Working Together to Address Global Drug Safety Issues with Packaging and Labeling

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  Member, Executive Committee, IMSN

IMSN INTERNATIONAL MEDICATION SAFETY NETWORK

www.intmedsafe.net/

Some important labeling and packaging problems

- Dangerous abbreviations
- Look-alike labeling
- Inconsistent and unclear expression of strength
- Cluttered labeling
- Highly stylized label graphics
- Overemphasis on company name and logos
- Lack of contrast on glass ampuls
- Inadequate prominence of reminders and warnings

Dangerous abbreviations and dose designations

60 Regular Insulin Now

New Zealand


HEPARIN INJECTION
heparin sod. (porcine mucous)
25 000 IU in 5 mL
IV/SC USE
Pfizer
HEPARIN INJECTION
heparin sod. (porcine mucous)
25 000 IU in 5 mL
IV/SC USE
Pfizer
HEPARIN INJECTION
heparin sod. (porcine mucous)
25 000 IU in 5 mL
IV/SC USE
Pfizer

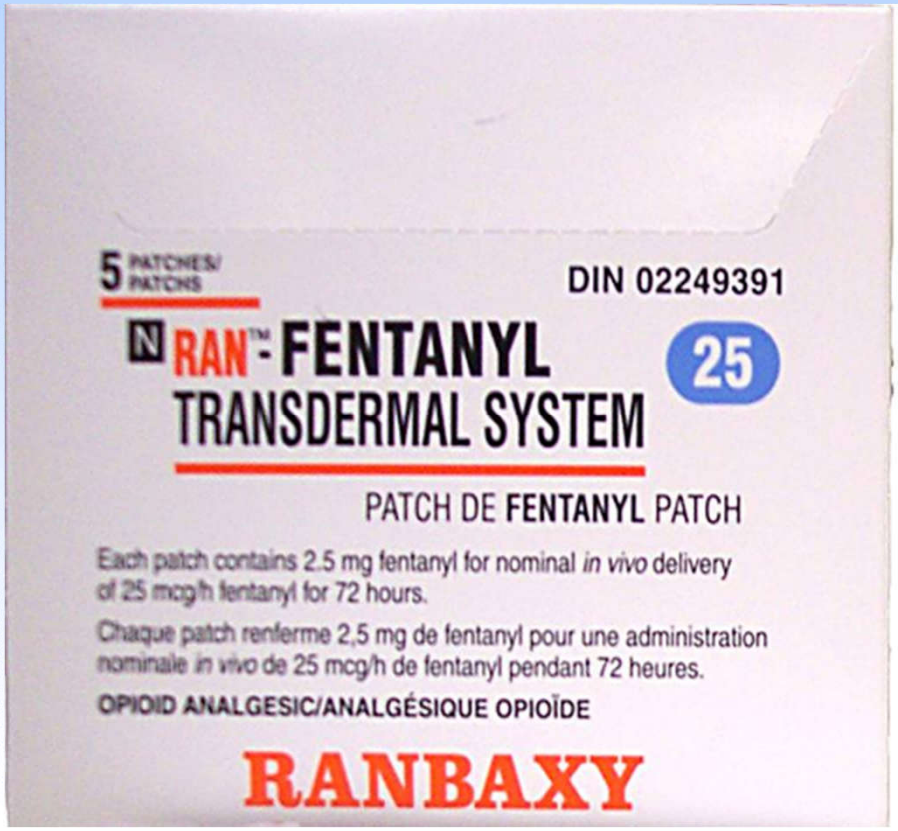

Exelon®
(rivastigmine tartrate)
Capsules
equivalent to
3.0 mg
base
100 Capsules
See bottom panel for lot number and expiration date.

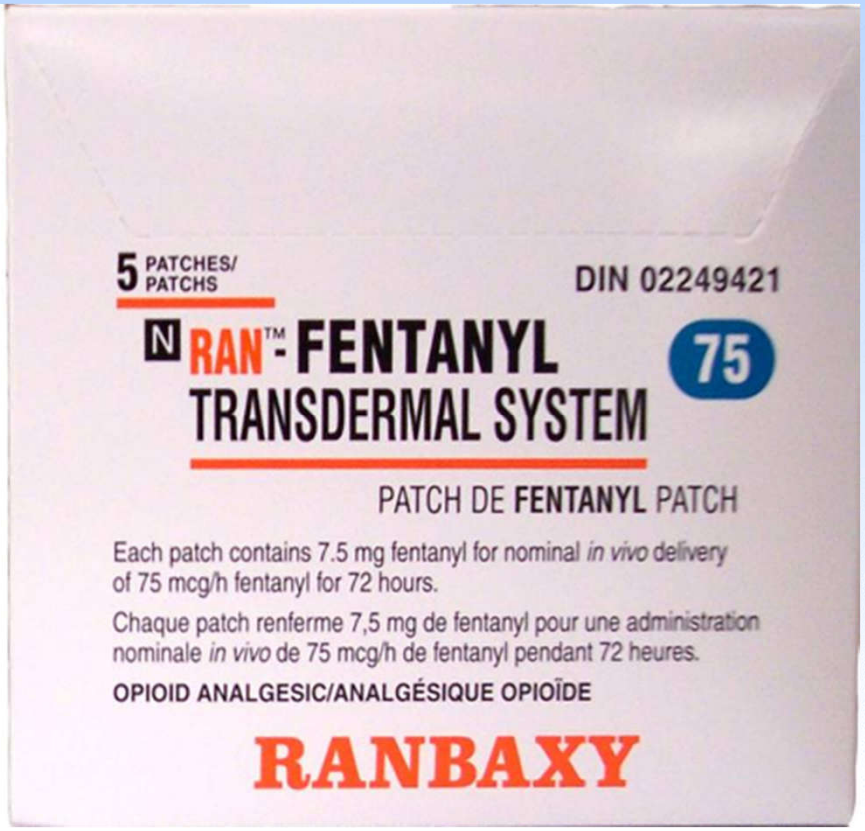
Look alike labeling

Belize

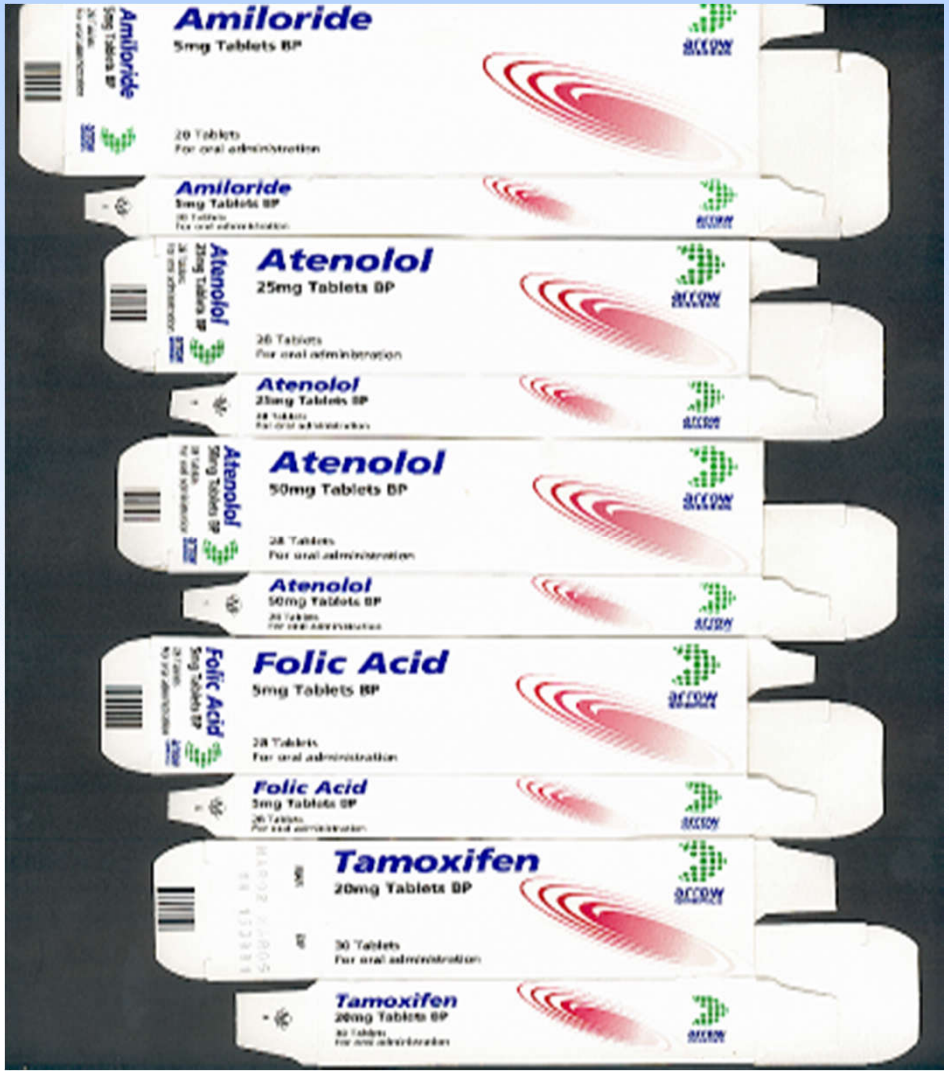

TROPIUM®-750
Solución para Nebulización
Bromuro de Ipratropium 750 mcg/mL
10 mL
ALBUGENOL®
Solución para Nebulización
Salbutamol 5mg/mL
10 mL

Canada

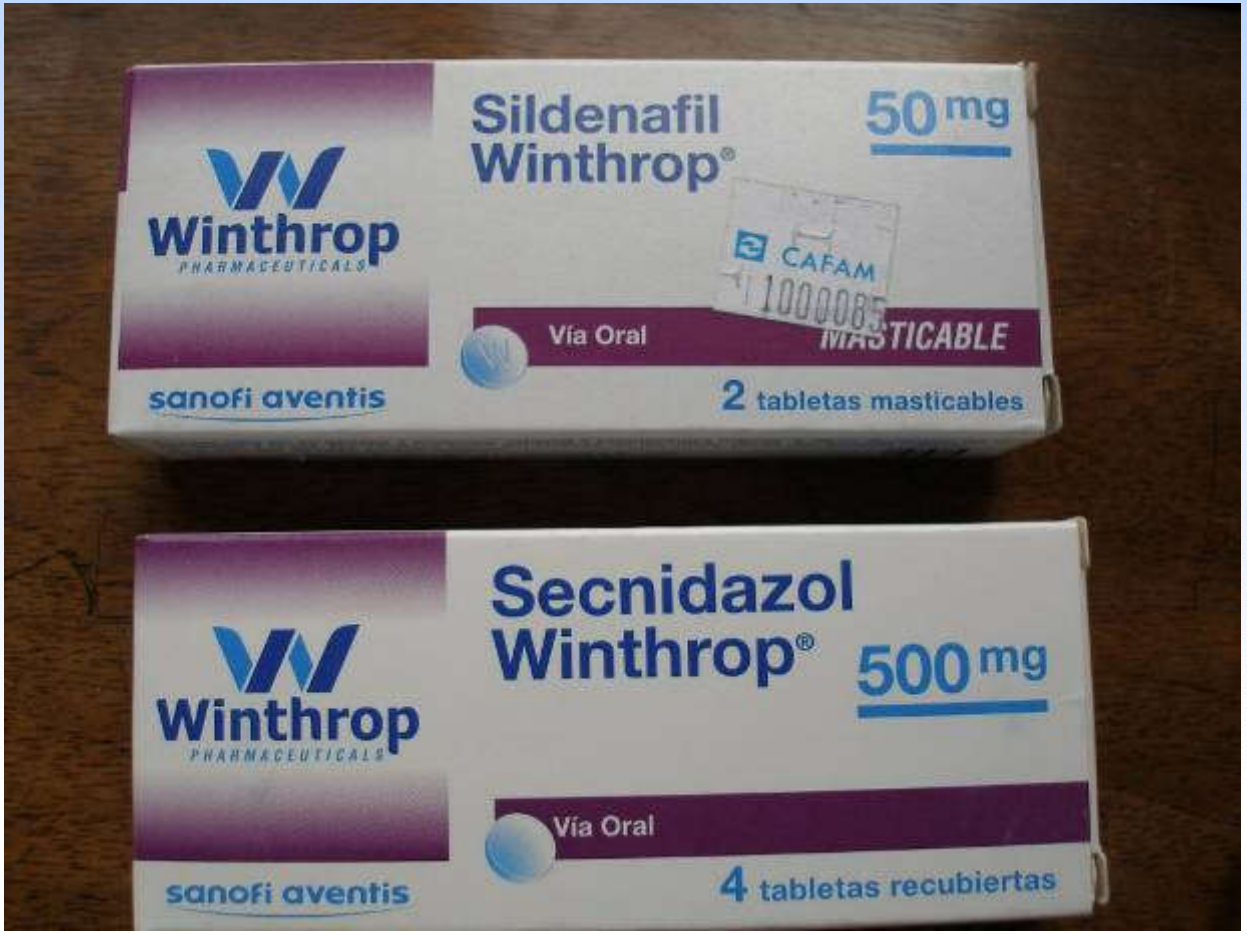

5 PATCHES/ PATCHS
DIN 02249391
RAN™-FENTANYL
TRANSDERMAL SYSTEM
25
PATCH DE FENTANYL PATCH
Each patch contains 2.5 mg fentanyl for nominal in vivo delivery of 25 mcg/h fentanyl for 72 hours.
Chaque patch renferme 2,5 mg de fentanyl pour une administration nominale in vivo de 25 mcg/h de fentanyl pendant 72 heures.
OPIOID ANALGESIC/ANALGÉSIQUE OPIOÏDE
RANBAXY


5 PATCHES/ PATCHS
DIN 02249421
RAN™-FENTANYL
TRANSDERMAL SYSTEM
75
PATCH DE FENTANYL PATCH
Each patch contains 7.5 mg fentanyl for nominal in vivo delivery of 75 mcg/h fentanyl for 72 hours.
Chaque patch renferme 7,5 mg de fentanyl pour une administration nominale in vivo de 75 mcg/h de fentanyl pendant 72 heures.
OPIOID ANALGESIC/ANALGÉSIQUE OPIOÏDE
RANBAXY

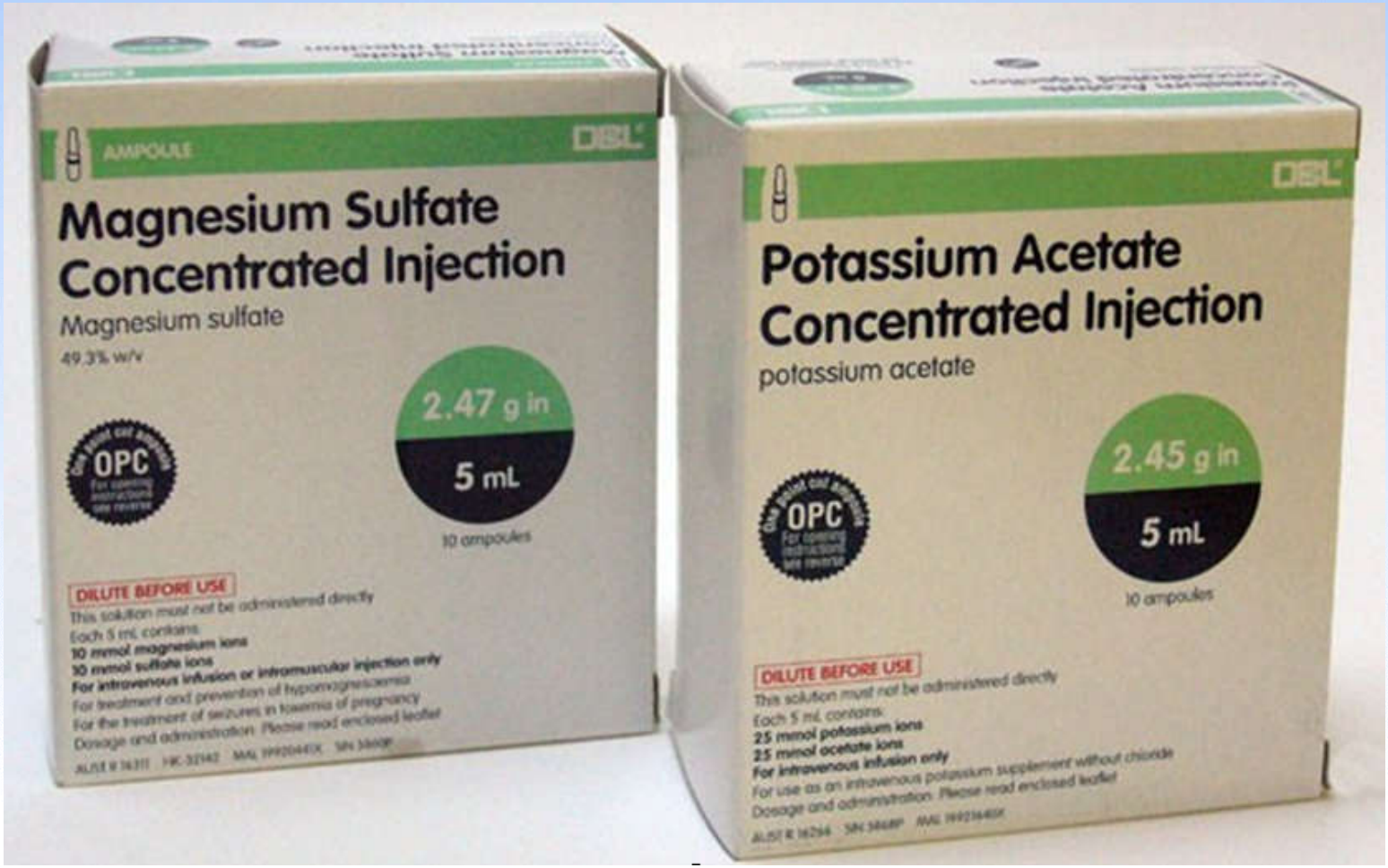
United Kingdom
Oral Generics



Latin America - Colombia



Australia


AMPOULE
DBL
Magnesium Sulfate
Concentrated Injection
Magnesium sulfate
49.3% w/v
2.47 g in
5 mL
10 ampoules
OPC
DILUTE BEFORE USE
This solution must not be administered directly
Each 5 mL contains:
10 mmol magnesium ions
10 mmol sulfate ions
For intravenous infusion or intramuscular injection only
For treatment and prevention of hypomagnesaemia
For the treatment of seizures in toxaemia of pregnancy
Dosage and administration: Please read enclosed leaflet
DBL
Potassium Acetate
Concentrated Injection
potassium acetate
2.45 g in
5 mL
10 ampoules
OPC
DILUTE BEFORE USE
This solution must not be administered directly
Each 5 mL contains:
25 mmol potassium ions
25 mmol acetate ions
For intravenous infusion only
For use as an intravenous potassium supplement without chloride
Dosage and administration: Please read enclosed leaflet

Denmark

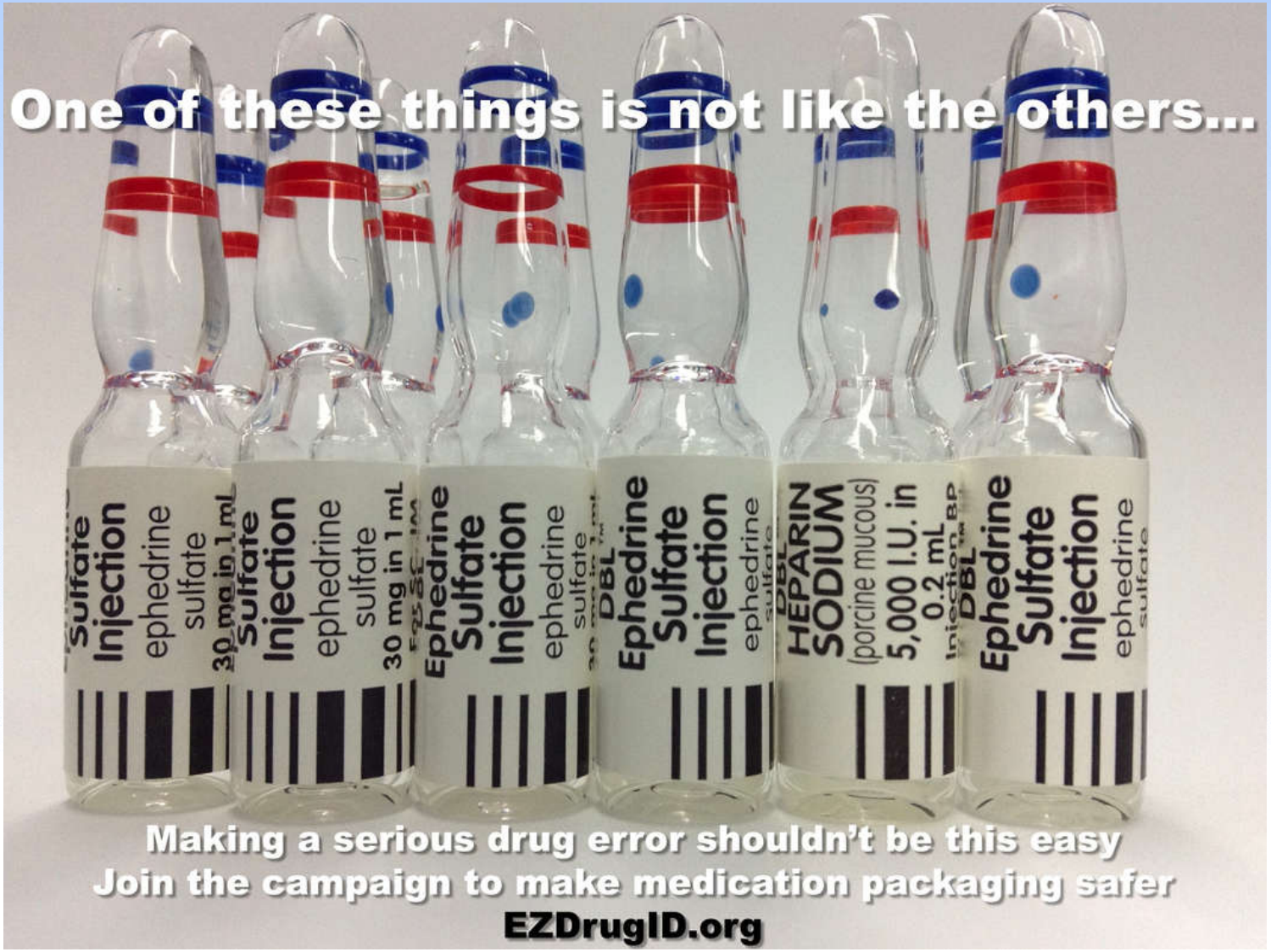

Klopoxid DAK
10 mg
100 tabletter
chlordiazepoxid
Vnr. 50 96 04
NYCOMED
Klopoxid DAK
25 mg
50 tabletter
chlordiazepoxid
Vnr. 50 96 38
NYCOMED

Contrast on glass ampuls

Spain

Note lack of label background – no contrast upon dark background

Australia


One of these things is not like the others...
Ephedrine Sulfate Injection ephedrine sulfate
HEPARIN SODIUM (porcine mucous) 5,000 I.U. in 0.2 mL
Making a serious drug error shouldn't be this easy
Join the campaign to make medication packaging safer
EZDrugID.org

Ampule labeling

Serious medication errors with ampules of bupivacaine and tranexamic acid

Figure 1. Look-alike ampoules: Tranexamic acid and bupivacaine.

- https://www.ejmanager.com/mnstemps/83/83-1444637751.pdf
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3371494/
- https://www.apsf.org/newsletters/html/2010/spring/02_inject.htm
- https://dokumen.tips/documents/01-danger-of-wrong-drug-administration-during-subarachnoid-blockpdfpdfcompressor.html

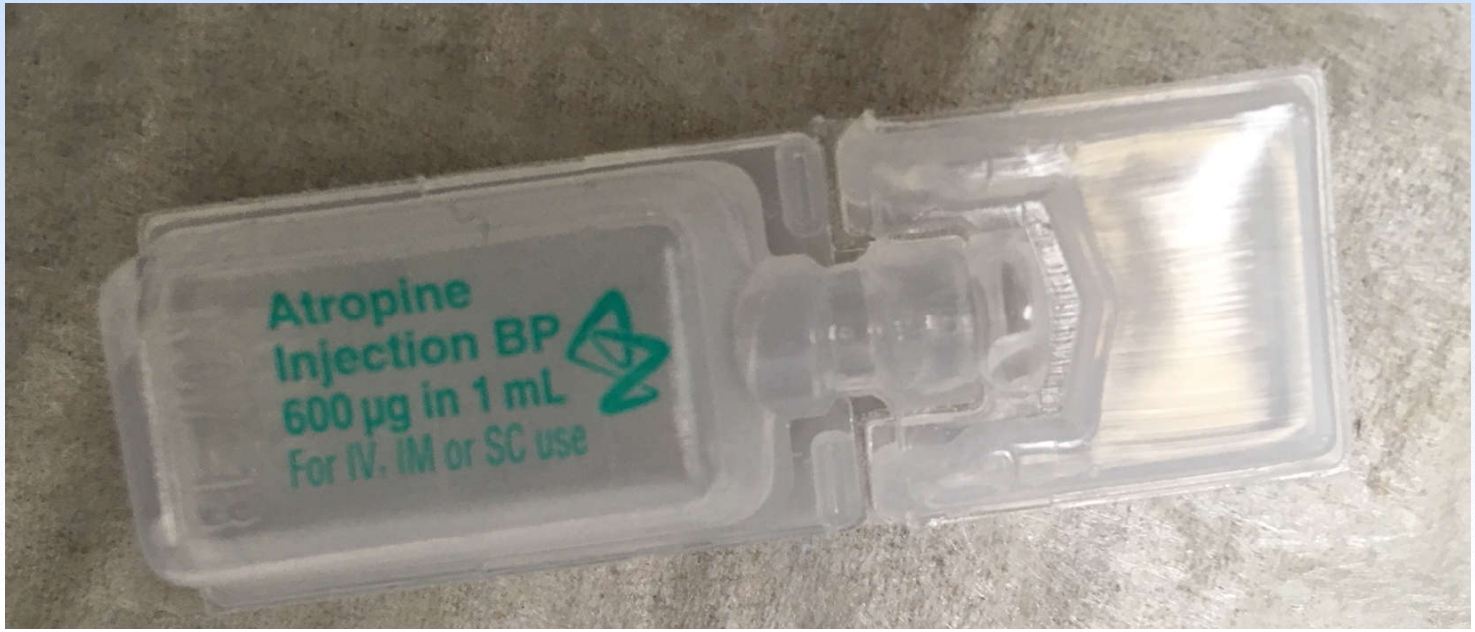
Germany and United States

Label position on ampuls and syringes

US ampul label for comparison

New Zealand

Readability of information on polypropylene ampules

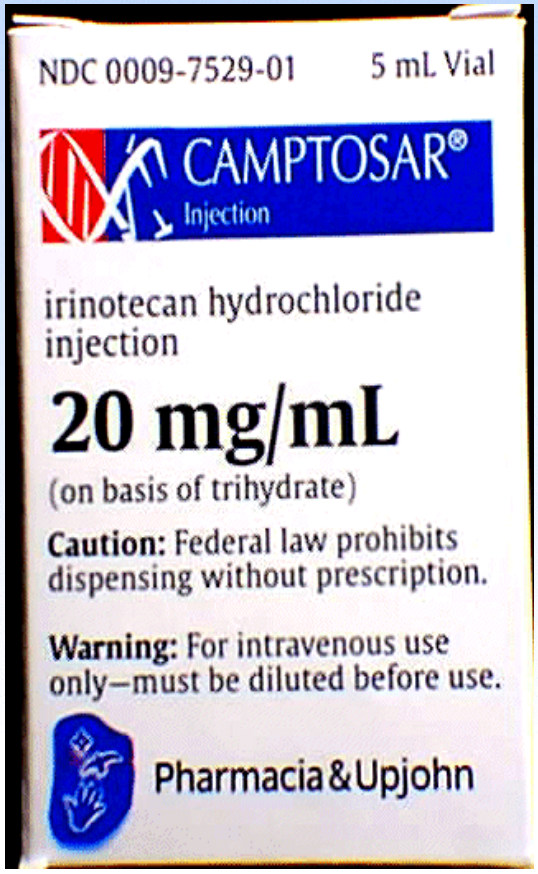


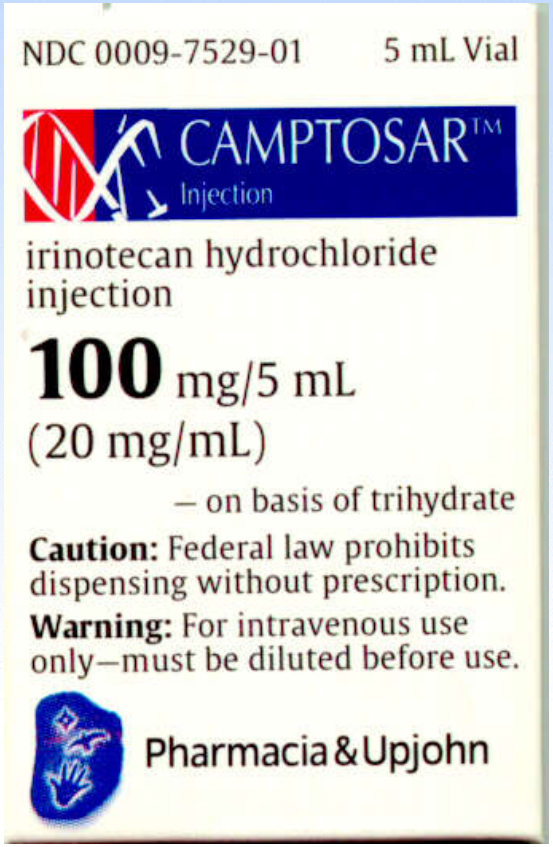

Clindamicina Fosfato 600 mg 4 mL I.M./I.V.
Diclofenaco Sódico 75 mg 3 mL I.M./Infusión I.V.
Gentamicina 160 mg 2 mL I.M./I.V.
Amikacina 100 mg 2 mL
Dexametasona Fosfato 8 mg 2 mL I.M./I.V.
Lincomicina 600 mg 2 mL
Betametasona 4 mg 1 mL I.M./I.V.
Lincomicina 300 mg 1 mL I.M./I.V.
traMADol Clorhidrato 50 mg 1 mL
Dexametasona Fosfato 4 mg 1 mL I.M./I.V.

Expression of concentration and strength

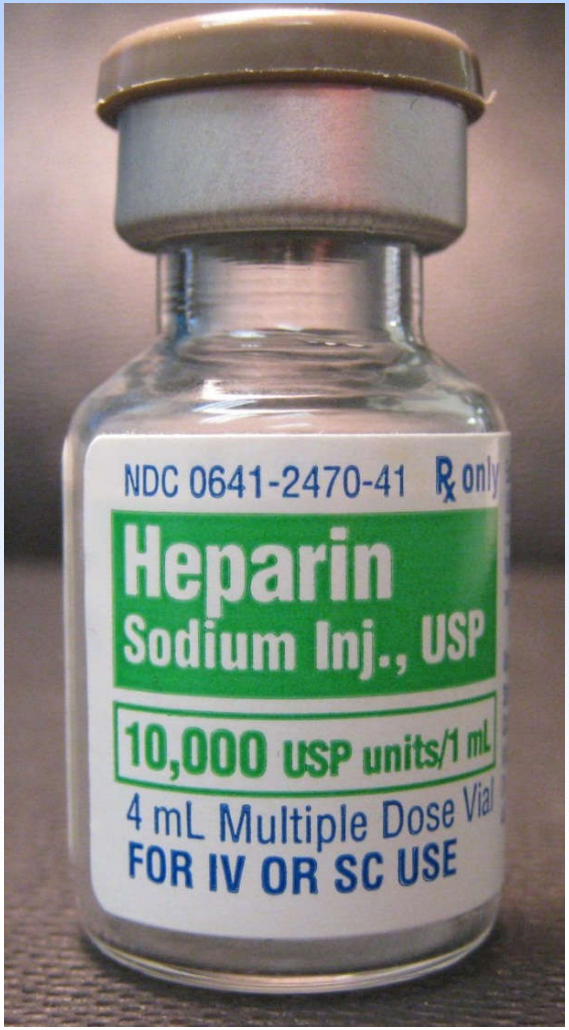
United States

Before and after – both are same strength





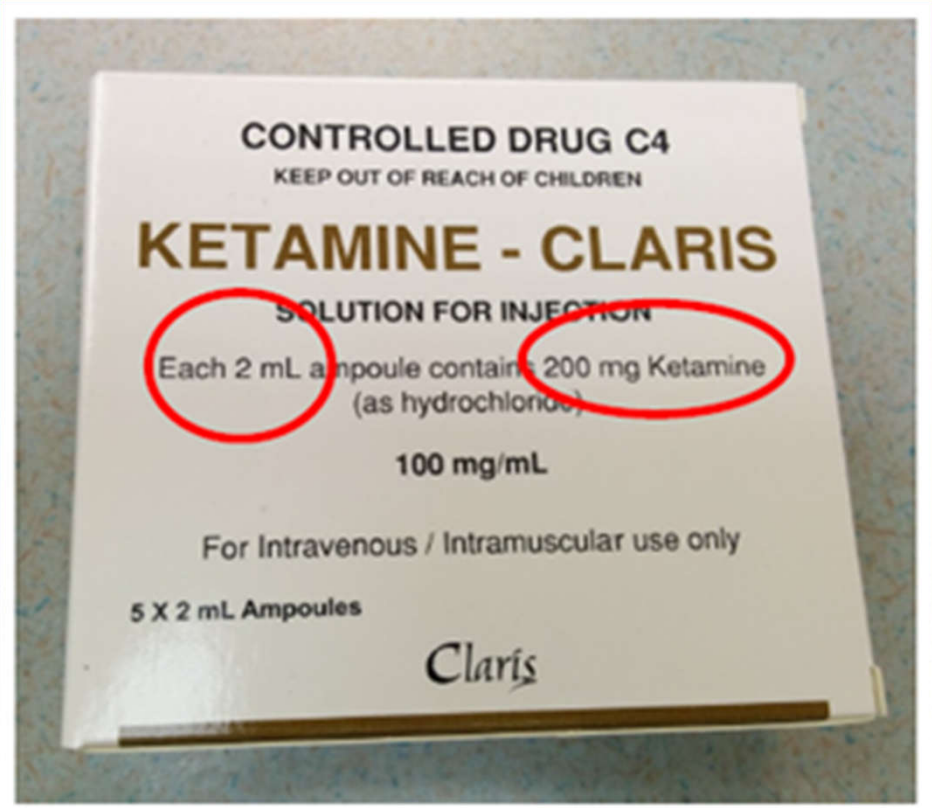
United States



Singapore


10 ml
KETAMINE HY
INJECTION US
50 mg Ketamine
for i.m./ i.v. injecti
Protect from light
Store below 30 °C
ROTE
TRITTAU • GERMA
29/04/201
ET13L087-1

New Zealand


CONTROLLED DRUG C4
KEEP OUT OF REACH OF CHILDREN
KETAMINE - CLARIS
SOLUTION FOR INJECTION
Each 2 mL ampoule contains 200 mg Ketamine
(as hydrochloride)
100 mg/mL
For Intravenous / Intramuscular use only
5 X 2 mL Ampoules
Claris


100 mg/mL
Claris

August 6, 2007

Direct Healthcare Professional Communication on Kaletra® (lopinavir/ritonavir) oral solution and accidental overdose in children

Dear Healthcare Professional,

Summary

Abbott was recently notified of an accidental overdose when an infant received a significantly large dose of Kaletra (lopinavirfritonavir) Oral Solution. The infant subsequently died.

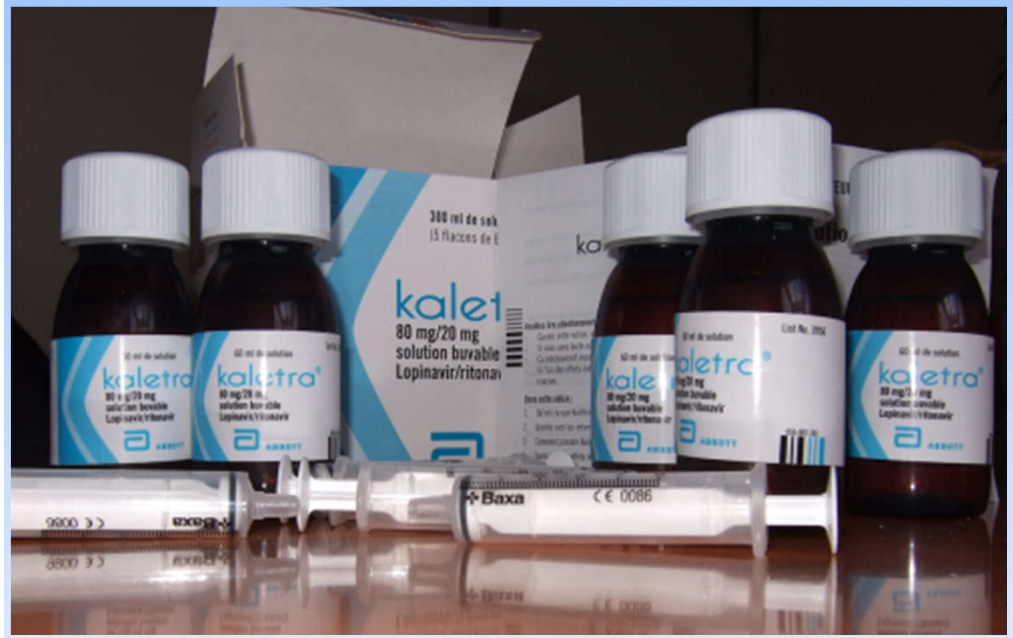
Abbott is reminding you that:

- Kaletra Oral Solution is highly concentrated, containing 80 mg lopinavir and 20 mg **ritonavir** per mL (not per bottle).
- Children dosages are calculated based on body weight. A child should receive **less** than 5 mL oral solution per dose unless they are also receiving certain concomitant **antiretroviral** medicines. Reference should be made to the attached prescribing information.

Further information on the safety concern

- **The accidental overdose occurred in a 44-day-old infant, born at 30 weeks gestation with HIV, who was given approximately 6.5 mL of Kaletra Oral Solution (this is about 10 times the calculated volume). The infant died nine days later of cardiogenic shock.**
- **Special attention must be paid to accurate calculation of the dose, transcription of the r instructions to minim be made to the attac recommendations in**

Please see accompanying **full pr**



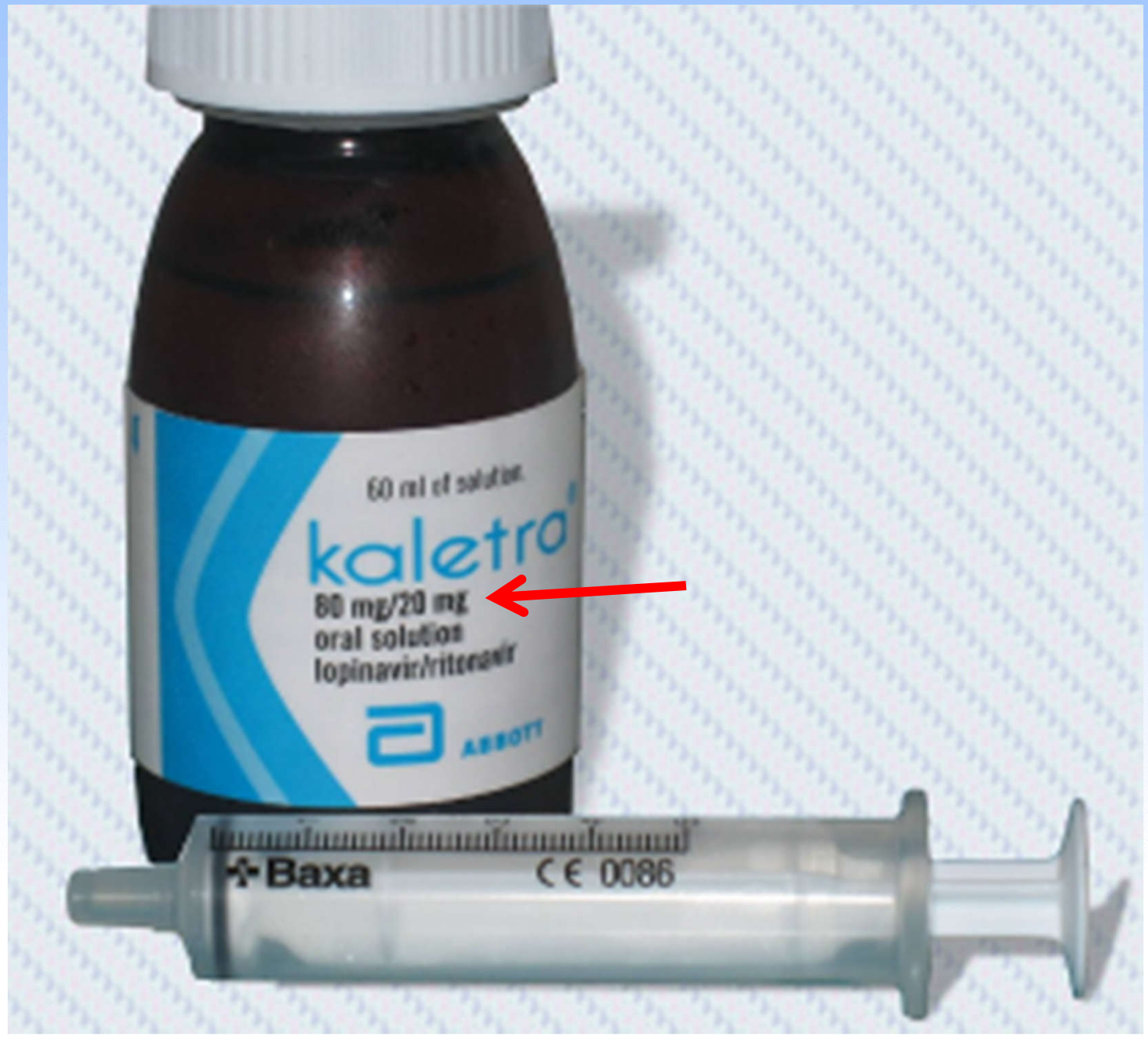
French label above

United Kingdom

France and French speaking African country

Spain

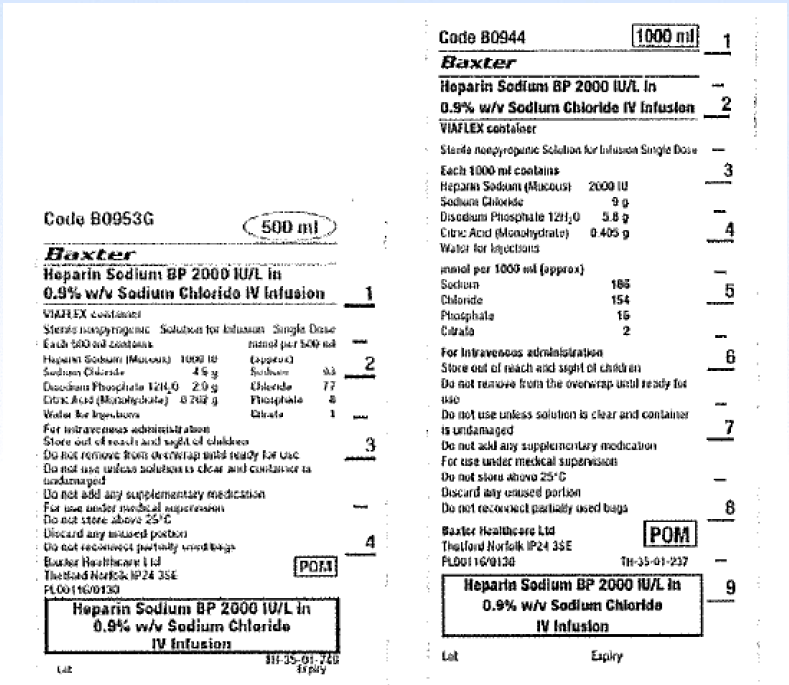
Greece

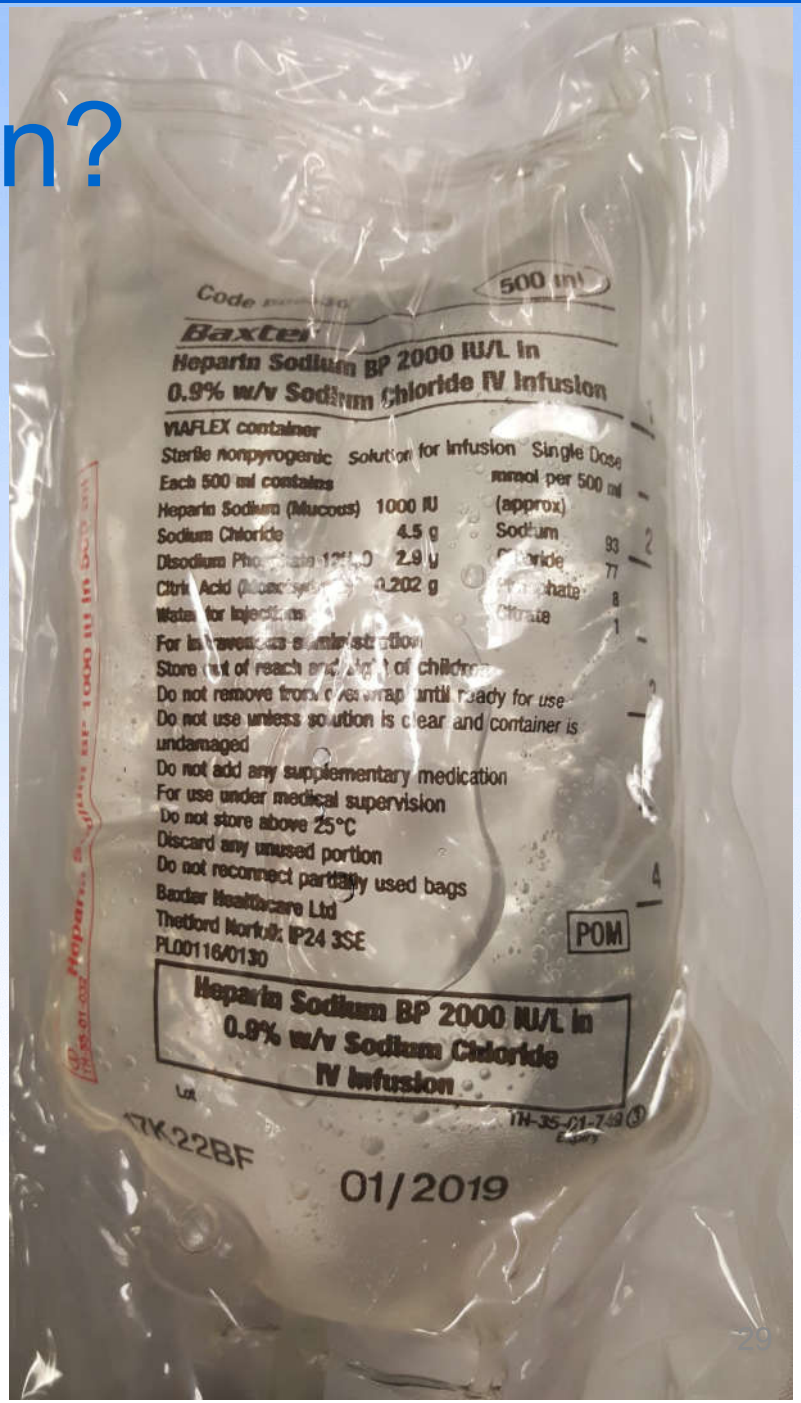

kaletra
80 mg/20 mg
oral solution
ABBOTT
Baxa
CE 0086

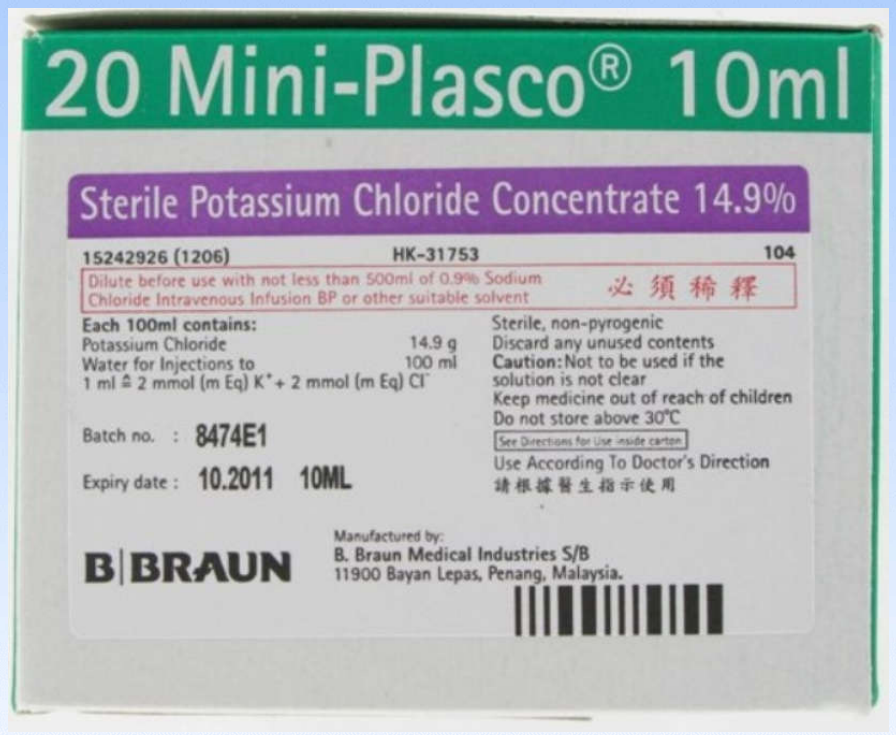

Baxter
1-0845
0.30% POTASSIUM CHLORIDE IN
5% DEXTROSE AND 0.45% SODIUM
CHLORIDE INJECTION USP
NDC 0264-7638-00
EXP-12/19 J7H087 L6380
1-0944
0.30% POTASSIUM CHLORIDE IN
5% DEXTROSE AND 0.45% SODIUM
CHLORIDE INJECTION USP
EXP-09/19 J7C124 L6380
Chloride
and
Chloride
REF L6380
1000 mL
NDC 0264-7638-00
DIN 01931571
CONTAINER
40 mEq K+/liter
Each 100 mL contains:
Hydrous Dextrose USP 5 g
Sodium Chloride USP 0.45 g
Water for Injection USP qs
pH 4.4 (3.5-6.5)

How much heparin?

- IU
- Bar code?
- Heparin in title is per liter while other heparin mention and electrolytes are per 500 mL







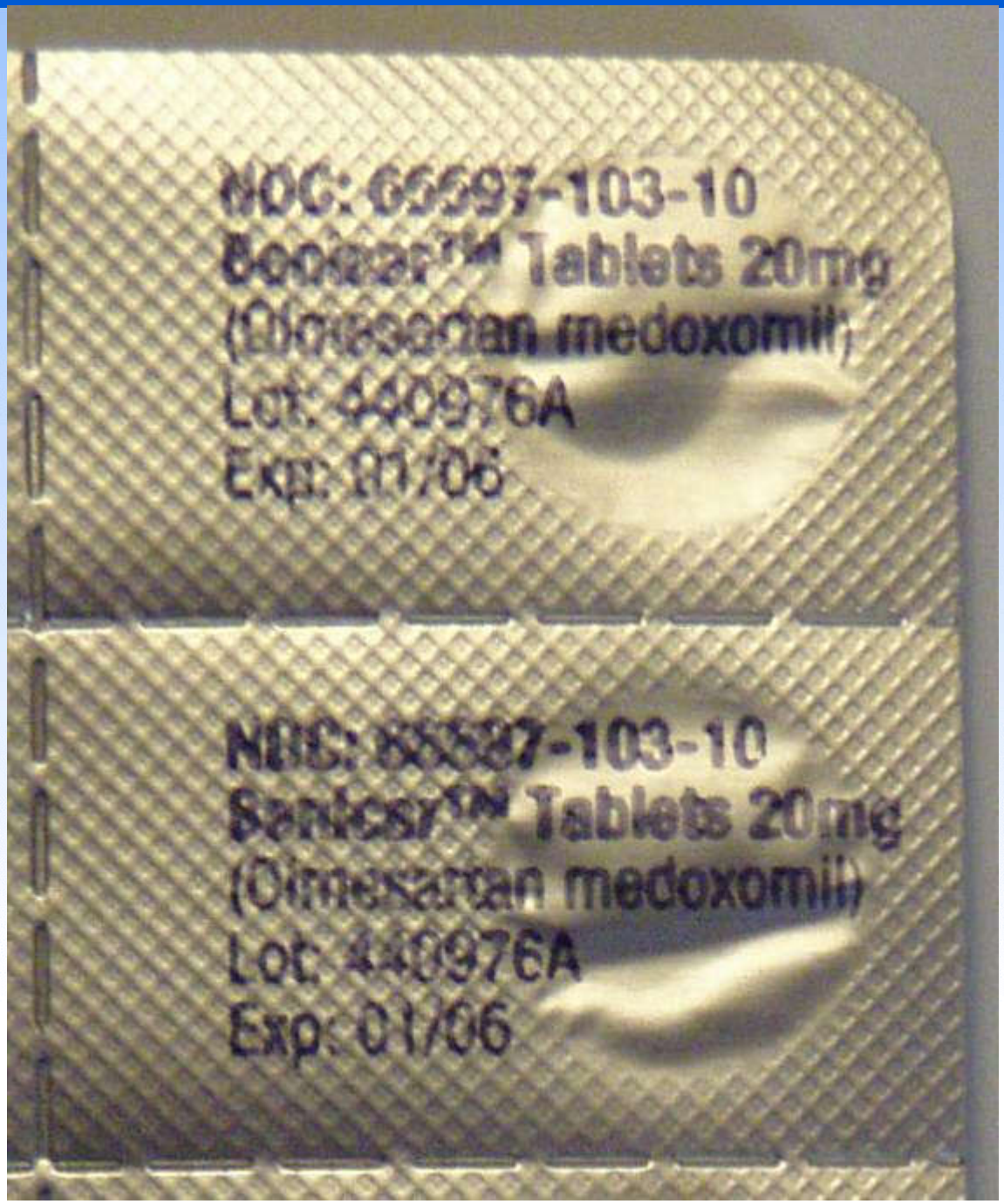
- Units not standardized to mEq or mmol
- Dilution warning barely visible

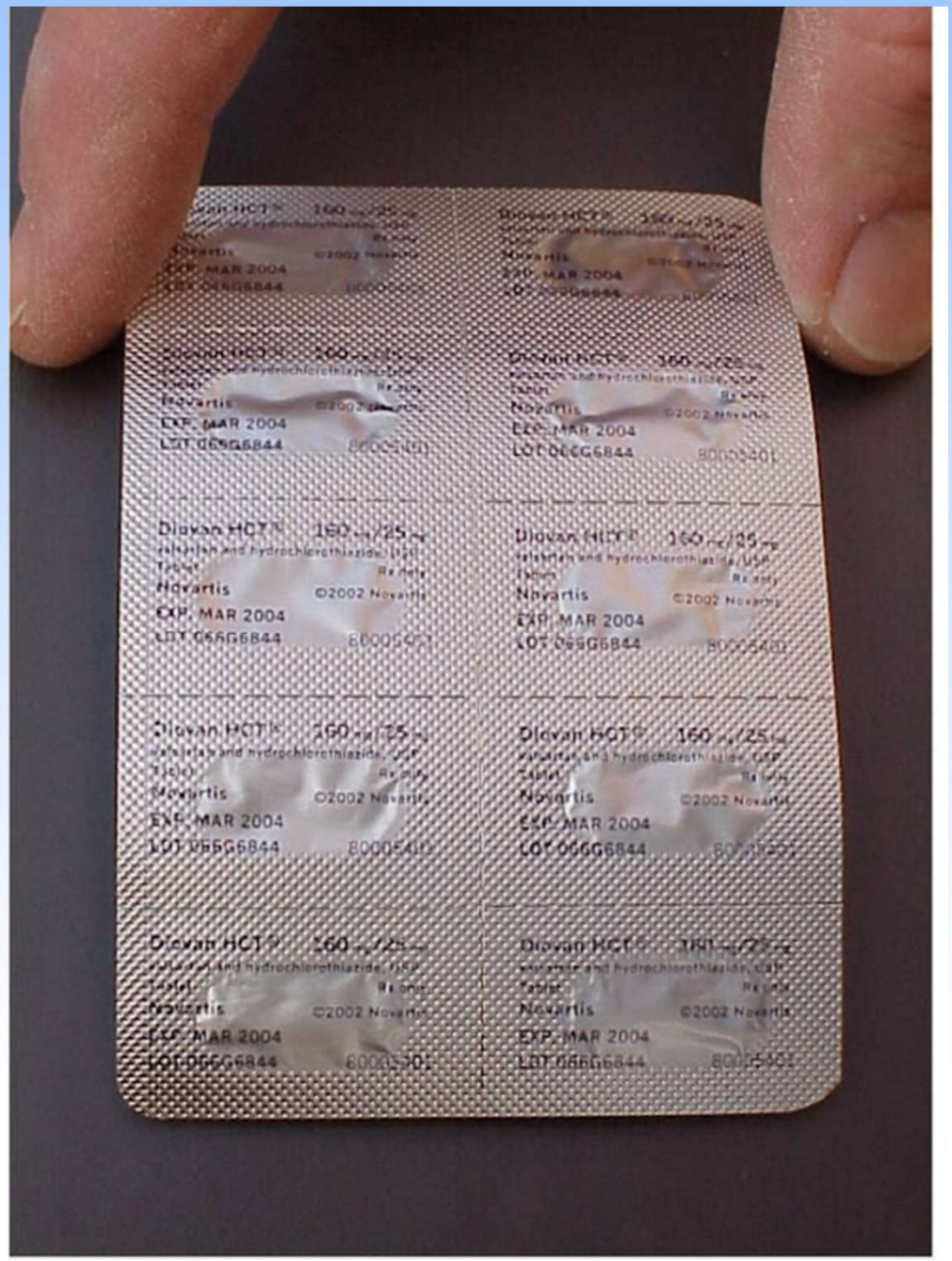

20 mL Single-dose For Intravenous use.
Potassium Chloride
for Injection Concentrate, USP
40 mEq/20 mL (2 mEq/mL)
CONCENTRATE
MUST BE DILUTED BEFORE USE.
Hospira, Inc., Lake Forest, IL 60045 USA


Potassium Chloride
for Injection
Concentrate, USP
Rx only
CONCENTRATE
MUST BE DILUTED BEFORE USE.
FOR INTRAVENOUS INFUSION ONLY;
MUST BE DILUTED PRIOR TO INJECTION.
Fliptop Vials
EN-3583
MUST BE DILUTED
Potassium Chloride
for Injection Concentrate, USP
20 mEq/10 mL (2 mEq/mL)
CONCENTRATE
MUST BE DILUTED BEFORE USE.
25 Units/NDC 0409-6651-06
Rx only
10 mL Single-dose
For Intravenous use.
LOT 62-225-DK
Hospira
IM-3545

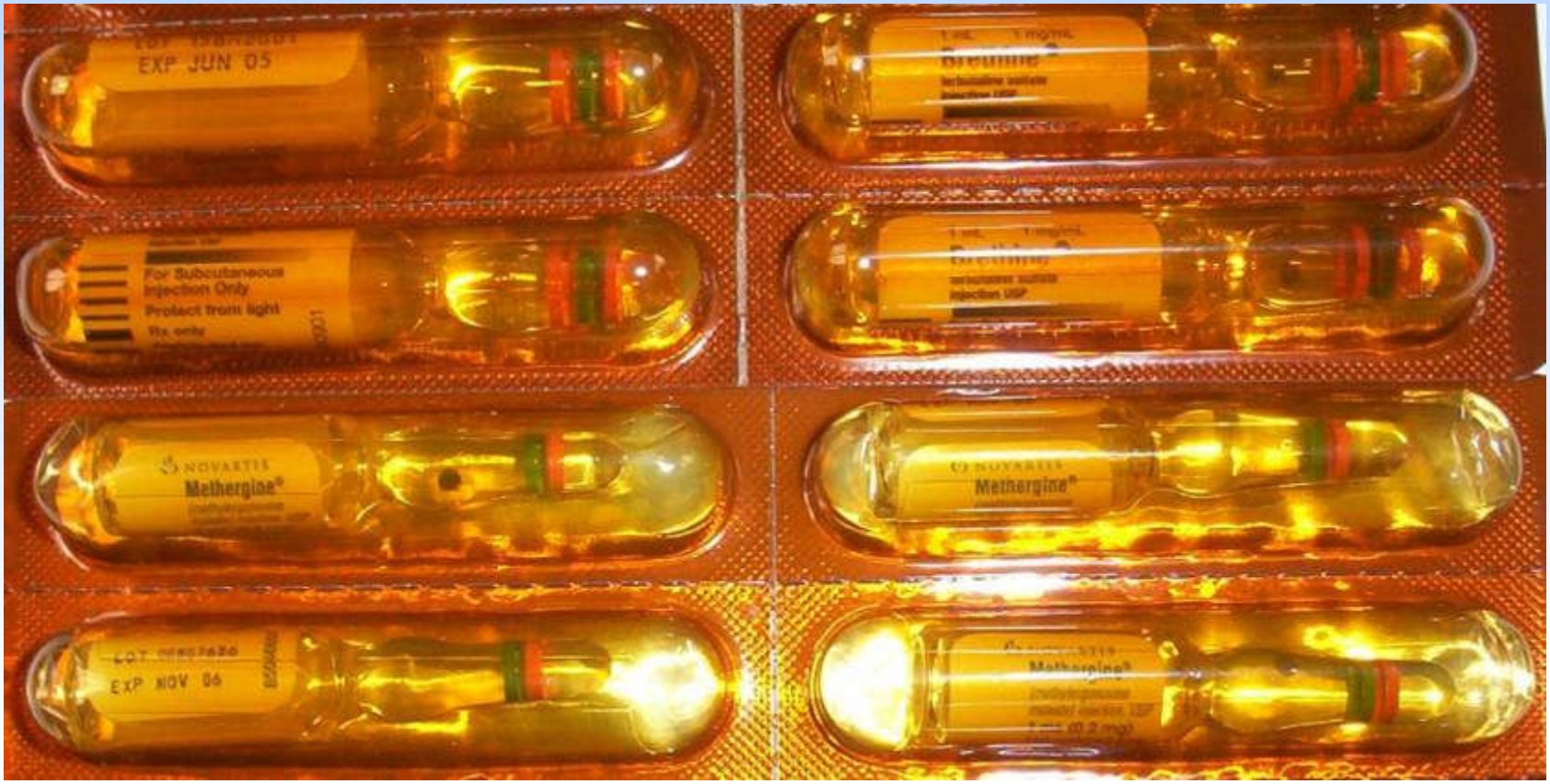
United States

Visibility of Information


NDC: 66697-103-10
Tablets 20mg
(Olmesartan medoxomil)
Lot: 440976A
Exp: 01/06
NDC: 66697-103-10
Tablets 20mg
(Olmesartan medoxomil)
Lot: 440976A
Exp: 01/06


Diovan HCT®
Novartis
©2002 Novartis
EXP. MAR 2004
LOT 066G6844

United States



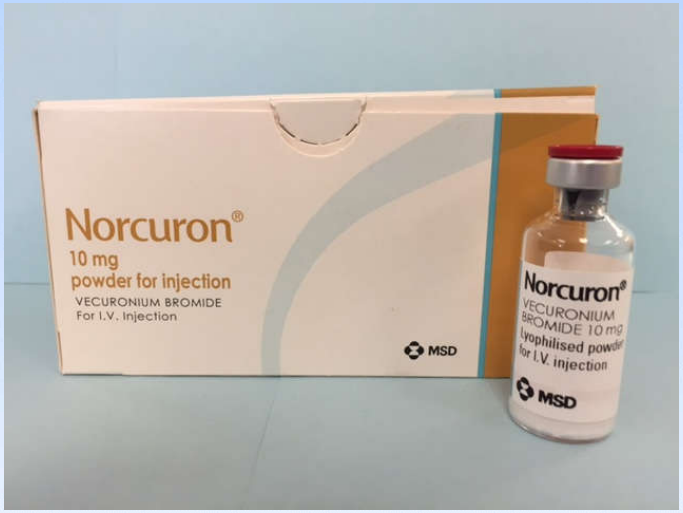
Color blocks view of drug name


SEALED FOR SAFETY
2 mL


Detrol
Pharmacia &
Upjohn Co
Detrol
Pharmacia &
Upjohn Co

Label reminders and warnings; communication of important information

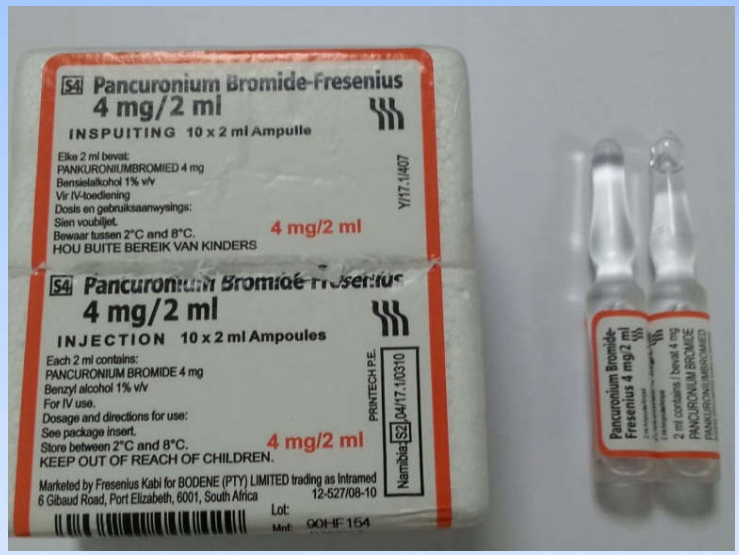
Neuromuscular Blockers

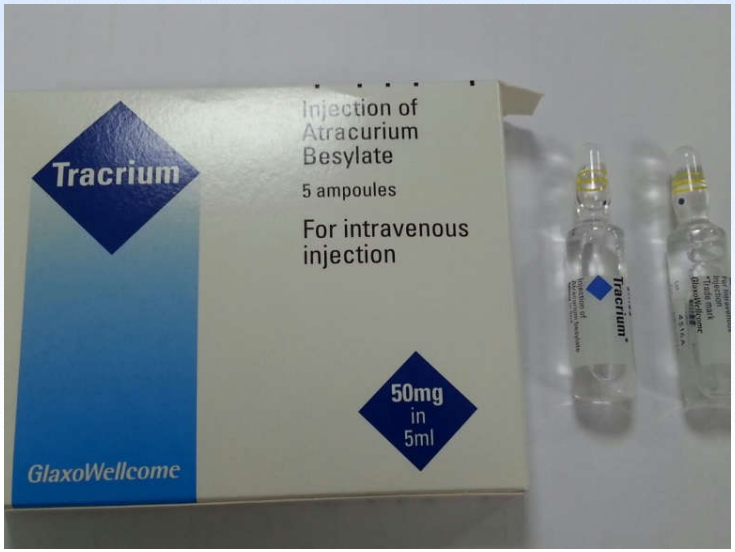


New Zealand

Unknown Country


Blok-L® İ.V. 10 mg
enjeksiyon için liyofilize toz içeren flakon
veküronyum bromür
İ.V. KULLANILIR
1 flakon
1 çözücü ampul
Mustafa Nevzat

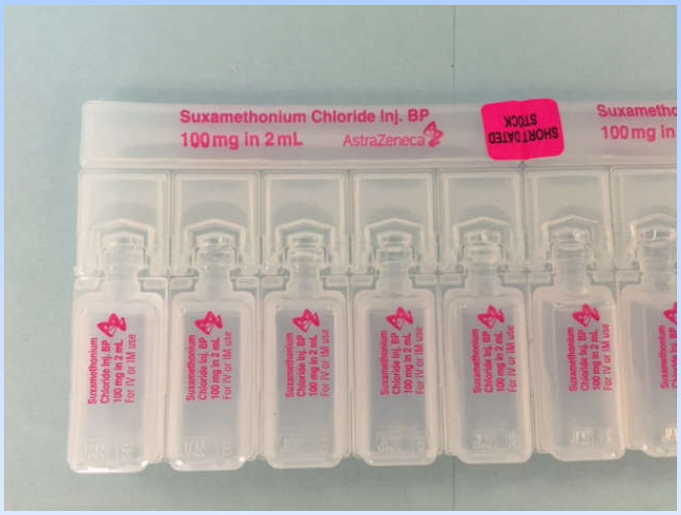

S4 Pancuronium Bromide-Fresenius
4 mg/2 ml
INSPUITING 10 x 2 ml Ampulle
Elke 2 ml bevat:
PANKURONIUMBROMIED 4 mg
Bensielalkohol 1% v/v
Vir IV-toediening
Dosis en gebruiksaanwysings:
Sien voubiljet.
Bewaar tussen 2°C and 8°C.
HOU BUITE BEREIK VAN KINDERS
4 mg/2 ml
Y/17.1/407
S4 Pancuronium Bromide Fresenius
4 mg/2 ml
INJECTION 10 x 2 ml Ampoules
Each 2 ml contains:
PANCURONIUM BROMIDE 4 mg
Benzyl alcohol 1% v/v
For IV use.
Dosage and directions for use:
See package insert.
Store between 2°C and 8°C.
KEEP OUT OF REACH OF CHILDREN.
4 mg/2 ml
PRINTECH P.E.
Namibia S2 04/17.10310
Marketed by Fresenius Kabi for BODENE (PTY) LIMITED trading as Intramed
6 Gibaud Road, Port Elizabeth, 6001, South Africa
12-527/08-10
Lot:
Mnf: 00HF154
Pancuronium Bromide-Fresenius 4 mg/2 ml
PANCURONIUM BROMIDE

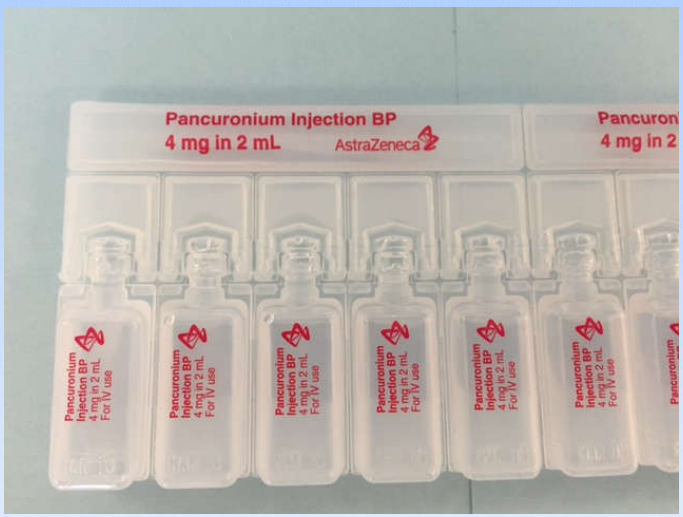

Tracrium
Injection of
Atracurium
Besylate
5 ampoules
For intravenous
injection
50mg
in
5ml
GlaxoWellcome


Lysthenon® 5 %
Injektionslösung
Suxamethoniumchlorid
5 Ampullen zu 2 ml Injektionslösung.
Zur intravenösen und intramuskulären Anwendung.
1 Ampulle enthält:
110 mg Suxamethoniumchlorid 2 H2O
(≙100 mg Suxamethoniumchlorid)
Wasser für Injektionszwecke.
Teil einer Bündelpackung -
Einzelverkauf unzulässig
Takeda

Why warning paralyzing agent on US and Canadian labels only?

New Zealand



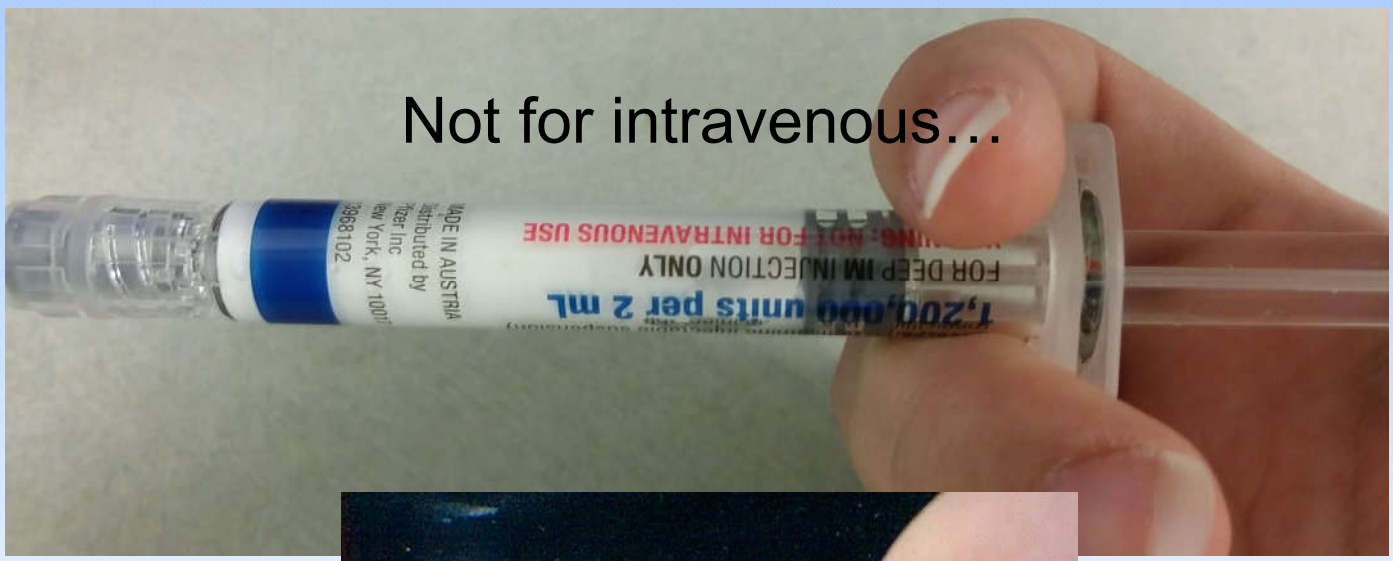


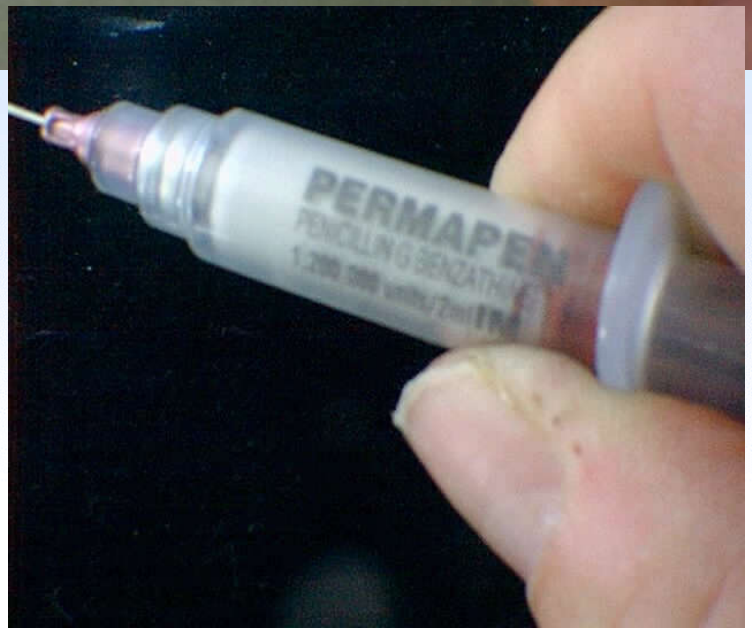
Neuromuscular Blocker look-alike

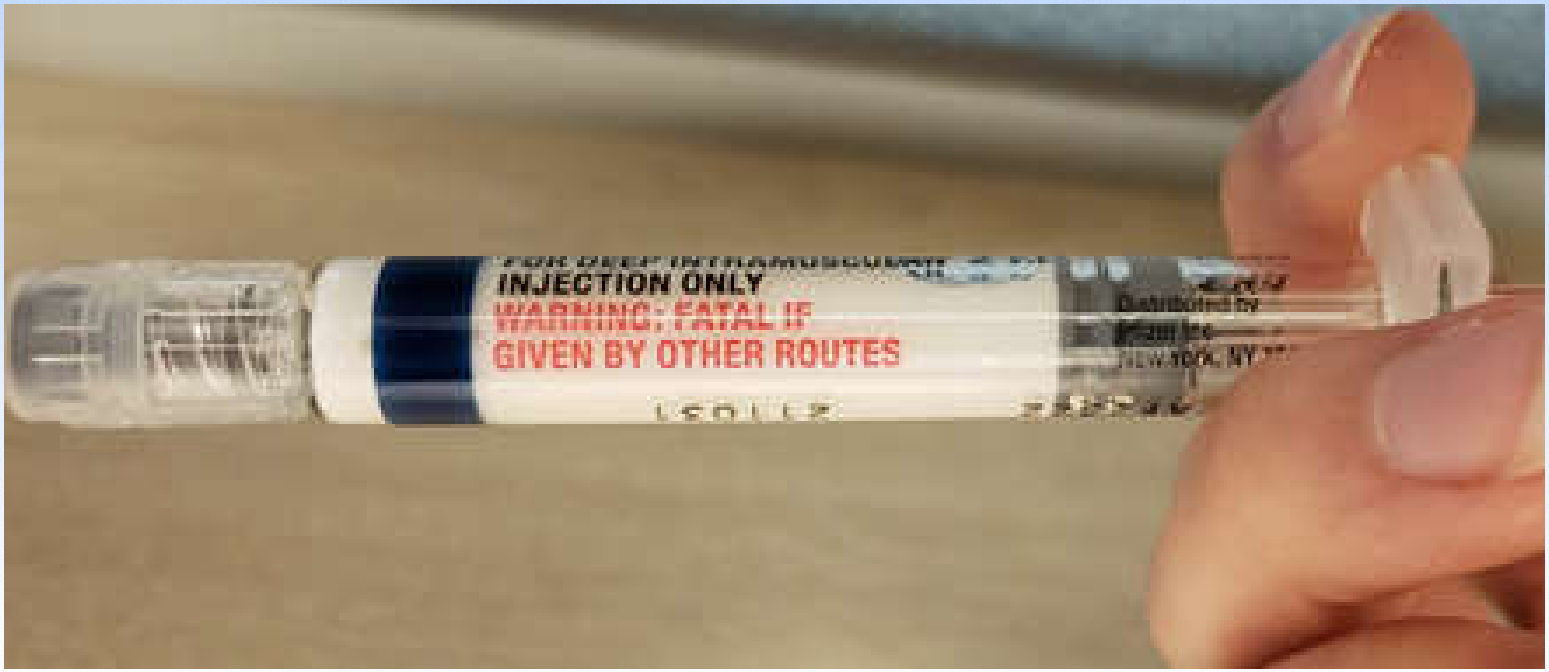
United States and Canada

Neuromuscular Blocker

United States






INJECTION ONLY
GIVEN BY OTHER ROUTES

IMSN INTERNATIONAL MEDICATION SAFETY NETWORK

HOME | ABOUT IMSN | IMSN ADVOCACY | PUBLIC EVENTS | MEMBERS RESOURCES | MEMBERS ONLY

13TH ANNUAL IMSN MEETING – CASCAIS 2018

The **International Medication Safety Network (IMSN)** is an international network of established safe medication practice centres, operating medication error reporting programmes and producing guidance to minimise preventable harms from medicine use in practice.
IMSN promotes safer medication practice to improve patient safety internationally. About IMSN

Global regulators and safety advocates meet about drug container labelling and packaging

FDA/IMSN SUMMIT *with* INTERNATIONAL DRUG REGULATORS *on*

LABELING & PACKAGING
to ADDRESS MEDICATION ERRORS

Sponsored by:

FDA U.S. FOOD & DRUG ADMINISTRATION | IMSN INTERNATIONAL MEDICATION SAFETY NETWORK

Participating regulators:

- Anvisa (Brasil)
- COFEPRIS (Mexico)
- European Medicines Agency
- Health Canada
- INFARMED (Portugal)
- Medicines Evaluation Board of Netherlands
- Medicines & Healthcare products Regulatory Agency (United Kingdom)
- Saudi Food and Drug Authority
- United States Food and Drug Administration
- World Health Organization

MAIN IMSN EVENTS

IMSN INTERNATIONAL MEDICATION SAFETY NETWORK

13th Annual IMSN Meeting - Cascais, Portugal 2018

- Global Meeting on Drug Product Labelling and Packaging Safety
- Pharmacovigilance Activities

MEDICATION SAFETY CURRICULA

ISMP INSTITUTE FOR SAFE MEDICATION PRACTICES

International Medication Safety Mentorship read more....

ismp CANADA

Practicum in Medication Safety for International Practitioners read more....

Saudi Medication Safety Center المركز السعودي لسلامة الدواء

Basic Medication Safety (BMS) Course read more....

2016 Toronto Global Regulatory Meeting

2013 Paris Conference on safer naming, labelling and packaging of medicines

FDA/IMSN SUMMIT *with* INTERNATIONAL DRUG REGULATORS *on*

LABELING & PACKAGING
to ADDRESS MEDICATION ERRORS

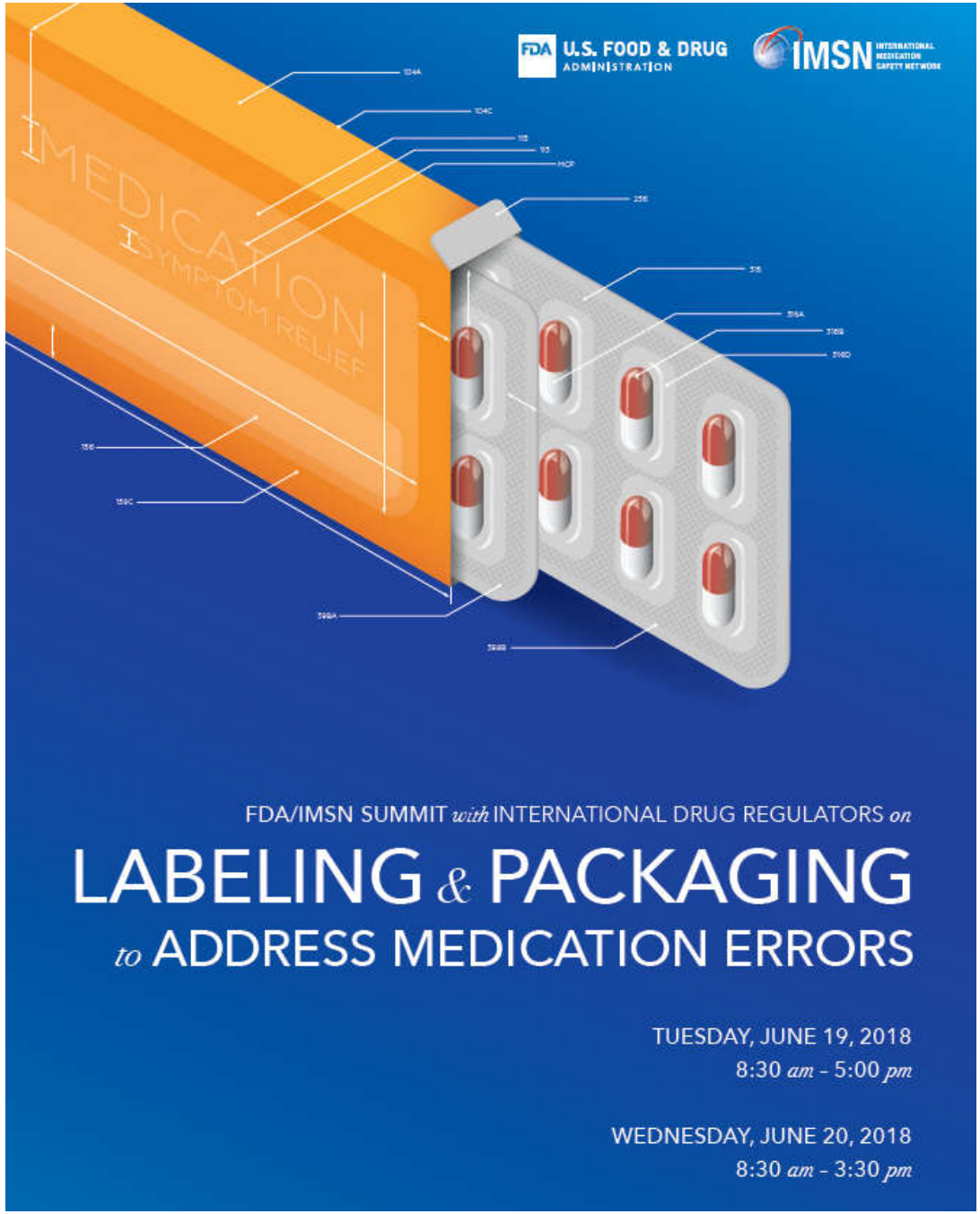
Sponsored by:

FDA U.S. FOOD & DRUG ADMINISTRATION

IMSN INTERNATIONAL MEDICATION SAFETY NETWORK

Participating regulators:

- Anvisa (Brasil)
- COFEPRIS (Mexico)
- European Medicines Agency
- Health Canada
- INFARMED (Portugal)
- Medicines Evaluation Board of Netherlands
- Medicines & Healthcare products Regulatory Agency (United Kingdom)
- Saudi Food and Drug Authority
- United States Food and Drug Administration
- World Health Organization



The purpose of the summit was to discuss and explore the potential for global harmonization of safe practices for labeling and packaging of regulated drug products between international drug regulators and how to minimize medication errors with labeling and packaging.

Advantages of Global Harmonization

- To achieve a reduction of overall harm related to medication errors, harmonization at the global level is necessary.

- Many of the product labeling, packaging and naming issues are common across the countries.
  - Thus, when practicable within the jurisdiction's regulation scheme, harmonization could help to reduce of overall harm related to medication errors
  - Working together toward understanding and improving drug naming, labeling and packaging issues around the globe.

- Work toward harmonizing a minimum set of safe medication practices as they impact labeling and packaging.

- This will not only help improve the quality of incoming submissions to regulators, making our reviews more efficient but will also help reducing potentially costly changes on industry and most importantly be a step in the right direction in addressing safety issues on a global scale.

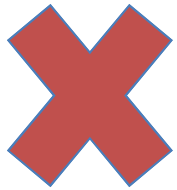
List of labeling recommendations discussed at the FDA/IMSN summit

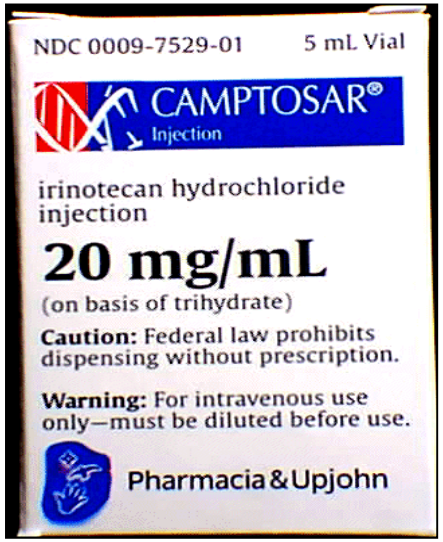
1. Include both the per mL and the per container quantity, not the per mL quantity alone, when presenting the concentration for injectables
2. Use metric units for products, and eliminate ratio expressions
3. Eliminate potentially error-prone abbreviations and dose designations on labels, such as U for units, IU for international units, or trailing zeros (e.g., 1.0) to express strength
4. Prominently display cautionary statements on carton and immediate container labels of neuromuscular blockers, potassium chloride concentrate injection, methotrexate, and other selected error-prone medications.
5. Use contrasting label backgrounds for the printing on glass ampules, and recommend font size and label orientation, to improve readability
6. Physically link or integrate diluents with drugs that are powders

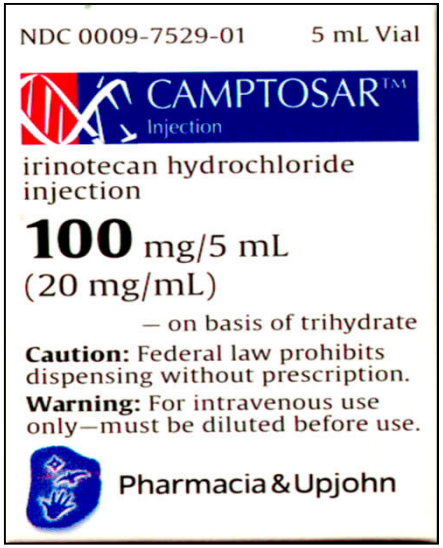
How product strength should be presented on labels

- **Small Volume Parenteral Products**
  - USP General Chapter <7> *Labeling*

    Total quantity per total volume followed by concentration per milliliter (mL)

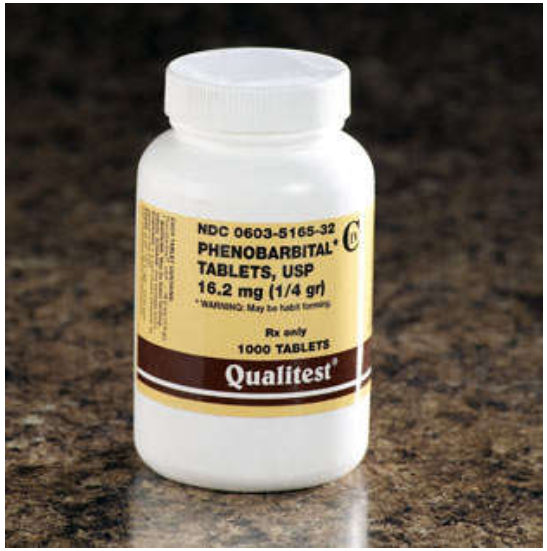






Express product strength in metric measurements

Dose or strength expression should appear in metric units of measure such as mL, mg, and mcg



1/4 gr?

Use consistent unit of measure across all elements of labels and labeling

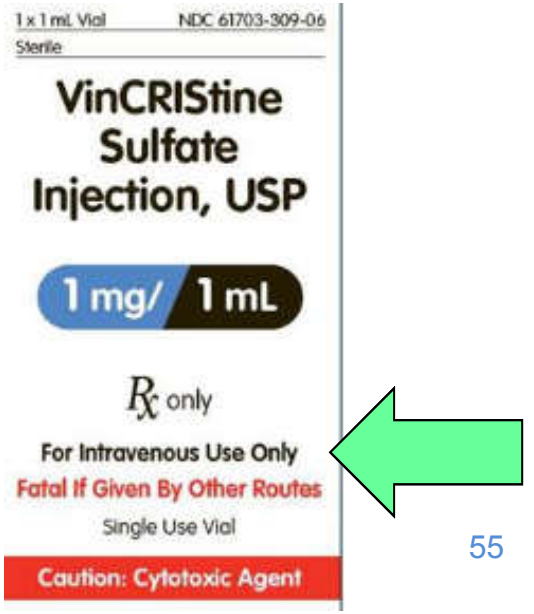
Dosing for Perioperative Hypotension

Intravenous bolus administration:
50 mcg to 250 mcg

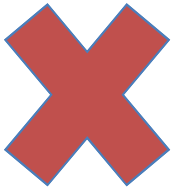
Inconsistent use of units

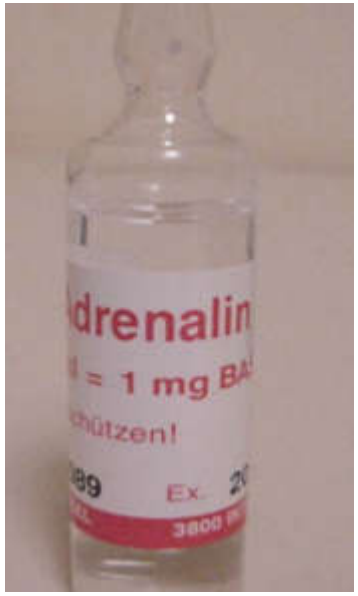
Prominently display cautionary statements on carton and immediate container labels

- Avoid use of abbreviations
- Use positive statements instead of negative statements
  - E.g., May overlook the word “not” in **NOT FOR INTRATHECAL USE**
  - Affirmative statements help to ensure readers understand the intended route of administration, even if they do not read every word



Use contrasting label backgrounds, font size and label orientation, to improve readability





List of labeling recommendations discussed at the FDA/IMSN summit

7. Increase the adoption of ready-to-use/ready-to-administer syringes, premixed IV solutions, unit-dose packaging, and other more efficient, safer packaging, while considering the overall cost of implementation
8. Develop product-specific world safety standards; for example, standard packaging for non-oncologic methotrexate to prevent accidental daily use and overdoses
9. Include barcodes on packages so they can be scanned at the bedside or other locations where medications are dispensed or administered by healthcare providers

Follow up with Industry

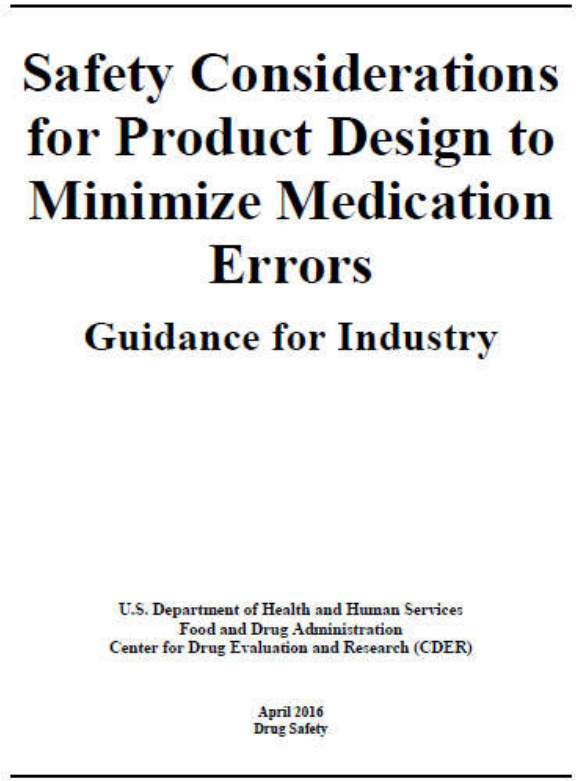
- A follow up meeting was held by IMSN in Portugal in October 2018 to discuss the recommendations
- Industry representatives also attended this meeting:
  - Abbvie – USA
  - Baxter – Portugal
  - BMS – USA
  - Eli Lilly – UK
  - Hikma – USA
  - Janssen, J&J – Netherlands
  - Novartis – USA
  - Pfizer – USA
  - UCB – USA

Current Status

- Drafted white paper outlining the rationale for these recommendations can be accessed at (https://www.intmedsafe.net/public-events/international-harmonization-in-progress/)
- Some regulators already have these recommendations in their guidances or best practices.
- Concurrence and feedback received from multiple regulators that attended the June FDA/IMSN and incorporated in the revised white paper
- Heard from other stakeholders such as International Society of Pharmacovigilance who are also interested in these recommendations
- Some regulators have started implementing these recommendations

Examples of Product Design Changes to Address Medication Errors

Safety Use of Drug Products: Unit-of-Use Packaging's Role



Safety Considerations for Product Design to Minimize Medication Errors

Guidance for Industry

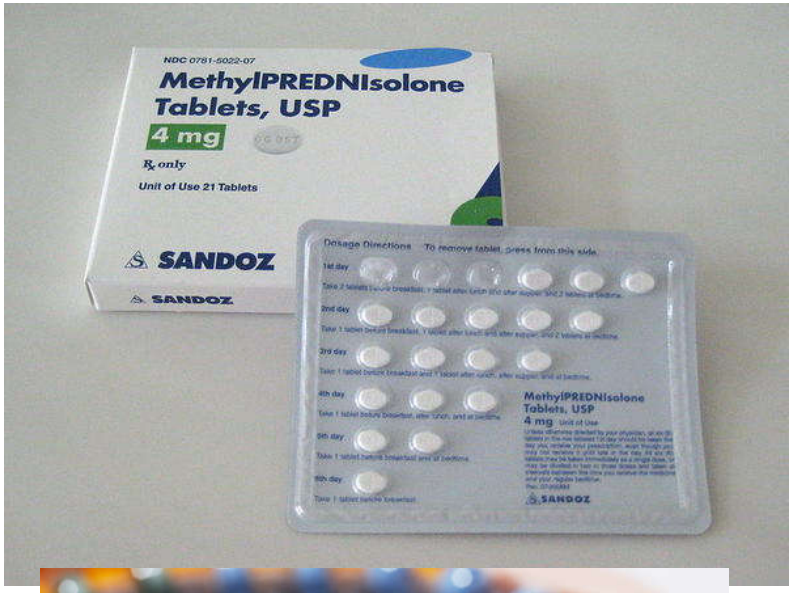
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

April 2016
Drug Safety

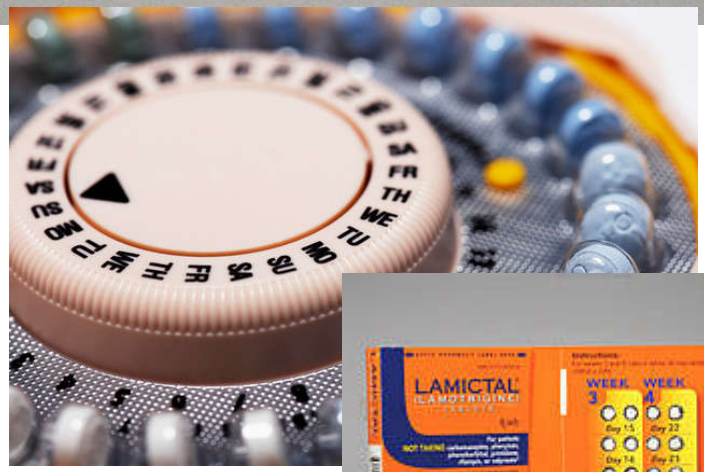
"Thoughtful use of unit-of-use container closures (e.g., blister packaging, calendar-packaging, sachets, and pouches) that can be dispensed intact to patients may help to reduce medication errors."

Patient-oriented Packaging for solid oral dosage forms

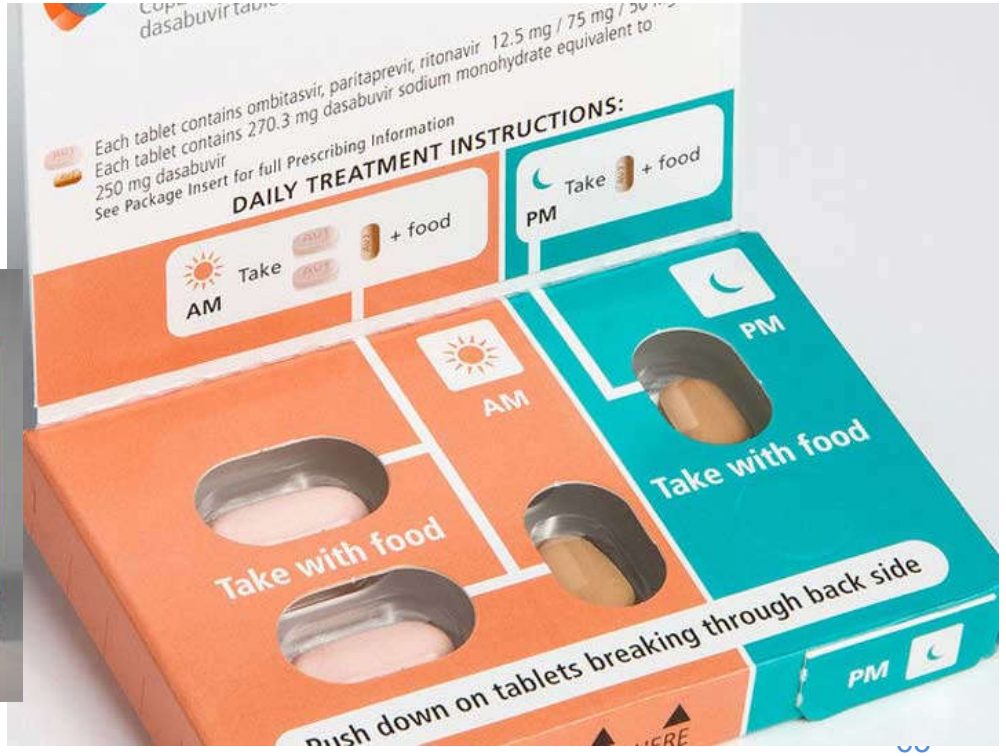
- **Adherence (compliance) packaging** designed to assist patients in taking their medication as prescribed.
  - typically employs one or more design or labeling elements that help to facilitate appropriate dosing and administration, such as warnings, dose sequencing, and administration instructions
- **Calendar packaging** organizes individual doses in a manner that resembles a calendar. (e.g., Mon., Tues., Weds.,) thereby providing a reminder as well as a visual record of medication administration.
- **Titration packaging** arranges doses to facilitate the escalation or de-escalation of doses in a manner congruent with the prescribing information.
- **Co-packaged product** design contains two or more drugs that distinctly in separate final dosage forms, but packaged together. For example, a package containing one or more tablets of Product A and one or more tablets of Product B would be considered co-packaged.


NDC 0781-5022-07
MethylPREDNIsolone
Tablets, USP
4 mg
Rx only
Unit of Use 21 Tablets
SANDOZ
Dosage Directions
To remove tablet, press from this side.
MethylPREDNIsolone
Tablets, USP
4 mg
SANDOZ

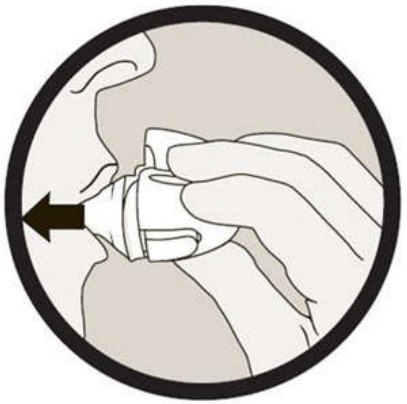

FOSAMAX PLUS
Take One Tablet Once A Week
4 tablets
MSD




LAMICTAL
STARTER KIT
WEEK 3
WEEK 4
WEEK 5


Each tablet contains ombitasvir, paritaprevir, ritonavir 12.5 mg / 75 mg /
Each tablet contains 270.3 mg dasabuvir sodium monohydrate equivalent to
250 mg dasabuvir
See Package Insert for full Prescribing Information
DAILY TREATMENT INSTRUCTIONS:
AM
Take
+ food
PM
Take
+ food
AM
PM
Take with food
Take with food
Push down on tablets breaking through back side
PM

Designing the Dosage Form



Step 1: Put the SPIRIVA capsule into the HandiHaler device.
Step 2: Inhale the medicine through your mouth.

Do NOT swallow SPIRIVA capsules.

Designing the Container

Topical products packaged in container/ closures that look similar to eye, ear, nasal, or oral products