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Prescrire's contribution to the WHO consultation on List 107 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 (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 107 of proposed INNs, which was published in June 2012 (7).

Our critical analysis of the proposed INNs. Our analysis of the 90 proposed INNs of List 107 was based on the 2011 list of common stems, 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 21 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 21 contentious INNs whether a simple comment or a formal objection was more appropriate, and listed their arguments.

Four INNs that were proposed in a previous list, then amended in response to an objection, were also examined: *elbimilast*, *rovatirelin*, *pictilisib* and *sonidegib*.

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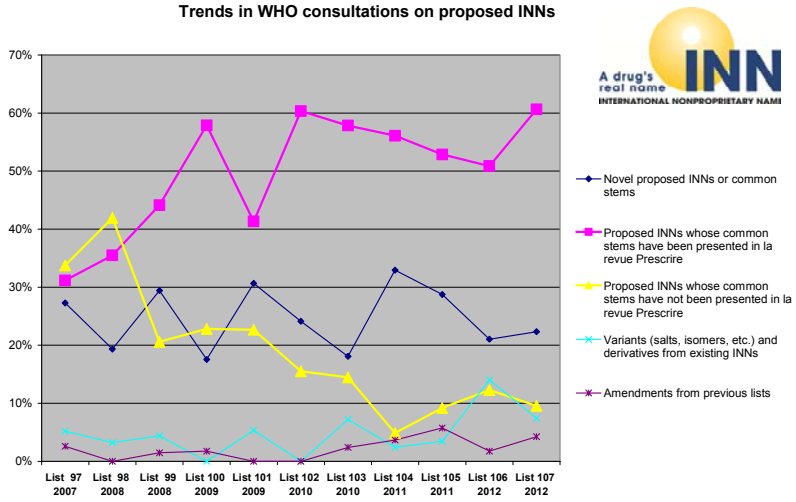
An unprecedented level of activity. This is the longest list of proposed INNs since *Prescrire* has been participating in the WHO's public consultations. These 94 proposed INNs comprise: 57 proposed INNs whose common stems have been presented in la revue *Prescrire* (61%); 9 proposed INNs whose common stems had not yet been presented at the start of our analysis of List 107 (10%); 21 novel proposed INNs or stems (22%); and 7 variants, such as salts and isomers (7%). The graph plotted to monitor *Prescrire*'s contributions to consultations on proposed INNs shows that this pattern of distribution has remained stable.



The examination of a list of proposed INNs provides an opportunity to discover some pre-stems, of which List 107 includes: **-buvir** (in *lomibuvir*) for RNA polymerase (NS5B) inhibitors; **-degib** (in *saridegib* and *sonidegib*) for antagonists of receptors associated with the smoothened protein (SMO receptor antagonists); **-lisib** (in *dactolisib*, *idelalisib*, *pictilisib* and *sonolisib*) for antineoplastic phosphatidylinositol 3-kinase inhibitors; **-lutamide** (in *enzalutamide*) for non-steroid antiandrogens; **peg-/pegol** (already in numerous INN as well in *empegfilgrastim*, *etirinotecan pegol*, *firtecan pegol* and *insulin peglispro*) for pegylated compounds; and **-rixin** (in *danirixin* and *elubrixin*) for chemokine CXCR receptor antagonists (7,10).

Formal objections

The risk of confusion or misunderstanding associated with some of the INNs proposed in List 107 was of sufficient concern to warrant a formal objection. These risks appear avoidable and resulted from similarity between INNs (*saridegib* and *sonidegib*) or similarity with existing common stems (*sepranolone*). We therefore request that these proposed INNs be re-examined, to prevent problems for patients and healthcare professionals in the future.

***Sonidegib* and *saridegib* too similar.** *Sonidegib* is the amended proposed INN for List 104's *erismodegib* (13). Although the suffix -ib in the pre-stem **-degib** helpfully indicates that these drugs are inhibitors, participants felt that the prefixes soni- and sari- were too similar, since they only differ by 2 letters. The proposed INNs *saridegib* and *sonidegib* therefore look and sound alike and are alphabetically close, so could be easily confused when written, spoken or selected from a list on a computer screen, etc.

Although erroneously substituting one of these antineoplastics for the other is unlikely to cause greater harm to the patient, it would be safer to abandon one of these INNs. We suggest amending *sonidegib,* due to its similarity with *sonolisib*, another INN proposed on List 107.

Foreseeable confusion between *sepranolone* and many other drugs. The stem **-olone** has been assigned to drugs with very different uses, which could cause *sepranolone* to be mistaken for a corticosteroid (e.g. *triamcinolone*), a hormone such as an androgen, or a quinolone. In addition, some participants misread *sepranolone* as *spironolactone*, or thought it might be mistaken for a beta-blocker such as *propranolol* through confusion with **-olol**, or for the selective serotonin reuptake inhibitor with the same prefix, *sertraline*.

All in all, we consider the risk of error in real-life healthcare situations to be very high, and such errors would have varied, unpredictable and potentially serious clinical consequences in view of the diversity of the indications of the drugs with which *sepranolone* is likely to be confused.

Other amendments to INNs proposed in previous lists

As a result of the objections filed, in addition to amending *erismodegib* (presented as an antineoplastic in List 104) to *sonidegib*, the INN programme changed: *pictrelisib* (presented as an antineoplastic in List 105) to *pictilisib*; *ravatirelin* (presented as a growth hormone release-stimulating peptide in List 104) to *rovatirelin*; and *ronomilast* (presented as a phosphodiesterase IV inhibitor in List 104) to *elbimilast*. These amendments were published in List 107 of proposed INNs (7). The participants who examined these amended INNs made the following comments.

The INN *elbimilast* replaces *ronomilast*, an INN proposed in List 104, to which *Prescrire* filed an objection due to its similarity with *roflumilast*, an anti-inflammatory drug that has been authorised in Europe and the US for chronic obstructive pulmonary disease (COPD) under the brand names Daxas° and Daliresp°.

The INN *pictilisib* replaces *pictrelisib*, an INN proposed in List 105. As for *rilpivirine*, the 4 ‘i’s in *pictilisib* make it special to pronounce.

The INN *rovatirelin* replaces *ravatirelin*, an INN proposed in List 104. *Rovatirelin* is the first INN to begin with "rova", and although it resembles the brand name Rovamycine° (*spiramycin*) should not pose any particular risk.

In summary, these three amended INNs seem acceptable.

Comments

Some proposed INNs generate a risk of medication errors, for a variety of reasons: some could be confused with other INNs, particularly when slightly deformed by a slip or lapse (misspelling, mispronunciation, misreading, mishearing or misremembering); some stems are easily confused with other stems; some INNs can be confused with brand names or with everyday, non-pharmaceutical terms; some common stems or INNs are difficult to interpret; and some INNs appear to have promotional connotations. Hence the following comments.

Confusion with other INNs. Some proposed INNs, such as *duligotumab, futuximab, latromotide* and *lirilumab*, could be confused with other INNs.

Latromotide and *lamotrigine* could be confused because both contain the sequence “la...mot.i.e”. Many participants were unfamiliar with the common stem **-motide**, which has not yet been presented in la revue *Prescrire*, so spontaneously thought of *lamotrigine* when speed reading. However, the distance between lam- and lat- on an alphabetical list of drugs on a computer screen should prevent selection errors, in spite of their visual and phonetic resemblance. And assuming that this peptide will only be injectable, their different routes of administration should also help prevent errors. Many INNs start with la-, and one participant mentioned potential confusion with one of these, *lanreotide*.

List 107 of proposed INNs contains 23 monoclonal antibodies, expanding an already overcrowded group, but we only identified risks of confusion for three of them: a risk of confusing *lirilumab* and *ipilimumab* would be generated by fonts in which upper case ‘i’

resembles lower case ‘L’; *futuximab* sounds like *rituximab*, but differ in the first syllable; and *duligotumab* was considered similar to *golimumab*.

We identified some other, more theoretical, risks of confusion between INNs: between *elubrixin* and *eribulin*; between *lifitegrast* and *filgrastim*; and between *neceprevir* and *boceprevir* (note that an accent is missing from the French version, which should read *nécéprévir*).

Confusion generated by slips and lapses. The participants identified certain slips and lapses that could create confusion between INNs, particularly with *lomibuvir*, *pradimotide* and *quisinostat*.

Inversion of just 2 consonants would generate a risk of confusion between *quisinostat* and *quinisocaine*.

Such slips or lapses occur more readily with unfamiliar stems, and when INNs share a similar beginning and end. The common stems **-motide** and **-buvir** have not yet been presented in la revue *Prescrire*, because no drugs of these types are yet marketed, hence the potential confusion identified between *lomibuvir* and *lopinavir*, and between *pradimotide* and *pralidoxime.*

Confusion between stems. Some of the proposed INNs could generate errors due to confusion between stems, e.g. *bevenopran* and *enobosarm*.

In *bevenopran*, the pre-stem -opran proposed by the United States Adopted Names Council (USANC) brings to mind *citalopram* and *escitalopram*. Although -opram is not a common stem (*citalopram* and *escitalopram* are exceptions of the stem -**oxetine**), this risk of confusion must be taken into account if the INN programme considers adopting -opran (-mopran or -nopran might be preferable).

The USANC has proposed the pre-stem -sarm for androgen receptor agonists (SARM: selective androgen receptor modulator). However, SARM is also the French acronym for meticillin-resistant *Staphylococcus aureus*, so some French-speaking healthcare professionals will assume that the suffix -sarm denotes an antibiotic.

In addition to –opran and –sarm, the examination of List 107 of proposed INNs provided an opportunity to discover other pre-stems proposed by USANC: -cirnon for CC chemokine receptor antagonists (CCR receptor antagonists), in *vercirnon*; -fol- for substances incorporating folic acid, in *vintafolide*; -golix for gonadorelin (GnRH) antagonists, in *relugolix*; -napant for inhibitors of inhibitor of apoptosis proteins (IAP inhibitors), in *birinapant*; -rian for ryanodine receptor modulators, in *aladorian*; -trombopag for thrombopoietin receptor agonists, in *avatrombopag*; and -unistat for nitric oxide synthase inhibitors, in *cindunistat*.

Confusion with brand names. Some proposed INNs resemble existing brand names, creating a risk of medication errors, in particular *ensereptide*, *fasiglifam*, *rovatirelin* and *vercirnon*.

Confusion between the following proposed INNs and drugs marketed in France were considered potentially dangerous: between *ensereptide* and Seretide° (a suspension for inhalation containing *salmeterol* + *fluticasone*, although their different routes of administration reduce the risk); between *fasiglifam* and Fasigyne° (*tinidazole*), firstly because they share the prefix fasig- and secondly because the "fam" suffix is phonetically identical to the French word for woman (*femme*), suggesting a gynaecological indication; between *rovatirelin* and Rovamycine° (*spiramycin*); and between *vercirnon* and Vercyte° (*pipobroman*).

A theoretical risk of confusion was suggested between *oprozomib* and Zomigoro° (*zolmitriptan*), but it would require two simultaneous slips: confusion between the common stem **-zomib** and zomig and inversion of the start and the end of the INN; the systematic use of INNs eliminates the possibility of errors of this kind.

Confusion with non-pharmaceutical terms. Some common stems (e.g. **-lisib**) and INNs (e.g. *auriclosene*) evoke everyday French terms. Other proposed INNs contain parts that have negative connotations in French (*bezlotoxumab*, *enobosarm* and *ibrutinib*), or contain proper nouns (*enobosarm*) or forenames (*aladorian*, *danirixin*, *lucitanib* and *omarigliptin*).

The pre-stem **-lisib**, denoting a phosphatidylinositol 3-kinase inhibitor, is similar to the French adjective "*lisible*" meaning legible (List 107 contains four such drugs: *dactolisib*, *idelalisib*, *pictilisib* and *sonolisib*).

"Auriclo" suggested "auriculo" to six participants, i.e. a treatment for auricular use. In fact, a number of French brand name drugs start with Auri: Auricularum° and Aurigoutte° are currently available on the French market.

The prefix "bez" in *bezlotoxumab* is phonetically identical to the French word "*baise*", a vulgar slang term meaning copulates, while its "loto" component, meaning lottery, suggests that the treatment will not necessarily work! Ultimately, the components of everyday language in this INN make it easier to remember.

In *enobosarm*, the prefix enobo is a common proper noun of African origin, also used by some businesses; furthermore, it brings to mind the bonobo chimpanzee, renowned for its sexual behaviour, which could help users remember its properties as an androgen receptor agonist!

The beginning of *ibrutinib* resembles the pejorative French word "*abruti*", meaning idiot.

Although unlikely to cause any problems, several INNs contain forenames used in French and other languages: Dani, the diminutive of Daniel, in *danirixin*; Dorian, derived from Théodore, in *aladorian*; Lucie in *lucitanib* (and also in *lucimycin*, a recommended INN); and Omar and Marie in *omarigliptin*.

INNs or common stems that are difficult to interpret. Some INNs were difficult to understand because their common stems provide no clues as to their potential use, e.g. *orticumab*. Some complex INNs appeared obscure to participants who did not know their chemical structure, which could lead to errors: *latanoprostene bunod*, *pefcalcitol* and *zoptarelin doxorubicin*.

In *orticumab*, the combination of the stem **-mab** with the sub-stems **u** and **-c(u)-** failed to suggest its anti-inflammatory activity, partly because participants lacked experience with the use of monoclonal antibodies for this function, and partly because List 107 also includes *enoticumab*, presented as an antineoplastic.

In *latanoprostene bunod*, the term *bunod* for the 4-(nitrooxy)butyl radical does not currently feature in the list of radicals, and several participants did not know what it meant. Confusion with *latanoprost* could lead to errors when selecting these drugs from a list on a computer screen, especially since the INN *latanoprostene bunod* is so long.

Participants who did not read the chemical description of *pefcalcitol* did not realise that pef refers to the pentafluoropropylacetamide that this substance contains; and read it as "pegcalcitol", which sounds like an INN but does not exist.

For *zoptarelin doxorubicin*, participants who understood that it is a complex linked by glutaric acid were concerned about the risk of prescribing errors due to confusion with *doxorubicin* when both substances become available.

When referring to *evogliptin* in French with the definite article (*l'évogliptine)*, it sounds like "lévogliptine", which does not exist but would be assumed to be an enantiomer.

Proposed INNs with promotional connotations? Most INN applications are submitted by pharmaceutical companies. Some of the INNs proposed appear to serve a marketing function: *cebranopadol*, *evogliptin*, *futuximab*, *fasiglifam*, *fasinumab* and *idelalisib*.

The following prefixes appear to have a promotional intent: the prefix cebrano in *cebranopadol* evokes a cerebral target, suggesting an analgesic promoted for headache; the prefix evo in *evogliptin* evokes “evolution”, suggesting that the drug belongs to the next generation of gliptins, therefore better; similarly, the prefix futu in *futuximab* suggests that it

is a drug of the "future"; and the prefix fasi in *fasiglifam* and *fasinumab* has the positive connotations of the French word "*facile*", meaning easy.

Idelalisib is difficult to pronounce and several participants read it as "ideallisib", or heard it as "ideal lysine" (the 'y' and the 'i' being phonetically identical in French). Again, the term ideal is very flattering.

In summary, our analysis of the long list of proposed INNs in List 107 raises many questions about INN comprehensibility and the associated risk of error. Our analysis of the pre-stems, most of which were proposed by the USANC, shows that future common stems should be chosen carefully. The problems identified reveal some occasionally complex mechanisms through which errors could arise, which should be carefully taken into account when educating healthcare professionals about INNs. Healthcare professionals and patients can only think successfully in terms of INNs when these names are devised and taught in a rigorous and consistent way.

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Review prepared and translated by the *Prescrire* Editorial Staff with the participation of healthcare professionals from the *Association Mieux Prescrire*.
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References

1- Prescrire Rédaction "Prescrire et penser en DCI: une bonne pratique professionnelle" *Rev Prescrire* 2000; **20** (209): 606-623.

2- Prescrire Rédaction "DCI: la priorité" *Rev Prescrire* 2005; **25** (265): 641.

3- Prescrire Rédaction "Patients-soignants: priorité à la DCI" http://www.prescrire.org/cahiers/dossierDciAccueil.php

4- International Society of Drug Bulletins (ISDB) "Special issue on INNs" *ISDB Newsletter* November 2006; **20** (3), 27 pages.

5- Prescrire Rédaction "Confusion entre noms commerciaux: entretenue par les agences du médicament" *Rev Prescrire* 2007; **27** (290): 941-945.

6- Council of Europe - Expert Group on Safe Medication Practices "Creation of a better medication safety culture in Europe: Building up safe medication practices" 19 March 2007: 257 pages.

7- WHO "Proposed International Nonproprietary Names: List 107" *WHO Drug Information* 2012; **26** (2): 157-235.

8- WHO "The use of stems in the selection of International Nonproprietary Names (INN) for pharmaceutical substances" WHO/EMP/QSM/2011.3 + Addendum 1, 187+3 pages.

9- WHO "International Nonproprietary Names (INN) for Pharmaceutical Substances" Site mednet.who.int.

10- WHO "Pre-stems: Suffixes used in the selection of INNs – June 2012" 7 June 2012; 5 pages.

11- WHO "International Nonproprietary Names (INN) for biological and biotechnological substances" Update 2011; 62 pages.

12- Thériaque database www.theriaque.org. Free access.

13- WHO "Proposed International Nonproprietary Names: List 104" *WHO Drug Information* 2010; **24** (4): 351-418.