Memantine is a relatively new addition to the therapeutic armamentarium in Alzheimer’s disease (AD). It was approved for use in Canada in late 2004, indicated for the symptomatic treatment of moderate-to-severe AD.

The pivotal studies that led to the drug’s approval included a placebo-controlled evaluation of memantine in 252 patients and a placebo-controlled evaluation of memantine as add-on therapy in 404 patients already taking a cholinesterase inhibitor. Both trials were conducted in patients with moderate-to-severe AD.

In the monotherapy trial, patients were treated with 20 mg of memantine or placebo daily for 28 weeks. The investigators found that patients receiving memantine had a better outcome than those receiving placebo, according to the results of the Clinician’s Interview Based Impression of Change with caregiver input (CIBIC-Plus), the Alzheimer’s Disease Cooperative Study Activities of Daily Living score, modified for severe dementia (ADCS-ADLsev) and the CIBIC-Plus. Memantine was well tolerated in both studies.

At the 2005 Meeting of the International Psychogeriatric Association (IPA), there were a number of studies presented that added to the evidence base with memantine, exploring the use of this agent in various AD domains (e.g., behaviour, function) and among patients with milder disease.

Data in Various AD Domains

Behaviour. An example of other endpoints examined were the three posters that presented evidence of memantine efficacy on behaviour in AD. One poster presented data drawn from the monotherapy pivotal trial, while another poster used data from both the monotherapy and add-on pivotal trials. The third poster included pooled data from six 24-to-28 week, randomized, placebo-controlled, double-blind memantine studies. Three of these studies were in mild to moderate AD; therefore including patients from across the AD spectrum.

All three posters presented data using the Neuropsychiatric Inventory (NPI), a tool that assesses several neuropsychiatric symptoms common in AD. In the monotherapy pivotal trial, the NPI total scores indicated a benefit of memantine treatment compared to placebo. The investigators of this analysis reported that the benefit was most prominent in the agitation and delusions domains.

In the analysis of both pivotal trials, the data presented at the IPA 2005 meeting showed that memantine was associated with statistical significant improvements in the overall NPI score, as well as in several individual items: agitation/aggression, irritability/lability, appetite/eating, and delusions. Improvements relative to placebo were found in terms of both preventing the emergence of symptoms and preventing worsening of symptoms.

The pooled analysis of memantine’s effect on behaviour across the AD spectrum included 1,242 patients taking memantine, and 1,069 taking placebo. Behavioural symptoms or this analysis were also evaluated with the NPI. Once again, memantine-treated patients were found to have a statistically significant benefit on the overall NPI score compared to placebo. Individual items reaching statistical significance were agitation/aggression,
delusions, irritability/lability, and disinhibition.

**Function** is another domain of AD in which memantine has been evaluated. There were two posters presented at the IPA 2005 meeting dealing specifically with functional improvements.6,7

One of the posters presented data on functional effects analyzed from two previous placebo-controlled studies (one pivotal trial1 and a 1999 trial by Winblad et al8) of memantine in AD. The effects were assessed by a single-item analysis of activities of daily living (ADL) rating scales in these trials.

The poster showed that in both studies, the total scores of these functional assessments favoured memantine treatment over placebo treatment. The single-item analysis demonstrated that patients treated with memantine showed a numerical advantage over placebo on all items.6

The other poster examining functional effects of memantine examined data from the two pivotal trials, both of which used the ADCS-ADL tool (19 items). The analysis showed significantly less functional deterioration in the memantine groups vs. placebo. In the monotherapy trial, the items showing statistical significance in favour of memantine were: makes conversation, clears a table, and disposes of litter. In the add-on therapy trial, items showing statistical significance in favour of memantine were: grooming, watching television, being left alone and finding belongings.

The investigators of this analysis also consolidated the individual items into four subgroups. In the monotherapy study, when the ADLs were consolidated, significance in favour of memantine was found in all four subgroups: basic ADLs, higher level functions, simple motor skills, and autonomy. In the add-on study, statistical significance was reached for two of the four subgroups: higher level functions and autonomy.

**Safety.** At the IPA 2005 meeting, researchers also presented data on the short- and long-term safety and tolerability of memantine in AD.9,10 The data for one poster were compiled from a number of double-blind, placebo-controlled trials and open-label extension studies.9

Short-term safety of memantine was evaluated in six placebo-controlled studies in mild-to-moderate AD patients (n = 1,306) and moderate-to-severe AD patients (n = 734). In mild-to-moderate AD, no adverse events (AEs) occurred in more than 5% of memantine-treated patients and at an incidence of at least twice that of placebo.

In moderate-to-severe AD, headache and confusion were reported in at least 5% of patients at an incidence of at least twice that of placebo.

In moderate-to-severe AD, long-term safety of memantine was assessed by pooling data from five open-label extension studies with moderate to severe AD and VaD patients (n = 1,416). The investigators found that the overall profile of AEs reported in the long-term was similar to that reported in the short-term.

No clinically relevant differences between memantine and placebo patients in vital signs or laboratory values were observed.

A separate investigation evaluated the safety and tolerability of a particular dosing regimen for memantine: weekly titration.10 For this prospective study, memantine was titrated up starting at 5 mg/day and subsequently increased weekly to 10 mg BID over a four-week period. A total of 238 patients were evaluated over this first month. Most of the patients were receiving memantine in addition to background cholinesterase inhibition (n = 226).

Investigators found that the rate of AEs associated with this titration method was 39.7% at one centre and 57.5% at another. The discontinuation rates due to adverse events were 15% and 10.6% at the two centres, respectively. All reported AEs were related to increased confusion, agitation or significant change in personality.

The investigators concluded that weekly titration is associated with significant AEs.

**New Efficacy Data**

**Data in mild-to-moderate AD.** One poster at the IPA 2005 meeting presented data from a prospective, randomized, placebo-controlled study of memantine in mild-to-moderate AD.11 The study enrolled 403 patients with an MMSE score of 10–22 at screening and baseline. Patients were randomized to placebo (n = 202) or memantine 10 mg b.i.d. (n = 201) and followed for 24 weeks.

The poster showed that memantine-treated patients showed statistically significant improvements compared to placebo-treated patients on the
primary endpoint of cognition as measured by the Alzheimer’s Disease Assessment Scale-Cognitive (ADAS-Cog). Four individual items on the ADAS-Cog also showed significantly superior results for memantine: commands, orientation, comprehension and recall of test instructions.

**Additional data in moderate-to-severe disease.** Three posters presented at the IPA 2005 added to the evidence base supporting the use of memantine in moderate-to-severe AD. These included a European post-marketing surveillance study \((n = 377)\), a retrospective evaluation of memantine among nursing home patients \((n = 81)\), and a small prospective uncontrolled study of 17 patients. All three posters validated the use of memantine in patients with advanced AD.

**Conclusion**

Memantine has proven to be an effective agent for improving cognition, behaviour and function in patients with moderate-to-severe AD, whether used in monotherapy or in combination with cholinesterase inhibition. Data presented at the 2005 IPA meeting not only add to the existing evidence base in moderate-to-severe AD, but also show that this agent has utility in mild-to-moderate disease.

**References:**