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Dear Dr Mattavelli:

This letter is in regards to nomenclature of antibody-drug conjugates

- **As you are aware, during the clinical trials of trastuzumab emtansine, deaths resulting from confusion with trastuzumab drew attention to the risks associated with International nonproprietary names (INNs) of such cytotoxic substances with a common part.**

- **The International Medication Safety Network (IMSN) was quickly alerted to these risks, and proposed that a new substitute INN should be examined by the WHO INN Programme, the only international body in charge eventually changing an INN. A proposal for substitution of trastuzumab emtansine is expected to be submitted by Canadian Healthcare authorities according to the international procedure.**

- **By studying the possibilities of preventing this type of error, the IMSN found that these risks of confusion apply to all antibody-drug conjugates. The IMSN is therefore calling on the WHO INN Programme to identify nomenclature that will reduce their potentially fatal similarities and define clear rules to help recognize products that include different substances, in order to make them safer. If necessary, the IMSN is ready to contribute to the assessment of this risk reduction and prevention strategy, essential but belonging to the sole authority of the WHO INN Programme.**

The trastuzumab emtansine case. In 2013 the confusion between trastuzumab and trastuzumab emtansine drew attention to the risks associated with the INNs of cytotoxic compounds with a common part. Trastuzumab emtansine contains an anti-HER-2 monoclonal antibody covalently linked to the microtubule inhibitory drug DM1, via the stable thioether linker MCC (4-[N-maleimidomethyl] cyclohexane-1-carboxylate); emtansine referring to the MCC-DM1 complex. Its maximum dose is less than twice the recommended dose of the trastuzumab alone, so the confusion between both drugs can lead to serious overdoses.

Deaths occurring during the clinical trials of trastuzumab emtansine confirmed the seriousness of this risk, and have led to alerts issued by IMSN members and by Drug Agencies (1-6). The US Food and Drug Administration (FDA) even demanded that the company change the name in ado-trastuzumab emtansine (3). Yet the procedure for the selection of International Nonproprietary Names for pharmaceutical substances, in particular Article 9 of WHO Resolution EB115.R4, state that only the WHO INN Programme may substitute an INN (7).

On May 8, 2014, the IMSN issued an Alert about the risk of confusion between the names trastuzumab emtansine and trastuzumab, recommending the use of both the INN and the brand name as an immediate measure to strengthen the differentiation between these products and advocating for a substitution of this INN in order to prevent such a potentially fatal similarity (8).

The IMSN is pleased to learn that the INN Committee decided to consider this issue brought by Health Canada forwarding concerns expressed by the Canadian Association of Provincial Cancer Agencies (CAPCA), and expects that the request for substitution submitted by the Canadian representative will be discussed during the 60th INN Consultation (April 14-16, 2015) (9).

Other INNs facing problems. Looking for proposals to contribute to safer INNs, a collaborative work was undertaken within the IMSN. It appears that other INNs of antibody-drug conjugates fall into the same problem, with 15 recommended INNs and 2 proposed INNs currently published in List 112:

INNs	Active moieties	Proposed in List	Recommended in List
trastuzumab emtansine	emtansine	103	RL 65*
vorsetuzumab mafodotin	mafodotin	107	RL 69*
denintuzumab mafodotin		111	
lorvotuzumab mertansine	mertansine	103	RL 65
cantuzumab mertansine		105 (ex 89)	RL 66
cantuzumab ravtansine	ravtansine	105	RL 66
indatuximab ravtansine		105	RL 67
anetumab ravtansine		109	RL 71
coltuximab ravtansine		109	RL 71
brentuximab vedotin	vedotin	103	RL 65
enfortumab vedotin		109	RL 71
polatuzumab vedotin		110 (ex 108)	RL 71
pinatuzumab vedotin		108	RL 70
lifastuzumab vedotin		110	RL 72
sofituzumab vedotin		110	RL 72
indusatumab vedotin		112	
vandortuzumab vedotin		112	

This inventory can identify the chances of two types of error occurring: a) confusion between a monoclonal antibody and its conjugate with an active moiety; and b) confusion between antibody-drug conjugates that have either the same monoclonal antibody or the same cytotoxic active moiety.

The trastuzumab emtansine case results from a confusion between the monoclonal antibody and its conjugate with an active moiety. This same type of error is likely to occur with the development of cytotoxic conjugates of monoclonal antibodies also available separately (in particular between indusatumab vedotin and indusatumab; between vorsetuzumab mafodotin and vorsetuzumab). This error is mainly due to the lack of knowledge as to the exact meaning of the second term of the INN by health caregivers, who believe it is an affix without specific pharmacological properties (as for 'a salt', or 'a version', or 'a full name' of the monoclonal antibody), while it is actually an active substance (**a**).

The list of proposed or recommended INN of antibody-drug conjugates also reveals the risk of confusion between conjugates, especially in the case of combinations of a same monoclonal antibody with different active moieties such as between cantuzumab mertansine and cantuzumab ravtansine.

How to reduce the risk of error? In this complex situation, an apparently relevant simple solution to prevent the first type of error could be switching the terms of the INN, with the drug name coming first, but it may prove to lead to the second type of error, strengthening the similarities between combinations to the same active moiety, for instance between cantuzumab ravtansine and indatuximab ravtansine (9).

Given these difficulties, the principles and conventions of naming all these antibody-drug conjugates have to be reconsidered by the WHO INN Programme in order to describe differently and clearly the conjugates and to help to recognize products including different substances, therefore having different potency and toxicity.

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a- One difficulty to access this knowledge may be that such cytotoxic compounds as emtansine, mafodotin, mertansine, ravtansine, vedotin are not exhaustively described as active substances in the INN Stembook rather than in an appendix to the list of names for radicals, groups & others (10). However some of these active moieties are well characterized by a stem: in particular, the stem **-dotin** describing synthetic derivatives of dolastatin series was selected as a prestem in April 2014 (11).

It is well known in fact that the rules adopted for fixed combinations of substances by national nomenclatures committees are not allowed by the WHO INN Programme (**b**). Respectful of the WHO INN Programme responsibility as well of the substitution procedure currently underway, the IMSN declines to make specific proposals (7). However, caring about an effective reduction of similarities between these INNs, IMSN stays at the disposal of the WHO INN Programme and is ready to participate, as necessary, to an assessment of the risk reduction solutions envisaged by the WHO INN Programme.

On this occasion, the IMSN urges the WHO INN Programme to focus in proactively identifying medicine names similarity to avoid name mix-ups and errors.

Best regards,

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About IMSN: The **International Medication Safety Network** (IMSN) is an international network involving medication safety organizations, and medication safety experts and advocates. Established in November 2006 by the "Salamanca Declaration to Promote Safe Medication Practices Globally", IMSN aims to prevent patient harm globally by promoting safe medication practices and collaboration between everyone involved in the medication use process. www.intmedsafe.net

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References:

1- Institute for Safe Medication Practices (ISPM) "Confusion between two HER2-targeted monoclonal antibodies" ISMP Medication Safety Alert! 7 March 2013; 18 (5): 2-3.
2- National Alert Network (NAN) "Confusion regarding the generic name of the HER2-targeted drug KADCYLA (ado-trastuzumab emtansine)" 17 April 2013; 2 pages.
3- US Food & Drug Administration (US 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.
4- 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.
5- ISMP Canada "Look-Alike / Sound-Alike ALERT: trastuzumab emtansine (Kadcyla) and trastuzumab (Herceptin)" ISMP Canada safety bulletin 4 November 2013 ; 13 (10) : 6.
6- Irish Medication Safety Network "Safety Alert. Confusion risk with trastuzumab emtansine (Kadcyla®) and trastuzumab" July 2014; 1 page.
7- World Health Organisation (WHO) "International Nonproprietary Names: revised procedure. Resolution WHO EB115.R4" 19 January 2005.
8- International Medication Safety Network "IMSN Alert – Risk of confusion between the names trastuzumab-emtansine and trastuzumab" 8 May 2014; 1 page.
9- World Health Organisation (WHO) "59th Consultation on International Nonproprietary Names for Pharmaceutical Substances Geneva, 14-16 October 2014 - Executive Summary"March 2015; 15 pages.
10- World Health Organisation (WHO) "International Nonproprietary Names (INN) for pharmaceutical substances. Names for radicals, groups & others. Comprehensive list" 2012: 80 pages.
11- World Health Organisation (WHO) "Addendum to "The use of stems in the selection of International Nonproprietary names (INN) for pharmaceutical substances"" 20 November 2014: 3 pages.

b British Approved Names (BAN) for substance combinations and United States Pharmacy Equivalent Names (PEN) for dosage forms containing two or more active ingredients start with the prefix 'Co-', for instance: co-amoxiclav for amoxicillin trihydrate + potassium clavulanate; co-codamol (BAN) ou co-codAPAP (PEN) for codeine phosphate + paracetamol; co-trimoxazol for trimethoprim + sulfamethoxazole.