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Prescrire's contribution to the WHO consultation on List 130 of proposed INNs

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Both independently since 1981, and as part of 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). Various reviewers, drawn from Prescrire's editorial staff and members of the IMSN, took part in this consultation phase and examined List 130 of proposed INNs, published in March 2024 (9).

Our critical analysis of the proposed INNs. Our analysis of the 219 INNs proposed in List 130, and two amendments to INNs proposed in previous lists, was based on the following resources: the WHO's Stem Book 2018 (and addendum), its database of INNs and 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 worldwide database of drugs; and Prescrire's in-house monitoring of the literature (10-18).

Our collective review is organised in such a way as to identify INNs or brand names of marketed drugs that could be confused with the INNs proposed in List 130. The 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. List 130 contains two lists: the main "standard" list of 215 proposed INNs, including two amendments, and an addendum containing an additional 6 proposed INNs, titled List 130 – COVID-19 (special edition).

The proposed INNs in these two lists feature numerous pre-stems: **-alkib** for anaplastic lymphoma kinase (ALK) inhibitors; **-drimer** for dendritic polymers (dendrimers); **-drostat** for aldosterone and cortisol synthesis inhibitors; **-gaptide** for gap junction protein channel modulators; **-gratinib** for fibroblast growth factor receptor (FGFR) inhibitors; **-kalner** for openers of calcium-activated (maxi-K) potassium channels; **-menib** for menin interaction inhibitors; **-metkib** for mesenchymal epithelial transition factor (MET) kinase inhibitors; **-ngitide** for angiogenesis-related peptides; **-noflast** for inflammasome protein NLRP3 inhibitors; **-nosine** for nucleoside analogues used as antiviral or antineoplastic drugs; and **-stinag** for stimulator of interferon genes (STING) agonists, used as antineoplastic drugs.

Some of these proposed INNs feature USAN stems: -gacestat for gamma-secretase inhibitors; -ramtide for antibody-recruiting molecules (ARMs); and -rian for ryanodine receptor (RyR) modulators.

Objections

Our review group identified risks of sufficient concern to warrant 14 formal objections against INNs proposed in List 130 for substances conjugated to a pharmacologically active agent such as a cytotoxic drug: *emiltatug ledadotin*, *micvotabart pelidotin*, *misitatug blivedotin*, *olintatug tesirine*, *opugotamig olatansine*, *precemtabart tocentecan*, *rinatabart sesutecan*, *samatatug zovodotin*, *tecotabart vedotin*, *telisotuzumab adizutecan*, *tilatamig samrotecan* and *trastuzumab envedotin*; as well as the immunostimulants *calotatug ginistinag* and *mozistobart zoratolimod*.

Two-word INNs for substances conjugated to pharmacologically active substances can cause medication errors of various types, in particular through confusion: between the standalone (unconjugated) substance and the same substance conjugated to a second substance; 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 have set out the arguments behind this objection in previous contributions, together with various examples, and we hope that the naming of substances conjugated to pharmacologically active substances will be revised or at least improved, in order to highlight their additional effects or toxicity (19).

Despite the presence of stems in some of these words, it is difficult to assess the severity of the consequences of medication errors caused by confusing a conjugate with the unconjugated substance, with the same substance conjugated to different substituents, or with a different conjugate in which the same substituent is coupled to a different substance. These uncertainties could be dispelled if lists of proposed INNs included the pharmacological properties of substituent groups and other chemical modifications, in addition to their names. While on this subject, we note the long-overdue publication in List 130 of *ravtansine*, a cytotoxic drug present as the payload in several antibody-drug conjugates that have already been published in previous lists: *cantuzumab ravtansine*, *indatuximab ravtansine*, *coltuximab ravtansine*, *anetumab ravtansine*, *oberotatug ravtansine*, *praluzatamab ravtansine* and *tusamitamab ravtansine*.

Our objection does not apply to other two-word INNs that do not expose patients to such a high risk of toxicity, such as *pregabalin naproxencarbil*, which combines the anticonvulsant drug *pregabalin* with an esterified form of the nonsteroidal anti-inflammatory drug *naproxen*. When this drug is introduced on the market, health professionals must be clearly informed that it contains these two active substances, so that they can take steps to minimise the risk of adverse effects and the risk of drug interactions.

Comments

Our review group identified a number of proposed INNs that could cause medication errors through confusion with a brand name, another INN or a stem.

Potential confusion with a brand name. Some INNs proposed in List 130, especially *aldastotug*, *bosakitug*, *foselutoclax*, *paluratide*, *talorasib*, *zomiradomide* and all the INNs ending in the stem **-mig**, could be confused with the brand names of other drugs.

The proposed INN *aldastotug* is strongly reminiscent of the brand names Aldactone° (*spironolactone*) and Aldactone Canrénoate° (*canrenone* in the form of *potassium canrenoate*), with which it shares the same first four letters and an almost identical sequence of vowels. Their similarity and proximity in an alphabetical menu could lead to wrong-drug errors. The potential for such errors is enhanced by the recent replacement of Soludactone° in France by Aldactone Canrénoate°, an injectable product, which is also the likely route of administration of *aldastotug* (20).

The proposed INN *bosakitug* shares phonetic and orthographic similarities with both the brand name Bosulif° and its INN *bosutinib*, primarily because they start with the same three letters. They are most likely to be confused when selecting drugs from an alphabetical menu.

The phonetic and orthographic similarity between the proposed INN *foselutoclax* and the brand name Koselugo° (*selumetinib*) could lead to confusion between the two, with confusion particularly likely during verbal communication.

The proposed INN *paluratide* looks and sounds like the brand name Paludrine° (*proguanil*). However, since the market withdrawal of Paludrine° in France and elsewhere, it is no longer possible to confuse the two in practice.

The proposed INN *talorasib* was considered too similar to the brand name Taloxa° (*felbamate*), with which it shares the same first four letters, creating a risk of confusion between the two when selecting drugs from an alphabetical menu.

The proposed INN *zomiradomide* is strongly reminiscent of both the brand name Zomig° and its INN *zolmitriptan*, mainly due to marked similarity at the start of their names. Wrong-drug errors are therefore particularly likely when selecting drugs from an alphabetical menu.

Some of our reviewers were confused about the pharmacological properties of drugs with the stem **-mig** (which actually denotes a bispecific or multispecific immunoglobulin), presuming them to be antimigraine drugs, because the stem **-mig** brought to mind “migraine”. This mental association is enhanced by the presence of “mig” in the brand names of some well-known antimigraine drugs, named long before the creation of this stem, such as Zomig° (*zolmitriptan*), Naramig° (*naratriptan*), Sanmigran° (*pizotifen*) and Imigrane° (*sumatriptan*).

Potential confusion with another INN or a stem. Some of the INNs proposed in List 130 could be confused with other proposed or recommended INNs, or contain a sequence of letters that could be confused with a stem, especially: *admilparant*, *ateganosine*, *brivekimig*, *claziprotamide*, *crelosidenib*, *dalmitamig*, *efparepoetin alfa*, *lonvoguran*, *luvomeran*, *lunbotinib*, *paluratide*, *sefaxersen*, *segigratinib* and *vixticibart*.

The suffix **-**parant of the proposed INN *admilparant* is too similar to the pre-stem **-parantag**, denoting antagonists of heparin, including low molecular weight heparins (LMWHs), used as heparin antidotes. Confusion between this suffix and pre-stem **-parantag** seems possible, and would in turn confuse health professionals over the expected pharmacological properties of the substances concerned.

The proposed INN *ateganosine* shares phonetic and orthographic similarities with the INN *adenosine*, with which it shares the same pre-stem **-nosine**, eight letters in common, and the phonetically similar prefixes ate**-** and ade**-**. Confusion between these two INNs in clinical practice

appears likely.

The proposed INN *brivekimig* was considered to resemble the INN *brigatinib*, with which it shares the same first three letters and phonetic similarity. Confusion between these two INNs seems possible despite their different routes of administration.

Marked resemblance was noted between the proposed INN *claziprotamide* and the INN *protamine* (*sulfate*), a drug used to rapidly neutralise the anticoagulant action of heparin, as well as to the brand name Protamine Choay°. The risk of confusion could be addressed by modifying the infix -prota-.

The proposed INN *crelosidenib* shares phonetic similarity with the INNs *pralsetinib* and *crizotinib*, creating a risk of confusion between them, especially in verbal communication.

Phonetic and orthographic resemblance was noted between the proposed INN *dalmitamig* and the INN *dalmelitinib* (List 127), with which it shares the same first four letters and overall phonetic similarity. These two INNs could be confused both during verbal communication and when selecting drugs from an alphabetical menu (21).

The proposed INN *efparepoetin alfa* shares phonetic and orthographic similarity with the INNs *darbepoetin alfa* and *pegdarbepoetin beta* (List 117) (22).

The suffix -guran in the proposed INN *lonvoguran* appears very similar to the stem **-glurant** and the pre-stem **-osuran**. Confusion between these stems and the suffix -guran seems possible, and would in turn confuse health professionals over the expected pharmacological properties of the substances concerned. Phonetic and orthographic similarities were also noted between *lonvoguran* and *luvomeran*, also proposed in List 130.

The suffix -botinib of the proposed INN *lunbotinib*, containing the stem **-tinib,** is very similar to the pre-stem **-batinib**. This resemblance accentuates the phonetic and orthographic similarities between *lunbotinib* and the INN *flumbatinib* (List 125) (22). The risk of confusion could be addressed by modifying the infix -bo-.

The proposed INN *paluratide* shares orthographic similarity with the INN *apalutamide*, which contains nine of its ten letters and the same sequence of vowels.

Our reviewers noted with concern that the prefix sef- of the proposed INN *sefaxersen* sounds like the stem **cef-**, used for cephalosporins. In verbal communication, this proposed INN could mislead health professionals over the precise nature of the drug, especially as the prefix sef- is followed by the letter -a-. Since no other INNs have the fantasy prefix sef-, refusing its use would ensure that antibiotics derived from cefalosporanic acid remain identifiable by the stem **cef-**, even in verbal communication.

The proposed INN *segigratinib* shares phonetic and orthographic similarities with the INN *resigratinib* (List 129), which contains the same sequence of vowels and the same stem (23).

The proposed INN *vixticibart* looks and sounds similar to the INN *vixtimotamab* (List 124), mainly because their first five letters are the same. This could lead to wrong-drug errors, especially when selecting drugs from an alphabetical menu (24).

Welcome amendments

We welcome the replacement of “milrebrutinib” with *docirbrutinib*. We pointed out the risk of confusion between “milrebrutinib” and the INNs *remibrutinib* (List 121) and *milrinone* in our contribution to the consultation on List 128 (19,25).

The replacement of “onvitrelin ucalontide” with *ucalolictide* is a welcome simplification. We stressed the risks of extending the use of two-word INNs to new therapeutic classes in our contribution to the consultation on List 128 (19,25). This replacement demonstrates the INN Programme’s ability to resolve the trend towards unnecessary complexity, by devising simple and understandable INNs.

In summary

Like the previous list, List 130 again demonstrates the ability of the WHO INN Programme to satisfy the need for drug names that are standardised throughout the world and make pharmaceutical products safer to use.

Since its inception over 70 years ago, the INN Programme has continually evolved to adapt to new substances. It also simplifies certain nomenclature rules in order to devise INNs that are easier to memorise and use in healthcare settings. It has already simplified the nomenclature scheme for monoclonal antibodies, and is about to do the same for gene and cell therapy substances (26).

However, we wish to express our concern yet again about the absence of a solution to the problem posed by drugs consisting of two active pharmacological entities, primarily monoclonal antibodies conjugated to cytotoxic drugs, because wrong-drug errors in situations such as these could have harmful and potentially serious consequences.

Review produced collectively by the *Prescrire* Editorial Staff:
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