Prescrire's contribution to the WHO consultation on List 121 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 growing number of INNs now in circulation and the number of applications for new INNs that sometimes remain unused. 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 121 in order to participate in the public consultation on this latest list of proposed INNs, published in August 2019 (a)(9).

Our critical analysis of the proposed INNs. Our analysis of the 143 INNs proposed in List 121, and 2 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 121. 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.
Ever longer lists. With 143 proposed INNs and 2 amendments, List 121 is the longest Prescrire has ever examined.

Our examination of List 121 identified the use of a number of pre-stems: -bep for engineered or synthetic protein scaffolds, non-immunoglobulin variable domain derived; -corat for glucocorticoid receptor agonists; -espi for heat shock protein (HSP) 90 inhibitors (other than -mycin), antineoplastics; -setrag for serotonin (5-HT3/4) receptor agonists, prokinetics; and -stinel for NMDA receptor co-agonists (15).

This list also includes some planned stems proposed by the US drug nomenclature committee, the USAN Council: -axine for antianxiety, antidepressant inhibitors of norepinephrine (noradrenaline) and dopamine reuptake; -etamine for amfetamine derivatives; and -nemdaz for N-methyl D-aspartate (NMDA) receptor antagonists (N2B subunit).

Objections

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 INNs mirzotamab clezutoxclax, patritumab deruxtecan and praluzatamab ravtansine 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 (19).

The proposed INN mirzotamab clezutoxclax is a perfect illustration of this type of ambiguity in List 121, with clezutoxclax listed as a radical on page 365, suggesting that it has no pharmacological activity, yet the full definition of mirzotamab clezutoxclax states that clezutoxclax is an inhibitor of BCL2L1. Furthermore, tapotoclox has been assigned a proposed INN in the same list, where it is clearly identified as an antineoplastic, as is the case for the 4 existing INNs ending in the stem -toclox: imlatoclox, navitoclax, obatoclax and venetoclox (marketed in Europe under the brand name Venclyxto®) (20). It is precisely this type of ambiguity that prevents health professionals from fully understanding drugs’ pharmacological properties from their INN.

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 (21). 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.

New monoclonal antibody nomenclature: signs of saturation? The new naming scheme for monoclonal antibodies, which omits the species substem, is a welcome development (22). However, the phonetic and visual similarity identified by some members of our review group between the proposed INNs manelimab and mavezelimab shows that a risk of saturation persists despite the 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, another INN or a related INN; confusion over the drug’s properties because it lacks a stem; confusion caused by the complexity of some two-term INNs; and finally the assignment of a single INN to cell therapies that are actually patient-specific.
Potential confusion with a brand name. Some INNs proposed in List 121 could be confused with a brand name, in particular: brepocitinib, cosibelimab, elexacaftor, felezonexor, sepopfarsen, sinbaglustrat and sovateltide.

One member of our review group pointed out that in French the proposed INN brépocitinib shares a certain visual and phonetic similarity with the brand name Dépocyté®.

The proposed INN cosibelimab shares visual and phonetical similarity with the brand name Cosimprel®.

Many of our reviewers felt that the proposed INN elexacaftor is liable to confusion with the brand name Effexor® , mainly because they sound alike.

The proposed INN felezonexor also resembles Effexor®.

A degree of resemblance was noticed in French between the proposed INN sepopfarsen and the brand name Époratio®.

The proposed INN sinbaglustrat shares predominantly phonetic similarity with the brand name Cymbalta®.

Several reviewers noticed phonetic and visual similarity between the proposed INN sovateltide and the brand name Solvadi®.

Potential confusion with another INN. Some of the INNs proposed in List 121 are liable to confusion with other INNs, in particular: arlipic acid, astegolimab, axatilimab, befovacimab, fosdenopterin, monomethyl fumarate, manelimab, mavezelimab, mirzotamab, obafistat, olpasiran, patritumab deruxtecan, and rebamipide mofetil.

Arlipoic acid could be confused with valproic acid, due to both phonetic and visual similarity.

The proposed INN astegolimab is liable to confusion with the INN golimumab as they both contain the syllable “go” with the stems -l(i) and -mab. It also resembles, to a lesser extent, the INN fingolimod. The same reviewer also pointed out the risk of confusion with the INN protolimib, proposed in List 119 (20).

The fact that the first 5 letters of axatilimab are almost identical to those of axitinib (“axali” vs “axiti”) creates a risk of selecting the wrong drug from an alphabetical menu, and a mix-up is all the more likely as both substances are antineoplastics.

The proposed INN befovacimab shares 4 of its 5 syllables with bevacizumab and bevacizumab beta, resulting in high phonetic and visual similarity and therefore a risk of confusion.

One reviewer pointed out the resemblance between fosdenopterin and fosphenytoin, which share the same first 3 letters and phonetic similarity.

The proposed INN monomethyl fumarate could be confused with dimethyl fumarate, marketed in many countries under the brand name Tefcidera®. It is puzzling that other fumaric acid esters have not been assigned an INN.

It was felt that the phonetic and visual similarity identified by some members of our review group between the proposed INNs manelimab and mavezelimab made them difficult to tell apart.

Two reviewers spotted a slight risk of confusion between the proposed INN mirzotamab and mirtazapine.

The strong phonetic and visual resemblance between the proposed INN obafistat and the INNs orlistat and cobicistat caused concern, particularly because of the risk of confusing orlistat or cobicistat with a drug that will potentially be used to treat cancer.

One reviewer felt that olpasiran looks and sounds sufficiently similar to patisiran to lead to confusion in routine clinical practice.

The monoclonal antibody patritumab deruxtecan could be confused with panitumumab, which resembles its first term, and with trastuzumab deruxtecan, which is conjugated to the same radical.

Many reviewers found the first term of the proposed INN rebamipide mofetil similar visually and phonetically to the INN repaglinide. And as with other 2-term INNs, rebamipide mofetil could also be confused with rebamipide, a drug mainly marketed in Asia for gastric ulcers.

Potential confusion with a related INN. Some of the INNs proposed in List 121 are liable to confusion with the INNs of substances to which they are chemically related, in particular efalumonagratim alfa, enmetazobactam, lomardexamfetamine, pregabalin arenacarbil, toludesvenlafaxine, and treprostinil palmitil.
The proposed INN ebemalenogristim alfa is liable to confusion with the INNs lenogristim and effenogristim alfa.

The proposed INN enmetazobactam could be confused with tazobactam, of which it is a methylated derivative. However, as their potencies will probably be similar, confusion between the two is unlikely to have severe consequences.

In addition to being surprised to learn that a pharmaceutical company is developing a new amphetamine, lornardexamfatine, our review group would have expected it to have the stem -orex rather than the old USAN Council stem -fetamin(e), which would have been a way for the INN Programme to help users keep in mind the drugs to which it is related and its probable high potential to cause harm. It could also be confused with amfetamine, dexamfatine and lisdexamfatine (20).

It appears that the compound pregabalin arenacarbil will have different kinetics from pregabalin. The very real risk of confusion between these two names, since the first term of the former is identical to the latter, could result in the wrong drug being selected from an alphabetical menu, causing patients to take their medication at the wrong dose and frequency. It could also be confused with the INN gabapentin enacarbil, because pregabalin is a gabapentin analogue and the names of their radicals are so similar. Our review group felt that toludesvenlafaxine is liable to confusion with the INNs venlafaxine and desvenlafaxine (venlafaxine’s major active metabolite), marketed in many countries under various brand names. Confusion with one of these drugs could cause a harmful dosing error, given the high risk of cardiac arrest associated with venlafaxine overdoses.

It appears that the aim of combining palmitil with treprostinil is to modify the kinetics of treprostinil. The risk of confusing treprostinil palmitil with treprostinil alone could result in patients taking their medication at both the wrong dose and the wrong frequency.

Confusion due to absence of a stem. The members of our review group were unable to identify a stem in the proposed INN otenaproxesul that would explain the drug’s nonsteroidal anti-inflammatory action, but it has an infix indicating that it is a derivative of naproxen, whose INN also lacks a stem but shares the letter sequence “naprox” with the INNs of two substances that are not currently marketed: cinaproxen and naproxcinod (20).

Complex two-term INNs: a great deal of educational effort required. 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. The gene therapy and cell therapy products in List 121 were considered particularly problematic in this regard: avaloctogene ontaparvovec, betibeglogene autotemcel, dirloctocogene samoparvovec, elivlrogenove autotemcel, ezalidigene resoparvovec, giroctogene fitelparvovec, letetresgene autoleucel, mipetresgene autoleucel, olitresgene autoleucel, tebrocabtagene autoleucel, and zildistogene varoparvovec. Although these INNs include all the information required to understand the nature of the substance, some reviewers identified a risk of confusion between the INNs of gene therapy or cell therapy products that share the same second term, as is the case for the 6 INNs proposed in List 121 that have autoleucel or autotemcel as their second term (letetresgene autoleucel, mipetresgene autoleucel, olitresgene autoleucel, tebrocabtagene autoleucel, betibeglogene autotemcel and elivlrogenove autotemcel).

As a consequence, 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 their INNs.

INNs and patient-specific cell therapies. List 121 contains 11 proposed INNs for cell therapy products (atiferasecotel, betibeglogene autotemcel, elivlrogenove autotemcel, firzotemcel, letetresgene autoleucel, mipetresgene autoleucel, olitresgene autoleucel, omidubicel, rovaleucel, stapudencel, and tebrocabtagene autoleucel), whereas previous lists contained far fewer (7 in List 115, 3 in List 116, 7 in List 117, 3 in List 118, 6 in List 119, and 1 in List 120) (2,20).

When the first “chimeric antigen receptor” (CAR) T-cell therapies were marketed, Prescrire’s editorial staff raised the issue that they had each been assigned an INN yet the composition of the treatment is specific to each patient, because it is produced from the patient’s own cells. In contrast to what this INN might suggest, CAR T-cell therapy is more
akin to a transfusion of autologous cells than a pharmacological treatment, and poses particular risks if administered to the wrong patient. Careful checks are therefore required when the patient’s cells are harvested, transported to the company, engineered, transported back to the bedside, and before administration, to ensure that the patient ID matches the information on the labelling at every stage (23).

**Welcome amendments.** The INN *fezagepras* replaces *setogepram*, eliminating the risk of confusion with the INNs *citalopram* and *escitalopram* that we pointed out in our response to List 119 of proposed INNs (19). However, one reviewer noticed a certain similarity in French to the INN *bezafibrate* and the brand name *Élaprase°*.

We have no particular comments to make about the replacement of *talditencept alfa* by *taldetfrope alfa*, except that the use of the pre-stem *-bep* provides some clarification on the nature of the substance (12).

**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. Many reviewers who were introduced to this complexity during this public consultation, without receiving additional instruction, reported that it will be preferable in routine practice to refer to these substances by their brand name, especially as they will be used on so few patients.

The nomenclature for monoclonal antibodies conjugated to pharmacologically active substances is an issue that remains unresolved and still concerns us, especially since List 121 continues to fuel ambiguity between radicals with and without pharmacological activity.

Issues identified by healthcare professionals are worth taking into account, such as: 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 are informative (about the drug’s indications and properties), 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 new INNs are easily intelligible and properly explained.

The recent launch of the “School of International Nonproprietary Names” website is a useful complement to the latest “Stem book” with its new, improved format, and the guide to INNs for students, which relates pharmacological classification to stems as an aid to learning pharmacology, giving even more substance to the School of INN (10,24,25). We heartily encourage the continued expansion of this new initiative and await the translation of these resources into the various official WHO languages, to increase their global reach.

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