2 August 2021[1]
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Pharmacovigilance Risk Assessment Committee (PRAC)

New product information wording – Extracts from PRAC recommendations on signals

Adopted at the 5-8 July 2021 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).

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

1. Donepezil – Cardiac conduction disorders including QT prolongation and Torsade de Pointes (EPITT no 19667)

Summary of product characteristics

4.4. Special warnings and precautions for use

Cardiovascular conditions

[…]

There have been post-marketing reports of QTc interval prolongation and Torsade de Pointes (see sections 4.5 and 4.8). Caution is advised in patients with pre-existing or family history of QTc prolongation, in patients treated with drugs affecting the QTc interval, or in patients with relevant pre-existing cardiac disease (e.g. uncompensated heart failure, recent myocardial infarction, bradyarrhythmias), or electrolyte disturbances (hypokalaemia, hypomagnesaemia). Clinical monitoring (ECG) may be required.

4.5. Interaction with other medicinal products and other forms of interaction

[1] Expected publication date. The actual publication date can be checked on the webpage dedicated to PRAC recommendations on safety signals.

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Cases of QTc interval prolongation and Torsade de Pointes have been reported for donepezil. Caution is advised when donepezil is used in combination with other medicinal products known to prolong the QTc interval and clinical monitoring (ECG) may be required. Examples include:

Class IA antiarrhythmics (e.g. quinidine)

Class III antiarrhythmics (e.g. amiodarone, sotalol)

Certain antidepressants (e.g. citalopram, escitalopram, amitriptyline)

Other antipsychotics (e.g. phenothiazine derivatives, sertindole, pimozide, ziprasidone)

Certain antibiotics (e.g. clarithromycin, erythromycin, levofloxacin, moxifloxacin)

4.8. Undesirable effects

Tabulated list of adverse reactions

Cardiac disorders

Frequency not known: Polymorphic ventricular tachycardia including Torsade de Pointes; Electrocardiogram QT interval prolonged

Injury and poisoning

common: Accidents including falls

Package leaflet

2. What you need to know before you take [product name]

Warnings and precautions

Talk to your doctor or pharmacist before taking [product name] if you have or have had:

a heart condition (such as irregular or very slow heart beat, heart failure, myocardial infarction)

a heart condition called 'prolonged QT interval' or a history of certain abnormal heart rhythms called Torsade de Pointes or if anyone in your family have 'prolonged QT interval'

low levels of magnesium or potassium in your blood

Other medicines and [product name]

In particular it is important to tell your doctor if you are taking any of the following types of medicines:

medicines for heart rhythm problems (e.g. amiodarone, sotalol, and quinidine)

depression (e.g. citalopram, escitalopram, amitriptyline), medicines for psychoses (e.g. pimozide, sertindole, ziprasidone), medicines for bacterial infections (such as clarithromycin, erythromycin, levofloxacin, moxifloxacin)

4. Possible side effects

Frequency not known:

Changes in the heart activity which can be seen on an electro-cardiogram (ECG) called 'prolonged QT interval'

Fast, irregular heart beat, fainting which could be symptoms of a life-threatening condition known as Torsade de Pointes

2. Immune checkpoint inhibitors: atezolizumab; avelumab; cemiplimab; durvalumab; ipilimumab; pembrolizumab; nivolumab – Immune-mediated cystitis (EPITT no 19610)

Keytruda (pembrolizumab)

Summary of product characteristics

4.4. Special warnings and precautions for use

Addition of 'cystitis noninfective' in the paragraph on other immune-related reactions with a cross-reference to sections 4.2 and 4.8.

4.8. Undesirable effects

Addition of 'cystitis noninfective' as ADR in the SOC Renal and urinary disorders with a frequency 'rare' in the column for monotherapy within table 2.

Package leaflet

4. Possible side effects

Addition of 'Inflammation of the bladder. Signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen.' among the list of adverse reactions with a frequency 'rare'.

Opdivo (nivolumab)

Summary of product characteristics

4.4. Special warnings and precautions for use

Addition of 'cystitis noninfective' in the paragraph on other immune-related reactions with a cross-reference to sections 4.2 and 4.8.

4.8. Undesirable effects

Addition of 'cystitis noninfective' as ADR in the SOC Renal and urinary disorders with a frequency 'rare' for nivolumab monotherapy in table 6.

Addition of 'cystitis noninfective' as ADR in the SOC Renal and urinary disorders with a frequency 'uncommon' for nivolumab in combination with ipilimumab in table 7 and in table 8.

Addition of 'cystitis noninfective' as ADR in the SOC Renal and urinary disorders with a frequency 'rare' in table 9.

Package leaflet

4. Possible side effects

Addition of 'Inflammation of the bladder. Signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen.' among the list of adverse reactions with a frequency 'rare' for treatment with Opdivo alone.

Addition of 'Inflammation of the bladder. Signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen.' among the list of adverse reactions with a frequency 'uncommon' for treatment with Opdivo in combination with other anti-cancer medicines.

Yervoy (ipilimumab)

Summary of product characteristics

4.4. Special warnings and precautions for use

Addition of 'cystitis noninfective' in the paragraph on other immune-related reactions with a cross-reference to sections 4.2 and 4.8.

4.8. Undesirable effects

Addition of 'cystitis noninfective' as ADR in the SOC Renal and urinary disorders with a frequency 'uncommon' in table 4.

Addition of 'cystitis noninfective' as ADR in the SOC Renal and urinary disorders with a frequency 'uncommon' for nivolumab in combination with ipilimumab in table 5 and in table 6.

Package leaflet

4. Possible side effects

Addition of 'Inflammation of the bladder. Signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen.' among the lists of adverse reactions with a frequency 'uncommon' for treatment with ipilimumab monotherapy respectively ipilimumab combination therapy.

Tecentriq (atezolizumab)

Summary of product characteristics

4.4. Special warnings and precautions for use

Other immune-related adverse reactions

Given the mechanism of action of atezolizumab, other potential immune-related adverse reactions may occur, including noninfective cystitis.

Evaluate all suspected immune-related adverse reactions to exclude other causes. Patients should be monitored for signs and symptoms of immune-related adverse reactions and, based on the severity of the reaction, managed with treatment modifications and corticosteroids as clinically indicated (see section 4.2 and section 4.8).

4.8. Undesirable effects

Addition of 'cystitis noninfective' as ADR in the SOC Renal and urinary disorders with a frequency 'not known' in the column for monotherapy within table 2.

Package leaflet

4. Possible side effects

[…]
Other side effects that have been reported (frequency not known):

Inflammation of the bladder. Signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen.

Bavencio (avelumab)

Summary of product characteristics

4.4. Special warnings and precautions for use

Addition of 'cystitis noninfective' in the paragraph on other immune-related reactions with a cross-reference to sections 4.2 and 4.8.

4.8. Undesirable effects

Addition of 'cystitis noninfective' as ADR in the SOC Renal and urinary disorders with a frequency 'rare' in table 2.

Package leaflet

4. Possible side effects

Rare (may affect up to 1 in 1000 people)

- Inflammation of the bladder. Signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen

Imfinzi (durvalumab)

Summary of product characteristics

4.4. Special warnings and precautions for use

Addition of 'cystitis noninfective' in the paragraph on other immune-related reactions with a cross-reference to sections 4.2 and 4.8.

4.8. Undesirable effects

Addition of 'cystitis noninfective' as ADR in the SOC Renal and urinary disorders with a frequency 'rare' in the column for Imfinzi monotherapy within table 3.

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4. Possible side effects

Addition of 'Inflammation of the bladder. Signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen.' among the list of adverse reactions with a frequency 'rare'.

Libtayo (cemiplimab)

Summary of product characteristics

4.4. Special warnings and precautions for use

Addition of 'cystitis noninfective' in the paragraph on other immune-related reactions with a cross-reference to sections 4.2 and 4.8.

4.8. Undesirable effects

Addition of 'cystitis noninfective' as ADR in the SOC Renal and urinary disorders with a frequency 'not known' in table 2.

Package leaflet

4. Possible side effects

Addition of 'Inflammation of the bladder. Signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen.' among the list of adverse reactions with a frequency 'not known'.

3. Octreotide – Pancreatic exocrine insufficiency (EPITT no 19661)

Summary of product characteristics

4.4. Special warnings and precautions for use

Pancreatic function:

Pancreatic exocrine insufficiency (PEI) has been observed in some patients receiving octreotide therapy for gastroenteropancreatic neuroendocrine tumours. Symptoms of PEI can include steatorrhea, loose stools, abdominal bloating and weight loss. Screening and appropriate treatment for PEI according to clinical guidelines should be considered in symptomatic patients.

Package leaflet

2. What you need to know before you take [product name]

Test and checks

Your doctor may wish to check your pancreatic enzyme function.