DIRECT HEALTHCARE PROFESSIONAL COMMUNICATION (DHPC)
IN AGREEMENT WITH THE ITALIAN MEDICINES AGENCY (AIFA)

07/02/2022

Donepezil containing medicinal products: Addition to the product safety information regarding cardiac conductions disorders including QT prolongation and Torsade de Pointes

Dear Healthcare professional,

The marketing authorization holders of donepezil containing medicinal products, in agreement with the Agenzia Italiana del Farmaco (AIFA), would like to inform you of the following updates to the product information of donepezil containing medicinal products. The purpose of this update is to amend the warnings, interactions and undesirable effects sections of the SmPCs EU product information for the use of donepezil.

Summary

- **There have been post-marketing reports of QTc interval prolongation and Torsade de Pointes in association with donepezil therapy**
- **Caution is advised in patients with pre-existing or family history of QTc prolongation**
- **Caution is advised in patients with concomitant treatment with medicinal products that affect the QTc interval or induce bradycardia**
- **Caution is advised in patients with relevant heart disease or electrolyte disturbances. At risk patients should be considered for monitoring with electrocardiograms (ECG).**
- **Addition of undesirable effects: Polymorphic ventricular tachycardia including Torsade de Pointes, Electrocardiogram QT interval prolonged**
- **Update of Drug interactions**

Background on the safety concern

Donepezil is a selective reversible inhibitor of acetylcholinesterase (Ache), in most European countries is indicated for the symptomatic treatment of mild to moderately severe Alzheimer's dementia and is available as 5mg, 10mg film coated tablets and as 5mg, 10mg orodispersible tablets.

The risk of cholinergic effects on heart rate is already known and the SmPCs EU product information contain a warning indicating that cholinesterase inhibitors may have vagotonic effects on heart rate (e.g. bradycardia) and that the potential for this action may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction conditions, such as sinoatrial or atrioventricular block.

The current changes to the product information for donepezil are a result of an assessment of post-marketing data and scientific literature. Reports of QTc interval prolongation and Torsade de Pointes associated with the use of donepezil were identified and evaluated and determined the causal relationship between donepezil and QT interval prolongation and Torsade de Pointes is at least a possibility.

The product information of donepezil will be updated accordingly as follows:

SmPC

Section 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 section 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.

Section 4.5: Interaction with other medicinal products and other forms of interaction

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 derivates, sertindole, pimozide, ziprasidone)*
- *Certain antibiotics (e.g. clarithromycin, erythromycin, levofloxacin, moxifloxacin)*

Section 4.8: Undesirable effects

Tabulated list of adverse reactions:

SOC Cardiac disorders

uncommon: Bradycardia

rare: Sino-atrial block; Atrioventricular block.

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

SOC Injury and poisoning:

common: Accidents including falls

The package leaflet will be updated accordingly. This communication is being disseminated at this time at the recommendation of AIFA.

Call for reporting

Healthcare professionals are reminded to continue to report suspected adverse reactions associated with donepezil containing medicinal products in accordance with the National spontaneous reporting system. Healthcare professionals are asked to report any suspected adverse reactions reactions via the Italian Medicines Agency reporting system: https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse

AIFA takes the opportunity to remind all Healthcare Professionals of the importance of reporting suspected adverse drug reactions, as an indispensable tool to confirm a favorable benefit/risk ratio in the real conditions of use.
Reports of Suspected Adverse Reaction from drugs should be sent to the Pharmacovigilance Manager of the Structure to which the Operator belongs.
This Direct Healthcare Professional Communication is also published on the AIFA website (http://www.agenziafarmaco.gov.it) and it's consultation is recommended for the best professional information and citizen service.