Prescrire’s contribution to the WHO consultation on List 113 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 routine 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, differntiation, 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). The editorial staff of Prescrire, joined by a group of pharmacy lecturers and students, at the initiative of a committed academic, as well as some hospital-based and front-line health professionals, are participating in this phase of the consultation on List 113, which was published in July 2015 (9).

Our critical analysis of the proposed INNs. Our analysis of the 97 proposed INNs and 4 amendments to previous lists presented in List 113 was based on the 2013 list of common stems, the INN database, a database of drugs marketed in France, which enables searches on both brand names and INNs, a reference database on drugs used throughout the world, and Prescrire’s own data search (10-16).

Prescrire used a two-step Delphi method. First, the participants compiled a list of potentially contentious INNs, along with the reasons for their doubts. For each of the 18 proposed INNs selected for further scrutiny in this first step, and for the 4 amendments, the participants assessed the risk of confusion and/or misunderstanding, along with the potential clinical consequences of such errors. Finally, they proposed comments for each of these 22 INNs, listing their arguments.

A long list. While List 112 contained 78 proposed INNs and 1 amendment, List 113 is longer and includes: 23 novel proposed INNs or common stems (23%); 56 proposed INNs whose common stems have been presented in the journal Prescrire (55%); 14 proposed INNs whose common stems have not yet been presented in Prescrire (14%); 4 variants (such as salts and isomers) and INNs that have undergone specific modifications
(4%); and 4 amendments to INNs proposed in previous lists (4%). The graph plotted to monitor Prescrire’s contributions to the WHO’s public consultations on proposed INNs shows that the number of novel proposed INNs or stems remains as high as in previous consultations.

Our examination of List 113 of proposed INNs also provided an opportunity to identify some future stems: -brutinib for Bruton tyrosine kinase inhibitors; -calcet/-calcet- for calcium-sensing receptor agonists; -dustat for hypoxia inducible factor (HIF) prolyl hydroxylase inhibitors; -gr(o)- a substem for monoclonal antibodies that target skeletal muscle mass related growth factors and receptors; -isant for histamine H$_3$ receptor antagonists; -ixibat for ileal bile acid transporter inhibitors; -parantag for antagonists of heparin and/or low molecular weight heparins; -prazan for proton pump inhibitors not dependent on acid activation; -sudil for Rho protein kinase inhibitors; and -tolimod for Toll-like receptor (TLR) agonists (12).

**Formal objections**

The risk of confusion or misunderstanding associated with some of the INNs proposed in List 113 was of sufficient concern to warrant four formal objections, relating to six proposed INNs: glembatumumab vedotin, labetuzumab govitcan, rovalpituzumab, rovalpituzumab tesirine, tisotumab and tisotumab vedotin. We also call for the revision of the INNs of all other monoclonal antibodies conjugated to cytotoxic agents.

Risks associated with the INNs of monoclonal antibodies conjugated to cytotoxic agents. Glembatumumab vedotin and tisotumab vedotin are monoclonal antibodies covalently bound to the cytotoxic agent monomethyl auristatin E (MMAE), a spindle poison referred to in INN nomenclature as vedotin. The toxic doses of these antibody-drug conjugates are likely to be much lower than those of their respective naked antibodies, glembatumumab and tisotumab.

Labetuzumab govitcan is a monoclonal antibody coupled to the active metabolite of the semisynthetic camptothecin derivative irinotecan. This antineoplastic agent, whose action is based on specific inhibition of DNA topoisomerase I, is referred to in INN nomenclature as govitcan. Again, this antibody-drug conjugate is likely to be toxic at much lower doses than naked labetuzumab.

Similarly, rovalpituzumab tesirine, a monoclonal antibody coupled to the pyrrolobenzodiazepine dimer, or tesirine, is probably toxic at much lower doses than
naked rovalpituzumab. In addition, some participants noticed a risk of confusion with the French drug brand name Rovalcyte°. We also wish to point out the discrepancy between tesarine in the radicals and groups section and tesirine, probably the result of a typing error (9).

Errors caused by confusion between a drug-conjugated antibody and the naked antibody have already occurred between trastuzumab emtansine and trastuzumab. The deaths caused by such errors while trastuzumab emtansine (List 103 of proposed INNs) was still undergoing clinical trials showed how serious the consequences of these errors can be, and prompted the IMSN, its members and various drug regulatory agencies to issue warnings about this risk (17-24).

We identified 26 recommended INNs for antibody-drug conjugates, and as well as the risk of confusing them with the respective naked antibody (e.g. rovalpituzumab tesirine versus rovalpituzumab), there is also a risk of confusion between the INNs of conjugates containing the same antibody but coupled to different active moieties (e.g. cantuzumab mertansine versus cantuzumab ravtansine) (25) or consisting of different antibodies coupled to the same active moiety (e.g. glembatumumab vedotin versus tsotumab vedotin) (b).

Better differentiation of monoclonal antibodies conjugated to cytotoxic agents is urgently needed. Training for health professionals is certainly required, given the dangers of these drugs. But if healthcare professionals do not know the precise meaning of the second term and assume it refers to a radical devoid of pharmacological activity rather than a second active substance, they may administer the wrong drug, resulting in a serious overdose. The fact that these cytotoxic moieties are described in the WHO list of radicals and groups trivialises their dangers (14). It would be better to present them more explicitly as active substances, especially since some contain common stems (such as -dotin, -tecan and -xetan) and the suffix “-tansine” also seems destined to become a stem.

The absence from List 113 of INNs for the naked form of the antibodies present in the antibody-drug conjugates cergutuzumab amunaleukin, clivatuzumab tetraxetan, mirvetuximab soravtansine, sacituzumab govitecan and vadastuximab talirine suggests that one method of preventing this risk of confusion is by not assigning an INN to the naked monoclonal antibody.

Other approaches exist for reducing these risks, as recently discussed by the IMSN (25). In Prescrire's opinion, the conjugated nature of these drugs must be clearly indicated through a specific prefix, such as “con” or “conj”, possibly combined with a specific typographic sign that clearly differentiates these INNs from those of fixed-dose combinations, for which specific typographic conventions exist. We leave it to the INN programme to devise appropriate measures, but urge it to do so before the number of such compounds becomes too great.

**Comments**

The participants identified a number of proposed INNs that could generate medication errors for a variety of reasons: some lack a stem but contain a sequence of letters resembling a stem; in one, the stem could be confused with a related derived stem; some INNs could be confused with another INN; and complex INNs are liable to be incomprehensible or misunderstood without full mastery of the INN system. INNs that lack a stem or contain a stem that is insufficiently obvious are hard to understand. Education about INNs for practising health professionals, students and patients is sorely needed.

**INNs that lack a common stem: risk of confusion with an existing stem.** The proposed INNs ezutromid and murepavadin lack a common stem but contain a sequence of letters resembling a stem, which could lead to confusion.

In ezutromid, the suffix “-tromid”, a possible candidate for stem status, could be confused with the suffix “-omide” present in about 30 INNs (especially in French, in which “omid” and “omide” are phonetically identical), and with the stem -zomib present in 6 INNs. Tromid® is also a brand name for the chemical dicyandiamide, while Nitromid® is a brand name for 3,5-dinitrobenzamide.
The main risk identified with murepavadin, and particularly with the French version murépavadine, is confusion between the suffix “-vadine” and the stem -tadine, denoting tricyclic H₁-antihistamines.

Confusion with a derived stem. In osimertinib, proposed as an amendment to replace mereletinib (List 112), the stem -tinib is preceded by “-mer-”, which could create confusion with the stem -metinib, derived from the stem -tinib and used to designate a subgroup of tyrosine kinase inhibitors that inhibit MEK (MAPK kinase). Such close resemblance requires a level of attention that, in practice, very busy health professionals cannot always provide.

Confusion with another INN. Some proposed INNs could be confused with other INNs, in particular: alofanib, ezutromid, monalizumab and murepavadin.

A high risk of confusion was identified between monalizumab and omalizumab: they look and sound alike, contain the same sequence of vowels and share all but one letter.

The phonetic similarity noted between alofanib and halofantrine (especially in French, in which the “h” is silent) could lead to medication errors; the consequences would depend on which of the drugs was mistaken for the other. If homophonic INNs are adopted, measures will be required to prevent transcription errors. In France this would be an issue for example for treatments discussed in multidisciplinary team meetings, given the format of these meetings here.

A risk was identified for ezutromid of erroneously selecting a name just above it in an alphabetical list in an electronic prescribing system, such as ezetimibe and its brand name Ezetrol⁶. A small risk of confusion was identified between murepavadin and the INN mupirocin. Both are antibiotics, although their routes of administration might be very different. The clinical consequences of confusing these two drugs are unlikely to be serious, although the treatment may be ineffective.

INNs, a language that must be learned. Many participants consider the complexity of certain INNs makes them difficult to memorise and pronounce, and hampers communication between health professionals when discussing patient care. A notable example in List 113 is the gene therapy product aglatimagene besadenovec, especially since the participants were not all entirely familiar with the rules governing the naming of these products. In reality, this INN contains all the information required to understand the nature of the drug. Prescrire helps health professionals learn the INN system through its regular “Common Stem” column: once they understand the rules of INN construction they can proceed to the next step, that of investing the effort required to memorise INNs.

Using INNs to describe chemical features useful to healthcare professionals. Some participants commented on the lack of (or ambiguous) information about the drug’s chemical characteristics in the proposed INNs alofanib, ezutromid, murepavadin and piclidenoson.

The presence of an aromatic nitro group is generally apparent from a drug’s INN, but is not indicated in the proposed INNs alofanib and tavilermide. This information would be helpful in highlighting the drug’s possible mutagenic potential.

Similarly, it would have been useful if the proposed INN ezutromid indicated the presence of a naphthalene nucleus, due to the possible risk of hepatotoxicity.

The presence of an aromatic iodo group is generally apparent from a drug’s INN, but is not indicated in the proposed INN piclidenoson. It would have constituted a helpful warning of the drug’s possible thyroid effects.

Finally, for the proposed INN murepavadin, the participants wondered why the stem -tide had been shunned, since the drug in question is a cyclic peptide.

Amendments. The participants identified no particular problems with 3 of the amendments to previous lists of proposed INNs.

We welcome the replacement of neladenoson dalanate by neladenoson bialanate since, as we commented in our response to the public consultation on List 112 of proposed INNs, the term dalanate has been used previously in a different sense. We also welcome the fact that bialanate has been introduced as a radical (26,27).
Similarly, we are pleased to see irbinitinib replaced by tucatinib, thereby preventing the risk of confusion with ibrutinib, about which we submitted a comment during the public consultation on List 11 of proposed INNs (29,30).

For maralixibat chloride, which replaces lopixibat chloride, we note that this prevents the risk of confusion with lopinavir, a risk identified by some participants during the public consultation on List 112, but which we did not include in our response to that consultation (27,28).

In summary. Although List 113 is longer than List 112, it attracted fewer comments, with the exception of the INNs proposed for monoclonal antibodies conjugated to cytotoxic agents. And as the numbers of these drugs are bound to grow, so will the risks of confusion and medication errors. We hope that a review of the rules governing their nomenclature will find effective solutions to clearly convey that these drugs are compounds of two active substances, so that health professionals are not forced to use brand names in clinical practice to better differentiate them from drugs with similar INNs. The INN programme has a responsibility to help health professionals and patients by assigning safe and fully informative INNs.
References


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