Donepezil 23 mg: Is it more advantageous compared to the original?

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ABSTRACT

The acetylcholinesterase inhibitor donepezil has been in clinical use for the treatment of Alzheimer's disease since 1996. The patent on the medication expired in November 2010, and at approximately the same time, a new dosage form of donepezil was FDA approved for moderate to severe Alzheimer's disease. This article discusses the benefits and risks of the new 23 mg sustained-release dosage form compared with donepezil 10 mg, based on the clinical trial data.

KEYWORDS

Alzheimer's disease, donepezil, acetylcholinesterase inhibitor

In December of 2010, a new FDA approved treatment for Alzheimer's disease emerged into the pharmacological arsenal for combating an illness for which limited pharmacotherapeutic treatments exist. The new approval was not for a novel chemical entity, but rather for a higher dose of a previous compound soon to lose patent exclusivity. Donepezil (Aricept®), an acetylcholinesterase inhibitor, has been in clinical use since 1996 for the treatment of Alzheimer's disease. After its arrival in 1996, donepezil soon became a blockbuster drug, as its safety and ease of administration greatly surpassed the first acetylcholinesterase inhibitor available in the United States, tacrine (Cognex®).

As with all chemical entities, expiration of patents is inevitable. The patent expired for donepezil in November 2010 ending Pfizer's ability to maintain exclusivity for the compound on the market. At approximately this same time, a new dosage form of donepezil, a 23 mg sustained-release dosage form, was FDA approved for moderate-to-severe Alzheimer's Disease.[1]

WITH A NEW HIGHER DOSAGE FORMULATION NOW AVAILABLE, ARE THERE ANY CLINICAL ADVANTAGES FOR USING THE 23 MG FORMULATION OF DONEPEZIL COMPARED TO THE PREVIOUS STANDARD FORMULATION?

The approval of the new dosage form is based on one large 24-week double-blind randomized clinical trial consisting of 1467 patients randomized to receive either donepezil 23 mg sustained release once daily or donepezil 10 mg once daily in a 2:1 ratio.[2] All of the patients enrolled in the study had moderate-to-severe impairment on the mini-mental status exam (MMSE) and were receiving donepezil 10 mg once daily for greater than or equal to 12 weeks prior to entering the study. The primary efficacy measures were change in cognition and global functioning from baseline, as assessed via the Severe Impairment Battery (SIB) and the Clinician's Interview-Based Impression of Change plus Caregiver Input scale (CIBIC+). The SIB is a standard assessment commonly used in clinical trials for moderate-to-severe Alzheimer's disease. It is a 40-item instrument that assesses cognition with scores from 0 (most impaired) to 100 (least impaired). The CIBIC+ is a multi-functional clinician rated assessment based on the interview with the patient and caregiver that evaluates the patient's functioning in several domains and represents a scale for global improvement. At the end of the 24 week treatment period, the change in the SIB score was significantly higher in the 23 mg group (+2.6) vs. the 10 mg group (+0.4), indicating a 2.2 difference ($p<0.001$). Although statistically significant, the changes in cognition most likely do not translate into a clinical improvement. Global functioning improvement based on the CIBIC+ was no different between groups (4.23 in the 23 mg group vs. 4.29 in the 10 mg group). Since statistical improvement is needed on both measures, the primary outcome was not achieved in the study. Also, no differences were seen between the two groups on any of the secondary end points as well, including the MMSE or Alzheimer's disease Cooperative Study-Activities of Daily Living scale. Thus, based on the data, a slight statistical improvement was seen in cognition for donepezil 23 mg over donepezil 10 mg, but no difference was evident for global improvement and the clinical trial did not achieve its primary outcome.

Although the efficacy of using donepezil 23 mg over the standard 10 mg dose is quite small, there is a greater price

to pay with the adverse effects of the higher dose compared to the lower dosage. The 23 mg dose is associated with a significantly higher incidence of nausea (11.8% vs. 3.4%), vomiting (9.2% vs. 2.5%), and diarrhea (1.7% vs. 0.4%), respectively compared to the 10 mg dose. Adverse events leading to discontinuation were also greater in the 23 mg/day group compared to the 10 mg/day group (18.6% vs.7.9%). GI bleeding, bradycardia, and weight loss were more frequently reported in the 23 mg donepezil group compared to the 10 mg group.[3]

Based on the clinical trial data, donepezil 23 mg offers little from a clinical standpoint compared to its 10 mg predecessor. When evaluating the utility of any medication, it is best to weigh the potential benefits of the medication with the potential risks. The sustained-release donepezil 23 mg formulation offers only a mild benefit in cognitive improvement and no difference in global improvement when compared to donepezil 10 mg formulation in the treatment of moderate-to-severe Alzheimer's disease. Consequently, the donepezil 23 mg has significantly higher adverse effects than the 10 mg/day dose, especially in regards to gastrointestinal adverse effects. Cost also raises an issue. The 23 mg formulation is only available as a brand product with an average wholesale price of $10.11 per unit. This is higher compared to multiple generic forms available for generic donepezil costing around $7.78 per unit.[4] Keeping this in mind, does the benefit of using the higher dose ultimately outweigh the risk in a fragile population with a chronically irreversible, deteriorating disease state? Doubtful.

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