Prescrire’s contribution to the WHO consultation on List 119 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 international nonproprietary names (INNs), which are clearer, safer and more informative than drug 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 sheer number of INNs now in circulation. 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, joined by lecturers in pharmacy and medicine from Marseille University Hospital and Marseille School of Pharmacy, has examined List 119 in order to participate in the public consultation on this latest list of proposed INNs, published in July 2018 (a)(9).

Our critical analysis of the proposed INNs. Our analysis of the 120 INNs proposed in List 119, and 4 amendments to INNs proposed in previous lists, was based on the following resources: the 2013 list of common stems and its addenda; the INN database and the WHO’s lists of pre-stems, biological and biotechnological substances, and radicals; the list of planned stems proposed by the United States Adopted Names (USAN) Council; a database of drugs marketed in France, which enables searches on both brand names and INNs; a reference database of drugs used throughout 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 119. In each case, the participants then assessed the likelihood and clinical consequences of a medication error 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 long list. With 120 proposed INNs and 4 amendments, List 119 is one of the longest Prescrire has examined.

Our examination of List 119 provided an opportunity to identify some pre-stems: -becestat for β secretase inhibitors; -cafor for cystic fibrosis transmembrane regulator (CFTR) protein modulators; -cerfont for corticotropin-releasing factor type-1 (CRF1) receptor antagonists; -ertinib for epidermal growth factor receptor (EGFR) inhibitors; -ixibat for ileal bile acid transporter (IBAT) inhibitors, bile acid reabsorption inhibitors; -pirdine for serotonin receptor antagonists; and -tirom(-) for antihyperlipidaemic thyromimetic derivatives.

This list also includes some planned stems proposed by the US drug nomenclature committee, the USAN Council: -alap for aldehyde traps; -cop for complement receptor inhibitors; -corilant for glucocorticoid receptor antagonists (not glucocorticoids); -dostat for indoleamine 2,3-dioxygenase inhibitors; -дутite for oxyntomodulin analogues; -frovent for histamine H4 receptor antagonists; -netile for peptides and glycopolypeptides for which neurological uses have been planned; -nod for nitrogen oxide donors; -padon for dopamine D1 receptor agonists/partial agonists; -purtide for peptides used as pulmonary surfactants; -semtiv for skeletal muscle troponin activators; -tristat for tryptophan hydroxylase inhibitors; and -vivint for WNT pathway inhibitors.

Formal objections

None of the risks of confusion or misunderstanding associated with the INNs proposed in List 119 were of sufficient concern to warrant a formal objection.

The abiding risk associated with the naming of monoclonal antibodies conjugated to active substances. We remain very concerned about the risks associated with the two-term INNs given to monoclonal antibodies conjugated to cytotoxic drugs. If healthcare professionals do not know the precise meaning of the second term, which they may assume refers to a radical devoid of pharmacological activity rather than a second active substance, dosing errors can occur through administration of the wrong product. The proposed INNs rolinsatamab talirine and tabituximab barzuxetan add to the list of similarly constructed INNs for antibody–drug conjugates against which Prescrire has filed objections in previous consultations (19).

We formally acknowledge that, while recognising the problem, the WHO INN Programme does not want to revise the nomenclature of these conjugated compounds, on the grounds that the rules that were established a long time ago (20). This amounts to shifting the task of risk mitigation onto pharmaceutical companies, regulatory agencies, healthcare establishments and organisations, and health professionals, requiring them to devise measures to reduce the number of patients harmed through confusion between these INNs, such as: aiding discrimination between these products through different packaging or labelling, and aiding discrimination between their INNs, for example by appending the brand name. This leads to the paradoxical situation in which it is safer to use brand names than INNs.

Why not take the revision of the monoclonal antibody nomenclature scheme further? The new nomenclature scheme for monoclonal antibodies, which includes discontinuation of the species substem, is a welcome development (21). However, some of the participants in our review group would like to see the "target class" substems of this new nomenclature developed further, to make the INNs of monoclonal antibodies more informative. For example, health professionals can tell from the substem -ci- in the proposed INNs abelacimab, dilipacimab, frovocimab, olivacimab and osocimab that these drugs target the cardiovascular system, but not that they also have immunomodulatory, antineoplastic, blood coagulation factor inhibiting, anticoagulant or lipid-lowering properties.

Similarly, some participants were concerned by the apparent lack of specificity of the target substems -li- and -ta- in the proposed INNs budigalimab, cemiplimab, dostarlimab, tabituximab [containing the -(li)-] target substem of the old nomenclature] and toripalimab, each described as an "immunomodulator, antineoplastic". Are they immunomodulators and/or antineoplastic? And in which therapeutic areas will they be used?
**Comments**

Our review group identified a number of proposed INNs that could generate medication errors for a variety of reasons: confusion with a brand name; confusion with another INN; confusion between their suffix and an existing stem; or confusion due to the absence of an expected stem.

**Confusion with a brand name.** Some INNs proposed in List 119 could be confused with a brand name, in particular: abelacimab, resmetirom, rovafovir etalafenamid and tirzepatide.

When selecting drugs from an alphabetical menu, the proposed INN abelacimab could be confused with Abelcet®, a brand name used for amphotericin B in many countries.

The proposed INN resmetirom could be confused with the brand name Esmeron® of the neuromuscular blocker rocuronium, marketed under this name in at least 38 countries. Without knowing the route of administration of resmetirom, it is difficult to assess the likelihood of confusion between these drugs. However, unintentional administration of a neuromuscular blocker would have catastrophic consequences for the patient.

The proposed INN rovafovir etalafenamid shares the first four letters of the brand name Rovalcyte® (valganciclovir). Despite the marked difference between the two INNs, the likelihood of confusing these drugs is increased by the fact that both have antiviral properties.

Resemblance was also noted between the proposed INN tirzepatide and the brand name Zepatier® (elbasvir+grazoprevir).

**Confusion with another INN.** Some of the INNs proposed in List 119 are liable to confusion with other INNs, in particular: abelacimab, asalhydromorphone, aticaprant, azelaprag, fosgemcitabine palabenamid, fosfoluxuridine nafalenbamid, frovocimab, masupirdine, mivavotinib, nomacopan, reproxalap, setogepram and tirzepatide.

The proposed INN abelacimab could be confused with the INN abciximab, as they have the same prefix and almost identical suffixes.

The proposed INN asalhydromorphone could be confused with the INN hydromorphone, with a risk of dosing errors, although the severity of the consequences is difficult to assess without knowing their relative potency. It is important that the INN Programme ensures drug regulatory agencies are aware of this risk, and that the strengths of all marketed products are expressed in the same way, as hydromorphone base for example.

A risk of confusion through visual and phonetic similarity was noted between the proposed INN aticaprant and the INNs apixaban and icatibant.

In an alphabetical menu, the proposed INN azelaprag would appear immediately above the INN azelastine and might therefore be selected in error in its place.

The proposed INN fosgemcitabine palabenamid could be confused with the INN gemcitabine, i.e. the drug from which it is derived. The severity of the consequences of such an error would depend on their relative potency. Similarly, a risk of confusion was noted between the proposed INN fosfoluxuridine nafalenbamid and the INN luxuridine, although the latter no longer appears to be marketed. When a drug is modified by a radical to form a salt or ester prodrug, it is crucial that health professionals understand how the radical modulates the dose received by altering its pharmacokinetics or pharmacodynamics.

A small risk of confusion was noted between the proposed INN masupirdine and the INNs mesudipine and manidipine, due to orthographic and phonetic similarities. The risk is compounded by the potential for confusion between the pre-stem -pirdine, used for serotonin receptor antagonists, and the stem -dipine, used for calcium channel blockers, which we reported in our responses to Lists 102 and 116 (19).

The similarity of the prefix of the proposed INN mivavotinib to that of the INN of the neuromuscular blocker mivacurium and its brand name Mivacron® caused concern. However, the probable route of administration of mivavotinib markedly reduces the likelihood of confusion errors. The consequences of errors involving neuromuscular blocking drugs are potentially catastrophic (risk of death through respiratory paralysis). In the interests of patient safety, INNs should never be liable to confusion with the INN or brand name of a neuromuscular blocker.
The proposed INN nomacopan, for a complement factor C5 inhibitor, could be confused with the INNs nonacog alfa, nonacog beta pegol and nonacog gamma. Five of the seven letters in the first term are shared with nomacopan, while the marked typographic resemblance between the two letters that differ (“n” versus “m”, and “g” versus “p”) enhances their visual similarity. The fact that blood products are usually stored together increases the likelihood of a confusion error.

The proposed INN reproxalap could be confused with the INN eprosartan, due to the similarity of their prefixes, apart from the initial letter “r”, and because reproxa- and eprosa-sound extremely similar in French.

Many of the participants in our review group reported a risk of confusion between the proposed INN setogepram and the INNs citalopram and escitalopram. It could also be confused with Séropram°, a brand name for citalopram. Furthermore, although setogepram is claimed to have anti-inflammatory and antifibrotic properties, it lacks a corresponding stem, and the participants in our review group assumed it to be a so-called “selective” serotonin reuptake inhibitor.

The proposed INN tirzepatide resembles the INN tinzaparin, a risk that will be compounded if their route of administration is similar.

Confusion between a suffix and a stem. Two INNs proposed in List 119 that lack a stem have suffixes, -oxazine and -gepram, that could be confused with existing stems.

The suffix -oxazine in the INN brilaroxazine could be confused with the stem -oxacin (-oxacine in French), used for antibiotics derived from nalidixic acid, also known as quinolones.

The suffix -gepram in the proposed INN setogepram could be confused with the new stem -gepant, used for calcitonin gene-related peptide (CGRP) receptor antagonists.

Confusion due to absence of an expected stem. The INNs bamadutide, cotadutide and tirzepatide have been proposed for antidiabetic drugs. The participants in our review group were surprised by the absence of the stem -gli-, which is generally present in the INNs of drugs for which this property is claimed. They felt that the absence of the expected stem in these proposed INNs compromises the ability of users to understand their pharmacological effect.

Amendments. Amendments to INNs proposed in previous lists are subjected to the same risk analysis as newly proposed INNs. Concerns were raised about two of the four amendments in List 119: lorecivivint and oxycodelogol.

The INN lorecivivint replaces adavivint, proposed in List 117. In our response to that list, we commented on the risk of wrong-drug errors when selecting drugs from an alphabetical menu due to its similarity and proximity to with Adavin° (19). However, the new name is liable to confusion with the brand name Recivit° (fentanyl), especially when written.

The INN oxycodelogol replaces loxicedegol (List 117). By dropping the initial “l” and replacing the “i” with a “y”, the amended name is liable to confusion with the INN oxycodone (the first 6 letters are identical) as well as its brand name Oxycontin°. Their proximity in an alphabetical menu creates a high risk of selection errors, compounded by the fact that they are both opioid receptor agonists. The consequences of confusing them are difficult to assess, but if their potencies differ, as is likely, a risk of overdose will exist.

In summary. Our examination of List 119 of proposed INNs confirms the major role of education in helping health professionals decipher and understand INNs. This list gave rise to fewer comments than previous lists to point out proposed INNs identified as liable to confusion or difficult to decipher. However, problems identified by health professionals must continue to be taken into account, including: the increasing complexity of INNs, an issue raised by many of our reviewers; the fact that some therapeutic classes have reached saturation point; the role of radicals in altering drugs’ pharmacokinetic or pharmacodynamic properties; and the advantages of INNs that provide more information about the drug’s indications and properties, while remaining simple and easy to memorise.

Despite the fact that our group considered no formal objections were necessary, the nomenclature for monoclonal antibodies conjugated to pharmacologically active drugs is an issue that remains unresolved and continues to concern us.
Healthcare professionals and patients can only think and act successfully in terms of INNs when these names are devised and taught in a rigorous, coherent and effective way, and when they are intelligible. The School of INN will undoubtedly occupy an important educational role in this teaching.

a- This response was prepared using the resources of the entire Prescrire team. Head of team analysis and preparation: Eric Bel (pharmacist). Members of the Prescrire editorial team who made a particular contribution to this review: Anne Americh (pharmacist); Élodie Artielle-Beaucamp (pharmacist); Julie Bontemps (pharmacist); Helen Genevier (translator); Christine Guibaud (pharmacist); Marie-France Gonzalez (pharmacist); Mélanie Hardy (pharmacist); Sébastien Hardy (pharmacist); Fabienne Jourdan (doctor); Laurence Le Quang Trieu (pharmacist); Loumi Nadjat (professor, pharmacologist); Vincent Walter (pharmacy residents).

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