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Prescrire's contribution to the WHO consultation on List 120 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 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 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). Our review group, consisting of members of *Prescrire*'s editorial staff, including hospital- and community-based health professionals, joined by lecturers in pharmacy and medicine from Marseille University Hospital and Marseille School of Pharmacy, has examined List 120 in order to participate in the public consultation on this latest list of proposed INNs, published in February 2019 (a)(9).

Our critical analysis of the proposed INNs. Our analysis of the 125 INNs proposed in List 120, and 4 amendments to INNs proposed in previous lists, was based on the following resources: the 2018 list of common stems and its addendum; the INN database and the WHO's lists of pre-stems, biological and biotechnological substances, and radicals; the list of planned stems proposed by the United States Adopted Names (USAN) Council; 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 120. In each case, the participants then assessed the likelihood and clinical consequences of a medication error 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.

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Ever longer lists. With 125 proposed INNs and 4 amendments, List 120 is one of the longest *Prescrire* has examined.

Our examination of List 120 provided an opportunity to identify some pre-stems: -adenant for adenosine receptor antagonists, -cerfont for corticotropin-releasing factor type-1 (CRF1) receptor antagonists, -sidenib for isocitrate dehydrogenase inhibitors; and -trectinib for tropomyosin receptor kinase (TRK) inhibitors.

This list also includes some planned stems proposed by the US drug nomenclature committee, the USAN Council: -camtiv for cardiac myosin activators, and -lanstat for lanosterol 14α -demethylase inhibitors.

Objections

The abiding risk associated with the naming of monoclonal antibodies conjugated to active substances. We remain deeply concerned about the risks associated with the two-term INNs given to monoclonal antibodies conjugated to cytotoxic drugs. 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, dosing errors can occur through administration of the wrong product. The proposed INNs disitamab vedotin, serclutamab talirine and tamrintamab pamozirine add to the ever-growing list of similarly constructed INNs for monoclonal antibodies conjugated to cytotoxic agents against which *Prescrire* has filed objections to the WHO INN Programme, mainly due to the risk of these cytotoxic moieties being mistaken for simple radicals (19).

Once again, we formally acknowledge that the WHO INN Programme is aware of the problem but has decided not revise the nomenclature for these conjugated compounds, on the grounds that the rules were established a long time ago (20). We regret that this shifts the responsibility for reducing the number of patients harmed through confusion between these INNs onto pharmaceutical companies, regulatory agencies, healthcare establishments and organisations, and health professionals, requiring them to devise measures to aid discrimination between the products concerned through their packaging, labelling, and the way they are listed in IT systems and on prescriptions. This leads to the paradoxical situation in which it is actually safer to use brand names than INNs.

New monoclonal antibody nomenclature: first signs of saturation? The new naming scheme for monoclonal antibodies, which omits the species substem, is a welcome development (21). However, the phonetic similarity identified by some members of our review group between the proposed INNs *ieramilimab* and *nidanilimab* indicates that there are early signs of saturation despite this new nomenclature.

Comments

Our review group identified a number of proposed INNs that could generate medication errors, for a variety of reasons: confusion with a brand name; confusion with another INN; confusion due to absence of a clearly identifiable stem; conflicts between the proposed INN and the indications claimed by the pharmaceutical company; the complexity of some two-term proposed INNs; and finally the assignment of a unique INN to therapies that are different for each patient.

Confusion with a brand name. Some INNs proposed in List 120 could be confused with a brand name, in particular: *aclimostat*, *aldafermin*, *clascoterone*, *danicamtiv*, *foscarbidopa*, *selitrectinib*, *taminadenant* and *teclistamab*.

The phonetic and visual similarity between the proposed INN *aclimostat* and the brand name Climaston° (*estradiol* + *dydrogesterone*) could lead to confusion errors.

The prefix "alda", used for the first time in the proposed INN *aldafermin*, has already been used in France as a prefix in brand names such as Aldactazine° (*altizide* + *spironolactone*), Aldactone° (*spironolactone*) and Aldara° (*imiquimod*), creating a risk of wrong-drug errors when selecting drugs from an alphabetical menu.

Some members of our review group felt that the proposed INN *clascoterone* is liable to confusion with the brand name Clastoban° (*clodronic acid*) as their first 4 letters are identical and they sound so similar. As in the previous case, this is the first time the prefix "clas" has

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been used in an INN.

The INN *danicamtiv* contains the USAN stem -camtiv, for cardiac myosin activators. This potential stem is very similar to the end of the brand name Hycamtin° (*topotecan*), a product marketed in many countries. If this suffix is used in future INNs, prefixes will have to be selected so as to avoid confusion with Hycamtin°.

The proposed INN *foscarbidopa* could be selected from an alphabetical menu instead of the brand name Foscavir° or its INN *foscarnet sodium*, as their first 5 or 6 letters, respectively, are identical.

One member of our review group pointed out that the proposed INN *selitrectinib* is phonetically similar to the brand name Zelitrex° (*valaciclovir*).

The proposed INN *taminadenant* shares visual and phonetic similarity with the brand name Tadenan° (*Pygeum africanum* extract) due to the combination of the prefix "ta" with the pre-stem **-adenant**.

Tecfidera° (dimethyl fumarate) is likely to be mis-selected from an alphabetical menu instead of the proposed INN teclistamab because the former would be listed first.

Confusion with another INN. Some of the INNs proposed in List 120 are liable to confusion with other INNs, in particular: *abrocitinib*, *amcipatricin*, *avanbulin*, *foscarbidopa*, *foslevodopa*, *serdexmethylphenidate* and *troriluzole*.

Accidental inversion of the first 2 letters of the proposed INN *abrocitinib* could result in confusion with the INN *baricitinib*. One member of our review group also pointed out its similarity to the INN *ibrutinib*.

Many of our reviewers pointed out the risk of confusion between the proposed INN amcipatricin and the INNs amifampridine, ampicillin and amphotericin B. They also felt it was unfortunate that the drug does not have a stem that clearly identifies it as an antifungal, even though use of the stem **-tricin** is perfectly justified on the basis of its chemical structure.

The proposed INN *avanbulin* is liable to confusion with the INN *lisavanbulin* (proposed in List 115), the consequences of which will depend on their relative potency (22).

List 120 contains several proposed INNs (described as "telescopic" by one member of our review group) created by adding prefixes to an existing INN. Although their construction cannot be faulted, in routine clinical practice they could be confused with the original INN they contain, i.e. foscarbidopa with carbidopa, foslevodopa with levodopa, serdexmethylphenidate with methylphenidate and dexmethylphenidate, and troriluzole with riluzole. To prevent dosing errors involving these new drugs, doses could be expressed as carbidopa, levodopa, methylphenidate and riluzole equivalents, respectively, similar to the measures taken in some countries to encourage doses of fosphenytoin to be expressed as phenytoin equivalents (23-27).

Confusion due to absence of a clearly identifiable stem. Our review group was unable to identify a stem more explicit that -mab in the proposed INN for the monoclonal antibody *volagidemab*, which they had expected would also contain the stem -li- or -gli- to indicate its claimed immunomodulating and antihyperglycaemic effects.

Conflicts between the proposed INN and the indications claimed by the pharmaceutical company. The proposed INN pepinemab contains the substem -ne- from the new monoclonal antibody nomenclature, signifying a neurological target, whereas the pharmaceutical company has only claimed immunomodulating properties for this drug. Our reviewers were therefore expecting it to contain the substem -li-.

Conversely, it makes sense that the substem **-ne-** was used rather than **-li-** in the proposed INN *cinpanemab*, for which both immunomodulating and antiparkinsonian properties are claimed.

Confusion caused by complex two-term INNs. Many of our reviewers considered that the complexity of certain INNs makes them difficult to memorise and pronounce, and hampers communication between health professionals when discussing patient care. In List 120, the gene therapy products in particular were considered problematic in this regard (adlinacogene civaparvovec, cadalimogene ixalentivec, devafidugene civaparvovec, etranacogene dezaparvovec, inlezifigene civaparvovec, inodiftagene vixteplasmid, ranuzifigene civaparvovec, resamirigene bilparvovec, rovoctocogene durparvovec, tefidsogene civaparvovec and volrubigene ralaparvovec), because the reviewers were

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unfamiliar with the rules governing the construction of their INNs.

Although these INNs include all the information required to understand the nature of the substance, some reviewers identified a risk of confusion between gene therapy INNs that share one of their 2 terms. For example, List 120 includes 5 proposed INNs that share the same second term *civaparvovec* (adlinacogene civaparvovec, devafidugene civaparvovec, inlezifigene civaparvovec, ranuzifigene civaparvovec and tefidsogene civaparvovec), and the INNs rilimogene galvacirepvec (proposed in List 107) and rilimogene glafolivec (proposed in List 113) share the same first term (28,29).

INNs and patient-specific cell therapies. List 120 only includes one proposed INN for a substance for cell therapy, *mocemestrocel*, whereas previous lists contained more (7 in List 115, 3 in List 116, 7 in List 117, 3 in List 118, and 6 in List 119) (2,30-33). At the time of their market introduction, *Prescrire*'s editorial staff raised concerns about the fact that each CAR-T therapy has an INN, whereas the composition of the treatment is specific to each patient, because it is produced from the patient's own T cells. In contrast to what this INN might suggest, these treatments are more akin to blood cell transfusions than drug therapy, and carry a particular risk of wrong-patient errors that require careful checks during production and transport, and before administration to the patient, to ensure that the patient ID matches the information on the labelling at each step of the way (34).

Amendments. We have no concerns to report regarding the 4 amendments included in List 120. We are pleased that our comments on the proposed INNs *abeprazan*, *nedisertib* and *nemorexant* were taken into account and that these names have been replaced respectively by *fexuprazan*, *peposertib* and *daridorexant* (35).

In summary. Two-term INNs are an elegant solution to the increasing complexity of biotechnology-derived pharmaceutical substances, but they generate new risks of confusion that we fear will only intensify as the number of such INNs increases. The same applies to substances for gene therapy and cell therapy. The nomenclature for monoclonal antibodies conjugated to pharmacologically active substances is an issue that has still not been unresolved and continues to concern us.

Issues identified by healthcare professionals are worth taking into account. These include: the increasing complexity of INNs, a problem mentioned by many of our reviewers; the fact that some therapeutic classes have reached saturation point; the role of radicals in altering drugs' pharmacokinetic or pharmacodynamic properties; and the advantages of INNs that provide more information about the drug's indications and properties, while remaining simple and easy to memorise. Healthcare professionals and patients can only think and act successfully in terms of INNs when these names are devised and taught in a rigorous, coherent and effective way, and when they are intelligible.

The recent publication of a guide to INNs for students usefully complements the well executed update of the "Stem book". It relates pharmacological classification to stems as an aid to learning pharmacology, giving more substance to the developing School of INN (10,36). We heartily encourage this initiative and await its translation into the various official WHO languages to increase its global reach.

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