National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response completed by Pfizer
2nd April, 2015

Executable Model

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept and tocilizumab for the treatment of rheumatoid arthritis (review of TA guidance 130, 186, 224, 234 and part review of TA guidance 225 and 247) [ID537]

The economic model enclosed and its contents are confidential and are protected by intellectual property rights, which are owned by ScHARR TAG It has been sent to you for information only. It cannot be used for any other purpose than to inform your understanding of the appraisal. Accordingly, neither the model nor its contents should be divulged to anyone other than those individuals within your organisation who need to see to them to enable you to prepare your response. Those to whom you do show the documents must be advised they are bound by the terms of the Confidentiality Agreement Form that has already been signed and returned to the Institute by your organisation.

You may not make copies of the file and you must delete the file from your records when the appraisal process, and any possible appeal, are complete. If asked, you must confirm to us in writing that you have done so. You may not publish it in whole or part, or use it to inform the development of other economic models.

The model must not be re-run for purposes other that the testing of its reliability.

Please set out your comments on reliability in writing providing separate justification, with supporting information, for each specific comment made. Where you have made an alteration to the model details of how this alteration was implemented in the model (e.g. in terms of programme code) must be given in sufficient detail to enable your changes to be replicated from the information provided. Please use the pro-forma to present your response.

Please prepare your response carefully. Responses which contain errors or are internally inconsistent (for example where we are unable to replicate the results claimed by implementing the changes said to have been made to the model) will be rejected without further consideration.

Results from amended versions of the model will only be accepted if their purpose is to test robustness and reliability of the economic model. Results calculated purely for the purpose of using alternative inputs will not be accepted.

Please upload and submit your response via NICE Docs/Appraisals. Any responses that are not sent via NICE Docs/Appraisals will not be accepted. No electronic versions of the economic model will be accepted with your response.

Responses should be provided in tabular format as suggested below (please add further tables if necessary).

March 2015

Issue 1 Overview of Pfizer concerns with the model

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
In the previous review of the Assessment Group (AG) economic model Pfizer identified a substantial number of errors and discrepancies between the AG model and reporting in the Technology Assessment Report (TAR). Based on these findings, Pfizer proposed that the economic model undergo an independent technical review to ensure that no further errors exist within the model. While many of the errors identified in Pfizer's review have been corrected (document 1a), several errors remain, including: 1. bDMARDs are not cost-effective at zero cost, despite being more effective, which shows large discrepancies between the AG and manufacturer models 2. The relationship between HAQ and pain used in the AG base case is not the most favourable for biological disease modifying anti-rheumatic drugs (bDMARDs). 3. Unrealistic monitoring assumptions for patients who receive bDMARDs 4. Implementation of mortality Furthermore, it is unclear whether the economic model has undergone independent review and validation, which is regarded as an important element of economic modelling best practice (Eddy et al. 2012). Consequently, Pfizer are concerned that unidentified errors	The Pfizer economic model underwent extensive validation, including primary verification by the model developer and further verification by an external health economist on two occasions (See section 4.3.6 of the Pfizer evidence dossier). The approach was also based upon one accepted in a previous Technology Appraisal. In the absence of independent validation of the AG model, Pfizer recommend that the Appraisal Committee compare results from the AG model to those submitted by manufacturers.	Not applicable

remain and that results do not accurately reflect the cost-effectiveness of bDMARDs when compared to conventional disease modifying anti-rheumatic drugs (cDMARDs).		

Issue 2 Model code and general transparency

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Pfizer are concerned that the economic model constructed by the AG remains extremely opaque (identified in issue 1 of our previous response), which limits the opportunity for consultees to review the accuracy of the model and the results it produces. Our main concerns include: a) **Model code:** fails to adhere to best practice with regards to Visual Basic for Applications (VBA) coding. For example in Module: sim_toshRA Ln 434 there is unclear text referring to: *"'Matt has added in these lines"* and Ln 540, *"JON NEW".* Insufficient labelling of the intended purpose has been included. b) **HAQ progression:** outputs on HAQ progression, estimated using Latent Class Growth Model (LCGM) techniques applied to the ERAS cohort, are not provided. For this important outcome it is unclear exactly how a simulated patient's HAQ progressed whilst receiving treatment. **c) Model inefficiency:** to simulate 20,000 patients can take over 12 hours (moderate, DMARD-IR population). This is impractical and requires consultees to trade-off precision when reviewing the models accuracy (i.e., fewer simulations) for pragmatism (i.e., maximising the number of potential	Several amendments could be included to improve transparency: a) Labelling within the VBA code should be revised to ensure the purpose is clear. b) The distribution of and mean HAQ scores at death for each sequence should be included as an additional model output. This was included in the Pfizer model and supported validation of our model projections. c) The coding approach should be reviewed to identify opportunities for greater efficiency. For example the Pfizer model is an individual patient level simulation capable of analysing 50,000 patients in 20 minutes.	Pfizer believe that the results produced by our model are a credible reflection of the cost-effectiveness of bDMARDs; therefore, in the interest of time, we would recommend the Appraisal Committee should use Pfizer's and other manufacturers' models to assess the cost-effectiveness of bDMARDs.

issues tested).		

Issue 3 In the AG base case bDMARDs (ADA, ETN and GOL) sequences are not considered cost-effective at zero cost

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Given the high ICERs estimated in the AG base case, Pfizer ran scenarios to validate the accurate inclusion of drug costs in the model. One scenario tested assumed that there was no cost associated for bDMARDs (i.e. prices at £0). The estimated ICER for the bDMARD sequences vs. the cDMARD sequence ranged between: ERAS HAQ progression: • approx. £24k to £33k* Linear HAQ progression • approx. £12k to £17k* Pfizer are extremely concerned that treatments acknowledged to be more effective than cDMARDs were not cost-effective at zero price. This emphasises differences between manufacturer evaluations presented as part of this appraisal and economic evaluations presented in previous technology appraisals (e.g., TA130, TA186, TA225.). *NOTE: For expediency simulations were undertaken with only 2,000 patients. Therefore, there is likely to be some variation in results.	The causes of the implausible results observed in this test scenario are unclear. However, Pfizer believe it relates to the non-representative sequence of treatment compared in the AG model (a concern raised in Pfizer's response to the TAR – 25/09/2013). Recent discussion in a DSU report on *Assessing technologies that are not cost-effective at a zero price* suggests that costs unrelated to the technology being appraised should be considered for exclusion from the analysis (Davis 2014). We reiterate that the AG model should be designed to examine the incremental impact of the first bDMARD and not a sequence of bDMARDs.	Pfizer anticipate that amending treatment sequences to reflect the incremental impact of the first bDMARD would reduce ICERs for bDMARDs.

Issue 4 Relationship between HAQ and Pain in the AG model has a significant impact on model results and few details of the relationship have been released to consultees for review

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
In Pfizer's previous review of the AG model we raised concerns regarding an error in how the relationship between HAQ and pain using the ERAS cohort was implemented (original issue 6). We requested further information on the analysis undertaken to estimate the aforementioned relationship as this had a large influence on results (original issue 7). While the AG addendum to the TAR (document 1a), Table 1, mentioned that an error in how the NDB data was applied in the AG model was corrected (correction 18), including a simple statement that: *"A third option, [NDB (updated 2014)] has been added to the model. In this option the value for pain has been divided by 10, compared with the previous NDB value, in order that the formula is correct"* Pfizer are concerned that the AG fail to appropriately describe in the TAR addendum or updated TAR where the data for this "third option" is sourced and how it differs to the original estimates. Furthermore, in Section 4 of document 1a, the AG state that: *"The data source used for establishing the relationship between HAQ and pain was also seen to influence the results markedly; the Assessment Group base case uses the estimate most favourable to the bDMARDs."* Upon further review Pfizer believe that the AG base case utilises the updated NDB data, which contradicts the above	Pfizer believe that the AG should report results for a scenario using the "NDB Quadratic Regression (Temporary)" estimate, which is most favourable to bDMARDs. This would show the impact of this variable in calculating ICERs and would more accurately illustrate the considerable uncertainty in the AG model results.	The impact on the ICER for the ETN+MTX sequence vs. cDMARD sequence of using the original NDB analysis to estimate the relationship between HAQ and pain is substantial compared to the updated NDB analysis: This correction changes the ICER by approximately £7k in the setting Pfizer consider most appropriate to assess the cost-effectiveness of bDMARDs (Linear HAQ progression and original NDB analysis). Linear HAQ progression (0.045) 1. Original NDB analysis – ICER approx. £29k 2. Updated NDB analysis – ICER approx. £36k ERAS HAQ progression: 1. Original NDB analysis – ICER approx. £48k 2. Updated NDB analysis – ICER approx. £65k NOTE: For expediency simulations were undertaken with only 2,000 patients.

statement, as the ICERs for bDMARD sequences compared to a cDMARD sequence are higher than the original NDB analysis option available in the updated model.		Therefore, there is likely to be some variation in results.

Issue 5 Unrealistic assumption that patients on bDMARDs will receive a hospital outpatient visit every month whilst on combination bDMARDs + MTX and bDMARD monotherapy

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
In Pfizer's previous review of the economic model it was highlighted (original issue 15) that the AG model assumed patients who receive bDMARDs require monthly outpatient appointments at an estimated cost of £134 following the initial 6 month response period. This included a full blood count (£3), hospital outpatient appointment (£128), and biochemical profile (£3). Pfizer note that this approach has not been updated and therefore continue to disagree with the updated AG model. The approach taken by the AG overestimates the monitoring costs of etanercept and other subcutaneous bDMARDs. Pfizer suggest that the original monitoring assumption used in TA130 is more appropriate and a better reflection of UK clinical practice (Chen et al. 2006). Chen and colleagues include monitoring costs for patients treated with subcutaneous bDMARDs every 3 months after the first 12 weeks of treatment.	Pfizer propose that the AG model be aligned with those accepted in previous appraisals. It should be amended to reflect outpatient appointments every 3 months post the initial 6 month response period (i.e., 4 per year) instead of the12 per year currently assumed.	The impact on the ICER for the ETN+MTX sequence vs. cDMARD sequence of amending the monitoring assumptions for bDMARDs to be more reflective of clinical practice is substantial. This correction changes the ICER by approximately £5k in the setting Pfizer consider most appropriate to assess the cost-effectiveness of bDMARDS (Linear HAQ progression and quarterly appointments). Linear HAQ progression (0.045) 1. Monthly appointments – ICER approx. £36k 2. Quarterly appointments – ICER approx. £31k ERAS HAQ progression: 1. Monthly appointments – ICER approx. £65k 2. Quarterly appointments – ICER approx. £57k

		NOTE: For expediency simulations were undertaken with only 2,000 patients. Therefore, there is likely to be some variation in results.

Issue 6 Despite corrections by the AG errors in how mortality has been implemented in the model are still present

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Sheet Name: Lifetables **Error:** vlookups used in cells M25:108. The AG has included an amendment to mortality calculations within the model (Issue 8 raised in our previous response). However, an error remains as the formula selects data from columns 3 and 5 from the selected range. Consequently, female mortality data is not used to inform the model, instead the male probability is applied to females and the rate (rather than probability) applied to males. This error also has implications for correction No. 13 in document 1a – correct application of hazard rates.	Change the formula from: a) =IF(basesex = 0, LOOKUP(L25,$A$9:$I$110,3),VLOOKUP(L25,$A$9:$I$110,5)); to b) =IF(basesex = 0, VLOOKUP(L25,$A$9:$I$110,5),VLOOKUP(L25,$A$9:$I$110,9))	Minimal

Issue 7 The mapping relationship of ACR to EULAR is still is not available for consultees to critique as this has been calculated outside of the model and values 'hard coded' into the model.

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
In our previous review of the AG economic model, we stated concerns that the details of mapping ACR to EULAR were not provided for consultees to appraise. Given our concerns regarding the inappropriate construction and use of the EULAR network – which combines both moderate and severe trials – we argue that the strength of the mapping relationship using the VARA database is fundamental to determining whether an ACR or EULAR based model is most appropriate to inform the decision question. Furthermore, Pfizer notes that due to this relationship being estimated outside of the model it means the uncertainty in this relationship is not characterised within the probabilistic sensitivity analysis (PSA).	Pfizer again requests that the detail and also how the ACR to EULAR relationship was estimated is released to consultees to allow an appraisal of the relationship to be undertaken. The relationship should be included in the model to ensure that any uncertainty in estimates is included within the probabilistic sensitivity analysis.	Uncertain

References

Chen Y-F, Jobanputra P, Barton P, Jowett SM, Bryan S, Clark W, et al. (2006) A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness*. Health Technology Assessment*. 10(42). p1–266. Available from - http://www.journalslibrary.nihr.ac.uk/hta/volume-10/issue-42. [Accessed: 01 April 2015]

Davis S. Assessing technologies that are not cost-effective at zero price. *NICE Decision Support Unit*. 2014. Available from - http://www.nicedsu.org.uk/Not-costeffective-at-0(2973292).htm. [Accessed: 01 April 2015]

Eddy EM, Hollingworth W, Caro JJ, Tsevat J, McDonald KM, and Wong JB. (2012) Model Transparency and Validation: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-7.*Value in Health*. 15(6).p843-50. Available from - http://www.ispor.org/workpaper/Model-Transparency-and-Validation.asp. [Accessed: 01 April 2015]