

## Single Technology Appraisals

A supplement to *Health Technology Assessment Journal*

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Gemcitabine for metastatic breast cancer

Varenicline for smoking cessation

Alteplase for acute ischaemic stroke

Rituximab for rheumatoid arthritis

Omalizumab for severe persistent allergic asthma

Rituximab for relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma

Adalimumab for psoriasis

Dabigatran etexilate for the prevention of venous thromboembolism

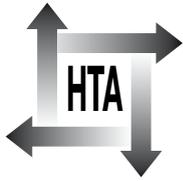
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Sunitinib for gastrointestinal stromal tumours

September 2009

**Health Technology Assessment**  
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The website also provides information about the HTA programme and lists the membership of the various committees.

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# NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needed in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy makers. TARs bring together evidence on the value of specific technologies.

This supplement to the Journal series contains a collection of summaries based on Evidence Review Group reports (ERGs), produced as part of NICE's Single Technology Appraisal (STA) process. The reports are mainly based on data submissions from manufacturers and do not undergo the standard peer-review process.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

## Criteria for inclusion in the HTA Journal series and Supplements

Reports are published in the Journal series and Supplements if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the supplement was commissioned and funded by the HTA programme on behalf of NICE. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report. The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

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## Supplement introduction

Welcome to the second Supplement to the *Health Technology Assessment* journal series. The series is now over 10 years old and has published more than 400 titles, covering a wide range of health technologies in a diverse set of applications. In general, the series publishes each technology assessment as a separate issue within each annual volume.

The Supplements depart from that format by containing a series of shorter articles. These are all products from a 'call-off contract', which the HTA programme holds with a range of academic centres around the UK, at the universities of Aberdeen, Birmingham, Exeter, Liverpool, Sheffield, Southampton and York. These centres are retained to provide a highly responsive resource, which meets the needs of national policy makers, notably the National Institute for Health and Clinical Excellence (NICE).

Until recently, these HTA Technology Assessment Review (TAR) centres provided academic input to policy making through independent analyses of the impact and value of health technologies. As many readers will be aware, the perception that the advice NICE provides to the NHS could be made more timely has led to the development of the 'Single Technology Appraisal' process. In this

approach, manufacturers of technologies, which are, in general, pharmaceuticals close to the time of launch, submit a dossier of evidence aiming to demonstrate effectiveness and cost-effectiveness. The independent academic input to NICE's process, which continues to be supported by the TAR centres around the UK under contract to the HTA programme, is to scrutinise, critique and explore this dossier of evidence.

The papers included in this Supplement report on this HTA programme funded work, and we hope that the summaries of the work carried out to inform the development of NICE guidance for these technologies will be of interest and value to readers.

Further details of each of the NICE Appraisals are available on the NICE website ([www.nice.org.uk](http://www.nice.org.uk)) and we welcome comments on the summaries via the HTA website ([www.hta.ac.uk/correspond](http://www.hta.ac.uk/correspond)).

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# Gemcitabine for the treatment of metastatic breast cancer

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**Declared competing interests of authors:** none

## Abstract

This paper presents a summary of the evidence review group (ERG) report into the evidence for the clinical effectiveness and cost-effectiveness of gemcitabine with paclitaxel for the first-line treatment of metastatic breast cancer (MBC) in patients who have already received chemotherapy treatment with an anthracycline, compared with current standard of care, based upon the manufacturer's submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The clinical evidence for gemcitabine as a treatment for MBC comes from the unpublished JHQQ trial (some data commercial-in-confidence): overall survival was 3 months longer for the gemcitabine/paclitaxel arm (18.5 months) than for the paclitaxel arm (15.8 months) ( $p = 0.0489$ ); gemcitabine/paclitaxel also improved tumour response and time to documented progression of disease compared with paclitaxel monotherapy, but haematological serious adverse events were more common. In the absence of any formal methods of indirect comparison there is insufficient robust evidence to compare the relative effectiveness of gemcitabine/paclitaxel with docetaxel monotherapy or docetaxel/capecitabine combination therapy. The manufacturers used a Markov state transition model to estimate the effect of treatment with five different chemotherapy regimes, adopting a 3-year time horizon with docetaxel monotherapy as the comparator. Health state utilities for different stages of disease progression and for patients experiencing treatment-related toxicity are used to derive quality-adjusted life expectancy with each treatment. The base-case cost-effectiveness estimate for gemcitabine/paclitaxel versus docetaxel is £17,168 per quality-adjusted life-year (QALY).

## HTA 06/16/01

### Date of ERG submission:

July 2006

### TAR Centre(s):

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The research reported in this article of the journal supplement was commissioned and funded by the HTA programme on behalf of NICE as project number 06/16/01. The assessment report began editorial review in July 2007 and was accepted for publication in November 2008. See the HTA programme web site for further project information ([www.hta.ac.uk](http://www.hta.ac.uk)). This summary of the ERG report was compiled after the Appraisal Committee's review.

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Discussion of ERG reports is invited. Visit the HTA website correspondence forum ([www.hta.ac.uk/correspond](http://www.hta.ac.uk/correspond)).

**This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.**



When longer survival with docetaxel is assumed in a sensitivity analysis, the incremental cost-effectiveness ratio (ICER) is £30,000 per QALY. Probabilistic sensitivity analysis estimates a 70% probability of gemcitabine/paclitaxel being cost-effective relative to docetaxel at a willingness-to-pay threshold of £35,000. There is considerable uncertainty over the results because of the lack of formal quality assessment or assessment of the comparability of the 15 trials included in the input data, and the questionable validity of the indirect comparison method adopted. An illustrative analysis using a different method for indirect comparison carried out by the ERG produces an ICER of £45,811 per QALY for gemcitabine/paclitaxel versus docetaxel. The guidance issued by NICE in November 2006 as a result of the STA states that gemcitabine in combination with paclitaxel, within its licensed indication, is recommended as an option for the treatment of MBC only when docetaxel monotherapy or docetaxel plus capecitabine is also considered appropriate.

## Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, for which most of the relevant evidence lies with one manufacturer or sponsor.<sup>1</sup> Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA of gemcitabine for advanced metastatic breast cancer.<sup>2</sup>

## Description of the underlying health problem

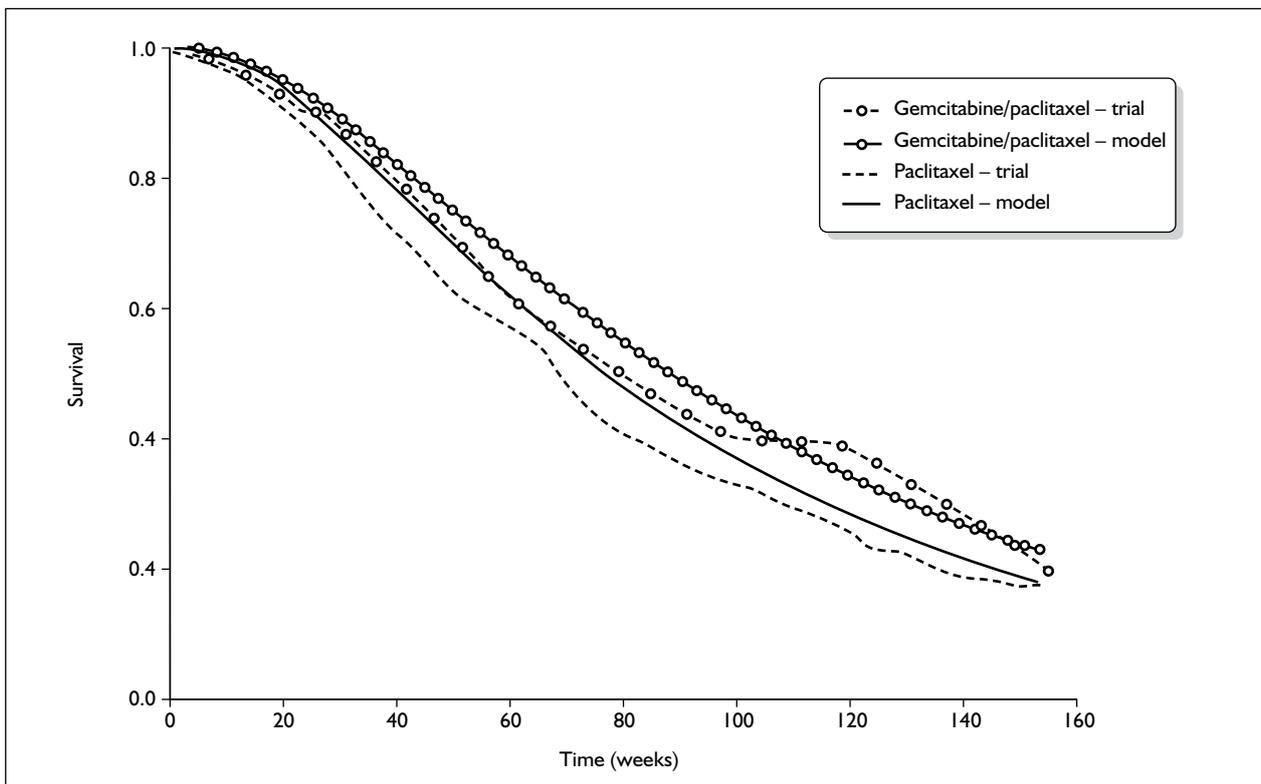
Breast cancer is classified into four clinical stages. Stages I and II are known as primary or early breast cancer, and stages III and IV represent advanced breast cancer. Stage IV is metastatic disease, characterised by the spread of secondary tumours to distant sites. A small proportion of incident breast cancers present as stage IV, i.e. they have overt metastases at the time of diagnosis. Approximately 40% of patients treated for early breast cancer will relapse and develop metastatic breast cancer (MBC). Patients who present with stage IV disease at first diagnosis are described by the manufacturer as being unsuitable for treatment with gemcitabine as they will not have received prior anthracycline therapy.

## Scope of the ERG report

The submission's scope is the use of gemcitabine with paclitaxel for the first-line treatment of MBC in patients who have already received chemotherapy treatment with an anthracycline, compared with current standard of care. This reflects the licensed indication, and is an appropriate question for the NHS within the context of the available evidence.

## Methods

The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process. It also included a critical assessment of the company's submitted economic model. The ERG examined the EXCEL model submitted by the manufacturer for accuracy and consistency and evaluated structural assumptions. In addition, the ERG estimated the survival probabilities and risk of disease progression for patients in the paclitaxel arm of the trial from survival plots reported in the conference presentation by Albain and colleagues,<sup>3</sup> and fitted a parametric survival function to these data using the outputs from an ordinary least squares regression on a log-cumulative hazard.<sup>4</sup> The ERG estimated the external validity of the manufacturer's model by running it with survival estimates from the JHQQ trial, and with median survival times for gemcitabine/paclitaxel and paclitaxel as shown in the JHQQ trial (*Figure 1*). In addition, one-way sensitivity analyses for key model parameters



**FIGURE 1** Estimated survival for gemcitabine/paclitaxel and paclitaxel predicted by the model compared with Kaplan–Meier curves from the JHQQ trial.

were carried out (Table 1), and key input data were replaced with pooled estimates from plausible alternative sources (e.g. the estimates observed in the JHQQ trial). A scenario analysis was conducted using effectiveness data from the JHQQ trial for both gemcitabine/paclitaxel and paclitaxel, and the pooled estimates from trials including anthracycline-pretreated patients for other chemotherapy regimes. To determine whether the results of the company's probabilistic sensitivity analysis are sensitive to the choice of included trials, the ERG reran the company's probabilistic sensitivity analysis using the pooled estimates for overall survival, time to disease progression and overall response rate for paclitaxel monotherapy with values from the JHQQ trial (Figure 2). The ERG constructed cost-effectiveness acceptability curves comparing each of four taxane-based chemotherapy regimes against each other (Figure 3).

## Results

### Summary of submitted clinical evidence

The clinical evidence for gemcitabine with paclitaxel compared with paclitaxel monotherapy as a treatment for MBC comes from the JHQQ

trial, which was published in conference abstracts<sup>5–7</sup> in 2003–4, but has not yet been fully published. The data in the industry submission come from the unpublished trial and so are mostly marked as commercial-in-confidence. Results from two other published trials are included in the submission to provide a comparison with docetaxel monotherapy<sup>8</sup> and docetaxel/capecitabine combined therapy.<sup>9</sup> The JHQQ trial compared gemcitabine/paclitaxel (GT) with paclitaxel (T) in patients with MBC. The trial by Jones and colleagues<sup>8</sup> compared docetaxel monotherapy with paclitaxel, and the trial by O'Shaughnessy and colleagues<sup>9</sup> compared docetaxel monotherapy with docetaxel/capecitabine combination therapy.

Overall survival, the primary outcome measure for the JHQQ trial, was approximately 3 months longer for the gemcitabine/paclitaxel arm (18.5 months in Albain *et al.* abstract,<sup>5</sup> 18.6 months in manufacturer's submission) than for the paclitaxel arm (15.8 months).<sup>7</sup> This difference is of borderline statistical significance ( $p = 0.0489$ ), but represents a clinically significant difference to patients. Results from the JHQQ trial suggest that gemcitabine added to paclitaxel also improves tumour response and time to documented progression of disease compared with paclitaxel monotherapy. Haematological serious adverse events were more

TABLE 1 Evidence review group one-way sensitivity analyses

Variable	Base case	Inputs		CE ratios (£)		Range (£)
		Lower	Upper	Lower input	Upper input	
Response rates (%)	46	39.0	52.9	17,199	17,052	147
Time to progression (weeks)	26	21.5	30.5	16,601	17,406	805
Overall survival (weeks)	80.60	CIC	CIC	30,446	12,310	18,136
AE discontinuation rate (%)	6.7	3.7	9.7	16,335	17,994	1659
Health state utilities:						
Stable	0.80	0.65	0.92	23,656	13,546	10,110
Response	0.72	0.60	0.83			
Progression	0.46	0.29	0.63			
Adverse event, e.g. stable neuropathy, utility rates	0.70	0.55	0.83	17,396	16,972	424
Non-drug costs						
Post-patient paclitaxel cost reduction (cost/course, £):		-25%	+25%	17,988	16,348	1640
Gemcitabine/paclitaxel	2442	1862	2442	5872	17,168	11,296
Paclitaxel	1462	862	1462			

AE, adverse events; CE, cost-effectiveness; CIC, commercial-in-confidence data removed.

common in the gemcitabine/paclitaxel arm than in the paclitaxel monotherapy arm.

In the absence of any formal methods of indirect comparison, there is insufficient robust evidence to compare the relative effectiveness of gemcitabine/paclitaxel with docetaxel monotherapy or docetaxel/capecitabine combination therapy.

### Summary of submitted cost-effectiveness evidence

The cost-effectiveness analysis in the manufacturer's submission uses a Markov state transition model to estimate the effect of treatment with five different chemotherapy regimes, adopting a 3-year time horizon. Base-case results are presented, with docetaxel monotherapy as the comparator for all interventions (assuming that docetaxel is the standard of care for UK practice). Additional scenario analyses are presented using alternative comparators and for a price reduction for paclitaxel once the patent expires. Treatment effects in the model are derived from pooling data from 15 clinical trials – only three of these are discussed in the clinical effectiveness section of the submission. No formal assessment of trial comparability or any quality assessment was presented. Health state utilities for different stages of disease progression and for patients experiencing treatment-related toxicity are

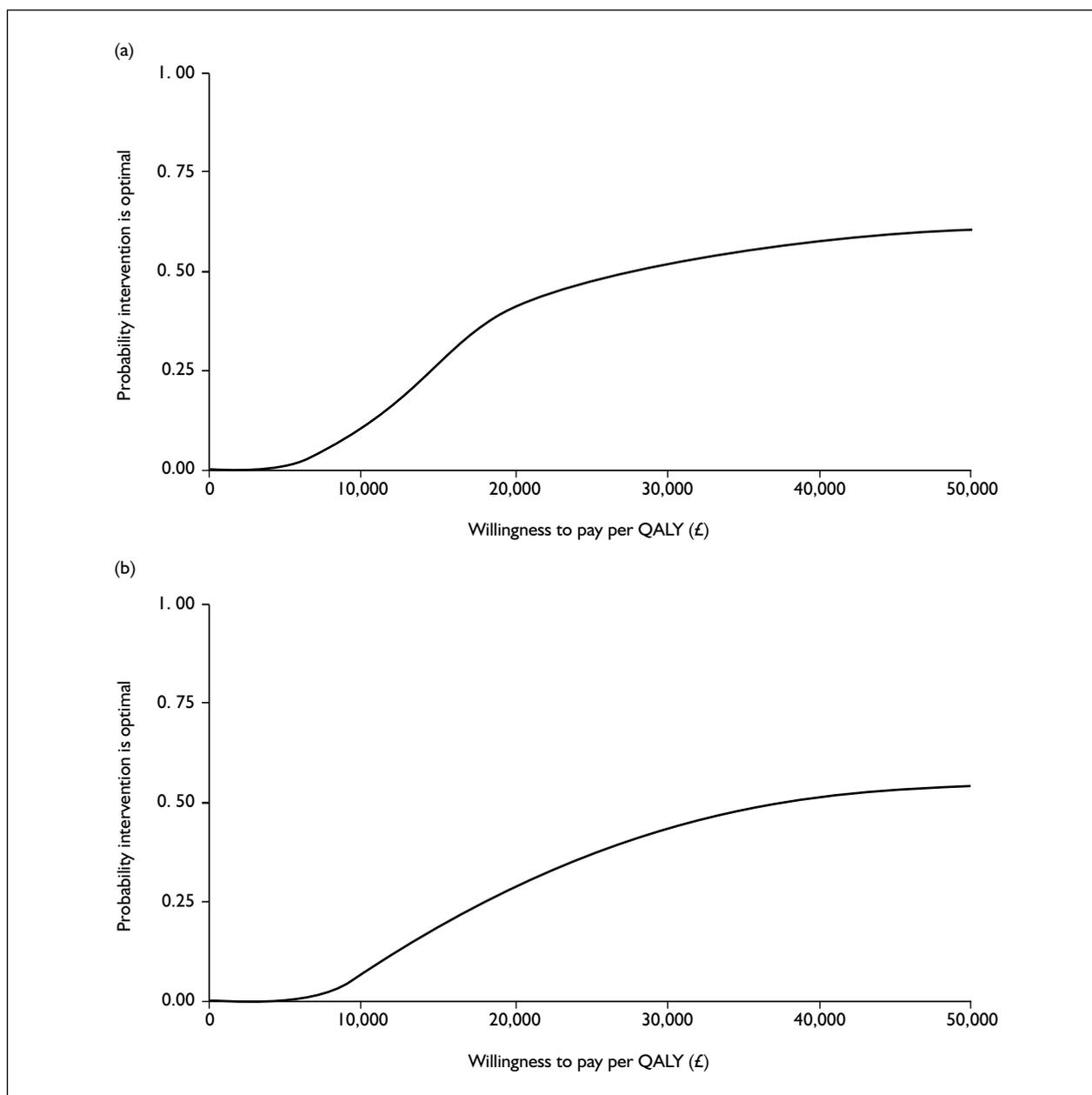
used in the model to derive quality-adjusted life expectancy with each treatment. The base-case cost-effectiveness estimate for gemcitabine/paclitaxel relative to docetaxel is £17,168 per quality-adjusted life-year (QALY). When longer survival with docetaxel is assumed in a sensitivity analysis, the incremental cost-effectiveness ratio (ICER) increases to approximately £30,000 per QALY. Probabilistic sensitivity analysis estimates a 70% probability of gemcitabine/paclitaxel being cost-effective relative to docetaxel at an arbitrary threshold willingness to pay of £35,000.

The lack of formal quality assessment or assessment of the comparability of trials included in the input data, and the questionable validity of the indirect comparison method adopted, leads to considerable uncertainty over the cost-effectiveness of gemcitabine/paclitaxel. An illustrative analysis using a different method for indirect comparison presented in this report produces an ICER of £45,811 per QALY for gemcitabine/paclitaxel relative to docetaxel.

### Commentary on the robustness of submitted evidence

#### Strengths

The structure of the manufacturer's economic model is appropriate for the stated decision problem and reflects accepted methodology.



**FIGURE 2** Cost-effectiveness acceptability curves for gemcitabine/paclitaxel versus paclitaxel using (a) pooled estimates used in the base-case analysis and (b) values from the JHQQ trial. QALY, quality-adjusted life-year.

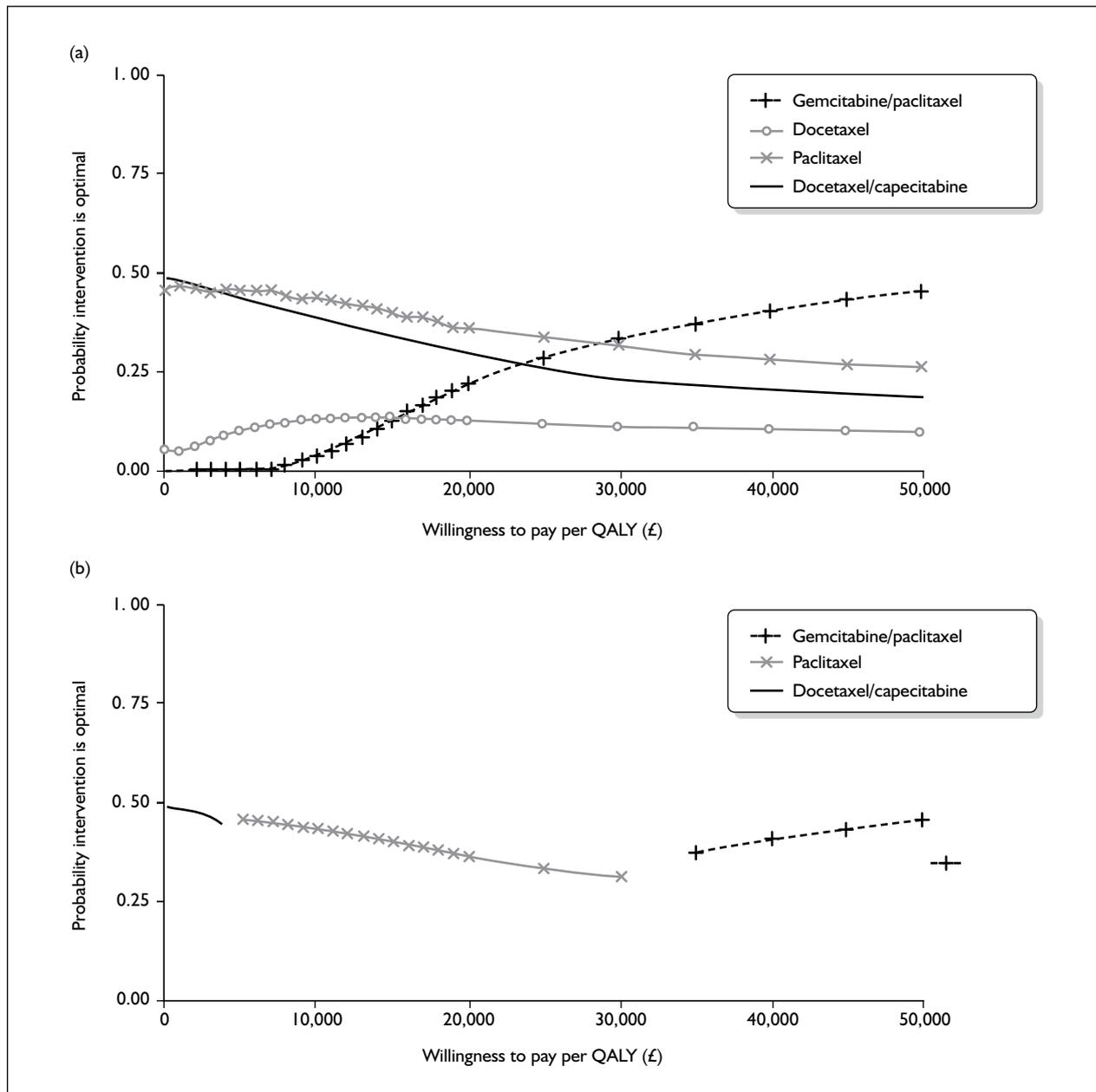
### Weaknesses

The manufacturer performed a systematic review, which identified two abstracts (and missed a third) reporting interim results of the JHQQ trial. However, commercial-in-confidence data were presented as ‘confidential – not to be cited’ in the manufacturer’s submission; they are due to be published later this year.

Although a systematic review was carried out, there is contradiction and a lack of methodological rigour regarding a number of the references included for the economic evaluation. The ERG therefore considers that, although the model’s

structure is appropriate, selection bias could potentially have affected the data inputs for the economic model.

The attempted indirect comparison in the clinical effectiveness section simply tabulates data from the JHQQ trial and the two comparator trials. It might have been possible to perform a formal statistical indirect comparison of the JHQQ trial with that by Jones and colleagues<sup>8</sup> (docetaxel monotherapy versus paclitaxel) as they have a common comparator arm. However, differences in the patient characteristics between the trials may have invalidated such an approach.



**FIGURE 3** (a) Multiple cost-effectiveness acceptability curves (CEAC) comparing four taxane-based chemotherapy regimens. (b) CEA frontier. QALY, quality-adjusted life-year.

## Conclusions

In the absence of a randomised controlled trial (RCT) directly comparing gemcitabine with docetaxel there does not appear to be sufficient evidence to compare the relative effectiveness of these treatments. The evidence for gemcitabine's clinical effectiveness comes from an RCT comparing gemcitabine/paclitaxel with paclitaxel. However, the economic evaluation uses docetaxel as the comparator in the reference case.

The manufacturer suggests that gemcitabine should be considered as one option for first-line therapy for MBC in some patients, but does not appear to advocate that it should replace any of the current taxane treatments.

## Summary of NICE guidance issued as a result of the STA

The guidance issued by NICE in November 2006 states that:

Gemcitabine in combination with paclitaxel, within its licensed indication, is recommended as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine is also considered appropriate.

## Acknowledgement

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# Varenicline in the management of smoking cessation: a single technology appraisal

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**Declared competing interests of authors:** the authors are not aware of any competing interests

## Abstract

This paper presents a summary of the submission's evidence for the clinical effectiveness and cost-effectiveness of varenicline for smoking cessation included four studies of varenicline (one of which was commercial-in-confidence) and a meta-analysis of varenicline versus nicotine replacement therapy (NRT), bupropion and placebo. Two controlled trials of 12 weeks of varenicline versus sustained-release bupropion and placebo suggested that varenicline results in a statistically significant improvement in the odds of quitting at 12 weeks [odds ratio (OR) for quit rate during last 4 weeks of the study: 1.90–1.93 ( $p < 0.001$ ) varenicline versus bupropion; 3.85 ( $p < 0.001$ ) varenicline versus placebo). The ORs for sustained abstinence (weeks 9–52) for varenicline versus bupropion were 1.77 ( $p = 0.004$ ) and 1.46 ( $p = 0.057$ ), and for varenicline versus placebo were 2.66–3.09 ( $p < 0.01$ ). A placebo-controlled maintenance trial examined whether a further 12 weeks of varenicline would maintain the rate of abstinence among those successfully treated on one 12-week course [OR = 2.48 at week 24 for varenicline versus placebo ( $p < 0.001$ )]. The meta-analysis suggested that varenicline was superior to placebo and bupropion at 1 year and 3 months. Based on indirect comparisons, varenicline was reported to be superior to NRT when compared with placebo or all controls at 1 year and 3 months. The submission presented a state transition model to estimate the incremental cost-effectiveness of varenicline compared with bupropion, NRT and placebo. The model suggests that varenicline dominates bupropion, NRT and placebo. Treatment efficacy was based on a pooled analysis of 1-year quit rates from the varenicline clinical trials. Assuming a willingness-to-pay threshold range

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of £20,000–30,000 per quality-adjusted life-year gained, the probabilistic sensitivity analysis suggests that the probability that varenicline produces the greatest amount of net benefit is 0.70. Weaknesses of the manufacturer's submission include the assumption that only a single quit attempt using a single smoking cessation intervention is made, the presence of multiple computational errors and a limited sensitivity analysis. In conclusion, varenicline is likely to be clinically and cost-effective for smoking cessation assuming that each user makes a single quit attempt. The key area of uncertainty concerns the long-term experience of subjects who have remained abstinent from smoking beyond 12 months. The guidance issued by the National Institute for Health and Clinical Excellence in July 2007 states that varenicline is recommended within its licensed indications as an option for smokers who have expressed a desire to quit smoking and that varenicline should normally be prescribed only as part of a programme of behavioral support.

## Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, for which most of the relevant evidence lies with one manufacturer or sponsor (Pfizer). Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA of varenicline for smoking cessation.

## Description of the underlying health problem

Three million deaths a year worldwide can be

attributed to smoking,<sup>1</sup> and it is a major etiological factor for lung cancer, cardiovascular disease and peripheral vascular disease. Smoking also causes respiratory disease, such as chronic obstructive pulmonary disease (COPD), including bronchitis and emphysema. Half of all smokers in the UK die prematurely of a smoking-related ailment, with the decrease in life expectancy for regular smokers under the age of 35 years who continue to smoke estimated to be about 8 years ([www.nice.org.uk](http://www.nice.org.uk); accessed 15 December 2006).<sup>2</sup> The annual cost to the NHS of treating patients with smoking-related disease is around £1.5 billion.<sup>3</sup>

The proportion of adults in the UK who smoked cigarettes fell substantially during the 1970s and the early 1980s, after which it declined gradually until the early 1990s. Since this time it has plateaued, and in 2003–4 26% of adults aged 16 or over smoked cigarettes, an identical rate to that in 2002/3. The gap between men and women smokers has narrowed, and in 2003–4 28% of men and 24% of women were cigarette smokers. In July 2004 the government set a new target to reduce the overall proportion of cigarette smokers in England to 21% or less by 2010 ([www.statistics.gov.uk](http://www.statistics.gov.uk); accessed 15 December 2006).

Inhaled nicotine is strongly addictive and stopping smoking results in craving and withdrawal symptoms. However, smokers who quit before the age of about 35 years have a life expectancy only slightly less than those who have never smoked. Even cessation in middle age improves health and substantially reduces the excess risk of death, and quitting at any age provides both immediate and long-term health benefits. It is estimated that about 4 million smokers a year attempt to quit, but that only 3–6% of these (1–2% of all smokers) succeed ([www.nice.org.uk](http://www.nice.org.uk); accessed 15 December 2006).

Smokers have a range of options when the decision has been made to attempt to quit, the most common of which is unaided cessation, so-called 'cold turkey'. Other alternatives are bupropion, counselling with or without pharmacotherapy, hypnosis, acupuncture or use of over-the-counter nicotine replacement therapy (NRT).

GPs in the UK maintain a record of the smoking habits of all patients and are encouraged to offer advice and support to smokers to help them quit. Smokers can be referred to a local smoking cessation service where counselling will be offered and, if deemed appropriate, pharmacological support prescribed.

## Scope of the ERG report

The principal research question is whether varenicline is clinically effective and cost-effective compared with NRT or bupropion, an antidepressant, in supporting smoking cessation in adults who smoke tobacco products and have indicated a desire to quit smoking. Varenicline is a selective nicotinic receptor partial agonist that is indicated for smoking cessation in adults. The recommended dose is 1 mg of varenicline twice daily following a 1-week titration period. At the time of writing of the ERG report the cost of varenicline was £1.95 per day per patient.

Key outcomes presented within the sponsor submission include: survival, morbidity related to smoking, quit rates, adverse effects of treatment, health-related quality of life and cost-effectiveness. Clinical effectiveness outcomes are presented only for the intention to treat populations within the clinical trials; subgroup analyses are not presented.<sup>4</sup>

## Methods

The ERG report<sup>3</sup> comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process.

The sponsor commissioned an independent review group to undertake a meta-analysis and indirect comparison of controlled trials. Aside from the indirect comparison, the McMaster review makes comparisons of clinical effectiveness previously undertaken in three (publicly funded) Cochrane reviews, the latest versions of which are by Silagy *et al.*<sup>5</sup> (NRT), Hughes *et al.*<sup>6</sup> (bupropion) and Cahill *et al.*<sup>7</sup> (varenicline). As these reviews were all relatively recent we did not undertake new searches. We used the Cochrane Tobacco Addiction Group to identify studies that were inappropriately excluded from the review. The ERG reran the meta-analyses and undertook an additional indirect comparison to validate the manufacturer's estimates of treatment effect.

A mathematical model to estimate the incremental cost-effectiveness of varenicline versus bupropion, NRT and placebo was presented by the sponsor; this model was made available to the ERG for scrutiny. The model was based upon an earlier smoking cessation model [the Health and Economic Consequences of Smoking (HECOS) model] previously reported by Orme *et al.*<sup>8</sup> The

model uses the state transition methodology to simulate the experiences of individuals following an initial attempt to quit smoking. The model includes five morbidities that are related to smoking: COPD, lung cancer, coronary heart disease (CHD) events, asthma and stroke. These morbidities were included in the model as they were reported by the sponsor to account for the greatest mortality, morbidity and cost associated with smoking. The ERG critically appraised the sponsor's model and undertook a detailed assessment of its internal and external consistency.

## Results

### Summary of submitted clinical evidence

The sponsor submission reported the methods and results of four clinical studies of varenicline. The first two studies were double-blind controlled trials of 12 weeks of varenicline versus sustained-release bupropion and placebo. These studies suggested that varenicline results in a statistically significant improvement in the odds of quitting at 12 weeks. The odds ratio (OR) for the quit rate during the last 4 weeks of the study was 1.90–1.93 ( $p < 0.001$ ) for varenicline versus bupropion, and 3.85 ( $p < 0.001$ ) for varenicline versus placebo. In terms of sustained abstinence (weeks 9–52), the OR for varenicline versus bupropion was significantly different in one study (OR = 1.77,  $p = 0.004$ ), but not in another (OR = 1.46,  $p = 0.057$ ). When compared against placebo, the OR for the sustained quit rate for varenicline versus placebo was 2.66–3.09; this improvement was statistically significant in both studies ( $p < 0.01$ ). The third study was a placebo-controlled maintenance trial that examined whether a further 12 weeks of varenicline treatment would maintain the rate of abstinence among those successfully treated on one 12-week course of varenicline. At week 24, patients who received varenicline had an OR of 2.48 of maintaining abstinence compared with patients who received placebo; this improvement was statistically significant ( $p < 0.001$ ). For weeks 13–52, the improvement remained significant (OR = 1.34,  $p < 0.02$ ). The fourth study was an open-label study that compared 12 weeks of varenicline therapy with 10 weeks of NRT transdermal patch. The results of this study were held as commercial-in-confidence.

The sponsor submission also detailed a large meta-analysis of varenicline versus NRT, bupropion and placebo. This analysis suggested that varenicline was superior to placebo and bupropion at 1 year and also at approximately 3 months. Based on

indirect comparisons, varenicline was reported to be superior to NRT when compared with placebo controls or to all controls at 1 year and at 3 months.

### **Summary of submitted cost-effectiveness evidence**

The submission reports the methods and results of a state transition model (the Benefits of Smoking Cessation on Outcomes or BENESCO model) to estimate the incremental cost-effectiveness of varenicline compared with bupropion, NRT and placebo. The model suggests that varenicline dominates (i.e. is more effective and less expensive than) bupropion, NRT and placebo. Treatment efficacy for each of the interventions is based on the results of a pooled analysis of 1-year quit rates sourced from the clinical trials of varenicline. Beyond this point the model assumes that short-term efficacy translates into long-term health gains and associated cost savings. This assumption of sustained benefit is subject to a substantial degree of uncertainty. Shorter time horizons may be less uncertain, but may underestimate the benefits of varenicline. Longer time horizons provide more favourable cost-effectiveness estimates for varenicline yet are subject to a much greater degree of uncertainty. Assuming a willingness-to-pay threshold range of £20,000–30,000 per quality-adjusted life-year gained, the probabilistic sensitivity analysis suggests that the probability that varenicline produces the greatest amount of net benefit is estimated to be 0.70.

### **Commentary on the robustness of submitted evidence**

#### **Strengths**

The manufacturers have recruited a team of researchers from McMaster University (Hamilton, Ontario) to produce and publish a systematic review, which they have used as the basis for their analysis.

The structural assumptions included in the submission model appear to be intuitively sensible, and the costs and consequences of most important smoking-related morbidities (lung cancer, COPD, asthma, CHD and stroke) are included in the analysis.

#### **Weaknesses**

The manufacturer's use of indirect comparisons is inappropriate because they had access to a direct comparison (the commercial-in-confidence randomised control trial). The indirect comparison was also flawed because it was based on a meta-analysis that inappropriately included and excluded studies, the effect of which would have been to exaggerate the effect size of varenicline.

The model assumes only a single quit attempt using a single smoking cessation intervention (varenicline, bupropion, NRT or placebo). In reality, smokers may attempt to quit more than once using several smoking cessation technologies. The costs and health outcomes of repeated quit attempts are not considered within the evaluation.

The model extrapolates lifetime outcomes for subjects attempting to quit smoking (up to 81 years of extrapolated costs and consequences) based on a pooled analysis of 1-year efficacy outcomes from clinical trials.

The model uses a large number of parameter values derived from US studies that may not reflect the smoking/abstinence behaviour of the population of England and Wales.

Methods for identifying and selecting costs and health utilities associated with morbidities are not reported or justified within the sponsor submission.

The presence of multiple computational errors should be borne in mind when considering cost-effectiveness results reported within the sponsor submission. Most notable was a structural error that violated a key condition of the Markov approach; consequently, the probability of being in any health state at any point in time does not consistently sum to 1 over the duration of the model time horizon.

The sensitivity analysis presented within the submission is very narrow and underestimates the true uncertainty surrounding the incremental cost-effectiveness of varenicline. In particular, the probabilistic sensitivity analysis was restricted to a limited number of parameters and is inherently flawed. The true uncertainty surrounding the incremental cost-effectiveness of varenicline has not been appropriately addressed within the submission.

The external validity of the model has not been demonstrated by the sponsor.

## Conclusions

Varenicline is likely to be clinically effective and cost-effective if one assumes, as the clinical trials and the manufacturer's model do, that each user makes a single quit attempt. The key area of uncertainty concerns the long-term experience of subjects who have remained abstinent from smoking beyond 12 months. The health economic model makes an assumption of sustained benefit for the remaining 81 years of the time horizon. The validity of the assumption of sustained benefit between treatment groups is unclear.

## Summary of NICE guidance issued as a result of the STA

At the time of writing the guidance document issued by NICE in July 2007<sup>9</sup> states that:

1. Varenicline is recommended within its licensed indications as an option for smokers who have expressed a desire to quit smoking.
2. Varenicline should normally be prescribed only as part of a programme of behavioral support.

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# Alteplase for the treatment of acute ischaemic stroke: a single technology appraisal

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## Abstract

This paper presents a summary of the evidence review group report into the clinical effectiveness and cost-effectiveness of alteplase for the treatment of acute ischaemic stroke, in accordance with the licensed indication, based upon the evidence submission from the manufacturer to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The submitted clinical evidence included several randomised controlled trials indicating that, in highly selected patients, alteplase administered at a licensed dose within 3 hours of the onset of acute ischaemic stroke is associated with a statistically significant reduction in the risk of death or dependency at 3 months compared with placebo, despite a significantly increased risk of symptomatic intracranial haemorrhage within the first 7–10 days. Data from the National Institute of Neurological Disorders and Stroke (NINDS) trial suggest that the benefit of treatment is sustained at 6 and 12 months. However, data from observational studies suggest that few patients with acute ischaemic stroke will be eligible for alteplase therapy under the terms of the current licensing agreement. In particular, many patients will be excluded by virtue of their age, and many more by the restriction of therapy to patients in whom treatment can be initiated within 3 hours of symptom onset. The manufacturer's submission included a state transition model evaluating the impact of treatment with alteplase within 3 hours of onset of stroke symptoms compared to standard treatment reporting that, in the base-case analysis, alteplase was both less costly and more effective than standard treatment. This increased to a maximum of approximately £4000 upon one-way sensitivity analysis of the parameters. The

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probabilistic sensitivity analysis presented within the submission suggests that the probability that alteplase has a cost-effectiveness ratio greater than £20,000 per quality-adjusted life-year (QALY) gained is close to 1 (0.99). The results of the short-term model demonstrate that alteplase is cost-effective over a 12-month period, with an incremental cost-effectiveness ratio of £14,026 per QALY gained. This increased to a maximum of £50,000 upon one-way sensitivity analysis of the parameters. At 12 months, the probabilistic sensitivity analysis presented within the submission suggests that the probability that alteplase has a cost-effectiveness ratio greater than £20,000 per QALY gained is approximately 0.7. The guidance issued by NICE in April 2007 as a result of the STA states that alteplase is recommended for the treatment of acute ischaemic stroke only when used by physicians trained and experienced in the management of acute stroke and in centres with the required facilities.

## Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, for which most of the relevant evidence lies with one manufacturer or sponsor.<sup>1</sup> Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG); an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA of alteplase for the treatment of acute ischaemic stroke.<sup>2</sup>

## Description of the underlying health problem

'Stroke' is a term used to refer to the clinical syndrome that results from the interruption of the blood supply to an area of the brain. Approximately 85% of all strokes occur when the

blood supply to the brain is blocked, either by a blood clot or by narrowing of the blood vessels: such strokes are termed *ischaemic* strokes.<sup>3</sup> Most other strokes occur when a blood vessel in or around the brain ruptures: these are termed *haemorrhagic* strokes.<sup>3</sup>

In England, stroke is one of the top three causes of death.<sup>3</sup> It is also the leading cause of adult disability;<sup>4</sup> at least 300,000 people in England live with moderate to severe disabilities as a result of stroke.<sup>3</sup>

Alteplase is an enzyme that causes blood clots to dissolve. It is therefore of potential value in ischaemic stroke because it may enable the restoration of the blood supply to the affected area of the brain. However, it is also associated with a risk of intracerebral haemorrhage. Moreover, because it dissolves blood clots, its use in haemorrhagic stroke is potentially fatal or disabling. Alteplase is not licensed for use in patients older than 80 years.

## Scope of the evidence review group report

The principal research question relates to the clinical effectiveness and cost-effectiveness of alteplase for the treatment of acute ischaemic stroke. The manufacturer's scope restricts the intervention to intravenous alteplase given to adults with ischaemic stroke within 3 hours of symptom onset, in a secondary care setting, under the guidance of experienced stroke and neuro-imaging specialists, and after prior exclusion of intracranial haemorrhage. The scope restricts the comparator to placebo or standard medical and supportive management without thrombolysis. This is because no thrombolytic treatment other than alteplase is licensed in the UK for use in acute ischaemic stroke, and other stroke treatment or prevention therapies that function in different ways would not be relevant comparators.

The single most clinically relevant and important outcome measure is the proportion of patients suffering death or dependency (reported as a score of 3–6 inclusive on the modified Rankin scale). This captures in one measure alteplase's impact on both the proportion of patients making a good functional recovery and the proportion suffering asymptomatic intracranial haemorrhage (SICH), an outcome associated with death or increased disability. Other relevant outcomes include survival; neurological deficit; mental health (including anxiety and depression); adverse effects of

treatment (including bleeding events); and health-related quality of life. Economic outcomes include cost per quality-adjusted life-year (QALY) gained.

## Methods

The ERG report comprised a critical review of the evidence for the clinical evidence and cost-effectiveness of the technology based upon the manufacturer's submission to NICE as part of the STA process. In addition, in an attempt to ensure that no relevant randomised controlled trials were overlooked, the ERG reran in MEDLINE both the manufacturer's search strategy and the search strategy previously used in the Cochrane review of thrombolysis for acute stroke.<sup>5</sup> This established that, while the manufacturer's MEDLINE search strategy identified the key publication relating to each of the included trials, it did not identify the important reanalysis of the National Institute of Neurological Disorders and Stroke (NINDS) study,<sup>6</sup> two supplementary analyses that the submission identified as relevant,<sup>7,8</sup> or the Cochrane review<sup>5</sup> on which the submission drew heavily.

The manufacturer's submission also drew on evidence from a number of observational studies. It is not clear how these were identified. The submission implied that the same search strategies were used to identify both randomised controlled trials and studies investigating or evaluating service delivery or provision of technology. However, as the manufacturer's EMBASE and MEDLINE search strategies both contained a term limiting the search to clinical trials, neither would have reliably identified observational studies. Supplementary data provided by the manufacturer stated that a systematic search was undertaken for observational studies, but did not provide a relevant search strategy and, within the time available, the ERG was not able to conduct supplementary searches to ensure that relevant observational studies were not missed. The manufacturer's exclusion criteria arbitrarily excluded observational studies that were small (< 100 patients) or added nothing to the conclusions that could be drawn from the larger studies. No indication was given as to the number of studies that were excluded for these reasons. Inclusion of those studies that were excluded because they did not contain a new message would have enabled estimation of the strength of evidence for the messages contained in the included studies.

The manufacturer did not undertake independent meta-analyses, but referred to those undertaken for the Cochrane review (which were calculated as odds

ratios using the Peto fixed-effects method),<sup>5</sup> and the pooled analysis of the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) A and B, European Cooperative Acute Stroke Study (ECASS) II, and NINDS 1 and 2 trials<sup>8</sup> (which again used the odds ratio). The ERG therefore carried out meta-analyses to explore the effects of excluding a study (ECASS I) that used an unlicensed dose of alteplase and of presenting the results as relative risks, as required by NICE, rather than as Peto odds ratios.

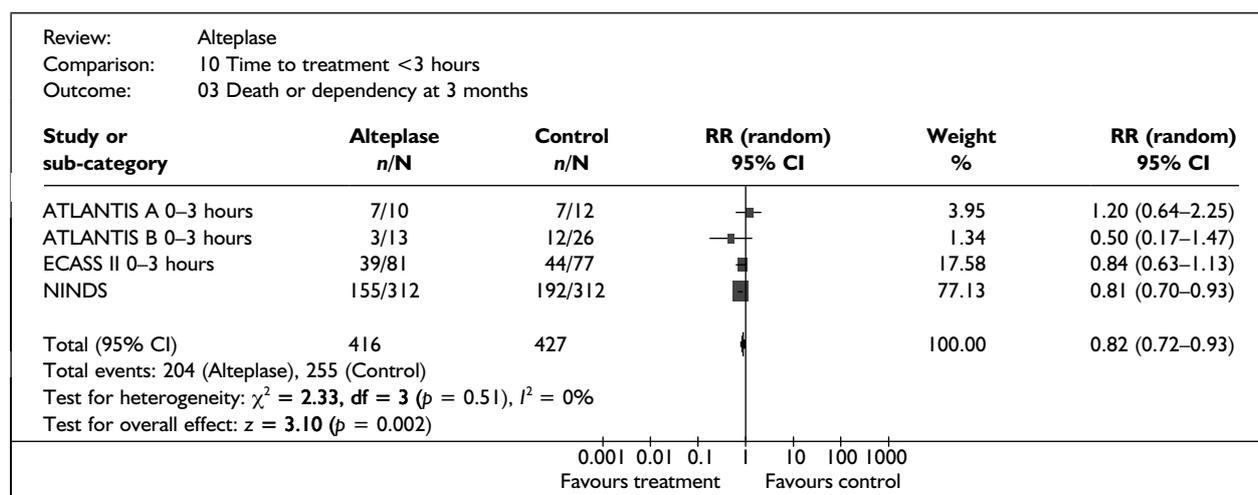
The ERG had concerns about some of the methods used by the manufacturer in the cost-effectiveness modelling. This included the use of odds ratios in the model instead of relative risks, and the length of the model cycle time. The manufacturers were asked to justify the use of these methods and were requested to perform additional analyses using methods considered by the ERG to be more appropriate. In all cases the manufacturers complied with these requests. The additional analyses showed no meaningful differences in either the direction or the magnitude of the results compared with the original work.

## Results

### Summary of submitted clinical evidence

Evidence from randomised controlled trials indicates that, in highly selected patients, alteplase administered at a licensed dose within 3 hours of the onset of acute ischaemic stroke is associated with a statistically significant reduction in the risk of death or dependency at 3 months compared with placebo [relative risk (RR) 0.82, 95% confidence interval (CI) 0.72 to 0.93, absolute risk reduction 11%; *Figure 1*], despite a significantly increased risk of SICH within the first 7–10 days [RR 4.24, 95% confidence interval (CI) 1.52 to 11.83, absolute risk increase 6%]. Data from the NINDS trial, the only study which presented data relating to a time point later than 3 months from stroke onset, suggest that the benefit of treatment is sustained at 6 and 12 months.

However, data from observational studies suggest that few patients with acute ischaemic stroke will be eligible for alteplase therapy under the terms of the current licensing agreement. In particular, many patients will be excluded by virtue of their age, and many more by the restriction of therapy to patients in whom treatment can be initiated within 3 hours of symptom onset. In principle, it may be possible to increase the proportion of patients who



**FIGURE 1** All patients treated within 3 hours: death or dependency at 3 months. ATLANTIS, Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke; CI, confidence interval; ECASS, European Cooperative Acute Stroke Study; NINDS, National Institute of Neurological Disorders and Stroke; RR, relative risk.

both reach hospital and are assessed for alteplase therapy within 3 hours, but to do so would require substantial investment in public education, and possibly also service reconfiguration. Moreover, the risk of major protocol violations in the administration of alteplase should be noted. In two comprehensive independent community-based studies, the Cleveland<sup>9</sup> and Connecticut<sup>10</sup> studies (of which only the former was cited in the manufacturer's submission), such violations, most of which appeared to have been accidental,<sup>10</sup> affected 67% of patients receiving alteplase in Connecticut and 50% in the Cleveland area.

### Summary of submitted cost-effectiveness evidence

A state transition model was used to evaluate the impact of treatment with alteplase within 3 hours of onset of stroke symptoms compared to standard treatment. The time horizon for this long-term model was 40 years. In addition, a short-term (12-month follow-up) model is included. The model is based on work published as part of the Health Technology Appraisal (HTA) of thrombolytic therapy by Sandercock *et al.*<sup>11</sup>

The main data source for the model is a Cochrane review meta-analysis of the NINDS,<sup>12</sup> ECASS I,<sup>13</sup> ECASS II,<sup>14</sup> ATLANTIS A,<sup>15</sup> ATLANTIS B<sup>16</sup> and Haley *et al.*<sup>17</sup> studies. Outcomes from this meta-analysis are extrapolated over a time horizon of 40 years in order to assess the long-term benefits and costs of alteplase. The model takes into account the increased rate of haemorrhage seen in alteplase-treated patients.

The health states used within the model and the costs and utilities associated with each health state are considered to be appropriate for the required analysis.

The Boehringer Ingelheim model estimated that, in the base-case analysis, alteplase was both less costly and more effective than standard treatment. This increased to a maximum of approximately £4000 upon one-way sensitivity analysis of the parameters.

The probabilistic sensitivity analysis presented within the submission suggests that the probability that alteplase has a cost-effectiveness ratio greater than £20,000 per QALY gained is close to 1 (0.99).

The results of the short-term model demonstrate that alteplase is cost-effective over a 12-month period, with an incremental cost-effectiveness ratio (ICER) of £14,026 per QALY gained. This increased to a maximum of £50,000 upon one-way sensitivity analysis of the parameters.

At 12 months, the probabilistic sensitivity analysis presented within the submission suggests that the probability that alteplase has a cost-effectiveness ratio greater than £20,000 per QALY gained is approximately 0.7.

### Commentary on the robustness of submitted evidence

The evidence for the clinical effectiveness of alteplase when used within the 3-hour licensed window for the treatment of acute ischaemic

stroke is not robust and, as noted in a recent Cochrane review,<sup>5</sup> should be treated with extreme caution. It is based on a total of only 416 patients who received the current licensed dose of alteplase within the 3-hour time window (see *Figure 1*). Moreover, 312 of these patients were enrolled in one trial, the NINDS trial, in which a substantial imbalance in baseline stroke severity, a key prognostic factor, favoured alteplase.<sup>11</sup> An additional analysis undertaken by the Cochrane reviewers suggested that the imbalance probably caused the effect of alteplase on death and dependency to be overestimated by around 3%.<sup>5</sup> However, a subsequent independent analysis of the NINDS data considered that there was no evidence that the imbalance in the distribution of baseline NIHSS (National Institute for Health Stroke Scale) scores had either a statistically or a clinically significant effect on the trial results.<sup>6</sup> The randomised trials were not stratified by any potential prognostic factor other than time to treatment, and therefore any post hoc analyses designed to explore the extent to which different groups might benefit from therapy can only be regarded as hypothesis generating. Nonetheless, it is interesting to note that a pooled analysis of data from the ATLANTIS A and B, ECASS II, and NINDS trials<sup>18</sup> appeared to indicate that alteplase therapy was of significant benefit in women, but not in men (*Table 1*).

The model structure is appropriate and allows sensitivity analysis to be carried out easily. Given a 40-year time horizon, one-way sensitivity analysis suggests that variations in the majority of the parameters do not have a large effect upon the ICER. Alteplase dominates (i.e. costs less and is more effective than) standard treatment; potential parameter variations are unlikely to increase the ICER beyond the currently accepted threshold values.<sup>19</sup>

The results at 12 months, when the full lifetime costs associated with disability due to stroke

and the QALY gain associated with increased survival are not captured, indicate that alteplase is still cost-effective. No weaknesses in the model structure were identified that would alter the results significantly. However, the model rests on evidence for the clinical effectiveness of alteplase administered with 3 hours of symptom onset which, as noted above, is not robust. Moreover, although the risks and benefits of alteplase are unknown beyond 12 months, the manufacturer's health economic model has used a lifetime horizon of 40 years. In addition, the economic evaluation relies heavily on the results of the NINDS trial in which, as noted above, a substantial imbalance in baseline stroke severity favoured alteplase. Thus, the results of the cost-effectiveness analysis should be treated with extreme caution.

One important issue which is not explicitly taken into account in the economic modelling is the possible impact of trying to increase the number of patients who could be treated within the 3-hour window. This could have a significant cost impact to the NHS in terms of both the need to educate the public on the importance of early treatment and potential substantial service reconfiguration.

## Conclusions

The evidence from randomised controlled trials suggests that, in highly selected patients, alteplase administered within 3 hours of the onset of acute ischaemic stroke is associated with a statistically significant reduction in the risk of death or dependency at 3 months compared with placebo, despite the statistically significant increase in the risk of early SICH. However, this evidence should be treated with extreme caution as it is based on a total of only 416 patients who received the current licensed dose of alteplase, and 312 of these patients were included in a trial in which a substantial imbalance in baseline stroke severity, a key prognostic factor, favoured alteplase.

**TABLE 1** Proportion of patients with a favourable outcome at 90 days [modified Rankin Scale (mRS) 0–1]: pooled analysis of data from the ATLANTIS A and B, ECASS II, and NINDS studies<sup>18</sup>

	Alteplase	Placebo	p-value (alteplase vs placebo)
Men	38.5%	36.7%	0.52
Women	40.5%	30.3%	<0.001
p-value (men vs women)	0.50	0.03	

Kent *et al.*<sup>18</sup> did not present these data in such a way as to allow the calculation of relative risks and confidence intervals.

Observational studies suggest that few patients with ischaemic stroke will be eligible for alteplase therapy under the terms of the current licensing agreement. In particular, many patients will be excluded because they are older than 80 years, and many more will be excluded because treatment cannot be initiated within 3 hours of symptom onset. Any increase in the number of patients in whom treatment can be initiated within 3 hours is likely to require substantial efforts in terms of public education and service reconfiguration.

The critical appraisal of the Boehringer Ingelheim model undertaken by the ERG suggests that alteplase can result in long-term cost savings and is more effective than standard treatment.

In the short-term, when the full lifetime costs associated with disability due to stroke and the QALY gain associated with increased survival are not captured, alteplase was still shown to be cost-effective compared to standard treatment.

## Summary of NICE guidance issued as a result of the STA

At the time of writing, the final appraisal determination document issued by NICE in April 2007 states that:

Alteplase is recommended for the treatment of acute ischaemic stroke when used by physicians trained and experienced in the management of acute stroke. It should only be administered in centres with facilities that enable it to be used in full accordance with its marketing authorisation.

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## Rituximab for the treatment of rheumatoid arthritis

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### Abstract

This paper presents a summary of the evidence review group's critical review of the evidence for the clinical effectiveness and cost-effectiveness of rituximab for the treatment of severe rheumatoid arthritis (RA) following failure of previous therapy, including one or more tumour necrosis factor- $\alpha$  inhibitors (TNFi), compared with current standards of care, based upon the manufacturer's submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The submission's clinical evidence came from one randomised, placebo-controlled, double-blind trial (REFLEX – Random Evaluation of Long-term Efficacy of Rituximab in Rheumatoid Arthritis) comparing rituximab plus methotrexate (MTX) with placebo plus MTX in 517 patients with long-standing refractory RA. Rituximab plus MTX was more effective than placebo plus MTX across a range of primary and secondary outcome measures, e.g. American College of Rheumatology (ACR) responses, Health Assessment Questionnaire (HAQ). However, this evidence cannot be used directly to address the manufacturer's analysis of the decision problem because, in the REFLEX trial, rituximab was not compared with a relevant comparator (e.g. leflunomide or second or third TNFi). Long-term efficacy data for retreatment with rituximab are favourable, with an estimated mean time to retreatment of 307 days ( $n = 164$ ). Evidence from a further five trials is presented as the basis for indirect comparisons with other disease-modifying antirheumatic drugs (DMARDs); however, it is not clear that all relevant clinical studies

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Discussion of ERG reports is invited. Visit the HTA website correspondence forum (<http://www.hta.ac.uk/correspond>).

have been included in the indirect comparison exercise, the rationale for the choice of indirect comparison method adopted is unclear and the indirect comparison method used to adjust the ACR responses only uses a single value for the reference placebo. The submitted microsimulation Markov model was based upon the REFLEX trial. For the 'NICE-recommended' scenario and the 'sequential TNFi' scenario, the original submission reports incremental cost-effectiveness ratios (ICERs) of £14,690 and £11,601 per quality-adjusted life-year (QALY) gained respectively. After model assumptions were adjusted to more realistic estimates by the ERG, the ICERs for the NICE-recommended scenario and the sequential use of TNFi range from £37,002 to £80,198 per QALY gained and from £28,553 to £65,558 per QALY gained respectively. The guidance issued by NICE in August 2007 states that rituximab in combination with methotrexate is recommended as an option for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to or intolerance of other DMARDs including treatment with at least one TNFi therapy.

## Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, for which most of the relevant evidence lies with one manufacturer or sponsor.<sup>1</sup> Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA of rituximab for the treatment of rheumatoid arthritis.<sup>2</sup>

## Description of the underlying health problem

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder, which is primarily characterised by inflammation and swelling of multiple synovial joints. The primary symptoms of pain, fatigue and disability are chronic and related to the underlying inflammatory disease process. Furthermore, patients with RA have a reduced life expectancy.<sup>3-7</sup> There is no cure for RA and so the therapeutic goals are a remission of symptoms involving the joints, a return of full function and the maintenance of remission.

RA affects between 0.5% and 1% of the population, equating to approximately 400,000 people in England and Wales, with the prevalence being three times higher in women than in men.<sup>8-11</sup> Diagnosis is generally between the ages of 40 and 80 years<sup>8-11</sup> and within 5 years one-third of patients are unable to work,<sup>12</sup> increasing the substantial economic burden of RA.

## Scope of the ERG report

The ERG report presents the results of the assessment of the manufacturer's (Roche Products) evidence submission regarding the use of rituximab for the treatment of severe RA following failure of previous therapy, including one or more tumour necrosis factor- $\alpha$  inhibitor (TNFi), compared with current standards of care. The report includes an assessment of both the clinical effectiveness and cost-effectiveness evidence submitted by the manufacturer.

Rituximab (known as MabThera<sup>®</sup> in the UK and Rituxan<sup>®</sup> in the USA) is a monoclonal antibody that depletes the CD20+ B cells implicated in the immunopathogenesis of RA. In July 2006 rituximab plus methotrexate (MTX) was licensed in Europe for the treatment of severe RA following the failure of conventional treatments, including at least one TNFi. The licensing submission was supported by a phase III study<sup>13</sup> comparing rituximab plus MTX with placebo plus MTX along with evidence from phase II trials.<sup>14-15</sup> It is restricted to use by specialist physicians experienced in the diagnosis and treatment of RA.

## Methods

The ERG report comprised a critical review of the evidence of the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process. The ERG assessed the quality of the manufacturer's clinical effectiveness review using a standard checklist. The ERG conducted a detailed evaluation of the manufacturer's economic model. Cost-utility estimates were recalculated taking changes in parameters and assumptions into account. For example, mortality rates, the evidence base for progression rates for Health Assessment Questionnaire (HAQ) scores, the calculation of treatment costs and errors/omissions in the estimation of inpatient costs were explored. Some other issues were identified as potentially influencing model results, and the ERG carried out sensitivity analyses to show their impact on model results.

## Results

### Summary of submitted clinical evidence

The manufacturer's submission provides clinical evidence from one randomised, placebo-controlled, double-blind trial (REFLEX – Random Evaluation of Long-term Efficacy of Rituximab in Rheumatoid Arthritis) that compares the effects of rituximab plus MTX with placebo plus MTX in a study population of 517 patients with long-standing refractory RA. Data from other randomised controlled trials (RCTs) are pooled to demonstrate the retreatment efficacy of rituximab and for the analysis of safety data. Evidence from a further five trials is presented as the basis for indirect comparisons with other disease-modifying antirheumatic drugs (DMARDs).

The results from the REFLEX trial at 24 and 48 weeks confirm that rituximab plus MTX is more effective than placebo plus MTX (*Table 1*). These findings are consistent across a range of primary and secondary outcome measures including American College of Rheumatology (ACR) responses (ACR20/50/70), disease activity score (DAS28), European League Against Rheumatism (EULAR) response, HAQ, disability index (DI) and radiographic scores. Given that the patients in the trial are difficult to treat and have severe disabling disease with marked impairment of quality of life, the results of the REFLEX trial are convincing for this trial population. However, whether or

not the patients in the REFLEX trial are similar enough to the patients described in the rituximab management strategies put forward in the manufacturer's submission is debateable, as 40% of the REFLEX trial patients had received at least two previous TNFi before receiving rituximab.

Long-term efficacy data for retreatment with rituximab from the REFLEX trial are favourable, but the results are limited by the small number of patients available for follow-up. The estimated mean time to retreatment from the REFLEX trial is 307 days ( $n = 164$ ). The available safety data from the REFLEX trial show that rituximab patients had slightly higher rates of adverse reactions than the placebo patients. The European Medicines Evaluation Agency (EMA) particularly stresses the risks of infusion reactions and infection associated with rituximab. This mirrors the belief that patients taking any of the newer biological drugs require close surveillance and monitoring.

The only RCT evidence available for rituximab is the comparison with placebo plus MTX. It is therefore appropriate for the manufacturer to conduct indirect comparisons to calculate absolute efficacy values for use in the economic model in order to answer the questions outlined in their statement of the decision problem. However, the ERG is not confident that the adjusted ACR scores described by the manufacturer are valid. In particular, it is not clear from the evidence presented by the manufacturer that all relevant clinical studies have been included in the indirect comparison exercise. The rationale for the choice of the indirect comparison method adopted is unclear and the indirect comparison method used to adjust the ACR responses only uses a single value for the reference placebo.

### Summary of submitted cost-effectiveness evidence

The economic model submitted in support of the manufacturer's submission is a microsimulation Markov model based upon the phase III RCT of rituximab plus MTX versus placebo plus MTX (REFLEX trial). Patient disease progression is tracked within the model according to HAQ score. By using microsimulation of 10,000 RA patients, patient history is kept in memory and cost-utility values are assigned to each individual at each cycle. The manufacturer concludes that rituximab is considered to be a cost-effective treatment option in RA. For the 'NICE-recommended' scenario, the original manufacturer's submission reports an incremental cost-effectiveness ratio (ICER)

TABLE 1 Key results from the REFLEX trial

Outcome <sup>a</sup>	Placebo (n = 201)	Rituximab (n = 298)
<b>Primary</b>		
ACR20 (%) 24 weeks	18	51
ACR20 (%) 48 weeks	4	19
<b>Secondary (24 weeks)</b>		
ACR50 (%)	5	27
ACR70 (%)	1	12
Change in DAS, mean (SD)	-0.4 (1.17)	-1.9 (1.6)
EULAR response (%):		
None	78	35
Moderate	20	50
Good	2	15
Change in ACR core set, mean (SD):		
Swollen joint count	-2.6 (10.35)	-10.4 (12.95)
Tender joint count	-2.7 (15.48)	-14.4 (17.48)
Patient global assessment	-5.3 (22.88)	-26.0 (29.56)
Physician global assessment	-6.2 (27.70)	-29.5 (27.40)
Health assessment questionnaire <sup>b</sup>	-0.1 (0.45)	-0.4 (0.60)
Pain assessment	-2.5 (23.30)	-23.4 (29.35)
CRP (mg/dl)	0.0 (3.59)	-2.1 (3.48)
ESR (mm/hour)	-4.1 (25.05)	-18.5 (22.56)
Change in SF-36 domains, mean (SD):		
Mental health <sup>c</sup>	1.3 (9.43)	4.7 (11.75)
Physical health <sup>d</sup>	0.9 (5.65)	5.8 (8.47)
Changes in FACIT-F, <sup>e</sup> mean (SD)	-0.5 (9.84)	-9.1 (11.3)

ACR, American College of Rheumatology; DAS, diseases activity score; EULAR, European League Against Rheumatism; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; SD, standard deviation; SF-36, Short Form-36 Health Survey.

a For SF-36 a positive change is an improvement; for all other continuous variables a negative change is an improvement.

b Clinically relevant improvement = decrease > 0.22.

c Clinically relevant improvement = increase > 6.33.

d Clinically relevant improvement = increase > 5.42.

e Clinically relevant improvement = decrease > 4.

of £14,690 per quality-adjusted life-year (QALY) gained. For the 'sequential TNFi' scenario, the ICER is estimated at £11,601 per QALY gained.

### Commentary on the robustness of submitted evidence

The main strength of the submitted evidence is that the manufacturer makes a convincing case for the use of rituximab plus MTX versus placebo plus MTX using clinical evidence from the REFLEX trial in a specific population who are difficult to treat and who have severe disabling disease with marked impairment of quality of life. However,

this evidence cannot be used directly to answer the questions raised in the manufacturer's analysis of the decision problem because, in the REFLEX trial, rituximab was not compared with a relevant comparator (e.g. leflunomide or second or third TNFi).

To compare the management strategies using rituximab described in their analysis of the decision problem the manufacturer carried out an indirect comparison exercise. However, given the criticisms previously outlined, the ERG is not confident that the adjusted ACR responses used in the economic evaluation are wholly valid.

**TABLE 2** Cost-effectiveness results incorporating the ERG corrections/amendments

Scenario	Rituximab simulation			Comparator simulation			Incremental			ICER	
	Life-years	QALYs	Costs	Life-years	QALYs	Costs	Life-years	QALYs	Costs	QALYs	Cost/QALY
Base case (no TNFi) – revised model	12.747	3.045	£41,279	12.568	2.318	£30,588	0.179	0.728	£10,691	0.728	£14,694
Base case – revised model + ERG changes	15.940	5.489	£44,636	15.890	5.157	£31,069	0.050	0.332	£13,567	0.332	£40,873
Base case – ERG changes – 50% HAQ gains	15.792	4.626	£44,793	15.767	4.456	£31,212	0.025	0.169	£13,581	0.169	£80,198
Base case – ERG changes + longer interval	15.940	5.489	£43,351	15.890	5.157	£31,069	0.050	0.332	£12,282	0.332	£37,002
Alternate (TNFi) – revised model	13.028	3.963	£69,901	12.866	3.457	£63,996	0.162	0.506	£5905	0.506	£11,666
Alternate – revised model + ERG changes	15.999	5.954	£77,701	15.947	5.684	£68,853	0.053	0.269	£8847	0.269	£32,855
Alternate – ERG changes – 50% HAQ gains	15.843	4.870	£77,800	15.823	4.737	£69,070	0.021	0.133	£8730	0.133	£65,558
Alternate – ERG changes + longer interval	15.999	5.948	£73,173	15.948	5.678	£65,456	0.051	0.270	£7717	0.270	£28,553

ERG, evidence review group; HAQ, Health Assessment Questionnaire; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years; TNFi, tumour necrosis factor- $\alpha$  inhibitor.

**Note:** all results are discounted at 3.5% per annum.

The ERG identified problems with the manufacturer's submitted model in two stages. Early examination by the ERG of the submitted economic model identified some aspects of its implementation that caused concern as to its reliability for generating estimates of cost-effectiveness. The manufacturer then submitted a revised model and addressed some of the ERG's concerns. However, the ERG subsequently identified a number of additional clinical and economic issues that called into question the validity of key assumptions in the revised economic model, and the credibility of the ICERs generated. In particular, the ERG commented upon the use of evidence for progression rates for HAQ scores, the calculation of treatment costs and the estimated duration of effective treatment for each of the active agents considered.

Most importantly, the ERG questioned whether the size of benefit from each RA treatment is overstated, because loss of efficacy is assumed to be instantaneous rather than cumulative. The manufacturer's probabilistic sensitivity analyses (original and revised), because of limitations described by the ERG, were also considered to be unreliable aids to decision-making.

In summary, after model assumptions were adjusted to more realistic estimates by the ERG, the ICER for the NICE-recommended scenario ranges from £37,002 per QALY gained to £80,198 per QALY gained and the ICER for the sequential use of TNFi ranges from £28,553 per QALY gained to £65,558 per QALY gained (Table 2).

## Conclusions

The consequences of the corrections and amendments made by the ERG demonstrate that the economic results for the use of rituximab no longer appear as unequivocally advantageous as suggested in the manufacturer's submission, and may more reasonably be termed 'borderline' at best. There remain important areas in which there is substantial uncertainty, which could easily invalidate economic results generated by the manufacturer's model, most especially in relation to the long-term progression of disease and its effect on HAQ scores, and the duration of effective treatment for each of the active agents considered.

The ERG concludes that the robustness of the evidence base used in the manufacturer's economic model is uncertain.

## Summary of NICE guidance issued as a result of the STA

At the time of writing the guidance issued by NICE (August 2007) states that:

Rituximab in combination with methotrexate is recommended as an option for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to or intolerance of other disease-modifying antirheumatic drugs (DMARDs), including treatment with at least one tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) inhibitor therapy.

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## Omalizumab for the treatment of severe persistent allergic asthma

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**Declared competing interests of authors:** none

### Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of omalizumab for the treatment of chronic severe persistent allergic asthma, in accordance with the licensed indication, based upon the evidence submission from Novartis to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The clinical evidence comes from a randomised controlled trial comparing omalizumab as an add-on to standard therapy with placebo and standard therapy over a 28-week treatment period. For the primary outcome of the rate of clinically significant asthma exacerbations, there was no statistically significant difference between treatment groups. However, after making a post hoc adjustment for a suggested 'clinically relevant' imbalance between trial arms in baseline exacerbation rate, the difference became marginally statistically significant. In terms of secondary outcomes, there were statistically significant differences favouring omalizumab over placebo in total emergency visits, Asthma Quality of Life Questionnaire scores, total symptom scores and lung function. Adverse events appeared to be similar between the trial arms. Results from three other publications are included in the manufacturer's submission as supporting evidence for the effectiveness of omalizumab, despite not meeting the inclusion criteria which adhere strictly to the licensed indication. The ERG checked and provided commentary on the manufacturer's model using standard checklists as well as undertook one-way sensitivity analysis, scenario analysis and a probabilistic sensitivity analysis.

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Discussion of ERG reports is invited. Visit the HTA website correspondence forum ([www.hta.ac.uk/correspond](http://www.hta.ac.uk/correspond)).

The cost-effectiveness analysis estimates the incremental costs and consequences of omalizumab as an add-on to standard therapy. The base-case analysis of the trial's primary intention-to-treat population estimates a cost per quality-adjusted life-year of £30,647. The ERG conducted one-way sensitivity analyses for parameters omitted from the manufacturer's submission sensitivity analysis. The results were most sensitive to variation in the utility values for omalizumab responders, and the unit cost of omalizumab. The guidance issued by NICE in November 2007 as a result of the STA states that omalizumab is recommended as a possible treatment for adults and young people over 12 years with severe persistent allergic asthma when their asthma meets certain conditions. Omalizumab treatment should be given along with the person's current asthma medicines. It should be prescribed by a doctor who is experienced in asthma and allergy medicine at a specialist centre. If omalizumab does not control the asthma after 16 weeks, treatment should be stopped.

## Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS which is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor.<sup>1</sup> Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG); an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA, omalizumab for severe persistent allergic asthma.

## Description of the underlying health problem

Asthma is characterised by symptoms such as dyspnoea, chest tightness, wheezing and cough associated with variable airflow obstruction and airway hyper-responsiveness. The development of

asthma occurs when a person comes into contact with a trigger; the bronchioles (small airways in the lungs) become inflamed, swollen and constricted and excess mucus is produced, which has an effect on the person's airway structure and function.

Asthma attacks vary in frequency and severity. Some people who have asthma are mostly symptom-free, with only occasional episodes of shortness of breath. Other people cough and wheeze most of the time and may have severe attacks after viral infections, exercise or irritants, including cigarette smoke; however, the absence of a cough or wheeze does not mean the attack is not severe. Asthma can have an allergic component resulting in overproduction of human immunoglobulin E (IgE) in response to environmental allergens, e.g. pollen, house dust mite. IgE binds to cell membrane receptors, resulting in the release of inflammatory mediators.

There are approximately 5.2 million people with asthma in the UK (4.7 million in England and Wales). The total for the UK includes 590,000 teenagers with asthma. Approximately 5% of asthma patients have severe asthma.

Current British guidelines from the British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) recommend a stepwise approach to treatment.<sup>2</sup> Control is maintained by stepping up treatment as necessary and stepping down when control is good.

## Scope of the evidence review group report

The ERG critically evaluated the evidence submission from Novartis on the use of omalizumab for the treatment of chronic severe persistent allergic asthma.

Omalizumab has a marketing authorisation for add-on therapy to improve asthma control in adult and adolescent patients (12 years of age and above) with severe persistent allergic asthma and ALL of the following:

- a positive skin test or in vitro reactivity to a perennial aeroallergen
- reduced lung function (forced expiratory volume in 1 second; FEV<sub>1</sub> < 80%), frequent daytime symptoms or night-time awakenings, multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids (ICS), plus a long-acting inhaled beta2-agonist (LABA)

- convincing IgE-mediated asthma.

The intervention specified in the decision problem was omalizumab as an add-on therapy to standard therapy, used within its licensed indication. The comparator was treatment without omalizumab. This means standard treatment such as ICS in combination with LABA, plus other medication as necessary in accordance with the BTS/SIGN guidelines. The population was adults and adolescent patients (12 years of age and above) with severe persistent allergic asthma under the conditions specified in the marketing authorisation. The outcome measures included objective measures of lung function [e.g. FEV<sub>1</sub>, peak expiratory flow (PEF)], symptom-free days and nights, incidence of acute exacerbations (e.g. unscheduled contact with health-care professional; hospitalisation or visit to accident and emergency department), levels of ICS, use of oral corticosteroids, reduction in IgE levels, adverse effects of treatment, health-related quality of life and mortality.

## Methods

The ERG report comprised a critical review of the evidence for the clinical evidence and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process.

The ERG checked the literature searches and applied the NICE critical appraisal checklist to the included studies and checked the quality of the manufacturer's submission with the Centre for Reviews and Dissemination (CRD) quality assessment criteria for a systematic review. In addition, the ERG checked and provided commentary on the manufacturer's model using standard checklists. A one-way sensitivity analysis, scenario analysis and a probabilistic sensitivity analysis were undertaken by the ERG.

## Results

### Summary of submitted clinical evidence

The manufacturer's submission presents clinical evidence for omalizumab in patients with severe persistent allergic asthma based on one published multicentre international double-blind randomised controlled trial (RCT) [known as the Investigation of Omalizumab in Severe Asthma Treatment (INNOVATE) trial].<sup>3</sup> (Table 1) This was the pivotal EU/UK licensing trial. The trial compares

omalizumab as an add-on to standard therapy (e.g. ICS and LABA) with placebo and standard therapy over a 28-week treatment period.

The efficacy analyses were carried out on the 'primary intention to treat' (PITT) population, which excludes 13% of randomised patients (excluded due to a trial protocol amendment). With the exception of safety results, 'true' intention to treat (ITT) results are not reported in the main manufacturer's submission report, or the INNOVATE journal publication. For the primary outcome of the rate of clinically significant asthma exacerbations, there was no statistically significant difference between treatment groups. However, after making a post hoc adjustment for a suggested 'clinically relevant' imbalance between trial arms in baseline exacerbation rate, the difference became marginally statistically significant.

In terms of secondary outcomes, there were statistically significant differences favouring omalizumab over placebo in total emergency visits, Asthma Quality of Life Questionnaire scores, total symptom scores and lung function. Adverse events appeared to be similar between the trial arms.

Results from three other publications are included in the manufacturer's submission as supporting evidence for the effectiveness of omalizumab, despite not meeting the inclusion criteria which adhere strictly to the licensed indication. These included a 12-month open-label 'naturalistic' RCT, a meta-analysis of seven pharmaceutical company sponsored trials, and a Cochrane systematic review of 14 RCTs of anti-IgE treatment. The results of these publications, in differing populations of asthmatics (e.g. mild to moderate asthma), are reported to support the findings of the INNOVATE trial.

### Summary of submitted cost-effectiveness evidence

The cost-effectiveness analysis (CEA) comprises a Markov state-transition model to estimate the incremental costs and consequences of omalizumab as an add-on to standard therapy. The model has been applied in a published Swedish<sup>4</sup> and a published Canadian<sup>5</sup> cost-effectiveness study and is reported to have been validated by asthma physicians and modelling experts.

Despite some limitations in reporting, the model is, in general, internally consistent and appropriate to severe asthma in terms of its structural assumptions. The CEA generally conforms to

TABLE 1 Characteristics of the INNOVATE trial

Study: Humbert et al. <sup>3</sup> (The INNOVATE trial)	
Methods	Outcomes
<p><b>Design:</b> RCT</p> <p><b>Interventions:</b> GripA: omalizumab – 0.016 (mg/kg)/(IU/ml) per 4-week period based on the patient's bodyweight and total serum IgE level at screening every 2 or 4 weeks for a 28-week treatment duration by subcutaneous injection GripB: placebo by subcutaneous injection for 28-week treatment duration by subcutaneous injection</p> <p><b>Number of centres:</b> 108 (14 countries)</p>	<p><b>Primary outcomes:</b> Rate of clinically significant asthma exacerbations</p> <p><b>Secondary outcomes:</b> Hospitalisation, emergency visit and unscheduled doctor's visits QoL<sup>3</sup> (weeks 0, 12 and 28) Clinical symptom score (weeks 0, 1, 2, 4, 12, 20, 24 and 28) Use of rescue medication Patients and investigators' global evaluations of treatment effectiveness Use of concomitant asthma medications Pulmonary function tests (FEV<sub>1</sub>, FVC, and FEF 25–75%); weeks 0, 2, 4, 12, 20, 24 and 28 PEF<sub>AM/PM</sub> and number of days with &gt; 20% improvement in AM PEF compared with personal best (diaries); weeks 0, 1, 2, 4, 12, 20, 24 and 28</p> <p><b>Other measures:</b> Haematological assessment, urine screening and blood chemistry; weeks 0, 12, 28 and during follow-up Vital signs and physical examination</p> <p><b>Length of follow-up:</b> 16 weeks (results not reported)</p>
<p><b>Participants</b> <b>Inclusion criteria:</b> Positive skin prick test to <math>\geq 1</math> perennial aeroallergen and total serum IgE level of <math>\geq 30</math>–<math>\leq 700</math> IU/ml Severe persistent asthma and regular treatment with &gt; 1000 <math>\mu</math>g/day BDP or equivalent and LABA (GINA step 4 treatment) Forced expiratory volume in 1 second (FEV<sub>1</sub>) <math>\geq 40</math> to &lt; 80% of predicted normal value and continuing asthma symptoms FEV<sub>1</sub> reversibility <math>\geq 12\%</math> from baseline within 30 minutes of inhaled (<math>\leq 400</math> <math>\mu</math>g) or nebulised (<math>\geq 5</math> mg) salbutamol More than two asthma exacerbations requiring systemic corticosteroids, or one severe exacerbation (PEF/FEV<sub>1</sub> &lt; 60% of personal best, requiring systemic corticosteroids) resulting in hospitalisation or emergency room treatment, in past 12 months Additional asthma medications taken regularly from &gt; 4 weeks prior to randomisation permitted, including theophyllines, oral <math>\beta_2</math>-agonists and anti-leukotrienes Maintenance oral corticosteroids (maximum 20 mg/day) permitted providing at least one of the exacerbations in the previous 12 months occurred whilst on this therapy</p>	

Study: Humbert et al. <sup>3</sup> (The INNOVATE trial)			
Methods	Participants	Outcomes	
	<p data-bbox="268 1279 292 1469"><b>Exclusion criteria:</b></p> <p data-bbox="320 1010 344 1469">Smokers or smoking history of <math>\geq 10</math> pack-years</p> <p data-bbox="373 965 453 1469">Treatment for an exacerbation within 4 weeks of randomisation (8-week run-in could be extended if necessary)</p> <p data-bbox="481 965 537 1469">Use of methotrexate, gold salts, troleandomycin or ciclosporin within 3 months of the first visit</p> <p data-bbox="566 1189 590 1469">Prior omalizumab treatment</p> <p data-bbox="619 1361 643 1469"><b>Numbers:</b></p> <p data-bbox="671 1032 695 1469">482 ITT; 419 (86.9%) PITT (efficacy analyses)</p> <p data-bbox="724 1256 748 1469">GrpA: 209; GrpB: 210</p> <p data-bbox="777 1144 801 1469"><b>Age: mean (SD, median, range):</b></p> <p data-bbox="829 1167 853 1469">GrpA: 43.4 (<math>\pm 13.29</math>, 44, 12–79)</p> <p data-bbox="882 1167 906 1469">GrpB: 43.3 (<math>\pm 13.49</math>, 44, 13–71)</p> <p data-bbox="935 1323 959 1469"><b>Discontinued:</b></p> <p data-bbox="987 1021 1011 1469">44 (10.8%), GrpA –30 (12.2%); GrpB –22 (9.3)</p> <p data-bbox="1040 1312 1064 1469"><b>Adverse events:</b></p> <p data-bbox="1093 1155 1117 1469">GrpA –11 (4.5%); GrpB –4 (1.7%)</p> <p data-bbox="1145 1279 1169 1469"><b>Lost to follow-up:</b></p> <p data-bbox="1198 1099 1222 1469">GrpA –2; GrpB –6. Reasons unknown</p>		<p data-bbox="1262 360 1334 2074">BDP, beclomethasone dipropionate; FEV<sub>1</sub>, forced expiratory volume in one second; FVC, forced vital capacity; GINA, Global Initiative for Asthma; IgE, human immunoglobulin E; ITT, intention to treat; LABA, long-acting beta<sub>2</sub> agonist; PEF, peak expiratory flow; PITT, primary intention to treat; QoL, quality of life; RCT, randomised controlled trial; SD, standard deviation.</p> <p data-bbox="1337 1541 1361 2074">a Juniper Adult Asthma Quality of Life Questionnaire.</p>

the NICE reference case and the scope/decision problem.

The model assumes that responders to omalizumab (those rated as 'excellent' or 'good' using the global evaluation of treatment effectiveness) at 16 weeks will continue to receive the drug for 5 years, after which they revert to standard therapy. Non-responders to omalizumab at 16 weeks revert to standard therapy at that point. The model has a lifetime horizon.

Data from the INNOVATE trial are used to estimate the proportion of patients with clinically significant exacerbations (both severe and non-severe), the utility associated with day-to-day symptoms, and treatment costs. Utility values for clinically significant exacerbations were taken from another study.<sup>6</sup>

The base-case analysis of the INNOVATE PITT population estimates a cost per quality-adjusted life-year (QALY) of £30,647. The base-case cost per QALY for a subgroup of 'high risk' patients hospitalised in the previous year was £26,509.

The base-case estimate for the INNOVATE PITT population rises as the mortality rate associated with clinically severe exacerbations decreases, with a cost per QALY of £73,177 when a 0% rate is used.

The ERG conducted one-way sensitivity analyses for parameters omitted from the manufacturer's submission sensitivity analysis. The results were most sensitive to variation in the utility values for omalizumab responders, and the unit cost of omalizumab.

The ERG conducted scenario analyses examining the cumulative effect of varying assumptions over the asthma mortality rate, costing of omalizumab, and utilities applied to the exacerbation states and to the day-to-day symptoms state for standard care. Using a lower mortality rate than in the base case and a more realistic approach to costing omalizumab in primary care produced less favourable incremental cost effectiveness ratios (ICERs) than in the base case. ICERs were more sensitive to assumptions over the difference in utility between omalizumab responders and standard care/non-responders than to utility associated with transient changes (such as exacerbations).

The probabilistic cost-utility analysis of the INNOVATE PITT population was £31,713 (confidence interval £23,178, £48,236) with a 50%

probability of the ICER being under £32,000. A replication of the probabilistic analysis by the ERG using a lower mortality rate (2%) and omalizumab cost per vial rather than per milligram, generated a mean ICER of £38,852. At a threshold willingness to pay of £30,000 per QALY, omalizumab add-on therapy has a 23.6% probability of being cost-effective (*Figure 1* and *Figure 2*).

## Commentary on the robustness of submitted evidence

### Strengths

The manufacturer's submission includes a systematic search for clinical effectiveness and cost-effectiveness studies of omalizumab. It appears unlikely that any additional trials would have met the inclusion criteria had the search been widened to include other databases.

The INNOVATE trial appears to be of reasonable methodological quality (with some limitations – see below) and measures a range of clinically relevant outcomes (e.g. exacerbations, day and night symptoms, health-related quality of life, emergency visits and adverse events). Taken together these outcomes accurately capture the impact of pharmacotherapy on the control of severe asthma.

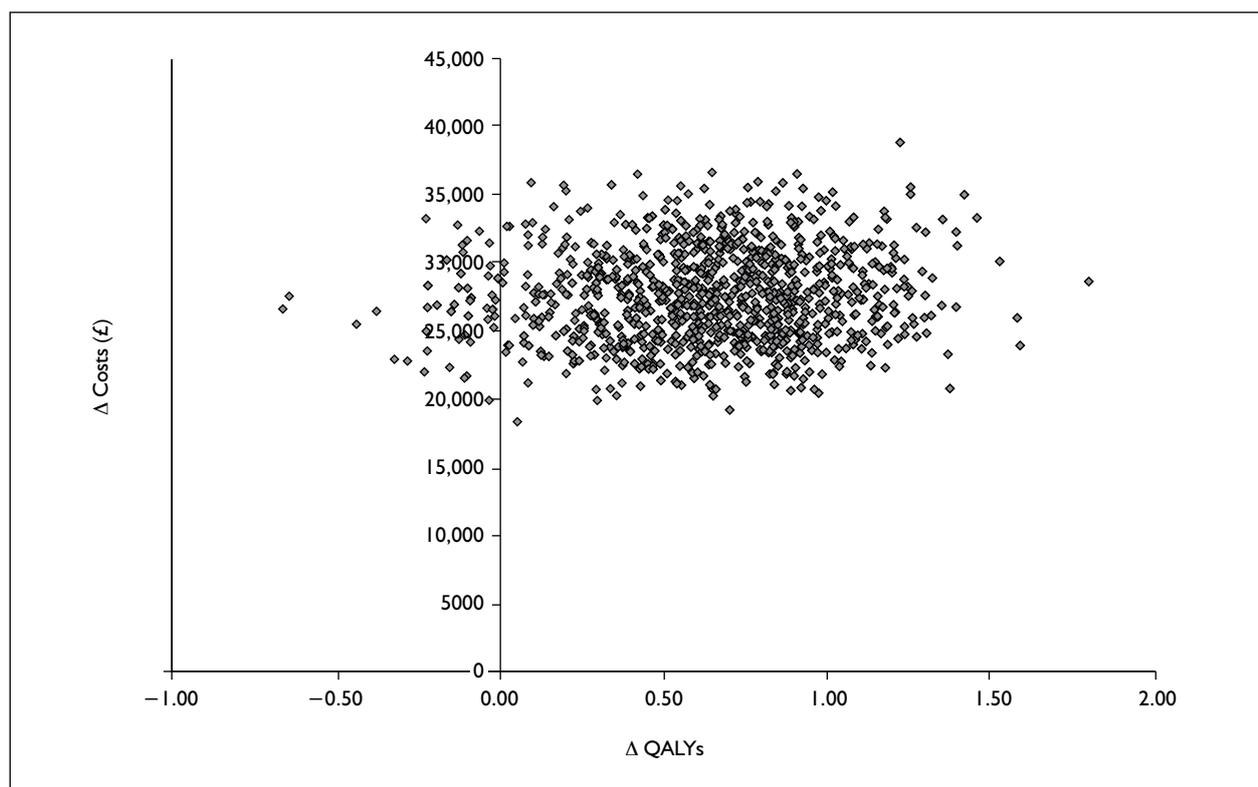
The economic model appears internally consistent and structurally appropriate, and the cost-effectiveness analysis is in accordance with the NICE reference case and the scope of the appraisal.

### Weaknesses

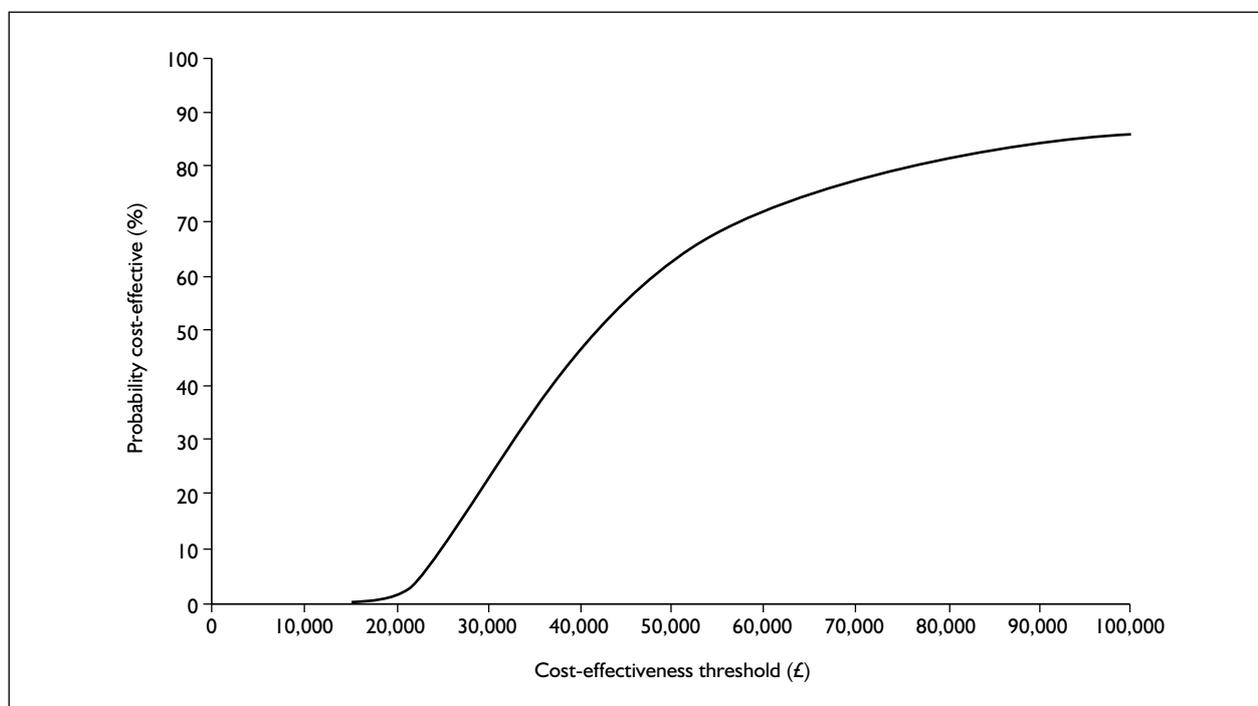
Despite a systematic search and screen of the literature, only one RCT was included. The manufacturer's submission is therefore largely dependent upon this one trial. Although the trial has merits there are also weaknesses, notably in the statistical analysis. Further high-quality RCT evidence for the effectiveness of omalizumab in the patient group meeting the licensed indication would be beneficial.

The INNOVATE trial was subject to protocol amendments which resulted in the exclusion of 13% of randomised patients from the PITT efficacy population (although it is reported that the results of the full ITT analysis are similar to the PITT).

As acknowledged in the manufacturer's submission, there was a strong placebo effect in the INNOVATE trial, exemplified by the relatively high physician rating of response for patients receiving placebo in addition to standard therapy. This is attributed to the optimised standard of care received by



**FIGURE 1** Scatter plot of the ERG probabilistic sensitivity analysis results. QALYs, quality-adjusted life-years.



**FIGURE 2** Cost-effectiveness acceptability curve from ERG probabilistic sensitivity analysis, INNOVATE primary intention-to-treat population.

patients in the clinical trial. Consequently, the manufacturer's submission regards the treatment effect to be an underestimate. Although an open-label RCT conducted in a setting more

representative of clinical practice was presented as supporting evidence, only around half of the randomised patients in this trial met the criteria for the licensed indication.

## Conclusions

### Areas of uncertainty

There is uncertainty about some of the statistical methods used in the analysis of the INNOVATE trial because of post hoc adjustments to the primary outcome to correct for suggested clinically relevant imbalances in baseline exacerbation history between trial arms. The manufacturer's submission reports that such adjustment was recommended by the Committee for Medicinal Products for Human Use. The validity of post hoc adjustments has to be viewed with caution, particularly as the difference in favour of omalizumab in the primary outcome only became statistically significant following adjustment.

The validity of including unpublished post hoc analysis for two subgroups ('high-risk' previously hospitalised patients, and omalizumab responders), is also questionable as both are likely to be underpowered.

Long-term published data on the effectiveness and safety of omalizumab are not yet available. The economic model extrapolates efficacy data from the 28-week INNOVATE trial over a 5-year period, and assumes full compliance. In practice, compliance is likely to vary with factors such as the standard of care, which may not be as optimal as within the context of a clinical trial.

There is no discussion in the manufacturer's submission of possible bias introduced due to missing response data on 14 omalizumab-treated patients. There is no discussion of the characteristics of these patients and the manufacturer's submission does not report the number of exacerbations for these patients separately.

The submission assumes that it is possible to store unused portions of vials of omalizumab and therefore costs the drug by the milligram rather than by the vial. It is unclear whether such a policy of re-use would be feasible in primary care, without incurring substantial additional costs for safe storage and managing this process.

There is substantial uncertainty over the excess mortality rate applied to severe exacerbations in the model. The rate used was derived from a Swedish observational study<sup>7</sup> in which definitions of severe and moderate asthma exacerbations were not clearly specified, and the patient population was substantially older (62.5 years) than the mean starting age for patients in the model (40

years). The manufacturer's submission contains no discussion or objective evidence on the extent to which the dimension that defines a clinically significant exacerbation as severe in the model (PEF or FEV<sub>1</sub> less than 60% of personal best) is a valid predictor of risk of asthma death.

### Key issues

Given that the inclusion criteria adhere strictly to the licensed indication, only one RCT was officially included in the manufacturer's submission (the pivotal licensing trial). In this trial the primary outcome became statistically significant in favour of omalizumab only once a post hoc adjustment had been made to correct for a 'clinically relevant' imbalance between trial arms.

The ICER is highly sensitive to assumptions about the mortality rate associated with severe exacerbations, and to a lesser extent to whether omalizumab is costed on a per vial or per milligram basis.

## Summary of NICE guidance issued as a result of the STA

The guidance issued by NICE in November 2007, TA133, states that:

Omalizumab is recommended as a possible treatment for adults and young people over 12 years with severe persistent allergic asthma when all of the following circumstances apply.

- When the person's asthma is still severe and unstable despite best efforts to control it with other asthma medicines taken as directed by their doctor.
- When the person has stopped smoking, if their doctor feels it is appropriate.
- When the person has allergic asthma. This should be confirmed by checking past symptoms and skin testing for allergies.
- When the person has had at least two asthma attacks within the past year that have needed admission to hospital, or when the person has had three or more severe asthma attacks within the past year, one of which has needed admission to hospital and the other two have needed additional treatment in an accident and emergency department.

Omalizumab treatment should be given along with the person's current asthma medicines. It should be prescribed by a doctor who is experienced in

asthma and allergy medicine at a specialist centre. If omalizumab does not control the asthma after 16 weeks, treatment should be stopped.

## Key references

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# Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma

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## Abstract

This paper presents a summary of the evidence review group report into the clinical effectiveness and cost-effectiveness of rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma (NHL), in accordance with the licensed indication, based upon the evidence submission from Roche Products Ltd to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The submitted clinical evidence included two randomised controlled trials [European Organisation for Research and Treatment of Cancer (EORTC) and German Low Grade Lymphoma Study Group – Fludarabine, Cyclophosphamide and Mitoxantrone and (GLSG-FCM)] comparing the clinical effects of chemotherapy with or without rituximab in the induction of remission at first or second relapse and the clinical benefits of rituximab maintenance therapy versus the NHS's current clinical practice of observation for follicular lymphoma (FL) patients. Both trials showed that in patients with relapsed FL the addition of rituximab to chemotherapy induction treatment increased overall response rates. Furthermore, rituximab maintenance therapy increased the median length of remission when compared with observation only. Safety data from the two trials showed that while the majority of patients reported some adverse events, the number of patients withdrawing from treatment in the EORTC trial was low, with rates not being reported for the GLSG-FCM trial.

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Discussion of ERG reports is invited. Visit the HTA website correspondence forum ([www.hta.ac.uk/correspond](http://www.hta.ac.uk/correspond)).

The most commonly reported adverse events were blood/bone marrow toxicity, skin rashes and allergies. The ERG reran the manufacturer's economic model after altering several of the assumptions and parameter values in order to recalculate the cost–utility ratios, quality-adjusted life-years (QALYs) and estimates of benefits. The manufacturer reported that maintenance therapy with rituximab was cost-effective compared with observation against commonly applied thresholds, with an incremental cost-effectiveness ratio of £7721 per QALY gained. The greatest clinical effectiveness is achieved by R-CHOP followed by rituximab maintenance (R-CHOP>R) and this treatment strategy had the greatest probability of being cost-effective for a QALY of approximately £18,000 or greater. The guidance issued by NICE as a result of the STA states that in people with relapsed stage III or IV follicular NHL, rituximab is now an option in combination with chemotherapy to induce remission or alone as maintenance therapy during remission. Rituximab monotherapy is also an option for people with relapsed or refractory disease when all alternative treatment options have been exhausted.

## Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor.<sup>1</sup> Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG); an external organisation independent of the Institute. This paper presents a summary of the ERG report for the STA entitled 'Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma'.<sup>2</sup>

## Description of the underlying health problem

Non-Hodgkin's lymphoma (NHL) represents about 3% of all cancers diagnosed in the UK. In 2002 there were 9443 people diagnosed with NHL in the UK<sup>3</sup> with an incidence of 16 per 100,000 in England and 15.6 per 100,000 in Wales. The overall rate is increasing at 3–4% per year, which is greater than would be expected from simply a combination of the effects of an ageing population plus improved diagnostic techniques.<sup>4</sup> Follicular lymphoma (FL) is the second most common type of NHL (22%) with a UK incidence of approximately 4 per 100,000<sup>5</sup> and a prevalence of about 40 per 100,000.<sup>4,5</sup>

Low-grade or indolent disease is differentiated from high-grade or aggressive disease by histology. Histological grading of the disease is determined by the World Health Organization classification grades I, II or IIIa or IIIb.<sup>5</sup> The grade is determined by the number and size of abnormal cells taken from lymph node biopsies. There is a growing consensus that histological grade III and, in particular, grade IIIb disease should be classified as aggressive and treated as such rather than treated as indolent disease.

Survival for patients with FL is prolonged. Different figures for median survival have been reported, but 8–10 years from diagnosis is typical.<sup>6,7</sup> However, these are likely to be underestimates as there is good evidence from recent large population-based<sup>8</sup> and single institution studies<sup>9,10</sup> that survival is improving.<sup>11</sup> This is probably as a consequence of improved treatment, especially the introduction of rituximab, which is the first drug treatment for this disease to demonstrate an ability to improve overall survival in randomised controlled trials.

## Scope of the evidence review group report

The ERG report presents the results of the assessment of the manufacturer's/sponsor's evidence submission regarding the use of rituximab for the treatment of relapsed/refractory FL. The ERG report includes an assessment of both the clinical and the cost-effectiveness evidence submitted by Roche Products Limited. The manufacturer's submission (MS) considers two ways of using rituximab: firstly, in conjunction with cytotoxic chemotherapy in order to induce remission in relapsed FL; and secondly, as maintenance therapy after successful induction of remission, regardless of the chemotherapy used to induce remission. The manufacturer presents

clinical evidence to support the use of (1) rituximab plus chemotherapy (e.g. R-CHOP and R-FCM) in the induction phase and (2) rituximab versus observation in the maintenance phase of treatment for FL patients. Only clinical evidence from the CHOP comparisons is used in the cost-effectiveness analyses. The MS claims that there is no new evidence for the use of rituximab in adult patients with stage III–IV FL who are chemoresistant or are in their second or subsequent relapse after chemotherapy. Therefore the MS presents no new case for the use of rituximab in this patient population.

## Methods

The ERG report comprised a critical review of the clinical and cost-effectiveness evidence presented in the MS to NICE as part of the STA process. The ERG assessed the quality of the clinical effectiveness review using a checklist, and attempted to replicate relevant clinical effectiveness and cost-effectiveness literature searches. The ERG re-ran the manufacturer's economic model after altering several of the assumptions and parameter values in order to recalculate the cost–utility ratios, quality-adjusted life-years (QALYs) and estimates of benefits.

## Results

### Summary of submitted clinical evidence

The MS provides clinical evidence from two randomized controlled trials (EORTC and GLSG-FCM). Both trials were included in the clinical systematic review and compare the clinical effects of chemotherapy with or without rituximab in the induction of remission at first or second relapse, and the clinical benefits of rituximab maintenance therapy versus the NHS's current clinical practice of observation for FL patients. Both trials had two points of randomisation. The induction phases included 465 and 147 patients with relapsed FL in EORTC and GLSG-FCM trials respectively. The maintenance phases included 395 and 176 patients who had responded to induction therapy in EORTC and GLSG-FCM trials respectively. Only 113 patients in the GLSG-FCM trial who received maintenance therapy or observation were FL patients. Both trials showed that in patients with relapsed FL the addition of rituximab to chemotherapy induction treatment increased overall response rates; 72.3% (CHOP) versus 85.1% (R-CHOP) in the EORTC trial and 70%

(FCM) versus 94% (R-FCM) in the GLSG-FCM trial. Furthermore, rituximab maintenance therapy increased the median length of remission when compared with observation only. In the EORTC trial, median progression-free survival (PFS) was 14.9 months for those on observation compared with 51.5 months for those receiving rituximab. In the GLSG-FCM trial for FL patients who received R-FCM, median PFS in the observation group was 26 months, and for those receiving rituximab median PFS was not reached.

Safety data from the two trials showed that while the majority of patients reported some adverse events, the number of patients withdrawing from treatment in the EORTC trial was low: 3% in each group at induction and 4% in the rituximab group at maintenance (rates were not reported for the GLSG-FCM trial). The most commonly reported adverse events were blood/bone marrow toxicity, skin rashes and allergies.

### Summary of submitted cost-effectiveness evidence

The MS presents the results of two sets of economic evaluations. The first compares the use of rituximab maintenance (following response to an induction therapy) with observation only (no treatment until relapse). This is referred to as the maintenance two-arm model. A three-state transition model (progression free, progressive disease and death) is used to capture the costs and benefits of relapsed/refractory FL.

The second model compares the use of rituximab maintenance therapy with observation only for patients responding to chemotherapy with or without rituximab, and tests whether the use of rituximab as an induction therapy in addition to maintenance therapy is cost-effective. This is referred to as the induction plus maintenance four-arm model. A five-state transition model (progression free in the induction setting, progression free in the maintenance setting, progression free but not in the induction or maintenance setting, progressive disease and death) captures the costs and benefits of relapsed/refractory FL.

Evidence from the EORTC trial is the principal source of clinical data used in the economic evaluations. A half-cycle correction is applied in both models. Patients in the economic evaluation are followed through the health states in monthly cycles over a period of 30 years in order to capture the entire lifetime costs and effects of the

population. Patients only exit the model due to death.

In the MS, the two-arm model is used to demonstrate that maintenance therapy with rituximab when compared with observation is cost-effective against commonly applied thresholds. The manufacturer reports an incremental cost-effectiveness ratio (ICER) of £7721 per QALY gained for this comparison. In the MS, when subject to extensive univariate and probabilistic sensitivity analysis (PSA), this ICER is shown to be robust (*Table 1*). In the MS, the four-arm economic model illustrates that the greatest clinical effectiveness is achieved by R-CHOP followed by rituximab maintenance (R-CHOP>R). The MS concludes that R-CHOP>R is cost-effective when compared with the second most clinically effective intervention of CHOP induction followed by rituximab maintenance therapy (CHOP>R); the estimated ICER is £16,749 per QALY gained. Again, in the MS this ICER is shown to be robust (*Table 2*).

For the PSA, scatter plots and cost-effectiveness acceptability curves were calculated. For the four-arm model, the manufacturer presents a scatter plot to illustrate the considerable overlap of costs and QALYs across the four treatment groups (*Figure 1*). The cost-effectiveness acceptability curve shows that at a willingness to pay (WTP) for a QALY of approximately £18,000 or greater, the R-CHOP>R treatment strategy had the greatest probability of being cost-effective (*Figure 2*).

## Commentary on the robustness of submitted evidence

### Strengths

The MS includes supporting clinical data from two randomised controlled trials, both of which closed early due to interim analyses showing a significant clinical benefit for rituximab treatment as induction and/or maintenance therapy before enrolment was complete.

The two economic models submitted by the manufacturer are implemented to a generally high standard, clearly presented and with a large amount of source information included to aid traceability. The layouts of the various elements of the models are generally logical, and the formulae employed are straightforward.

### Weakness

The systematic review (SR) reported in the MS does not clearly specify the inclusion and exclusion criteria employed, which results in ambiguity regarding reasons for the exclusion of some trials. In addition, the MS fails to describe adequately the existing clinical evidence for the use of rituximab monotherapy in the treatment of relapsed FL.

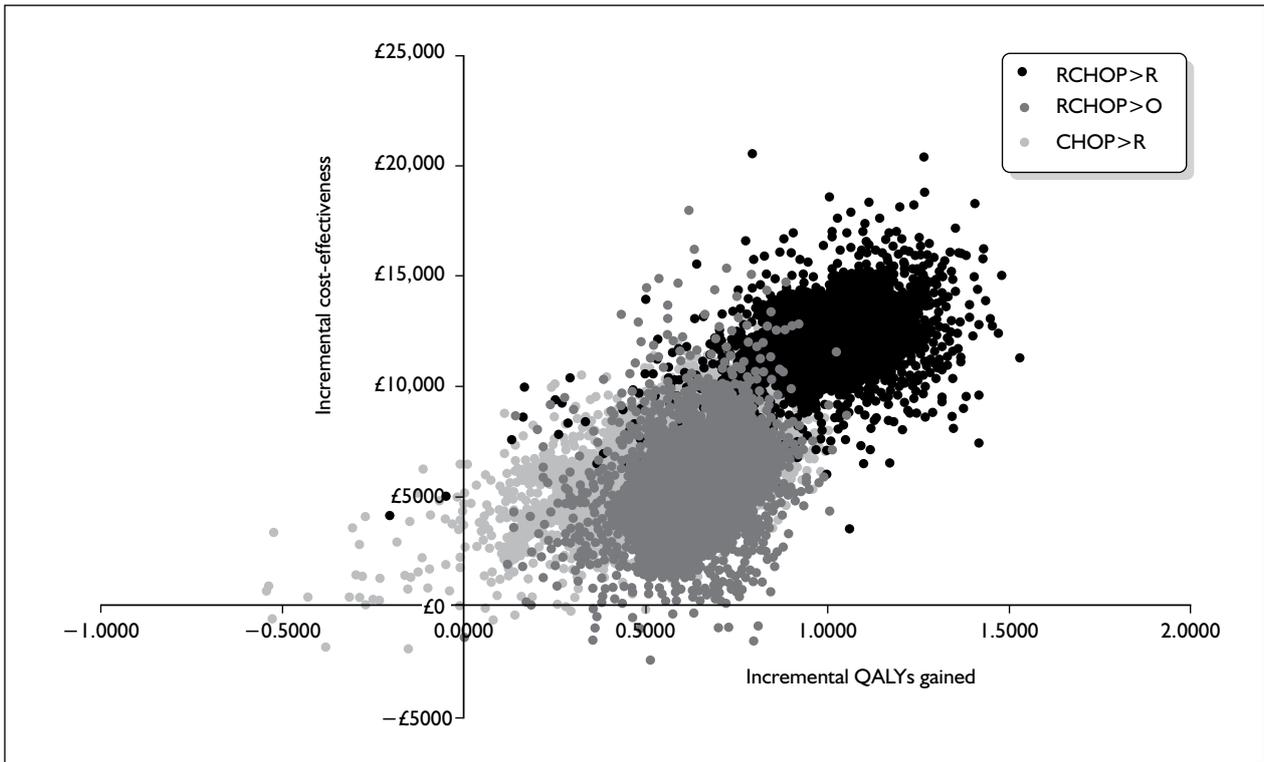
The GLSG-FCM trial includes FL, mantle cell and lymphocytoid lymphoma patients. Evidence to support the use of rituximab as maintenance from the GLSG-FCM trial is inconclusive due to missing clinical data for FL patients only.

**TABLE 1** Incremental cost-effectiveness of rituximab maintenance compared with observation

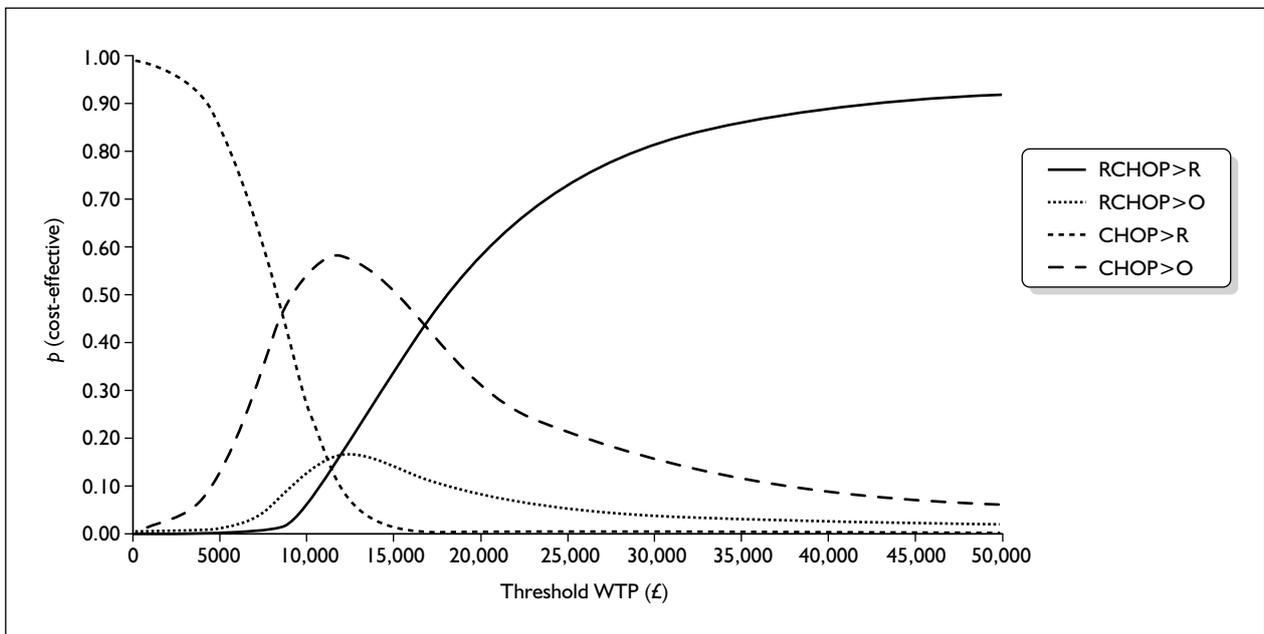
Treatment group	Total costs	QALYs gained	Incremental cost per QALY gained
Rituximab	£21,608	4.2250	
'Observation'	£14,722	3.3331	
Incremental	£6886	0.8919	£7721
QALY(s), quality-adjusted life-years(s).			

**TABLE 2** Incremental cost-effectiveness of a treatment strategy of R-CHOP>R versus a treatment strategy of CHOP>R in patients presenting for induction therapy

Treatment and comparator groups	Costs	QALYs gained	Incremental cost per QALY gained
R-CHOP>R	£28,585	4.0906	
CHOP>R	£22,389	3.7207	
Incremental	£6196	0.3699	£16,749
QALY(s), quality-adjusted life-years(s).			



**FIGURE 1** Scatter plot showing incremental cost and effect of maintenance therapy over CHOP>observation across 2000 simulations of the economic model.



**FIGURE 2** Cost-effectiveness acceptability curve – probability that each treatment practice is cost-effective at a given willingness-to-pay (WTP) threshold.

From the available clinical evidence, the ERG concludes that the maintenance two-arm economic model is too simplistic and therefore the ERG concentrates on the results generated by the induction plus maintenance four-arm model.

**Uncertainty**

The clinical effectiveness of R-CHOP induction in patients previously treated with rituximab cannot be assessed from this STA as patients in the EORTC trial are rituximab naive at entry. In

**TABLE 3** Combined effect on cost-effectiveness of applying ERG modifications to the submitted four-arm

Comparison	Model projections			ERG modifications but using original outcome projections			ERG modifications including K-M outcome estimates		
	IC	IQ	ICER	IC	IQ	ICER	IC	IQ	ICER
R-CHOP>R vs CHOP>R	£6196	0.3699	£16,749	£8849	0.3705	£23,882	£8660	0.2015	£42,982
R-CHOP>R vs R-CHOP>O	£5531	0.4646	£11,904	£7686	0.4656	£16,509	£7289	0.1728	£42,192
R-CHOP>R vs CHOP>O	£11,927	1.0014	£11,910	£12,149	1.0034	£12,108	£12,157	0.4680	£25,978
CHOP>R vs R-CHOP>O	-£665	0.0947	Dominant	-£1,163	0.0951	-£12,232	-£1371	-0.0287	£47,734
CHOP>R vs CHOP>O	£5731	0.6315	£9076	£3300	0.6329	£5,214	£3497	0.2665	£13,122
R-CHOP>O vs CHOP>O	£6396	0.5368	£11,916	£4463	0.5378	£8,298	£4867	0.2952	£16,488

ERG, evidence review group; IC, incremental discounted cost per patient; ICER, incremental cost-effectiveness ratio; IQ, incremental discounted QALYs per patient; ICER, incremental cost per QALY gained; K-M, Kaplan-Meier; QALY(s), quality-adjusted life-year(s).

a ERG modifications: amended discounting logic; increased cost of drug administration; revised calculation of relapsed treatment costs; inclusion of £5000 per patient terminal care costs; replace projected overall and progression-free survival estimates with K-M estimates at 1500 days (right-hand section of table only).

2006, R-CVP was approved by NICE<sup>12</sup> as a first-line treatment for patients with FL. It is therefore unlikely that future patients with relapsed FL in the NHS in England and Wales will be rituximab naive.

The ERG raised some concerns about the modelling of the survival data. The ERG was unable to overcome such concerns (e.g. by conducting PSA) as the manufacturer did not provide the requested additional information on the disposition of patients in the EORTC trial and the mean time spent in each segment of the treatment pathway.

## Conclusions

The ERG acknowledges that the economic models submitted by the manufacturer are implemented to a generally high standard, clearly presented and with a large amount of source information included to aid traceability. The layouts of the various elements of the models are generally logical, and the formulae employed are straightforward.

On detailed examination of the models, the ERG identified a minor anomaly in the model coding that affected estimates of both costs and outcomes. Correction of this anomaly favoured the rituximab patients. In terms of costs, the ERG made two adjustments which increased the R-CHOP>R versus CHOP>R ICER. Firstly, the outpatient cost (£86) is replaced by a chemotherapy administration cost (£504) in order to reflect that demanding chemotherapy regimens are typically given within a day-case setting and the ICER increases from £16,749 to £18,204. Secondly, the calculation of alternative postprogression treatment costs by the ERG also increases the ICER from £16,749 to £22,688.

In terms of utilities, changing the postprogression utility values does not have a major impact on the ICERs. However, the preferred approach to survival modelling does impact on the size of the ICER for every possible combination in the four-arm model. The ERG identifies four areas of concern regarding the manufacturer's estimation of lifetime benefits from use of rituximab. In order to overcome such concerns, the ERG requested additional information from the manufacturer about the disposition of patients and the mean time spent in each segment of the treatment pathway. The manufacturer declined to provide this information. Consequently, the ERG used the observed and reported evidence on PFS and overall

survival (OS) from the EORTC trial rather than the manufacturer's projections. In doing so, the ICERs for the six possible combinations now range from £13,895 to £73,140.

The ERG calculated the cumulative effect of all of the changes on the ICERs (*Table 3*). It is clear that the single-use strategies are the most cost-effective options, i.e. use of rituximab for induction of remission (£13,122 per QALY gained) or for maintenance of remission (£16,488 per QALY gained). Dual-use strategies compared with single-use strategies are the least cost-effective options at around £42,000 per QALY gained. A comparison of dual use of rituximab with no use of rituximab also appears to be moderately cost-effective (£26,000 per QALY gained). However, in order to fully inform decision-making about the preferred use of rituximab for FL, a comprehensive PSA in the form of a cost-effectiveness acceptability plot is required. However, as all of the necessary data were not available to the ERG, it was not possible to carry out this assessment.

In summary, the ERG agrees that the use of rituximab for the treatment of FL is probably cost-effective, but cannot confidently recommend either or both single-use strategies over the dual-use strategy, based on the available data.

## Summary of NICE guidance issued February 2008 as a result of the STA

In people with relapsed stage III or IV follicular NHL, rituximab is now an option in combination with chemotherapy to induce remission or alone as maintenance therapy during remission. Rituximab monotherapy is also an option for people with relapsed or refractory disease when all alternative treatment options have been exhausted.

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# Adalimumab for the treatment of psoriasis

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**Declared competing interests of authors:** none

## Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical and cost-effectiveness of adalimumab for the treatment of moderate to severe plaque psoriasis based upon a review of the manufacturer's submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The submission's clinical evidence came from three randomised controlled trials comparing adalimumab with placebo, two extension studies and one ongoing open-label extension study. The studies were of reasonable quality and measured a range of clinically relevant outcomes. A higher proportion of patients on 40 mg adalimumab every other week achieved an improvement on the Psoriasis Area and Severity Index (PASI) of at least 75% (PASI 75) compared with placebo groups after 12 or 16 weeks of treatment, and there was a statistically significant difference in favour of adalimumab for the proportion of patients achieving a PASI 50 and a PASI 90. In a mixed treatment comparison, for each PASI outcome the probability of a response was greater for infliximab than for adalimumab, but the probability of response with adalimumab was greater than that with etanercept, efalizumab and non-biological systemic therapies. Adverse event rates were similar in the treatment and placebo arms and discontinuations because of adverse events were low and comparable between groups. The submission's economic model presents treatment effectiveness for adalimumab versus other biological therapies based upon utility values obtained from two clinical trials. The model is generally internally consistent and appropriate to psoriasis in terms of structural assumptions and the methods used are appropriate. The base-case

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### Date of ERG submission:

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Discussion of ERG reports is invited. Visit the HTA website correspondence forum ([www.hta.ac.uk/correspond](http://www.hta.ac.uk/correspond)).

incremental cost-effectiveness ratio for adalimumab compared with supportive care for patients with severe psoriasis was £30,538 per quality-adjusted life-year. Scenario analysis shows that the model was most sensitive to the utility values used. Weaknesses of the clinical evidence included not undertaking a systematic review of the comparator trials, providing very little in the way of a narrative synthesis of outcome data from the key trials and not performing a meta-analysis so that the overall treatment effect of adalimumab achieved across the trials is unknown. Weaknesses of the economic model included that the assumptions made to estimate the cost-effectiveness of intermittent etanercept used inconsistent methodology for costs and benefits and there were no clear data on the amount of inpatient care required under supportive care. The NICE guidance issued as a result of the STA states that adalimumab is recommended as a treatment option for adults with plaque psoriasis in whom anti-tumour necrosis factor treatment is being considered and when the disease is severe and when the psoriasis has not responded to standard systemic therapies or the person is intolerant to or has a contraindication to these treatments.

## Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, for which most of the relevant evidence lies with one manufacturer or sponsor.<sup>1</sup> Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA of adalimumab for the treatment of psoriasis.

## Description of the underlying health problem

Psoriasis is an inflammatory skin disease that can take several forms. The most common type is plaque psoriasis, characterised by exacerbations of thickened, erythematous, scaly patches of skin that can occur anywhere on the body. The severity of psoriasis can vary from mild through to moderate and severe. The disease impacts on quality of life at all levels of disease severity.

It is well recognised that obtaining estimates for psoriasis prevalence is difficult. NICE guidance on the use of etanercept and efalizumab indicates that approximately 2% of the UK population have psoriasis.<sup>2</sup> Defining what constitutes mild, moderate and severe psoriasis is also problematic as a number of different criteria are available and differing approaches are taken. One of the main accepted systems for classifying the severity of psoriasis is the Psoriasis Area and Severity Index (PASI). The limitations of this measure have been well documented,<sup>3</sup> but despite its shortcomings it is the measure used in most clinical trials. Body surface area (BSA) and the Dermatology Life Quality Index (DLQI) are also commonly used as systems for classifying the severity of psoriasis. The guidance for the use of biological therapies in psoriasis issued by NICE in July 2006<sup>2</sup> defines severe psoriasis as a PASI of  $\geq 10$  combined with a DLQI  $> 10$ . A 2005 review<sup>4</sup> of the PASI alone (i.e. without DLQI or BSA) as an instrument in determining the severity of chronic plaque-type psoriasis defines severe psoriasis as a PASI  $> 12$  and moderate psoriasis as a PASI ranging from 7 to 12.

## Scope of the ERG report

The ERG critically evaluated the evidence submission from Abbott Laboratories on the use of adalimumab for the treatment of moderate to severe plaque psoriasis. At the time of the evaluation adalimumab had not yet been licensed for this indication.

Adalimumab is a recombinant human immunoglobulin monoclonal antibody that binds to the proinflammatory cytokine tumour necrosis factor-alpha (TNF- $\alpha$ ). Adalimumab neutralises the biological function of TNF- $\alpha$  by blocking its interaction with the p55 and p75 cell-surface TNF receptors.

The anticipated licensed indication for adalimumab is the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to or who are intolerant to other systemic therapy including ciclosporin, methotrexate or PUVA.

The outcomes stated in the manufacturer's definition of the decision problem were measures of severity of psoriasis, remission rate, adverse effects of treatment and health-related quality of life.

## Methods

The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process.

The ERG checked the literature searches and applied the NICE critical appraisal checklist to the included studies and checked the quality of the manufacturer's submission with the Centre for Reviews and Dissemination (CRD) quality assessment criteria for a systematic review. In addition, the ERG checked and provided commentary on the manufacturer's model using standard checklists. A one-way sensitivity analysis, scenario analysis and a probabilistic sensitivity analysis (*Figure 1*) were undertaken by the ERG.

## Results

### Summary of submitted clinical evidence

The main evidence on efficacy in the submission comes from three randomised controlled trials (RCTs) comparing adalimumab with placebo. One of these RCTs also compares adalimumab with methotrexate. One further RCT contributes evidence on efficacy and time to relapse. Additionally two extension studies and one ongoing open-label extension study were included. Other than the one RCT mentioned above, which included a methotrexate arm, no trials of potential comparator treatments were included.

A higher proportion of patients on 40 mg adalimumab every other week achieved an improvement on the PASI of at least 75% (PASI 75) compared with placebo groups after either 12 weeks (two trials) or 16 weeks (two trials) of treatment. There was also a statistically significant

difference in favour of adalimumab for the proportion of patients achieving a PASI 50 (three trials) and a PASI 90 (four trials).

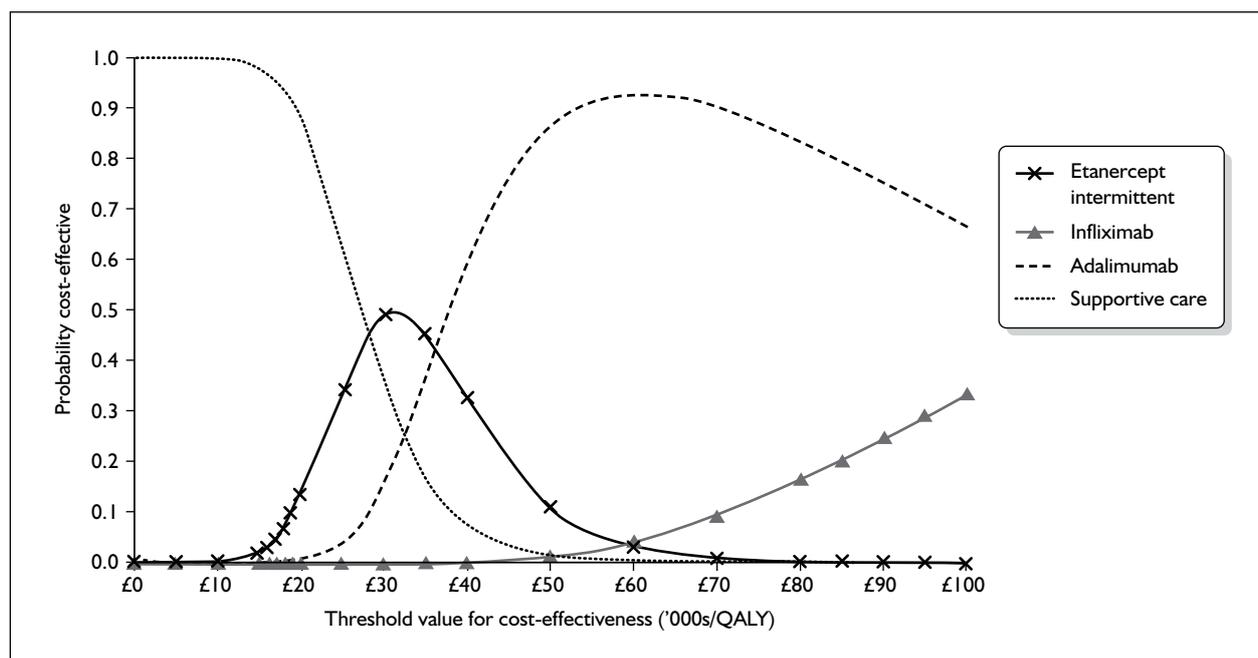
The manufacturer's submission did not present a narrative or quantitative synthesis of the data from the four trials except in the mixed treatment comparison. The mixed treatment comparison result for treatment with 40 mg adalimumab every other week was a mean probability of achieving a PASI 75 response to treatment of 67% (2.5–97.5% credible interval of 57–74%), compared with a mean probability of achieving a PASI 75 of 5% (2.5–97.5% credible interval of 4–6%) with supportive care. The mixed treatment comparison results for PASI 50 and PASI 90 were also in favour of adalimumab over supportive care. For each PASI outcome in the mixed treatment comparison the probability of a response was greater for infliximab 5 mg/kg/day than for adalimumab, but the probability of response with adalimumab was greater than the probability of response with etanercept, efalizumab and the non-biological systemic therapies.

In terms of secondary outcomes there were statistically significant differences between adalimumab and placebo in Physician's Global Assessment (PGA) score, DLQI, the EuroQoL quality of life questionnaire (EQ-5D) and the short-form version 36 (SF-36) quality of life outcomes. The incidence of any adverse event was similar in the treatment and placebo arms, serious adverse events were comparable and discontinuations because of adverse events were low and comparable between groups.

### Summary of submitted cost-effectiveness evidence

The cost-effectiveness analysis estimates the mean length of time that an individual would respond to treatment, and the utility gains associated with this response. The model is based closely upon the model reported in the NICE appraisal of etanercept and efalizumab for psoriasis.<sup>2</sup> The results are presented for adalimumab compared with other biological therapies, including intermittent etanercept, based upon utility values obtained from two clinical trials.

The model is generally internally consistent and appropriate to psoriasis in terms of structural assumptions. The cost-effectiveness analysis generally conforms to the NICE reference case, the scope and the decision problem.



**FIGURE 1** Cost-effectiveness acceptability curve for ERG probabilistic sensitivity analysis. QALY, quality-adjusted life-year.

Treatment effectiveness is reported in terms of the numbers of patients achieving PASI 50, 75 and 90 goals at the end of the trial period. Evidence was synthesised from a variety of trials for all therapies considered in the model using a mixed treatment comparison model. Patients who achieve improvements in PASI score were assigned an associated improvement in quality of life with higher responses associated with larger improvements in quality of life.

The base-case incremental cost-effectiveness ratio (ICER) for adalimumab compared with supportive care for patients with severe psoriasis was £30,538 per quality-adjusted life-year (QALY). Scenario analysis reported in the manufacturer's submission shows that the model was most sensitive to the utility values used (with DLQI  $\leq 10$  having much higher cost-effectiveness ratios than DLQI  $> 10$ ).

## Commentary on the robustness of submitted evidence

### Strengths

The manufacturer conducted a systematic search for clinical effectiveness and cost-effectiveness studies of adalimumab. It appears unlikely that the searches missed any additional trials that would have met the inclusion criteria. The four key adalimumab trials identified were of reasonable methodological quality and measured a range of

outcomes that are as appropriate and clinically relevant as possible. Overall, the manufacturer's submission presents an unbiased estimate of treatment efficacy for adalimumab based on the results of the placebo-controlled trials.

The economic model presented with the manufacturer's submission used an appropriate approach for the disease area given the available data. The measure of utility gain was taken from two randomised clinical trials that directly linked changes in PASI score to changes in utility using the EQ-5D.

### Weaknesses

The processes undertaken by the manufacturer for screening references, data extraction and quality assessment of included studies were not well reported in the manufacturer's submission. However, the manufacturer was able to provide details when requested.

The manufacturer did not undertake a systematic review of the comparator trials and reported very limited information on the comparator trials that were included in the mixed treatment comparison. The manufacturer's submission provided very little in the way of a narrative synthesis of outcome data from the key trials and did not perform a meta-analysis. A mixed treatment comparison was conducted, but few methodological details were provided on this.

The assumptions made to estimate the cost-effectiveness of intermittent etanercept used inconsistent methodology for costs and benefits. The estimation of QALYs and costs generated were based upon different estimates of the length of time that individuals would spend on etanercept, with the estimate used for costs greater than that used for QALYs.

There were no clear data on the amount of inpatient care required under supportive care.

A fourth infusion for infliximab was included in the trial period at 14 weeks. This would last for the first 8 weeks of the treatment period and hence is most appropriately included in the treatment period costs. The clinical expert consulted believed that generally in clinical practice the fourth infusion would be given only after the individual's response category was assessed.

## Conclusions

### Areas of uncertainty

As a standard meta-analysis was not conducted the overall treatment effect of adalimumab achieved across the trials is unknown. A meta-analysis might also have identified whether there is heterogeneity across the trials. If heterogeneity was found to be present the appropriateness of conducting a mixed treatment comparison would need to be reconsidered.

The limited descriptions of both the comparator trials included in the mixed treatment comparison and the methodological assumptions underlying the mixed treatment comparison make it difficult for the ERG to critique the model outputs.

The extent to which the trial populations of the included adalimumab trials match the population specified in the decision problem, in terms of previous treatment with systemic therapy, is uncertain.

A regression model was used to relate changes in PASI score to EQ-5D data. However, few details were given of this model and so the ERG could not be sure of the appropriateness of the approach taken.

Uncertainty exists as to the correct way to model key alternatives to adalimumab, particularly intermittent etanercept. It is unclear how widely intermittent etanercept is used in clinical practice and the degree to which costs are avoided with

intermittent therapy. It is also unclear as to how much utility is lost because of psoriasis flare-ups.

There appears to be a paucity of data regarding the need for inpatient stays in psoriasis patients. The assumption is that individuals who are not responders to treatment receive 21 days per year and those who are on treatment receive no inpatient stays. The model is sensitive to changes in the length of supportive care inpatient stay.

### Key issues

The majority of the trials of adalimumab efficacy presented in the manufacturer's submission were placebo-controlled trials. Only one head-to-head RCT was included that directly compared adalimumab with methotrexate. No studies were identified that directly compared adalimumab with the other possible comparators listed in the scope. The manufacturer carried out an indirect comparison, but because of the limited information presented on the included comparison trials and the methodological assumptions the ERG have reservations about this.

The precise definition of the severity of the psoriasis patients included in the model is unclear. A clear specification of this and a tailoring of the effectiveness, quality of life and cost data, to reflect specific severities, would improve the applicability of the model.

There is a need for better data relating to the need for inpatient stays for non-responders with various severities of disease.

The assumptions made in estimating the values for key parameters used for the comparators are important in determining the relative cost-effectiveness of adalimumab compared with other biological treatments, particularly the costing assumptions made for intermittent etanercept.

## Summary of NICE guidance issued as a result of the STA

NICE issued an Appraisal Consultation Document in January 2008 which states that:

1.1 Adalimumab is recommended as a treatment option for adults with plaque psoriasis in whom anti-tumour necrosis factor (TNF) treatment is being considered and when the following criteria are both met.

- The disease is severe as defined by a total Psoriasis Area Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10.
- The psoriasis has not responded to standard systemic therapies including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation); or the person is intolerant to, or has a contraindication to, these treatments.

1.2 It is recommended that adalimumab is discontinued in people whose psoriasis has not responded adequately at 12 weeks. An adequate response is defined as either:

- a 75% reduction in the PASI score (PASI 75) from when treatment started, or
- a 50% reduction in the PASI score (PASI 50) and a five-point reduction in DLQI from start of treatment.

1.3 It is recommended that, when using the DLQI, healthcare professionals take care to ensure that a person's disabilities (such as physical impairments) and linguistic or other communication difficulties are taken into account when reaching conclusions on the severity of plaque psoriasis. In such cases, healthcare professionals should ensure that their use of the DLQI continues to be a sufficiently

accurate measure. The same approach should apply in the context of a decision about whether to continue the use of the drug in accordance with section 1.2.

## Key references

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# Dabigatran etexilate for the prevention of venous thromboembolism in patients undergoing elective hip and knee surgery: a single technology appraisal

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## Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of dabigatran etexilate (DBG) for the prevention of venous thromboembolism (VTE) in patients undergoing elective hip and knee surgery based upon a review of the manufacturer's submission to the NICE as part of the single technology appraisal (STA) process. The submission's evidence came from three reasonable-quality trials comparing DBG with enoxaparin, and a comparison of DBG with fondaparinux based on the relative efficacy and safety as derived from a mixed treatment comparison (MTC) meta-analysis. DBG (220 mg and 150 mg once daily) is not inferior to enoxaparin (40 mg once daily and 30 mg twice daily) in terms of major VTE or VTE-related events (secondary outcome). Meta-analysis shows that 220 mg DBG is not inferior to enoxaparin (40 mg once daily or 30 mg twice daily) in reducing total VTE and all-cause mortality (primary outcome) in total hip or knee replacement, whereas there is uncertainty around the clinical effectiveness of 150 mg DBG for this outcome. In the MTC analysis DBG compared favourably with the other interventions, with the exception of extended enoxaparin and fondaparinux. The adverse event profile was not significantly different in those receiving DBG and those receiving enoxaparin.

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Discussion of ERG reports is invited. Visit the HTA website correspondence forum ([www.hta.ac.uk/correspond](http://www.hta.ac.uk/correspond)).

The submitted two-phase economic model compares DBG with enoxaparin and fondaparinux in total hip and knee replacement. The model structure is appropriate and the model assumptions are reasonable. The health states, costs, utilities and recurrence rates used are considered to be appropriate for the required analysis. The model estimated that at the licensed dose of 220 mg once daily DBG dominates enoxaparin in both total hip replacement and total knee replacement and that at the lower dose of 150 mg once daily DBG dominates enoxaparin in total hip replacement and enoxaparin dominates DBG in total knee replacement. DBG is less cost-effective than fondaparinux in total hip replacement at both doses; the cost per quality-adjusted life-year of fondaparinux versus DBG is £11,111 and £6857 for the higher and lower doses of DBG respectively. In total knee replacement, both DBG doses are dominated by fondaparinux. For DBG versus all comparators in all cases the cost-effectiveness results are based on small incremental cost and health benefits. Weaknesses of the submitted evidence include that methods used for screening studies, data extraction and applying quality assessment criteria to included studies, as well as key details of trials included in the MTC, were not adequately described. In addition, some input parameters into the modelling process are incorrect. The ERG was unable to correct all of these mistakes and the impact on the model results is therefore unknown. The National Institute for Health and Clinical Excellence guidance issued as a result of the STA states that DBG is recommended as an option for the primary prevention of VTE events in adults who have undergone elective total hip or knee replacement surgery.

## Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, for which most of the relevant evidence lies with one manufacturer or sponsor.<sup>1</sup> Typically,

it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA of dabigatran etexilate for the prevention of venous thromboembolism in patients undergoing elective hip and knee surgery.<sup>2</sup>

## Description of the underlying health problem

Venous thromboembolism (VTE) is the formation of a blood clot (thrombus) in a vein, which may dislodge from its site of origin to cause an embolism. Most thrombi occur in the deep veins of the legs; this is called deep vein thrombosis (DVT). Dislodged thrombi may travel to the lungs; this is called a pulmonary embolism (PE) and can be fatal. Thrombi can also cause long-term morbidity due to venous insufficiency and post-thrombotic syndrome, potentially leading to venous ulceration.

Recurrence of DVT is common. Studies have shown that up to 30% of patients who have experienced an acute DVT will experience one or more recurrences over the following 10–15 years.<sup>3–5</sup>

Total hip or knee replacement surgery is a strong risk factor for VTE. In the absence of thromboprophylaxis the risk of developing a DVT after a primary total hip replacement and after a primary total knee replacement is 50% and 60% respectively.<sup>6</sup>

Mortality due to VTE is significant. Long-term follow-up of patients who have experienced an episode of VTE (usually acute DVT) has shown that there is a high mortality rate over the subsequent 10–15 years.<sup>3,5,7,8</sup>

PE has a high mortality rate with 13% proving fatal in elderly patients 1 month after onset<sup>9</sup> and 17.5% within 3 months.<sup>10</sup>

The National Joint Registry for England and Wales recorded 61,456 hip replacement procedures, of which 10% were revisions or reoperations, and 60,986 knee replacement procedures, of which 8% were revisions or reoperations, undertaken between 1 January and 31 December 2006.<sup>11</sup>

## Scope of the ERG report

The objective of the appraisal is to evaluate the clinical effectiveness and cost-effectiveness of dabigatran etexilate (DBG) within its licensed indication for the prevention of VTE after elective hip or knee replacement surgery in adults. The comparators are enoxaparin (a low-molecular-weight heparin) and fondaparinux.

In total hip replacement, the recommended standard dose of DBG is 110 mg within 1–4 hours of surgery, continuing with 220 mg daily thereafter for a total of 28–35 days. In total knee replacement, the recommended standard dose is 110 mg within 1–4 hours of surgery, continuing with 220 mg daily thereafter for a total of 10 days. A reduced dose of 150 mg once a day is recommended for special populations: those aged 75 years and older, those with moderate renal impairment and those taking amiodarone.

The outcomes measured are mortality, incidence of DVT, incidence of PE, post DVT complications including post-thrombotic syndrome, length of hospital stay, health-related quality of life and adverse effects of treatment including bleeding events (minor and major).

The comparison with enoxaparin is based on the evidence from two pivotal head-to-head DBG phase III clinical trials: RE-NOVATE<sup>12</sup> in a total hip replacement population and RE-MODEL<sup>13</sup> in a total knee replacement population. There are no head-to-head trials comparing DBG with fondaparinux. This comparison is based on the relative efficacy and safety as derived from a mixed treatment comparison (MTC) meta-analysis.

The economic evaluation presented a cost-utility analysis with cost-effectiveness expressed in terms of incremental cost per quality-adjusted life-years (QALYs). Given the potential chronic nature of some complications arising from VTE, the time horizon of the model was lifetime. Costs were considered from an NHS and personal social services perspective.

## Methods

The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process.

The only additional work undertaken by the ERG was a series of meta-analyses on the primary safety outcomes. There was no difference between DBG and enoxaparin in any of these outcomes.

The ERG requested the manufacturers to repeat the cost-effectiveness analysis with the inclusion of the RE-MOBILIZE study,<sup>14</sup> a second trial in a total knee replacement population. The inclusion of the RE-MOBILIZE study reverses the results, from DBG dominating to DBG being dominated for both dosages. However, the manufacturers do not believe that the RE-MOBILIZE study is generalisable to the England and Wales setting. It is their opinion that these analyses are therefore inappropriate for this submission. The ERG's clinical advisors agree with this opinion.

## Results

### Summary of submitted clinical evidence

The main evidence in the submission is derived from three head-to-head, phase III, multi-arm, randomised, double-blind, controlled, non-inferiority trials (RE-NOVATE, RE-MODEL and RE-MOBILIZE). These trials compared the efficacy and safety of DBG at doses of 220 mg and 150 mg once daily with that of enoxaparin [40 mg once daily in RE-NOVATE and RE-MODEL, 30 mg twice daily in RE-MOBILIZE] in patients undergoing total knee replacement (RE-MODEL and RE-MOBILIZE) or total hip replacement (RE-NOVATE). Follow-up was 12–14 weeks.

DBG (at both 220 mg once daily and 150 mg once daily) does not appear to be inferior to enoxaparin (40 mg once daily and 30 mg twice daily) in terms of the secondary efficacy outcome of major VTE or VTE-related events.

The meta-analysis of the primary efficacy outcome across all three trials, and across combinations of these trials, appears to show that the intervention DBG at a dose of 220 mg once daily was not inferior to the comparator enoxaparin (at either 40 mg once daily or 30 mg twice daily) in reducing levels of total VTE and all-cause mortality among patients undergoing total hip replacement and total knee replacement.

Evidence from post hoc subgroup analyses of the included trials indicates that the 150-mg once daily dose may be less effective in terms of incidence of total VTE and all-cause mortality than the 220-mg

once daily dose in the special populations indicated for this lower dose and for whom the lower dose is specifically licensed. Safety outcomes were not reported for these subgroups.

The meta-analysis of the RE-MODEL and RE-NOVATE trials appears to show that the 150-mg once daily dose of DBG is not inferior to the comparator enoxaparin (at either 40 mg once daily or 30 mg twice daily) in reducing levels of total VTE and all-cause mortality among patients undergoing total hip replacement and total knee replacement.

The meta-analyses of the two total knee replacement trials combined (RE-MODEL and RE-MOBILIZE) and the three total knee replacement and total hip replacement trials combined (RE-NOVATE, RE-MODEL and RE-MOBILIZE) appear to show that the 150-mg once daily dose of DBG is inferior to the comparator enoxaparin (at both 40 mg once daily and 30 mg twice daily) in reducing levels of total VTE and all-cause mortality among patients undergoing total hip replacement and total knee replacement.

An MTC analysis compared the results of these trials of DBG with results for all other available interventions for patients undergoing surgery and at risk of DVT and found that DBG compared favourably with the other interventions, with the exception of extended enoxaparin and fondaparinux, which appear to be relatively more effective (level of statistical significance of difference not reported).

The adverse event profile was not significantly different in those receiving DBG compared with those receiving enoxaparin. The primary safety end point was major bleeding. Clinically relevant bleeding, any bleeding and liver function were also measured (secondary end points).

### Summary of submitted cost-effectiveness evidence

The model developed by Boehringer Ingelheim has an acute phase that starts at the time of surgery and ends at 10 weeks post surgery and a chronic phase with a lifetime horizon. The model compares DBG with enoxaparin and fondaparinux in both total hip replacement and total knee replacement. The acute phase model is a decision tree which predicts the health states that patients will be in at 10 weeks based on evidence from phase III trials of DBG compared with enoxaparin and from an MTC of DBG compared with fondaparinux. At 10 weeks

patients enter a chronic phase Markov model in the same health state in which they terminated the decision tree model. No further treatment effect is applied in the chronic phase model. Transition between states in the chronic phase model is dependent on VTE recurrence rates obtained from the literature.

The health states, costs, utilities and recurrence rates used within the model are considered to be appropriate for the required analysis.

The Boehringer Ingelheim model estimated that:

- at the licensed dose of 220 mg once daily DBG dominates enoxaparin in both total hip replacement and total knee replacement
- at the lower dose of 150 mg once daily DBG dominates enoxaparin in total hip replacement and enoxaparin dominates DBG in total knee replacement
- DBG is less cost-effective than fondaparinux in total hip replacement at both doses of DBG. The cost/QALY of fondaparinux versus DBG is £11,111 and £6857, respectively, for the higher and lower doses of DBG.
- In total knee replacement, both DBG doses are dominated by fondaparinux.

Table 1 presents a summary of the cost-effectiveness results. For DBG versus all comparators it should be noted that in all cases the cost-effectiveness results are based on small incremental cost and health benefits.

## Commentary on the robustness of submitted evidence

### Strengths

The manufacturer conducted a limited, but systematic search for clinical and cost-effectiveness studies of DBG for the prevention of VTE in patients undergoing total knee replacement and total hip replacement. It appears unlikely that any additional trials would have met the inclusion criteria had the search been widened to include more free-text terms or to include other databases.

The three identified trials, which represent the main clinical efficacy evidence, were of reasonable methodological quality, with some limitations, and measured a range of outcomes that were appropriate and clinically relevant.

TABLE 1 Summary of deterministic and probabilistic sensitivity analysis results

	Deterministic	Probability cost-effective at threshold:	
		£20,000/QALY	£30,000/QALY
<b>DBG compared with enoxaparin in THR patients</b>			
<i>DBG 220mg</i>			
Incremental cost	-£99	99%	98%
Incremental QALYs	0.010		
ICER	DBG dominant		
<i>DBG 150mg</i>			
Incremental cost	-£83	76%	71%
Incremental QALYs	0.001		
ICER	DBG dominant		
<b>DBG compared with enoxaparin in TKR patients</b>			
<i>DBG 220mg</i>			
Incremental cost	-£18	82%	82%
Incremental QALYs	0.011		
ICER	DBG dominant		
<i>DBG 150mg</i>			
Incremental cost	£20	38%	39%
Incremental QALYs	-0.002		
ICER	DBG dominated		
<b>DBG compared with fondaparinux in THR patients</b>			
<i>DBG 220mg</i>			
Incremental cost	-£200	40%	35%
Incremental QALYs	-0.018		
ICER	£11,111 <sup>a</sup>		
<i>DBG 150mg</i>			
Incremental cost	-£192	32%	27%
Incremental QALYs	-0.028		
ICER	£6857 <sup>a</sup>		
<b>DBG compared with fondaparinux in TKR patients</b>			
<i>DBG 220mg</i>			
Incremental cost	£16	0%	0%
Incremental QALYs	-0.016		
ICER	DBG dominated		
<i>DBG 150mg</i>			
Incremental cost	£25	0%	0%
Incremental QALYs	-0.019		
ICER	DBG dominated		

DBG, dabigatran etexilate; ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s); THR, total hip replacement; TKR, total knee replacement.

a Note that this ICER is in the 'south/west' quadrant of the cost-effectiveness plane.

The meta-analyses demonstrated the non-inferiority of DBG 220 mg once daily versus enoxaparin in terms of the efficacy and safety end points, and acknowledged the apparent inferiority of the 150-mg once daily dose in terms of the primary efficacy outcome.

An MTC analysis compared DBG with all other available interventions for patients undergoing surgery and at risk of DVT and found that DBG compared favourably with the other interventions, with the exception of extended low-molecular-weight heparins and fondaparinux, which appear to be more effective.

The model structure is appropriate and allows sensitivity analysis to be carried out easily.

The model assumptions are reasonable.

The univariate sensitivity analysis is extensive and is performed on appropriate parameters.

The probabilistic sensitivity analysis is performed correctly.

### **Weaknesses**

The processes undertaken by the manufacturer for screening studies, data extraction and applying quality assessment criteria to included studies were not made explicitly clear in the submission. These factors limit the robustness of the systematic review.

Quality assessment of the included studies should have been undertaken using a checklist appropriate to the types of study included (non-inferiority randomised trials).

One of the trials used in the clinical effectiveness section is published only as an abstract (RE-MOBILIZE); much of the key data employed are unpublished.

A simple pooled analysis of the patient level data from the two pivotal trials, as well as all three head-to-head trials, was reported. However, the methods used for this data pooling were not described; the statistical approach for combining the data appears to be inappropriate as it fails to preserve randomisation and introduces bias and confounding. The resulting pooled data should therefore be treated with caution.

Elements of the MTC reported in the manufacturer's submission are reproduced from documents produced by organisations other

than the manufacturer, rather than specifically in response to the scope. The key details of trials included in the MTC, and issues relating to heterogeneity of trials, are neither reported nor discussed. The resulting MTC should therefore be treated with caution.

The economic results for DBG compared with enoxaparin in total hip replacement and total knee replacement both rely on one trial each. These trials indicate that DBG is not inferior to enoxaparin. The small numerical difference seen in these trials is reproduced in the model in terms of both incremental costs and incremental health benefits (see *Table 1*). A small change in the direction of the trial results could significantly change the cost-effectiveness conclusions.

The economic results for DBG versus fondaparinux in total hip replacement are based on one study for which the manufacturer appears to have used an incorrect relative risk estimate. However, the difference is small and the impact on the results is likely to be small.

VTE recurrence rates, post-thrombotic syndrome rates and quality of life utilities used in the model are based on a literature review limited to economic studies. It is therefore possible that non-economic studies reporting these data in sources such as MEDLINE have not been identified.

Some input parameters into the modelling process are incorrect. These include using the underlying risk of DVT instead of the underlying risk of VTE for the comparison of DBG with fondaparinux, wrongly estimating the recurrence rates for VTE, wrongly estimating the probability of PE being severe, not including intensive care unit costs in PE post discharge and including the cost of informal care when it should be excluded. The ERG was unable to correct all of these mistakes and the impact on the model results is therefore unknown.

## **Conclusions**

### **Key issues**

The external validity of the evidence is limited. Only a single randomised controlled trial (RCT) using a comparator and dose applied in England and Wales has been conducted on each of the relevant total hip replacement and total knee replacement populations. The addition of evidence from any future RCTs may alter the results regarding the non-inferiority of DBG. Small changes in key parameters could markedly alter

the conclusions with respect to cost and clinical effectiveness.

The results of the RE-MOBILIZE total knee replacement trial indicate that both the 220-mg once daily and the 150-mg once daily dose of DBG are inferior to enoxaparin in terms of the primary efficacy outcome of total VTE and all-cause mortality. When the pivotal trials (RE-MODEL and RE-NOVATE) are combined with this trial in a meta-analysis the 150-mg once daily dose of DBG is found to be inferior to enoxaparin in terms of the primary efficacy outcome. The 150-mg once daily dose may therefore not be suitable for use in the special populations indicated. Post hoc subgroup analyses for total VTE and all-cause mortality conducted on the special populations indicated also suggest that this dose may be less effective than the 220-mg once daily dose in terms of the primary efficacy outcome.

The economic results for DBG compared with enoxaparin in total hip replacement and total knee replacement both rely on one trial each. These trials indicate that DBG is not inferior to enoxaparin. Although at the licensed dose of 220 mg once daily DBG dominates enoxaparin, a small change in the direction of the trial results could significantly alter the cost-effectiveness conclusions.

The cost-effectiveness analysis based on a meta-analysis of the RE-MODEL plus the RE-MOBILIZE trials reverses the direction of the results, that is, DBG is now dominated by enoxaparin for both doses. However, it is the manufacturer's opinion that the RE-MOBILIZE study is not generalisable to the England and Wales setting. This is also the opinion of the clinical advisors to the ERG.

### Areas of uncertainty

There is uncertainty around the clinical effectiveness and cost-effectiveness of DBG compared with other relevant treatments included in the scope, especially fondaparinux and standard and extended low-molecular-weight heparins other than enoxaparin, especially with respect to the 150-mg once daily dose. The 150-mg once daily dose may be less effective than the 220-mg once daily dose for the special populations for whom this lower dose is licensed.

The economic results for DBG compared with enoxaparin in total hip replacement and total knee replacement both rely on one trial each. The small numerical difference seen in these

trials is reproduced in the model in terms of both incremental costs and incremental health benefits. The conclusions of the cost-effectiveness analysis could be significantly changed with only a small change in the direction of the trial results.

### Summary of NICE guidance issued as a result of the STA

At the time of writing, the final appraisal determination issued by NICE on 21 July 2008 states that:

Dabigatran etexilate, within its marketing authorisation, is recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery.

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# Romiplostim for the treatment of chronic immune or idiopathic thrombocytopenic purpura: a single technology appraisal

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## Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical and cost-effectiveness of romiplostim for the treatment of adults with chronic immune or idiopathic thrombocytopenic purpura (ITP) based upon a review of the manufacturer's submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The submission's evidence came from two relatively high-quality randomised controlled trials (RCTs). The ERG found no evidence that any important data were missed or that data extraction was inaccurate. In both RCTs more patients in the romiplostim than in the placebo group achieved a durable platelet response [non-splenectomised patients: romiplostim 25/41 (61%), placebo 1/21 (5%), odds ratio (OR) 24.45, 95% confidence interval (CI) 3.34 to 179.18; splenectomised patients: romiplostim 16/42 (38%), placebo 0/21 (0%), OR 8.5 (95% CI 1.15 to 372)] and an overall platelet response [non-splenectomised patients: romiplostim 36/41 (88%), placebo 3/21 (14%), OR 34.74, 95% CI 7.77 to 155.38; splenectomised patients: romiplostim 33/42 (79%), placebo 0/21 (0%), OR 16.6 (95% CI 2.37 to 706)]. The difference in mean period with a platelet response was 13.9 weeks (95% CI 10.5 to 17.4) in favour of romiplostim in the RCT of non-splenectomised patients and 12.1 weeks (95% CI 8.7 to 15.6) in favour of romiplostim in the RCT of splenectomised patients. The manufacturer's economic model evaluated the cost-effectiveness of romiplostim compared with standard care. The

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Discussion of ERG reports is invited. Visit the HTA website correspondence forum ([www.hta.ac.uk/correspond](http://www.hta.ac.uk/correspond)).

ERG had concerns about the way the decision problem was addressed in the economic model and about the non-adjustment of findings for confounding factors. In non-splenectomised patients, using romiplostim as a first option treatment, the base-case incremental cost-effectiveness ratio (ICER) was £14,840 per quality-adjusted life-year (QALY). In splenectomised patients the ICER was £14,655 per QALY. Additional sensitivity analyses performed by the ERG identified two issues of importance: whether individuals entered the model on watch and rescue or on active therapy in the comparator arm (ICER £21,674 per QALY for non-splenectomised patients, £29,771 per QALY for splenectomised patients); whether it was assumed that any unused medicine would be wasted. Combining all of the separate sensitivity analyses, and assuming that watch and rescue was not the first-line treatment, increased the ICERs further (non-splenectomised £37,290 per QALY; splenectomised £131,017 per QALY). In conclusion, the manufacturer's submission and additional work conducted by the ERG suggest that romiplostim has short-term efficacy for the treatment of ITP, but there is no robust evidence on long-term effectiveness or cost-effectiveness of romiplostim compared with relevant comparators.

## Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, for which most of the relevant evidence lies with one manufacturer or sponsor.<sup>1</sup> Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA of romiplostim for the treatment of chronic immune or idiopathic thrombocytopenic purpura (ITP).

## Description of the underlying health problem

Immune thrombocytopenic purpura is a condition in which autoantibodies are formed against platelets. ITP may present as bleeding and/or bruising or may be asymptomatic and picked up on blood counts taken for other reasons. The incidence rates quoted for adult ITP in the UK/USA range from 1.13<sup>2</sup> to 6.6<sup>3</sup> per 100,000 per year. Licensed treatments for ITP are steroids, intravenous immunoglobulin and anti-D immunoglobulin. Other treatments include splenectomy (a surgical treatment), cyclophosphamide, vinca alkaloids, danazol, azathioprine, ciclosporin, rituximab, mycophenolate mofetil, dapsone, alemtuzumab, autologous stem cell transplantation, interferon and combination chemotherapy. More recent novel treatments include the thrombopoietin analogues (romiplostim and eltrombopag), which appear to increase platelet production.

## Scope of the ERG report

The manufacturer's submission assessed the efficacy, safety and cost-effectiveness of romiplostim for the treatment of chronic ITP in adult patients with platelet counts of less than  $30 \times 10^9/l$ . Two subgroups were assessed: non-splenectomised patients with inadequate response to initial corticosteroid treatment, in whom splenectomy was medically contraindicated, and ITP patients refractory to splenectomy. The primary outcome was the incidence of durable response, defined as achieving at least six weekly platelet responses (platelets  $\geq 50 \times 10^9/l$ ) during the last 8 weeks of treatment with no rescue medications administered at any time during the 24-week treatment period.

The data used to assess the efficacy and safety of romiplostim came from two small randomised controlled trials (RCTs) by Kuter and colleagues<sup>4</sup> comparing romiplostim with placebo in (1) non-splenectomised patients and (2) splenectomised patients. In addition, data were also reported for an 'ITP safety set' consisting of a number of other non-randomised phase II studies.

The manufacturer submitted an economic evaluation. The economic model was a cohort-type model constructed in Microsoft EXCEL in which the two patient populations were modelled. The model evaluated the cost-effectiveness of romiplostim compared with standard care, defined by reference to international guidelines in the treatment of

ITP and the manufacturer's own commissioned survey. In the model, patients initially enter a watch and rescue state or are treated first with romiplostim. The model was populated with a variety of observational data for the effectiveness of alternative treatments from a number of small studies. The RCT data on romiplostim were also treated as observational data within the economic model.

Romiplostim is designed to increase the production of platelets at a rate that outpaces their destruction by the immune system. The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) positive opinion for romiplostim (Nplate™, Amgen) stated that Nplate was indicated for adult chronic ITP splenectomised patients who were refractory to other treatments, and that Nplate could also be considered as second-line treatment for adult non-splenectomised patients in whom surgery was contraindicated.

## Methods

The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process.

Following submission of the manufacturer's report the ERG:

- requested clarification from the manufacturer on a number of points, mainly relating to the clinical effectiveness and cost-effectiveness aspects of the submission
- assessed the clinical effectiveness part of the manufacturer's submission for its quality as a systematic review using the questions in the Centre for Reviews and Dissemination (CRD) Report No. 4<sup>5</sup>
- replicated the manufacturer's MEDLINE search strategy with the inclusion of the term 'nplate.tw,rn' and adapted the searches for the other databases using the appropriate subject heading terms
- undertook complementary searches for additional evidence on each comparator
- requested the manufacturer to rerun the economic model for a number of additional analyses, and
- performed additional sensitivity analyses on the economic model.

## Results

### Summary of submitted clinical evidence

Evidence on the efficacy of romiplostim came from two RCTs by Kuter and colleagues with a 24-week follow-up.<sup>4</sup> In the RCT of non-splenectomised patients, 25/41 (61%) patients in the romiplostim group and 1/21 (5%) in the placebo group achieved a durable platelet response [odds ratio (OR) 24.45, 95% confidence interval (CI) 3.34 to 179.18]. An overall platelet response was achieved by 36/41 (88%) patients in the romiplostim group and 3/21 (14%) in the placebo group (OR 34.74, 95% CI 7.77 to 155.38). The Kaplan–Meier estimated median time to the first platelet response was 2.0 weeks and the mean period with a platelet response was 15.2 weeks for romiplostim and 1.3 weeks for placebo (difference 13.9 weeks, 95% CI 10.5 to 17.4 weeks).

In the RCT of splenectomised patients, 16/42 (38%) patients in the romiplostim group and 0/21 (0%) in the placebo group achieved a durable platelet response. The OR estimated by the ERG using an assumption of one event in the placebo group was 8.5 (95% CI 1.15 to 372). An overall platelet response was achieved by 33/42 (79%) patients in the romiplostim group and 0/21 (0%) in the placebo group. The OR estimated by the ERG using the same assumption above was 16.6 (95% CI 2.37 to 706). The Kaplan–Meier estimated median time to the first platelet response was 3.0 weeks and the mean period with a platelet response was 12.3 weeks for romiplostim and 0.2 weeks for placebo (difference 12.1 weeks, 95% CI 8.7 to 15.6 weeks).

The efficacy of 24-week administration of romiplostim was significantly better than that of placebo in the above outcomes and also in reduction of concurrent ITP therapy. Across both studies headache (29/84, 35%) was the most common adverse drug reaction amongst romiplostim patients, followed by arthralgia (22/84, 26%), dizziness (14/84, 17%) and insomnia (13/84, 15%). In the RCT of splenectomised patients three patients in the placebo group died, with causes of death pneumonia, pulmonary embolism and cerebral haemorrhage. In the RCT of non-splenectomised patients one patient in the romiplostim group died, the cause of death being an intracranial haemorrhage.

The manufacturer used evidence from existing reviews and primary studies from complementary searches to report the efficacy and safety of

comparator drugs. The majority of the efficacy and safety data came from non-randomised studies or case series.

### Summary of submitted cost-effectiveness evidence

The manufacturer's economic model evaluated the cost-effectiveness of romiplostim compared with standard care, defined by reference to international guidelines on the treatment of ITP and the manufacturer's own commissioned survey. In the model, patients initially entered a watch and rescue state or were treated first with romiplostim.

The results from the manufacturer's revised base-case analysis showed that, in non-splenectomised patients, using romiplostim as a first option treatment resulted in an incremental cost-effectiveness ratio (ICER) of £14,840 per quality-adjusted life-year (QALY). In splenectomised patients the ICER was £14,655 per QALY. Additional sensitivity analyses were performed by the ERG (Tables 1 and 2). The combined sensitivity analysis provided far larger changes in the ICER than were reflected in one-way sensitivity analysis. The two issues of most importance were

(1) whether individuals entered the model on watch and rescue or on an active therapy in the comparator arm (ICER £21,674 per QALY for non-splenectomised patients, £29,771 per QALY for splenectomised patients) and (2) as vials of the drug came in a fixed size, whether it was assumed that any unused medicine would be wasted. Combining all of the separate sensitivity analyses, with the additional assumption that watch and rescue was not the first-line treatment, increased the ICERs further (non-splenectomised £37,290 per QALY; splenectomised £131,017 per QALY).

### Commentary on the robustness of submitted evidence

Overall the quality of the RCTs reporting romiplostim was relatively high and the ERG found no evidence that any data of consequence were missed in the reviews or that data extraction was inaccurate. The evidence base for both romiplostim and the comparator treatments was limited.

Although the decision problem, description of alternatives and perspective were all well outlined

**TABLE 1** ERG's exploratory sensitivity analyses (non-splenectomised patients)

Scenario	ICER (£ per QALY gained)	
	Watch and rescue is initial comparator intervention (as adopted by manufacturer)	Rituximab is initial comparator intervention (ERG analysis using manufacturer's model)
Base case	14,633	21,674
1. Use of EQ-5D data from RCTs	16,503	24,426
2. Change in number of vials (from 0.93 to 1.0)	21,214	28,556
3. Serious adverse events +50%	14,623	21,658
4. Serious adverse events -50%	14,641	29,741
5. Cost of bone marrow test included	14,663	21,706
6. Cost of blood assessment included	19,230	36,131
7. Reducing frequency of physician visits	14,669	21,701
8. Combining 1 and 2 and 4-7	29,179	37,290
9. Response rate for romiplostim (worst case for censoring)	16,258	57,593
10. Response rate for romiplostim (best case for censoring)	14,152	18,776
11. Combining 8 and 9	29,934	76,728
12. Romiplostim effectiveness reduced to 0.25 of base case	16,354	165,129
13. Romiplostim effectiveness reduced to 0.75 of base case	14,884	26,439

EQ-5D, EuroQol 5 dimensions questionnaire; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; RCTs, randomised controlled trials.

**TABLE 2** ERG's exploratory sensitivity analyses (splenectomised patients)

Scenario	ICER (£ per QALY gained)	
	Watch and rescue is initial comparator intervention (as adopted by manufacturer)	Rituximab is initial comparator intervention (ERG analysis using manufacturer's model)
Base case	15,595	29,771
1. Use of EQ-5D data from RCTs	17,580	33,558
2. Change in number of vials (from 1.38 to 2.0)	91,406	109,802
3. Serious adverse events +50%	15,580	21,687
4. Serious adverse events -50%	15,608	29,796
5. Cost of bone marrow test included	15,639	29,817
6. Cost of blood assessment included	22,068	26,154
7. Reducing frequency of physician visits	15,642	29,803
8. Combining 1 and 2 and 4-7	110,352	131,017
9. Response rate for romiplostim (worst case for censoring)	17,501	106,703
10. Response rate for romiplostim (best case for censoring)	15,367	24,669
11. Combining 8 and 9	106,515	233,106
12. Romiplostim effectiveness reduced to 0.25 of base case	17,245	446,204
13. Romiplostim effectiveness reduced to 0.75 of base case	15,808	39,268

EQ-5D, EuroQol-5 dimensions questionnaire; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; RCTs, randomised controlled trials.

in the submission, there were some concerns about the way that the decision problem was addressed in the economic model, which related to the structure of the model and whether patients entered the model on watch and rescue or on an active treatment.

The ERG raised a number of concerns about the pre-model data analyses and the statistical and epidemiological techniques employed. These concerns related to the manufacturer not adjusting the findings for confounding factors (e.g. severity of ITP, age, number of previous treatments, concurrent treatments, and withdrawal rates), which might affect the reliability and size of the treatment effect.

## Conclusions

Based on the manufacturer's submission and the additional work conducted by the ERG the evidence available for romiplostim for both non-splenectomised and splenectomised patient groups suggests that:

- romiplostim appears to be a safe treatment for ITP, although no long-term data exist

- romiplostim has short-term efficacy for the treatment of ITP
- there is no robust evidence on long-term efficacy of romiplostim
- there is no robust evidence on long-term effectiveness of romiplostim compared with relevant comparators
- there is no robust evidence on long-term cost-effectiveness of romiplostim compared with relevant comparators.

Key issues for the decision-making process are:

- Will the use of romiplostim lead to wastage of the drug? Within the base-case industry submission it was assumed that there would be no wastage, but if there is then the cost-effectiveness of romiplostim will be reduced.
- Is the appropriate comparison for romiplostim an active treatment rather than watch and rescue? If so then the use of romiplostim is far less likely to be considered cost-effective.
- Can the results of an international study be extrapolated to the UK population? There appeared to be differences between the study population and the average UK patient.
- Is it plausible that patients in the romiplostim trial who were censored were more likely to

cease to respond to romiplostim? If so then the use of romiplostim is far less likely to be considered cost-effective.

- What is the extent and direction of bias caused by the use of indirect comparisons of non-comparative observational data? If the current data, as used in the manufacturer's submission, overestimate the relative effectiveness of romiplostim then it is far less likely to be considered cost-effective.

## Summary of NICE guidance issued as a result of the STA

At the time of writing, the guidance had not been issued by NICE .

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# Sunitinib for the treatment of gastrointestinal stromal tumours: a critique of the submission from Pfizer

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## Abstract

The submission's evidence for the clinical effectiveness and cost-effectiveness of sunitinib for the treatment of gastrointestinal stromal tumours (GISTs) is based on a randomised controlled trial (RCT) comparing sunitinib with placebo for people with unresectable and/or metastatic GIST after failure of imatinib and with Eastern Cooperative Oncology Group (ECOG) progression status 0–1, and an ongoing, non-comparative cohort study of a similar population but with ECOG progression status 0–4. The searches are appropriate and include all relevant studies and the RCT is of high quality. In the RCT sunitinib arm overall survival was 73 median weeks [95% confidence interval (CI) 61 to 83] versus 75 median weeks (95% CI 68 to 84) for the cohort study. However, time to tumour progression in the cohort study was different from that in the RCT sunitinib arm [41 (95% CI 36 to 47) versus 29 (95% CI 22 to 41) median weeks respectively]. Median progression-free survival with sunitinib was 24.6 weeks (95% CI 12.1 to 28.4) versus 6.4 weeks (95% CI 4.4 to 10.0) on placebo (hazard ratio 0.333, 95% CI 0.238 to 0.467,  $p < 0.001$ ). The manufacturer used a three-state Markov model to model the cost-effectiveness of sunitinib compared with best supportive care for GIST patients; the modelling approach and sources and justification of estimates are reasonable. The base-case incremental cost-effectiveness ratio (ICER) was £27,365 per quality-adjusted life-year (QALY) with the first cycle of sunitinib treatment not costed; when we included the cost of the first treatment cycle we estimated a base-case

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ICER of £32,636 per QALY. Pfizer's sensitivity analysis produced a range of ICERs from £15,536 per QALY to £59,002 per QALY. Weaknesses of the manufacturer's submission include that the evidence is based on only one published RCT; that 84% of the RCT control population crossed over to the intervention group, giving rise to the use of unusual rank preserved structural failure time (RPSFT) analysis to correct for possible bias; and that a number of errors and omissions were made in the probabilistic sensitivity analysis, meaning that it is not possible to come to firm conclusions about the cost-effectiveness of sunitinib for GIST in this patient population. In conclusion, during the blinded phase of the RCT, overall survival was significantly longer in the sunitinib arm than in the placebo arm (hazard ratio 0.491, 95% CI 0.290 to 0.831,  $p < 0.007$ ). However, intention-to-treat analysis of the entire study showed no statistically significant difference in overall survival for those who received sunitinib (73 weeks) versus those who received placebo (65 weeks) (hazard ratio 0.876, 95% CI 0.679 to 1.129,  $p = 0.306$ ).

## Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, for which most of the relevant evidence lies with one manufacturer or sponsor.<sup>1</sup> Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report<sup>2</sup> for the STA of the clinical and cost-effectiveness of sunitinib for gastrointestinal stromal tumours.

## Description of the underlying health problem

Gastrointestinal stromal tumours (GISTs) represent the most common mesenchymal neoplasms of the gastrointestinal tract.<sup>3,4</sup> GISTs are believed to originate from an intestinal pacemaker cell called the interstitial cell of Cajal.<sup>5</sup> The incidence of GIST is estimated at 11–14.5 cases per million per year.<sup>6,7</sup> The most frequent primary sites are gastric (50%) and small bowel (25%). Colorectal, oesophageal and peritoneal GISTs are less frequent. GIST can be diagnosed at any age, with a median age at diagnosis of 60 years.<sup>8</sup>

Estimates vary widely on the incidence of new cases of GIST, with figures between 200 and 2000 quoted<sup>9</sup> with an apparent acceptance of an upper limit of 240. Approximately half of new cases of GIST are likely to be metastatic and/or unresectable on first presentation, the prognosis of which is poor, with few, if any, people surviving beyond 5 years in the absence of effective treatment.<sup>9</sup>

The clinical presentation of GIST is highly variable according to site and tumour size.<sup>10</sup> GIST often remains clinically silent until tumours reach a large size, when mass effects, bleeding or rupture may ensue.<sup>11</sup>

## Scope of the ERG report

### Research question

The research question that Pfizer addressed was: 'What is the clinical and cost-effectiveness of sunitinib for unresectable and/or metastatic GISTs after the failure of imatinib mesylate treatment due to resistance or intolerance?'

### Intervention

The intervention is a multitargeted tyrosine kinase inhibitor produced by Pfizer with the brand name of Sutent<sup>®</sup> and the approved name of sunitinib malate.

### Outcomes

The outcomes measured for clinical effectiveness are overall survival, progression-free survival, time to tumour progression, response rates, adverse effects of treatment and health-related quality of life. Those measured for cost-effectiveness are incremental cost per quality-adjusted life-year (QALY), incremental cost per life-year gained,

resource utilisation and the cost of treating adverse events.

### Type of clinical/cost-effectiveness data used

In the clinical effectiveness evidence the type of data used is 'time to event'; this is reported as median time in weeks with the point estimates expressed as hazard ratios and 95% confidence intervals. To provide cost-effectiveness evidence Pfizer built a Markov model. The model was parameterised by effectiveness data and health state utilities [derived from the EuroQol 5 dimensions (EQ-5D) questionnaire] from a randomised controlled trial (RCT) by Demetri *et al.*<sup>12,13</sup> and longer follow-up unpublished data from the same trial. Costs were based on an NHS and personal social services perspective.

### Stated potential health effects

Pfizer stated that sunitinib potentially benefits patients as a second-line treatment for GIST by increasing the time to tumour progression, progression-free survival and overall survival through inhibiting vascular endothelial growth factor/platelet-derived growth factor receptors on cancer cells, vascular endothelial cells and pericytes, thus constraining the proliferation of tumour cells and the development of tumour blood vessels.

### Stated costs

Pfizer reported that sunitinib malate is available at the following costs: 12.5-mg 28-capsule pack = £784.70; 25-mg 28-capsule pack = £1569.40; 50-mg 28-capsule pack = £3138.80; 12.5-mg 30-capsule pack = £840.75; 25-mg 30-capsule pack = £1681.50; and 50-mg 30-capsule pack = £3363.

## Methods

The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process.

The manufacturer's search strategy was reviewed by an Information Scientist and the searches were rerun with a more extensive RCT filter to see if any relevant trials had been omitted. The methods used by the manufacturer to report the clinical effectiveness were critiqued using the

principles found in the Centre for Reviews and Dissemination's guidance for undertaking reviews in health care.<sup>14</sup> We considered Pfizer's economic evaluation against the following study quality checklists: NICE reference case,<sup>15</sup> Drummond *et al.*<sup>16</sup> and Philips *et al.*<sup>17</sup> for decision model-based economic evaluations. The model was rerun to check for wiring and parameterisation errors.

## Results

### Summary of submitted clinical evidence

The evidence for this submission is based on one RCT<sup>12,13</sup> that compares sunitinib with placebo for people with unresectable and/or metastatic GIST after failure of imatinib due to resistance or intolerance and with Eastern Cooperative Oncology Group (ECOG) progression status 0–1 (the most physically able), and one, ongoing, non-comparative cohort study<sup>18</sup> that gives expanded access to a similar population but with ECOG progression status 0–4.

The RCT was a double-blind, placebo-controlled, parallel-group, multicentre, phase III clinical trial. The blinded phase became open-label upon disease progression or at the time of interim analysis (54 weeks) when patients were allowed to cross over from placebo to treatment group.

The results for overall survival are similar in both studies with the RCT reporting results for the sunitinib arm of 73 median weeks [95% confidence interval (CI) 61 to 83 weeks] in comparison to 75 median weeks 95% CI 68 to 84 weeks] for the cohort study. However, the results for time to tumour progression in the cohort study (median weeks = 41, 95% CI 36 to 47 weeks) are quite different from those of the sunitinib arm of the RCT (median weeks = 29, 95% CI 22 to 41 weeks). These results may be influenced by the different ECOG performance status of the two study populations and a greater median overall survival for the ECOG grade 0–1 in the cohort study [RCT 73 weeks (95% CI 61 to 83 weeks), cohort 88 weeks (95% CI 77 to 97 weeks)].

The interim RCT results for progression-free survival showed that those in the sunitinib group had a significantly better chance of being alive and free from progressive disease than those in the placebo group. Median progression-free survival with sunitinib was 24.6 weeks (95% CI 12.1 to 28.4 weeks) compared with 6.4 weeks (95% CI 4.4 to

10.0 weeks) on placebo (hazard ratio 0.333, 95% CI 0.238 to 0.467,  $p < 0.001$ ).

### Summary of submitted cost-effectiveness evidence

The manufacturer used a Markov model, based on the renal cell carcinoma (RCC) model developed by the Peninsula Technology Assessment Group (PenTAG), to model the cost-effectiveness of sunitinib compared with best supportive care for GIST patients. This had a three-state structure: progression-free survival, progressive disease and death.

Pfizer's base-case analysis produced an incremental cost-effectiveness ratio (ICER) of £27,365 per QALY with the first cycle of sunitinib treatment not costed and using effectiveness estimates from their rank preserved structural failure time (RPSFT) analysis. When we included the cost of the first cycle of treatment we estimated that the value of the base-case ICER was £32,636 per QALY, again using RPSFT effectiveness data. Pfizer's sensitivity analysis produced a range of ICERs from £15,536 per QALY to £59,002 per QALY.

When a conventional method of unadjusted intention-to-treat (ITT) analysis is used to calculate the base-case ICER, values of £93,062 per QALY (first cycle costed) and £77,107 per QALY (first cycle free) are produced. However, this method does not account for the overestimated effectiveness results in the placebo arm due to crossovers; independent expert statistical opinion favours the RPSFT method.

## Commentary on the robustness of submitted evidence

### Clinical effectiveness

The searches are appropriate and include all relevant studies and the RCT is of high quality.

### Cost-effectiveness

The approach taken to modelling is reasonable and the sources and justification of estimates are also generally reasonable.

### Weaknesses

The evidence is based on only one completed and published RCT. The expanded access cohort

study is ongoing, is not comparative and is only published as an abstract at the time of this report.

The majority of the control population (84%) in the RCT crossed over to the intervention group. This gave rise to the use of unusual methods of analysis (RPSFT) to correct for the bias that this may have introduced. Although we believe this to be the correct approach we have been unable to check that it was applied correctly.

In their economic evaluation, Pfizer have presented a miscalculation of cost-effectiveness using the ITT overall survival data for best supportive care (Kaplan–Meier analysis). The stated ICER is £34,649 per QALY when it should have been £93,062 per QALY with sunitinib fully costed (or £77,107 per QALY if the first cycle of treatment is free). (Pfizer corrected this error following questions from us.)

A number of errors and omissions were also made in the probabilistic sensitivity analysis:

- Pfizer used the standard deviation rather than the standard error for the utilities
- in the model, Pfizer assume a standard deviation of 0.02 for progression-free survival, whereas the report says 0.20
- importantly, Pfizer have not modelled all of the uncertainty in the treatment effect for progression-free survival and overall survival
- there are errors in the Cholesky matrix decompositions in modelling the uncertainty of the fit of the Weibull curves for treatment effectiveness in worksheets 'PFS', 'overall survival\_RPSFT analysis' and 'overall survival\_ITT analysis'.

## Conclusions

During the blinded phase of the RCT, overall survival was significantly longer for those in the sunitinib arm than for those who received placebo, with a hazard ratio of 0.491 (95% CI 0.290 to 0.831,  $p < 0.007$ ). However, the ITT analysis of the entire study showed that there was no statistically significant difference in overall survival for those who received sunitinib (73 weeks) compared with those who received placebo (65 weeks), with a hazard ratio of 0.876 (95% CI 0.679 to 1.129,  $p = 0.306$ ).

The degree of uncertainty (listed in the next section) in the cost-effectiveness analysis means

that it is not possible to come to firm conclusions about the cost-effectiveness of sunitinib for GIST in this patient population.

### Areas of uncertainty

Given that there are several major errors in the probabilistic sensitivity analysis the precise degree of uncertainty in the base-case ICER is unknown. However, we can say that the uncertainty in the base-case ICER (reported as £27,365 per QALY – first cycle free) is substantial, given the wide (95%) CI for the hazard ratio of overall survival of 0.262 to 1.234 (using the RPSFT method).

The use of the RPSFT method of analysis has had a very large impact on cost-effectiveness; the ICER using this method (£32,636 per QALY – first cycle costed) is a great deal less than that based on the unadjusted ITT data analysis (£93,062 per QALY – first cycle costed). Expert statistical advice from Ian White (MRC Biostatistics Unit, Cambridge) indicates that the RPSFT is the correct method for analysis and that it appears to have been correctly applied. However, we cannot be sure of this.

We caution that the base-case ICERs may be slightly too low as Pfizer's calculation does not include the cost of sunitinib in progressive disease for some patients randomised to sunitinib (54 patients in the sunitinib arm carried on with this treatment after disease progression) who theoretically may have benefited.

### Key issues

The use of the RPSFT method of analysis (instead of the conventional approach of censoring participants at the point of crossover) greatly affects the estimated cost-effectiveness of sunitinib for GIST. However, this is a common analysis issue in trials of cancer drugs that are found to be effective mid-trial, and the use of the RPSFT seems appropriate.

The lack of costing of sunitinib in progressive disease for patients initially randomised to sunitinib does not reflect the treatment of some patients in the RCT (22% continued with sunitinib after disease progression).

There is a large amount of uncertainty in the relative treatment effectiveness for overall survival between sunitinib and best supportive care under the RPSFT method.

Whether to assume that the first cycle of sunitinib is free to the NHS.

Patients in the expanded access cohort study had a longer median time to tumour progression than those in the RCT.

## Summary of NICE guidance issued as a result of the STA

The Appraisal Consultation Document has yet to be issued by NICE.

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***We look forward to hearing from you.***