Dr R. Balocco Mattavelli
International Nonproprietary Name (INN)
Programme and Classification of Medical Products
Health Products Policy and Standards (HPS)
Access to Medicines and Health Products Division (MHP)
World Health Organization (WHO)
CH 1211 GENEVA 27
Switzerland

Paris, November 14, 2022

Prescrire's contribution to the WHO consultation on List 127 of proposed INNs

Prescrire
83 boulevard Voltaire
75558 PARIS CEDEX 11
FRANCE

Tél. : (33) (0)1 49 23 72 80

contact@prescrire.org

Site internet
Web site
www.prescrire.org

Relations Abonnés :

Abonnements
Subscription Department
Tél. : (33) (0)1 49 23 72 86
Fax : (33) (0)1 49 23 76 48
relationsabonnes@prescrire.org
international@prescrire.org

Formations Prescrire
Tél. : (33) (0)1 49 23 72 90
Fax : (33) (0)1 49 23 76 48
formations@prescrire.org

Association Mieux Prescrire

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Independant organisation continuing education for health professionals

Association loi de 1901
n° 86/4331 - JO 21/01/1987
(Statuts sur demande)
Org DPC n° 1358
Org FC 11 751 711 075
N° TVA : FR 48 340647619
SIRET 340 647 619 00014
Code NAF : 9499Z
RIB La Banque Postale Paris
BIC : PSST FRPPPAR
IBAN :
FR44 2004 1000 0100 6120 5H02 022

Prescrire is an independent organisation that provides information and continuing education for healthcare professionals. It is wholly funded by its subscribers, carries no advertising, has no shareholders, and receives no other financial support whatsoever.

Both independently since 1981, and with others as part of the Medicines in Europe Forum, the International Society of Drug Bulletins (ISDB) and the International Medication Safety Network (IMSN), *Prescrire* has been advocating the systematic use by healthcare professionals and patients of drugs' international nonproprietary names (INNs). INNs are intended to be more informative, safer and clearer than brand names (1-6).

Making INNs safer. The principles underlying the creation of INNs are the same that apply to the prevention of medication errors: standardisation, differentiation, and facilitation of logic and redundancy checks (7).

However, even with the INN system there is a residual risk of confusion, partly owing to the escalating number of INNs in circulation and the sheer number of applications for new INNs, some of which are never used. A report from the Council of Europe, which recommends the use of INNs, calls for active participation in the public consultations on proposed INNs organised by the World Health Organization (WHO), in order to identify any risk of confusion during their clinical use (8). Our review group (including hospital- and community-based health professionals on *Prescrire*'s editorial staff, and lecturers in medicine and pharmacy from Marseille University Hospital and School of Pharmacy) examined List 127 in order to participate in the public consultation on this latest list of proposed INNs, published in July 2022 (**a**)(9).

Our critical analysis of the proposed INNs. Our analysis of the 247 INNs proposed in List 127, and 1 amendment to an INN proposed in a previous list, was based on the following resources: the WHO's Stem Book 2018 (and its addendum), INN database and its lists of pre-stems, biological substances and radicals; the United States Adopted Names (USAN) stem list; databases of drugs marketed in France, which enable searches on both brand names and INNs; a reference database of drugs used around the world; and *Prescrire*'s in-house monitoring of the literature (10-18).

The first step of *Prescrire*'s collective review was to identify INNs or brand names of marketed drugs that could be confused with the INNs proposed in List 127. In each case, our reviewers then assessed the potential clinical consequences of a medication error arising

through this mechanism, listing their arguments. When clinical consequences were foreseeable, reviewers were also invited to suggest solutions to reduce the risk of confusion.

Two lists in one. There are actually two lists within List 127: a “standard” list of 236 proposed INNs and its addendum, titled “List 127 - COVID-19 (special edition)”, containing 11 proposed INNs. We were unable to examine the proposed INNs *ibacovavec* and *nisfevitug*, because they were not present in the version of List 127 published on 21 July and, regrettably, we were not informed of their subsequent inclusion. We only came across them online while performing the final checks on our contribution, by which time it was too late to subject them to our method of analysis.

Our examination of List 127 of proposed INNs identified the use of many pre-stems: **-caltamide** for T-type calcium channel blockers; **-capavir** for viral capsid and nucleocapsid inhibitors; **-corilant** for non-steroidal glucocorticoid receptor antagonists; **-delpar** for peroxisome proliferator-activated receptor (PPAR) delta agonists; **-dirsen** for splice-switching oligonucleotides for muscular dystrophies; **-folastat** for inhibitors of folate hydrolase 1 (prostate-specific membrane antigen, PSMA); **-ganan** for antimicrobials that are permeability-increasing peptides; **-gliatin** for glucokinase activators; **-inurad** for urate transporter inhibitors; **-nersen** for antisense oligonucleotides targeting neurological functions; **-pixant** for purinoreceptor (P2X) antagonists; **-protafib** for protein tyrosine phosphatase (HPTP) inhibitors; **-rasib** for Ras protein inhibitors; **-tacicept** for TACI (TNFRSF13B)-derived TNF receptors; **-trelvir** for antiviral 3CL protease inhibitors; and **-virimat** for antivirals that are disruptors of viral maturation.

List 127 also features some proposed INNs containing a USAN stem: -alap for aldehyde traps; -aniten for androgen receptor inhibitors (N-terminal domain inhibitors); -desivir for adenosine analogues acting as RNA polymerase inhibitors; -forant for H4 histamine receptor antagonists; -lanstat for lanosterol 14α-demethylase inhibitors; -melagon for melanocortin-1 receptor (MC1R) agonists; -netap for neurotoxic protein translation inhibitors; -padon for dopamine D1-like receptor agonists/partial agonists and potentiators; and -paratide for parathyroid hormone related peptides. Several reviewers considered the potential future stems -melagon and -padon, present in the proposed INNs *resomelagon* and *razpipadon*, too similar and liable to confusion if the descender of the “g” were accidentally replaced by an ascender, or the ascender of the “d” were replaced by a descender.

Objections

Our review group identified risks of sufficient concern to warrant 9 formal objections against INNs proposed in List 127 for monoclonal antibodies conjugated to pharmacologically active substances, such as a cytotoxic agent or corticosteroid, namely: *adalimumab fosimdesonide*, *anvatabart opadotin*, *anvatabart pactil*, *delpacibart etedesiran*, *ispectamab tazide*, *izeltabart tapatansine*, *raludotatug deruxtecan*, *trastuzumab imbotolimod*, and *trastuzumab rezetecan*.

Two-term INNs for substances conjugated to other pharmacologically active substances can cause wrong-drug errors of various types, with List 127 containing several proposed INNs that could be confused with INNs from previous lists. The first type of error results from confusion between a standalone substance and the same substance conjugated to another drug, for example between *adalimumab* and *adalimumab fosimdesonide*, *delpacibart* and *delpacibart etedesiran*, *izeltabart* and *izeltabart tapatansine*, *raludotatug* and *raludotatug deruxtecan*, and *trastuzumab, trastuzumab imbotolimod* and *trastuzumab rezetecan*. The second is confusion between conjugates containing the same substance but coupled to different active moieties, such as between *anvatabart opadotin* and *anvatabart pactil*, and *trastuzumab imbotolimod, trastuzumab rezetecan* and the other four *trastuzumab*-drug conjugates that have already been named, at least one of which is already

marketed (**b**). The third is between conjugates in which different substances are coupled to the same active moiety, in particular between *ispectamab tazide* and *luveltamab tazide* (List 126), and between *raludotatug deruxtecan*, *datopotamab deruxtecan* (List 123), *ifinatamab deruxtecan* (List 126), *patritumab deruxtecan* (List 121) and *trastuzumab deruxtecan* (19-21).

Conjugation to active substances not identified as such: dangerous for patients. If healthcare professionals do not know the precise meaning of the second term of a two-term INN, which is often assumed to refer to a component devoid of pharmacological activity rather than a second active substance, they may prescribe, dispense or administer the drug at the wrong dose or for the wrong indication. *Prescrire* has already filed objections against such conjugates in previous consultations, mainly when an active substance could be mistaken for an innocuous "radical" (22).

The fact that pharmacologically active substances such as *berdoxam, etedesiran, fosimdesonide, imbotolimod, opadotin, pactil, rezetecan, tapatansine* and *tazide* are explained in a section of the list called "Names for chemical modifications of INN (substituent groups, counterions, adduct partners, etc.)" downplays their pharmacological activity, thus trivialising their risks. Yet some, such as *fosimdesonide* and *tapatansine*, are themselves INNs, listed in the Mednet Search Tool under request numbers 11645 and 12301, respectively, and incidentally were only listed here after publication of the version of List 127 dated 21 July 2022. Why these and not the others?

One potential solution, or at least an idea to explore, is based on the way certain French INNs include the preposition "*de*", such as in *obaluronate de paclitaxel* (for *paclitaxel obaluronate*, from List 126) and *ursodésoxycholate de berbérine* (for *berberine ursodeoxycholate*), where the preposition "de" signals the union of the two components of the conjugate. A more universal approach would be to use a mathematical symbol to link the two components rather than a preposition, such as the union symbol ∪ (e.g. *adalimumab* ∪ *fosimdesonide*). This symbol would be used only when both components of the conjugate are pharmacologically active and if the second term is itself an INN (19).

While waiting for the nomenclature for conjugates containing pharmacologically active substances to be revised in order to highlight their greater toxicity, *obaluronate de paclitaxel* and *ursodésoxycholate de berbérine* suggest one way the WHO INN Programme could improve the naming of these types of compound.

Comments

Our review group identified a number of proposed INNs that could generate medication errors through various mechanisms: confusion caused by the meaning of a prefix in French; confusion between overly complex INNs; confusion with a brand name; and confusion with another INN or another stem.

A prefix whose meaning in French could cause errors. Most of our reviewers feel that the INNs for isotopic variants incorporating deuterium ^{2}H are problematic in French, the latest example being the INN *deulinoleic acid* proposed in List 127. As the prefix deu- is pronounced the same as "deux" in French, meaning two, this prefix could cause misunderstandings in verbal communication between healthcare professionals, especially if INNs with and without the prefix deu- coexist. We have already reported this risk of confusion in our responses to Lists 118, 124 and 126, and filed an objection against the INN *deutivacaftor* which in French sounds like "two *ivacaftors*" and could result in serious *ivacaftor* overdoses (22). The INN Programme did not take our objection into account. There are currently 11 substances with the prefix deu-, and most of them are also marketed without deuterium. Examples include *deudextromethorphan* and *dextromethorphan*,

deudomperidone and *domperidone*, *deutenzalutamide* and *enzalutamide*, *deutivacaftor* and *ivacaftor*, *deuruxolitinib* and *ruxolitinib*, and *deutetrabenazine* and *tetrabenazine*.

Complex INNs. Our reviewers considered a number of two-term INNs proposed in List 127 too complex to memorise and use in clinical practice, especially those proposed for gene therapy products, in particular: *alnugranogene aldeparvovec*, *alvamemugene sulseparvovec*, *anbalcabtagene autoleucel*, *cretostimogene grenadenorepvec*, *crosigalcogene omlixparvovec*, *enekinragene inzadenovec*, *equecabtagene autoleucel*, *esepapogene zalarnarepvec*, *igrelimogene litadenorepvec*, *ixoberogene soroparvovec*, *linvekinogene treniplasmid*, *ninsipapogene sibarnarepvec*, *pomlucabtagene autoleucel*, *raxorulimogene belzovacirepvec*, *rivunatpagene miziparvovec*, *satricabtagene autoleucel*, *seglebegagene dasniparvovec*, *tezemlimogene daxadenorepvec*, *tidagixagene derxeparvovec*, *torulimogene lonferencel*, *tremtelectogene empogeditemcel*, *umitrelimorgene autodencel*, *varnimcabtagene autoleucel* and *zocaglusagene nuzaparvovec*. However, those that are ultimately marketed will only be used by specialised healthcare professionals in highly specific situations and obtained through specific supply channels and processes, thus reducing the risk of confusion between different substances. Under these circumstances, the brand name, which is bound to be simpler, will undoubtedly be used in preference to the INN, which means that the complexity of these INNs is counterproductive and will undermine efforts to promote the use of INNs.

Potential confusion with a brand name. Some INNs proposed in List 127 could be confused with a brand name, especially *acloproxalap*, *amelenodor*, *becotatug*, *certepetide*, *divarasib*, *inixaciclib*, *izuforant* and *nexiguran*.

The INN *acloproxalap* could be confused with two different brand names, especially when selecting drugs from an alphabetical menu, because their first 5 letters are identical, namely Aclop° (*clopidogrel* or *aceclofenac* + *paracetamol*) and Aclophen° (*phenylephrine hydrochloride* + *paracetamol* + *chlorphenamine maleate*). One reviewer also remarked that the potential future stem -alap in this proposed INN, preceded by the letter “x”, brought to mind the brand name Xalatan° (the prostaglandin *latanoprost*), a mental association reinforced by the inclusion of -pro- in the INN; it is also worth noting that the brand name Xalaprost° is used in Greece and Australia.

The proposed INN *amelenodor* contains every letter of the brand name Melenor° (*risedronic acid*), used in Greece, the Netherlands and the Czech Republic, creating a risk of confusion in these countries.

For several reviewers, the prefix beco- of the proposed INN *becotatug* brought to mind the brand name Becotide° (*beclometasone*). Although their routes of administration probably differ, thus reducing the risk of confusion, the wrong drug could be selected from an alphabetical menu, especially as *becotatug* will appear first in an alphabetical list.

The proposed INN *certepetide* could be confused with the brand name Seretide° (*fluticasone* + *salmeterol*), and vice versa, due to their orthographic similarity (same sequence of vowels) and phonetic similarity.

The proposed INN *divarasib* starts with the same 5 letters as the brand name Divarius° (*paroxetine*), which could lead to confusion between the two, according to two of our reviewers, and a risk of selecting the wrong drug from an alphabetical menu.

The first 5 letters of the proposed INN *inixaciclib* are almost identical to the brand name Inhixa° (*enoxaparin*), which could cause errors when selecting drugs from an alphabetical menu, and are pronounced identically in French.

The proposed INN *izuforant* could be confused with Forane°, a brand name used for *isoflurane* in many countries. The INN of this halogenated anaesthetic is also phonetically similar to *izuforant* in French.

The proposed INN *nexiguran* and the brand name Nexium° (*esomeprazole*) start with the same 4 letters, creating a risk of confusion between the two and errors when selecting drugs from an alphabetical menu.

Potential confusion with another INN or another stem. Some of the INNs proposed in List 127 could be confused with other proposed or recommended INNs, especially: *dimebutic acid*, *acloproxalap*, *aroxybutynin*, *berberine ursodeoxycholate*, *ciduvectamig*, *dalmelitinib*, *dalzanemdor*, *delpacibart*, *misetionamide*, *tilpisertib fosmecarbil, ulefnersen*, *ultevursen*, *zandatrigine*, *zanzalintinib*, *zerlasiran*, *zifcasiran* and *zifibancimig*.

Many reviewers noted the phonetic and orthographic similarity between the first term of the proposed INN *dimebutic acid* and the INN *trimebutine*. One reviewer also noted a slight resemblance with the INN *dimecrotic acid*, a drug that does not currently appear to be marketed.

The proposed INN *acloproxalap* is perfectly constructed for a derivative of *reproxalap* (RL 81), from which a chlorine atom has been removed. As confusion between these two is possible in practice, well differentiated labelling will be required to prevent errors if they are eventually marketed at the same time (23).

The proposed INN *aroxybutynin* is perfectly constructed, but all of our reviewers who analysed it found it very similar phonetically and orthographically to the INNs *oxybutynin* and *esoxybutynin* (RL 54). The similarity makes perfect sense, since *aroxybutynin* and *esoxybutynin* are enantiomers of *oxybutynin*. Well differentiated labelling will be required to prevent confusion if these substances are eventually marketed at the same time (24).

The proposed INN *berberine ursodeoxycholate* is very similar to *ursodeoxycholic acid*, and many reviewers felt this similarity could cause confusion in everyday practice.

One reviewer, on recognising the presence of the substem **-vec** in the proposed INN of the monoclonal antibody *ciduvectamig*, asked us about the precise nature of this drug, wondering whether it is a gene therapy product involving a monoclonal antibody with a viral vector.

One reviewer pointed out the potential for confusion between the proposed INN *dalmelitinib* and the INN *trametinib,* resulting from the strong resemblance between the suffix -melitinib and the stem **-metinib**.

The proposed INN *dalzanemdor* could be confused with the INN *plazinemdor* (RL 86), which has the same pharmacological property, because they share 9 of their 11 letters (25). Accidental inversion of the ascender of the “d” would further enhance their similarity.

In addition to the risk of confusion between the proposed INN *delpacibart* and its conjugate *delpacibart etedesiran*, pointed out in our formal objection, several reviewers reported the strong resemblance of the prefix delpa- to the pre-stem **-delpar**.

In French, the proposed INN *misetionamide* is very similar phonetically and orthographically to the INNs *ethionamide* and *nicotinamide*, yet their properties are very different: the first being an antineoplastic drug, the second an antituberculous drug and the third a vitamin. Any confusion between them would have consequences for patients.

The proposed INN *tilpisertib fosmecarbil* could be confused with the INN *tilpisertib* (RL 85)(26). *Fosmecarbil* appears to be a radical with no pharmacological action of its own. It is nevertheless important that healthcare professionals understand that a change of radical can affect the dose of the pharmacologically active substance to be used, and is sometimes simply a ploy by the drug company to keep copies at bay.

The proposed INNs *ulefnersen* and *ultevursen* were considered too similar, due to the presence of the same stem, **-rsen**, and the similarity of the prefixes ule- and ulte-, an impression accentuated by their proximity in this alphabetical list. In addition, several reviewers found the prefix uléf- difficult to pronounce.

Similarly, but to a lesser degree, our reviewers found the proposed INNs *zandatrigine* and *zanzalintinib* very similar, an impression probably accentuated by their proximity in this alphabetical list.

The proposed INNs *zerlasiran*, *zifcasiran* and *zifibancimig* were also considered too similar, the first two because they both start with "z" and end in -asiran (which includes the stem **-siran**), and the second two because they share the prefix zif-.

Amendments.

Our review group raised no objections to replacing *ensomafusp alfa* (proposed in List 123) with *englumafusp alfa*, but neither did we submit any concerns about *ensomafusp alfa* in our response to List 123 (20,22).

In summary

Continuing along the same lines as the previous list, List 127 again illustrates the ability of the WHO INN programme to respond swiftly when names for substances used in the treatment of COVID-19 are urgently required, and to make this universal language available to healthcare professionals.

However, we yet again regret the absence of a solution to the problem posed by drugs consisting of two pharmacological active entities, mostly monoclonal antibodies conjugated to cytotoxic agents, given that the consequences of confusing them would most certainly be serious for the patients concerned.

Prescrire acknowledges the remarkable efforts made by the INN Programme to assign names to the increasing number of biological products it has to accommodate in each successive list, which it achieves by updating its naming schemes, as evidenced by the fact that List 127 includes more than 60 proposed INNs for monoclonal antibodies based on its new nomenclature scheme for these molecules, as compared with 6 in List 126. Despite these efforts, *Prescrire* is concerned that it will eventually become impossible to devise distinctive, memorisable INNs for drugs of these classes. The INN Programme has so far managed to meet the challenges posed by the escalating number of substances it is called upon to name, generated by therapeutic innovation and personalised therapies, by deploying imagination and originality.

Review produced collectively by the *Prescrire* Editorial Staff:
no conflicts of interest

a- *This response was prepared using the resources of the entire Prescrire team. Éric Bel (pharmacist) headed the group analysis and drafted this response. The following members of Prescrire's editorial team made a particular contribution: Élodie Artielle-Beaucamp (pharmacist), Karine Begnaud (pharmacist), Julie Bontemps (pharmacist), Helen Genevier (translator), Christine Guilbaud (pharmacist), Mélanie Hardy (pharmacist), Fabienne Jourdan (doctor), Laurence Le Quang Trieu (pharmacist), Nadjat Loumi (pharmacologist), Florent Macé (pharmacist), Ève Parry (pharmacist), Gabriel Perraud (doctor), Agnès Rouzes (pharmacist) and Étienne Schmitt (pharmacist). The contributors from Marseille University*

Hospital Pharmacy and Marseille School of Pharmacy were Pascal Rathelot (professor, hospital consultant), Caroline Castera-Ducros and Christophe Curti (senior lecturers, hospital consultants), Nicolas Primas (lecturer, hospital practitioner), Laura Dubois and Pierre Giacalone (pharmacy residents), and Noémie Cauvet, Louise Cayez and Noémie Raynaud (5th-year pharmacy students).
***b**- The 4 INNs in question are trastuzumab emtansine (List 103), trastuzumab duocarmazine (List 115), trastuzumab deruxtecan (List 116) and trastuzumab corixetan (List 126) (refs 19,27,28).*

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