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# Prescrire's contribution to the WHO consultation on List 128 of proposed INNs

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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 of drugs' international nonproprietary names (INNs) by both healthcare professionals and patients. 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, which consisted of hospital- and community-based health professionals on *Prescrire*'s editorial staff, examined List 128 in order to participate in the public consultation on this latest list of proposed INNs, published in January 2023 (**a**)(9).

**Our critical analysis of the proposed INNs.** Our analysis of the 196 INNs proposed in List 128 and 3 amendments to INNs proposed in previous lists, 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 128. 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.

**Four lists in one.** List 128 contains four lists, i.e. a main "standard" list of 188 proposed INNs

including 3 amendments, and three addenda containing an additional 14 proposed INNs: List 128 - COVID-19 (special edition), List 128 - COVID-19 (special edition - ADDENDUM 1), and List 128 - COVID-19 (special edition – ADDENDUM 2). Prescrire already analysed and commented on the proposed INNs *davesomeran*, *famtozinameran* and *secelasomeran* within the required 2 weeks of their publication (on 15 September and 8 August 2022, respectively) prior to the release of the full List 128.

List 128 contains many pre-stems: **-afine** for squalene monooxygenase inhibitors, used as antifungals; **-alkib** for ALK (anaplastic lymphoma kinase) inhibitors; **-caprant** for kappa-opioid receptor antagonists; **-cirnon** for CC chemokine receptor (CCR) antagonists; **-citide** for peptides and glycopeptides with a cardiovascular target; **-corvir** for core protein (Cp) inhibitors); **-covatein** for protein vaccine substances for coronavirus immunisation; **-desivir** for adenosine analogues that act as RNA polymerase inhibitors; **-drimer** for dendritic polymers (dendrimers); **-glipron** for glucagon-like peptide-1 receptor (GLP1R) agonists; **-gratinib** for fibroblast growth factor receptor (FGFR) inhibitors; **-kalner** for openers of calcium-activated (maxi-K) potassium channels; **-metkib** for MET (mesenchymal epithelial transition factor) kinase inhibitors; **-podect** for phosphodiesterase 10A (PDE10A) inhibitors; **-protafib** for protein tyrosine phosphatase (HPTP) inhibitors; **-rasib** for Ras protein inhibitors; **-rogant** for retinoic acid receptor-related orphan receptor gamma (RORγ) antagonists and inverse agonists; **-rpacept** for SIRPα receptor proteins; and **-scein(e)** for fluorescein-derived fluorescent imaging agents.

List 128 also features some proposed INNs containing a USAN stem: -borole for substances containing boron; and -brodib for inhibitors of the histone acetyltransferase p300 and CREB-binding protein.

**Objections**

Our review group identified risks of sufficient concern to warrant 6 formal objections against INNs proposed in List 128 for monoclonal antibodies conjugated to a pharmacologically active substance, such as a cytotoxic agent or a glucagon-like peptide-1 (GLP-1) receptor agonist: *oberotatug ravtansine*, *puxitatug samrotecan*, *trastuzumab botidotin*, *trastuzumab vedotin*, *upinitatug rilsodotin* (which replaces *upifitamab rilsodotin*) and *maridebart cafraglutide*, although the clinical consequences of confusion between *maridebart* and *maridebart cafraglutide* are likely to be less serious, because *cafraglutide* is not a cytotoxic agent.

Our objection to the proposed INN *onvitrelin ucalontide* reflects our concern that the phenomenon of assigning two-term INNs that make it insufficiently clear that the second term denotes a second pharmacologically active substance is now being extended to other therapeutic classes.

Two-term INNs for substances conjugated to pharmacologically active substances can cause wrong-drug errors of various types, in particular through confusion between a standalone (unconjugated) substance and the same substance conjugated to another drug, between conjugates containing the same substance but coupled to different active moieties, and between conjugates in which different substances are coupled to the same active moiety.

We will not repeat the arguments and examples already given in our previous contributions, but we hope that the naming of conjugates containing pharmacologically active substances will be revised or at least improved, in order to highlight their greater toxicity (19).

**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 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 *deupirfenidone,* proposed in List 128. 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. However, this risk of confusion, specific to the French language, is attenuated when -deu- is used as an infix, as in the proposed INN *mindeudesivir*.

**Potential confusion with a brand name.** Some INNs proposed in List 128 could be confused with a brand name, especially *duvakitug*, *pralurbactam*, *renvistobart*, *rovadicitinib*, *verzistobart* and *riticovatein*.

Several of our reviewers noted a resemblance between the proposed INN *duvakitug* and the brand name Duvadilan° (*isoxsuprine*), resulting from the fact that their first 6 letters are almost identical. Confusion between the two will no longer be possible however in the many countries where Duvadilan° has been withdrawn from the market. One reviewer also noted a certain phonetic similarity between *duvakitug* and the brand name Ayvakyt° (*avapritinib*).

All of our reviewers considered the proposed INN *pralurbactam* far too similar to the brand name Praluent° (*alirocumab*), with which is shares the same first 5 letters. This level of similarity at the start of their names can cause wrong-drug errors, especially when selecting drugs from an alphabetical menu.

Several reviewers considered *renvistobart* and *verzistobart* too similar, orthographically and phonetically, to the brand name Vistogard° (*uridine triacetate*), creating a risk of confusion in both written and verbal communication.

Several reviewers considered that the orthographic and phonetic similarity of *rovadicitinib* to the brand name Rovalcyte° (*ganciclovir*) could lead to confusion in written and verbal communication.

Several reviewers considered *riticovatein* too similar, orthographically and phonetically, to the brand name Ticovac° (a tick-borne encephalitis vaccine). The mental association will only be reinforced by the fact that they are both vaccines, increasing the risk of confusing the two. Some of our reviewers even felt that healthcare professionals might think that *riticovatein* is the INN of the vaccine substance present in Ticovac°.

**Potential confusion with another INN or another stem.** Some of the INNs proposed in List 128 could be confused with other proposed or recommended INNs: *acimtamig*, *brigimadlin*, *davutamig*, *enlonstobart*, *ersodetug*, *erzotabart*, *eurestobart*, *ifebemtinib*, *lirafugratinib*, *maridebart*, *milrebrutinib*, *nebratamig*, *oberotatug*, *obertamig*, *risvodetinib*, *ritivixibat* and *rovadicitinib.*

The proposed INN *acimtamig* ends in the stem **-ta-mig**, denoting a multispecific immunoglobulin with a tumour target. The phonetic similarity noted in French between **-ta-mig** and the stem **-lutamide**, denoting nonsteroid antiandrogens, could mislead healthcare professionals over the true nature of these substances. As a precautionary measure, the use of the infix -lu- in front of the stem **-ta-mig** should be forbidden, to avoid increasing this similarity still further.

All of our reviewers considered the proposed INN *brigimadlin* too similar to the INN *brigatinib*. As their first 4 letters are identical, and as *brigatinib* would be displayed just above *brigimadlin* in an alphabetical menu, *brigatinib* could be accidentally selected instead of *brigimadlin.*

Excessive similarity was noted between the proposed INN *davutamig* and the INN *darunavir*, resulting from the fact that they share the same sequence of vowels. Several reviewers considered that wrong-drug errors involving these two INNs would be highly likely.

Many reviewers considered the proposed INNs *enlonstobart*, *ersodetug*, *erzotabart* and *eurestobart* too similar. Their similarities are admittedly accentuated by the fact that WHO's lists of proposed INNs are alphabetical. Nevertheless, the following shared features, particularly in spoken French, make wrong-drug errors in clinical practice possible, if not probable: the first 4 letters of *ersodetug* and *erzotabart* are phonetically identical in French; *enlonstobart* and *eurestobart* sound alike in French and

share the stem **-sto-bart**, which also strongly resembles the stem **-ta-bart**. Could this level of similarity be a sign that the new nomenclature for monoclonal antibodies is already reaching saturation point?

The proposed INN *ifebemtinib* looks and sounds like the INN *fedratinib*. The reviewer who reported this similarity felt that it could cause wrong-drug errors.

Several reviewers identified the potential for confusion between *lirafugratinib* and the INN *liraglutide*, because they share the same first 4 letters, and similar infixes (-fug- and -glu-).

The identical prefixes of *maridebart* and *maribavir* could lead to wrong-drug errors when selecting drugs from an alphabetical menu.

One reviewer commented on the similarity between *milrebrutinib* and *remibrutinib* (List 121), and another considered that *milrebrutinib* could be confused with the INN *milrinone* when selecting drugs from an alphabetical menu (20).

One reviewer noted orthographic and phonetic similarity between *nebratamig* and the INN *neratinib*, a result of the fact that their prefixes are almost identical and their stems sound similar.

All of our reviewers considered the proposed INNs *oberotatug* and *obertamig*, both antineoplastics, too similar, due to the fact that they have the same 4 first letters and contain the substem **-ta-**.

Two reviewers identified slight orthographic and phonetic similarity between the proposed INN *risvodetinib* and the INNs *crizotinib* and *ruxolitinib*.

At least two reviewers considered the orthographic similarity between the proposed INN *ritivixibat* and the INN *rituximab* sufficiently marked to create a risk of wrong-drug errors when selecting drugs from an alphabetical menu.

One reviewer noted that the proposed INN *rovadicitinib* has the same stem and the same sequence of vowels as the INN *tofacitinib*, making wrong-drug errors a possibility.

**Amendments**

The previously proposed INNs *upifitamab* (List 122) and *upifitamab rilsodotin* (List 123) have been replaced by *upinitatug* and *upinitatug rilsodotin*, respectively, an amendment that does nothing to resolve the issue of the naming of monoclonal antibodies conjugated to cytotoxic agents. The replacement of *encukalner* (List 126) by *azetukalner* is a welcome amendment (21-23)!

**In summary**

Like the previous list, List 128 again illustrates the ability of the WHO INN programme to respond swiftly when names for substances used in the prevention or 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. However, Prescrire is concerned that the limits of these schemes are already being approached. We are also concerned about the increasing complexity of certain INNs, especially those for gene therapy products, due to the risk that their brand names, which are bound to be simpler, will be used in preference to their INNs. Although complex INNs are highly informative for those who know how to decipher them, the growing complexity of new INNs could ultimately prove counterproductive and undermine efforts to promote the use of INNs.

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

***a-*** *This review was produced collectively by Prescrire's editorial staff. Éric Bel (pharmacist) led the project and prepared this response. The following members of the Prescrire team took part in the review: Élodie Artielle-Beaucamp (pharmacist), Karine Begnaud (pharmacist), Julie Bontemps (pharmacist), Helen Genevier (translator), Sophie Ginolhac (pharmacist), 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).*

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