

rivastigmine

New Indication

Dementia and Parkinson's disease: no thank you!

● In patients with both Parkinson's disease and dementia, a placebo-controlled trial has confirmed that the adverse effects of rivastigmine outweigh its benefits. It is better to carefully adjust ongoing antiparkinsonian treatments than to add an anticholinesterase.



NOT ACCEPTABLE

Anticholinesterases such as rivastigmine are used in the treatment of dementia caused by Alzheimer's disease, despite their limited benefits. In general, clinical improvement occurs in only around 10% of patients and lasts only a few months (1,2). This class of drugs is associated with cholinergic and extrapyramidal adverse effects (3).

In patients with Parkinson's disease, atropinic agents (anticholinergics) have a positive impact on symptoms but a limited effect on motor disorders. It does not make sense, therefore, to use an anticholinesterase in these patients, as it tends to increase acetylcholine levels in the brain (1).

A two-stage marketing authorisation procedure. Novartis nonetheless applied for European marketing authorisation for rivastigmine in the symptomatic treatment of dementia in patients with Parkinson's disease. Initially, on the basis of the only available placebo-controlled trial (EXPRESS trial), the marketing authorisation committee of the European Medicines Agency did not recommend approval of the drug. The manufacturer appealed the decision and the Agency convened an ad-hoc expert group to re-examine the trial data. In the end, rivastigmine was approved for this indication (4,5).

More adverse effects than benefits.

This double-blind randomised trial included 541 patients who had Parkinson's disease and mild to moderate dementia defined by an MMSE score (Mini-Mental State Examination) of between 10 and 24 (6,7). After randomisation they were treated for 24 weeks with either rivastigmine (3 mg to 12 mg/day) or placebo. A marked or moderate cognitive improvement was seen in 19.8% of patients on rivastigmine and in 14.5% of patients on placebo. This small difference (about 5% in absolute terms) confirms the limited efficacy of rivastigmine in the treatment of symptoms of dementia that has been observed in other trials.

This trial also confirmed the known adverse effect profile of rivastigmine: 17% of patients taking rivastigmine withdrew from the trial because of adverse events, versus 8% of patients on placebo. Nausea (29% versus 11.2%), vomiting (16.6% versus 1.7%) and tremor (10.2% versus 3.9%) occurred more frequently with rivastigmine. All differences were statistically significant.

In practice: focus on treating Parkinson's disease. About 5% of patients with dementia treated with rivastigmine showed a cognitive improvement, but the treatment also caused nausea and vomiting in about 15% of patients and tremor in about 6%.

It is better to fine-tune ongoing treatment for Parkinson's disease as the disease progresses than to add rivastigmine. After all, what is the point of exposing patients to a risk of adverse effects and drug-drug interactions when there is little if any chance of a therapeutic benefit?

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rivastigmine (Exelon®)

Capsules

• **1.5 to 6 mg** of rivastigmine per capsule

• **2 mg** of rivastigmine per milliliter of oral solution

■ **New indication:** "Symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease."

[EU marketing authorisation, centralised procedure]

anticholinesterase

Selected references from Prescrire's literature search.

In response to our request for information, Novartis provided us with abundant and pertinent data.

1- Prescrire Editorial Staff "Anticholinesterases in Alzheimer's disease" *Prescrire Int* 2003; 12 (68): 230-231.

2- Prescrire Editorial Staff "Rivastigmine" *Prescrire Int* 1999; 8 (40): 47-48.

3- Prescrire Rédaction "Maladie d'Alzheimer: gare aux interactions avec les anticholinestérasiques" *Rev Prescrire* 2006; 26 (269): 111-115.

4- "Novartis overturns CHMP negative opinion for Exelon" *Scrip* 2006; (3128): 19.

5- European Medicines Agency - CHMP "European Public Assessment Report (first published) Exelon - Scientific discussion: 25 pages: published on the EMEA website on 28 February 2006.

6- Novartis "A 24-week prospective, randomized, multicenter, double-blind, placebo-controlled, parallel-group study of the efficacy, tolerability, and safety of 3-12 mg/day of Exelon® (rivastigmine) capsules in patients with Parkinson's disease dementia" 10 November 2004: 65 pages.

7- Emre M et al. "Rivastigmine for dementia associated with Parkinson's disease" *N Engl J Med* 2004; 351 (24): 2509-2518 + 352 (13): 1387.