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Prescrire's contribution to the WHO consultation on List 129 of proposed INNs

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Both independently since 1981, and with others as part of the Medicines in Europe Forum and later 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, joined by lecturers in pharmacy and medicine from Marseille University Hospital and Marseille School of Pharmacy and members of the IMSN, examined List 129 in order to participate in the public consultation on this latest list of proposed INNs, published in August 2023 (**a**)(9).

Our critical analysis of the proposed INNs. Our analysis of the 214 INNs proposed in List 129 and 3 amendments to INNs proposed in previous lists, was based on the following resources: the WHO's Stem Book 2018 (and addendum), 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).

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 129. 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.

Three lists in one. List 129 contains three lists: the main "standard" list of 205 proposed INNs, including 3 amendments, and two addenda containing an additional 18 proposed INNs, titled List 129 – COVID-19 (special edition) and List 129 – COVID-19 (special edition – ADDENDUM 1).

Prescrire already analysed and commented on the 6 INNs (*andusomeran*, *pitozinameran*, *raxtozinameran*, *tegrenmeran*, *upalsecovatein* and *vintesomeran*) proposed in List 129 - COVID-19 (special edition) in July, within the required 2 weeks of its publication on 30 June 2023, prior to the release of the full List 129.

List 129 features numerous pre-stems: **-afine** for squalene monooxygenase inhibitors (antifungals); **-ampator** for α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor modulators; **-capavir** for viral capsid and nucleocapsid inhibitors; **-caprant** for kappa-opioid receptor (KOR) antagonists; **-caserin** for serotonin receptor agonists (mostly 5-HT_2); **-depsin** for depsipeptide derivatives; **-dirsen** for splice-switching oligonucleotides for muscular dystrophies; **-gliatin** for glucokinase activators; **-glipron** for glucagon-like peptide-1 receptor (GLP1R) agonists; **-gratinib** for fibroblast growth factor receptor (FGFR) inhibitors; **-inapant** for inhibitors of inhibition-of-apoptosis proteins (IAPs); **-lintide** for amylin derivatives and analogues; **-melagon** for non-peptidic melanocortin receptor agonists; **-menib** for menin interaction inhibitors; **-nod** for nitrogen monoxide (nitric oxide, NO) donors; **-noflast** for inflammasome protein NLRP3 inhibitors; **-nontrine** for phosphodiesterase 9 (PDE9) inhibitors; **-pivat** for pyruvate kinase activators; **-plam** for SMN2 gene splicing modulators (small molecules); **-protafib** for protein tyrosine phosphatase (HPTP) inhibitors; **-rasib** for Ras protein inhibitors; **-trelvir** for antiviral 3CL protease inhibitors; and **-xian** for blood coagulation factor XI inhibitors.

List 129 also features some proposed INNs containing a USAN stem: -borole for the boron-containing substances; -cap for viral capsids; -ifan for hypoxia-inducible factor (HIF) inhibitors; -piravir for treatments of SARS-CoV-2 infection, inhibiting viral RNA replication; and -potide for peptides with prostate cancer indications.

Objections

Our review group identified risks of sufficient concern to warrant 7 formal objections against INNs proposed in List 129 for substances conjugated to a pharmacologically active substance such as a cytotoxic agent: *bezetabart debotansine*, *izalontamab brengitecan*, *opelkibart elmanitin*, *sacituzumab tirumotecan*, *sigvotatug vedotin*, *trastuzumab brengitecan* and *zelenectide pevedotin.*

Two-term INNs for substances conjugated to pharmacologically active substances can cause medication 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 additional effects or toxicity (19).

Our objection does not apply to other two-term INNs, such as *abefolastat tesaroxetan*, *bimatoprost grenod*, *ucasareotide dasaroxetan*, *zeleciment basivarsen* and *zeleciment rostudirsen* (although, for the latter two, the order in which the two terms have been placed creates uncertainty about which moiety is pharmacologically active and which has a drug targeting role). We lack sufficient information about the substituent groups in these substances, and in particular their pharmacological property, but we presume them to be less toxic than cytotoxic substances. Despite the presence of stems in some of these terms, it is difficult to assess the severity of the

consequences of medication errors caused by confusing a given 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, counterions, adduct partners, etc., in addition to their names.

Comments

Our review group identified a number of proposed INNs that could generate medication errors through various mechanisms: confusion with a brand name; confusion with another INN or a stem; confusion caused by the meaning of a prefix in French; by fantasy prefixes used as memory cues; by the presence of a possibly incomplete pre-stem; by overly complex INNs; or by a prefix that indicates the substance's chemical structure.

Potential confusion with a brand name. Some INNs proposed in List 129, especially *lixumistat*, *rapirosiran* and *uplarafenib*, could be confused with a brand name.

The proposed INN *lixumistat* is similar to the brand name LYXUMIA°, as their first 5 letters are almost identical, and also resembles this product's INN, *lixisenatide*. This could cause wrong-drug errors, in particular when selecting drugs from an alphabetical menu, especially if the letter "Y" is unwittingly transformed into an "I". These drugs could also be confused in verbal communication, because "Y" and "I" are phonetically identical in French.

The proposed INN *rapirosiran* is not easily distinguishable from the brand name RAPISCAN° (*regadenoson*). This notable similarity is due to the fact that they share the same first four letters, and because the suffix **-**iscan resembles the stem **-siran**. The prefix of the proposed INN *rapirosiran* must be changed to prevent confusion between the two.

The proposed INN *uplarafenib* is similar to the brand name UPLIZNA° (*alirocumab*), which has the same first 3 letters. This could lead to wrong-drug errors, especially when selecting drugs from an alphabetical menu.

Potential confusion with another INN or a stem. Some of the INNs proposed in List 129 could be confused with other proposed or recommended INNs, or contain a sequence of letters that could be confused with a stem, especially: *bimatoprost grenod*, *clofutriben*, *envuretcel*, *evruleucel*, *firmonertinib*, *icalcaprant*, *mivelsiran*, *negalstobart*, *nelmastobart*, *pobrolitide*, *sutidiazine*, *tacaciclib*, *tagtociclib*, *uplarafenib*, and *zaloganan*.

The pre-stem **-nod** present in the proposed INN *bimatoprost grenod* could be confused with the stem **-imod**, particularly when preceded by the letter "I". Confusion between **-**inod and **-imod** can potentially mislead healthcare professionals over the true nature of the substance. Fortunately, as of late 2023, *naproxcinod* (proposed in List 95) is the only INN that ends with this sequence of letters, and it has not yet been marketed (20).

The proposed INN *clofutriben* and the INN *clomifene* share the same first 3 letters, and also sound and look alike in French (*clofutribène and clomifène*, respectively). This similarity can lead to wrong-drug errors, in particular when selecting drugs from an alphabetical menu, or in verbal communication in French.

The proposed INNs *envuretcel* and *evruleucel* were perceived as similar, in part because lists of proposed INNs are arranged in alphabetical order. However, confusion between the two is possible.

The proposed INN *firmonertinib* shares orthographic similarity with *mifanertinib* (proposed in List 128), as well as phonetic similarity, especially in French. Their similarity, due to the presence of the same stem and their overall visual resemblance, could lead to confusion between the two, in

particular through inversion of the first two syllables, especially for people with dyslexia (21). Similarity with the INN *osimertinib* was also identified.

Strong resemblance was noted between the proposed INN *icalcaprant* and the INN *milnacipran*, due to orthographic similarities, and phonetic similarities in French. Similarity was also identified with the INN *icatibant*.

The proposed INN *mivelsiran* was considered similar to the proposed INN *divesiran*, as they contain the same stem and the same sequence of vowels. Confusion between the two is possible.

The proposed INNs *negalstobart* and *nelmastobart* were considered very similar. Their proximity in an alphabetical list may have accentuated their resemblance, but it is important to note that the presence of the same sequence of vowels and the same stem, **-sto-bart**, are contributary factors. Confusion between these INNs in practice is possible if not probable, especially during verbal communication. These two proposed INNs were also considered very similar to *benmelstobart*, proposed in List 128. These multiple similarities raise questions about whether the new nomenclature for monoclonal antibodies has reached saturation point (21).

The suffix **-**litide in the proposed INN *pobrolitide*, which contains the stem **-tide**, was perceived as nearly identical to the stem **-ilide** as well as the pre-stem **-lintide**. These similarities could mislead healthcare professionals over the true nature of *pobrolitide*.

The proposed INN *sutidiazine* was considered too similar to the INN *sulfadiazine*, both orthographically and phonetically in French, with which it shares the suffix **-**diazine, indicating the presence of a 6-membered aromatic heterocycle (4 carbon atoms and 2 nitrogen atoms), as well as 9 of its 11 letters. Confusion between these two INNs appears highly likely.

The prefixes of the proposed INNs *tacaciclib* and *tagtociclib* are too similar to prevent confusion between the two, especially when selecting drugs from an alphabetical menu.

The proposed INN *uplarafenib* has an almost identical prefix to the INN *upadacitinib*, and is very similar phonetically. Confusion between these two INN appears probable, especially in verbal communication in French.

The proposed INN *zaloganan* is phonetically and orthographically similar to the INN *zaloglanstat* (proposed in List 124), since both start with zalog**-** and end in similar stems. This similarity could lead to confusion when prescribing and dispensing these drugs, especially when selecting them from an alphabetical menu or in verbal communication (22).

A prefix whose meaning in French could cause errors. The INNs for isotopic variants incorporating deuterium ^{2}H are problematic in French, the latest examples being *deupsilocin* and *deunirmatrelvir*, proposed in List 129. As the prefix deu**-** is pronounced the same as "*deux*" in French, meaning two, healthcare professionals may wrongly understand this prefix as a quantity during verbal communication, especially if INNs with and without the prefix deu- coexist.

Fantasy prefixes used as memory cues: a source of confusion. Many INNs include a "fantasy" prefix with no intrinsic meaning. For healthcare professionals, some of these prefixes have been adopted as mnemonic cues, as an aid to learning and memorisation. This can lead to confusion between INNs with the same prefix, especially when selecting drugs from an alphabetical menu or in verbal communication, through mental association.

The identical or near-identical prefixes of the proposed INN *cabotamig* and the INNs *cabozantinib*, *cabotegravir* and *carboplatin* create a risk that the wrong drug will be selected from a menu.

The orthographic and phonetic similarity between the proposed INN *dorocubicel* and the INNs *doxorubicin* and *daunorubicin* was considered significant. Their prefixes are almost identical, and sound very similar in French.

The fantasy prefix émi**-** of the French proposed INNs *émidurdar* and *émiluménib* (*emidurdar* and *emilumenib* in English) is pronounced the same as the prefix *hémi***-** in French, meaning half. 14 INNs

currently start with émi-, only one of which, *émicizumab*, appears to be marketed. This prefix is also sometimes used in brand names, e.g. HEMI-DAONIL° and HEMIGOXINE NATIVELLE°.

A possibly incomplete pre-stem. The proposed French INN *limantrafine* appears to contain the pre-stem **-afine**. However, in its English version, *limantrafin*, this pre-stem appears to be absent or truncated, through omission of the final letter. This omission may not be an error, however, because the drug in question is claimed to be an antineoplastic agent, whereas the pre-stem **-afine** denotes squalene monooxygenase inhibitors used as antifungals.

INNs that are too complex to be usable in routine practice. Our review group considered a number of INNs proposed in List 129 for gene therapy substances and cell-based gene therapy substances to be too complex to be easily usable in practice (and often very similar): *brinretigene vesgedparvovec*, *cemacabtagene ansegedleucel*, *clemidsogene lanparvovec*, *dazagamglogene autogedtemcel*, *fencabtagene autoleucel*, *firicabtagene autoleucel*, *nimatpagene pariparvovec*, *pozetaldogene ormesparvovec*, *renizgamglogene autogedtemcel* and *ribrecabtagene complexautoleucel*. Although the INN programme has embarked on efforts to simplify the nomenclature of these substances, it is likely that the brand name will continue to be used in preference to the INN, because the safety of the medication-use process for these substances relies primarily on measures to ensure that they are given to the individual patient for whom they are intended, rather than on their INN (23).

Prefixes indicating a chemical structure? It might be surmised from the prefix oxim- of the proposed INN *oximbomotide* that its chemical structure includes an oxime, a type of imine with the general structure R2C=NOH (where R may or may not be H). However, *oximbomotide* is a peptide. The presence of an oxime structure is clearly indicated by the suffix -oxime in some INNs, e.g. *cefuroxime* and *pralidoxime iodide*. And in the case of *oxiconazole*, this chemical characteristic appears to be denoted by the prefix oxi-. The use of the prefix oxim- in *oximbomotide* may therefore mislead health professionals over the true chemical nature of the substance.

On the other hand, the INN *davelizomib* has been proposed for a substance whose chemical structure includes an azetidine ring, a saturated four-membered heterocycle containing one nitrogen atom. This ring is present in β-lactam antibiotics (such as penicillins and cephalosporins) and is essential to their antimicrobial activity. By replacing the fantasy prefix daveli- with dazeti- to form “dazetizomib”, its INN would reflect this characteristic.

The points outlined above, raised by our review group, show the importance of maintaining a minimal amount of significant chemical terminology within the INN system, as an additional aid to understanding the potential effects of the substances concerned.

Amendments

As mentioned above, *divesiran*, the proposed replacement for *manusiran*, was considered too similar to the proposed INN *mivelsiran*.

We welcome the spelling corrections in one of the languages to the INNs *ganfeborolum* and *rademikibartum*.

In summary

Like the previous list, List 129 again demonstrates 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, in so doing, to make a universal language available to healthcare professionals.

The fact that the INN *demannose* was proposed for D-mannopyranose clearly reflects this determination to establish a universal language, even for substances described a long time ago that may prove useful therapeutically. This approach helps harmonise communication within the medical community, while also helping health professionals to understand the therapeutic properties of these substances, be they new or old.

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 agents. The consequences of confusion in this context can be extremely serious for patients.

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