REVIEW OF THE BRISTOL-MYERS SQUIBB / ASTRAZENECA RESPONSE TO THE ACD ON DAPAGLIFLOZIN FOR TYPE 2 DIABETES

REPORT BY THE DECISION SUPPORT UNIT

4th March 2013

Sarah Davis
School of Health and Related Research, University of Sheffield
Jefferson Sheard
Jefferson Sheard Consultancy, Sheffield

Decision Support Unit, ScHARR, University of Sheffield, Regent Court, 30 Regent Street
Sheffield, S1 4DA

Tel (+44) (0)114 222 0734
E-mail dsuadmin@sheffield.ac.uk
Website www.nicedsu.org.uk

ABOUT THE DECISION SUPPORT UNIT

The Decision Support Unit (DSU) is a collaboration between the Universities of Sheffield, York and Leicester. We also have members at the University of Bristol, London School of Hygiene and Tropical Medicine and Brunel University. The DSU is commissioned by The National Institute for Health and Clinical Excellence (NICE) to provide a research and training resource to support the Institute's Technology Appraisal Programme. Please see our website for further information www.nicedsu.org.uk

The production of this document was funded by NICE through its Decision Support Unit. The views, and any errors or omissions, expressed in this document are of the authors only. NICE may take account of part or all of this document if it considers it appropriate, but it is not bound to do so.

EXECUTIVE SUMMARY

The DSU has reviewed the Bristol-Myers Squibb / AstraZeneca (BMS/AZ) response to the appraisal consultation document (ACD) and the technical aspects of the revised economic models. The manufacturer has addressed all of the significant areas of concern identified in the previous DSU report.

In particular;

- The DSU were able to validate that the source code provided was that used to generate the DLLs provided with the submitted models.
- The results generated by the PSA version of the model (diab2sampling DLL) when no parameters are sampled and the model version which uses mean parameter values (diabetes2 DLL) are comparable.
- The results are now based on 1,000 model replications which the DSU considers to be a sufficient number to provide stable estimates of the ICER.
- The mortality equations have been updated to use those reported by UKPDS and therefore all-cause mortality is now appropriately adjusted for diabetes related mortality.
- Various inconsistencies between the event and risk factor equations used and those reported by the UKPDS have been corrected or accounted for.
- The PSA model now uses the sampled lifetime BMI profiles to calculate 'delta BMI' which determines the utility impact of weight changes from baseline.
- The weight changes attributable to treatment are now applied gradually over the first year of the model.
- Further checks have been made regarding the QALY decrements applied for the hypoglycaemia, UTI and GI adverse events and the DSU are satisfied that the utility decrements described in the MS are being applied for the appropriate time period.
- The process used to sample from beta and gamma distributed parameters within the PSA now produces appropriately distributed samples. Although it should be noted that the standard errors applied for the costs and utility decrements are assumed to be 10% of the mean parameter value rather than 20% of the mean as previously reported.

CONTENTS

TABLES & FIGURES

ABBREVIATIONS AND DEFINITIONS

BMI	Body mass index
BMS/AZ	Bristol-Myers Squibb / AstraZeneca
CHF	Congestive heart failure
DLLs	Dynamic link library
DPP-4	Dipeptidyl peptidase-4
GLP1	Glucagon-like peptide 1
HbA1c	Glycosylated haemoglobin
HDL	High density lipoprotein
ICER	Incremental cost-effectiveness ratio
IHD	Ischaemic heart disease
INS	Insulin
MET	Metformin
MS	Manufacturer submission
MI	Myocardial infarction
PSA	Probabilistic sensitivity analysis
SBP	Systolic blood pressure
TC	Total cholesterol
TZD	Thiazolidinedione
UKPDS	United Kingdom Prospective Diabetes Study
UTI	Urinary tract infection
VBA	Visual basic application
QALY	Quality adjusted life-years

1. INTRODUCTION

1.1. BACKGROUND

Bristol-Myers Squibb / AstraZeneca (BMS/AZ) submitted a response to the Dapagliflozin Appraisal Consultation Document (ACD) which included revised economic models. The DSU has reviewed the manufacturer's written response to the ACD (MRACD) and the technical aspects of the revised economic model to determine whether the manufacturer has provided a satisfactory response to the following concerns raised by the DSU in their review[1] of the original economic models:

- differences between the economic model described in the submission and the executable model provided
- several aspects of the executable model that were not described in the manufacturers' submission
- inability to reproduce the results of the probabilistic sensitivity analyses reported in the manufacturers' submission on the basis of the C++

1.2. STRUCTURE OF THIS REPORT

Section 2 of this report reviews section 3.1.1 of the MRACD which specifically addresses the concerns previously raised by the DSU. Section 3 of this report describes whether those concerns not specifically addressed in section 3.1.1 of the MRACD have been adequately addressed. This report should be read in context with the previous DSU report[1] related to this appraisal and the MRACD.

2. REVIEW OF SECTION 3.1.1 OF THE MRACD

The sections below follow the headers used in section 3.1.1 of the MRACD.

2.1.1. Compiling the source code

The DSU is satisfied that the source provided for the revised DLLs is equivalent to that used to generate the DLLs provided in the revised economic models that accompany the MRACD. This is based on the fact that we have been able to demonstrate that the results produced by the DLLs provided in the revised models, are identical to the results produced by the DLLs generated by compiling the source code provided in the MRACD. We were therefore able to proceed to checking that the changes to the source code since the last submission are as described in the MRACD and that they adequately address the concerns expressed in the DSU's first report[1].

2.1.2. Model stability and convergence

The DSU assessed model convergence for three example models within the 'DCEM for base case' zip file. When these models were submitted they were set up to run 1,000 replication of 1,000 patients using mean parameter values. One model was selected for each indication (dual therapy add-on to MET, dual therapy add-on to INS, triple therapy) and in each case the comparison with the smallest incremental QALY gain was selected as the MRACD states that the number of runs required increases for smaller effect sizes. The three models selected were:

- 'DCEM v2.2 (Model 1) NMA_.xls' in the INS+DPP4 folder (no changes to spreadsheet)
- 'DCEM v2.2 (Model 2) NMA_.xls' in the 'MET+DDP4_TZD' folder (sole change was to select MET+TZD as comparator on demographics sheet)
- 'DCEM v2.2 (Model 1) NMA_UK_triple.xls' in the 'triple therapy' folder (sole change was to select MET+GLP1 as comparator in the demographics sheet)

In all three cases, the DSU were satisfied that a stable estimate of the ICER was produced by 1,000 runs of 1,000 patients.

The DSU then ran the PSA version of the model for the spreadsheets in the 'vs INS_DPP4' folder and the 'vs MET+TZD' folder. Based on these results we are satisfied that the PSA model provides a stable estimate of the ICER for 1,000 runs of 10,000 patients.

2.1.3. Comparability of mean values (Diabetes2) and PSA (Diab2Sampling) DLLs

The MRACD presents figures in Table 3.1.1.1 which show identical outputs for the Diabetes2 and Diab2Sampling DLLs. They state that these have been generated using 10 runs of 1000 patients. No further detail is provided by the manufacturer regarding the model used to generate these results. The DSU would not expect the results to be identical as reported, as the source code for the two versions of the model compared differs in the order in which certain events are sampled and would therefore not attribute the same random numbers to each event even though the random number stream is fixed. As the model behaviour being reported in Table 3.1.1.1 was unexpected, the DSU performed a comparison using 10 runs of 1000 patients for the model named "DCEM v2.2 (Model 1)_INSvDPP4". The DSU switched off all parameter sampling by setting each dark blue cell to zero in the worksheet called 'PSA'. The results generated when selecting 'run model using mean values' were then compared with the results generated when selecting 'run probabilistic sensitivity analysis' on the demographics sheet. As expected, the results were not identical. The DSU would expect comparable (but still not identical) results to be achieved over a larger sample size. The results in Table 1 show the same comparison for 1,000 runs of 10,000 patients. The confidence intervals for the incremental costs and QALYs overlap, suggesting reasonable agreement between the two models.

The DSU noted a significant discrepancy between the results generated by the diabetes2 and diab2sampling DLL which was that the PSA version does not report any deaths from non-diabetes related mortality. After further investigation, this was discovered to be an error in the reporting of model outcomes within the diab2sampling DLL rather than an error in the way the model estimates mortality. In effect, the deaths resulting from equations 9 and 10 (see 2.1.5 below for a description of these equations) have been included in the tally of UTIs events and not in the tally of 'other' deaths. This error would not affect the estimation of mean QALYs within the model and so does not invalidate the ICERs.

Table 1 Comparison of incremental QALYs and costs when using the 'run model with mean values' and 'run probabilistic sensitivity analysis' with no parameters sampled*

	Mean Values (Diabetes2.dll)	**PSA Values (Diab2Sampling.dll)**
Cost	£281 (£262.48 to £299.73)	£263 (£244.35 to £281.85)
Benefit	0.112 (0.109 to 0.115)	0.115 (0.112 to 0.118)
ICER	£2,501	£2,286

*generated using the DCEM v2.2 (Model 1)_INSvDPP4, 1000 runs of 10,000 patients

2.1.4. Risk-Factor Progression

The manufacturer claims to have implemented changes to the risk factor progression equations and event equations, so that the input values for SBP, TC:HDL, HbA1c and BMI are taken from the initial cohort baseline profile. Example source code for HbA1c is provided in section 3.2 of Appendix 1. The DSU can verify that these changes have been implemented correctly and the risk factor equations now refer to the baseline risk factor values as specified in the UKPDS equations.

2.1.5. Event Equations

Mortality event equations have been updated to use UKPDS[2] equations 8, 9 and 10. When an MI, Stroke, CHF, renal failure or amputation event occurs, equation 8 is applied to determine if the event itself is fatal. Equation 9 is applied once each cycle to determine diabetes related mortality from the events in previous cycles. Equation 10 is applied to determine non-diabetes related mortality and this replaces the all-cause mortality data based on UK lifetables. The DSU have checked the revised equations which are confirmed to be correct with the exception of one coefficient in equation 9 which has been mistyped into the code as 2.087 instead of 2.807. This error was corrected in the source code and the model was run for the add-on to insulin comparison. This did not result in any changes to the ICERs, suggesting that this equation is either not used or that its impact on the ICER is insignificant. The DSU did not have sufficient time to investigate why the ICER did not vary when this covariate was corrected.

2.1.6. Parameter sampling

The DSU repeated their previous check of the gamma samples for the cost of MI and the beta samples for the utility decrement following MI. In both cases, the samples extracted

(N=10,000) had an appropriate mean, but the standard error was 10% of the mean and not 20% as reported in Table 72 of the original MS. This appears to be due to the standard errors being set at 10% of the mean within the 'PSA' sheet of the spreadsheet model.

The DSU are satisfied that the gamma and beta functions used by the model produce appropriately distributed samples, but it should be noted that the standard errors for the costs and utility decrements are assumed to be 10% of their mean value and not 20% as described in the original submission.

2.1.7. Hypoglycaemia

We have made further validation checks to assess the utility decrements applied in the model for hypoglycaemia and we are satisfied with the manufacturer's response.

2.1.8. Event Probabilities

The DSU are satisfied with the changes made to the source code to correct the calculation of transition probabilities from the cumulative hazard functions provided by the event and mortality functions.

2.1.9. All-cause mortality

The DSU are satisfied with the changes made to the source code. The all-cause mortality data taken from the life-tables is now adjusted for all diabetes related mortality as estimated by equations 8 and 9. It should be noted that this amendment to the source code does not affect the model results unless the user selects an option to use the life-table data instead of equation 10 (see 2.1.5 above) to estimate all-cause mortality.

2.1.10. Applying transformations to risk factors and moving averages

In section 3.2 of the DSU report[1], some inconsistencies were noted between the event equations applied in the model and those reported in the UKPDS paper[2]. The MRACD directs the reader to a spreadsheet embedded in Appendix 5, which describes how the UKPDS equations are implemented in practice and claims that their implementation is coded in line with this spreadsheet. The DSU did not have sufficient time to examine the

spreadsheet embedded in Appendix 5 in detail, but they note that it wasn't possible to verify all of the discrepancies previously identified by the DSU (in section 3.2 of the previous DSU report[1]) as not all UKPDS equations were included in the spreadsheet.

The DSU have not checked the spreadsheet attached to Appendix 5 of the MRACD to assess the validity of not using moving averages.

3. OTHER CONCERNS NOT DISCUSSED IN 3.1.1 OF THE MRACD

3.1. SOURCE CODE CHANGES DESCRIBED IN THE APPENDIX 1 OF THE MRACD

Appendix 1 of the MRACD describes several changes to the code which are not explicitly discussed in section 3.1.1 of the MRACD.

3.1.1. Delta BMI values in PSA model

The DSU had previously noted that the utility gain associated with body mass index (BMI) changes within the PSA model was based on the BMI profile generated using mean parameter values whilst the rest of the simulation used a BMI profile that was sampled within the PSA. The source code for the PSA model has been updated such that the change in BMI since baseline is based on the simulated BMI profile as requested by the DSU.

3.1.2. BMI value used in risk equations

The DSU had previously noted that in the CHF equation, the current BMI value was being used to evaluate the risk of CHF rather than BMI at diagnosis as specified in UKPDS 68.[2] The DSU are satisfied that this concern has been addressed by the changes described in appendix 1 of the MRACD.

3.1.3. Weight profiles

The DSU were previously concerned that the treatment effect on weight was being applied immediately within the model and not gradually as might be expected. This code has been changed as described in Appendix 1 of the MRACD and the weight reduction is spread linearly across two 6 month periods.

3.2. CONCERNS NOT EXPLICITLY ADDRESSED IN THE MRACD

3.2.1. Time periods over which adverse event utilities are applied

The DSU has previously expressed some uncertainty regarding the time periods over which the utility decrements are applied for the adverse events of hypoglycaemia, UTI and GI. The MRACD has specifically addressed the DSU's uncertainty regarding the application of utility

values for hypoglycaemia (see 2.1.7 above). The DSU has also made further checks to the time period over which the utility values are applied following UTI and GI and is satisfied that these are appropriate.

3.2.2. Fatality equation for CHF, amputation and renal events

The fatality equations have been updated to match those reported in the UKPDS paper. [2] This addresses the DSU's concern described in section 3.2 of the DSU report[1] with the exception of a sole covariate which appears to have been mistyped in the source code (see 2.1.5 above).

3.2.3. SBP risk factor equation

The risk equation for updating SBP (UKPDS equation 12) now uses the baseline SBP value as specified in the UKPDS paper[2]. The DSU are no longer concerned with the discrepancy described in section 3.3.1 of their previous report[1].

4. CONCLUSIONS

The manufacturer has addressed all of the significant areas of concern identified in the previous DSU report[1]. No new areas of significant concern were identified when reviewing changes made to the model since the previous submission, although an exhaustive check of all changes to the model was not feasible.

REFERENCES

1. Davis S, Sheard J. A review of the Bristol-Myers Squibb / AstraZeneca economic model on the cost-effectiveness of Dapagliflozin: Report by the Decision Support Unit. November 2012 [http://www.nice.org.uk/nicemedia/live/13722/62588/62588.pdf]

2. Clarke PM, Gray AM, Briggs A, Farmer AJ, Fenn P, Stevens RJ, *et al.*A model to estimate the lifetime health outcomes of patients with Type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). *Diabetologia 2004.* 47(10):1747-1759.