

## E-learning on Adverse Reactions

According to recent research by the **SCOPE** (Strengthening Collaboration for Operating Pharmacovigilance in Europe) project, educational materials on adverse drug reaction (ADR) reporting are not easily available. An e-learning module has been developed to fill that gap. It is available on the project's website and includes case studies. It aims to support healthcare professionals in **obtaining clear information and guidance on ADR reporting**.

This online course will also help healthcare professionals to understand the impact their ADR reports have on the safety assessment of medicinal products through the National Pharmacovigilance System.

The e-learning targets healthcare professionals at any stage of their careers, and is accredited by the European Accreditation Council for Continuing Medical Education (EACCME) for the EU and other countries, as a CME (continuing medical education) activity. Its completion awards 1 European credit (ECMC).

Click [here](#) now to start the course.



## Loperamide Serious adverse cardiac reactions from abuse and misuse



### Quick Read

Very high doses of loperamide may be associated with the occurrence of serious adverse cardiac reactions, such as QT interval prolongation, torsades de pointes, other ventricular arrhythmias and even cardiac arrest. These reactions have been reported in the USA in cases of abuse and misuse. No cases have been reported in Portugal.

*Loperamide is a GI motility modifying drug that belongs to the group of opioids. By binding to the  $\mu$  receptors in the intestinal wall it inhibits the release of acetylcholine and prostaglandins and reduces propulsive peristalsis, thus prolonging intestinal transit time and increasing anal sphincter tonus, which in turn reduces faecal incontinence. Loperamide is used therefore, for the treatment of acute and chronic diarrhoea, as it decreases the number and volume of stools and increases its consistency.*

Based on an alert from the US Food and Drug Administration (FDA), a safety signal (suspected problem) was raised in Europe regarding an association between abuse and misuse of loperamide in high doses and the occurrence of serious cardiac events.

Due to its high affinity to the gut wall and its significant first pass metabolism, therapeutic doses of loperamide hardly reach the systemic circulation at all. However, when used in doses higher than those recommended, loperamide can cause serious adverse cardiac events, namely QT interval prolongation, torsades de pointes or other ventricular arrhythmias, syncope and even cardiac arrest.

Most cases that were reported in the USA occurred in individuals who had intentionally misused or abused the medicine in an attempt to find relief for opioid withdrawal syndrome or to reach a state of euphoria. In Portugal no cases of abuse or misuse have been reported.

Once all available data had been assessed, the PRAC recommended an update of the information of products containing loperamide (see overleaf).

## INDEX CARD

Director: Fátima Canedo  
Editor: Rui Pombal

Assistant Editor: Leonor Nogueira Guerra

Contributors: Ana Sofia Martins, António Leandro Ponte, Cristina Mousinho, Fátima Bragança, Fátima Hergy, Leonor Nogueira Guerra, Magda Pedro, Márcia Silva, Sílvia Duarte, Vanda Araújo

Publishing Assistant: Inocência Pinto

Advisory Board: Conselho Diretivo do INFARMED, I.P. – Comissão de Avaliação de Medicamentos  
INFARMED – Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.  
Parque de Saúde de Lisboa, Av. do Brasil, N.º 53, 1749-004 Lisboa

Phone: +351 217 987 100

E-mail: [infarmed@infarmed.pt](mailto:infarmed@infarmed.pt)

Design and production: Letras & Sinais, Comunicação e Imagem, Lda.  
ISSN: 0873-7118

# Loperamide

## Serious adverse cardiac reactions from abuse and misuse



### Summary of product characteristics

#### 4.4. Special warnings and precautions for use

Cardiac events including QT prolongation and torsades de pointes have been reported in association with overdose. Some cases had a fatal outcome (see section 4.9). Patients should not exceed the recommended dose and/or the recommended duration of treatment.

#### 4.9. Overdose

In individuals who have ingested overdoses of loperamide HCl, cardiac events such as QT interval prolongation, torsades de pointes, other serious ventricular arrhythmias, cardiac arrest and syncope have been observed (see section 4.4). Fatal cases have also been reported.

#### 5.3. Preclinical safety data

Non-clinical in vitro and in vivo evaluation of loperamide indicates no significant cardiac electrophysiological effects within its therapeutically relevant concentration range and at significant multiples of this range (up to 47-fold). However, at extremely high concentrations associated with overdoses (see section 4.4), loperamide has cardiac electrophysiological actions consisting of inhibition of potassium (hERG) and sodium currents, and arrhythmias.

Beatriz Tavares da Costa

## ADRs in the Literature

### Antidepressants in pregnancy not associated with autism spectrum disorders



A retrospective cohort study (Brown HK et al, 2017) , within the scope of the public provincial health system of Ontario (Canada), included children born to mothers who received prescriptions of serotonergic antidepressants while pregnant between 2002 and 2010. This cohort of newborns corresponds to 4.2% of all births in that period. The children were followed up until early 2014.

**No statistically significant association** was found between exposure to those drugs in pregnancy and occurrence of **autism spectrum** disorders, namely when compared with children born to non-exposed mothers.

In another retrospective cohort study involving over a million and a half Swedish newborns whose mothers had taken antidepressants during the first trimester of pregnancy, multiple statistical and methodological approaches to adjust for confounding factors led the authors to conclude that there was an association between exposure to antidepressants in the first trimester and a **small increase in the risk of premature birth** (odds ratio 1.3 in the comparison between siblings analysis). However, no association was found with a risk of **small for gestational age babies** or later occurrence of **autism spectrum** or **hyperactivity / attention deficit disorders**.

*Association Between Serotonergic Antidepressant Use During Pregnancy and Autism Spectrum Disorder in Children. Brown HK et al. JAMA. 2017;317(15):1544-1552.*

*Associations of Maternal Antidepressant Use During the First Trimester of Pregnancy With Preterm Birth, Small for Gestational Age, Autism Spectrum Disorder, and Attention-Deficit/Hyperactivity Disorder in Offspring.*

*Sujan AC et al. JAMA. 2017;317(15):1553-1562.*

## Educational Materials published in the Infomed product information webpage



Medicinal product (DCI)	Click on the links (in Portuguese)
<p><b>Cerdelga (eliglustat)</b></p>	<p><b>Educational materials for healthcare professionals</b></p> <p><a href="#">Guia para o prescriptor – 1.ª versão</a></p> <p>For paediatricians, haematologists, internists, neurologists and hepatologists (gastroenterologists).</p> <p><b>Educational materials for patients</b></p> <p><a href="#">Cartão de alerta do doente – 1.ª versão</a></p> <p>Published on 28-04-2017</p>
<p><b>Erivedge (vismodegib)</b></p>	<p><b>Educational materials for healthcare professionals</b></p> <p><a href="#">Cartão de informação de Erivedge® para o profissional de saúde – 2.ª Versão</a></p> <p><a href="#">Erivedge: Formulário de Notificação de Gravidez – 2.ª Versão</a></p> <p><a href="#">Programa de Prevenção de Gravidez de Erivedge®: Informação para os médicos prescritores – 2.ª Versão</a></p> <p>For physician specialists in dermatology, oncology, plastic surgery and radiotherapy.</p> <p><b>Educational materials for patients</b></p> <p><a href="#">Erivedge: Cartão de informação para o doente – 2.ª Versão</a></p> <p><a href="#">Formulário de Verificação de Aconselhamento de Erivedge – 2.ª Versão</a></p> <p><a href="#">Programa de Prevenção de Gravidez de Erivedge®: Informação importante sobre a prevenção de gravidez e contraceção para mulheres e homens – 2.ª Versão</a></p> <p>To be handed out to patients by hospital doctors or pharmaceutical services.</p> <p>Published on 28-04-2017</p>
<p><b>Valdoxan (agomelatine)</b></p>	<p><b>Educational materials for healthcare professionals</b></p> <p><a href="#">Valdoxan – Informação de Segurança para os Profissionais de Saúde: Monitorização da função hepática – 6.ª Versão</a></p> <p>For psychiatrists, neurologists, internists and family doctors.</p> <p>Published on 19-04-2017</p>
<p><b>Vpriv (velaglucerase alfa)</b></p>	<p><b>Educational materials for healthcare professionals</b></p> <p><a href="#">Guia para Profissionais de Saúde que tratam doentes com a Doença de Gaucher – 1.ª Versão</a></p> <p>For doctors who prescribe or may potentially prescribe this medicinal product, namely paediatricians, haematologists, gastroenterologists, internists, and pharmacists involved in the treatment of haemophilia.</p> <p><b>Educational materials for patients</b></p> <p><a href="#">Manual para doentes com doença de Gaucher que recebem VPRIV® por perfusão no domicílio: Risco de reações relacionadas com a perfusão, incluindo reações de hipersensibilidade do tipo alérgico no enquadramento domiciliário – 1.ª Versão</a></p> <p>To be handed out to patients by hospital doctors or pharmaceutical services.</p> <p>Published on 10-04-2017</p>

## Communications to Healthcare Professionals published on the Infarmed [website](#)



Medicinal product (DCI)	Click on topic for details (in Portuguese)
<b>Herceptin (trastuzumab)</b>	<p><a href="#"><b>Warning on importance of cardiac monitoring during therapy to reduce the frequency and seriousness of left ventricular dysfunction and congestive heart failure</b></a></p> <p>For physician specialists in oncology, radiotherapy, general surgery, gynaecology, and internal medicine, who are in charge of senology services and who are experienced in the use of anti-HER2 therapies.</p> <p>Published on 07-04-2017</p>
<b>Lovenox (enoxaparin sodium)</b>	<p><a href="#"><b>Harmonization of expressions of expressed dosage, both in international units (IU) of anti-Xa activity and in milligrams (mg)</b></a></p> <p><b>1 mg of enoxaparin sodium is equivalent to 100 UI of anti-Xa activity</b></p> <p><b>Harmonization of dosing regimes for the treatment of deep venous thromboembolism (DVT) and pulmonary embolism (PE) and use in patients with severe renal impairment</b></p> <p>For physicians specialists in: general practice/family medicine, orthopaedic surgery, internal medicine, cardiology, haematology, surgery, neurology, anaesthetics, gynaecology, intensive care medicine, pneumology, immunology, oncology, technical heads of community and hospital pharmacies, and head nurses of national hospital nursing services.</p> <p>Published on 10-04-2017</p>

Compiled by Magda Pedro

## What do they mean?

**ADR** Adverse Drug Reaction

**EMA** European Medicines Agency

**MA** Marketing Authorization

**PIL** Patient Information Leaflet

**PRAC** Pharmacovigilance Risk Assessment Committee (EMA)

**SmPC** Summary of Product Characteristics