DONEPEZIL, RIVASTIGMINE, GALANTAMINE AND MEMANTINE FOR THE TREATMENT OF ALZHEIMER'S DISEASE:

A REVIEW OF COMMENTS SUBMITTED BY CONSULTEES ON THE RELIABILITY OF ECONOMIC MODEL

REPORT BY THE DECISION SUPPORT UNIT

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10 March 2009

EXECUTIVE SUMMARY

The current NICE guidance on the use of drugs for the treatment of Alzheimer's disease was published in September 2007. An economic model was developed by the assessment group, SHTAC, to inform the development of the guidance. This model was later amended by the NICE secretariat at the request of the Appraisal Committee. Following a judicial review, NICE was requested by the Court of Appeal to offer the release of the executable version of the model for consideration of its reliability. The models for donepezil (mild and moderate disease) and galantamine (moderate and mild disease) were released following requests by consultees.

The Decision Support Unit was asked by NICE to provide a view on whether the comments received on the executable models provide a justifiable challenge to the reliability of the models used for the formulation of the guidance. 'Reliability' is viewed as the executable model being consistent with the description of it provided to the Appraisal Committee. It does not include commenting on those inputs or assumptions documented in the appraisal papers and accepted by the Appraisal Committee.

Following a review of the comments received during consultation, the DSU agreed that the following amendments were appropriate:

1. Correction to the implementation of the hazard for the transition to full time care.
2. Correction to separate out the characterisations of uncertainty and variability in the model so that the model only samples parameter values and not patient characteristics. Patient characteristics have been set at their mean values and results presented as subgroups by age.
3. Correction to the implementation of discounting.
4. Correction to implementation of the 'augmented benefit'.

In addition, sensitivity analyses were conducted to explore the sensitivity of the model to the following amendments.

1. Inclusion of carer benefits in the standard care arm of the model.

2. Amendment to the estimates of behavioural symptoms in the mild disease model.
3. Amendment to the utility values included in the model.

After implementing the four changes in the basecase analysis the ICERs for moderate disease (donepezil) change from £35,500 to between £28,600 and £41,000 depending on age. For mild disease (donepezil) the ICERs change from a mean of £63,750 to between £51,700 and £77,500 depending on age. For mild disease (galantamine) the ICERs change from a mean of £59,100 to between £48,600 and £71,400 depending on age. The sensitivity analysis including carer benefits in the control arm of the model makes very little difference to the results. The sensitivity analysis including an increased probability of behavioural symptoms and improved effectiveness of the drugs in treating those symptoms decreased the ICERs by approximately £5,000 to £10,000 (mild disease model only). The sensitivity analysis on the utility estimates slightly reduced the mean ICERs for mild disease by approximately £5,000 to £10,000 and increased the ICERs for moderate disease by approximately £5,000 to £7,000 .

The amendments to the model for mild disease as a result of the comments do not affect the ICERs so substantially that they fall within the £20,000 to £30,000 range usually considered cost-effectiveness by NICE. Given that the guidance for moderate disease was based on estimates of cost-effectiveness at the very top of the range usually considered cost-effective by NICE, the effect of small changes in the ICER is less clear.

CONTENTS

ABBREVIATIONS AND DEFINITIONS

AC	Appraisal Committee
AChEI	Acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale-cognitive subscale
Consultee	Organisations that accept an invitation to participate in the appraisal.
DSU	Decision Support Unit
FAD	Final Appraisal Determination
FTC	Full time care
ICER	Incremental cost effectiveness ratio
MMSE	Mini mental state examination
NICE	National Institute for Health and Clinical Excellence
PSA	Probabilistic sensitivity analysis
QALY	Quality Adjusted Life Year
ScHARR	School of Health and Related Research
SE	Standard error
SHTAC	Southampton Health Technology Assessments Centre

1. INTRODUCTION

1.1. BACKGROUND

A NICE technology appraisal of drugs for the treatment of Alzheimer's disease (AD) was published in 2005. An economic model was developed by the assessment group SHTAC. During the course of the appraisal the SHTAC model was amended by NICE to reflect considerations considered appropriate by the Appraisal Committee (AC). The amended economic model is referred to as the 'augmented basecase model'.

The guidance was reissued in September 2007 following a judicial review.[1] The reissued guidance included a clarification of the steps healthcare professionals should take when assessing whether Alzheimer's disease is of moderate severity and highlights that clinicians should be mindful of the need to secure equality of access to treatment. In addition, at a subsequent hearing the Court of Appeal requested the release of the executable economic model for the AChEIs for consideration of its reliability. Four versions of the economic model were released following requests by consultees. Two models related to analyses of donepezil for the treatment of mild Alzheimer's disease and for the treatment of moderate Alzheimer's disease and two models related to the analysis of galantamine for the treatment of mild Alzheimer's disease and of moderate disease. Comments from five consultee organisations were received by NICE: Alzheimer's Society, British Geriatrics Society, EisaiLtd, Lundbeck Ltd and the Research Institute for the Care of Older People (RICE). The comments relating to the model for galantamine focussed upon the analysis of mild disease. Therefore the model relating to galantamine for the treatment of moderate disease is not considered further in this report.

This review

The Decision Support Unit was requested by NICE to provide a view on whether the comments received on the executable model provide a justifiable challenge to the reliability of the models used for the formulation of the guidance. In this context, 'reliability' is viewed as the executable model being consistent with the description of it provided to the Appraisal Committee. The role of the DSU was not to provide an

opinion on those inputs or assumptions used in the model of which the Committee were aware and accepted. In addition, the DSU's consideration of comments provided by consultees is limited to those which relate to the analyses used for the formulation of the guidance and does not include consideration of comments relating to analyses based on other sets of inputs or assumptions which were disregarded by the Committee during the appraisal process.

2. METHODS

All of the comments submitted by the five consultee organisations have been considered as to whether they meet the criteria for consideration by the DSU as outlined in the project specification. That is, relating to the reliability of the model (the executable model being consistent with the description of it provided to the Appraisal Committee) AND relating to the analyses used for the formulation of the guidance.

Those comments considered to potentially meet the criteria have been assessed and a response provided below. Comments not meeting both of these criteria are considered outside of the scope for this report as they do not relate to the reliability of the model used to formulate the guidance and are not considered further in this document.

An assessment of those comments considered to potentially fulfil the criteria following the initial screen of comments has been made. A summary of the relevant comments and a DSU response is provided below. The organisation(s) raising the issue and the number of the issue (where provided) are included in parenthesis for ease of reference. Where corrections to the model were considered appropriate, amendments have been made to the models to demonstrate the impact.

The ICER as a result of each individual amendment is reported in the text below in order to demonstrate the impact on the results. The cumulative impact of all the amendments for all three models is reported in Section 4.2 (see Tables 4 to 6).

3. RESULTS FROM THE ECONOMIC MODELS AS REPORTED IN THE FINAL APPRAISAL CONSULTATION DOCUMENT AND ISSUED TO CONSULTEES

The results from the three models as issued to consultees are reported below.

Table 1: Results as sent to consultees: donepezil (moderate disease)

	Mean Cost	Mean QALYs
Non-Drug Treatment	£20,302	1.72
Donepezil	£22,234	1.78
Difference	£1,931	0.061
ICER	£31,550	per QALY

Table 2: Results as sent to consultees: donepezil (mild disease)

	Mean Cost	Mean QALYs
Non-Drug Treatment	£13,912	2.23
Donepezil	£17,825	2.29
Difference	£3,913	0.061
ICER	£63,749	per QALY

Table 3: Results as sent to consultees: galantamine (mild disease)

	Mean Cost	Mean QALYs
Non-Drug Treatment	£14,084.07	2.21
Galantamine	£17,741.88	2.28
Difference	£3,657.80	0.062
ICER	£59,108	per QALY

It should be noted that one of the consultees (Eisai) made amendments to the basecase of the model prior to implementing the changes reported in their comments. The amendments made by DSU have been made directly to the version issued to consultees, which is compatible with the figures reported in the FAD (although there is a small difference for the results for the donezepil mild disease model – see section A.9). Therefore changes made to the model reported here will not produce the same results as those submitted by Eisai.

4. SUMMARY OF AMENDMENTS TO THE AUGMETED BASECASE MODELS

The DSU has made the following amendments to the augmented basecase models following the review of the comments and proposed corrections sent by consultees in response to the release of the executable model.

1. Correction to the implementation of the hazard for the transition to full time care
2. Correction to separate out the characterisations of uncertainty and heterogeneity in the model so that the model only samples parameter values and not patient characteristics. Patient characteristics have been set at their mean values and results presented as subgroups by age.
3. Correction to the implementation of discounting
4. Correction to implementation of 'augmented benefit'

4.1. AMENDMENTS MADE TO THE AUGMENTED BASECASE

4.1.1. Hazard for transition to full time care (FTC)

Comment: Eisai (issue 2)

Summary: The model calculates the hazard of transitioning to FTC but then applies the hazards as if it was a probability.

DSU response: The point made is correct and this also applies to the mortality hazard, although the latter only has an impact on the model outputs when the relevant option is selected. The model treats an instantaneous hazard rate as a probability (see Briggs, Sculpher and Claxton p.51).[2] We agree that the change has negligible impact on the ICERs. Correcting the model yields an ICER of £63,164 for the donepezil mild patient subgroup, £31,556 for the donepezil moderate subgroup and £59,400 for the galantamine mild subgroup.

4.1.2. Conflation of heterogeneity with uncertainty

Comment: Eisai (not numbered), Alzheimer's Society (Issue 1), Shire (Issue 6)

Summary: The model conflates variability with uncertainty. It is structured as a probabilistic sensitivity analysis (PSA). A PSA should include only those variables for which values are intrinsically unknown for any patient so as to examine the true uncertainties in a health economic model. The model includes variables for which the true value is known at any time for an individual patient: age, sex and Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) score. These values should not be used in a PSA and should be subject to separate cohort analysis.

DSU response: The model uses PSA to represent uncertainty. It samples both from parameter values and also patient characteristics. The latter represent heterogeneity, not uncertainty. The DSU agrees that it is incorrect to sample in this manner and the approach to dealing with heterogeneity between patients that should be taken to dealing with this is by subgroup analysis. The DSU does not have the expertise to specify appropriate subgroups in this situation.

The following results are presented to highlight the potential impact of the modelling approach adopted by SHTAC:

- Setting all patient characteristics at their mean values, including those which relate to indicator variables in the regression e.g. sex.
- Subgroups by ADAS-cog score and age.

For ADAS-cog we use only the two mean values already used in the economic model that distinguish mild and moderate disease (12.5 for mild, 34 for moderate).

There are 2 ways in which age influences the results of the model. Firstly, because “young at onset” is a covariate into the FTC index regression, which in turn depends on age, the probability of transition to FTC is age dependent. The model distinguished between those diagnosed <65 versus >=65, which given the mean time from onset to diagnosis results in difference ICERS for those aged <66 versus >=66.

Secondly, the functions that are used to fit the hazard over time are different according to whether a patient is <=73 or >73. This is the case both for the FTC and

death hazards, although the latter is not used in the base case. Thus, ICERs will differ according to patients aged less than 65yrs, 65 to 73, and those greater than 73.

Note that in order to accurately calculate the ICERs for these patient subgroups, the changes made in point 0 above must be made.

Results:

- In the donepezil mild model, when the sampling of patient characteristics is removed (in addition to the corrections in 0) the ICERs are £84659, £73804, £55779 for the ages less than 65yrs, 65 to 73 yrs and over 73 yrs respectively
- In the donepezil moderate model, when the sampling of patients is removed (in addition to the corrections in 0) the ICERs are £37384, £43863 and £30999.
- In the galantamine mild model, when the sampling of patients is removed (in addition to the corrections in 4.1.1) the ICERs are £80755, £69856 and £51978.

4.1.3. Discounting and half cycle correction

Comment: Eisai (Issue 5)
Summary: Discounting is applied incorrectly and inconsistently in the model as it does not properly account for the first 6 months of treatment, nor make a half-cycle correction for the discounting period.

DSU response: The point regarding discounting is correct. The first 6 months of treatment has not been taken into account in the discounting of costs and benefits. The model appears to discount seemingly from the end of the first year, however because of the pre-treatment costs and benefits included in the model, this is actually the end of the first 18 months (one year plus 6 month pre-treatment). The proposal to discount midway through each year has been implemented. In addition, discounting was applied inconsistently for part of the QALY calculation as it discounted some QALYs from the end of the first year and other QALYs from the beginning of the first year. This has also been amended.

Results:

- In the donepezil mild disease model, correcting the discounting decreases the ICER from £63,749 to £60,607.
- In the donepezil moderate disease model, correcting the discounting decreases the ICER from £31,550 to £31,053.
- In the galantamine mild disease model, correcting the discounting decreases the ICER from £59,108 to £57,941.

We agree that there is no half cycle correction included in the model. However the documentation does not state that a half cycle correction was included and it is questionable whether such an amendment would be appropriate. Therefore, no change has been made.

4.1.4. Implementation of augmented benefits

Comment: Alzheimer's Society (issue 8)
Summary: The model gives the augmented benefit to patients in the treatment arm by multiplying the number of patients who remain out of FTC during the five-year span in the non-treatment arm (cell 'ADProgBase B66') by 0.01. It should apply to the difference between the treatment and control arm. This comment was raised as part of a related comment, which is discussed in section 4.2.1 below.

DSU response: The comment is correct in that the model gives benefit to patients in the treatment arm based on the number who remain out of FTC during the five-year span in the non-treatment arm. This applies not only to the additional benefit for carers (0.01) but to the whole of the augmented benefit (0.01+0.03=0.04). The model should refer to the number of patients who remain out of FTC in the treatment arm when calculating the additional benefit for people on treatment who have not entered full time care within 5 years. Whether the model should also be amended to also include the additional benefit in the no treatment group is discussed in 4.2.1 below.

Results:

- In the donepezil mild disease model, correcting the discounting decreases the ICER from £63,749 to £61,060.
- In the donepezil moderate disease model, correcting the discounting decreases the ICER from £31,550 to £30,287.
- In the galantamine mild disease model, correcting the discounting decreases the ICER from £59,108 to £56,866.

The results from each of the models as a result of making these four amendments cumulatively are shown in Tables 4 to 6.

4.2. CUMULATIVE RESULTS OF AMENDMENTS TO THE AUGMETED BASECASE MODELS

Table 4: Cumulative results for donepezil – mild disease

Change	Costs		QALYs		Cost diff	QALY diff	ICER
	No drugs	Donepezil	No drugs	Donepezil			
Augmented Basecase	£13,912	£17,825	2.23	2.29	£3,913	0.061	£63,749
1. Hazard for FTC	£13,695	£17,640	2.22	2.28	£3,945	0.062	£63,164
2. No sampling patient characteristics							
Age 64	£15,155	£18,811	2.146	2.190	£3,657	0.043	£84,659
Age 70	£12,795	£16,929	2.288	2.344	£4,134	0.056	£73,804
Age 74	£14,359	£18,168	2.187	2.255	£3,809	0.068	£55,779
3. Discounting							
Age 64	£14,574	£18,145	2.160	2.204	£3,571	0.043	£82,653
Age 70	£12,411	£16,436	2.256	2.312	£4,025	0.056	£71,903
Age 74	£13,938	£17,644	2.170	2.238	£3,706	0.068	£54,542
4. Augmented benefit							
Age 64	£14,497	£18,067	2.143	2.189	£3,569	0.046	£77,464
Age 70	£12,442	£16,461	2.261	2.321	£4,019	0.060	£67,408
Age 74	£13,767	£17,489	2.176	2.248	£3,722	0.072	£51,660

Table 5: Cumulative results for donepezil – moderate disease

Change	**Costs**		**QALYs**		**Cost diff**	**QALY diff**	**ICER**
	No drugs	Donepezil	No drugs	Donepezil			
Augmented Basecase	£20,302	£22,234	1.72	1.78	£1,931	0.061	£31,550
1. Hazard for FTC	£20,310	£22,239	1.726	1.787	£1,929	0.061	£31,556
2. No sampling patient characteristics							
Age 64	£21,539	£23,359	1.668	1.717	£1,820	0.049	£37,384
Age 70	£18,728	£21,047	1.775	1.828	£2,319	0.053	£43,863
Age 74	£21,230	£23,039	1.688	1.746	£1,809	0.058	£30,999
3. Discounting							
Age 64	£20,704	£22,524	1.659	1.707	£1,820	0.048	£37,629
Age 70	£17,876	£20,144	1.761	1.813	£2,268	0.052	£43,480
Age 74	£20,605	£22,327	1.678	1.737	£1,722	0.059	£29,163
4. Augmented benefit							
Age 64	£20,580	£22,369	1.668	1.718	£1,789	0.049	£36,334
Age 70	£18,277	£20,547	1.758	1.813	£2,270	0.055	£41,041
Age 74	£20,447	£22,193	1.677	1.738	£1,746	0.061	£28,561

Table 6: Cumulative results for galantamine – mild disease

Change	**Costs**		**QALYs**		**Cost diff**	**QALY diff**	**ICER**
	No drugs	Galantamine	No drugs	Galantamine			
Augmented Basecase	£14,084	£17,742	2.21	2.28	£3,658	0.062	£59,108
1. Hazard for FTC	£13,705	£17,386	2.224	2.285	£3,680	0.062	£59,500
2. No sampling patient characteristics							
Age 64	£14,781	£18,236	2.158	2.201	£3,455	0.043	£80,755
Age 70	£12,972	£16,843	2.258	2.314	£3,871	0.055	£69,856
Age 74	£14,217	£17,783	2.188	2.256	£3,566	0.069	£51,978
3. Discounting							
Age 64	£14,384	£17,732	2.147	2.190	£3,348	0.043	£78,708
Age 70	£12,724	£16,475	2.238	2.293	£3,752	0.055	£68,110
Age 74	£13,956	£17,416	2.180	2.248	£3,459	0.068	£50,970
4. Augmented benefit							
Age 64	£14,533	£17,852	2.152	2.198	£3,319	0.046	£71,404
Age 70	£12,418	£16,188	2.243	2.302	£3,770	0.059	£63,916
Age 74	£13,888	£17,358	2.180	2.252	£3,469	0.071	£48,574

4.3. EXPLORATORY ANALYSES ON THE AMENDMENTS TO THE AUGMENTED BASECASE

In addition exploratory analyses have been conducted in response to the comments received.

1. Inclusion of carer benefits in the standard care arm of the model.
2. Amendment to the estimates of behavioural symptoms in the mild disease model.
3. Amendment to the utility values included in the model.

Each of the individual (one-way) sensitivity analyses have been applied to the cumulative amendments described in Section 4.1. The results are reported in Tables 7 to 9.

4.3.1. Implementation of 'additional' and carer benefits

Comment: Alzheimer's Society (issue 8)
Summary: Patients that stay in the pre-FTC state for the five years of the model receive a utility benefit of 0.01 quality-adjusted life-years (QALYs) to reflect the benefit to carers. However, the SHTAC model gives benefit to patients in the treatment arm by multiplying the number of patients who remain out of FTC during the five-year span in the non-treatment arm. The benefit should be applied to the difference between the number of patients that avoid FTC in the non-treatment arm and the number of patients that avoid FTC in the treatment arm. It is proposed that the benefit be included as an increase in utility for the pre-FTC state and applied to both arms in the model.

DSU response: The NICE augmented basecase model includes amendments made at the request of the Appraisal Committee for extra QALY gains to be included in the results for some patients. Gains representing additional benefits to patients (increase in utility of 0.03) and additional benefits to carers (utility benefit of 0.01) have been combined and implemented in the model together as an additional 0.04 utility benefit for patients meeting specific criteria.

The criteria for the inclusion of the extra gains are described in Technical Report no.1 (see 3a and 3d in the request from the Appraisal Committee to the Secretariat - reproduced below) and the FAD sections 4.3.10.1 and 4.3.10.2.

Extract from the request from the Appraisal Committee to the Secretariat (Tech report No 1):

3a) Establish the impact of incorporating benefits to those who, during or at the end of the model, have not been able to benefit from the interventions. More specifically, those people who are on treatment and:

1. are still in the pre-FTC health state at the end of the model, or

2. transit from the pre-FTC health state to the death state at any time during the model.

d) Establish the impact of incorporating carer benefits;

1) Review the estimates of utilities associated with caring for people with Alzheimer's disease.

2) Establish the impact of using carer (dis)utilities associated with health states while accepting the Augmented Base Case.

The request states that the additional benefits for people who "have not been able to benefit from the interventions" should be applied only to those people who are on treatment. Whilst the rationale for applying this only to people in the treatment arm is not clear from the document, the model does indeed apply an additional benefit (of an increase in utility of 0.03 in pre-FTC) to those the patients in the treatment arm described within 3a (once the correction detailed in section 4.1.4 has been implemented).

The NICE-model also incorporates a utility benefit of 0.01 to represent the benefit to carers. The model includes the extra 0.01 utility in exactly the same way as the additional 0.03 utility described above. Consequently, the additional 0.01 benefit is allocated to people who are not in full-time care at the end of 5 years (including those who die within 5 years) and is included only in the treatment arm.

The inclusion of carer benefit only for people who are not in full-time care at the end of 5 years (including those who die within 5 years) is consistent with the Committee's

intentions as described in the FAD section 4.3.10.2. Therefore, it is considered inappropriate to make the proposed change by applying the increase in utility to the whole of the pre-FTC period for all patients.

Whether the Committee's intention was for this benefit to be applied only to the treatment arm, or whether it should also be applied to the no treatment arm, is not clear from the FAD. The technical reports do not clarify this point. Technical report no.1 describes applying a ***reduction*** of 0.01 in utility during the pre-FTC period based on a previously published study. However, the approach to including carer (dis)benefits differs in the description in Technical Report No.2 which refers to an ***increase*** in utility of 0.01 for carers (p15). The reasoning for this is not clear. In addition, it is not clear to which patients or health states this should be applied. Therefore, it has not been possible to establish precisely what the Committee intended to reflect by the addition of the carer benefit in the model ion terms of whether the benefit should be included in one or both arms of the model.

The effect of including an additional benefit for carers in the no treatment arm for people who do not enter full time care in 5 years (including those who die) is included as a sensitivity analysis.

4.3.2. Estimates of behavioural symptoms

Comment: Eisai (not numbered)

Summary: Contrary to the footnote on page 7 of Technical Report #2 which states that all analyses used a 30% estimate for the prevalence of behavioural symptoms and a 20% reduction in these symptoms with AChE inhibitors, the mild disease model as sent had the prevalence of behavioural symptoms set to 10% and the reduction in these symptoms with treatment set to 0% (in both probabilistic and deterministic settings).

DSU response: Comment is correct. These estimates are reported as values for a sensitivity analysis in the FAD (4.2.6.4 and 4.3.10.4). The results are reported in the

FAD only for patients with moderate disease. An additional sensitivity analysis has been conducted using these values for the mild disease model.

4.3.3. Model structure – utility data

Comment: Alzheimer's Society (Issue 7), Shire (related to issues 2 and 6), Eisai (not numbered), RICE (issue 3)

Summary: The utility value of 0.69 used in mild pre-FTC patients relates to an ADAS-cog score of 24. This value should be updated when considering the individual ADAS-cog starting scores for the separate models for moderate and mild disease.

DSU response: The utilities included in the model are consistent with those reported in Technical Report No 2. (See p15). These values have been derived from two equations external to the model and are dependent upon the ADAS-cog score. Therefore, we agree that given the way the model was structured, where patient characteristics including ADAS-cog score are sampled, it would have been better to also update the utility score for the pre FTC state.

This is also relevant where subgroup analyses are conducted defined in terms of ADAS-cog score, as is the case in the distinction between mild and moderate disease. We agree that the utility values corresponding to the ADAS-cog scores of 21, 12.5 and 4 determined by the two equations used are 0.72, 0.83 and 0.94 respectively. However, it should also be noted that the scores generated may be considered inappropriately high. For patients with a mean age of 75 yrs the generated value is in excess of that for the otherwise healthy population (75yrs and over =0.73 according to the MVH study reported in Kind et al 1998).[3] Indeed, the mean at age 45-54 is only 0.85. This change is therefore implemented as a sensitivity analysis.

It should also be noted that this change does not affect the number of health states in the model. For example, in the mild disease models, patients continue with the utility for pre-FTC (sensitivity analysis value for mild disease = 0.833) until they reach FTC. That is, the value for mild disease is assumed to apply for the whole of the pre-FTC period in the mild disease model. If an additional health state (e.g. moderate disease)

were included to reflect that patients' utility decreases before reaching full time care, the ICERs would decrease by a smaller amount (assuming the pattern of progression is not different between the two arms)

4.4. RESULTS OF ONE-WAY SENSITIVTY ANALYSIS

Table 7: One-way sensitivity analysis for donepezil – mild disease

Change	**Costs**		**QALYs**		**Cost diff**	**QALY diff**	**ICER**
	No drugs	Donepezil	No drugs	Donepezil			
Original Augmented Basecase	£13,912	£17,825	2.23	2.29	£3,913	0.061	£63,749
DSU amended basecase							
Age 64	£14,497	£18,067	2.143	2.189	£3,569	0.046	£77,464
Age 70	£12,442	£16,461	2.261	2.321	£4,019	0.060	£67,408
Age 74	£13,767	£17,489	2.176	2.248	£3,722	0.072	£51,660
Sensitivity analysis 1 (carer benefits):							
Age 64	£14,569	£18,148	2.168	2.215	£3,579	0.047	£75,796
Age 70	£12,818	£16,835	2.273	2.333	£4,017	0.060	£67,142
Age 74	£13,968	£17,679	2.215	2.287	£3,710	0.073	£50,922
Sensitivity analysis 2 (behavioural symptoms): Age 64	£14,938	£18,341	2.142	2.193	£3,403	0.051	£66,445
Age 70	£12,699	£16,583	2.222	2.285	£3,883	0.063	£61,479
Age 74	£14,059	£17,606	2.176	2.253	£3,547	0.077	£45,973
Sensitivity analysis 3 (utility data):							
Age 64	£14,675	£18,249	2.517	2.573	£3,574	0.056	£63,855

Age 70	£12,477	£16,488	2.669	2.736	£4,010	0.068	£59,403
Age 74	£14,162	£17,854	2.572	2.654	£3,692	0.082	£44,830

Table 8: One-way sensitivity analysis for donepezil – moderate disease

Change	Costs		QALYs		Cost diff	QALY diff	ICER
	No drugs	Donepezil	No drugs	Donepezil			
Original Basecase	£20,302	£22,234	1.72	1.78	£1,931	0.061	£31,550
DSU amended basecase							
Age 64	£20,580	£22,369	1.668	1.718	£1,789	0.049	£36,334
Age 70	£18,277	£20,547	1.758	1.813	£2,270	0.055	£41,041
Age 74	£20,447	£22,193	1.677	1.738	£1,746	0.061	£28,561
Sensitivity analysis 1 (carer benefits):							
Age 64	£21,095	£22,891	1.684	1.734	£1,796	0.050	£35,959
Age 70	£18,067	£20,329	1.761	1.816	£2,262	0.055	£40,795
Age 74	£20,006	£21,811	1.685	1.746	£1,805	0.061	£29,626
Sensitivity analysis 3 (utility data):							
Age 64	£20,403	£22,205	1.592	1.634	£1,802	0.042	£43,102
Age 70	£18,394	£20,628	1.675	1.722	£2,234	0.048	£47,037
Age 74	£20,063	£21,870	1.606	1.659	£1,807	0.053	£33,838

Table 9: One-way sensitivity analysis for galantamine – mild disease

Change	Costs		QALYs		Cost diff	QALY diff	ICER
	No drugs	galantamine	No drugs	galantamine			
Original Basecase	£14,084	£17,742	2.21	2.28	£3,658	0.062	£59,108
DSU amended basecase							
Age 64	£14,533	£17,852	2.152	2.198	£3,319	0.046	£71,404
Age 70	£12,418	£16,188	2.243	2.302	£3,770	0.059	£63,916
Age 74	£13,888	£17,358	2.180	2.252	£3,469	0.071	£48,574
Sensitivity analysis 1 (carer benefits):							
Age 64	£14,568	£17,881	2.142	2.188	£3,313	0.045	£73,520
Age 70	£12,464	£16,228	2.246	2.305	£3,764	0.059	£63,584
Age 74	£13,747	£17,216	2.217	2.290	£3,469	0.073	£47,643
Sensitivity analysis 2 (behavioural symptoms): Age 64	£14,855	£18,007	2.127	2.178	£3,152	0.051	£61,661
Age 70	£12,696	£16,328	2.218	2.280	£3,632	0.062	£58,505
Age 74	£14,253	£17,553	2.181	2.258	£3,300	0.077	£42,661
Sensitivity analysis 3 (utility data):							
Age 64	£14,322	£17,675	2.520	2.575	£3,353	0.055	£61,111
Age 70	£12,687	£16,443	2.669	2.736	£3,756	0.067	£56,260
Age 74	£14,223	£17,668	2.569	2.651	£3,445	0.082	£41,933

5. CONCLUSIONS

The combined results of the changes make very little difference to the incremental cost-effectiveness estimates. For moderate disease (donepezil) the ICERs change from a mean of £35,500 to between £28,600 and £41,000 depending on age. For mild disease (donepezil) the ICERs change from a mean of £63,750 to between £51,700 and £77,500 depending on age. For mild disease (galantamine) the ICERs change from a mean of £59,100 to between £48,600 and £71,400 depending on age.

The sensitivity analysis including carer benefits in the control arm of the model makes very little difference to the results. The sensitivity analysis for the mild disease model of including increases to the probability of behavioural symptoms and the effectiveness of the drugs in treating those symptoms decreases the ICERs in the region of £5,000 to £10,000 in the models for mild disease. The ICERs for the mild disease models reduce by a similar magnitude as a result of the sensitivity analysis linking the utility estimates for pre-FTC with the starting ADAS-cog score. For the moderate disease model this sensitivity analysis on the utility estimates increases the ICERs by approximately £5,000 to £7,000 depending on age. This is because the utility value used in the sensitivity analysis for pre-FTC for the moderate model (0.558) is lower than that used in the main analysis (0.6).

Removing the sampling of patient characteristics shows that the treatments appear to be more cost-effective for people aged 74 and over compared to the younger age groups. For people aged 74 and over with moderate disease, the ICER of £28,500 is towards the upper end of the £20,000 to £30,000 cost-effectiveness threshold range reportedly used by NICE.[4] The ICERs for the other age groups are higher than this. The other changes made in the main analysis to the model for moderate disease do not substantially impact on the results. The sensitivity analysis on carer benefits has little effect and the sensitivity analysis on utility estimates increases the ICERs further.

For the mild disease models, none of the changes made to the augmented base case or in the one-way sensitivity analysis reduce the ICERs for the treatment of mild disease

to the £20,000 to £30,000 threshold range reportedly considered cost-effective by NICE.

Taking the definition of reliability as noted earlier (that is, does the model do what the Committee belived it did as described in the documentation), the amendments to the model for mild disease as a result of the comments do not render the guidance unreliable. Given that the guidance for moderate disease was based on estimates of cost-effectiveness at the very top borderline of the range usually considered cost-effective by NICE, the effect of small changes in the ICER is less clear. In coming to these conclusions DSU has not judged the inputs or assumptions used in the model of which the Committee were aware and accepted.

6. REFERENCES

Reference List

(1) National Institute for Health and Clinical Excellence. Technology appraisal guidance 111: Donepezil, galantamine, rivastigamine (review) and memantine for the treatment of Alzheimer's disease (amended). 2007. NICE, London.
Ref Type: Report

(2) Briggs A, Sculpher M, Claxton K. Decision modelling for Health Economic Evaluation. Oxford: Oxford University Press; 2006.

(3) Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. BMJ 1998; 316(7133):736-741.

(4) National Institute for Health and Clinical Excellence. Guide to the Methods of Technology Appraisal. 2008. London, NICE.
Ref Type: Report

APPENDIX: RESPONSES TO PROPOSED CHANGES NOT IMPLEMENTED IN THE BASECASE ANALYSIS

The following comments were considered to potentially relate to the reliability (see definition in Section 1) following an initial review of all the comments submitted to NICE. Following further investigation, amendments to the model were not considered appropriate because the comment did not relate to the reliability of the model, the comment did not relate to the analysis used to formulate the guidance, the change was not warranted or the changes made in response to other comments and described in the main report render further amendment unnecessary.

Where the results following amendments to the model are described, the model for donezepil for mild Alzheimer's disease has been used for illustrative purposes unless stated otherwise.

A.1 HAZARD MORTALITY

Comment: Eisai (Issue 1 and 3)

Summary: Consultees raised concerns about the implementation of the hazard of mortality in the model if the 'death index' option is selected. The index for older patients is applied to younger patients (and vice versa). The other problem is that the model uses an age of 72 to select which index to use, when in fact the age cut-off to be used is 73.

DSU response: The point made relates to a sensitivity analysis. The model was incorrect. The proposed implementation to rectify the error is similar to that suggested by Eisai with an additional amendment. The DSU amendment increases the ICER by approximately £2k for the sensitivity analysis. The ICER in the donepezil mild model (sensitivity analysis) changes from £56,683 to £58,430 and the ICER for the donepezil mild model (sensitivity analysis) changes from £27,131 to £28,184 in the donepezil moderate model).

This change does not affect the basecase results and is therefore not included in the analysis reported in Sections 4 and 5.

Details of correction:
Using "Aug BC + Extra work Q3 05 DON Mild 4268b FAD"
Starting ICER is £56,683, from the above model with "death hazard" set to 1, B82 of Inputs sheet.
Original in cell AF7, ADProgbase (but applies to entire column) and also applies to AP7 and entire column in ADProgTx
=IF(age>72,(0.0108*EXP(0.0498*A7)),(0.0195*EXP(0.0415*A7)))
Eisai suggest cell change to
=IF(age<73,(0.0108*EXP(0.0498*A7)),(0.0195*EXP(0.0415*A7)))
DSU suggest change should be
=IF(age<=73,(0.0108*EXP(0.0498*A7)),(0.0195*EXP(0.0415*A7)))

A.2 HAZARDS MORTALITY

Comment: Shire (Issue 8), RICE (Issue 2), Eisai (not numbered)

Summary: The model uses a constant probability of death regardless of age, disease severity etc.

DSU response: The model does assign a constant probability of death regardless of patient characteristics including age or whether pre FTC or not. The AC were aware of this and is discussed in the FAD 4.3.10.5. The annual probability of death is 0.112 and this is correctly converted into a monthly probability. An exploratory sensitivity analysis halving the mortality probability applied yields an ICER of £54,026 (donepezil mild model). The model outputs are not very sensitive to the mortality rate.

A.3 DISTRIBUTION OF ADAS-COG SCORES

Comment: Shire (Issue 3)

Summary: The distribution of ADAS-cog score over the AD population in the SHTAC model was assumed to be a gamma distribution. However the augmented

NICE model assumes that the ADAS-cog score is uniformly distributed over the range of scores and the reason for this is not clear from the NICE documentation.

DSU response: The consultee refers to the distribution for the reduction in the ADAS-cog score as a result of treatment (Inputs sheet, cell E23). In the original SHTAC model this assumed a gamma distribution. In the NICE-augmented base case model a normal distribution is used. The data are reported on page 11 of Technical report No.2 (mild model: mean = 1.86, standard error [SE] = 0.53; moderate model mean = 3.98, SE = 0.39). The notation on the spreadsheet has not been amended to state that a normal distribution has been used in place of the gamma distribution & no reference has been found to explain the choice of distribution. However, there is no reason to assume that the distribution would be skewed with minimum of zero (which is what a gamma distribution would typically be used for). .

A.4 RANGE OF ADAS-COG SCORES

Comment: Shire (Issue 4)

Summary: In addition, the selection of ADAS-cog score in cell 'Inputs L15 'is invalid. The formula which samples moderate patient values, RAND()*(47-21)+21, includes values for patients with an ADAS-cog score of 21 which is outside the intended range for moderate patients. In the mild version of the model, the formula RAND()*(21-4)+4 does not give full value to patients at 21 or 4 (range should select from >3.5 to <21.5 to give equal weighting to all the values).

DSU response: This comment is no longer relevant once the amendment to remove the sampling of patient characteristics has been made (See section 4.2). However, for completeness, a response is noted below.

The definition of moderate disease is reported in Tech Report no.2 (p7) and the ranges of ADAS-cog scores used are also reported in the project specification for additional work (July 2005). It is stated that moderate disease uses the range of 21 to 47. The implied cut-off between mild and moderate disease is therefore less than but not equal to 21.

The model includes the following possible ranges for ADAS-cog scores:
Mild disease: 4 to 21
Moderate disease: 21 to 47

There range of ADAS-cog scores are implemented incorrectly in the mild disease model, however the proposed amendment is not that suggested by the consultee. The model for moderate disease should not be amended. However, an amendment should be made to the mild model to reflect that the definition for mild disease does not include 21.

Details of amendment:
Amendment to Inputs L15 : RAND()*(20-4)+4
Results: The change makes minimal differences to the results. The ICER for donepezil decreases from £63,749 to £62,438.

A.5 IMPLEMENTATION OF AUGMENTED BENEFIT

Comment: Eisai (not numbered) and Alzheimer's Society (Issue 9)
Summary: The implementation of augmented benefit does not rectify short comings of the model. In particular that the costs for pre-FTC are not amended, a single utility is assigned to pre-FTC, and no amendment has been made to utility within the mild model.

DSU response: We note that the addition of the augmented benefit in the model does not alter the underlying structure to the model. However the consultees do not raise issues that have not been reported in the available documentation.

A.6 COST DATA

Comment: Eisai (not numbered)

Summary: The model appears to allow for general practitioner (GP) monitoring visits but the frequency is hardwired to 0. Also, the model includes a distribution around some unit cost estimates rather around the quantity of resources used.

DSU response: The model has been set up to enable additional GP visits associated with monitoring patients to be included (for example as is reported in a sensitivity analysis – AR p175). It is not inconsistent with the information provided to the Appraisal Committee. The AC was informed that in the basecase, resource-use associated with monitoring was assumed to be outpatient visits only (mean =2, gamma distribution). The model is therefore consistent with the documentation and no change has been implemented.

The way in which the distributions around the cost estimates rather than resource use estimates have been applied in the model is also consistent with the documentation (see page 169 AR). No change

A.7 DISCONTINUATION/STOPPING RULE

Comment: Eisai (not numbered)
Summary: If discontinuation is selected, patients cannot die or transit to FTC in the month of discontinuation if they drop out of treatment.

Response from DSU: Discontinuation was not included in the model that underpins the NICE guidance. No change.

A.8 IMPLEMENTATION OF FULL TIME CARE (FTC) INDEX

Comment: Eisai (Issue 4)
Summary: The selection of FTC index calculation to use (for younger or older patients) was set to 74 years, but should have been set to 73 years. (Eisai)

DSU response: The FTC index calculation varies depending upon whether the person's age is less than or equal to 73 years, or over 73 years. (Cells AC3 to AG3 in ADprogTx and Z3 to AD3 in ADProgBase). This is compatible with the

description in the AR (p163) and the publication on which the model is based and therefore no change is needed.

A.9 INCORRECT CELL CODING FOR PROPORTION IN FTC

Comment: Alzheimer's Society (Issue 3) and Shire (Issue 5)

Comment: The model contains a cell ('Inputs B56') in which the proportion of full-time care (FTC) patients that are treated in the community should be entered. The cell 'COST DATA H30' is supposed to use this percentage to calculate the cost of long-term care. However, the value in cell 'COST DATA H30' is hard coded to 0.52, so whenever the input sheet is amended, the change is not propagated through the model.

DSU response: The comment is correct in that the value in cell 'Cost data H30' of 0.52 is directly entered rather than linked to cell Inputs B56' which also contains the value 0.52. Any change to the value of 0.52 would require it being directly entered into 'Cost data H30' or linked to the inputs sheet. This makes no difference to the estimates included in the basecase analysis of the model.

A.10 USE OF EFFECTIVENESS DATA BASED ON 6 MONTHS

Comment: Shire (Issue 9) and Eisai (not numbered)

Summary: Interrogation of the model has shown that the SHTAC model is not structured to calculate continued improvement beyond 6 months. The model assumes that patients receive no additional treatment benefit beyond 6 months - but data from long-term studies suggest that treatment effect (active vs no treatment) increases over time for milder patients.

DSU response: The documentation makes it clear the effectiveness data are based on 6 month trials. This is reported in Technical Report no.2 (Table 4 page 11). The effectiveness data over 6 months is used to estimate the risk index, which in turn is used to predict the proportion of people who die or enter full time care at each cycle. No change.

A.11 UNABLE TO REPLICATE RESULTS

Comment: Eisai (not numbered)

Comment: Eisai state that the inputs and assumptions included in the models as sent to them were not set up to replicate the results included in the technical reports and that they have had difficulties amending the model to reproduce these results.

DSU response: The models have been set up to produce the estimates considered most appropriate by the Appraisal Committee, and relate to the lower end of the range of estimates reported in 4.2.6.8 of the FAD. A discrepancy has been found between the ICER noted in the FAD and the model for donepezil (mild disease). The FAD states that the ICER is £61,000 however the estimates in the model are £64,000.

A.12 INCORRECT MEAN AGE INCLUDED IN THE MODEL

Comment: Eisai (not numbered)

Comment: The NICE report states that a mean baseline age of 74 was used in the model, but in both deterministic and probabilistic settings, the model as sent uses a mean age of 75.

DSU response: Agree with the point. The model uses a mean age of 75 years and the Assessment Report refers to a mean age of 74. However, this comment is no longer relevant once the amendment to remove the sampling of patient characteristics has been made (See section 4.2). For completeness, a response is noted below.

Amendments:

Change 'Inputs Cell F10' to 74.

The change makes minimal differences to the results. The ICER for donepezil (mild disease) increases from £63,749 to £64,244 and for donepezil (moderate disease) decreases from £31,550 to £30,842.

A.13 PRIOR DISEASE DURATION

Comment: Eisai (not numbered)

Summary: A mean duration of disease of 1 year prior to commencement of treatment is assumed, although the delay to diagnosis of Alzheimer's disease in the United Kingdom has been reported to be almost 3 years.

DSU response: Committee were aware of this. See AR p169. No change.

A.14 ARBITRARY SELECTION OF PROBABILISTIC PARAMETERS RANGES

Comment: Eisai (not numbered)

Summary: The ranges used for many of the probabilistic parameters appear to be arbitrary, and in many cases so wide that nonsensical replications arise.

DSU response: It is noted that the selection of some of the probabilistic parameter ranges appear to be arbitrary however, the ranges are reported in the AR. See p169.