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The dangers of INNs for antibody-drug conjugates should not be overlooked

- **The International Medication Safety Network (IMSN) is particularly concerned by the risks of error related to antibody-drug conjugates and quickly alerted to these risks.**

- **Beyond the trastuzumab emtansine case, no longer on the WHO INN Programme agenda for a substitution, the IMSN recalls again that other INNs of antibody-drug conjugates fall into the same problem.**

- **In March 2015, the IMSN called on the WHO INN Programme to change the names of antibody-drug conjugates to reduce their potentially fatal similarities and define clear rules helping to recognize products including different substances and to make them safer.**

- **In the lack of any risk reduction solutions envisaged by the WHO INN Programme, the IMSN goes further by proposing several approaches: 1st make awareness on active moieties; 2nd change the way of expressing the conjugate compound (taking in account human factor principles, the names of active substances should include a specific prefix for conjugated compound, such as con-, and/or be concatenated by "+","plus" or "/" without space); 3rd avoid attribution of INN to corresponding naked antibodies when antibody-drug conjugates are considered.**

- **If requested, 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 International Medication Safety Network (IMSN) is particularly concerned by the risks of confusion and error related to antibody-drug conjugates. We remember the Alert issued by the IMSN in May 8, 2014, about the risk of confusion between the names trastuzumab emtansine and trastuzumab, following the alerts issued by IMSN members and by Drug Agencies (1-7); and also our letter of March 23, 2015, noting that these risks of confusion apply to all antibody-drug conjugates and calling on the WHO INN Programme to change their names to reduce their potentially fatal similarities and define clear rules helping to recognize products including different substances and to make them safer (8).

During the last meeting, held on 30 September and 1st October 2015 in Cartagena, Colombia, the IMSN discussed about the decisions taken during the 59th and the 60th INN Consultations, respectively held on 14-16 October 2014 and on 13-15 April 2015 (9,10). Knowing that "*until there is a proper introduction of risk mitigation strategies, Heath Canada will not be moving towards a name change*", it appears that a substitution procedure for trastuzumab emtansine is no longer on the agenda, contrary to what had suggested Canadian

and Irish efforts (9). The IMSN appreciated that the INN Expert Group established a "conjugates working group", recognising that "*there are real clinical and naming issues which need to be addressed*" regarding conjugated compounds containing two active substances (10).

Beyond the trastuzumab emtansine case, the IMSN recalls that other INNs of antibody-drug conjugates fall into the same problem, with 17 recommended INNs and 9 proposed INNs currently published in List 113:

INNs of antibody-drug conjugates (conjugated mAb)	Active moieties	Proposed in List	Recommended in List	Monoclonal antibodies (naked mAb)	Proposed in List	Recommended in List
cergutuzumab amunaleukin	amunaleukin	113		cergutuzumab	Not requested	
trastuzumab emtansine	emtansine	103	RL 65*	trastuzumab	78	RL 40
labetuzumab govitecan	govitecan	113		labetuzumab	85	RL 47
sacituzumab govitecan		113		sacituzumab	Not requested	
vorsetuzumab mafodotin	mafodotin	107	RL 69*	vorsetuzumab	107	RL 69
denintuzumab mafodotin		111	RL 73	denintuzumab	Not requested	
lorvotuzumab mertansine	mertansine	103	RL 65	lorvotuzumab	Not requested	
cantuzumab mertansine		105 (ex 89)	RL 66	cantuzumab	Not requested	
cantuzumab ravtansine	ravtansine	105	RL 66	cantuzumab	Not requested	
indatuximab ravtansine		105	RL 67	indatuximab	Not requested	
anetumab ravtansine		109	RL 71	anetumab	Not requested	
coltuximab ravtansine		109	RL 71	coltuximab	Not requested	
mirvetuximab soravtansine	soravtansine	113		mirvetuximab	Not requested	
vadastuximab talirine	talirine/telirine	113		vadastuximab	Not requested	
rovalpituzumab tesirine	tesirine/tesarine	113		rovalpituzumab	113	
clivatuzumab tetraxetan	tetraxetan	113		clivatuzumab	Not requested	
brentuximab vedotin	vedotin	103	RL 65	brentuximab	Not requested	
enfortumab vedotin		109	RL 71	enfortumab	Not requested	
polatuzumab vedotin		110 (ex 108)	RL 71	polatuzumab	Not requested	
pinatuzumab vedotin		108	RL 70	pinatuzumab	Not requested	
lifastuzumab vedotin		110	RL 72	lifastuzumab	Not requested	
sofituzumab vedotin		110	RL 72	sofituzumab	Not requested	
indusatumab vedotin		112	RL 74	indusatumab	112	RL 74
vandortuzumab vedotin		112	RL 74	vandortuzumab	Not requested	
glembatumumab vedotin		113		glembatumumab	102	RL 64
tisotumab vedotin		113		tisotumab	113	

IMSN members have distinguished 3 types of errors regarding INNs of antibody-drug conjugates:

- Confusion between the naked mAb and the conjugated mAb, in 7 cases:
  - trastuzumab emtansine (103, RL 65) # trastuzumab (78, RL 40)
  - vorsetuzumab mafodotin (107, RL 69) # vorsetuzumab (107, RL 69)
  - indusatumab vedotin (112, RL 74) # indusatumab (112, RL 74)
  - labetuzumab govitecan (113) # labetuzumab (85, RL 47)
  - glembatumumab vedotin (113) # glembatumumab (102, RL 64)
  - rovalpituzumab tesirine (113) # rovalpituzumab (113)
  - tisotumab vedotin (113) # tisotumab (113)
- Confusion between several conjugated mAb from the same naked mAb conjugated with different active moieties (1 case):
  - cantuzumab mertansine (105 (ex 89), RL 66) # cantuzumab ravtansine (105, RL 66)
- Confusion between several conjugated mAb from different antibodies conjugated with the same active moiety (5 cases):
  - 10 mAb conjugated with vedotin
  - 2 mAb conjugated with mertansine
  - 4 mAb conjugated with ravtansine
  - 2 mAb conjugated with mafodotin
  - 2 mAb conjugated with govitecan

Beyond the risk of selection error in computer programs, the main cause of these errors is 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. The most serious are the confusions between the monoclonal antibodies and their conjugates with an active moiety, because such errors can lead to serious overdoses and toxicity. This type of error is likely to occur with the development of cytotoxic conjugates of

monoclonal antibodies also available separately. Although a simple prevention of this risk could be to avoid the later and concerns already expressed by IMSN before the 60th INN Consultation, IMSN members felt a growing concern with the 4 new risky pairs published in the List 113 of proposed INN, putting in question the approach of the safety of these INNs of antibody-drug conjugates and their proactive risk management by the WHO INN Programme.

In our 23 March, 2015, letter, respectful of the WHO INN Programme remit, the IMSN declined to make specific proposals and declared staying at the disposal of the WHO INN Programme for seeking an effective reduction of similarities between these INNs (8). In the lack of any risk reduction solutions envisaged by the WHO INN Programme, IMSN members have wished to go further by proposing several approaches.

1st make awareness on active moieties. One difficulty to access this knowledge may be that such cytotoxic compounds as amunaleukin, emtansine, govitecan, mafodotin, mertansine, ravtansine, soravtansine, talirine, tesarine, 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 (11,12). 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 and as a stem in June 2015, the stem -tecan describing antineoplastics, topoisomerase I inhibitors, the stem – xetan describing chelating agents selected as prestem in June 2015 (11-13). A widely use suffix such as –tansine should be recognized as a stem. The designations for selected active moieties should be presented in the INN Stembook instead of the INN Radicalbook and be a matter of continuing education programmes for healthcare givers.

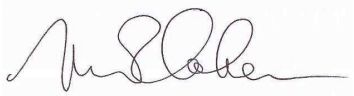
2nd change the way of expressing the conjugate compound. The principles and conventions of naming all these antibody-drug conjugates have to be reconsidered by the WHO INN Programme in order to describe differently and clearly the conjugates and to help to recognize products including different substances, therefore having different potency and toxicity. Several solutions have been considered by IMSN members taking in account human factor principles: using a specific prefix, such as con- (for conjugated compound); concatenating the names of active substances by “+”,“plus” or “/” without space.

3rd avoid attribution of INN to corresponding naked antibodies when antibody-drug conjugates are considered. As evidenced in the table provided, the risk of confusion between the monoclonal antibodies and their conjugates with an active moiety is simply avoided in 19 cases, no INN having been requested for corresponding naked antibodies. IMSN members interpreted the 4 pairs published in the List 113 of proposed INNs as a lack of awareness of this safety principle by the WHO INN Programme.

The dangers of INNs for antibody-drug conjugates in current care conditions should not be overlooked. It would be a failure for the WHO INN Programme effectiveness reputation to accept recommending the use of both the INN and the brand name as an immediate measure to strengthen the differentiation between these products. INNs of these antibody-drug conjugates should be both designed to help to understand what they are really and to prevent any type of confusion.

From the time that error risks are identified, it is the responsibility of the WHO INN Programme to review these INNs of antibody-drug conjugates to make them more safer. Once again, the IMSN urges the WHO INN Programme to care about an effective reduction of similarities between these INNs.

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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