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Prescrire's contribution to the WHO consultation on List 125 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 by healthcare professionals and patients of drugs' international nonproprietary names (INNs). They are clearer, safer and more informative 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, consisting of members of *Prescrire*'s editorial staff, including hospital- and community-based health professionals, has examined List 125 in order to participate in the public consultation on this latest list of proposed INNs, published in July 2021 (**a**)(9).

Our critical analysis of the proposed INNs. Our analysis of the 225 INNs proposed in List 125, an amendment to an INN proposed in a previous list, and a modified INN (INNM) 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 potentially be confused with the INNs proposed in List 125. In each case, the participants then assessed the likelihood and clinical consequences of a medication

error and/or misunderstanding arising through this mechanism, listing their arguments. When clinical consequences were foreseeable, the participants were also invited to suggest solutions to reduce the risk of confusion.

Another huge list. Our examination of List 125 identified the use of a number of pre-stems: **-amimab** for monoclonal antibodies targeting serum amyloid protein (SAP)/amyloidosis; **-batinib** for BCR-ABL kinase inhibitors; **-borbactam** for boronic acid-derived β-lactamase inhibitors; **-cianine** for indocyanine-derived fluorescent dyes; **-corilant** for non-steroidal glucocorticoid receptor antagonists; **-dacin** for DNA gyrase and topoisomerase IV inhibitors used as antibiotics; **-enatide** for glucagon-like peptide-1 receptor (GLP-1R) agonists, *exenatide* (exendin-4) and analogues; **-gratinib** for fibroblast growth factor receptor (FGFR) inhibitors; **-inurad** for urate transporter inhibitors; **-nersen** for antisense oligonucleotides targeting neurological functions; **-nesib** for kinesin inhibitors; **-pertin** for glycine transporter inhibitors; **-ralstat** for kallikrein inhibitors; **-rogant** for retinoic acid receptor-related orphan receptor gamma (RORγ) antagonists; **-sopasem** for superoxide dismutase (SOD) mimetics; **-terkib** for extracellular signal-regulated kinase (ERK) inhibitors; and **-turev** for therapies based on oncolytic viruses.

This list also features some proposed INNs that include a USAN stem: -esatide for erythropoiesis-stimulating agents and/or erythropoietin mimetic peptides; -filam for filamin A binders; -glenastat for glutaminase inhibitors; -loride for *amiloride*-derived epithelial sodium channel (ENaC) inhibitors; -netide for neuropeptide Y (NPY) receptors and analogues; -nontrine for phosphodiesterase type 9 (PDE9) inhibitors; -votide for prostate-specific membrane antigen (PSMA) binding peptides; and -zolac for pyrazole acetic acid-derived anti-inflammatory agents.

Objections

Prescrire identified risks of sufficient concern to warrant formal objections against two of the INNs proposed in List 125, both for substances conjugated to cytotoxic agents: *farletuzumab ecteribulin* and *pivekimab sunirine*.

Conjugation to active substances not identified as such: a danger to patients. We remain deeply concerned about the risks associated with the two-term INNs given to substances conjugated to cytotoxic agents. The list of these conjugates continues to grow, creating a worrying and ever-increasing risk of confusion between the INNs of: a standalone (unconjugated) substance and its conjugated counterparts; conjugates containing the same substance coupled to different active moieties; and conjugates containing the same active moiety coupled to different substances.

If healthcare professionals do not know the precise meaning of the second term, 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 wrong dose or even a drug with an unintended pharmacological action. The proposed INNs *farletuzumab ecteribulin* and *pivekimab sunirine* add to the ever-growing list of similarly constructed INNs for substances conjugated to cytotoxic agents, against which *Prescrire* has filed objections in previous consultations, mainly due to the risk that the cytotoxic component will be mistaken for an innocuous component (19).

New principles for the naming of monoclonal antibodies were discussed in April 2021 at the 72nd INN Consultation, and published in November 2021, in order to address the overcrowding within this class that has made it increasingly difficult to devise distinctive INNs for new antibody-based drugs. However, despite acknowledging that the current approach to naming antibody-drug conjugates could cause medication errors, the INN expert group rejected the idea of modifying their INNs by adding an infix such as -con-, a prefix or a suffix, concluding that no change to their nomenclature was required at this time (20, 21).

We regret that this opportunity to revise the nomenclature for substances conjugated to cytotoxic agents was missed, but remain confident in the INN Programme's ability to improve the naming of this particular type of conjugate. It is an issue that remains unresolved and will need to be revisited.

Comments

Our review group identified a number of proposed INNs that could generate medication errors, for a variety of reasons: the potential for confusion with a brand name or another INN; the absence of an identifiable stem; and potential confusion between stems.

Potential confusion with a brand name. Some INNs proposed in List 125 could be confused with a brand name, especially *farudodstat*, *omilancor* and *pegsitacianine*.

A slight risk of confusion exists between the proposed INN *farudodstat* and the brand name Farydak°, due to their similar prefixes, reinforced by association with its INN *panobinostat*.

The proposed INN *omilancor*, which lacks a stem or pre-stem, could be confused with the visually and phonetically similar brand name Omacor°.

The proposed INN *pegsitacianine* could be confused with the brand name Pyostacine° (*pristinamycin*) and vice versa, due to visual and phonetic similarity, especially in French.

Potential confusion with another INN. Some of the INNs proposed in List 125 could be confused with other proposed or recommended INNs, especially: *amubarvimab*, *atuzabrutinib*, *bafisontamab*, *doxecitine*, *doxribtimine*, *emraclidine*, *escibenzoline*, *famitinib*, *mupadolimab*, *pegloxenatide*, *pegmolesatide*, *riletamotide*, *tagitanlimab*, *tamgiblimab*, *ubamatamab*, *ulenistamab*, *upanovimab* and *vornorexant*.

The slight visual similarity between the proposed INN *amubarvimab* and the INN *bamlanivimab* could lead to confusion between the two.

A slight risk of confusion was noted between the proposed INN *atuzabrutinib* and the INN *zanubrutinib*, based on inverting letters in their prefixes. A higher risk of confusion with the INN *atuzaginstat* (List 124) was noted, especially when selecting drugs from an alphabetical menu, because their first 5 letters are identical (22).

One member of our review group noticed slight similarity between the proposed INN *bafisontamab* and the INN *tafasitamab*.

Our reviewers felt that the prefix dox-, shared by the proposed INNs *doxecitine* and *doxribtimine* and some very familiar INNs, could contribute to errors. As a result, *doxecitine* could be confused with the INNs *doxorubicin* or *doxycycline*, a risk accentuated by their phonetic similarity. One reviewer also pointed out a slight risk of confusion between *doxecitine* and the INN *duloxetine*. The proposed INN *doxribtimine* could also be confused with the INN *doxorubicin*. However, because these nucleotide precursors are components of biological substances such as mRNA vaccines, and are therefore unlikely to be referred to in therapy, the risk of confusing them with drugs is very slim in practice.

The proposed INN *emraclidine* is liable to confusion with the INN *emtricitabine* due to a combination of phonetic similarity in French and their identical first 2 letters.

Although the INN proposed for *escibenzoline*, an enantiomer of *cibenzoline*, is perfectly constructed, the two drugs could be confused in practice, exposing patients to a risk of dosing errors. Preventive measures will therefore be required at the point of care, and their labelling will need to be designed in a way that helps users distinguish between the two substances.

The proposed INN *famitinib* resembles the INN *famotidine*. However, the likelihood of mistaking a cancer drug for a histamine H2-antagonist, used as an anti-ulcer treatment, seems low.

All of our reviewers found that some of the INNs proposed in List 125 for monoclonal antibodies were not sufficiently distinctive, with excessive similarity noted between *mupadolimab, ubamatamab*, *ulenistamab* and *upanovimab*, and between *tagitanlimab* and *tamgiblimab*. This is a consequence of the overcrowding within this group, currently comprising over 750 named monoclonal antibodies, which the new nomenclature scheme should help resolve. As the stem **-mab** is well known and easily recognised by healthcare professionals, educational efforts will be required when it is no longer used for all INNs of monoclonal antibodies and the four new planned groups are launched (20,21).

All of our reviewers considered the proposed INNs *pegloxenatide* and *pegmolesatide* too similar, due to the fact that 10 of their 13 letters are identical, including the prefix peg- and the suffix -atide. They are likely to be confused when written or spoken and when selecting drugs from an alphabetical menu.

One reviewer noted strong resemblance between the proposed INN *riletamotide* and the INN *rilematovir* (List 122), and considered that, if both substances were marketed, a risk of selecting the wrong drug from an alphabetical menu could not be ruled out (23).

The proposed INN *vornorexant* could lead to wrong-drug errors through confusion with *vorinostat* when selecting drugs from an alphabetical menu.

Risk of confusion through lack of an identifiable stem. This was a particular concern for one of the INNs proposed in List 125: *ivospemin*.

The suffix -pemin of the proposed INN *ivospemin* is liable to confusion with the stem **-ermin** and by extension with the stems: **-bermin, -dermin**, **-fermin**, **-filermin**, **-nermin**, **-otermin**, **-plermin**, **-sermin** and **-termin**.

Potential confusion between stems. One INN proposed in List 125, *anumigilimab*, contains a sequence of letters that could be mistaken for a stem.

The presence of -gil- in the proposed INN *anumigilimab*, resulting from the juxtaposition of -gi- and the substem **-li-**, was misinterpreted by some of our reviewers as the stem **gli**. As a result, they wrongly concluded that this monoclonal antibody has antihyperglycaemic effects.

A slight amendment: risk persists. The previously proposed INN *pavunalimab* has been amended to *bavunalimab*. In our contribution to the consultation on List 123, we pointed out the risk of confusion between the proposed INN *pavunalimab* and the INN *pavurutamab*. However, simply replacing a descender with an ascender, to turn a “p” into a “b”, is insufficient to eliminate the risk of confusion between *bavunalimab* and *pavurutamab* (19,24).

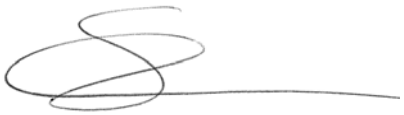
In summary

List 125 is much in the same vein as previous lists: an unprecedented 226 INNs have been proposed, a significant proportion of these are biological pharmaceutical substances, and many of the proposed INNs lack an established stem.

Two-term INNs are certainly a pragmatic solution to the increasing complexity of biotechnology-derived pharmaceutical substances, but they can generate new risks of confusion that we fear will only intensify as the number of such INNs increases. The same applies to gene therapy substances and cell therapy products, which have such complex INNs that it is often preferable to use their brand names. While the new nomenclature scheme for monoclonal antibodies should address the overcrowding in this class, the issue of monoclonal antibodies conjugated to pharmacologically active substances remains unresolved and continues to concern us as it spreads beyond the monoclonal antibody group. We regret the fact that the 72nd INN Consultation missed this opportunity to make these modified INNs more clearly comprehensible to INN users.

Prescrire has been deeply concerned since 2015 that these active substances were relegated to the status of substituents in the “Radical book”, rather than included in the lists of proposed INNs. An example from List 125 is the proposed INN *ecteribulin*, a cytotoxic agent modified for conjugation to a monoclonal antibody. Admittedly this section of the consultations has acquired a new heading since the publication of List 123: “*Names for chemical modifications of INN (substituent groups, counterions, adduct partners, etc.)*”; and as such the publication of this modified INN cannot be considered inaccurate. We maintain however that if a clearer distinction were made between active substances and components devoid of pharmacological properties, healthcare professionals would better understand their nature and their dangers. A new version of the Radical Book, last updated in 2015, that clearly distinguishes pharmacologically active substances from other radicals, would be a welcome development (14,19).

We yet again commend the INN Programme’s remarkable efforts, which enable health professionals to make independent treatment choices, focusing on what really matters (the choice of substance, then the dose and the pharmaceutical form), while also providing information about each drug’s therapeutic class and/or mechanism of action, and therefore about its foreseeable adverse effects and interactions.



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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: Anne Americh (pharmacist), Élodie Artielle-Beaucamp (pharmacist), Julie Bontemps (pharmacist), Christine Guilbaud (pharmacist), Mélanie Hardy (pharmacist), Sébastien Hardy (pharmacist), Fabienne Jourdan (doctor), Laurence Le Quang Trieu (pharmacist), Florent Macé (pharmacist), Ève Parry (pharmacist) and Étienne Schmitt (pharmacist). The other contributors were Imene Beghriche (pharmacologist), Helen Genevier (translator) and Nadjat Loumi (pharmacologist).

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