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
contact@prescrire.org

Site internet
Web site
www.prescrire.org

Relations Abonnés :

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

Formations Prescrire
Tél. : (33) (0)1 49 23 72 90
Fax : (33) (0)1 49 23 76 48
formations@prescrire.org

Association Mieux Prescrire

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Independant organisation
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World Health Organization
Raffaella Balocco
INN Programme Manager
Quality Assurance & Safety: Medecines
CH 1211 GENEVA 27
Switzerland

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Prescrire's contribution to the WHO consultation on List 112 of proposed INNs

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Since 1981, and also 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 been advocating the routine use, by both healthcare professionals and patients, of international nonproprietary names (INNs), which are clearer, safer and more informative than 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).

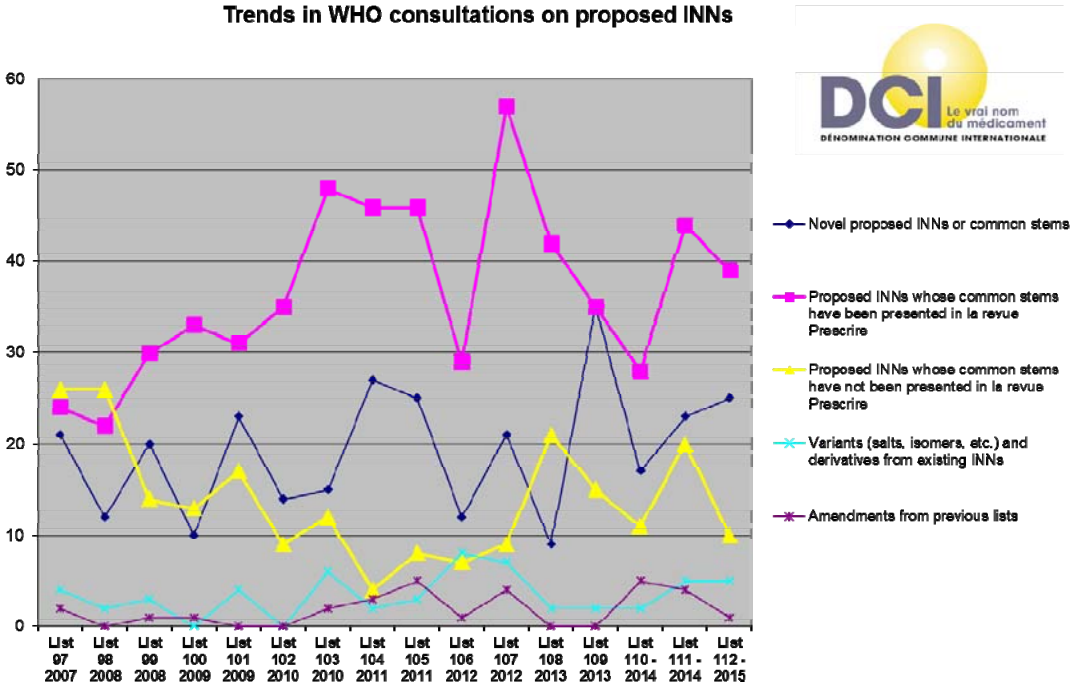
However, even with the INN system there is a residual risk of confusion, partly owing to the sheer number of INNs now in circulation. A report from the Council of Europe, which recommends the use of INNs, calls for active participation in the public consultations on proposed INNs organised by the World Health Organization (WHO), in order to identify any risk of confusion during their clinical use (8). The editorial staff of *Prescrire*, joined by a group of lecturers and students from a school of pharmacy, at the initiative of a committed academic, and some hospital-based and primary care health professionals, are participating in this phase of the consultation on List 112, which was published in January 2015 (**a**)(9).

Our critical analysis of the proposed INNs. Our analysis of the 78 proposed INNs and one amendment to a previous list presented in List 112 was based on the 2013 list of common stems, the INN database, a database of drugs marketed in France, which enables searches on both brand names and INNs, and *Prescrire*'s own data search (10-15).

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 amendment, 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 22 INNs, listing their arguments.

Fewer INNs than the previous list. While List 111 contained 92 proposed INNs and 4 amendments, List 112 is shorter and includes: 25 novel proposed INNs or common stems (32%); 39 proposed INNs whose common stems have been presented in the journal

Prescrire (49%); 10 proposed INNs whose common stems have not yet been presented in *Prescrire* (12%); 5 variants (such as salts and isomers) and INNs that have undergone specific modifications (6%); and 1 amendment to an INN proposed in a previous list (1%). The graph plotted to monitor *Prescrire*'s contributions to the WHO's public consultations on proposed INNs shows that, in comparison with the previous consultation, List 112 includes a few more novel proposed INNs or stems.



Our examination of List 112 of proposed INNs also identified two planned pre-stems proposed by the United States Adopted Names Council (USANC): -becestat for beta-secretase inhibitors, in *verubecestat*, and -forant for histamine H_4 receptor antagonists, in *toreforant*.

Formal objections

The risk of confusion or misunderstanding associated with some of the INNs proposed in List 112 was of sufficient concern to warrant 3 formal objections, relating to 6 proposed INNs: *indusatumab*, *indusatumab vedotin* and *vandortuzumab vedotin*, and more generally to the INNs of other monoclonal antibodies conjugated to cytotoxic drugs; *erlosiban*, due to the risk of confusion with *erlotinib*; and *crisaborole* and *epetraborole*, in which the suffix "-borole" deserves consideration as a possible common stem.

Risks associated with the naming of monoclonal antibodies conjugated to cytotoxic drugs. *Indusatumab vedotin* is a monoclonal antibody covalently bound to the cytotoxic drug monomethyl auristatin E (MMAE), a spindle poison also known as *vedotin*. It is likely that the toxic dose of *indusatumab vedotin* is much lower than that of *indusatumab* used alone. If healthcare professionals do not know the precise meaning of the second term, and assume it refers to a harmless substituent rather than a second active substance, this proposed INN could cause overdoses when *indusatumab vedotin* would be administered at a dose of *indusatumab*. This type of error has already occurred with *trastuzumab emtansine*, due to confusion with *trastuzumab*, including deaths during the clinical trials of *trastuzumab emtansine* (List 103 of proposed INNs), prompting the IMSN, its members and various drug regulatory agencies to issue safety alerts about the serious consequences of this error (16-23). The Canadian authorities have already expressed their

concerns to the WHO, and a substitution process of the INN *trastuzumab emtansine* is expected (24).

One way of drawing attention to the cytotoxic moiety and of differentiating these conjugated antibodies more clearly from the unconjugated form would be to reverse the order of the terms to state the cytotoxic moiety first. However, this solution is unfeasible given that several antibodies conjugated to the same cytotoxic drugs have already been named, and List 112 contains another one, *vandortuzumab vedotin*. The IMSN has identified 15 recommended INNs of conjugated monoclonal antibodies affected by this problem and recently asked the INN programme to review the rules governing the nomenclature of combination drugs containing a cytotoxic moiety, to enable healthcare professionals to recognise them more easily (**b**)(25).

***Erlosiban*: risky prefix.** *Erlosiban* and *erlotinib* could be confused because they share the same prefix, creating a risk of error when selecting one of these drugs from an alphabetical list on a computer screen. Such an error could lead to the administration of the cytotoxic drug *erlotinib* to a pregnant woman, harming the unborn child by inhibiting the tyrosine kinase associated with the human type I epidermal growth factor receptor. *Erlosiban* could also be confused with *retosiban* (not yet marketed) through a slip, involving inversion of the first two letters of *retosiban* to produce “ertosiban”, which closely resembles *erlosiban*. Some participants suggested replacing the prefix “erlo-” with a more informative prefix, signalling the presence of the biphenyl ring that characterises the chemical structure of *erlosiban*.

-**borole: a waste of a potential stem?** All the participants perceived the suffix “-borole” in *crisaborole* and *epetraborole* as a stem and, indeed, both drugs contain a benzoxaborole ring, as does *tavaborole* (proposed in List 106). However, the potential therapeutic uses claimed by the pharmaceutical companies for these three drugs are different: *crisaborole* is listed as a nonsteroidal anti-inflammatory drug, *epetraborole* as an antibacterial, and *tavaborole* is an antifungal. This would preclude any future use of -borole as a common stem to denote a specific pharmacological activity. The participants therefore felt that this choice is not conducive to the use of INNs by healthcare professionals in their everyday practice. The aim of our objection to the INNs *crisaborole* and *epetraborole* is to prevent the risks of incomprehension and misinterpretation, while also safeguarding a potentially useful stem.

Comments

Some proposed INNs could generate medication errors, for a variety of reasons: some contain stems or pre-stems that could be confused with other stems; some lack a stem but contain a sequence of letters resembling a stem; some INNs could be confused with other INNs; others are incomprehensible or liable to be misunderstood because they are too complex or have an uninformative or misleading prefix; and some are confusing due to a resemblance to a brand name. So many reasons reveal the need for a broad teaching of INN.

Confusion between stems or pre-stems. Some of the proposed INNs could generate errors due to similarity between their stem or pre-stem and another stem, in particular the proposed INNs containing the stem -**ciclib** or the pre-stem -**fadine**.

The stem -**ciclib,** adopted for cyclin-dependent kinase inhibitors and present in *abemaciclib*, was felt to be too similar to the common stem -**cycline**. This risk of confusion was noticed by all the participants, and will have to be taken into account, especially since tetracycline antibiotics are so numerous and commonly used.

The pre-stem -**fadine**, proposed for monoamine transport inhibitors and present in *centanafadine*, was felt to look and sound too similar to the stem -**tadine**, adopted for tricyclic histamine-H_1 antagonists.

During their analysis, the participants were surprised by some similarities between stems, in particular: -**nercept** and -**bercept** (*asinercept* and *aflibercept* containing a sequence of similar syllables); -**nicline** and -**cycline**; remarks that denote a lack of awareness about common stems and still require pedagogy among health professionals.

INNs without a stem that contain a sequence of letters resembling a stem. Some of the proposed INNs in List 112 could create confusion because they lack a stem but contain a sequence of letters resembling a stem, for example: *eleclazine*, *emeramide*, *gepotidacin* and *ridinilazole*.

The suffix “-azine” in *eleclazine* resembles several stems: -**dralazine**, denoting hydrazinephthalazine derivatives used as antihypertensive drugs which can be conceived as *eleclazine* also seems to have vasodilatory effects; -**salazine**, used for certain salicylic acid derivatives; and especially a large number of substances whose INN ends with “-azine” and pertaining to various pharmacologic classes (phenothiazines used for antihistamines, or neuroleptics; cytotoxics; antibacterials; etc.).

The suffix “-ramide” in *emeramide* resembles the stems -**lutamide**, used for non-steroid antiandrogens, and -**pamide**, denoting sulfamoylbenzoic acid derivatives used as diuretics. The presence of “-mer-” was interpreted as the stem -**mer**-, used to identify polymers. Many INNs end in “-amide” (over 200 INNs identified). In other words, the INN *emeramide* do not provides pharmacotherapeutic information on the substance.

The suffix “-dacin” in *gepotidacin* resembled the stems: -**oxacin**, used for quinolones; -**kacin**, denoting the subgroup of drugs produced by *Streptomyces kanamyceticus*. The List 112 does not explain if *gepotidacin* is close from these antibiotics.

The suffix “-nilazole” in *ridinilazole* resembles the stem -**nidazole**, denoting antibacterial and antiparasitic drugs derived from *metronidazole*. This is understandable since its denotes also imidazole derivatives. A risk of confusion was identified between *ridinilazole* and *tinidazole,* which has 8 letters in common with *ridinilazole* and a very similar sequence of syllables.

In summary, it is difficult to understand INNs that lack a stem or contain a stem that is insufficiently obvious.

Confusion with other INNs. Some proposed INNs could be confused with other INNs, in particular: *ibiglustat* and *nemolizumab*.

A risk of confusion was identified between the phonetically and visually similar *ibiglustat* and *eliglustat*, identical in all but their first two letters.

Nemolizumab, *mepolizumab* and *vedolizumab* all contain the same sequence of vowels and the same common stem, -**lizumab**. The risk of confusing the prefixes “nemo-”, “mepo-” and “vedo-” through a slip is enhanced by the fact that these eleven-letter INNs vary at only two positions.

Overly complex INNs. Many participants also pointed out that some of the proposed INNs are too complex, which would make them difficult to memorise and pronounce, and would hamper communication about patient care between health professionals, especially since the some of the rules governing their construction were not yet known to the participants, for example for: *axalimogene filolisbac*, *neladenoson dalanate* and *spanlecortemlocel*.

As well as being difficult to memorise due to its complexity, the gene therapy product *axalimogene filolisbac* contains some substems that have not yet been described by the INN programme, such as “-lis-” and “-bac” (13).

The participants did not understand the significance of the term *dalanate* in *neladenoson dalanate*, corresponding to a L-alanyl-L-alaninate ester, a term that they did not found in the list of radicals and which has had a different meaning in *dalanated insulin*.

As the rules for constructing INNs for cell therapy products are currently being developed, the participants found *spanlecortemlocel* incomprehensible. When these drugs becomes available for clinical use, the syntax used to devise their INNs will therefore have to be explained.

A misleading prefixe from a chemical point of view. Some INNs suggested chemical features that the drug does not possess, in particular: the prefix “indi-” in *indimilast* misleadingly suggests the presence of an indole, indane or indene ring.

It would be helpful if INN prefixes provided a little more information about the chemical characteristics of the drugs concerned when these characteristics probably have a decisive result on the clinical or therapeutic effects.

Confusion with brand names. Some of the proposed INNs resemble the brand names of drugs already marketed in France, in particular: *asinercept* and *avoralstat*.

The risk of confusion between *asinercept* and Aricept° (a brand name used for *donepezil* in many countries), which start and end almost identically, is mitigated by major differences in their indications and INNs.

The same applied to the risk of confusion between *avoralstat* and Avodart° (*dutasteride*), a risk compounded by the fact that they start with the same three letters, increasing the likelihood of selecting the wrong drug from an alphabetical list on a computer screen.

Amendments. The participants identified no problems with the single amendment to an INN presented in a previous list. We welcome the replacement of *velcalcetide* by *etelcalcetide*, since it eliminates the risk of confusion with Velcade° (*bortezomib)*, about which we submitted a comment in the public consultation on List 109 of proposed INNs (26,27).

In summary. Our analysis of List 112 of proposed INNs identified more problems with INN comprehensibility and potential confusion than for previous lists.

Our formal objections and comments highlight some problems with INN nomenclature: certain drug groups, such as monoclonal antibodies and tyrosine kinase inhibitors, are overpopulated, depleting the supply of available prefixes and distinct names; some new drug groups, for example cell therapy products, require the use of complex, compound stems; and finally, there is an urgent need for new rules concerning the naming of drugs containing two active moieties, in order to differentiate them more clearly from their individual components, in particular monoclonal antibodies conjugated to cytotoxic drugs (25).

Having identified these problems, we can anticipate some occasionally complex mechanisms through which errors could arise. It also highlights the growing importance of effective teaching the principles and the limits of INNs in order to provide safer care to patients.

Bruno Toussaint
Publishing Director

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b- *trastuzumab emtansine, vorsetuzumab mafodotin, denintuzumab mafodotin, lorvotuzumab mertansine, cantuzumab mertansine, cantuzumab ravtansine, indatuximab ravtansine, anetumab ravtansine, coltuximab ravtansine, brentuximab vedotin, enfortumab vedotin, polatuzumab vedotin, pinatuzumab vedotin, lifastuzumab vedotin, and sofituzumab vedotin (ref.25).*

References

1- Prescrire Editorial Staff “Think INN, prescribe INN, dispense INN” Prescrire Int 2000; 9(50): 184-190.

2- Prescrire Editorial Staff “Informed decisions: think of the INN” Prescrire Int 2005; 14(78): 122.

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- International Medication Safety Network (IMSN) “Improving the Safety of International Non-proprietary Names of Medicines (INNs)” November 2011; 5 pages.

6- Prescrire Rédaction “Ordonnance: la dénomination commune internationale (DCI) au quotidien” *Rev Prescrire* 2012; **32** (346): 586-591.

7- Prescrire Editorial Staff “Drug regulatory agencies maintain confusion between brand names” Prescrire Int 2008; 17(94): 83-86.

8- 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.

9- WHO “Proposed International Nonproprietary Names: List 112” *WHO Drug Information* 2014; **28** (4): 485-563.

10- WHO “The use of stems in the selection of International Nonproprietary Names (INN) for pharmaceutical substances” WHO/EMP/RHT/TSN/2013.1 + Addendum November 2014, 192+3 pages.

11- WHO “International Nonproprietary Names (INN) for Pharmaceutical Substances” mednet.who.int.

12- WHO “Pre-stems: Suffixes used in the selection of INNs – November 2014” 8 January 2015; 6 pages.

13- WHO “International Nonproprietary Names (INN) for biological and biotechnological substances” Update 2013; 74 pages.

14- WHO “International Nonproprietary Names (INN) for pharmaceutical substances. Names for radicals, groups & others. Comprehensive list” 2012; 80 pages.

15- Thériaque database www.theriaque.org.

16- WHO “Proposed international nonproprietary names: List 103” *WHO Drug Information* 2010; **24** (2): 125-198.

17- Institute for Safe Medication Practices (ISMP) “Confusion between two HER2-targeted monoclonal antibodies” *ISMP Medication Safety Alert!* 7 March 2013; **18** (5): 2-3.

18- National Alert Network (NAN) “Confusion regarding the generic name of the HER2-targeted drug KADCYLA (ado-trastuzumab emtansine)” 17 April 2013; 2 pages.

19- US Food & Drug Administration (FDA) “FDA warns about potential medication errors resulting from confusion regarding nonproprietary name for breast cancer drug Kadcyla (ado-trastuzumab emtansine)” FDA Drug Safety Communication 6 May 2013; 3 pages.

20- Health Canada “Kadcyla (trastuzumab emtansine) and Herceptin (trastuzumab) - Potential Risk for Medication Error Due to Name Confusion” Dear Healthcare Professional Letter from Hoffmann-La Roche Limited 9 October 2013; 2 pages.

21- ISMP Canada “Look-Alike / Sound-Alike ALERT: trastuzumab emtansine (Kadcyla) and trastuzumab (Herceptin)” *ISMP Canada Safety Bulletin* 4 November 2013; **13** (10): 6.

22- International Medication Safety Network (IMSN) “IMSN Alert – Risk of confusion between the names trastuzumab-emtansine and trastuzumab” 8 May 2014; 1 page.

23- Irish Medication Safety Network “Safety Alert. Confusion risk with trastuzumab emtansine (Kadcyla®) and trastuzumab” July 2014; 1 page.

24- World Health Organisation (WHO) “59th Consultation on International Nonproprietary Names for Pharmaceutical Substances Geneva, 14-16 October 2014 - Executive Summary” March 2015; 15 pages.

25- International Medication Safety Network (IMSN) “Letter to the INN Programme regarding the nomenclature of antibody-drug conjugates” 23 March 2015; 3 pages.

26- WHO “Proposed international Nonproprietary Names: List 109” *WHO Drug Information* 2013; **27** (2): 135-209.

27- Prescrire Editorial Staff “Prescrire’s contribution to the WHO consultation on List 109 of proposed INNs” 25 October 2013; 5 pages, 18 references.