Donepezil – Risk of neuroleptic malignant syndrome (but insufficient evidence on causal relationship with serotonin syndrome)

Based on all information assessed, the PhVWP concluded that modifications to the summaries of product characteristics (SmPCs) and package leaflets (PLs) of all donepezil-containing medicinal products authorised in the EU are necessary to include:

in SmPC section 4.8 (under Nervous system disorders):
- NMS as an adverse reaction;

in SmPC section 4.4:
- that NMS is a potentially life-threatening condition and characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels; additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure;
- that NMS has been reported to occur very rarely in association with donepezil, particularly in patients also receiving concomitant antipsychotics;
- that if a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, treatment should be discontinued;

in PL (under Serious side effects):
- advice to tell a physician immediately if as a patient one notices fever with muscle stiffness, sweating or a lowered level of consciousness (a disorder called "Neuroleptic Malignant Syndrome"), as urgent medical treatment may be needed.

Dutch translation
SmPC
-Neuroleptisch maligne syndroom (NMS) NMS is potentieel levensbedreigend en kenmerkt zich door hyperthermie, stijfheid van de spieren, autonome instabiliteit, veranderd bewustzijn en een verhoogde concentratie kreatinekinase in het serum; andere tekenen kunnen myoglobinurie (rhabdomyolysie) en acuut nierfalen zijn.
-NMS is slechts zeer zelden in combinatie met donepezil waargenomen, met name bij patiënten die gelijktijdig antipsychotica krijgen toegediend.
-Indien een patiënt tekenen en symptomen ontwikkeld die op NMS wijzen, of onverklaarbaar hoge koorts krijgt zonder de overige klinische manifestaties van NMS, dient de behandeling te worden gestaakt.

PL
Ernstige bijwerkingen
Onmiddellijk bijwerkingen
Onmiddellijk op de hoogte met een arts als er bij koorts in combinatie met spierstijfheid wordt opgemerkt, verder nog zweten of een verlaagd bewustzijnsniveau (een aandoening met de naam "Neuroleptisch maligne syndroom"), aangezien dringende medische behandeling nodig kan zijn.

See Annex
Annex

Summary Assessment Report of the PhVWP July 2012

Donepezil – Risk of neuroleptic malignant syndrome (but insufficient evidence on causal relationship with serotonin syndrome)

Key message

Neuroleptic malignant syndrome (NMS) has been reported in patients treated with donepezil with or without concomitant antipsychotic medication, and if a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, donepezil should be discontinued.

Safety concern and reason for current safety review

The PhVWP became aware of serotonin syndrome (SS) in association with donepezil as a possible safety concern and agreed to assess this signal. The PhVWP expanded their review to include neuroleptic malignant syndrome (NMS), since the diagnosis of NMS may include symptoms of SS in addition to other symptoms such as muscle stiffness and very high temperature.

Clinical setting

Donepezil is authorised for the treatment of Alzheimer’s disease. It is a specific and reversible inhibitor of acetyl-cholinesterase and its efficacy is believed to be attained through the augmentation of acetylcholine-mediated synaptic transmission.

The overall exposure worldwide is estimated as approximately 18 million patient-years since 1997.

Information on the data assessed

Pre-clinical, clinical trial and spontaneous reporting data (from the originator marketing authorisation holder and the EudraVigilance adverse reaction database maintained by the agency) were assessed in addition to information from the medical literature [1-4]. Data held in the adverse reaction database of the UK competent authority were also reviewed.

Outcome of the assessment

Having reviewed all evidence from pre-clinical studies, clinical trials and spontaneous reporting, the evidence to support an association between donepezil and SS was not considered strong. There were no case reports of SS from clinical trials and very few spontaneous case reports of SS. In all of the 4 cases reported by the marketing authorisation holder co-suspect medication (paroxetine, sertraline or trazodone) occurred.

There were 3 cases of NMS from the marketing authorisation holder’s clinical trial database and considerably more cases of NMS (67) than of SS (4) from the marketing authorisation holder’s spontaneous report database. The PhVWP considered that there was reasonably good evidence that NMS occurs in causal relation with donepezil, both when used alone and together with other medication, usually antipsychotics. Factors that suggested causality included positive dechallenge in 42 cases and positive rechallenge in 1 case. In addition there were several cases where the clinical event
occurred in a plausible time relationship to administration and there were at least 5 cases where NMS developed after a dose increase. Review of data held in the adverse reaction database of the UK competent authority and EudraVigilance data and of cases published in the medical literature [1-4] supported the PhVWP's view.

Further, it was considered that there are plausible biological mechanisms. The neuropathophysiology of NMS is thought to relate to dysregulation of cortical-subcortical circuits between motor cortex and basal ganglia. Blockage of the striatal D2-receptors relative to regulatory cholinergic pathways was considered to be the most likely neurochemical cause. Thus an NMS-like syndrome may be precipitated by increasing cholinergic functioning in the presence of a compromised dopaminergic system.

Based on all information assessed, the PhVWP concluded that modifications to the summaries of product characteristics (SmPCs) and package leaflets (PLs) of all donepezil-containing medicinal products authorised in the EU are necessary to include:

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References


