

World Health Organization
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Prescrire's contribution to the WHO consultation on List 105 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 105 of proposed INNs, which was published in June 2011 (7).

Our critical analysis of the proposed INNs. Our analysis of 77 proposed INNs of List 105 was based on the 2009 list of common stems and its updates, on the INN database, on a database of drugs marketed in France, which enables searches on both brand names and INNs, and on *Prescrire's* own data search (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 37 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 37 contentious INNs whether a simple comment or a formal objection was more appropriate, and listed their arguments.

Five INNs that were proposed in previous lists, then amended in response to objections lodged by *Prescrire*, among others, were also examined: *bitopertin*, *fabomotizole*, *nintedanib*, *pegadricase* and *tofacitinib*.

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Formal objection

List 105 of proposed INNs includes *sepantronium bromide*, which correctly denotes a quaternary ammonium compound. However, this proposed INN of a cytotoxic could be confused with an antibacterial quaternary ammonium compound and also, due to some similarity between its "tronium" portion and the common stem **-tropium**, it could be confused with an atropine derivative used as a bronchodilator, like *ipratropium*, *tiotropium* and *oxitropium*. The consequences of confusing a cytotoxic antineoplastic with another type of drug are potentially fatal, so we are lodging a formal objection and requesting that this proposed INN be changed.

Amendments to previously proposed INNs

As a result of the objections lodged, the INN programme have changed *intedanib* (presented as an antineoplastic in List 102) to *nintedanib*; *obenoxazine* (presented as an anxiolytic in List 103) to *fabomotizole*; *paliflutine* (presented as a neuroleptic in List 103) to *bitopertin*; *pegsiticase* (an enzyme presented in List 103) to *pegadricase*; and *tasocitinib* (presented as an anti-inflammatory in List 103) to *tofacitinib*. These amendments were published in List 105 of proposed INNs (7). The participants who examined these amended INNs made the following comments.

Replacing *intedanib* (List 102) with *nintedanib* reduces the previously identified risk of confusion between *intedanib* and *indapamide*. This change eliminates the risk of selecting the wrong drug from an alphabetical list where the two look-alike INNs are in close proximity, but *nintedanib* and *indapamide* still sound alike in French, so a mix-up could still arise during verbal communication (13).

Tasocitinib (List 103) exposed patients to the risk of serious adverse effects due to potential confusion with the brand name Tazocilline^o (a combination of *piperacillin* and *tazobactam*) and with the antineoplastic *dacomitinib* (also from List 103), which contain the same sequence of vowels; *Prescrire* therefore lodged a formal objection (14). However, changing it to *tofacitinib* does not completely eliminate the risk of mistakenly administering a cytotoxic antineoplastic instead of an anti-inflammatory drug. If *tofacitinib* also proves to be an immunosuppressant, INN users will have to be appropriately informed.

Fabomotizole is the amended proposed INN for *obenoxazine* (List 103) against which *Prescrire* had lodged an objection in view of the serious consequences of confusing this proposed INN with *enoxacin*, a quinolone that contains the same sequence of vowels, and with *garenoxacin* and *ozenoxacin* (14). However, most of the participants understood *fabomotizole* to be an antifungal because it ends in "zole", like several common stems of drugs with antifungal properties (**-bendazole**, **-nidazole** and **-conazole**) (8).

The possibility of confusing the proposed INN *paliflutine* (List 103) with *palifermin* was identified during *Prescrire*'s proposed INNs workshop, although the risk was considered too low to warrant comment in *Prescrire*'s contribution. It has been amended to *bitopertin*, but the beginning of this word has vulgar connotations in French slang, denoting the male sex.

Other comments

Some proposed INNs generate a risk of medication errors, for a variety of reasons: some could be confused with other INNs; the sheer number of INNs in certain groups creates similarity; 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 brand names. Hence the following comments.

Risks of confusion with other INNs. Some proposed INNs, such as *amilomotide*, *etoxybamide*, *facinicine*, *ladarixin*, *lexibulin*, *lurbinctedin*, *navarixine* and *naloxegol* could be confused with other INNs.

Amilomotide closely resembles *amiloride* and, to a lesser extent, *amlodipine*. The risk of confusion is all the more insidious since the sub-stem **-motide** is not well known, as no immunostimulants of this type are in therapeutic use. When the first of these drugs becomes available, INN users will require clear information to address this issue.

A risk of confusion was identified between *etoxybamide* and *hydroxycarbamide*. It warrants mention because of the serious consequences of confusing a cytotoxic antineoplastic with a hypnotic. This risk of error will have to be managed by informing INN users and by clear labelling, perhaps by highlighting the parts of the INN that differ from *hydroxycarbamide* with capital letters, for instance *HYDRoxyCARbamide*.

A risk of mainly sound-alike confusion was identified between *ladarixin* and *navarixin* within list 105; this will have to be managed through clear labelling and package leaflets when these drugs are marketed.

A number of other proposed INNs could be confused with existing INNs: *facinicine* with *famotidine*, *lexibulin* with *eribulin*, *lurbinctedin* with *ivermectin*, and *naloxegol* with *naloxone* (where potential confusion already exists between *naloxone* and *naltrexone*); very clear labelling and package leaflets will therefore be required for all of these drugs when they are marketed.

The sheer number of INNs in certain groups creates similarity. Within-group similarity is particularly marked among monoclonal antibodies, and *ozoralizumab*, *pateclizumab* and *vatelizumab* are new examples of this problem.

There are now 36 humanised immunomodulatory monoclonal antibodies whose INN ends in **-lizumab** (8 of which are marketed in France). As the list grows, so does the risk of confusing sound-alike and look-alike INNs: *ozoralizumab* with *omalizumab*; *pateclizumab* with *palivizumab*; and *vatelizumab* with *pateclizumab*, which sound alike because they contain the same sequence of vowels.

Risks of confusion between common stems. Some of the proposed INNs could generate errors due to similarity between their common stems, for example *asunaprevir*, *lexibulin*, *milciclib* and *safotibant*.

The proposed INN *lexibulin* contains the same sequence of vowels as *desirudin* and *lepirudin*. The phonetic similarity between the suffix “-ibulin”, which contains the common stem **-bulin**, and the common stem **-irudin** that denotes *hirudin* derivatives, generates a risk of confusion. It could result in an antineoplastic being administered instead of an anticoagulant, a situation the participants considered critical.

The pre-stem **-ciclib** (denoting cyclin dependant kinase inhibitors) was considered very similar to the common stem **-cycline**, creating phonetic similarity between *milciclib* and *minocycline* that could cause errors when substituting one product for another or selecting a drug from a list on a computer screen. In view of the potentially serious consequences of such a mix-up, special attention will have to be paid to making **-ciclib** clearly legible in INNs containing this common stem.

While examining *safotibant*, we identified some common stems that sound and like similar to **-tibant**, the pre-stem for bradykinin receptor antagonists. One was **-fiban**, denoting antagonists of platelet-surface glycoprotein IIb/IIIa receptors (other than peptides or monoclonal antibodies), which are used as platelet aggregation inhibitors, and another was **-siban**, a pre-stem for oxytocin antagonists. These risks of confusion could be managed by highlighting the common stems in the labelling of the drugs concerned.

The common stem **-previr** is used for hepatitis C virus protease inhibitors. Inversion of the first two syllables of “-naprevir” in *asunaprevir* could lead to confusion with *amprenavir*. Such a slip would result in a patient with hepatitis C infection receiving treatment for HIV infection, as the common stem **-navir** is used for HIV protease inhibitors.

INNs that lack expected common stems. Inconsistent use of common stems and sub-stems causes confusion between INNs and uncertainty over the drug's therapeutic activity. This is particularly common among monoclonal antibodies when the general policies are apparently not applied, such as *crenezumab* and *blosozumab* (8,11).

Although *crenezumab* is listed as an immunomodulator, it does not contain the sub-stem for immunomodulatory activity, **-l(i)**. It is not clear whether this proposed INN contains the sub-stem **-n(e)-**, which is still under discussion and corresponds to neural activity. One participant suggested renaming it "crelizumab".

The same applies to *blosozumab*, which although listed as an immunomodulator lacks the sub-stem **-l(i)-**, and contains the sub-stem **-s(o)-**, denoting bone activity, although its potential therapeutic target is not indicated.

Risks of confusion with brand names. Some proposed INNs resemble existing brand names, creating risks of medication errors, in particular *cenderitide*, *evacetrapib*, *pegnivacogin* and *serelaxin*.

In contravention of resolution WHA46-19, INNs and common stems are used in many brand names (15). For example, the common stem for peptides and glycopeptides, **-tide**, is inappropriately used in the French brand names Bécotide°, Cetrotide°, Flixotide°, Seretide° and Vistide°. However, confusion between *cenderitide* and Seretide° is unlikely because they are administered by different routes. *Serelaxin* could be confused with Relaxine°, a valerian-containing drug that "Martindale: The Complete Drug Reference" lists as being available in Belgium, although no longer marketed in France.

A risk of confusion was also identified between the stem **-cetrapi-**, listed in USAN, and an *insulin* brand name, Actrapid° (16). This will have to be taken into consideration if *evacetrapib* is administered by injection. Finally, potential confusion between *pegnivacogin* and Nivaquine° (*chloroquine*) would be easily prevented by the systematic use of INNs.

Promotional connotations of some proposed INNs Most INN applications are submitted by pharmaceutical companies and sometimes serve their marketing strategy. The flattering overtones of several proposed INNs raised suspicions of a promotional intent, in particular *facinicline*, and *serelaxin*.

Whereas smoking cessation is far from easy, in French *facinicline* evokes "faci"le, meaning easy, as well as "fasci"nation. The proposed INN for relaxin H2, *serelaxin*, could infer that the drug has a relaxing or anxiolytic effect due to similarity to "serenity".

Poorly comprehensible proposed INNs: foreseeable problems. Most of the participants found the proposed INNs *cantuzumab ravtansine* and *indatuximab ravtansine* too long, complicated, and hard to pronounce and to remember, especially since *ravtansine* is not described in List 105 or the "Names for radicals, groups & others" list that was available during the consultation period (7,17).

Common stems that are difficult to understand. Contradictory or imprecise common stems are hard to understand and cause confusion about the drug's potential use. Problems of this nature were identified with *calaspargase pegol*, *conbercept*, *exeporfinium chloride* and *lenomorelin*.

Most participants did not understand the difference between *pegaspargase* and *calaspargase pegol*, but as they can only be prescribed by specialists in similar therapeutic indications, any mix-up between the two would have somewhat limited consequences.

Some of the participants are more familiar with the common stem **-relin** in GnRH (gonadotrophin releasing hormone) analogues (alias LH-RH analogues) and suggested there was a risk of mainly sound-alike confusion between *lenomorelin* and *leuprorelin*.

The presence of the common stem **-porfin**, which denotes benzoporphyrin derivatives, in the proposed INN of the bis-quaternary ammonium compound *exeporfinium chloride* indicates the substance's chemical structure and draws attention to the risk of photosensitisation. Although its antibacterial activity is related to the typical antiseptic activity of other quaternary ammonium compounds, the grounds for confusion put forward by the participants showed that they had an insufficient grasp of the chemistry of the substance to understand its name.

Angiogenesis inhibitors are identified either by the common stem **-anib-** or by their action on VEGF (vascular endothelial growth factor) receptors, indicated by the sub-stem **-ber-** of the common stem **-cept**, as in *conbercept*. As for all drugs with more than one activity and therapeutic indication, the common stem **-cept** can cause confusion with other classes of drug for INN users who are unfamiliar with its sub-stems.

Our analysis therefore exposes several pitfalls that hinder immediate comprehension of INNs: difficulty understanding sometimes complex chemical structures, falsely assuming that drugs whose INNs contain the same common stem act through the same mechanism, the existence of more than one common stem denoting the same potential use, etc.

A common stem can also be an effective means of promoting a particular mechanism of action. This was felt to be the case for the common stem **-flapon**, since it places so much emphasis on the substance's inhibitory action on 5-lipoxygenase activating protein (alias FLAP).

In summary, our analysis of List 105 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. In particular it reveals some counterintuitive mechanisms through which errors could arise, which should be taken into account when educating healthcare professionals about INNs. Prescribers and users can only think in terms of INNs when these names are devised and taught in a rigorous and consistent way.

A handwritten signature in black ink, appearing to read 'Bruno Toussaint'.

Bruno Toussaint
Publishing Director

**Review prepared and translated by the *Prescrire*
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