



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

23 March 2017  
EMA/PRAC/146563/2017  
Pharmacovigilance Risk Assessment Committee (PRAC)

## New product information wording – Extracts from PRAC recommendations on signals

Adopted at the 6-9 March 2017 PRAC

The product information wording in this document is extracted from the document entitled 'PRAC recommendations on signals' which contains the whole text of the PRAC recommendations for product information update, as well as some general guidance on the handling of signals. It can be found [here](#) (in English only).

### 1. Loperamide – Serious cardiac events with high doses of loperamide from abuse and misuse (EPITT no 18339)

#### 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.



## Package leaflet

2 - What you need to know before you take <brand name>

### Warnings and precautions

Do not take this product for anything other than its intended use (see section 1) and never take more than the recommended amount (see section 3). Serious heart problems (symptoms of which include fast or irregular heartbeat) have been reported in patients who have taken too much loperamide, the active ingredient in <brand name>.

3 - If you take more <brand name> than you should

If you have taken too many <brand name>, immediately contact a doctor or hospital for advice. Symptoms may include: increased heart rate, irregular heartbeat, changes to your heartbeat (these symptoms can have potentially serious, life-threatening consequences), muscle stiffness, uncoordinated movements, drowsiness, difficulty urinating, or weak breathing.

Children react more strongly to large amounts of <brand name> than adults. If a child takes too much or shows any of the above symptoms, call a doctor immediately.

## 2. Nivolumab; pembrolizumab – Transplant rejection (EPITT no 18781)

New text to be added to the product information is underlined. Current text to be deleted is ~~struck through~~.

### Opdivo (nivolumab)

#### Summary of product characteristics

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

##### Other immune-related adverse reactions

Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with nivolumab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with nivolumab versus the risk of possible organ rejection should be considered in these patients.

##### 4.8. Undesirable effects

##### Immune system disorders

##### Nivolumab monotherapy

Frequency 'not known': Solid organ transplant rejection

##### Nivolumab in combination with ipilimumab

Frequency 'not known': Solid organ transplant rejection

## Package leaflet

2 - What you need to know before you use OPDIVO

Warnings and precautions

Talk to your doctor before using OPDIVO as it may cause:

Solid organ transplant rejection

## Keytruda (pembrolizumab)

### Summary of product characteristics

4.4. Special warnings and precautions for use

Other immune-related adverse reactions

Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with pembrolizumab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with pembrolizumab versus the risk of possible organ rejection should be considered in these patients.

4.8. Undesirable effects

Immune system disorders

Frequency 'not known': Solid organ transplant rejection

## Package leaflet

2 - What you need to know before you are given KEYTRUDA

Warnings and precautions

Before you get KEYTRUDA, tell your doctor if you:

- have liver damage ~~or have had a liver transplant~~
- have kidney damage ~~or have had a kidney transplant~~
- have a solid organ transplant