Prescrire’s contribution to the WHO consultation on List 104 of proposed INNs

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As an active member of the Medicines in Europe Forum, the International Society of Drug Bulletins (ISDB), and the International Medication Safety Network (IMSN), Prescrire has long been advocating the routine use, by both healthcare professionals and patients, of international nonproprietary names (INNs), which are more informative, safer and clearer than brand names (1-4).

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. INNs make pharmaceutical substances easier to identify and are less frequently confused than brand names (5).

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 public consultations on proposed INNs, in order to identify any risk of confusion during their clinical use (6). The editorial staff of Prescrire and members of the not-for-profit organisation Association Mieux Prescrire are participating in this phase of the consultation and have examined List 104 of proposed INNs, which was published in January 2011 (7).

Our critical analysis of the proposed INNs. Our analysis of List 104 of proposed INNs was based on the 2009 list of common stems and its updates, on the INN database, on Prescrire’s own data search, and on a database of drugs marketed in France, which enables searches on both brand names and INNs (8–12).

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 38 proposed INNs selected for further scrutiny in this first step, the participants assessed the risk of confusion and/or misunderstanding, along with the potential clinical consequences of such errors. Finally they decided for each of these 38 contentious INNs whether a simple comment or a formal objection was more appropriate, and listed their arguments.

We also examined three INNs, darexaban, tedizolid and vosaroxin, that had been proposed in previous lists, then amended in response to objections lodged by Prescrire and others.
Formal objections

We identified some risks of mix-ups or misunderstandings among the proposed INNs in List 104 that were of sufficient concern to warrant a formal objection. These risks of error appear avoidable and are caused by similarities between INNs (ronomilast), similarities with existing common stems (elobixibat, ordopidine and seridopidine), or an insufficiently obvious common stem, creating the potential for confusion with brand names (orteronel). We therefore request that these proposed INNs be re-examined, to prevent problems for patients and healthcare professionals in the future.

**ronomilast too similar to roflumilast.** Many participants identified the strong resemblance between ronomilast and the existing INN roflumilast, an anti-inflammatory drug approved in Europe and the US in chronic obstructive pulmonary disease (COPD) marketed under the brand names Daxas® and Daliresp®. These drugs have the same therapeutic indications, but by sharing three of their four syllables, including the prefix, the similarity is excessive. Given the current proliferation of phosphodiesterase IV inhibitors (11 INNs already end in −milast), the INNs adopted must be more distinctive to prevent mix-ups between them, resulting in medication errors, and particularly dosing errors (9).

**elobixibat could be mistaken for a monoclonal antibody.** This proposed INN could be confused with chimeric monoclonal antibodies that end in −iximab, such as abciximab, basiliximab, dacliximab (replaced by daclizumab) and infliximab. The phonetic similarity results from the fact that −ibat and −imab, and −ixat and −iximab have too many letters in common. Given this potential for error, the INN Expert Group will need to take great care when considering the prestem −ibat, proposed by the United States Adopted Names (USAN) Council, and may need to find a more distinctive common stem for ileal bile acid transporter inhibitors (13).

**−dopidine: too many risks for this proposed prestem.** The USAN has proposed the prestem −dopidine for dopamine D\textsubscript{2} receptor modulators such as ordopidine and seridopidine (13). The clinical risk from confusing these INNs with ticlopidine includes serious bleeding. Potential for confusion also exists between −dopidine and −dipine, the stem for nifedipine derivatives used as calcium-channel blockers, such as amlodipine, felodipine, isradipine, lacidipine, lercanidipine, nicardipine and nitrendipine. The same concerns had already prompted Prescrire to lodge a formal objection against pridopidine in its contribution to List 102 of proposed INNs (14), to which the reply was that “the INN Expert Group commonly agreed that there was no conflict with ticlopidine” (15). These additional objections provide further reason against adopting −dopidine as a future prestem, due to the risk of confusion with many look-alike, sound-alike INNs; and for the immediate development of an alternative to the USAN’s proposal.

**orteronel: one “l” too many.** The “l” at the end of this INN conceals the common stem −terone, and most of the participants suggested that “orterone” would be more explicit for this antiandrogen. Furthermore, the end of this INN is reminiscent of and could be confused with the brand names of some bisphosphonates, such as Actonel® and Didronel®.

### Amendments to previously proposed INNs

As a result of the objections lodged, the INN programme changed tanexaban (presented in List 101 as a blood coagulation factor Xa inhibitor) to darexaban, torezolid (presented in List 101 as an antibiotic) to tedizolid, and voreloxin (presented in List 100 as an antineoplastic) to vosaroxin. These amendments were published in List 104 of proposed INNs (7). Prescrire had lodged a following formal objection to voreloxin: “a name that does not evoke a cytotoxic drug, could be confused with INNs ending in "xine", including
venlafaxine, gitaloxine and quarfloxine; vorelixin is more evocative of an antibiotic, given the similarity with the common stem –oxacin" (16).

The participants who examined these amended INNs made no comments about the changes.

Other comments

Some proposed INNs generate a risk of medication errors, for a variety of reasons: some could be confused with other INNs; indeed, the sheer number of INNs in certain groups creates similarity; some could be transformed into another by a slip or a lapse; some have common stems that are difficult to learn, are missing, easily confused with other common stems, insufficiently obvious or that depart from existing guidance on INN design; and some can be confused with everyday, non-pharmaceutical terms or brand names. Hence the following comments.

Risks of confusion with other INNs. Some proposed INNs, such as luseogliflozin, plecanatide and solithromycin, could be confused with other INNs.

The confusion between luseogliflozin and griseofulvin looking and sounding alike when written or spoken could lead to medication errors. It was considered that the potential frequency and seriousness of such errors did not justify an objection, although several participants suggested reducing the risk by replacing "seo" with "so".

The risk of look-alike confusion between plecanatide and flecainide should be addressed by ensuring that the indications are clearly marked on labelling and package leaflets.

Risks of confusion were identified between solithromycin and: roxithromycin, which contains the same sequence of vowels, creating a sound-alike risk that was considered potentially frequent; and more rarely with telithromycin, which only differs by one syllable, but the fact that it is the first syllable enables adequate differentiation of the two INNs.

The sheer number of INNs in certain groups creates similarity. Within-group similarity is particularly marked among antineoplastic tyrosine kinase inhibitors (lenvatinib, linsitinib) and monoclonal antibodies (etrolizumab).

Against the background of the current proliferation of tyrosine kinase inhibitors (List 104 included 6 proposed INNs ending in –tinib), a risk of confusion was identified between lenvatinib, the existing INN lapatinib, and the proposed INN linsitinib.

There are now 33 monoclonal antibodies whose INN ends in –lizumab (8 of which are marketed in France). As the list grows, so does the risk of confusing these sounding or looking alike INNs, for example etrolizumab and certolizumab.

Mix-ups created by a slip or a lapse. The participants identified certain INNs, such as mericitabine and naronapride, where a slip or a lapse would create a risk of confusion.

Some participants identified the risk of medication error generated by inversion of the first two letters of mericitabine or emtricitabine. As they belong to the same therapeutic class, the consequences of such a slip were not considered sufficiently serious to justify a formal objection although there is still a risk of dosing errors. It does highlight the risk created when INNs share too many letters (all but one letter “t” in this example), and should prompt the INN Expert Group to pre-empt such errors and develop programmes to detect situations where they could arise. One participant pointed out that changing a single letter of the proposed INN (to “maricitabine” for example) would dispel this risk.

A switch of consonants while writing naronapride could lead to confusion with nadroparin (particularly in French, where the INN is nadroparine). If, like prucalopride, marketed under the brand name Resolor°, naronapride is an oral formulation for the treatment of constipation or irritable bowel syndrome, the practical risk of confusing it with a low molecular weight heparin seems minimal however.
−tapide: help users to learn this stem. The prestem −tapide, used in granotapide and usistapide, is envisaged for microsomal triglyceride transfer protein inhibitors (10). Several participants found it sufficiently similar to −pride, the common stem for sulpiride derivatives, most of which are neuroleptics, particularly cinitapride (not marketed in France). INN users will require clear information about the stem −tapide to help them differentiate it from the stem −pride.

Misleading absence of common stems. The practice of using INN common stems to highlight the structural or pharmacological relationship between drugs of the same series can suggest that a stem is present when it is not, for example cadazolid, delamanid, setipiprant and vidupiprant.

One participant identified the potential for confusion between the antibacterial cadazolid and −azoline, the common stem used for antazoline derivatives used as antihistamines or local vasoconstrictors, and cited cefazolin (céfazoline in French) in which this stem has been used, but not in accordance with its definition. The risk appeared plausible to other participants, particularly on handwritten prescriptions, but the drugs’ very different conditions of use greatly reduce its likelihood, especially since the rare new antibiotics that are developed are subject to restricted use.

As delamanid contains no identifiable common stem, there are no clues as to its antibacterial activity, and instead this proposed INN brings to mind common stems such as −anib, −anide and −tinib; or substances ending in anin or anine (such as melanin or alanine). However, the participants did not identify any specific INNs liable to be confused with delamanid.

The risk of confusion between setipiprant, vidupiprant and aprepitant caused several participants to infer a risk of error between the common stem −pitant, used for neurokinin NK1 receptor antagonists (the receptors for the neurotransmitter, substance P) and what appears, from the two proposed INNs from List 104, to be a future prestem “−piprant”. It is noteworthy that the proposed indication is given for vidupiprant, while the mechanism of action is indicated for setipiprant: it is confusing to present proposed INNs in this way, without a common stem, and it ought to be harmonised.

Insufficiently obvious common stems. When common stems are insufficiently obvious, as in atopaxar and irosustat, the INN provides no clues as to the drug’s potential use.

The prestem −paxar was constructed on the basis of the English description of these drugs’ mechanism of action (protease activated receptor type 1 (PAR1) antagonists) (10). Participants who expected the INN for a platelet aggregation inhibitor to include the common stem −grel− were surprised. The inconsistency created by stems that focus sometimes on a drug’s mechanism of action, sometimes on its therapeutic use, makes it harder for healthcare professionals to learn INNs in a consistent way.

Several participants were unsure as to whether the antineoplastic irosustat is actually an enzyme inhibitor, warranting the use of the common stem −stat; and some are concerned about this common stem losing its significance and becoming less informative.

INNs that lack expected common stems. Uncertainty remains over a drug’s therapeutic activity when common stems are insufficiently obvious. This is particularly common among monoclonal antibodies when the general policies are apparently not applied: atinumab, enokizumab, gevokizumab, icrucumab, vesencumab (8).

Although atinumab is listed as an immunomodulator, it does not contain the common stem for immunomodulatory activity, −l(i). It is not clear that this INN contains the substem −n(e), which is still under review and corresponds to neural activity.

For icrucumab and vesencumab, the substem −c(t)− applies to cardiovascular drugs; some participants made the point that, as antineoplastics, the substem t(u) should have been expected instead. The −encu− portion of vesencumab calls to mind a swear word in French, which could shock French-speaking users.
In *enokizumab* and *gevokizumab*, the substem −k(i)− denotes the fact that the target is an interleukin. However, several participants identified a risk of confusion with antineoplastics, especially since no clinical information have been given for *gevokizumab*.

**Poorly comprehensible proposed INNs: foreseeable problems.** Most of the participants found *pomaglumetad methionil* long, complicated, hard to pronounce and to remember as nothing in the INN conveys its psychotropic activity.

**Risks of confusion with non-pharmaceutical terms.** Regarding *erteberel*, the participants were surprised not to find the common stem *estr* which is used for oestrogens because they were unaware of the prestem −berel for beta oestrogen receptor agonists. Some suggested “estreberel” or “estroberel” as alternatives. In addition, risks of confusion were identified with the brand name Enbrel®, and the medical term "vertebral".

**Risks of confusion with brand names.** Some proposed INNs resemble brand names, creating risks of medication errors, in particular: *bisegliptin*, *burixafor*, *egaptivon pegol* and *ixazombi*.

Bisepthine® is a French brand name for an antiseptic spray or solution, so the risk of mistakenly using an oral tablet for topical application or inadvertently swallowing antiseptic instead of *bisegliptin* is probably very low. The French drug regulatory agency (Afssaps) should be informed however, so that the information on the packaging and package leaflet can be consolidated; and the brand name changed if errors occur.

Several participants found *egaptivon pegol* similar to Septivon®, a French brand name for an antiseptic solution. The risk of confusion appears low given their different uses and dosage forms, but the clinical consequences could be serious because of the potential systemic effects of mistakenly injecting a quaternary ammonium compound.

The prestem −zomib is being considered for proteasome inhibitors (10). Several participants found it similar to the brand names Zomig® and ZomigOro® (*zolmitriptan*). Their different therapeutic indications greatly reduce the likelihood of confusion, which would be easily prevented by the routine use of INNs.

**In short,** our analysis of List 104 of proposed INNs shows that progress can still be made to improve the safety of INNs and that future common stems should be carefully chosen. Prescribers and users can only think in terms of INNs when these names are devised in a rigorous and consistent way.
References


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