

**Rapporteur's
Public Assessment Report
for paediatric studies submitted in accordance
with Article 46 of Regulation (EC) No1901/2006, as amended**

**Donepezil (Aricept)
UK/W/025/pdWS/001**

Rapporteur:	UK
Day 120	27th November 2010

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Aricept
INN (or common name) of the active substance(s):	Donepezil/Donepezil hydrochloride
MAH:	Eisai Limited
Currently approved Indication(s)	Symptomatic treatment of mild to moderately severe Alzheimer's dementia
Pharmaco-therapeutic group (ATC Code):	Anti-dementia drugs; anticholinesterases ATC code N06DA02
Pharmaceutical form(s) and strength(s):	5 & 10 mg Film Coated Tablets & Liquid 1mg/ml Oral Solution

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I. EXECUTIVE SUMMARY AND RECOMMENDATION

I.1 Introduction

This is an assessment of data for donepezil, as part of the Article 46 EU work-sharing procedure for assessment of paediatric studies completed after the Paediatric Regulation entered into force (26 Jan 2007). The UK is Rapporteur for this product; the initial assessment report (day 70) is due to be circulated to concerned Member States on 30 September 2010.

On 27 May 2010 the MAH submitted 5 clinical studies for donepezil, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use. In addition, a critical expert overview has been provided. The submitted studies are for the use of donepezil for the treatment of attention impairment in paediatric cancer survivors and Down's syndrome in children and adolescents. The MAH stated that the submitted paediatric studies do not influence the benefit risk for donepezil and that there is no consequential regulatory action.

Donepezil, a selective inhibitor of acetylcholinesterase, has been developed for the treatment of Alzheimer's disease (AD) in adults. There is no evidence that donepezil is currently prescribed for use in children for the treatment of cognitive impairment, attention deficit hyperactivity disorder (ADHD), Down's syndrome or any other medical condition in the EU

Clinical data submitted

The following studies were submitted:

Pharmacokinetic study E2020-A001-101-randomized, double-blind, placebo-controlled, single-dose, sequential-group study in children with ADHD.

Pharmacokinetic study E2020-A001-106 -randomized, double-blind, ascending multiple-dose, placebo-controlled, parallel-group study in children with ADHD.

Study E2020-A001-219 - a double-blind, ascending dose, placebo-controlled Phase II proof-of-concept study in 129 children to evaluate the efficacy and safety of donepezil hydrochloride in the treatment of the cognitive dysfunction exhibited by children with Down's syndrome

E2020-G000-333 (Study 333) and the concurrent and identical companion study **E2020-G000-334 (Study 334)**- Randomized, Double-Blind, Placebo-Controlled Study of Efficacy and Safety of Donepezil Hydrochloride in Preadolescent and Adolescent Children with Attention Impairment Following Cancer Treatment.

Conclusions

The results of the Phase III trials in a small sample of paediatric and adolescent cancer survivors did not provide evidence that donepezil is superior to placebo for attention deficits. In addition, there was no evidence that donepezil was efficacious in the treatment of Down's syndrome.

In the five submitted studies, donepezil, the safety profile was surprisingly good; the drug was also generally well-tolerated. However, only limited long term safety data were provided.

From the data provided, there is no change in the benefit/risk of donepezil with respect to the treatment of the paediatric population.

Day 85 MS Comments

Comments were only received from Sweden, who endorsed the Rapporteur's recommendations

I.2 Recommendations

The Rapporteur recommends that no changes in the product information are required. In addition, no further regulatory action is required.

II. INTRODUCTION

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III. REGULATORY ASPECTS

III.1 Regulatory History

Donepezil,(±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl] methyl]-1H-inden-1-one hydrochloride, a selective inhibitor of acetylcholinesterase, has been developed for the treatment of Alzheimer's disease (AD) in adults. The approved-for-market formulations of donepezil hydrochloride for oral administration in the EU include immediate release (IR) film-coated tablets and uncoated orodispersible tablets (ODTs), containing 5 or 10 mg of donepezil hydrochloride. A 1 mg/ml oral solution has also been approved in the EU, but is not marketed.

In 2007, the MA holder submitted a Paediatric Investigation Plan including Requests for Waiver for donepezil hydrochloride to the EMEA/PDCO (EMEA-000108-PIP-01-07). The PIP was intended to support the indication of donepezil for the treatment of attention impairment in paediatric cancer survivors. However, the PIP was withdrawn in 2008, following the receipt of D60 comments. For the clinical program in Down's syndrome, no PIP was submitted. However, the Phase III studies were intended to be conducted in the EU, and clinical trial authorisations were underway at the time that the program was terminated due to lack of efficacy demonstrated in the Phase II proof-of-concept study. A Class Waiver has been obtained for donepezil for the indication of Alzheimer's disease.

There is no evidence that donepezil is currently prescribed for use in children for the treatment of cognitive impairment, attention deficit hyperactivity disorder (ADHD), Down's syndrome or any other medical condition in the EU.

IV. SCIENTIFIC DISCUSSION

IV.1 Introduction

Attention impairment in paediatric cancer survivors

There is currently an unmet medical need for effective treatment of attention impairment in children who have been treated for and survived cancer. In children treated for systemic cancers or brain tumours, cranial irradiation and chemotherapy may produce significant long term adverse effects, which include intellectual deterioration that may have important implications for functional status and quality of life. Until recently, the limited survival of children with either systemic cancer or brain tumours meant that their intellectual deterioration received little attention. However, as the prognosis has improved for children with certain types of brain tumours and cancers, this long-term and possibly remediable late effect has become increasingly important (Duffner, 2004; Regine et al., 2004; Kondziolka et al., 2005).

Attention impairment consequent to cancer therapy is an important factor in the quality of life for patients who survive their cancer (Ahles and Saykin, 2002). Children are in the midst of peak learning and skills acquisition, so interruption of this process by the effects of chemotherapy and/or radiotherapy not only stalls the process, but can cause permanent damage to the central nervous system (CNS) and the tracts associated with attention, memory, and cognition in general. These impairments can translate into poor academic performance, which may have amplified effects on a child's future employment and independence. The cognitive consequences of cancer therapy are also shared by the family, who must cope with the impact of cognitive deficits on the paediatric patient. Cognitive dysfunction has been recognised as an important problem by the US National Cancer Institute and is considered a significant challenge facing cancer survivors by the National Coalition for Cancer Survivorship (NCIDEA: President's Cancer Panel, 1999; Ferrell BR et al., 1997).

Cholinergic Hypothesis and the Use of Cholinesterase Inhibitors

The aetiological mechanisms of cognitive and attention impairments associated with cancer treatments are likely to be variable, dependent on radiation doses and delivery and chemotherapeutic agents. There are, however, commonalities among organic disorders such as AD or dementia associated with Parkinson's disease and acquired diseases such as the one under study. The underlying concept is that the neuronal damage from whatever source (neuritic plaques, neurofibrillary tangles, inflammatory responses, toxic effects) leads to a cholinergic deficit that would be amenable to cholinergic enhancement.

The role of acetylcholine (ACh) and the brain cholinergic system in attention, learning, and memory is well established (Gron et al., 2005). Evidence for the important function of ACh in cognition has been provided by a variety of experimental approaches showing that interference with cholinergic function generally impairs, and augmenting such function generally enhances, learning and memory (Pepeu et al., 2006, Hasselmo, 2006; Hasselmo and Giocomo, 2006). Cholinergic modulation of frontal cortical brain regions associated with learning and memory during neuroimaging studies in humans has shown that memory-impairing or –promoting effects of cholinergic drugs may be linked to modulation of frontal cortical neuronal activity (Theil, 2003). These findings suggest an important role for cholinergic activation in stimulus processing and attention function (Theil, 2003).

However, the cognitive impairment associated with non-dementing conditions such as those following chemotherapy or radiotherapy is acquired, and the role of cholinergic deficit in its pathophysiology has not yet been clearly established. There have been no studies on cholinergic deficits in human subjects who have been treated with chemotherapy or radiotherapy, although exposure of mice to ionizing radiation has been found to decrease both choline esterase (ChAT) and ACh levels (Dimberg et al). Nevertheless, radiation-induced injury shares some clinical, radiographic, and pathologic features with AD (Frytak et al., 1989). Children with leukaemia who receive chemotherapy alone may have a high prevalence of leukoencephalopathy, which occurs in as many as 80% of patients on some treatment regimens (Montour-Proulx et al., 2005; Reddick et al., 2005).

Several potential mechanisms underlying chemotherapy-induced neurological injury include microvascular injury and secondary injury as a result of immune-mediated inflammatory responses, which are also hypothesized to play a role in AD. Chemotherapy-induced inflammation leads to direct injury of both cerebral gray and white matter (Mulhern et al., 2004; Tuxen MK, Hansen SW, 1994). Taken together, the commonalities in clinical and neuropathological features between AD and the cognitive dysfunction associated with chemotherapy or radiotherapy suggest that the cholinergic deficit underlying dementia may also be involved in the latter condition. Therefore, cancer treatment is hypothesized to result in neuronal injury that, in turn, causes an ACh deficiency.

Increasing evidence indicates that cholinergic therapy may improve cognition. There are two possible mechanisms by which enhancement of cholinergic function may provide clinical benefits for children and adolescents with attention and other cognitive difficulties associated with cancer therapies: (1) through the general role of acetylcholine (ACh) in cognitive function and/or (2) through an impact on symptoms resulting from underlying brain pathology. Although no studies in children have been undertaken, an open-label study in adults who have received cranial irradiation for brain tumours (Shaw et al., 2006) provided limited evidence that donepezil may improve certain cognitive functions, including attention impairment.

Down's syndrome

Down's syndrome (DS) is the most common genetic disorder diagnosed at birth that involves adaptive and cognitive deficits. It occurs in 1 in 700 to 800 live births. The current estimated prevalence of DS in the US is 350,000. Today, the potential lifespan of individuals with DS is extended significantly, leading to greater participation of DS patients within the social community. Thus, maximizing functional potential is an immediate need. For children with DS, evolving educational policies and early intervention have helped to place emphasis on abilities, rather than disabilities. However, the cognitive defects that are associated with DS represent a major obstacle to progression toward greater independence and productivity (Yang et al., 2002).

To this end, medical, and in particular pharmacological, intervention strategies are needed. Currently, no treatment for improved cognition or function in paediatric DS patients is approved. At present, parents of DS children have only limited off-label medication usage as treatment options for DS-related cognitive and functional impairment. The development of effective treatments would be of particular benefit for children with DS precisely because their effects would occur during the development process when the impact may be maximized.

Several lines of evidence support the cholinergic deficit hypothesis in DS: (1)

Data from transgenic mouse models of DS that support the potential for cholinergic dysfunction and possibly degeneration across the lifespan, which are thus pertinent to treating children; (2) data from autopsy; and (3) data from two small open-label trials of cholinesterase inhibitors that showed treatment benefits.

Two small open-label studies that have been completed with cholinesterase inhibitors in children suffering from DS; one studied donepezil (Spiridigliozzi et al., 2007), the second investigated rivastigmine (Heller et al, 2006). Overall in both trials, the drug was considered to be well-tolerated. It was noted that in the donepezil study, in addition to expected cholinergic side effects, there was some apparent increased stubbornness or assertiveness in several subjects. Efficacy measures of memory and attention seemed to show the most improvement, in addition to the language measures previously reported.

IV.2 Pharmaceutical aspects

The 1 mg/ml oral solution that has been approved in the EU, but is not marketed was used for the studies.

IV.3 Non-clinical aspects

No data were submitted.

IV.4 Clinical aspects

IV.4.1 Submitted clinical studies

The following studies were submitted:

Pharmacokinetic study E2020-A001-101-randomized, double-blind, placebo-controlled, single-dose, sequential-group study in children with ADHD.

Pharmacokinetic study E2020-A001-106 -randomized, double-blind, ascending multiple-dose, placebo-controlled, parallel-group study in children with ADHD.

Study E2020-A001-219 - a double-blind, ascending dose, placebo-controlled Phase II proof-of-concept study in 129 children to evaluate the efficacy and safety of donepezil hydrochloride in the treatment of the cognitive dysfunction exhibited by children with Down's syndrome

E2020-G000-333 (Study 333) and the concurrent and identical companion study **E2020-G000-334 (Study 334)**- Randomized, Double-Blind, Placebo-Controlled Study of Efficacy and Safety of Donepezil Hydrochloride in Preadolescent and Adolescent Children with Attention Impairment Following Cancer Treatment.

IV.4.2 Assessment of submitted studies.

IV.4.2.1 Pharmacokinetics

Data on paediatric PK are derived from two studies in children with ADHD and one study conducted in children with Down syndrome (DS). It should be noted that the studies were conducted with liquid donepezil hydrochloride in a 5 mg/5 ml formulation that has been shown to be bioequivalent to the film-coated tablets currently marketed.

Study E2020-A001-101 was a two-centre, randomized, double-blind, placebo-controlled, single-dose, sequential-group study in 33 ambulatory children (26 males and 7 females; 31 White and 2 Black; aged 7-14 years; weight 22-60 kg) with an established diagnosis of ADHD for ≥ 3 months based on DSM-IV criteria. Donepezil was administered in a 20% sorbitol solution to four single-dose groups of 0.025, 0.05, 0.075, and 0.10 mg/kg. Over a 4-fold range of doses, mean values for AUC_{0-last} and C_{max} generally increased proportionally with dose. Across the four donepezil dose groups, T_{max} ranged from 2.5 to 4.0 hours and the mean t_{1/2} ranged from 63 to 83 hours. There was no apparent dose effect for t_{1/2}.

Study E2020-A001-106 was a randomized, double-blind, ascending multiple-dose, placebo-controlled, parallel-group study in 32 ambulatory children (27 males and 5 females; aged 7-15 years; weight 22-73 kg) with an established diagnosis of ADHD for ≥ 3 months based on DSM-IV criteria. The treatment groups were as follows: Group 1= placebo for 8 weeks; Group 2 = for those ≤ 35 kg (mean weight 28.0 kg), donepezil 2.5 mg/day for 4 weeks then 5.0 mg/day for 4 weeks; and Group 3 = for those > 35 kg (mean weight 51.3 kg), donepezil 5.0 mg/day for 4 weeks, followed by 10.0 mg/day for 4 weeks. There was little difference in PK findings between the two weight/dose groups of children, suggesting linear PK in children.

Study E2020-A001-219 was a double-blind, ascending dose, placebo-controlled Phase II proof-of-concept study in 129 ambulatory children to evaluate the efficacy and safety of donepezil hydrochloride in the treatment of the cognitive dysfunction exhibited by children with Down's syndrome confirmed by chromosome analysis (free trisomy 21).

A total of 127 children (66 males and 61 females; aged 10 to 17 years; weight 20-100 kg) comprised the intent-to-treat (ITT) population. Donepezil or matching placebo was administered orally as liquid formulation followed by a full glass of water. Dosing was based on body weight: 2.5 mg/day for subjects from >20 kg to <25 kg, 5 mg/day for subjects from 25 to <50 kg, and 10 mg/day for subjects \geq 50 kg. The intent was to achieve maximum doses between 0.1 mg/kg/day to 0.2 mg/kg/day for at least 4 weeks. The average daily dose of donepezil administered during the maintenance phase was 5.0 mg/day.

Results

Table 2 compares the steady state results in children with those following 5 or 10 mg donepezil immediate release (IR) tablets once nightly for 28 days in healthy young adults (Study E2020-A001-011). Results suggest a relatively lower clearance in paediatric patients compared with healthy young adults after dosing to steady state (apparent clearance approximately 0.07 - 0.08 versus 0.11 L/h/kg, respectively). There was little difference in pharmacokinetic findings between the two weight/dose groups of children, suggesting linear PK in children. Linear PK is also observed in adults.

Study	Dose (mg)	Age (years)	Weight (kg)	C _{max} (ng/ml)	AUC ₀₋₂₄ (ng•h/ml)	t _{1/2} (h)
A001-106	5	8.7	28.0	67.7 ± 26.2	2293 ± 1015	56.4 ± 13.4
	10	11.7	51.3	79.8 ± 48.0	2879 ± 2086	58.2 ± 12.1
A001-011	5	40.1	70.8	34.1 ± 7.3	635 ± 92	72.7 ± 10.6
	10	36.1	80.2	60.5 ± 10.0	1128 ± 196	73.5 ± 11.8

Results presented as mean ± standard deviation

Based upon the most relevant PK data from multiple dosing in paediatric subjects from Study A001-106, doses of 5 mg in children <35 kg and 10 mg in children >35 kg gave exposures greater than those expected to be efficacious (target daily exposure, or AUC₀₋₂₄), between 1-2 µg•h/mL compared to observed values of between 2.3-2.9 µg•h/mL.

Assessor's comments:

PK data the 3 submitted studies provide limited information:

The results of Study E2020-A001-101 showed that plasma donepezil concentrations increased in proportion to dose, and the mean apparent plasma clearance in paediatric subjects was similar to that reported for adults.

Limited data from Study E2020-A001-106 suggest that donepezil exposure at comparable doses is greater in paediatric patients with ADHD relative to healthy adults, but donepezil may be eliminated at a faster rate in paediatric patients compared with adults.

However, as donepezil is not prescribed in children, the assessor considers that no changes to the product information are required.

IV.4.2.2 Efficacy study of donepezil for the treatment of attention impairment in paediatric cancer survivors.

Study Design

The clinical program for the assessment of the efficacy of donepezil for the treatment of attention impairment in paediatric cancer survivors was comprised of two Phase III studies, **E2020-G000-333 (Study 333)** and the concurrent and identical companion study **E2020-G000-334 (Study 334)**.

Each study was a randomized, double-blind, placebo-controlled, parallel-group, multicentre study (that was undertaken in 2008-9), of the efficacy and safety of donepezil hydrochloride in 70 children and adolescents aged 6-17.5 years with attention impairment following cancer treatment,. These were double-blind, placebo-controlled, parallel-group studies in a total of 70 male and female paediatric subjects.

The primary objective of each study was to evaluate the efficacy of donepezil in children with attention impairment that was present at least 12 months after the completion of cancer treatment.

The secondary objective was to evaluate the safety and tolerability of donepezil in children. Safety parameters included AEs, discontinuation from treatment, study compliance, extent of exposure, clinical laboratory data, physical examination findings, and vital sign assessments.

The trials had three phases: (1) pre-randomization to establish eligibility, (2) a 12-week, double-blind, placebo-controlled, parallel-group phase with dose escalation based on body weight, (3) a 12-week, blinded extension phase during which all subjects received active drug. Subjects who met inclusion/exclusion criteria were randomized to receive placebo or donepezil.

All subjects randomized to receive donepezil started on 3 mg/day. Subjects who weighed 35 to 49.9 kg were titrated up to 5 mg/day final dose three weeks later. Subjects weighing 50.0 kg or more were titrated up after three weeks to 5 mg/day, then to a final dose of 10 mg/day three weeks later. No down-titrations were allowed.

The studies required both a subjective complaint and objective corroboration of the complaint, as measured by scores at least one standard deviation below the norm for age and gender on the d' statistic from the Test of Variables of Attention – Continuous Performance Test (TOVA-CPT).

Key inclusion criteria were age 6-17.5 years, with subjective parental complaint of their child's attention impairment present at least one year following successful treatment for underlying cancer.

The primary efficacy variable was the d-prime (d') standard score from the Test of Variables of Attention-Continuous Performance Test (TOVA-CPT) at 12 weeks (see Annex 3 for full details regarding efficacy variables). This computerised test was developed to measure attention and impulse control processes in four areas: inattention or omissions; impulse control or commissions; response time; and response time variability.

Other efficacy assessments used were the TOVA-CPT response time and response time variability, Paired Associates Learning (PAL) test; Decision Speed Test; Woodcock Johnson Mathematics Fluency Test; Go/No-Go Task, the Behavioural Rating Inventory of Executive Functioning (BRIEF) test (Gioia et al., 2000), Conners' Parent Rating Scale – Revised (CPRS-R(S); Conners et al., 1998), Delis-Kaplan Executive Function System Trail Making Test (D-KEFS TMT) (Tombaugh, 2004), Treatment Expectation Scale (TES); and Treatment Outcome Scale (TOS).

The efficacy and safety analyses used pooled data from Studies 333 and 334. An analysis of covariance (ANCOVA) model with a factor for treatment and the screening value as covariate was used as the primary model for estimating and testing treatment effects of the primary endpoint. Except for the TOS and TES, efficacy endpoints were analysed using a similar ANCOVA model. The TOS was analyzed using the Cochran-Mantel- Haenszel test.

Donepezil plasma concentration data were analyzed. Full pharmacokinetic analysis was not performed because too few samples were collected to allow for any meaningful pharmacokinetic parameter estimation.

Efficacy Results

Primary Efficacy Assessment

The primary efficacy endpoint for the ITT population was the TOVA-CPT d' standard score change from baseline to Week 12 (last observation carried forward [LOCF]) of the Double- Blind Phase. At Week 12, subjects assigned to the donepezil treatment group in pooled Studies 333 and 334 demonstrated a mean change from baseline in the TOVA-CPT d' standard score that was slightly greater than placebo, but the difference between treatment groups was not statistically significant. Both donepezil and placebo subjects improved slightly versus baseline (least squares [LS] mean 5.2 ± 1.32 points and 4.4 ± 1.51 points, respectively), and LS mean difference was 0.8 points between donepezil subjects and placebo subjects ($P=0.6940$). The results of the primary efficacy analysis did not demonstrate the superiority of donepezil as compared to placebo for the treatment of preadolescent and adolescent children with attention impairment following cancer treatment.

Secondary Efficacy Assessments

Subjects assigned to the donepezil treatment group demonstrated no statistically significant differences in change from baseline in comparison to placebo for the TOVA-CPT secondary efficacy variables, including change from baseline to Week 6 for the d' standard score, and change from baseline to Weeks 6 and 12 for the Reaction Time Variability standard score and Response Time standard score.

There were no notable differences in TOVA-CPT secondary efficacy endpoints in pooled Studies 333 and 334. For the BRIEF secondary endpoints, donepezil subjects also demonstrated no statistically significant differences in change from Baseline to Week 12 for the Global Executive Composite Score, Behavioral Regulation Index, Metacognition Index, or Working Memory Scale.

Exploratory Assessments, Double-Blind Phase

Exploratory efficacy assessments during the Double-Blind Phase were the D-KEFS TMT, Go/No-Go Task, and TOS. There were no statistically significant differences on any parameter between groups.

Efficacy Conclusions

The results of the primary efficacy analysis for pooled Studies 333 and 334 did not demonstrate superiority of donepezil as compared to placebo for the treatment of preadolescent and adolescent children with attention impairment following cancer treatment.

The results of the secondary efficacy analyses for the pooled studies demonstrated no statistically significant difference in change from Baseline to Week 6 and Week 12 endpoints for donepezil and placebo subjects. Efficacy data analyses also showed no important differences between treatment groups during the blinded extension phase (Weeks 12-24).

Assessor's comments:

The appropriateness of the primary outcome assessment instrument (TOVA-CPT) is questionable. This is a validated tool for the clinical diagnosis of children with ADHD; however, the assessor considers that its use in the research setting is limited.

Also, the Conners rating scale was only measured by parents, not externally (by teachers for instance), thus limiting the usefulness of this as an efficacy measure.

Efficacy was not demonstrated in this study either clinically or statistically; no change in the SmPC is required.

IV.4.2.3 Efficacy study for the treatment of Down's syndrome

Study Design

The objective of this study (E2020-A001-219) was to evaluate the efficacy and safety of donepezil hydrochloride in the treatment of the cognitive dysfunction exhibited by children with Down's syndrome as assessed in the domains of communication, daily living skills, and socialization.

It was a 10-week, multicenter, randomized, double-blind, placebo-controlled study, with a planned interim analysis using group sequential design. Approximately 35 sites in the US and 150 subjects were planned. Subjects (male or female) resided in the community, were 10 to 17 years of age, ambulatory or ambulatory-aided, with a diagnosis of Down syndrome (trisomy 21) documented by chromosomal analysis and staging of mild or moderate mental retardation as indicated by a Vineland-II composite adaptive behaviour standard score of >55 at screening.

Maximum dosing was based on body weight: 2.5 mg/day orally for subjects < 25 kg, 5 mg/day orally for subjects 25- <50 kg, and 10 mg/day for subjects > 50 kg. All subjects started with a dose of 2.5 mg/day (2.5 ml donepezil or placebo); dose escalations occurred in 2.5 mg/d (2.5 ml) increments every 2 weeks (steady state levels reached) to a maximum of 10 mg/day (10 ml donepezil or placebo), as per the clinician's judgment. Blinded 5 mg donepezil/5 ml and placebo liquid were supplied as liquid formulations. The study duration was 10 weeks of double-blind treatment.

The primary outcome measure was the change in Vineland-II Adaptive Behaviour Scale (VABS-II), Parent/Caregiver Rating Form (PCRF) sum of the 9 sub-domain v-scores (3 scores for each of the communication, daily living skills, and socialization domains) from baseline to week 10 using last observation carried forward (LOCF) in the intent-to-treat (ITT) population. The VABS is an assessment tool for children aged pre-school to 18 years old. It measures the social abilities five domains: communication, daily living skills, socialization, motor skills, and maladaptive behaviour (see Annex 4 for further details).

Secondary outcome measures included (1) additional analyses of the VABS-II/PCRF including the composite score and domain and sub-domain raw and standardized scores; and (2) The Test of Verbal Expression and Reasoning (TOVER), a subject-performance-based evaluation of language function. Pharmacokinetic analyses were conducted based on with plasma donepezil levels measured pre-dose at Visits 2 and 3. Safety was assessed by evaluation of the subject's medical history, physical exam, vital signs and neurological examinations, clinical laboratory tests, ECG, concomitant medications and adverse event (AE)/serious adverse event (SAE) reporting.

Efficacy Results

Primary Efficacy Assessment

This was the change from baseline to Week 10 LOCF of the VABS-II/PCRF sum of the 9 sub-domain v-scores. In both treatment groups, there was an increase in mean scores from baseline to Week 10 LOCF (donepezil mean change = 4.74; placebo mean change = 4.22); these differences were statistically significant compared with baseline in both groups ($p < 0.0001$). However, the least squares (LS) mean change difference between the 2 groups (donepezil = 4.43; placebo = 4.42) was virtually zero and the p value for this primary efficacy comparison was 0.999.

Secondary Efficacy Assessments

All mean scores, except personal at Week 4, increased, with greater increases at Week 10 than at Week 4. For 22 of the 54 comparisons to baseline, the p value was <0.05. All mean increases were <1.0. The LS mean change treatment difference generally favoured donepezil for the written, personal, domestic, and play and leisure time sub-domains; placebo was generally favoured in the receptive, expressive, community, interpersonal relationships, and coping skills sub-domains. The Week 10 domestic sub-domain LS mean change treatment difference p-value was 0.047, also favouring donepezil. None of the other treatment difference comparisons showed p values <0.05.

Efficacy Conclusions

In most efficacy measures, there were mean increases from baseline to Week 4, Week 10, and Week 10 LOCF study time points that were statistically significant in both treatment groups. In most efficacy measures, treatment differences between the donepezil and the placebo group at these time points were not statistically significant.

On both the primary efficacy measure, the VABS-II/PCRF, a broad functional assessment rated by parents or caregivers and the secondary efficacy measure, the TOVER, a subject performance-based measure of expressive language function, both the donepezil group and the placebo group had mean scores that increased from baseline over the course of the study. However, within each group, these increases were usually statistically significant. As a result of such similar improvements, the differences between treatments were small and not significant.

Thus, this study failed to demonstrate any benefit for donepezil versus placebo in children and adolescents with Down's syndrome. Donepezil appeared to be safe and well-tolerated in this study.

Assessor's comments:

Efficacy was not demonstrated in this study either clinically or statistically; however donepezil appeared to be well tolerated. The assessor considers that no change in the SmPC is required.

IV.4.2.4 Safety

Data on the safety of donepezil in children from the five submitted studies were provided in the clinical expert report.

Safety in phase 1 studies

Donepezil was well-tolerated in Study E2020-A001-101, in which 33 children aged 7-14 years received single doses of donepezil 0.025, 0.05, 0.075, or 0.10 mg/kg or placebo. The incidence of adverse events (AEs), as defined by treatment-emergent signs and symptoms (TESS) and treatment-emergent abnormal laboratory values (TEAVs), was similar across the five treatment groups. Most AEs were judged by the investigator to be mild in intensity. There were no unexpected events or serious adverse events (SAEs), and no subject withdrew from the study due to AEs. There were no clinically meaningful changes in other safety parameters including clinical laboratory tests, vital signs, physical examination, or electrocardiogram (ECG) recordings.

Donepezil was well tolerated in Study E2020-A001-106, in which 32 children aged 7-15 years received, over 8 weeks, placebo, donepezil 2.5 mg/day rising to 5 mg/day, or donepezil 5 mg/day rising to 10 mg/day (depending on body weight).

In the donepezil groups, nine (64.3%) subjects in the 2.5-5 mg dose group (≤ 35 kg) and 10 (90.9%) subjects in the 5-10 mg dose group (> 35 kg) experienced one or more AEs, as defined by TESS. In the placebo group, six (85.7%) subjects experienced one or more AEs. Most AEs were judged by the investigator to be mild or moderate in intensity. The most common AEs occurring with greater frequency in donepezil treatment groups than in the placebo group were vomiting, abdominal pain, and headache. These AEs are consistent with the known safety profile of donepezil. There were no SAEs or unexpected AEs. Four subjects withdrew from the study due to AEs: two (14.3%) in the 2.5-5 mg dose group and two (18.2%) in the 5-10 mg dose group. There were no clinically meaningful changes in other safety parameters (clinical laboratory tests, vital signs, physical examination, or ECG recordings).

Safety in phase II studies

Double-blind Study in Paediatric Down's Syndrome (DS)

During the DS Phase II double-blind Study 219, 129 patients were randomized to donepezil or placebo. The median duration of treatment was 69.0 days for the donepezil group and 70.0 days for the placebo group. In the safety population, the majority of subjects (55) in the donepezil group and the majority of subjects (63) in the placebo group received study drug for 61 to 90 days. The average daily dose was 5.0 mg in the donepezil group and 5.6 mg in the placebo group. Mean compliance was high in both groups.

Forty-five (70.3%) donepezil-treated subjects and 42 (64.6%) placebo-treated subjects experienced AEs during the study. The most common AEs (occurring in $> 5\%$, regardless of relationship to study drug) were diarrhoea (17.2%), vomiting (12.5%), upper respiratory tract infection (9.4%), headache (7.8%), nausea (7.8%), and cough (6.3%) in the donepezil group and diarrhoea (15.4%), upper respiratory tract infection (7.7%), and nasopharyngitis (6.2%) in the placebo group. With the exception of upper respiratory infection and cough, the most common donepezil AEs were consistent with the known cholinergic AE profile of donepezil and similar in incidence to those reported in AD studies.

No severe AEs were reported during the study. The majority of AEs in both treatment groups were reported as mild in both treatment groups. No deaths occurred during this study. There was 1 subject in the placebo group who had 2 SAEs: a single hospitalization for gastroenteritis and dehydration. Both SAEs were assessed by the investigator as not related to study drug, both were moderately severe, and both resolved. Study drug was not changed due to gastroenteritis; study drug was adjusted/interrupted due to dehydration.

There was one donepezil-treated subject who discontinued due to TEAEs during the study. This subject developed mild pollakiuria (increased urinary frequency) assessed as not related to study drug, which resolved. Evaluation of changes in vital signs, physical and neurological examinations, clinical laboratory tests, and ECGs did not find any cause for safety concerns.

Following the double-blind study, 117 subjects entered the 42 week open-label extension study (Study E2020-A001-220). This study was terminated early by the sponsor since donepezil was not found to be effective in the treatment of DS patients during the Phase II double-blind study.

Safety in phase III studies in paediatric cancer survivors

In the double-blind phase of the two studies E2020-G000-333 and E2020-G000- 334 more subjects in the donepezil group experienced treatment emergent adverse events (TEAEs) than subjects in the placebo group (75.0% vs. 64.5%). During the Blinded Extension Phase, the incidence of TEAEs was similar between the groups of subjects who received donepezil during both the double-blind and blinded extension phases of the studies (donepezil/donepezil) and those who received placebo during the double-blind phase and switched to donepezil in the blinded extension phase (placebo/donepezil) (61.8% and 60.0%, respectively). As expected, most TEAEs that occurred at relatively higher incidence rates were cholinergic-related and were consistent with the known clinical profile of donepezil.

There were few discontinuations due to TEAEs in pooled studies E2020-G000-333 and E2020-G000-334. During the Double-Blind Phase of pooled studies E2020-G000-333 and E2020-G000-334, four donepezil subjects experienced 5 severe TEAEs (1 event each of headache, muscle spasms, nightmare, somnolence, and syncope) versus 1 placebo subject (1 event of nightmare).

During the blinded extension phase, 1 donepezil/donepezil subject experienced a severe TEAE (aggression) compared to no subjects in the placebo/donepezil group. Therefore, the severity of TEAEs did not appear to be correlated to the donepezil treatment. Across both studies, there were two SAEs. An SAE of neutropenia was reported for one subject and was considered possibly related to study medication. An SAE of high-grade central nervous system sarcoma with rhabdomyoblastic differentiation was considered not related to study medication.

Among subjects in the pooled studies E2020-G000-333 and E2020-G000-334, and among subjects in study E2020-G000-333 alone, there were no clinically important differences between treatment groups in the incidence of abnormalities for any laboratory parameter or vital sign.

A total of 15 subjects discontinued from the pooled studies due to TEAE. Five subjects (12.5%) in the donepezil group and 4 subjects (12.9%) in the placebo group discontinued from the study due to TEAE during the Double-Blind Phase. During the Blinded Extension Phase, 2 subjects (5.9%) in the donepezil/donepezil group and 4 subjects (16.0%) in the placebo/donepezil group discontinued from the study due to TEAE.

Assessor's comments:

At the dosage studied, donepezil appeared to be well tolerated. As expected, most of the adverse events that occurred at relatively higher incidence rates were cholinergic-related and were consistent with the known clinical profile of donepezil. There are limited long term safety data provided; no data beyond 24 weeks are available.

No changes in the SmPC are required.

V. RAPPORTEUR'S OVERALL CONCLUSIONS

The results of the Phase III trials in a small sample of paediatric and adolescent cancer survivors did not provide evidence that donepezil is superior to placebo for attention deficits. In addition, there was no evidence that donepezil was efficacious in the treatment of Down's syndrome.

In the five submitted studies, donepezil, the safety profile was surprisingly good; the drug was also generally well-tolerated. However, only limited long term safety data were provided.

Currently, there is no evidence that donepezil is prescribed for use in children or adolescents for the treatment of cognitive impairment, attention deficit hyperactivity disorder (ADHD), Down's syndrome or any other medical condition in the EU.

From the data provided, there is no change in the benefit/risk of donepezil with respect to the treatment of the paediatric population.

VI. DAY 85 MS COMMENTS

Comments were only received from Sweden, who endorsed the Rapporteur's recommendations.

VII. RAPPORTEUR'S RECOMMENDATIONS

The Rapporteur therefore recommends no changes in the product information are required. In addition, no further regulatory action is required.