Naming, labelling and packaging of medicines put patients at risk

Findings from Prescrire

Assessing therapeutic advance

Providing healthcare professionals with the information they need about drugs and therapeutic strategies

- efficacy
- adverse reactions
- **convenience**
  - **safety**
  - **usability**

  of packaging, labelling (leaflet and associated devices included)

Systematic analysis by Prescrire's Packaging Working Group

- Every item of the packaging is examined in detail using a standardised form.
- When the drug is part of an umbrella range, we compare its appearance with the other products in the range.
- We check the labelling for the legibility and position of key information (INN, dose strength, storage, etc.).
- We test whether tablets are easily divisible.
- We prepare formulations that require reconstitution.
- We test the quality of blister pack films and bottle caps, especially for dangerous drugs.
- We try out dosing devices, referring to the patient leaflet.
- We check whether oral delivery syringes could be attached to an injection needle.
- We analyse the usability and safety of the information provided, especially in the patient leaflet, including symbols, pictograms and dosing schedules.

The Prescrire Packaging Awards

Prescrire analyses the packaging of about 150 drugs every year, and has examined over 5000 products in the past 30 years.

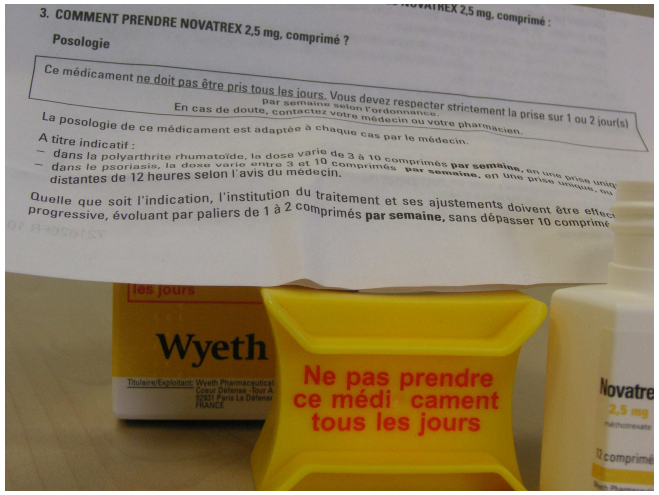
The Packaging Awards focus on the quality of packaging for drugs evaluated during the previous year in the New Products section of our French edition

-  Packaging Awards
-  Yellow cards
-  Red cards

Packaging, labelling and naming issues beyond "New products" and changes

- Medication errors reported to Prescrire Programme Éviter l'Évitable (Preventing the Preventable)
- In-deepth analysis of types of errors or packaging problems
- Prescrire' responses to public consultations (European Commission, European and national medicines agencies, others)

Oral methotrexate



Translated from ***Rev Prescrire*** **February 2013; 33 (352): 101**

Weekly oral methotrexate therapy: raise awareness of fatal dosing errors

● **France's decision to remove all sentences referring to fractionation of the weekly dose from the summaries of product characteristics (SPCs) for products based on oral *methotrexate* does not go far enough: the packaging must also be improved. *Methotrexate* dosing errors can be fatal.**

Methotrexate, a cytotoxic agent, is used as an anticancer drug and also as an immunosuppressant, at low weekly doses, for severe forms of rheumatoid arthritis and psoriasis (1,2). *Methotrexate* overdose can cause severe and even life-threatening disorders, including mouth ulceration as well as haematological, hepatic, renal, gastrointestinal, cutaneous and pulmonary disorders (1).

In early 2013, three brands of oral *methotrexate* were available in France: Imeth° tablets (10 mg), Méthotrexate Bellon° tablets (2.5 mg) and Novatrex° tablets (2.5 mg) (3).

The use of bulk bottles without a safety cap creates a risk that children may accidentally ingest massive amounts of *methotrexate*, with fatal consequences (2).

The weekly dosing schedule of oral *methotrexate* is unusual (2), and a common cause of oral *methotrexate* overdose is daily ingestion of entire weekly doses. Deaths are regularly reported (see inset, right) (4).

SPCs: a single weekly dose. In 2011, in an attempt to prevent overdose due to dosing errors, the marketing authorisation committee of the French health products agency (ANSM, formerly Afssaps) recommended that the SPCs of products based on oral *methotrexate* should no longer mention the possibility of splitting the weekly dose for patients who do not tolerate the single weekly dose (5). In early 2013 the SPCs and patient leaflets of Méthotrexate Bellon° and Novatrex°, but not those of Imeth°, were modified accordingly (**a**)(3,6). The phrase (our translation) "*take the prescribed dose only once a week*" now appears on the boxes and bottles of all three brands but is not always easy to read, especially on the bottles of Méthotrexate Bellon°.

In practice. Splitting the weekly dose of oral *methotrexate* may be useful for some patients who do not tolerate the single weekly dose (5). However, simply removing sentences mentioning this possibility from the SPCs does not eliminate the risk of error: it would be better to provide specific information on how to split the weekly dose, along with packaging appropriate for once-weekly dosing. In addition, patients, family members and caregivers must be properly alerted to this danger.

Healthcare professionals must take care when writing prescriptions and when adding written information to the packaging; they must also take time to inform patients, family members and caregivers of the risk (7). These warnings must be repeated until the severity of *methotrexate* dosing errors is fully grasped.

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a- Méthotrexate Bellon° and Novatrex° were licensed through the French national marketing authorisation procedure, and the French authorities can therefore decide whether to remove parts of the SPCs. Imeth° was authorised through the European decentralised procedure, meaning that changes to the SPC must be discussed at the European level (ref 8). On 7 January 2013, the possibility of splitting the weekly dose with a different schedule was still mentioned in the Imeth° SPC (ref 3).

Selected references from Prescrire's literature search.
1- Prescrire Rédaction "20-1-4. Patients sous méthotrexate" *Rev Prescrire* 2012; **32** (350 suppl. interactions médicamenteuses).
2- Prescrire Rédaction "Méthotrexate oral: flacons-vrac dangereux pour un cytotoxique" *Rev Prescrire* 2011; **31** (331): 346-347.
3- Afssaps "RCP-Imeth" 27 March 2012 + "RCP+notice-Méthotrexate Bellon" 7 February 2012 + "RCP+notice-Novatrex" 27 December 2011: 33 pages.
4- Prescrire Editorial Staff "Weekly methotrexate: still more deaths in France in 2011" *Prescrire Int* 2012; **21** (123): 15.
5- Afssaps "Commission d'AMM du 1er December 2011 "Verbatim"": 47 pages.
6- Nordic Pharma "Courriel à *Prescrire*" 14 December 2012: 2 pages.
7- Prescrire Rédaction "Méthotrexate une fois par semaine: attention !" Infos-Patients Prescrire July 2012: 1 page.
8- HMA "Pharmacovigilance working party. December 2011 plenary meeting" 10 January 2012: 20 pages.

PREVENTING THE PREVENTABLE

Fatal methotrexate overdose

● **A case reported through Prescrire's Preventing the Preventable programme (evitable.prescrire.org).**

A 90-year-old man was admitted to hospital, via a busy emergency unit, for a fracture. He was dependent and had difficulty expressing himself (1).

Consulted a few days later for a suspected infection of the surgical wound, a doctor, on examining his ongoing treatments and laboratory results (showing neutropenia), realised that the patient had received a *methotrexate* overdose due to daily administration of the weekly dose.

A junior doctor, on reading a prescription for « *Novatrex° 2.5 mg - 6 tab/d (once/week)* », entered « *Novatrex° 2.5 mg 2 tab morning, midday, evening* » into the ward's prescribing software. The dosing error was not detected on the patient's transfer to a surgical ward, or when his drug regimen was analysed.

The *methotrexate* thus administered had not been dispensed by the hospital pharmacy but had been brought along by the patient himself. The nursing staff had administered *methotrexate* from the patient's box, but had failed to notice the warning printed on the box and the patient leaflet (our translation): "*Do not take this drug every day*". Thus, instead of 15 mg once a week, the patient had received a total of about 50 mg of *methotrexate* over 5 days.

Despite *methotrexate* withdrawal and *folic acid and filgrastim* administration, the patient died 5 days after the error was first detected (1).

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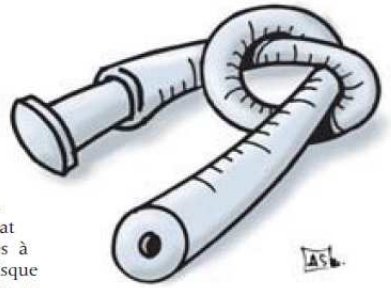
1- Programme Éviter l'Évitable "Signalement n° ee120118215 - observation anonymisée" 22 November 2012: 3 pages.

Inaccurate dosing devices

Médicaments : règles et pièges ..... *Quelques concepts*

Dispositifs doseurs : pour éviter les erreurs de doses



Le dispositif doseur d'un médicament buvable nécessite une attention particulière. Ses caractéristiques, son maniement, ses dangers sont à connaître pour un usage à bon escient.

Rev Prescrire 2011 ; 31 (334) : 580-581.

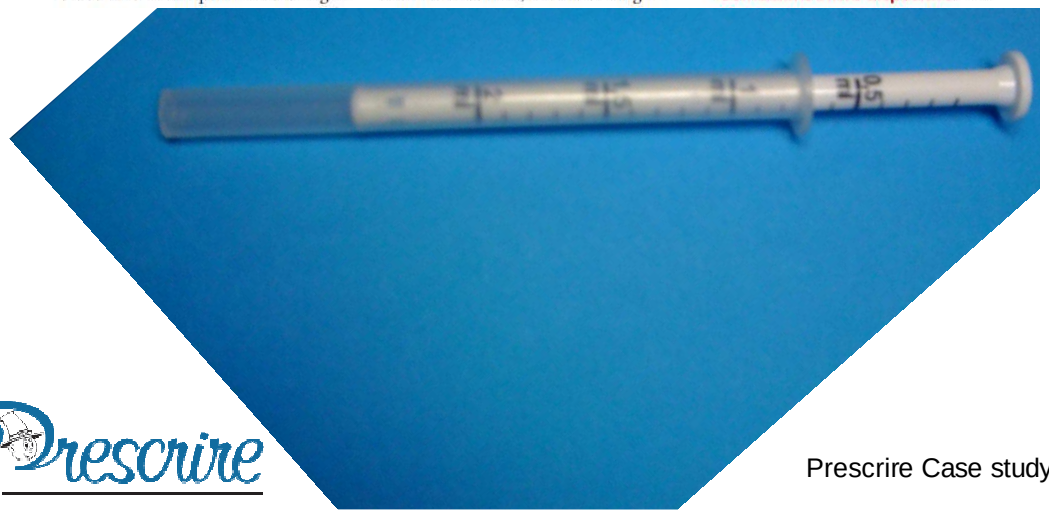
La balance bénéfices-risques d'un médicament dépend des doses utilisées. Les formes buvables sont utiles pour adapter finement les doses en fonction du poids, chez les enfants par exemple, et en cas de difficultés à avaler des comprimés ou des gé-

Les limites du compte-gouttes. Le compte-gouttes permet une mesure fine (4). Mais son usage devient délicat quand le nombre de gouttes à compter est élevé. Il existe un risque d'imprécision, parfois importante, en cas d'erreur sur le compte des gouttes, en cas de pression trop forte sur l'embout du compte-gouttes, et quand le dispositif n'est pas utilisé tout à fait verticalement.

Gare aux graduations. Les manières de graduer les dispositifs doseurs sont variées, et sont à l'origine par patient. Elles font perdre de vue la quantité réelle administrée (9).

Les mentions figurant sur les dispositifs doseurs (graduation, dénomination, concentration) sont parfois difficilement lisibles (1,2,7,10).

Confusions entre dispositifs. Les



COMPLÉMENT DE GAMME

Oxycodone buvable : attention aux erreurs lors de la préparation des doses

Ce qui fait la nouveauté	Ce qui existe aussi
Hôpital **OXYNORM° 10 mg/ml** solution buvable ***oxycodone*** 10 mg/ml 1 flacon de 30 ml ... 13,50 € (**a**) Agréé collect. **Stupéfiant (b)** Mundipharma	**Sous le nom d'Oxynorm°** : les gélules à 5 mg, 10 mg et 20 mg, en boîtes de 14 ; la solution injectable IV et SC à 10 mg/ml (10 mg/1 ml, 20 mg/2 ml et 200 mg/20 ml) et à 50 mg/1 ml, en boîtes de 4 ou 5 ampoules. **Sous le nom d'Oxycontin° LP** : les comprimés à libération prolongée à 5 mg, 10 mg, 20 mg, 40 mg, 80 mg et 120 mg, en boîtes de 28. **Sous le nom d'Oxynormoro°** : les comprimés orodispersibles à 5 mg, 10 mg et 20 mg, en boîtes de 14. La gamme Oxycontin° LP, les gélules Oxynorm° et la gamme Oxynormoro° sont remboursables à 65 % par la Sécurité sociale, agréées aux collectivités et inscrites sur la liste des stupéfiants (**b**,**c**). Les solutions injectables Oxynorm° sont agréées aux collectivités et inscrites sur la liste des stupéfiants (**d**).

a- Prix hors taxes.
b- Prescription sur une ordonnance sécurisée, pour une durée maximale limitée à 28 jours.
c- Remboursables uniquement dans l'indication « douleurs d'origine cancéreuse, intenses ou rebelles aux antalgiques de niveau plus faible, chez l'adulte à partir de 18 ans ». Non remboursables dans l'indication « traitement des douleurs sévères qui ne peuvent être correctement traitées que par des analgésiques opioïdes forts, en particulier les douleurs d'origine cancéreuses ».
d- Prescription sur une ordonnance sécurisée, pour une durée maximale limitée à 7 jours, ou à 28 jours en cas d'administration à l'aide de systèmes actifs pour perfusion.

En France, l'*oxycodone*, un opioïde fort, est commercialisée pour le traitement des douleurs cancéreuses des adultes (1,2). Il n'est pas démontré que l'*oxycodone* présente une meilleure balance bénéfices-risques que la *morphine*, la référence (2).

Mi-2011, la firme Mundipharma a commercialisé une forme buvable multidoses d'*oxycodone* à libération immédiate sous le nom Oxynorm°, que nous avons tardé à présenter (1).

Un conditionnement à risque d'erreur. Le piston de la seringue doseuse est gradué en ml (de 0,1 ml à 2 ml, soit de 1 mg à 20 mg d'*oxycodone*), ce qui oblige à une conversion en ml de la dose d'*oxycodone* prescrite en mg (1,3). De plus, la mention du volume ne figure que tous les 0,5 ml (soit 5 mg). En l'absence de graduation à 0,25 ml, il s'avère impossible de mesurer précisément 2,5 mg d'*oxycodone*, dose pourtant prévue dans le RCP (1).

En outre, la concentration élevée de la solution à 10 mg/ml fait prévoir des surdoses, avec par exemple administration d'une dose de 20 mg (soit 2 ml) au lieu de 2 mg (soit 0,2 ml).

Le flacon multidoses contient 300 mg d'*oxycodone*, une quantité importante pour ce stupéfiant, et dangereuse en cas d'ingestion massive volontaire ou accidentelle. Cette quantité importante expose de surcroît à un risque de contamination microbienne en raison du nombre élevé de prélèvements par seringue doseuse (1,3).

Le programme Prescrire Éviter l'Évitable a reçu un signalement corroborant que ces défauts de praticité s'avèrent sources d'erreur de dose en pratique courante de soins (3). En particulier, cette présentation expose à un risque d'erreur de dose lors d'une prescription de 1 mg ou 2 mg, souvent suffisante au moment d'un soin douloureux chez des patients âgés.

En pratique. La *morphine* est l'opioïde fort de premier choix (2). Et elle est aussi disponible sous forme buvable et en unidoses (Oramorph°) (4).

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Extraits de la veille documentaire Prescrire.
1- ANSM "RCP-Oxynorm 10 mg/ml, solution buvable" 21 décembre 2010 ; 7 pages.
2- Prescrire Rédaction "5-1-4. Patients sous opioïde" *Rev Prescrire* 2011 ; **31** (338 suppl. interactions médicamenteuses).
3- Programme Éviter l'Évitable "Signalement n° ee120316234. Observation détaillée" 24 mai 2012 : 4 pages.
4- Prescrire Rédaction "morphine buvable-Oramorph°. Des unidoses bienvenues, mais à mieux étiqueter" *Rev Prescrire* 2006 ; **26** (275) : 570.

Prescrire calls for patient safety

Medicines in Europe Forum

Outlook

Translated from Rev Prescrire June 2012; 32 (344): 458-459

Packaging of medicines for paediatric use: Prescrire's constructive proposals

Abstract

● In May 2011, the European Medicines Agency (EMA) released for public consultation a draft guideline on the pharmaceutical development of medicines for paediatric use. Prescrire made 20 constructive proposals.

2. Improve surveillance of supplementary protection certificates

For medicines that are candidates for a 6-month extension of their supplementary protection certificate under the European Paediatric Regulation, impose stric-

5. Improve public information on packaging

Improve the information provided by health authorities for healthcare professionals and patients: provide descriptions of packaging items and instructions for their use in the summaries of product

Prescrire

Paris, 17 December 2012

Open letter

To Patricia Brunko

Head of Unit, Medicinal Products – Authorisation

European Commission

Is there a need for insulin at 200 units per ml?

Why use a new and poorly established analogue?

Dear Mrs Brunko,

Prescrire

Confusion between commercial names: EMA more concerned with defending trademarks than patient safety

Prescrire's response to the EMA consultation on drug brand names (August 2013)

Summary

● Prescrire has examined the proposed revision of the European Medicines Agency (EMA) guideline on the acceptability of brand names for drugs processed through the centralised procedure (revision 6) released for public consultation in June 2013.

The growing awareness of the risk of errors and adverse effects caused by confusion between brand names owes much to independent medication error-reporting programmes, such as the Institutes for Safe Medication Practices (ISMP), that alert health professionals, patients and health authorities by reporting the most significant cases (1). The lists of potentially confusing drug names pairs, compiled by these pro-

The North American drug regulatory agencies have raised their standards

Although it was long considered impossible to predict confusion between drug names, the development of psycholinguistic methods and human factors engineering has led the North American drug regulatory agencies to reconsider their methodology for assessing the acceptability of proposed drug names and to impose

Prescrire

Paris, 29 November 2012

Safety and usability of packaging and labelling: assessment is required prior to marketing authorisation for all medicinal products, not just for copies of existing drugs

- *Poor packaging is a major cause of medication errors. In its response to the European Medicines Agency's public consultation on potential medication errors in the context of benefit risk balance and risk minimisation measures (1), Prescrire calls for the safety and usability of the packaging and labelling of new medicines to be assessed as part of the evaluation of marketing applications. Prescrire calls also for a re-examination of all the packaging of existing medicinal products.*

Summary:

- The draft position paper that the European Medicines Agency (EMA) released for consultation on 1st June 2012 is not about considering potential medication errors as part of the evaluation of all medicinal products before marketing authorisation is granted. It focuses on the risks generated by copies containing the same active substance as a medicinal product that is already marketed. The draft does not specify whether "umbrella" brands fall under the scope of this position paper, despite their dangers.

responses to public consultations
http://english.prescrire.org
Dossiers > Theme: Medicines in Europe

Prescrire

Prescrire International Editorial

Translated from *Rev Prescrire* June 2012; 32 (344): 401

Think about drug packaging