

World Health Organization  
**Raffaella Balocco**  
INN Programme Manager  
Quality Assurance & Safety :  
Medecines  
CH 1211 GENEVA 27  
SUISSE

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## Prescrire's contribution to the WHO consultation on List 114 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 routine 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 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 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). A group of committed pharmacy lecturers and students, and hospital-based and front-line health professionals joined *Prescrire's* editorial staff to participate in this phase of the consultation on List 114, which was published in December 2015 (a)(9).

**Our critical analysis of the proposed INNs.** Our analysis of the 91 INNs proposed in List 114 and the 3 amendments to INNs proposed in previous lists was based on the following resources: the 2013 list of common stems and its addenda; 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; a database of drugs marketed in France, which enables 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 (10-17).

*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, and for the 3 amendments, the participants assessed the risk of confusion and/or misunderstanding, along with the potential clinical consequences of such errors. Finally, they proposed comments for each of these 24 INNs, listing their arguments.

**Prescrire**  
83 boulevard Voltaire  
75558 PARIS CEDEX 11  
FRANCE  
Tél. : (33) (0)1 49 23 72 80  
Fax : (33) (0)1 49 00 33 20  
contact@prescrire.org

Site internet  
Web site  
www.prescrire.org

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Tél. : (33) (0)1 49 23 72 86  
Fax : (33) (0)1 49 23 76 48  
relationsabonnes@prescrire.org  
international@prescrire.org

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Fax : (33) (0)1 49 23 76 48  
formations@prescrire.org

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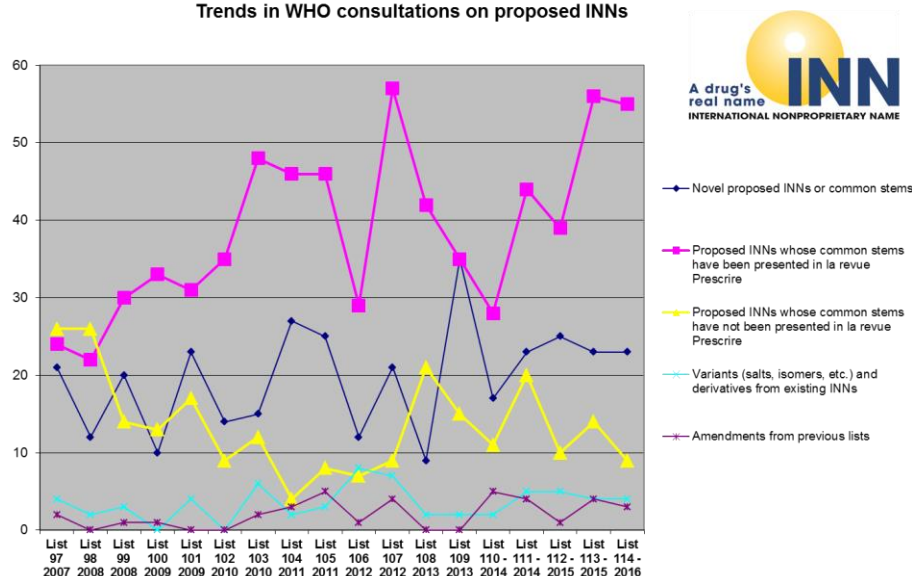
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**A long list.** The previous list was among the longest we have examined and contained 97 proposed INNs and 4 amendments. List 114 contains a similar number and includes: 23 novel proposed INNs or common stems (24%); 55 proposed INNs whose common stems have been presented in the journal *Prescrire* (59%); 9 proposed INNs whose common stems have not yet been presented in *Prescrire* (10%); 4 variants (such as salts and isomers) and INNs that have undergone specific modifications (4%); and 3 amendments to INNs proposed in a previous list (3%). The graph plotted to monitor *Prescrire's* contributions to the WHO's public consultations on proposed INNs shows that the number of novel proposed INNs or stems remains as high as in previous consultations.

Trends in WHO consultations on proposed INNs



**Prescrire**  
83 boulevard Voltaire  
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FRANCE

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Our examination of List 114 of proposed INNs also provided an opportunity to familiarise ourselves with some future stems: **-caftor** for CFTR protein modulators; **-closporin** for drugs derived from *ciclosporin*; **-dacin** for antibiotics that are DNA gyrase and topoisomerase IV inhibitors; **-dustat** for hypoxia inducible factor (HIF) prolyl hydroxylase inhibitors; **-gr(o)-**, a substem for monoclonal antibodies that target skeletal muscle mass related growth factors and receptors; **-pirdine** for serotonin (5-HT<sub>6</sub>) receptor antagonists; **-siban** for oxytocin antagonists; **-teronel** for non-steroid antiandrogens; **-trigine** for sodium channel blockers, signal transduction modulators; and **-vet-**, a substem for monoclonal antibodies for veterinary use (12).

This list also includes some planned stems proposed by the US drug nomenclature committee, the USAN Council: **-dostat** for indoleamine 2,3-dioxygenase 1 (IDO1) inhibitors; **-glustat** for glycosyltransferase inhibitors; **-netide** for peptides and glycopeptides for which neurological uses have been claimed; **-potide** for peptides and glycopeptides for which uses in prostate cancer have been claimed; and **-toran** for Toll-like 4 receptor (TLR4) antagonists (15).

### Formal objections

The risk of confusion or misunderstanding associated with some of the INNs proposed in List 114 was of sufficient concern to warrant 3 formal objections.

Our first two objections relate to INNs proposed for monoclonal antibodies conjugated to cytotoxic active substances: *laprituximab emtansine* and *naratuximab emtansine*. These two-term proposed INNs add to the list of similarly constructed INNs for monoclonal antibodies conjugated to cytotoxic agents for which *Prescrire* has already filed objections in previous consultations (18,19). We therefore repeat our request for the revision of the INNs of all monoclonal antibodies conjugated to cytotoxic agents.

Our third objection concerns *nalbuphine sebacate*, on the grounds that the proposed INN does not reflect the fact that each molecule of *nalbuphine sebacate* contains 2 molecules of *nalbuphine*. The absence of any indication of this “2 in 1” composition makes misunderstandings and overdoses far too easy.

**Two-term INNs for monoclonal antibodies conjugated to cytotoxic agents are not safe.** As in our previous contributions, we would like to draw the attention of the INN programme once more to the dangerous current approach to the naming of monoclonal antibodies conjugated to cytotoxic active substances, a risk identified by all of the participants in our analysis (18,19).

If healthcare professionals do not know the precise meaning of the second term and assume it refers to a radical devoid of pharmacological activity rather than a second active substance, they may administer the conjugate instead of the naked antibody, resulting in a serious overdose. The fact that these cytotoxic moieties are described in the WHO list of radicals and groups trivialises their dangers (14). It would make more sense to present them more explicitly as active substances, especially since some contain stems or pre-stems (such as **-dotin**, **-tecan** and **-xetan**), and the suffix “-tansine” also seems destined to become a stem.

We urge the INN programme once more to devise appropriate measures to make the INNs of monoclonal antibodies conjugated to cytotoxic agents more distinctive, and to do so urgently before this group becomes too large to assign them all a safer INN.

**Clearly indicate the presence of two molecules in one.** *nalbuphine sebacate* consists of two molecules of *nalbuphine* linked by the *sebacate* radical described at the end of List 114. It is important that the INN indicates this fact, to make healthcare professionals aware that it is not to be used at the same dose as *nalbuphine hydrochloride*, a drug marketed in many countries. Since each molecule of *nalbuphine sebacate* is more than likely to release two molecules of *nalbuphine* into the body, confusion with *nalbuphine hydrochloride* would result in an overdose.

Some participants suggested the addition of the prefix “di” or “bi” to the term “nalbuphine” to signal the presence of a double dose. The likelihood of confusion seems even greater in English than in French, because “nalbuphine” is the first term in both *nalbuphine sebacate* and *nalbuphine hydrochloride*.

Prescrire  
83 boulevard Voltaire  
75558 PARIS CEDEX 11  
FRANCE  
  
Tél. : (33) (0)1 49 23 72 80  
Fax : (33) (0)1 47 00 33 20  
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## Comments

The participants identified a number of proposed INNs that could generate medication errors for a variety of reasons: confusion with a brand name; confusion with another INN; confusion between their stem, pre-stem or suffix and another stem, pre-stem or planned stem proposed by the USAN Council; and the complexity of certain INNs.

**Risk of confusion with a brand name.** Many participants felt that one of the proposed INNs is particularly liable to confusion with a brand name: *avacopan*, which looks and sounds like the brand name *Acupan*° (*nefopam*). INN prescribing would not eliminate this risk entirely, due to similarity between the suffix “fopam” in *nefopam* and the suffix “copan” in *avacopan*.

**Risk of confusion with another INN.** Some proposed INNs could be confused with other INNs, in particular: *fonadelpar*, *lendalizumab*, *leniolisib*, *pogalizumab*, *raxatrigine* and *ruclosporin*.

Some participants identified a risk of confusion between *fonadelpar* and *fondaparinux*, due firstly to similarity between the prefixes “fonad-” and “fonda-”, and secondly to the presence in both of “par”, which in *fondaparinux* hints at its use as a heparin substitute but is not the case for *fonadelpar*.

The potential for confusion identified between *lendalizumab* and *benralizumab* (List 102) derives from the fact that they have 10 out of 12 letters in common (20).

A risk of confusion was identified between the proposed INN *leniolisib* and the proposed INN *tenalisib*, due to visual resemblance between “len” and “ten”, accentuated

by their identical stem, and with the INN *lenvatinib*, which starts with the same three letters and due to the similarity we have previously highlighted between the stems **-tinib** and **-lisib** (21,22).

Phonetic and visual resemblance was identified between *pogalizumab* and both *plozalizumab* and *omalizumab*, and between *raxatrigine* and *rasagiline*.

Finally, although the company has claimed that *ruclosporin* will be for veterinary use, there is a high likelihood of confusion with *ciclosporin* if one day it is used in human medicine.

**Risks of confusion associated with stems and pre-stems.** Visual and phonetic similarity between the pre-stem **-pirdine** and the stem **-dipine** could cause *intepirdine* to be confused in particular with *nifedipine* and *nitrendipine*. We already reported this risk in our contributions to Lists 102 and 106 (23,24).

In *olumacostat glasaretil*, the suffix “costat” containing the stem **-stat** could lead to confusion with the stems **-inostat** and **-mostat**, with the pre-stem **-dustat** present in the proposed INN *vadadustat*, and also with the planned stem **-dostat**, proposed by the USAN Council, present in the proposed INN *epacadostat*.

The stem **-siran**, present in *cemdisiran*, *givosiran* and *inclisiran*, is very similar to the pre-stem **-siban**, present in the amendment *nolasiban*, a similarity we have already reported (21,25).

In *acebilustat*, the suffix “lustat” containing the stem **-stat** could be confused with the pre-stem **-dustat** present in *vadadustat* and with the planned stem **-glustat** present for example in the amendment *venglustat*.

**Complex INNs: education required.** Many participants consider the complexity of certain INNs makes them difficult to memorise and pronounce, and hampers communication between health professionals when discussing patient care. Notable examples in List 114 are the gene therapy products *lenadogene nolparvovec* and *mesmulogene ancovacivec*, especially since the participants were not all entirely familiar with the rules governing the naming of these products. In reality, these INNs contain all the information required to understand the nature of the drug. *Prescrire* helps health professionals learn the INN system through its regular “Common Stem” column: once they understand the rules of INN construction they can proceed to the next step, that of investing the effort required to memorise INNs.

Additional help is now available in the form of the INN programme’s “School of INN”, a welcome initiative to promote education in INN nomenclature for health professionals from their initial university training (26).

**Amendments.** Amendments to INNs proposed in previous lists are subjected to risk analysis in the same way as newly proposed INNs. Having received no feedback from the INN programme since our contribution to the public consultation on List 111, we do not know whether the amendments in List 114 to INNs proposed in List 112 were a result of our comments on List 112 (27).

The proposed INN *ibiglustat* has now been replaced by *venglustat*, eliminating the potential for confusion we reported with *eliglustat* (18,28).

We filed an objection for *erlosiban* because of the risk of confusion with *erlotinib*. Its replacement by *nolasiban* eliminates this risk (18,28).

The replacement of *asinercept* by *asunercept* certainly reduces the risk of confusion we reported with the brand name Aricept® (18,28). However, the new prefix could lead to selection errors when using electronic prescribing systems, by confusing *asunaprevir* with *asunercept* in an alphabetical list.

**In summary.** List 114 shows that the nomenclature of monoclonal antibodies conjugated to cytotoxic agents remains a serious problem. If our objection is not taken into account, the risks of confusion will only intensify as the number of such conjugates increases, as it inevitably will.

Prescrire  
83 boulevard Voltaire  
75558 PARIS CEDEX 11  
FRANCE

Tél. : (33) (0)1 49 23 72 80  
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*Prescrire* is proud to have contributed for many years to the work undertaken by the WHO to instigate and maintain a common international language for drugs. We trust that the creativity and perseverance of which the INN programme is capable will be mobilised to address the issues we have raised, in order to improve the quality and safety of drug treatment, in the interest of patients.



Bruno Toussaint  
Publishing Director

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