATC4, such as chlormadinone has been associated with carcinogenicity in animals, or desogestrel, gestodene and drospirenone, which have a higher risk of venous thromboembolism. So, if the SqB symbol is not restricted, the decision to include one combination or another in the National EMLs can have consequences due to the different toxicity profile of the listed combinations.

3.11 Diazepam for anxiety disorders

Diazepam is listed for the treatment of anxiety disorders with an unrestricted SqB symbol. The Expert Committee recommended that "*any long-acting benzodiazepine (half-life> 12 hours) can be used*".

Diazepam has been classified under the N05BA therapeutic subgroup, which includes 22 active ingredients belonging to the same pharmacological family.

Section	Medicine (RoA)	ATC5	ATC4	Active ingredients [a]
24.3	Diazepam (O)	N05BA01	N05BA Benzodiazepine derivatives	chlordiazepoxide (O, P), medazepam (O), **oxazepam** (O), potassium clorazepate (O), lorazepam (O, P, SL), adinazolam (?), bromazepam (O), clobazam (O), ketazolam (?), prazepam (O), alprazolam (O), halazepam (O), pinazepam (?), **camazepam** (O), nordazepam (O), fludiazepam (O), ethyl loflazepate (O), etizolam (?), clotiazepam (?), cloxazolam (?), tofisopam (?), bentazepam (O)

Under N05BA, the plasma half-lives of the listed medicines are intermediate to high (i.e., >12 hours in most cases). Despite this, as the plasma half-life uses to be specified as a range, in some cases (oxazepam, lorazepam and alprazolam), the lower range described is less than 12 hours. Finally, camazepam is a short to intermediate half-life benzodiazepine (i.e., <12 hours) and it has been withdrawn in some countries for its risk of dermatological adverse drug reactions.

3.12 Salbutamol for asthma and COPD

Salbutamol is listed as a medicine for asthma and chronic pulmonary obstructive disease with an SqB symbol.

Section	Medicine (RoA)	ATC5	ATC4	Active ingredients [a]
25.1	Salbutamol (Inh)	R03AC02	R03AC Selective beta-2-adrenorecept or agonists	**terbutaline (Inh), fenoterol (Inh), rimiterol (Inh), hexoprenaline (Inh),** isoetarine, **pirbuterol (Inh),** tretoquinol, carbuterol, **tulobuterol (Inh), salmeterol (Inh), formoterol (Inh),** clenbuterol, reproterol, **procaterol (Inh),** bitolterol, **indacaterol (Inh), olodaterol (Inh)**

According to the ATC4 therapeutic subgroup, there are 16 active ingredients listed under R03AC, but five don't have a DDD value assigned. Eleven products are available as inhaled medicines. Notwithstanding this, it should be noted that not all medicines have the same pharmacokinetic characteristics, which make them slightly different. For example, formoterol, indacaterol, olodaterol and salmeterol are classified as long-acting selective β_2-adrenoceptor agonists. But salbutamol is a short-acting selective β_2-adrenoceptor agonist, as terbutaline.

Then, an unrestricted SqB can lead to the selection of active ingredients with slightly different clinical actions. Last but not least, this ATC4 subgroup includes fenoterol, a medicine which was associated with exacerbation of asthma and mortality, especially in New Zealand during the 1990s.

In conclusion, guidance or restriction of the SqB symbol, in this case, could be helpful for the selection of alternatives by different countries.

3.13 Nicotinamide

Nicotinamide (a form of vitamin B_3)is listed as "Vitamins and minerals", and it is indicated for pellagra with an SqB symbol.

As nicotinamide belongs to ATC4 subgroup A11HA, it is listed together with ten additional active ingredients. In this case, it should be noted that the therapeutic subgroup includes other vitamins B (B_6 B_2), but also vitamin E and derivates.

Section	Medicine (RoA)	ATC5	ATC4	Active ingredients [a]
25	Nicotinamide (O)	A11HA01	A11HA Other plain vitamin preparations	pyridoxine (Vit B6) (O, P), tocopherol (Vit E) (O, P), riboflavin (Vit B2), biotin, pyridoxal phosphate, inositol, tocofersolan (O), dexpanthenol, calcium pantothenate, pantethine

Specification of appropriate alternatives (if any) could help to avoid mistakes in the selection process.

3.14 Otological drops of ciprofloxacin

The last example is the entry of ciprofloxacin to be administered topically for infectious diseases of the external ear.

Section	Medicine (RoA)	ATC5	ATC4	Active ingredients [a]
28	Ciprofloxacin T otic	S02AA15	S02AA Antiinfectives	chloramphenicol, nitrofural, boric acid, aluminium acetotartrate, clioquinol, hydrogen peroxide, neomycin, tetracycline, chlorhexidine, acetic acid, polymyxin B, rifamycin, miconazole, gentamicin, ofloxacin

The ATC4 subgroup for ciprofloxacin is S02AA; it includes 15 active ingredients besides ciprofloxacin. The only additional fluoroquinolone is ofloxacin. But this ATC4 also lists different classes of antibacterials, antiseptics or antifungals. Note that clioquinol is also listed, a halogenated quinolone withdrawn from the market due to subacute myelo-optic neuropathy (SMON) in Japan. Nitrofural is another antimicrobial withdrawn from several countries due to its mutagenic and carcinogenic effect in animal studies.

This is another example where specific alternatives should be listed to ensure that the original spirit of the inclusion of otic ciprofloxacin in the EML is maintained in other national EMLs.

D. Discussion and recommendations

The concept of the square box symbol applied to entries of the EML as a way to allow listed a medicine seen as a representative example from a group of clinically equivalent medicines within a pharmacological class is useful. It allows the countries' selection committees to choose which medicine list in their national EML, taking into account variations in the availability of molecules or even uses of the prescribers due to pharmaceutical market differences.

To ensure that the process is efficient, that decisions at the country level are taken following the evidence-based principles, and to minimise misunderstandings during the process to adapt and adopt the WHO-EML to the needs and characteristics of any given country, three conditions are envisaged that:

(1) The square box symbol is consistently used in the WHO EML, which will be taken as a model.
(2) That the members of the national selection committees know the uses of the square box symbol, are familiar with the therapeutic equivalents available for each listed medicine, and know the process to select and list medicines to the NEML.
(3) The information about the therapeutic alternatives suggested by the WHO Expert Committee on Selection and Use of Essential Medicines is accessible and easy to find.

Then, the following recommendations arose from the present analysis and will be addressed to improve those three aspects.

1. Improvement of the use of the SqB symbol by the Expert Committee on Selection and Use of Essential Medicines

Sixteen years and seven iterations after the previous analysis of the square box symbol conducted by Drs Sue Hill and Leo Offerhaus, the use of this symbol in the 2019 EML showed heterogeneity, some inconsistencies and some areas lacking definition which could lead to the selection of an inappropriate alternative at the country level.

The following table summarises the main findings by category, as well as the proposed actions to improve the situation:

FINDING	DESCRIPTION	EXAMPLES	ACTIONS
Heterogeneity	In some cases, the '*' symbol is used to name some alternative medicines or therapeutic equivalents	propofol	To consider converting entries with the '*' symbol to qualified square box listings
		clarithromycin	
		meropenem	
	The '*' symbol is used to specify: "including quality-assured biosimilars."	rituximab	To revise the criteria to accept biosimilars, thus avoiding the need to specify it in each case. The same was done with generic medicines in the case of small molecules in the past.
		trastuzumab	
Inconsistencies	Unrestricted SqB become qualified or restricted SqB in the full EC meeting report	simvastatin	To consider converting these entries to qualified square box listing, specifying the alternatives defined in the EC recommendations
		ofloxacin (ocular)	
		lisinopril + hydrochlorothiazide	
		medroxyprogesterone acetate	
Lack of definition (if ATC4 is being used as a proxy to therapeutic equivalent)	Products with no defined daily dose	dexrabeprazole (omeprazole)	To specify that medicines of the same ATC4 class with no assigned DDD are not suitable alternatives.
		diphenadione (warfarin)	
	Products lacking one or more listed routes of administration	midazolam (O, P), but brotizolam (O)	To address this potential limitation in the definition of suitable or eligible therapeutic alternative.
		omeprazole (O, P), but lansoprazole (O)	
	Products with safety warnings or withdrawn in some countries	cerivastatin (simvastatin)	As some discontinued products continue to be listed in the ATC/DDD Index, a limited list of alternatives can help to avoid that these toxic products are mistakenly included in NEML
		oxyphenisatine (senna)	
		zimeldine (fluoxetine)	
	Double SqB symbol in fixed-dose combinations	ethinylestradiol + levonorgestrel	To specify if the SqB refers to an equivalent fixed-dose combination (instead of the combination of therapeutic equivalents of both components).
	The ATC4 class includes a mixture of products	Nicotinamide (the ATC4 includes a mixture of vitamins and minerals)	To specify the best alternatives, according to the evidence on therapeutic equivalence.
		Otic ciprofloxacin (the ATC4 includes other classes of antibacterials and antifungals	

Given the highlighted limitations and potential problems derived from the interpretation of the SqB symbol by the different members of the expert committees at the country level, we suggest:

- To rename the square box symbol as "therapeutic equivalent" (a name which can confuse experts in some countries) or "suitable therapeutic alternative", or any other more accurate name.
- To try to review and restrict the proposed alternatives in all WHO-EML entries progressively.

2. Updating the skills to improve the medicines selection process based on the WHO-EML model and principles at the country level

The process to select a medicine and decide whether and how to include it in the national essential medicines list requires different skills, including the critical appraisal of the available published scientific evidence. The decision of excluding a specific medicine also requires knowledge in therapeutics, skills in the critical analyses of evidence and even skills to argue the decision in front of the stakeholders interested in its inclusion.

Within the frame of the training courses to be developed by the WHO-EML Secretariat, it could be interesting to include:

- Courses to strengthen the skills for the selection of medicines addressed to members of the local expert committees.
- Short courses and messages addressed to the population, journalists and lawyers, to modify the negative attitudes towards the WHO-EML and national EMLs, as well as how to turn into a positive message the fact of excluding medicines from the list because of their insufficient evidence.

The WHO Academy initiative could be an excellent framework to develop these pieces of training.

3. To ensure that the information about the proposed alternatives (specific medicines, evidence supporting them) are clearly specified in the e-EML.

The new *e*-EML (https://list.essentialmeds.org/) is an excellent tool, easily searchable, which allows easy and fast consultations of the EML listed medicines as well as their indications of use, formulations, evidence supporting the inclusion, etc.

The site also includes information regarding therapeutic equivalents (the SqB symbol). In most cases, the information appearing in the highlighted box is the sentence: "*Medicines within the same pharmacological class can be used*", although a careful reading of the 'Summary of evidence and Expert Committee recommendations' paragraph details specific alternatives, in some cases.

Due to the versatility of the *e*-EML, as well as the expected growth of visitors, it is recommended to:

- Limit the unspecific recommendations in the 'Therapeutic equivalent' entry as much as possible.
- Improve the legibility of the additional information section (including the 'Summary of evidence and Expert Committee recommendations') with simple graphic modifications, such as including headings in bold type (e.g., Background, References, Evidences, Therapeutic equivalents, Use in children, Safety warnings, among others, depending on the medicine).

4. To know the variations in the inclusion of therapeutic equivalents and uses of the SqB symbol in the national EMLs.

A recent analysis of 137 national EML concluded that "Most national lists of essential medicines had more than 200 differences compared with WHO's model list. These differences were only partly explained by the countries' characteristics we investigated. Most of the medicines were listed by a small number of countries."[15]

A closer analysis of the individual medicines selected in the national EMLs focusing on those which have an SqB symbol in the WHO-EML could help to understand how the national selection committee interprets the therapeutic equivalent (SqB symbol) concept. It can also help to detect inaccuracies in that interpretation which could lead to an inappropriate prescription. Additionally, **this knowledge will be helpful to develop the courses and short courses** suggested in the previous paragraph.

Actions to help to improve the rationalisation of the medicines included in a country's EML is a critical way to improve the use of medicines available for prescription and also to ensure the most efficient use of the economic resources needed to pay for them.

[15] Persaud N, *et al*. Comparison of essential medicines lists in 137 countries. *Bull World Health Organ* 2019;97:394–404C doi: http://dx.doi.org/10.2471/BLT.18.222448

APPENDIX 1: Square box listings without qualification ("unrestricted") on the 2019 WHO Model Lists of Essential Medicines

Section	Medicine (RoA)	ATC5	ATC4	Active ingredients [a]	Nr in ATC4**	Nr in ATC4 (=RoA)
1.2 Local anaesthetics	Bupivacaine (I, ISpA)	N01BB01	N01BB Amides	mepivacaine, prilocaine, butanilicaine, cinchocaine, etidocaine, articaine, ropivacaine, levobupivacaine	10	0 (no DDD)
	Lidocaine (I, ISpA, T)	N01BB02			10	0 (no DDD)
1.3 Preoperative medication and sedation for short-term procedures	Midazolam I, Ol, T (O, P)	N05CD08	N05CD BZD derivatives	Flurazepam (O), nitrazepam (O), **flunitrazepam (O,P)**, estazolam (O), triazolam (O, SL), lormetazepam (O), temazepam (O), brotizolam (O), quazepam (O), loprazolam (O), doxefazepam?, cinolazepam?, remimazolam?	14	1
2.3 Medicines for common symptoms palliative care	Ondansetron I, Ol, T (O, P)	A04AA01	A04AA Serotonin antagonists	**Granisetron (O, P, TD), tropisetron (O, P), dolasetron (O, P), palonosetron (O, P)**	4	4
3 Antiallergics and medicines used in anaphylaxis	Prednisolone Ol, T (O)	H02AB06	H02AB Glucocorticoids	**Betamethasone (O, P, Psr), dexamethasone (O,P) , fluocortolone (O), methylprednisolone (O,P), paramethasone (O,P), prednisone (O), triamcinolone (O,P), hydrocortisone (O,P), cortisone (O,P), prednylidene (O), deflazacort (O**), cloprednol?, meprednisone?, cortivazol?	14	11
	Loratadine Ol, T (O)	R06AX13	R06AX Other antihistamines for systemic use	**Bamipine (O), cyproheptadine (O)** thenalidine (?) phenindamine (?) **antazoline (O, P) triprolidine (O**) pyrrobutamine (?) **azatadine (O) astemizole (O) terfenadine (O) mebhydrolin (O) deptropine (O) ketotifen (O) acrivastine (O) azelastine (O)** tritoqualine (?) **ebastine (O)** pimethixene (?) epinastine (?) **mizolastine (O) fexofenadine (O) desloratadine (O) rupatadine (O) bilastine (O)** quifenadine ? sequifenadine ?	26	18
5 Anticonvulsants /antiepileptics	Lorazepam (P)	N05BA06[b]	N05BA BZD derivatives (Attention, clonazepam)	**diazepam (O, P, R)**, **chlordiazepoxide (O, P)**, medazepam (O), oxazepam (O), potassium clorazepate (O), adinazolam (?), bromazepam (O), clobazam (O), ketazolam (?), prazepam (O), alprazolam (O), halazepam (O), pinazepam (?), camazepam (O), nordazepam (O), fludiazepam (O), ethyl loflazepate (O), etizolam (?), clotiazepam (?), cloxazolam (?), tobenoxaebrbuforfisopam (?), bentazepam (O)	22	2
6.4.1 Antiherpes medicines	aciclovir (Ol, I, T) (O, P)	J05AB01	J05AB Nucleos. and nucleot. excl. rev. transcr. inhibitors	idoxuridine (?) vidarabine (P) **ganciclovir (O, P)** famciclovir (O) valaciclovir (O) cidofovir (P) penciclovir ? valganciclovir (O) brivudine (O)	9	1

6.5.1 Antiamoebic and antigiardiasis medicines	metronidazole (I, Ol, T) (O, P)	P01AB01 Metro P is J01XD01	P01AB Nitroimidazole derivatives J01XD Imidazole derivatives	tinidazole (O, R), ornidazole (O), azanidazole ?, propenidazole ?, nimorazole (O), secnidazole (O) J01XD02 tinidazole (P) J01XD03 ornidazole (P)	6 (+2)	0
7.2 Antimigraine – for prophylaxis	Propranolol (O)	C07AA05	C07AA Beta blocking agents, non-selective	**alprenolol (O,P) oxprenolol (O,P) pindolol (O,P) timolol (O,P) sotalol (O,P) nadolol O mepindolol O carteolol O tertatolol O** bopindolol ? bupranolol ? **penbutolol O** cloranolol ?	13	10
9 Antiparkinsonism medicines	biperiden (O,P)	N04AA02	N04AA Tertiary amines	trihexyphenidyl (O), metixene (O), **procyclidine (O, P),** profenamine ?, **dexetimide (O, P),** phenglutarimide ?, mazaticol ?, bornaprine ?, tropatepine ?	9	2
	levodopa + o **carbidopa** (T)	N04BA02 levodopa + decarboxylase inhibitor	N04BA Dopa and dopa derivatives	No ATC for carbidopa. No decarboxylase inhibitors specified		0
10.2 Medicines affecting coagulation	warfarin (O)	B01AA03	B01AA Vitamin K antagonists	**dicoumarol (O), phenindione (O), phenprocoumon (O), acenocoumarol (O), ethyl biscoumacetate (O)**, clorindione ?, diphenadione ?, tioclomarol ?, fluindione ?	9	5
12.1 Antianginal medicines	isosorbide dinitrate (O sl)	C01DA08	C01DA Organic nitrates	glyceryl trinitrate (O, oral aerosol SL, TD), methylpropylpropanediol dinitrate ?, pentaerithrityl tetranitrate (O), propatylnitrate (O), isosorbide dinitrate (O, SL, oral aerosol, TD), trolnitrate (O), eritrityl tetranitrate (O), isosorbide mononitrate (O), tenitramine ?	9	2?
12.3 Antihypertensive medicines	amlodipine (O)	C08CA01	C08CA Dihydropyridine derivatives	**felodipine (O), isradipine (O, P), nicardipine (O, P), nifedipine (O, P), nimodipine (O, P), nisoldipine (O), nitrendipine (O), lacidipine (O), nilvadipine (O), manidipine (O), barnidipine (O), lercanidipine (O), cilnidipine (O)**, benidipine ?, clevidipine ?	15	13
	enalapril (O)	C09AA02	C09AA ACE inhibitors, plain	**captopril (O), lisinopril (O), perindopril (O), ramipril (O), quinapril (O, P), benazepril (O), cilazapril (O), fosinopril (O), trandolapril (O), spirapril (O), delapril (O), moexipril (O), temocapril (O), zofenopril (O), imidapril (O)**	15	15
	hydrochlorothiazide (O)	C03AA03	C03AA Thiazides, plain	**bendroflumethiazide (O), hydroflumethiazide (O), chlorothiazide (O), polythiazide (O), trichlormethiazide (O), cyclopenthiazide (O), methyclothiazide (O), cyclothiazide (O)**, mebutizide ?	9	8
	lisinopril + amlodipine (O)	C09BB03[c]	C09BB ACE inhibitors and calcium channel blockers	enalapril and lercanidipine?, lisinopril and amlodipine?, perindopril and amlodipine?, ramipril and felodipine?, enalapril and nitrendipine?, ramipril and amlodipine?, trandolapril and verapamil?, delapril and manidipine?	8	?
	lisinopril + hydrochlorothiazide (O)	C09BA03[c]	C09BA ACE inhibitors and diuretics	captopril and diuretics, enalapril and diuretics, perindopril and diuretics, ramipril and diuretics, quinapril and diuretics, benazepril and diuretics, cilazapril and diuretics, fosinopril and diuretics, delapril and diuretics, moexipril and diuretics, zofenopril and diuretics	11	?

	losartan (O)	C09CA01	C09CA Angiotensin II receptor blockers (ARBs), plain	**eprosartan (O), valsartan (O), irbesartan (O)**, tasosartan ?, **candesartan (O), telmisartán (O), olmesartan medoxomil (O), azilsartan medoxomil (O), fimasartan (O)**	9	8
	telmisartan + amlodipine (O)	C09DB04**c**	C09DB ARBs and calcium channel blockers	valsartan and amlodipine?, olmesartan medoxomil and amlodipine?, irbesartan and amlodipine?, losartan and amlodipine?, candesartan and amlodipine?, valsartan and lercanidipine?, fimasartan and amlodipine?	8	?
	telmisartan + hydrochlorothiazide (O)	C09DA07**c**	C09DA ARBs and diuretics	losartan and diuretics?, eprosartan and diuretics?, valsartan and diuretics?, irbesartan and diuretics?, candesartan and diuretics?, olmesartan medoxomil and diuretics?, azilsartan medoxomil and diuretics?, fimasartan and diuretics?	8	?
12.4 Medicines used in heart failure	enalapril (O)	C09AA02	C09AA ACE inhibitors, plain	(see 12.3)		
	furosemide (O, P)	C03CA01	C03CA Sulfonamides, plain	**bumetanide (O,P)**, piretanide ?, **torasemide (O,P)**	3	2
	hydrochlorothiazide (O)	C03AA03	C03AA Thiazides, plain	(see 12.3)		
	Losartan (T)	C09CA01	C09CA Angiotensin II receptor blockers (ARBs), plain	(see 10.3)		
12.6 Lipid-lowering agents	simvastatin (O) (* for use in high risk patients)	C10AA01	C10AA HMG CoA reductase inhibitors	**lovastatin (O) pravastatin (O) fluvastatin (O) atorvastatin (O) cerivastatin[16] (O) rosuvastatin[17] (O) pitavastatin (O)**	7	7
13.1 Dermatological - antifungal medicines	miconazole Cr, Oin	D01AC02	D01AC Imidazole and triazole derivatives	clotrimazole?, miconazole?, econazole?, chlormidazole?, isoconazole?, tiabendazole?, tioconazole?, ketoconazole?, sulconazole?, bifonazole?, oxiconazole?, fenticonazole?, omoconazole?, sertaconazole?, fluconazole?, flutrimazole?, eberconazole?, luliconazole?, efinaconazole?	19	?
13.3 Dermatological - anti-inflammatory medicines	betamethasone a Cr Oin **a** hydrocortis preferred in neonates	D07AC01	D07AC Corticosteroids, potent (group III)	fluclorolone? desoximetasone? fluocinolone acetonide? fluocortolone? diflucortolone? fludroxycortide? fluocinonide? budesonide? diflorasone? amcinonide? halometasone? mometasone? methylprednisolone aceponate? beclometasone? hydrocortisone aceponate? fluticasone? prednicarbate? difluprednate? ulobetasol?	19	?
	calamine Lot	----	---			
	hydrocortisone Cr, Oin	D07AA02	D07AA Corticosteroids, weak (group I)	methylprednisolone?, prednisolone?	2	?
13.4 Medicines affecting skin differentiation and proliferation	podophyllum resin Sol	D06BB04	D06BB Antivirals	idoxuridine?, tromantadine?, aciclovir?, inosine?, penciclovir?, lysozyme?, ibacitabine?, edoxudine?, imiquimod?, docosanol?, sinecatechins?	11	¿
13.5 Scabicides and pediculicides	benzyl benzoate Lot	P03AX01	P03AX Other ectoparasiticides, incl. scabicides	copper oleinate?, malathion?, quassia?, dimeticone?, benzyl alcohol?	5	?

[16] Withdrawal of cerivastatin from the world market https://www.ncbi.nlm.nih.gov/pmc/articles/PMC59524/

[17] https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/21366slr005lbl.pdf

14.1 Diagnostic agents - ophtalmic	tropicamide Oc	S01FA06	S01FA Anticholinergics	atropine?, scopolamine?, methylscopolamine?, cyclopentolate?, homatropine?	5	?
14.2 Radiocontrast media	Amidotrizoate I	-----	No ATC	No ATC		
	Iohexol I	V08AB02	V08AB Watersoluble, nephrotropic, low osmolar X-ray contrast media	metrizamide, ioxaglic acid, iopamidol, iopromide, iotrolan, ioversol, iopentol, iodixanol, iomeprol, iobitridol, ioxilan	11	?
15.1 Antiseptics	Chlorhexidine Sol	D08AC02	D08AC Biguanides and amidines	phepropamidine, propamidine, hexamidine, polyhexanide	4	?
	Ethanol Sol	D08AX08	D08AX Other antiseptics and disinfectants	hydrogen peroxide, eosin, propanol, tosylchloramide sodium, isopropanol, potassium permanganate, sodium hypochlorite	7	?
	povidone iodine Sol	D08AG02	D08AG Iodine products	iodine/octylphenoxypolyglycolether, iodine, diiodohydroxypropane	3	?
15.2 Disinfectants	chlorine base compound Sol	¿	¿	¿		
	Chloroxylenol Sol	D08AE05	D08AE Phenol and derivatives	hexachlorophene, policresulen, phenol, triclosan, biphenylol	5	?
16 Diuretics	furosemide (O, P)	C03CA01	C03CA Sulfonamides, plain	**bumetanide (O, P)**, piretanide ?, **torasemide (O, P)**	3	2
	hydrochlorothiazide (0)	C03AA03	C03AA Thiazides, plain	**bendroflumethiazide (O), hydroflumethiazide (O), chlorothiazide (O), polythiazide (O), trichlormethiazide (O), cyclopenthiazide (O), methyclothiazide (O), cyclothiazide (O)**, mebutizide ?	9	8
17.1 Antiulcer medicines	omeprazole (O,P)	A02BC01	A02BC Proton pump inhibitors	**pantoprazole (O, P),** lansoprazole (O), rabeprazole (O), **esomeprazole (O, P),** dexlansoprazole (O), dexrabeprazole ?, vonoprazan ?	7	2
	ranitidine (O, P)	A02BA02	A02BA H2-receptor antagonists	**cimetidine (O, P), famotidine (O, P), nizatidine (O, P),** niperotidine ?, roxatidine (O), ranitidine bismuth citrate (O), lafutidine (O)	7	3
17.2 Antiemetic medicines	ondansetron (O, P)	A04AA01	A04AA 5HT3 antagonists	**granisetron (O, P, TD), tropisetron (O, P), dolasetron (O, P), palonosetron (O, P)**	4	4
17.3 Gastrointestinal - anti-inflammatory medicines	Sulfasalazine (O, R)	A07EC01	A07EC aminosalicylic acid and similar agents	**sulfasalazine (O, R), mesalazine (O, R)**, olsalazine (O), balsalazide (O)	4	2
17.4 Laxatives	Senna (O)	A06AB06	A06AB contact laxatives	**oxyphenisatine (O), bisacodyl (O, R), dantron (O), phenolphthalein (O), castor oil (O),** senna glycosides?, cascara?, **sodium picosulfate (O), bisoxatin (O)**	9	7
18.4 Progestogens	medroxyprogesterone acetate (O)	G03DA02	G03DA Pregnen (4) derivatives	gestonorone (P), hydroxyprogesterone (P), **progesterone (O, P, R, V)**	3	1
20 Muscle relaxants and cholinesterase inhibitors	Atracurium (P)	M03AC04	M03AC Other quaternary ammonium compounds	pancuronium, gallamine, vecuronium, atracurium, hexafluronium, pipecuronium bromide, doxacurium chloride, fazadinium bromide, rocuronium bromide, mivacurium chloride, cisatracurium	10	?
	Vecuronium (P)	M03AC03			10	?
	Gentamicin Oc	S01AA11	S01AA Antibiotics		24	?

21.1 Ophtalmological preparations - anti-infective	Tetracycline Oc oin	S01AA09		chloramphenicol, chlortetracycline, neomycin, oxytetracycline, tyrothricin, framycetin, tetracycline, natamycin, gentamicin, tobramycin, fusidic acid, benzylpenicillin, dihydrostreptomycin, rifamycin, erythromycin, polymyxin B, ampicillin, amikacin, micronomicin, netilmicin, kanamycin, azidamfenicol, azithromycin, cefuroxime, vancomycin	24	?
	Ofloxacin Oc	S01AE03	S01AE Fluoroquinolones	norfloxacin, ciprofloxacin, lomefloxacin, levofloxacin, gatifloxacin, moxifloxacin, besifloxacin	7	?
21.2 Ophtalmological preparations - anti-inflammatory agents	Prednisolone Oc	S01BA04	S01BA Corticosteroids, plain	dexamethasone, hydrocortisone, cortisone, triamcinolone, betamethasone, fluorometholone, medrysone, clobetasone, alclometasone, desonide, formocortal, rimexolone, loteprednol, fluocinolone acetonide	14	?
21.3 Ophtalmological preparations - local anaesthetics	Tetracaine Oc	S01HA03	S01HA Local anesthetics	cocaine, oxybuprocaine, proxymetacaine, procaine, cinchocaine, lidocaine	6	?
21.4 Ophtalmologic preparations - miotics and antiglaucoma	Pilocarpine Oc	S01EB01	S01EB Parasympathomimetics	carbachol, ecothiopate, demecarium, physostigmine, neostigmine (ointment), fluostigmine, aceclidine, acetylcholine, paraoxon	9	(9)
	Timolol Oc	S01ED01	S01ED Beta block agents	betaxolol, levobunolol, metipranonaftlol, carteolol, befunolol	5	?
22.1.1 Oral hormonal contraceptives	ethinylestradiol + levonorgestrel (O)	G03AA07	G03AA Progestogens and estrogens, fixed combinations	etynodiol + ethinylestradiol, quingestanol + ethinylestradiol, lynestrenol + ethinylestradiol, megestrol + ethinylestradiol, norethisterone + ethinylestradiol, norgestrel + ethinylestradiol, levonorgestrel + ethinylestradiol, medroxyprogesterone + ethinylestradiol, desogestrel + ethinylestradiol, gestodene + ethinylestradiol, norgestimate + ethinylestradiol, drospirenone + ethinylestradiol, norelgestromin + ethinylestradiol, nomegestrol + estradiol, chlormadinone + ethinylestradiolcisa, dienogest + ethinylestradiol, medroxyprogesterone + estradiol	16	?
	ethinylestradiol + norethisterone (O)	G03AA05			16	?
22.3 Uterotonics	Ergometrine (P)	G02AB03	G02AB Ergot alkaloids	**methylergometrine (O, P),** ergot alkaloids,	2	1
24.1 Medicines used in psychotic disorders	Chlopromazine (O, P)	N05AA01	N05AA Phenothiazines with aliphatic side-chain	**levomepromazine (O, P), promazine (O, P), acepromazine (O, P), triflupromazine (O, P)**, cyamemazine, chlorproethazine	6	4
	Fluphenazine (P)	N05AB02	N05AB Phenothiazines with piperazine structure	**dixyrazine (O, P), perphenazine (O, P, depot, R), prochlorperazine (O, P, R)**, thiopropazate (O), **trifluoperazine (O, P, R**), acetophenazine (O), **thioproperazine (O, P),** butaperazine (O), **perazine (O, P)**	9	6
	Haloperidol (O,P)	N05AD01	N05AD Butyrophenone derivatives	trifluperidol (O), **melperone (O, P), moperone (O, P),** pipamperone (O), **bromperidol (O, P depot),** benperidol (O), droperidol (P), fluanisone?	8	3

24.2.1 Medicines used in depressive disorders	Amitriptyline (O)	N06AA09	N06AA Non-selective monoamine reuptake inhibitors	**desipramine (O), imipramine (O, P), imipramine oxide (O), clomipramine (O, P), opipramol (O), trimipramine (O, P), lofepramine (O), dibenzepin (O), nortriptyline (O, P), protriptyline (O), doxepin (O, P), iprindole (O), melitracen (O, P), butriptyline (O), dosulepin (O), amoxapine (O), dimetacrine (O),** amineptine, **maprotiline (O, P),** quinupramine	20	18
	Fluoxetine (O)	N06AB03	N06AB Selective serotonin reuptake inhibitors	**zimeldine (O), citalopram (O, P), paroxetine (O), sertraline (O),** alaproclate, **fluvoxamine (O),** etoperidone, **escitalopram (O)**	8	6
24.3 Medicines for anxiety disorders	Diazepam (O)	N05BA01	N05BA Benzodiazepine derivatives	**chlordiazepoxide (O, P), medazepam (O), oxazepam (O), potassium clorazepate (O), lorazepam (O, P, SL)**, adinazolam (?), **bromazepam (O), clobazam (O),** ketazolam (?), **prazepam (O), alprazolam (O), halazepam (O),** pinazepam (?), **camazepam (O), nordazepam (O), fludiazepam (O), ethyl loflazepate (O),** etizolam (?), clotiazepam (?), cloxazolam (?), tofisopam (?), **bentazepam (O)**	22	15
25.1 Antiasthmatic medicines and medicines for chronic obstructive	Beclometasone Inh	R03BA01	R03BA Glucocorticoids	**Beclometasone (inh), budesonide (Inh), flunisolide (Inh),** betamethasone, **fluticasone (Inh)**, triamcinolone, **mometasone (Inh), ciclesonide (Inh),** fluticasone furoate	8	5
	Budesonide Inh	R03BA02			8	5
	budesonide + formoterol Inh	R03AK07	R03AK Adrenergics + corticosteroids or other drugs, excl. anticholinergics	epinephrine and other drugs for obstructive airway diseases, isoprenaline and other drugs for obstructive airway diseases, salbutamol and sodium cromoglicate, reproterol and sodium cromoglicate, salmeterol and fluticasone, formoterol and budesonide, formoterol and beclometasone, formoterol and mometasone, vilanterol and fluticasone furoate, formoterol and fluticasone, salmeterol and budesonide, salbutamol and beclometasone, indacaterol and mometasone	12	?
	Salbutamol (Inh)	R03AC02	R03AC Selective beta-2-adrenoreceptor agonists	**terbutaline (Inh), fenoterol (Inh), rimiterol (Inh), hexoprenaline (Inh),** isoetarine, **pirbuterol (Inh),** tretoquinol, carbuterol, **tulobuterol (Inh), salmeterol (Inh), formoterol (Inh),** clenbuterol, reproterol, **procaterol (Inh),** bitolterol, **indacaterol (Inh), olodaterol (Inh)**	16	11
	Tiotropium Inh	R03BB04	R03BB Anticholinergics	**ipratropium bromide (Inh), oxitropium bromide (Inh),** stramoni preparations, **aclidinium bromide (Inh**), **glycopyrronium bromide (Inh)**, **umeclidinium bromide (Inh)**, revefenacin	7	5
26.2 Solutions correcting water, electrolyte and acid-base disturbances - parenteral	sodium lactate, compound solution I	---	---			
27 Vitamins and minerals	Ergocalciferol (O)	A11CC01	A11CC Vitamin D and analogues	Ergocalciferol (no DDD!), **dihydrotachysterol (O), alfacalcidol (O, P), calcitriol (O, P), colecalciferol (O),** calcifediol	5	4
	Nicotinamide (O)	A11HA01	A11HA Other plain vitamin preparations	**pyridoxine (vit B6) (O, P), tocopherol (vit E) (O, P), riboflavin (vit B2),** biotin, pyridoxal phosphate, inositol, **tocofersolan (O),** dexpanthenol, calcium pantothenate, pantethine	10	4?

28 Ear, nose and throat medicines	budesonide Inh	R01AD05	R01AD corticosteroids	**beclometasone (N),** prednisolone, dexamethasone, **flunisolide (N)**, **betamethasone (N), tixocortol (N), fluticasone (N), mometasone (N), triamcinolone (N), fluticasone furoate (N), ciclesonide (N)**	11	9
	Ciprofloxacin T ot	S02AA15	S02AA Antiinfectives	chloramphenicol, nitrofural, boric acid , aluminium acetotartrate, clioquinol, hydrogen peroxide, neomycin, tetracycline, chlorhexidine, acetic acid, polymyxin B, rifamycin, miconazole, gentamicin, ciprofloxacin, ofloxacin	16	?
	Xylometazoline Inh	R01AA07	R01AA Sympathomimetics, plain	cyclopentamine, **ephedrine (N), phenylephrine (N), oxymetazoline (N), tetryzoline (N**), **naphazoline (N),** tramazoline, metizoline, tuaminoheptane, fenoxazoline, tymazoline, epinephrine, indanazoline	13	5