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Prescrire's contribution to the WHO consultation on List 122 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 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 122 in order to participate in the public consultation on this latest list of proposed INNs, published in January 2020 (a)(9).

Our critical analysis of the proposed INNs. Our analysis of the 134 INNs proposed in List 122, and 1 amendment to an INN proposed in a previous list, 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 122. 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.

Growing number of biological substances. More than 60 of the 134 INNs proposed in List 122 are for biological substances, including 42 monoclonal antibodies, 9 gene therapy or cell therapy products, and 4 substances with an engineered or synthetic protein scaffold, derived from a non-immunoglobulin variable domain.

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A number of pre-stems have been used in the INNs proposed in List 122: **-atovir** for RSV fusion protein inhibitors; **-bep** for engineered or synthetic protein scaffolds, non-immunoglobulin variable domain derived; **-capavir** for viral capsid inhibitors; **-estrant** for oestrogen antagonists; **-gratinib** for fibroblast growth factor receptor (FGFR) inhibitors; and **-meran** for messenger RNA (mRNA) (12).

This list also features some proposed INNs that include a USAN stem: **-luren** for inducers of ribosomal readthrough on nonsense mutation mRNA stop codons; **-napant** for inhibitors of apoptosis protein (IAPs); and **-sarm** for nonsteroidal selective androgen receptor modulators (15).

Objections

The risk of confusion or misunderstanding associated with two INNs proposed in List 122 was of sufficient concern to warrant a formal objection: *datopotamab deruxtecan*, a monoclonal antibody conjugated to a cytotoxic drug, and *rulabricin alfa*.

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. 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 INN *datopotamab deruxtecan* adds 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 (19).

Once again, we acknowledge that the WHO INN Programme is aware of the problem but has decided not to revise the nomenclature for these conjugated compounds, on the grounds that the rules were established a long time ago (20). Unfortunately however, 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.

A confusing combination. Similarity between the proposed INN *rulabricin alfa* and the INNs *idarubicin* and *aclarubicin* was noticed by many members of our review group, who assumed *rulabricin alfa* to be an antineoplastic drug. This proposed INN has no known stem or pre-stem applicable to a drug derived from human proteoglycan 4, a molecule present in human synovial fluid and otherwise known as lubricin, which we assume to be the origin of the suffix “-bricin”. Confusion is likely with the stem **-rubicin**, used for antineoplastics derived from *daunorubicin*, due to the presence of the syllable “ru” in the prefix “rula-”, and the similarity between the suffixes “-bricin” and “-bicin”. At least 4 drugs with the stem **-rubicin** in their INN (*daunorubicin*, *doxorubicin*, *epirubicin* and *idarubicin*) are currently marketed in France, and *aclarubicin* is marketed in many other countries. As *rulabricin alfa* seems intended as a treatment for osteoarthritis, for administration by intra-articular injection, confusion with an antineoplastic drug could cause severe harm to patients. Although the suffix “-bricin” helps users identify the nature of this drug, it would be prudent to never combine it with the prefix or infix “(-)ru-”. The aim of our objection is to amend this proposed INN while it is still possible to do so.

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, especially for proposed INNs derived from a recommended INN; confusion with another stem; or confusion over the drug’s indication or properties.

Potential confusion with a brand name. One proposed INN in particular could be confused with a brand name. At least two members of our review group noted the risk of confusing *vonafexor* with the brand name Effexor^o (*venlafaxine*), due to the close phonetic

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similarity in both French and English between the suffix “-afexor” and the brand name Effexor^o.

Potential confusion with another INN. Some of the INNs proposed in List 122 could be confused with existing INNs, in particular: *aramisulpride*, *belzutifan*, *esamisulpride*, *felzartamab*, *fosciclopirox*, *fosfidancitinib* and *velufenacin*.

The proposed INN *belzutifan* could be confused with the INN *busulfan* due to their slight, mainly phonetic, similarity, particularly in French.

Several participants identified a risk of confusion between the proposed INN *felzartamab* and the INN *felbamate*, due to the fact that they start with the same three letters and sound alike. However, their different routes of administration would lessen the risk of an error reaching the patient.

There is a small risk of confusion between the proposed INN *velufenacin* and the INNs *venlafaxine* and *fexofenadine*.

List 122 features several proposed INNs, mainly for enantiomers or ester prodrugs, derived from the INNs of existing substances. Although their construction cannot be faulted, in routine practice they could be confused with the original INN they contain, i.e. *aramisulpride* or *esamisulpride* with *amisulpride*, *fosciclopirox* with *ciclopirox*, and *fosfidancitinib* with *ifidancitinib* (also proposed in List 122).

Given that List 122 contains some proposed INNs for dihydrogen phosphates, identifiable by their prefix fos-, it is worth considering the errors that have occurred with *fosphenytoin*. Admittedly, confusion between the INNs *phenytoin* and *fosphenytoin* was not the only factor: confusion between the brand names Dilantin^o and Prodilantin^o also played a role, as did the way their concentrations are expressed, and prominently displayed in the name and labelling (50 mg/mL and 75 mg/mL respectively, rather than 500 mg/10 mL and 750 mg/10 mL), resulting in calculation and conversion errors at every stage from prescribing to the preparation and administration of these drugs (21). In France, 41 errors linked to Prodilantin^o were listed in the medication errors database of the French Health Products Agency (ANSM) for the period from 1st January 2005 to 13 March 2015 and in the national pharmacovigilance database from 1985 to 13 March 2015. The error resulted in an adverse effect in 39 cases, notably 32 overdoses rated as serious, 4 of which were fatal (22). Similar errors were reported in other countries, in particular in the United States (23-26). In early 2017, the ANSM warned healthcare professionals about these sometimes-fatal errors, particularly in children younger than 5 years old, and stressed the importance of prescribing and administering *fosphenytoin sodium* as *phenytoin sodium* equivalents (PSE) (27).

Pharmaceutical companies, agencies and healthcare professionals could reduce the risk of dosing errors involving these new substances by expressing doses as *amisulpride*, *ciclopirox* or *ifidancitinib* equivalents, respectively.

Potential confusion with another stem. The presence of the suffix “-pixant” in the proposed INNs *eliapixant* and *filapixant* suggests it may become a stem for purinoreceptor antagonists. This suffix is very similar to the stems **-pitant**, used for neurokinin NK1 (substance P) receptor antagonists, **-piprant**, used for non-prostanoid prostaglandin receptor antagonists and, to a lesser degree, to the stem **-triptan**, used for serotonin (5-HT₁) receptor agonists derived from *sumatriptan*. Similarities between stems create a risk of confusion between drugs from different pharmacotherapeutic classes, with potentially serious clinical consequences. These similarities are a reminder that when new suffixes are chosen for INNs, they must be distinctive and easily identifiable.

These similarities are also a reminder of the importance of educational efforts to ensure users understand the information conveyed by INNs.

Potential confusion over the drug’s indication or properties. Some INNs proposed in List 122 could lead to confusion over the drug’s indication or properties, in particular: *ebopiprant*, *lazuvapagon*, *pexopiprant* and *vosilasarm*.

The proposed INNs *ebopiprant* and *pexopiprant* contain the stem **-piprant**, used for non-prostanoid prostaglandin receptor antagonists. Many of our reviewers identified these drugs as antibiotics on account of their familiarity with Pipram^o, a brand name for *pipemidic acid* in France.

The proposed INN *lazuvapagon*, for a drug described as a vasopressin V₂ receptor agonist, suggests that it may contain a future stem for these agonists. The similarity between *lazuvapagon* and the INN *glucagon* caused some reviewers to wonder whether it was a glycoconjugate hormone.

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The proposed INN *vosilasarm* has the USAN stem *-sarm*, used for nonsteroidal selective androgen receptor modulators. This potential stem is also the acronym in French for methicillin-resistant *Staphylococcus aureus* (MRSA), which could lead to confusion over the indications or properties of drugs ending in *-sarm*.

Complex two-term INNs: a great deal of educational effort required. Many of our reviewers considered that the complexity of some new INNs makes them difficult to memorise and pronounce, and hampers communication between health professionals when discussing patient care. The gene therapy and cell therapy products in List 122 were considered particularly problematic in this regard: *afamitresgene autoleuvel*, *autogene cevumeran*, *ciltacabtagene autoleuvel*, *dapatifagene navolactibac*, *olvimulogene nanivacirepvec*, *orvacabtagene autoleuvel*, *rocakinogene sifuplasmid*, *simoladagene autotemcel*, and *verbrinacogene setparovec*. Many hospital-based healthcare professionals say they will refer to gene therapy and/or cell therapy products by their brand names in clinical practice rather than by their INNs, especially as they will be used on so few patients.

This highlights yet again the importance of active, sustained efforts to educate users about the INN system in general, and about recent INNs in particular.

Welcome amendment. The proposed INN *nadunolimab* replaces *nidanilimab*, a welcome amendment that eliminates the risk created by the phonetic resemblance between *nidanilimab* and the INN *ieramilimab*, pointed out in our response to List 120 of proposed INNs (19).

In summary

List 122 reflects the continuing boom in biological substances, which accounted for almost half of these newly proposed INNs.

The INN Programme has implemented many solutions and revisions to the naming of these substances, such as the nomenclature scheme for fusion proteins, monoclonal antibodies, insulins, and gene therapy and cell therapy products. We appreciate the INN Programme's efforts to provide clear and concise explanations of some of its solutions for naming biologicals, while also recognising a number of limitations and necessary revisions (28). However, many members of our review group, confronted with the full complexity of INN nomenclature for biologics for the first time during this consultation, without explanations, reported being reluctant to use these INNs in routine practice.

Yet it is crucial that the use of INNs continues to improve the quality and safety of medical treatment throughout the world, for the benefit of patients. And, therefore, that INNs continue to be informative, concise, easy on the ear, easy to pronounce and memorable, and that, as soon as INNs are introduced, their stems are made clear and explained, through highlighting and hyperlinks for example.

We feel sure that the creativity and perseverance of which the INN Programme is capable are up to this challenge.

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