SHIRE PHARMACEUTICALS LIMITED

TA111: DRUGS FOR THE TREATMENT OF ALZHEIMER'S DISEASE REVIEW OF GALANTAMINE DATA

MARCH 2010

EXECUTIVE SUMMARY

1 The efficacy of galantamine is confirmed from RCTs in mild and moderate AD, with ('mixed dementia') or without concomitant cerebrovascular disease. Efficacy is demonstrated across various domains (cognition, function, behaviour, global measures and caregiver burden).

2 RCT evidence confirms that galantamine is effective for 6 and 12 months of treatment; open label studies indicate that this efficacy is extended for several years in a minority of patients.

3 Galantamine has a beneficial effect on cognition for patients with severe AD.

4 Shire does not utilise a new Health Economic model for this review but identifies data that were not implemented in the previous review. Results from interrogation of the AHEAD (Shire) and SHTAC (NICE) models are revisited and issues are raised which, if addressed in the current review and applied to a reliable model, it is believed would show that galantamine treatment is cost effective for patients with mild and moderate Alzheimer's Disease:

- Galantamine treatment is clinically effective for 12 months, or much longer for a minority of patients
- Galantamine treatment delays admission to Nursing Homes
- Mortality was over-estimated in the SHTAC model
- Cost data for patient care should be current and appropriate for the UK situation
- 'No change' on global efficacy score should be recognised as a treatment success in this progressive deteriorating disease after 6 months or longer
- Caregiver time and costs should be considered in any overall cost-effectiveness analysis
- Responder analyses are worth exploration

5 Shire strongly supports issue of further guidance at the earliest opportunity for the benefit of patients and caregivers, undertaken by an overall fresh team, utilising a new and reliable HE model and considering all available evidence.

1 INTRODUCTION

Shire welcomes the opportunity to participate further in the appraisal of drugs (in particular galantamine) for the treatment of Alzheimer's disease (AD).

Galantamine has been licensed in the UK for the treatment of mild to moderate AD for more than nine years and was investigated in randomised clinical trials (RCTs) involving more than 4300 AD patients for a similar number of years prior to gaining marketing authorisation **[1-5]**. The drug has therefore reached a stage of maturity at which few new data are emerging.

In this review of TA111, Shire will rely mainly on data submitted in June 2004 to the first review of TA111 **[6]**, together with further data submitted during the protracted appraisal process **[7-16]** which was concluded, following appeals to the Court, in the Guidance of August 2009 **[17]**.

In the 2009 Guidance, NICE again recognised that galantamine is clinically effective for the treatment of both mild and moderate AD, consistent with its licensed indications. This conclusion was reached from RCT data **[1-5, 18]**, across various clinical end-points for this population of patients, including those with concomitant cerebrovascular disease ('mixed' dementia) **[19]**.

In this review Shire will refer largely in Section 2 to the established RCT data mentioned above. Results from open label clinical studies will be discussed with reference to long term efficacy of galantamine treatment **[20-25]** and its propensity to delay patient admission to nursing homes **[26]**.

In the 2009 Guidance **[17]**, NICE estimated that galantamine was not cost effective for the treatment of patients with mild AD. However, Shire estimated using their AHEAD health economic (HE) model **[6]** that galantamine was cost effective for treatment of both mild and moderate AD patients. Interrogation of NICE's SHTAC model by Shire confirmed this conclusion **[15, 16]**.

Shire will not utilise a new HE model for this review but will emphasise data in Section 3 that were not implemented in the previous review. Flaws in the SHTAC model were acknowledged **[27]** in the Final Appraisal Determination (FAD) and Shire requests in this review that any new model used by NICE be challenged with inputs and assumptions previously suggested by Shire.

Shire will not present confidential data in this submission.

Shire strongly supports issue of further guidance at the earliest opportunity for the benefit of patients and caregivers, undertaken by an overall fresh team, utilising a new and reliable HE model and considering all available evidence.

2 CLINICAL EFFECTIVENESS

2.1 Randomised placebo controlled studies

NICE has recognised in its previous two TA111 Guidances that the acetylcholinesterase inhibitors (AChEIs) are clinically effective in the treatment of mild and moderate AD, according to their licensed indications, as shown in a long series of randomised, placebo controlled clinical trials. The submission to NICE in June 2004 by Shire and Johnson and Johnson **[6]** described the published

galantamine studies in AD, at which time the Phase 3 clinical programme was largely complete. Further published studies, including those for patients with 'mixed' dementia **[19, 23]**, have been described in the various galantamine submissions to NICE leading to the August 2009 Guidance **[7-16]**. One study reports data from treatment with the once daily galantamine formulation, introduced post-2004, showing the once and twice formulations to be equivalent in efficacy **[18]**. There are 7 randomised placebo-controlled studies reported in total **[1-5, 18, 19]**.

Shire emphasises that data from early galantamine studies **[1, 4]** which employed dosing regimens outside the product label should be used with caution. The clinical development of galantamine evolved from high doses (32mg) and fast (weekly) titration, to lower dosing (16 & 24mg) with a slower (4-weekly) titration schedule to improve the risk/benefit of treatment. By including data for non-licensed doses and failing to adhere to product labelling, NICE presented inappropriately high AE and discontinuation rates in the 2009 Guidance. The Protocol for the current review **[28, section 4.7]** discounts analyses from off-label dosing.

Efficacy data from galantamine studies demonstrate efficacy obtained across various domains (cognition, function, behaviour, global measures and caregiver burden). These data demonstrated efficacy of galantamine across a broad range of symptoms and patient populations.

2.2 Results according to disease severity

Subsequent to the initial SHTAC analysis, NICE asked Shire and the other manufacturers to provide a breakdown of responses according to severity of disease. We had already performed these analyses (pages 9-22, Tables 1.1-1.4 and 2.1 of the June 2004 submission) **[6, see attached]** for the main efficacy parameters. Shire's detailed analyses demonstrated galantamine efficacy over several domains of disease activity and over the whole range of disease severity (mild, moderate, advanced moderate and overall mild to moderate patients).

2.3 Comparative studies

Regarding comparisons of benefits between interventions, NICE have given only cursory reference to results from the largest and longest comparative study of galantamine vs. donepezil **[29]**. Hence relevant evidence has not been considered. This is a 12-month, rater-blinded, randomized, parallel-group, multi-centre UK trial, involving 188 AD patients. The given reason for exclusion was that the patient population had a baseline MMSE outside the range 10-26 **[27, Section 4.1.5.1]**. However only two patients had an MMSE of 9 and information relating to the remaining 186 patients is therefore excluded by rigid adherence to the 'moderate' MMSE definition. The results from the excluded study show largely similar efficacy for the 2 drugs but with some evidence to support better long-term MMSE outcomes for patients treated with galantamine vs. donepezil. Safety and tolerability of the two drugs were similar.

This comparative study is particularly important in that it demonstrates success after 12 months of galantamine treatment in maintaining MMSE at baseline levels **(*i.e.* treatment success at 12 months)**.

Furthermore, the short-term comparative study **[30]**, which was included in the donepezil analysis, suffered from the same shortcoming in that it entered patients with a baseline MMSE range of 8-25 (see Table 1, page 61 of the publication). The

patient population is not entirely mild-to-moderate as stated in the publication summary. In addition, patients in the galantamine arm were placed on a forced dose titration schedule (all patients were escalated from 16 to 24mg daily), contrary to the product label; and galantamine patients had only been on an effective dose for 2 months at the end of the study, compared with 3 months for donepezil.

2.4 Severe Alzheimer's disease

A 6-month randomised placebo controlled trial has been performed in patients with severe AD (MMSE 5-12) **[31]**:*'The data showed that galantamine can be started and used safely in elderly patients with severe AD. Galantamine improved cognitive function but failed to significantly improve the co-primary parameter of overall activities of daily living.'*

2.5 Open label studies

When products have been marketed for several years, TAs have the opportunity to assess long-term data and utilise economic models. Although long-term data require cautious interpretation, they provide both complementary and comparative data for economic models, which by necessity make long-term predictions based on short-term clinical data.

Long-term clinical trials are difficult to conduct and future long-term placebo-controlled trials are unlikely to occur. Long-term placebo treatment is not considered ethical, given the availability of licensed treatments for AD. Further there are difficulties of maintaining interest and participation by frail elderly people and their caregivers, who are often frail and elderly themselves.

Shire regards several open label studies as providing useful data for this current review **[20-26]**. Comparison of observed decline in cognition for galantamine treated patients compared with predicted decline without treatment for periods of 3 years and beyond **[20-22]** leads to a conclusion that galantamine treatment is efficacious over long periods for a substantial minority of patients (see also section 3 below: 'Issues to be addressed').

One open study, involving 548 AD patients with or without cerebrovascular disease, demonstrated a significant association between galantamine treatment and delay to nursing home placement **[26]**.

3 COST EFFECTIVENESS

Shire appreciates that a new health economic model will be utilised in this TA review but nevertheless draws attention below to perceived shortcomings in the previous model and suggests issues that remain to be addressed.

3.1 SHTAC Model

Following a long process which commenced in June 2004 with submissions by stakeholders, NICE was instructed by the Court of Appeal to release the Fully Executable Version (FEV) of the SHTAC HE model **[32]**. Consultees, including Shire, interrogated the model for the first time and tested various assumptions and inputs as permitted by the Court. Shire reported in their submission of 15 January 2009 **[15]**

results of this analysis (in particular a cumulative analysis), using valid amended inputs and assumptions. ICERs well below £30,000 were estimated for mild patients.

Shire's findings reinforced the importance of testing the reliability and robustness of the model by reference to alternative assumptions from those applied by NICE. **For the avoidance of doubt, the Court of Appeal judgement clearly permitted consultees to re-run the FEV on this basis.**

The Decision Support Unit (DSU) reviewed the model **[33]** but was denied by NICE the capability of checking Shire's analyses, which we contend would have shown galantamine to be cost effective for mild AD patients.

Subsequently, the appraisal committee acknowledged flaws in the model at various paragraphs in the FAD [**28, sections 4.3.17, 4.3.19, 4.3.20, 4.3.22, 4.3.23, 4.3.24, 4.3.25, 4.3.27, 4.3.28, 4.3.29, 4.3.37]**. Errors in the model had been identified in the DSU report (*qv* section 4.2.8 of the FAD) and by consultees. Shire's request for further analyses was dismissed in paragraphs 4.3.30 and 4.3.37 of the FAD.

3.2 Issues to be addressed

We list below issues arising from the SHTAC analysis **[7-16]** that we believe should be addressed in the construction and interrogation of the new AD model.

1. Interrogation of the FEV showed that the SHTAC model was not structured to calculate continued improvement beyond 6 months. The model assumes that patients receive no additional treatment benefit beyond 6 months - but long-term data suggest that treatment effect (active *vs.* no treatment) is maintained for longer periods, supported by a 12 month comparative study **[29]** and by open label studies conducted over 3 years or longer and employing reasonable projected data for untreated patients [**20-26]**.

   Consequently the SHTAC model underestimates long-term cost-effectiveness for mild patients. The use of only 6 month RCT evidence of treatment effect in the model to project long-term ICER values makes the drugs appear less cost effective. The HE analysis should consider evidence from relevant sources, including long term observational studies which provide several years follow up data **[20-26]** as well as the 6 and 12 month RCT evidence **[1-5,18,19,29]**.

   An international retrospective study in the UK and 6 other countries of 548 galantamine-treated AD patients (22% of whom had concomitant cerebrovascular disease) including retrieved drop-outs, investigated the effects of long-term treatment on delay to permanent residential or nursing home placement **[26]**. Sensitivity analyses were conducted to examine the robustness of results to differing assumptions and analytical methods. A statistically significant reduction ($p<0.05$) in permanent admissions was shown for patients treated long-term with galantamine. The reduction in relative risk of Nursing Home admissions was 31% for each additional year of galantamine treatment.

   This result has a bearing on a patient's ability to remain independent, which was specified in the protocol **[28, Section 4.6]** for this review as an outcome to be addressed.

We acknowledge that the above long-term data constitute lower tier evidence *vs.* well-designed placebo-controlled RCTs that maintain long-term patient participation and treatment adherence. However, the studies can provide complementary and comparative data *vs.* current model predictions and we ask that the Committee consider them as relevant evidence.

2. Untreated decline for mild AD patients in practice settings is likely to be much greater than that observed in clinical trials since the patients will not only be denied medication but also specialist treatment.

3. Mortality was over-estimated in the SHTAC model, reducing treatment effect, thus making the drugs look less cost effective. The evidence does not support the estimates used. Baseline severity is a well known predictor of time to death in AD.

4. Cost data employed in the model were inaccurate and out of date - and relevant data were omitted. Data were employed from an old study and not updated for inflation and location. The cost estimates for both pre-full-time care and full-time care states did not reflect current best estimates, thus making the drugs look less cost effective. Late stage AD is associated with increased physical dependency and increased neuropsychiatric symptoms but estimates chosen by the NICE Secretariat did not take these issues into account. NHS/PSS costs should be indexed to 2010 levels if earlier cost data are employed.

5. The exclusion of institutional costs for patients who pay out of pocket is perverse, inequitable and contrary to NICE's own guidance to manufacturers. This misrepresents the cost-effectiveness of treatment.

6. Limiting the definition of treatment success to 'improvement' on the global CIBIC score is too restrictive, as it does not reflect the goals of clinical management in AD patients and makes AChEIs look less cost effective. 'No change' in CIBIC score is a treatment success after 6 months or more, in this progressive deteriorating disease.

7. Shire believes that due account of caregiver time and costs **[34, 35]** should be given in any overall cost-effectiveness analysis.

8. NICE did not accept Shire's suggestion of performing responder analyses, with stopping rules **[10]**. We believe that this concept is worth exploring.

3.3 Issues arising from DSU review

Shire contends that the new model should be challenged with inputs of all rational parameters, so that optimum ICERs can be derived. Within the terms of their remit from NICE the DSU did not address Shire Issues 6, 7, 10 and 11 in their review [**15, attached]**. In particular, the cumulative analysis (Issue 11) combined all Shire's suggested amendments and derived an ICER for mild patients of £12,000 -15,000, well below the recognised £30,000 cut-off.

The overall effect of addressing the above Shire concerns (*qv* points in 3.2 and 3.3 above) regarding the model would have been to lower the ICERs and tend towards cost-effectiveness for mild patients.

If NICE does not properly take Shire's Issues into account in the current review of the Guidance, this will be considered by Shire as unfair and irrational conduct.

4 CONCLUSIONS

The efficacy of galantamine is confirmed from RCTs in mild and moderate AD, with (‘mixed dementia’) or without concomitant cerebrovascular disease. Efficacy is demonstrated across various domains (cognition, function, behaviour, global measures and caregiver burden).

RCT evidence confirms that galantamine is effective for 6 and 12 months of treatment; and open label studies indicate that this efficacy is extended for several years in a minority of patients.

Galantamine has a beneficial effect on cognition for patients with severe AD.

The DSU review was denied the capability (permitted by the Court of Appeal) of checking Shire’s analyses, performed for the first time on the FEV of the Model. Shire believes that, had a series of listed issues been addressed via interrogation of the previous SHTAC model with valid inputs, galantamine would have been shown to be a cost effective treatment for mild, as well as, moderate AD patients. If NICE were to address these issues for the new model in this current review, there is no reason to believe that cost effectiveness will not be demonstrated for mild and moderate AD.

Galantamine treatment delays patient admission to Nursing Homes.

The Consultees and the DSU report have identified a large number of deficiencies in the SHTAC HE Model which therefore did not reach the required standard of a key component in the important cost-effectiveness analysis affecting the treatment and quality of life of many patients with mild AD, together with their caregivers. The Model had not been adequately checked for defects before use.

If NICE does not properly take Shire's Issues 6, 7, 10 and 11 of their January 2009 submission **[15]** into account in the current review of the Guidance, this will be regarded by Shire as unfair and irrational conduct.

5 REFERENCES

1. Wilkinson D, Murray J. Galantamine: a randomized, double-blind, dose comparison in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* 2001;16:852-7.

2. Tariot PN, Solomon PR, Morris JC, Kershaw P, Lilienfeld S, Ding C. A 5 month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. *Neurology* 2000;54:2269-76.

3. Wilcock GK, Lilienfeld S, Gaens E. Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. Galantamine International-1 Study Group. *BMJ* 2000;321:1445-9.

4. Rockwood K, Mintzer J, Truyen L, Wessel T, Wilkinson D. Effects of a flexible galantamine dose in Alzheimer's disease: a randomized, controlled trial. *J Neurol Neurosurg Psychiatry* 2001;71:589-95.

5. Raskind MA, Peskind ER, Wessel T, Yuan W. Galantamine in AD: a 6-month randomized, placebo-controlled trial with a 6-month extension. The Galantamine USA-1 Study Group. *Neurology* 2000;54:2261-8.

6. HTA111: Drugs for the treatment of Alzheimer's Disease. Submission to the National Institute of Clinical Excellence. *Shire Pharmaceuticals and Johnson & Johnson.* 03 June 2004.

7. HTA111: Drugs for the treatment of Alzheimer's Disease. Comments on SHTAC Report to the National Institute of Clinical Excellence. *Shire Pharmaceuticals and Johnson & Johnson.* 06 October 2004.

8. HTA111: Drugs for the treatment of Alzheimer's Disease. Comments on Technical Report to the National Institute of Clinical Excellence. *Shire Pharmaceuticals and Johnson & Johnson. (Extra Work on Appraisal of Drugs for Alzheimer's Disease, by Southampton HTA Centre).* 21 January 2005.

9. HTA111: Drugs for the treatment of Alzheimer's Disease. Comments on Appraisal Consultation Document to the National Institute of Clinical Excellence. *Shire Pharmaceuticals and Johnson & Johnson.* 22 March 2005.

10. HTA111: Drugs for the treatment of Alzheimer's Disease. Response to the Request from the National Institute of Health and Clinical Excellence for Additional Analyses (July 2005). *Shire Pharmaceuticals and Johnson & Johnson*. 21 October 2005.

11. HTA111: Drugs for the treatment of Alzheimer's Disease. Comments on MRC Statistical Analysis and NICE Technical Report 2; Drugs for the Treatment of Alzheimer's Disease (review). *Shire Pharmaceuticals and Johnson & Johnson.* 09 December 2005.

12. HTA111: Drugs for the treatment of Alzheimer's Disease. Comments on Addenda to MRC Statistical Analysis and NICE Technical Report 2; Drugs for the Treatment of Alzheimer's Disease (review). *Shire Pharmaceuticals and Johnson & Johnson*. 16 December 2005.

13. HTA111: Drugs for the treatment of Alzheimer's Disease. Comments on Further Appraisal Consultation Document to the National Institute of Health and Clinical Excellence. *Shire Pharmaceuticals and Johnson & Johnson.* 13 February 2006.

14. Shire Pharmaceuticals Limited: Grounds of Appeal against the Final Appraisal Determination for Donepezil, Galantamine, Rivastigmine (review) and Memantine for the Treatment of Alzheimer's Disease. 15 June 2006

15. TA111. Shire Pharmaceuticals Limited. Drugs for the treatment of Alzheimer's Disease. Comments to the National Institute for Health and Clinical Excellence on the reliability of the fully executable version of the economic model created for assessing the cost-effectiveness of AChEIs. 15 January 2009

16. TA111. ShirePharmaceuticals Limited. Comments on the Decision Support Unit Review (March 2009) of the Fully Executable Version of the Health Economic Model employed by NICE for Cost-effectiveness Analyses of Alzheimer's Drugs. 08 April 2009

17. NICE technology appraisal guidance 111 (amended September 2007, August 2009) Donepezil, galantamine, rivastigmine (review) and memantine for the treatment of Alzheimer's disease (amended)

18. Brodaty H, Corey-Bloom J, Potocnik FC, Truyen L, Gold M, Damaraju CR. Galantamine prolonged-release formulation in the treatment of mild to moderate Alzheimer's disease. *Dement.Geriatr.Cogn Disord.* 2005;20:120-32.

19. Erkinjuntti T, Kurz A, Gauthier S, Bullock R, Lilienfeld S, Damaraju CV. Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. *Lancet* 2002;359:1283-90.

20. Raskind MA, Peskind ER, Truyen L, Kershaw P, Damaraju CV. The cognitive benefits of galantamine are sustained for at least 36 months: a long-term extension trial. *Arch Neurol* 2004;61:252-6.

21. Rockwood K. Dai D. Mitnitski A. Patterns of decline and evidence of subgroups in patients with Alzheimer's disease taking galantamine for up to 48 months. *International Journal of Geriatric Psychiatry* 2008;23:207-214).

22. Truyen L, Lilienfeld S, Kershaw P. Safety and efficacy of galantamine in Alzheimer's Disease after treatment for 4 years. Poster presented at the 18th Annual Conference of Alzheimer's Disease International, Barcelona, Spain, 2002.

23. Erkinjuntti T, Kurz A, Small GW, Bullock R, Lilienfeld S, Damaraju CV. An open-label extension trial of galantamine in patients with probable vascular dementia and mixed dementia. *Clin Ther* 2003;25:1765-82.

24. Bullock R, Erkinjuntti T, Lilienfeld S. Management of patients with Alzheimer's disease plus cerebrovascular disease: 12-month treatment with galantamine. *Dement Geriatr Cogn Disord* 2004;17:29-34.

25. Lyketsos C.G. Reichman W.E. Kershaw P. Zhu Y. Long-term outcomes of galantamine treatment in patients with Alzheimer disease. *American Journal of Geriatric Psychiatry* 2004;12 473-482).

26. Feldman HH, Pirttila T, Dartigues JF, Everitt B, Van Baelen B, Schwalen S, Kavanagh S. Treatment with galantamine and time to nursing home placement in Alzheimer's disease patients with and without cerebrovascular disease. *Int J Geriatr Psychiatry* 2009; 24: 479-488.

27. TA111: National Institute for Health and Clinical Excellence. Final Appraisal Determination. Donepezil, galantamine, rivastigmine (review) and memantine for the treatment of Alzheimer's disease (amended). 11 June 2009

28. Technology Assessment Report commissioned by the NETSCC HTA Programme on behalf of the National Institute for Health and Clinical Excellence. HTA 09/87/01: Final Protocol. November 2009

29. Wilcock G, Howe I, Coles H et al. A long-term comparison of galantamine and donepezil in the treatment of Alzheimer's disease. *Drugs Aging* 2003;20:777-89.

30. Jones RW, Soininen H, Hager K et al. A multinational, randomised, 12-week study comparing the effects of donepezil and galantamine in patients with mild to moderate Alzheimer's disease. *Int J Geriatr Psychiatry* 2004;19:58-67.

31. Burns A. Bernabei R. Bullock R. Jentoft A.J.C. Frolich L. Hock C. Raivio M. Triau E. Vandewoude M. Wimo A. Came E. Van Baelen B. Hammond G.L. van Oene J.C. Schwalen S. Safety and efficacy of galantamine (Reminyl) in severe Alzheimer's disease (the SERAD study): a randomised, placebo-controlled, double-blind trial. *Lancet Neurology* 2009;8: 39-47.

32. SHTAC (Southampton Health Technology Assessment Centre) health economic model, utilised to prepare the TA111 Guidance, June 2009

33. DSU (Decision Support Unit) review of Fully Executable Version of NICE health economic (SHTAC) model March 2009.

34. Sano M, Wilcock GK, Van Baelen B. The effects of galantamine treatment on caregiver time in Alzheimer's disease. *Int J Geriatr Psychiatry* 2003;18:942-50.

35. Cummings JL, Schneider L, Tariot PN, Kershaw PR, Yuan W. Reduction of behavioral disturbances and caregiver distress by galantamine in patients with Alzheimer's disease. *Am J Psychiatry* 2004;161:532-8.