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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 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 123 in order to participate in the public consultation on this latest list of proposed INNs, published in July 2020 (a)(9).

Our critical analysis of the proposed INNs. Our analysis of the 163 INNs proposed in List 123, and 2 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 of pre-stems, biological and biotechnological 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 123. 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.

A huge list. This is a very long list, comprising 163 proposed INNs and 2 amendments. Naming this many new drugs is a real challenge!

Our examination of List 123 identified the use of a number of pre-stems: -batinib for BCR-ABL kinase inhibitors; -bep for engineered or synthetic protein scaffolds, non-immunoglobulin variable domain derived; -bresib for inhibitors of bromodomain proteins; -cianine for fluorescent dyes derived from indocyanine; -espib for heat shock protein (HSP) 90 inhibitors (other than -mycin); -lintide for amylin derivatives and analogues; -meran for messenger RNA (mRNA); -metostat for histone N-methyltransferase inhibitors; -pixant for purinoreceptor (P2X) antagonists; -saicin for analogues, capsaicin analogues; -sudil for Rho protein kinase inhibitors; -terkib for ERK (extracellular signal-regulated kinase) inhibitors; and -vivint for Wnt signalling inhibitors (12).

This list also features some proposed INNs that include a USAN stem: -ciron for chemokine receptor (CCR) antagonists, not antivirals; -polstat for DNA polymerases; and -xian for coagulation factor Xa inhibitors (15).

Objections
The risk of confusion or misunderstanding associated with seven INNs proposed in List 123 was of sufficient concern to warrant a formal objection: the prefix “adren-”, present in the proposed INN adrenomedullin pegol, and six INNs proposed for monoclonal antibodies conjugated to cytotoxic drugs, namely dafsolimab setaritox, grisnilimab setaritox, mipasetamab uzoptirine, tusamitamab ravtansine, upifitamab rilsodotin, and zanidatamab zovodotin.

“adren-”: a prefix with a history, to be used with caution. Most of the members of our review group felt that the immediately recognisable prefix “adren-” in the proposed INN adrenomedullin pegol could lead to confusion with adrenaline, used as a nonproprietary name for epinephrine in many countries, including France (19,20). Confusion between these two drugs would expose patients to the opposite pharmacological effect to the one intended — vasodilation with adrenomedullin pegol, peripheral vasoconstriction, among other effects, with epinephrine — which could have particularly dangerous consequences in a life-threatening emergency. The prefix “adren-” has only been used once before in an INN, namely adrenalone (21). In view of the risk of confusion over the pharmacological effect of this drug, it would be better to amend this proposed INN, dropping the prefix “adren-”, and possibly making use of the stem -dil to indicate the drug’s vasodilatory effect.

The abiding risk associated with the naming of monoclonal antibodies conjugated to active substances. We are still deeply concerned about the risks associated with the two-term INNs given to monoclonal antibodies conjugated to cytotoxic drugs. The list of these conjugates continues to grow, creating a worrying and ever-increasing risk of confusion between the INNs of: naked antibodies and their conjugated counterparts; conjugates containing the same antibody coupled to different active moieties; and conjugates containing the same active moiety coupled to different antibodies. To give two examples, trastuzumab emtansine (List 103), trastuzumab duocarmazine (List 115) and
trastuzumab deruxtecan (List 115) all contain the antibody trastuzumab but conjugated to different cytotoxic drugs, while the list of compounds containing the cytotoxic moiety raviglione conjugated to an antibody continues to grow: 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)(9,22-26).

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, they may prescribe, dispense or administer the wrong product, causing dosing errors. The proposed INNs dafsolimab setaritox, grisniliimab setaritox, mipasetamab uzoptirine, tusamitamab ravtansine, upifitamab rilsodotin and zanidatamab zovodotin add to the ever-growing list of similarly constructed INNs for monoclonal antibodies 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 a pharmacologically inactive radical (27).

For example, the chances of suspecting that uzoptirine is a cytotoxic drug are low in the absence of a stem indicative of this property. The ability of healthcare professionals to immediately identify the precise nature of the moiety referred to by the second term is vital, especially when it is pivotal to the conjugate’s pharmacological action. Yet it remains very difficult to tell whether the second term refers to a pharmacologically active product or a radical with no particular pharmacological action. Although the other cytotoxic agents conjugated to monoclonal antibodies in List 123 contain a stem indicative of their activity, such as -dotin (in rilsodotin and zovodotin), -tansine (in ravtansine), and -tox (in setaritox), their inclusion in the section of List 123 on radicals and other substituent groups underplays their toxicity.

The WHO INN Programme has decided not to improve this particular aspect of the nomenclature for these conjugated compounds, on the grounds that the rules for naming them were established a long time ago and that few errors have been reported (28). And it is content to shift the responsibility for measures to prevent any confusion between INNs onto pharmaceutical companies, regulatory agencies, healthcare establishments and organisations, and health professionals, requiring them for example to adapt the packaging and labelling of the products concerned, and the way they are listed in IT systems and on prescriptions, to help users tell them apart. Unfortunately, this leads to the paradoxical situation in which it is actually safer to use brand names than INNs.

Comments

Our review group identified a number of proposed INNs that could generate medication errors for a variety of reasons: the potential for confusion with a brand name; confusion with another INN; or uncertainty over their meaning.

Potential confusion with a brand name. Some INNs proposed in List 123 could be confused with a brand name, especially aldumastat, cagrilintide, danavorexton, firazorexton and hepcidin.

The first three syllables of the proposed INN aldumastat and of the brand name Aldurazyme® (laronidase) are very similar. This could cause the wrong drug to be selected from an alphabetical menu. In addition, phonetic similarity, in French, was identified between aldumastat and the brand name Haldol décanoas® (haloperidol).

One member of our review group identified phonetic similarity between the proposed INN cagrilintide and the brand name Integrilin® (eptifibatide).
A risk of selecting the wrong drug from an alphabetical menu was reported with the proposed INN danavorexton and the brand name Danatrol® as well as the INN of Danatrol®’s active substance danazol.

Similarly, several participants reported the risk of selecting the wrong drug from an alphabetical menu with the proposed INN firazorexton through confusion with the brand name Firazyx® (icatibant), which starts with the same 5 letters.

Resemblance was noted between the proposed INN hepcidin (especially the proposed French INN hepcidine) and Hélicidine®, the brand name of a cough suppressant syrup.

**Potential confusion with another INN.** Some of the INNs proposed in List 123 could be confused with another existing or proposed INN, especially valiloxibic acid, asundexian, cagrilintide, dapiglutide, darigabat, flubentyllosin, garivulimab, pavunalamib, pavurutamab, and tenofovir amibufenamide.

A minor risk of visual or phonetic confusion was identified between the proposed INN valiloxibic acid and the INN valproic acid, which could cause the wrong drug to be selected from an alphabetical menu.

The proposed INN asundexian contains the USAN stem -xian, for coagulation factor XIa inhibitors, preceded by the letters “de”, which could cause it to be mistaken for a dextran.

One participant noted phonetic similarity between the proposed INN cagrilintide and the INN anagrelide.

Several participants felt that the proposed INN dapiglutide is too similar to the INN albiglutide, as they contain the same sequence of vowels.

The proposed INN darigabat shares strong visual and phonetic resemblance in French with the INN dabigatran and, to a lesser degree, with the brand name Débridat® (trimebutine).

Although the construction of the proposed INN flubentyllosin cannot be faulted, many participants noted the risk of confusion with the INN flubendazole, because they share the same prefix, “fluben-”.

A high likelihood of confusion was noted between the proposed INN garivulimab and the INN sarilumab, as they share the same stem, the same sequence of vowels and have 8 letters in common.

Similarly, many members of our review group found the phonetic and visual similarity between pavunalamib and pavurutamab (both proposed in this list) too strong.

The INN tenofovir amibufenamide was proposed in List 123 for a new prodrug of tenofovir. Many reviewers were concerned that yet another drug with tenofovir in its name would increase still further the risk of confusion that already exists between tenofovir alafenamide, tenofovir exalidex and tenofovir disopropil fumarate (an alternative name for tenofovir), and wondered whether these “copies” offered any real advantages to patients. This risk of confusion is particularly high between tenofovir amibufenamide and tenofovir alafenamide, due to the similarity of their second terms. Confusion between the two drugs would probably result in dosing errors. It is important that healthcare professionals understand the modulatory role these radicals have on the pharmacologically active substance to which they have been added, whether they convert it to a prodrug or alter its pharmacokinetic or pharmacodynamic properties.

**Confusing proposed INNs.** Some of the INNs proposed in List 123 confused certain members of our review group, especially valiloxibic acid, icapamespib, oplunofusp, pirepemat and resiniferatoxin.

It surprised our reviewers that the proposed INN valiloxibic acid, described as referring to a GABA<sub>5</sub> receptor agonist, lacked the stem gab.
Some reviewers, who consider it useful when INNs also reflect the drug’s chemical composition, felt that the proposed INN capamespib could have indicated the presence of iodine in its chemical structure more clearly, and would have preferred to see “io” or “iod” in the prefix.

The proposed INN oplunofusp, and in particular its infix -o-, does not convey this fusion protein’s antiviral action. Many of our reviewers would have preferred a more informative INN.

Given pirepemat’s chemical structure and the claim that it is a nootropic, one reviewer wondered why this proposed INN lacked the stem -racetam. This reviewer also noted that the presence of fluorine and a benzene ring is indicated in the proposed INN flubentyllosin but not in pirepemat.

One reviewer noted the presence of a vanillyl group within the chemical structure of resiniferatoxin. This group, present in vanilloids, is also found in the chemical structure of capsaicin. If resiniferatoxin turns out to be a capsaicin analogue, it would be a pity not to have used the stem -saicin in its INN.

Welcome amendments. The proposed INN favezelimab is a welcome replacement for mavezelimab. In our response to List 121, we pointed out that the phonetic and visual similarities between mavezelimab and the INN manelimab could cause errors (27,29).

Our review group raised no objections to replacing diroleuton (List 118) with daleuton, but neither did we submit any concerns about diroleuton in our response to List 118 (27,30).

In summary. List 123 reflects the continuing rise of complex two- or even three-term INNs, often used, for example, for gene therapy products. Faced with the growing demand for new INNs, we salute the INN Programme for having managed to preserve the system’s intrinsic qualities of universality and simplicity, while remaining sufficiently informative for healthcare professionals, able to evolve, and independent of the pharmaceutical industry.

However, our reviewers sometimes expressed surprise, incomprehension, or even disappointment, with comments such as “Overly complex INN”, “Impossible to remember”, “It will be simpler to use the brand name”, “Three words for one molecule… with 10 or 11 syllables…”. Without knowing how many of these complex INNs will culminate in a marketed product, used perhaps to treat only a handful of patients managed by highly specialised healthcare professionals.

Solid, effective INN teaching programmes are as important as ever.

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Review produced collectively by the Prescrire Editorial Staff: no conflicts of interest ©Prescrire

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