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Prescrire's contribution to the WHO consultation on List 124 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 now 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, joined by other contributors, including lecturers in pharmacy and medicine, has examined List 124 in order to participate in the public consultation on this latest list of proposed INNs, published in January 2021 (**a**)(9).

Our critical analysis of the proposed INNs. Our analysis of the 154 INNs proposed in List 124, 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 lists 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 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 124. 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 124 identified the use of a number of pre-stems: **-cianine** for indocyanine-derived fluorescence dyes; **-ectedin** for ecteinascidin (also known as trabectedin) derivatives; **-gratinib** for fibroblast growth factor receptor (FGFR) inhibitors; **-inapant** for inhibitors of inhibition-of-apoptosis proteins (IAPs); **-madlin** for E3 ubiquitin-protein ligase Mdm2 inhibitors; **-meran** for messenger RNA (mRNA); **-nersen** for antisense oligonucleotides targeting neurological function; **-rasib** for Ras protein inhibitors; **-terkib** for extracellular signal-regulated kinase (ERK) inhibitors; **-toran** for toll-like receptor antagonists; and **-vivint** for Wnt signalling inhibitors.

This list also features some proposed INNs that include a USAN stem: -costat for acetyl CoA carboxylase (ACC) inhibitors; -paratide for parathyroid hormone related peptides; -pivat for pyruvate kinase activators; -podun for phosphodiesterase 1 (PDE1) inhibitors; -taront for trace amine-associated receptor (TAAR) agonists; -vatrep for vanilloid subtype 1 receptor antagonists; and -xostat for xanthine oxidase/dehydrogenase inhibitors.

Objections

Prescrire wishes to file a formal objection to one INN proposed in List 124 that contains a stem not justified by the nature of the substance in question. We identified risks of sufficient concern to warrant three more formal objections, all involving substances conjugated to a cytotoxic agent, namely *lonigutamab ugodotin*, *nendratareotide uzatansine* and *zilovertamab vedotin*.

Presence of the stem -io- in the absence of iodine. The presence of the stem **-io-** in the proposed INN *idroxioleic acid* caused our reviewers to mistakenly identify this substance ($C_{18}H_{34}O_3$) as an iodine-containing drug. Iodine has an important role in thyroid conditions; a stem indicating the presence of iodine should be used without ambiguity. It would probably cause less confusion if this INN were to be amended to *idroxoleic acid*.

Conjugation to active substances not identified as such: a danger to patients. This risk now extends beyond the monoclonal antibodies, as evidenced by the proposed INN *nendratareotide uzatansine*, a somatostatin analogue conjugated to *uzatansine*. 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 substance alone 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.

To give two examples, the conjugates *trastuzumab emtansine* (List 103), *trastuzumab duocarmazine* (List 115) and *trastuzumab deruxtecan* (List 115) all contain the monoclonal antibody *trastuzumab* but conjugated to different cytotoxic drugs, while *cantuzumab ravtansine* (List 105), *indatuximab ravtansine* (List 105), *anetumab ravtansine* (List 109), *coltuximab ravtansine* (List 109), *praluzatamab ravtansine* (List 121) and *tusamitamab ravtansine* (List 123) all contain the cytotoxic moiety *ravtansine* but conjugated to different antibodies (9,19-23).

If healthcare professionals do not know the precise meaning of the second term, which is often assumed to refer to a radical 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 *lonigutamab ugodotin*, *nendratareotide uzatansine* and *zilovertamab vedotin* 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 moiety will be mistaken for an innocuous radical (24).

We are confident in the ability of the WHO's INN Programme to re-examine and improve this particular aspect of the nomenclature for such conjugated compounds.

Comments

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

Absence of an existing stem consistent with the action or use claimed by the company. Most of our reviewers felt that the INN of a drug intended for use as an antiviral should contain the stem **vir** or the substem **-vi-** or **-v(i)-**, and found the absence of this stem from *tomligisiran*, proposed as an INN for an antiviral agent, unhelpful.

Potential confusion with a brand name. Some INNs proposed in List 124 could be confused with a brand name, especially *adagrasib*, *aficamten*, *firzacorvir*, *labuvirtide*, *navtemadlin* and *zavegepant*.

The proposed INN *adagrasib* poses two risks: it could be confused with the brand name Agrastat° (*tirofiban*), and it could be mistakenly selected from an alphabetical menu instead of the brand name Advagraf° (*tacrolimus*).

In a discussion, the proposed INN *aficamten* could be confused with the brand name Hycamtin° (*topotecan*) and vice versa, due to their phonetic similarity in French.

Several participants felt that the visual resemblance between the proposed INN *firzacorvir* and the brand name Firazyr° (*icatibant*) could cause the wrong drug to be selected from an alphabetical menu.

The proposed INN *labuvirtide* could be confused with the brand name Laburide° (*pheneturide*) when written or spoken or when selecting drugs from an alphabetical menu.

Several participants felt that, in French, the strong visual and phonetic resemblance between the proposed INN *navtémadline* (*navtemadlin* in English) and the brand name of another antineoplastic drug, Navelbine° (*vinorelbine*), could cause medication errors.

In an alphabetical menu containing both INNs and brand names, Zavedos° (*idarubicin*) would be listed just above the proposed INN *zavegepant*, and could be accidentally selected instead as they start with the same four letters (although the proposed French INN *zavégépant* has an accent on the "e").

Potential confusion with another INN. Some of the INNs proposed in List 124 could be confused with other proposed or recommended INNs: *ansuvimab*, *aumolertinib*, *botensilimab*, *deudomperidone*, *deuruxolitinib*, *deutarserine*, *eganelisib*, *elraglusib*, *labuvirtide*, *orludodstat*, *tolinapant*, *torudokimab* and *tozorakimab*.

The proposed INN *ansuvimab* could be confused with the INN *suvizumab* (proposed in List 102), although the risk is currently theoretical since *suvizumab* is not marketed to the best of our knowledge (25).

A risk of sound-alike confusion was detected between the proposed INN *aumolertinib* and the

INN *osimertinib* due to the phonetic similarity in French of the vowels “o” and “au”.

The proposed INN *botensilimab* could possibly be confused with the INN *bortezomib*, as well as with the INN *bosentan* when selecting drugs from an alphabetical menu.

List 124 includes three proposed INNs for isotopic variants incorporating deuterium ^{2}H starting with deu-, namely *deudomperidone*, *deuruxolitinib* and *deutarserine*. In French, deu- sounds like *deux*, meaning two, creating a risk of potentially serious overdoses, identified by most of our reviewers, if these proposed INNs were understood as “two *domperidones*", “two *ruxolitinibs*" and, possibly, “two *mianserins*", respectively. In addition, the proposed INN *deuruxolitinib* could also be confused with the INNs *doxorubicin* and *duloxetine*, and the proposed INN *deutarserine* with the INN *dutasteride*.

Visual and phonetic similarity in French was identified between the two proposed INNs *eganelisib* and *elraglusib*.

The risk of confusion between the proposed INN *elraglusib* and the INNs *liraglutide* and *glepaglutide* (proposed in List 116) due to similarities in their prefixes, is enhanced by the resemblance, particularly in French, between the stem **-glutide** and the suffix -glusib (26).

The proposed INN *labuvirtide* could be confused with the INN *bulevirtide* due to similarity between their first two syllables.

As the prefix orl- in the proposed INN *orludodstat* has only been used once before, in the INN *orlistat*, and they share the same stem **-stat**, confusion between these two INNs cannot be ruled out.

A high risk of confusion exists between the proposed INN *tolinapant*, when written or spoken, and the INN *tolvaptan*, with which it shares the first three letters and possibly a phonetically similar ending in French.

Many participants identified visual and phonetic similarity between *torudokimab* and *tozorakimab*, both proposed in List 124. One reviewer also pointed out a risk of confusion between *tozorakimab* and the INN *tocilizumab*.

Welcome amendments. In our contribution to the consultation on List 122, we pointed out the risk of confusion between *rulabricin alfa* and the INNs *idarubicin* and *aclarubicin*. We therefore welcome the replacement of *rulabricin alfa* by *ledelabricin alfa* (24,27).

We are also pleased to see that *valiloxibic acid*, proposed in List 123, has been replaced, because, as we pointed out in our contribution to the consultation on that list, its phonetic and visual similarity to *valproic acid* could have caused medication errors (23,24). However, the INN chosen to replace it, *valiloxybate*, has the disadvantage of containing the letter “y”.

Our review group raised no objections to replacing *icatolimab* (proposed in List 122) with *tifcemalimab,* but neither did we submit any concerns about *icatolimab* in our response to List 122 (24,27).

In summary

List 124 is much in the same vein as previous lists: a considerable number of INNs are proposed, a significant proportion of these are biological pharmaceutical substances, and many of the INNs proposed have no established stem. Yet again, the INN Programme’s remarkable efforts enable health professionals to make independent treatment choices, focusing on what really matters: first the choice of drug, then the dose and the pharmaceutical form. INNs also convey information about a drug’s therapeutic class and/or mechanism of action, and therefore about its foreseeable adverse effects and interactions.

However, many of our reviewers reported that it is becoming increasingly difficult to learn and use certain future INNs. The INNs that present most difficulty are those for so-called “advanced” therapies: cell and gene therapies; fusion proteins; monoclonal antibodies; and treatments based on messenger RNA or antisense oligonucleotides. If the INN system is to be used more widely and by everyone, the principles underpinning INN construction will need to be taught early on in university

training, clinical pharmacology teaching will need to incorporate INNs and their stems, and particular attention will need to be paid to learning the INNs of biological pharmaceutical substances and advanced therapies. In addition, as soon as a new pharmaceutical substance is introduced on the market, regulators will need to refer to it unfailingly, without compromise, by its INN, so that health professionals and patients become familiar with the drug's nonproprietary name.

We note that the French version of the School of INN is now available as an aid to these educational efforts. It offers a range of courses with supporting videos, self-administered tests, documents and tools, for example to help identify stems in an INN. This translation is a welcome development, awaited since the WHO INN Programme launched the English version in October 2019, that *Prescrire* intends to announce to its French speaking subscribers (11).

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Publishing Director

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