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Issues from the systematic assessment of error risks related to new drugs and to packaging, naming, labeling, dosing devices, etc. by the Prescrire's Packaging Working Group

- Withdrawal of premixed potassium injectable solutions
- Tranexamic acid mix-ups: with amps too Prescrire's annual review
- Failed unit-dose syringes or pens requiring multiple injections at the same time
- Expression of dosages in the seases of fixed-dose combinations and of parenteral preparations



Premixed potassium injectable solutions withdrawn in France, although promoted (1)

- 2012 concentrated potassium administration in error classified as a 'never event' by the French Ministry of Health
- 2015 IV potassium only available on prescription
- 2015 marketing autorisation granted to 1L and 0.5L bags of KCl NaCl Kabi 0.3% 0.9% sol inj
- 2017 French Medicine Agency (ANSM) called to "*prefer premixed potassium IV bags*"







### Premixed potassium injectable solutions withdrawn in France, although promoted (2)

Potassium mectaple preunue : abandonné dans un silence révélateur Potassium injectable prédilué :

de multiples défaillances

- Mid 2020: cessation of the marketing of the product due to a lack of buyers Fresenius Kabi has informed the ANSM that it will stop the marketing of the product Chlorure de potassium 0,3 % et chlorure de sodium 0,9 % Kabi° "due to low sales volumes"
- 2022: protest by Prescrire and some subscribers

Potassium injectable prédilué prêt à perfuser : une barrière de sécurité à remettre à disposition

En France, des injections mortelles, par erreur de solutions de potassium concentrées continuent d'être rapportées.

• Une solution prédiluée de chlorure de potassium est une barrière de sécurité évitant le recours aux ampoules de solution concentrée de *potassium*, et donc le risque mortel auque elles exposent. La seule spécialité prédiluée et autorisée dans les hypokaliémies n'est plus commercialisée, faute d'incitation forte à l'utiliser : une régression en matière de sécurité de

es solutions concentrées de chlorure de potassiun injectables sont couramment utilisées à l'hôpital. notamment pour la préparation extemporanée de solutions pour perfusion. En France, elles sont disponibles en ampoules contenant le plus souvent 1 g, 2 g ou 4 g de chlorure de potassium (1à3).

Solutions concentrées de chlorure de potassium un risque mortel. L'administration intraveineuse du contenu de ces ampoules expose à des arrêts cardiaques (1à3). De nombreuses alertes à ce sujet ont été émises depuis les années 2000, et des cas continuent d'être rapportés. Selon l'Agence française du médicament (ANSM), 28 « erreurs avérées » ont été signalées entre 2017 et fin 2020. Trois patients sont morts. Parmi les causes de ces injections par fois mortelles, on retrouve le plus souvent : une confusion avec d'autres ampoules similaires, par exemple de glucose, ou de diluant pour la reconstitution de solutions injectables à partir de poudres ; une erreur de calcul lors de la préparation de per fusions ou du réglage du débit de perfusion (1à5).

Prévention "prioritaire"... à pas comptés. En France depuis une quinzaine d'années, des mesures ont été prises par l'ANSM dans l'objectif de limiter les njections par erreur de solution concentrée de otassium (3). En 2007, l'étiquetage des ampoules de chlorure de notassium a été modifié : mentions en rouge et quadruple expression du dosage (quan tité totale par rapport au volume total, pourcentage oncentration (g/ml) et concentration molaire) (6 En 2011, les résumés des caractéristiques (BCP) et les notices des spécialités concernées ont été mo difiés, notamment pour ajouter le risque d'arrê cardiaque en cas d'administration rapide. Une affichette à destination des établissements de santé a été publiée pour rappeler de « lire toutes les mentions de l'étiquetage ; toujours diluer (les ampoules de KCI] ; perfuser lentement ; surveiller les para mètres cliniques et biologiques » (7). À partir de 2012, les erreurs d'administration de solution oncentrée de chlorure de potassium ont été considérées par les autorités sanitaires comme « des événements qui ne devraient iamais arriver » (aussi dénommés "never events" en anglais) et dont la prévention « doit constituer une priorité pour le établissements » (8,9). C'est aussi à cette é que l'ANSM a informé qu'elle engage flexion sur la pertinence de la mise à o poches de KCI prédiluées » (7). En 2015, a été inscrit sur la liste l des substan « sous toutes ses formes lorsqu'il e par voie injectable (...) » (a)(10).

Solution prédiluée prête à l'emploi nassive hienvenue. Dans la préventie ment de l'hypokaliémie, c'est seuler qu'a été commercialisée en France Chlorure de potassium 0,3 % et chloru 0,9 % Kabi°, en solution diluée prête à flacons contenaient 3 grammes par litr de potassium dans une solution de sodium, et constituaient une alternat aux ampoules de solutions concentré de potassium (3.11).

Cette spécialité répondait à la rec de l'ANSM de préférer le potassium une forme diluée prête à l'emploi da la voie orale n'est pas utilisable (8). De à disposition de cette présentation di le retrait des stocks d'ampoules dar hospitaliers en prévention d'erreurs tion. L'application simultanée de cette retrait des stocks d'ampoules de chlo sium injectable concentré dans les se taliers érigeait une barrière de sécuri un moven qui s'oppose à, ou ralenti d'un accident (1,2).

1000 mL

POTASSIUM 0.3 %

ROAD VERILIARY

3.01079.0

KCI 0'3 %

D'autres solutions diluées de chl sium (à la concentration de 2 g/l, ave et du chlorure de sodium) pour p disponibles en France depuis de nombr mais elles sont autorisées par exen déshydratation, et pas dans le traiter vention des hypokaliémies (11).

a. En France durant une vingtaine d'années le circuit du médicament à l'hôpital était régi par la réglementation substances vénéneuses, ce qui exemptait les médicaments "hors liste" mis à disposition sans prescription, ni contrôle rticuller, notamment de leur détention. Un arrêté d'avri 2011 a corrigé cette lacune en étendant les dispositions antérieures à tous les médicaments et a rangé les solutions d'électrolytes concentrés dans la catégorie des "médicaments à risque" (réf. 9,16).

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échanges

### Tranexamic acid mix-ups: with amps too (1)

- In North America, confusions with tranexamic acid occur mostly between vials
- The existence of ampoules in Canada has even been proposed as a mode of differentiation

**FIGURE 3.** An example of tranexamic acid supplied in an ampoule.



FIGURE 1. The tranexamic acid (at left) and bupivacaine (at right) products involved in the described incident.

FIGURE 2. Tranexamic acid (middle product) and local anesthetics (bupivacaine on the left and ropivacaine on the right) involved in drug mix-ups in the US NAN Alert.







### Tranexamic acid mix-ups: with amps too (2)

 However, in the rest of the world, ampoules are widely used and prone to errors



Figure 1 Similarity of tranexamic acid and hyperbaric bupivacaine ampoules.

Journal of Clinical Anesthesia 58 (2019) 48-49



Fig. 1. Ampoules of bupivacaine 4 ml and tranexamic acid 5 ml

#### S Afr Med J 2019;109(11):841-844.



Fig. 1. Tranexamic acid, hyperbaric bupivacaine and isobaric bupivacaine.



Fig. 2. Tranexamic acid and spinal bupivacaine stored in the same container in a private hospital.

#### FIGURE 1

Ampoules of local anesthetic and tranexamic acid with similar appearance



Moran. Tranexamic acid at cesarean delivery: drug-error deaths. Am J Obstet Gynecol 2022.

FIGURE 2 Ampoules of local anesthetic and tranexamic acid with similar size and shape



Moran. Tranexamic acid at cesarean delivery: drug-error deaths. Am J Obstet Gynecol 2022.





International labeling and packaging standardization: a long and difficult path

- Tranexamic acid mix-up issue points the lack of standardization at a global level
- Due to shortages, foreign packages obtained during the pandemic where used (and discovered) by carers with error risks related to poor identification and packaging
- A good reason to resume the IMSN previous initiative?



FDA/IMSN SUMMIT with INTERNATIONAL DRUG REGULATORS OF LABELING & PACKAGING to ADDRESS MEDICATION ERRORS Sponsored by:

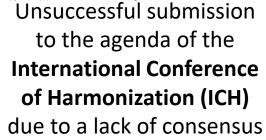
White-Paper-outlining-Safety-Considerations-for-Pharmaceutical-Container-Labelling-and-Packaging-Design-to-Minimize-Medication-Errors-for-International-Harmonization¶

To reduce owerall-harm related to medication-errors, harmonization at the global-level-in-accessary. Many yorduct containers exhibit labelling and packaging issues that contribute to errors invariouscontrinse. Allo, domestic drug manufacturing does not easily in Imany countries, so drugs are commonly imported, often with features that can esuit in-safety issues. Some internationalregulators have undertaken successful packaging and labelling changes that have reduced the risk of errors. §

To-advance global-harmonization of container-labeling and packaging standards and reduce overallharm associated with medication errors, the international Medication Safety-Network (MSN) andthe US-Food and Day Administration(FQA) held a summit for regulators on drug container labelling and packaging-safety-in sume 2018.1 link to t<u>ittps://www.stmtodafa.net/public-events/imsn-</u> members-events/food-advant-to-labelling-and-packaging/16

articipants agreed to create white paper to promulgate a minimum set of best practices for harmaceutical container labeling and packaging aimed at reducing medication errors and the mplementation of support for safety technologies such as label barcodes to be used with scanning quipment hor reduce medication errors. The proceedings from the June 2018 meeting were also liscs set during of follow-upmenting facility pair for dis 312 shows the support of the safety facility of the Cascal, Portugal). (Inix to <u>three//www.inimedic</u> ummt on drugs product sheeling - and packaten legulators and industry participants in the safety of the safety facility of the safety of the s

container <u>Habeling</u> and packaging recommendations which here to download the IMSN White Paper (https://www.intmediate.net/wpicontent/upload/s103/09/6-14-19-0RAFT-WHITE-PAPER-Harmonizing-Safe-Medication-Contain





#### Failed unit-dose syringes or pens requiring multiple injections at the same time!

| Solution injectable en seringue préremplie<br>tralokinumab<br>bie sous-cutanée<br>2 atrigues privergées<br>Adtralza°<br>(tralokinumab)<br>Prefilled syringes<br>Prefilled syringes<br>150 mg<br>150 mg<br>150 mg<br>150 mg<br>300 mg SC<br>every 2 weeks<br>bie very 2 weeks  | Adtralza 150 mg  | Products  | Presentations      | Dosages | Authorized<br>dosing<br>regimen | Simultaneous<br>injections<br>needed | répéter  |
|---|--|-----------|--------------------|---------|---------------------------------|--------------------------------------|--|
| Main 2000       Main 2000 | tralokinumab   |           | Prefilled syringes | 150 mg  | then<br>300 mg SC               | 4 then 2                             | seringues<br>Pour une dose de 300 mg,<br>deux seringues de 150 mg sont<br>reicossaires.<br>Injectez la première seringue, et |
| Bimzelx*       160 mg       320 mg SC       2         Bimzelx*       Prefilled syringes       160 mg       320 mg SC       2         Bimzelx*       Prefilled syringes       160 mg       320 mg SC       2         Bimzelx*       Prefilled syringes       160 mg       320 mg SC       2         Bimzelx*       Prefilled syringes       160 mg       320 mg SC       2         Bimzelx*       Prefilled syringes       160 mg       320 mg SC       2         Bimzelx*       Prefilled syringes       160 mg       320 mg SC       2         Bimzelx*       Prefilled syringes       160 mg       320 mg SC       2         Bimzelx*       Prefilled syringes       160 mg       320 mg SC       2         Bimzelx*       Prefilled syringes       160 mg       320 mg SC       2       2         Bimzelx*       Prefilled syringes       400 mg       800 mg IM for       2 then 1  | solution for injection   | -         | Prefilled syringes | 150 mg  | -                               | 2                                    |  |
| Abilify Prefilled syringes 400 mg 800 mg IM for 2 then 1  | Auf as fair higheritas in prov filled perio<br>Amerikasumab 2 pro-filled perio 2 pro-filled | -         | , .                | 160 mg  |                                 | 2                                    | <ul> <li>sont nécessaires pour</li> </ul>  |
|   |  | Maintena° | Prefilled syringes | 400 mg  |                                 | 2 then 1                             | Ready to inject,<br>indeed?  |

2022 Update from Prescrire

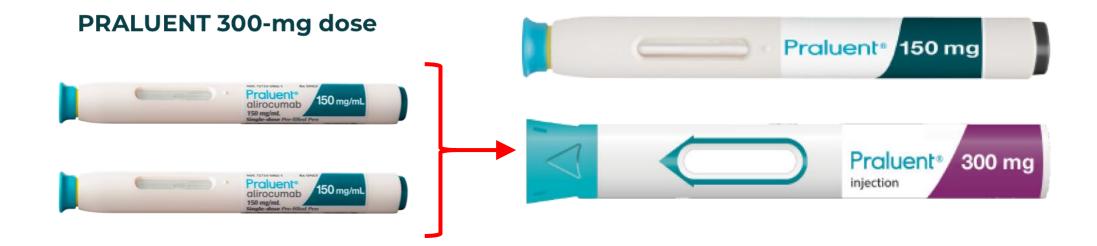
Maresorire

8

# Failures that can be corrected, however: Praluent° (alirocumab), a recent example

Since mid-2021, prefilled pens dosed at 300 mg are also marketed, which avoids the need for two successive injections when the 300 mg dose is chosen.



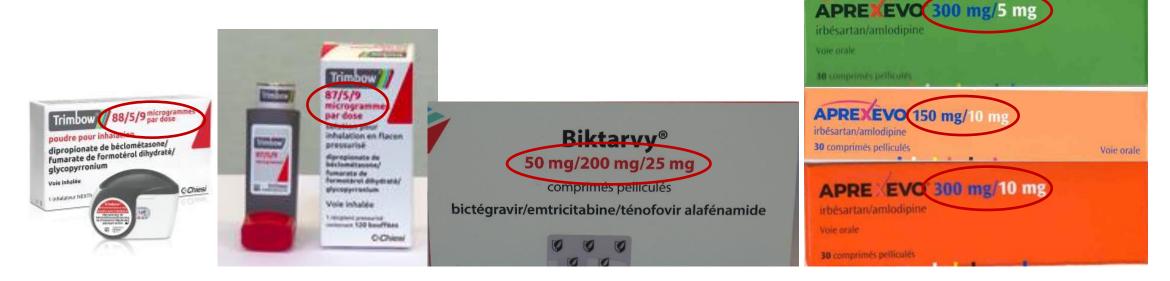




## Expression of dosages in the names of fixed-dose combinations

#### **Error prone labeling:**

the dosage of each substance is unclear because the dosages do not follow the INNs and are even far from them





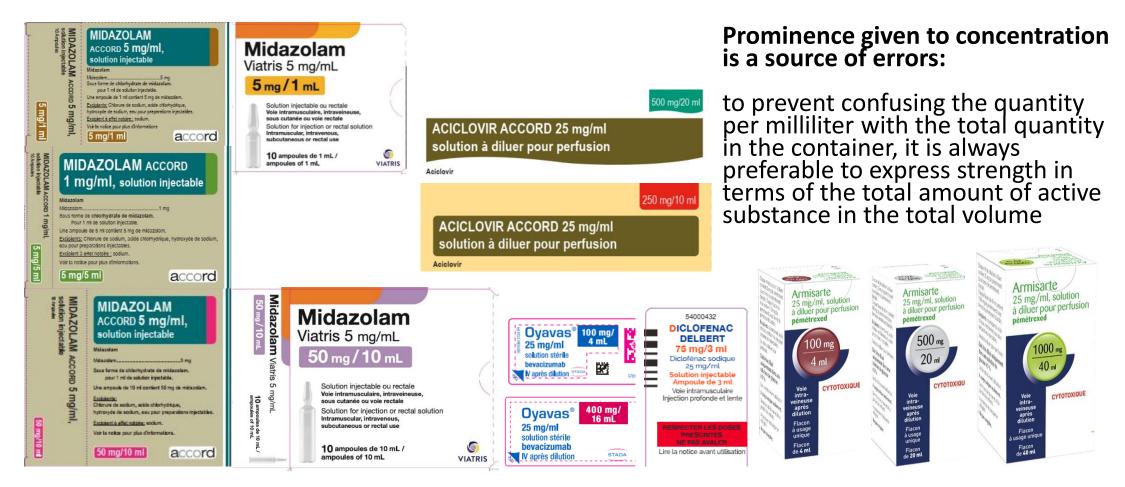
Voie orale

APREXEVO 150 mg/

irbésartan/amlodipine

30 comprimés pelliculés

# Expression of dosages in the names of parenteral preparations





2022 Update from Prescrire

## Expression of dosages in the names: error prone recommendations in Europe

- Application of the EMA's "QRD Recommendations on the expression of strength in the name of centrally authorised human medicinal products"
- The use of the "full name" required by the EMA is problematic and a constant source of error

|  | ondon, 18 November 2009<br>sc. Ref. EMA/707229/2009 |  | EMEA<br>EUROFEAN MEDICINES AGENCY<br>7 Westferry Corcos<br>Carara Wharf   | 2013  |
|--|---|--|---|---|
| QUALITY REVIEW OF DOCUMENTS GROUP (QRI   | ))  |  | Loodox E14 4HB<br>United Kingdom<br>Pans, May 28, 2009  |   |
| QED RECOMMENDATIONS ON THE EXPRESSION OF STRENGTH<br>CENTRALLY AUTHORISED BUGAN MEDICINAL PRODUCTS<br>SECTION 1 OF SPC, AND IN THE NAME SECTION OF LABELI  | AS STATED IN  |  | Prescrite's comments on GRD Recommendations EMEA/200304/2009<br>Preventing errors initiated to the expression of strength on drug packaging<br>The European Commission has produced detailed definitions of drug strengths because<br>of their impact on the fees paid by pharmacellacit companies (a)(1)(5-4). These definitions<br>are not intended to gody to the expression of strength in the summary of product   | POSITION STATEMENT<br>Making Medicines Naming, Labeling and Packaging Safer |
| ADOPTION BY QRD FOR RELEASE FOR CONSULTATION   | March 2009  |  | characteristics (SPC), the package leaflet or on drug packaging (1p2). However these<br>administrative definitions have entered into normal usage in these various situations, leading  | Making Medicines Naming, Labeling and Packaging Safer                       |
| RELEASE FOR CONSULTATION   | 07 April 2009                                       |  | to overdoses and confusion between different strengths of the same drug, unnecessarily<br>exposing European citizens to preventable adverse effects.  |   |
| END OF CONSULTATION (DEADLINE FOR COMMENTS)  | 29 May 2009   | President<br>83, bookerund Voltaine<br>75558 Realts CEOEX 11<br>PRANCE   | The European Medicines Agency (EMEA) has produced recommendations on the<br>expression of strength in the name of centrally authorised human medicinal products, "not   |   |
| ASSESSMENT OF COMMENTS   | June-August 2009                                    | Yel, (232) (951 49 23 72 90<br>Fee (232) (951 49 27 72 90  | only in order to achieve harmonisation across similar medicinal products and pharmaceutical   |   |
| FINAL ADOPTION BY QRD  | 17 September 2009                                   | Gewact@preconv.org   | forms, but especially in order to make improvements to medicines labelling to ensure the<br>correct and safe use of medicines and minimise medication errors" (2).  |   |
| PUBLIC RELEASE ON EMEA WEBSITE   | January 2010  | Web and president and  | These draft recommendations are currently the subject of a public consultation (2). They<br>are all the more important since national drug regulatory agencies and the Co-ordination  |   |
| ENTER INTO FORCE   | 01 March 2010                                       | Service and Absends<br>Subscription (Jeportment<br>Yet. (23)-(9)1 49 23 72 46<br>Page (23)-(9)1 49 23 78 48  | Group for Mutual Recognition and Decentralised Procedures (CMD) align themselves with the<br>EMEA's position.   |   |
|  |   | alexene manta@genection.org<br>Forewardiness Prescrime<br>T41.(133)(0)(1473372400<br>Pasa.(122)(0)(1473372400<br>Pasa.(122)(0)(147337240)<br>formations@genectrin.org                                      | Prescrite is responding to this public consultation to push for safer and cleater naming of<br>drugs (3).<br>The emphasis on concentration is a source of error   |   |
|  |   | Anastation Heart Proceive<br>Organization independent<br>de services particulation<br>de services particulation<br>de services de services<br>de services de services<br>per heating pageoreach            | As of 2009, in accordance with European Commission guidelines, drugs are labelled<br>with the brand name + the strength + the phenocentral form and, underwaht, the<br>international nogramitative name (MN) (dp 12). But these guidelines are analyzed,<br>rescence's systematic analyzes of drug packaging reveal that in fact phenocentical<br>compares place, greater emphasis on commercial details, invented names, logos and<br>company graphics (54). |   |
| 7 Westlerry Circos, Canary Wharf, London, E14 4HB, UK<br>Tet (44-20) 74 15 44 400 E Raz (44-30) 75 23 71 29<br>E-mail: crig@terma.coc.au / www.come.coc.au |   | Appriments (HRC, L17 et submit<br>Ong HC 11: 701 - 711 - 071<br>HF Two, H16 HG (HAAR-10)<br>TRET F WEINER ANY DEDX<br>Class And SPR72<br>HIS (a Transport Pressure Ferro<br>30041 (2004) (DB1-2201402) 323 | Prominence given to concentration. The strength of liquid forms in particular is<br>expressed as the amount of active substance in each militize (concentration) rather than as<br>the amount of active substance in the total volume. Analyses of the packaging of contrally<br>authorised medicinal products have revealed that the amount of active substance in the total   |   |
|  |   | Autoration for the 1901<br>of 664(3): - 33 210(1787  |   |   |

Strength of single dose injectables and liquid preparations should be stated as the total quantity of the active pharmaceutical substance per total volume and per ml.<sup>14</sup> If the volume in the container exceeds 1ml, the concentration (quantity of active pharmaceutical substance per one ml) should be indicated immediately below the strength, either in brackets or in less prominent letters.

IMSN Position Statement | Making Medicines Naming, Labeling and Packaging Safer 5



## Looking at mutual aid between IMSN members: just browse *Prescrire & Prescrire International* (1)

| Topics                  | Prescrire  | IMSN source  |
|-------------------------|--|--|
| COVID-19 Vaccines       | "Tozinameran (Comirnaty <sup>°</sup> ) and covid-19 in children aged<br>5-11 years" <i>Prescrire International</i> 2022; <b>31</b> (236): 97.<br>Excerpt from <i>Rev Prescrire</i> 2022; <b>42</b> (460): 94-95.<br>"Packaging of covid-19 vaccines: flexibility to respond to | <ul> <li>ISMP "Age-related covid-19 vaccine mix-ups" ISMP Medication Safety Alert!</li> <li>18 November 2021; 26 (23): 1-2.</li> <li>ISMP "Learning from errors with the new COVID-19 vaccines" ISMP</li> </ul>                |
|                         | the health emergency" <i>Rev. Prescrire</i> 2022; <b>42</b> (463): 378.  | Medication Safety Alert! 2021; <b>26</b> (1): 1-7.   |
| Patient safety literacy | "Learning from Healthcare Error Experiences. Potential contribution of relatives to the occurrence of errors during care" <i>Rev Prescrire</i> 2022; <b>42</b> (460): 157-158.   | <b>ISMP</b> "Parents staying with their hospitalized child can help detect some errors – but may contribute to others" <i>ISMP Safe Medicine</i> 2021; <b>19</b> (5): 1-2.   |
| Pneumococcal vaccines   | "Pneumococcal vaccine errors: infants poorly protected"<br><i>Prescrire International</i> 2022; <b>31</b> (234): 48-49.  | <b>ISMP</b> "2017-2018 Biannual Report. The ISMP National Vaccine Errors Reporting Program (VERP)" 2019: 38 pages.   |
| Tranexamic acid         | "Confusing tranexamic acid for a local anaesthetic: fatal<br>spinal injections" <i>Prescrire International</i> 2022; <b>31</b> (235):<br>75-76   | <b>National Alert Network</b> (NAN) "NAN Alert : Dangerous wrong-route errors with tranexamic acid" 9 September 2020 : 2 pages.  |
| Clinical trials         | "Medication errors during clinical trials: to be reported and<br>analyzed to improve safety of care" <i>Rev Prescrire</i> 2022; <b>42</b><br>(462): 277-278.   | <b>ISMP</b> "Investigational drugs: strategies for sponsors, FDA, and clinical sites to prevent product-related errors (Part II)" <i>ISMP Medication safety Alert</i> ! 2018: <b>23</b> (9): 1-5.                              |
| Potassium concentrate   | "Ready-to-infuse pre-diluted potassium: a safety barrier to<br>be urgently made available" <i>Rev Prescrire</i> 2022; <b>42</b> (463):<br>339-340.   | International Medication Safety Network (IMSN) "Global Targeted<br>Medication Safety Best Practices 1: Remove potassium concentrate injection<br>from drug storage areas on all inpatient nursing units/wards" June 2019: 5-6. |



## Looking at mutual aid between IMSN members: just browse *Prescrire & Prescrire International* (2)

| Topics                        | Prescrire  | IMSN source  |
|-------------------------------|--|--|
| Tacrolimus                    | "Learning from Healthcare Error Experiences. Transplant<br>patients: exposed to immunosuppressant dose errors" <i>Rev</i><br><i>Prescrire</i> 2022; <b>42</b> (462): 316-317.  | <ul> <li>ISMP "Multifactorial causes of tacrolimus errors : confusion with strength/formulation, look-alike names, preparation errors, and more" <i>ISMP Medication Safety Alert!</i> 2017; 22 (16) : 1-4.</li> <li>Health Canada "Tacrolimus and the Risk of Graft Rejection due to Medication Errors: Inadvertent Switching between Different Oral Formulations" 22 July 2019</li> </ul> |
| Administration<br>turnarounds | "Oral administration of an injectable form: a little-studied<br>practice with known risks" <i>Prescrire International</i> 2022; <b>31</b><br>(241): 245. Excerpt from <i>Rev Prescrire</i> 2022; <b>42</b> (463): 347-<br>352. | <b>ISMP</b> "Vancomycin injection for oral use given IM" <i>ISMP Medication Safety Alert! Long-Term Care Advise-ERR</i> 2014; <b>2</b> (5) : 2-3.  |
| Paxlovid°                     | "Nirmatrelvir + ritonavir (Paxlovid°) in covid-19. For certain patients at risk of developing severe disease" <i>Prescrire International</i> 2022; <b>31</b> (238): 145-148.   | <ul> <li>ISMP Canada "Mitigating Risk for Medication Errors Involving Paxlovid" ISMP Canada Safety Bulletin 2022; 22 (2): 1-2.</li> <li>ISMP "Numerous wrong dose errors with Paxlovid" " ISMP Medication Safety Alert! 2022 ; 27 (13) : 1-3.</li> </ul>   |
| Clozapine                     | "Clozapine: danger from sudden reintroduction" <i>Prescrire</i><br>International 2022; <b>31</b> (240): 215.   | <ul> <li>Zekarias A. (UMC) "Clozapine – Drug dose titration not performed" WHO<br/>Pharmaceuticals Newsletter 2020; (3): 11-13.</li> <li>ISMP "Potential for severe cardiovascular effects when restarting clozapine"<br/>ISMP Medication Safety Alert! 2022; 27 (1): 1-2.</li> </ul>  |





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