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Health Technology Assessment

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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 needs led 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 third 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) and we welcome comments on the summaries via the HTA website (www.hta.ac.uk/correspond).

Prof. Tom Walley
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Lapatinib for the treatment of HER2-overexpressing 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 clinical effectiveness and cost-effectiveness of lapatinib for the treatment of advanced or metastatic HER2-overexpressing breast cancer 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 scope included women with advanced, metastatic or recurrent HER2-overexpressing breast cancer who have had previous therapy that includes trastuzumab. Outcomes were time to progression, progression-free survival, response rates, overall survival, health-related quality of life and adverse effects. The submission's evidence came from one randomised controlled trial (RCT) of reasonable methodological quality, although it was not powered to detect a statistically significant difference in mean overall survival. Median time to progression was longer in the lapatinib plus capecitabine arm than in the capecitabine monotherapy arm {27.1 [95% confidence interval (CI) 17.4 to 49.4] versus 18.6 [95% CI 9.1 to 36.9] weeks; hazard ratio 0.57 [95% CI 0.43 to 0.77; $p = 0.00013$]}. Median overall survival was very similar between the groups [67.7 (95% CI 58.9 to 91.6) versus 66.6 (95% CI 49.1 to 75.0) weeks; hazard ratio 0.78 (95% CI 0.55 to 1.12; $p = 0.177$)]. Median progression-free survival was statistically significantly longer in the lapatinib plus capecitabine group than in the capecitabine monotherapy group [27.1 (95% CI 24.1 to 36.9) versus 17.6 (95% CI 13.3 to 20.1) weeks; hazard ratio 0.55 (95% CI 0.41 to 0.74); $p = 0.000033$]. The manufacturer's economic model to estimate progression-free and overall

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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 07/10/01. The assessment report began editorial review in May 2008 and was accepted for publication in May 2009. See the HTA programme web site for further project information (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).

survival for patients with HER2-positive advanced/metastatic breast cancer who had relapsed following treatment with an anthracycline, a taxane and trastuzumab was appropriate for the disease area. The base-case incremental cost-effectiveness ratios (ICERs) for lapatinib plus capecitabine compared with capecitabine monotherapy or vinorelbine monotherapy were higher than would conventionally be considered cost-effective. When compared with trastuzumab-containing regimes, lapatinib plus capecitabine dominated. In sensitivity analyses the ICER for lapatinib plus capecitabine compared with capecitabine monotherapy or vinorelbine monotherapy was robust to variation in assumptions. In all sensitivity analyses the ICERs remained higher than would conventionally be considered cost-effective. ICERs for trastuzumab-containing regimes were particularly sensitive to assumptions over the frequency of treatment, which had a large effect on the cost-effectiveness of lapatinib plus capecitabine. In conclusion, there was a general lack of evidence on the effectiveness of comparators included in the model and on key parameters such as dose adjustments and the model outputs need to be interpreted in the light of this uncertainty. At the time of writing, NICE were still considering the available evidence for this appraisal.

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.[1] 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 the clinical effectiveness and cost-effectiveness of lapatinib for the treatment of metastatic breast cancer.

Description of the underlying health problem

Breast cancer is the most common cancer in the UK, accounting for one-third of all cancers in women.[2] Increasing age is the strongest risk factor for breast cancer, and the disease is rare in women under the age of 40.

In 2004 there were 36,939 new cases of breast cancer in women in England, which represents a crude rate of 144.6 per 100,000 women.[3] In 2005 there were 2364 new registrations in Wales, giving a rate of 155.4 per 100,000 women. These figures equate to age-standardised rates per 100,000 population of 120.7 [95% confidence interval (CI) 119.5 to 121.9] for England and 120.8 (95% CI 115.9 to 125.7) for Wales.[4] A recent review by the Office for National Statistics[5] found a 20-year survival rate of 64% for women diagnosed with breast cancer between the ages of 50 and 69 years.

Breast cancer is classified on a clinical basis according to the internationally recognised tumour, node, metastases (TNM) staging system.[6] The TNM system is based on three sets of codes relating to the primary tumour, involvement of lymph nodes and evidence of distant metastases. Four clinical stages are defined by particular combinations of these codes. Stage IV is metastatic disease, regardless of lymph node assessment or size of primary tumour. Approximately 25–30% of people with metastatic breast cancer have HER2-positive disease, that is, their tumours overexpress the *HER2* gene.[7]

Scope of the ERG report

The ERG critically evaluated the evidence submission from GlaxoSmithKline UK for the use of lapatinib for the treatment of advanced or metastatic ErbB2 (HER2: human epidermal growth factor receptor 2)-overexpressing breast cancer, in accordance with the predicted licensed indication. Lapatinib is a dual kinase inhibitor of epidermal growth factor receptor (ErbB1) and HER2 (ErbB2). It works intracellularly and, unlike monoclonal antibodies, it can block signalling through receptors that have lost or mutated their extracellular domains. Lapatinib is administered orally, in conjunction with capecitabine.

At the time of writing, lapatinib had not yet received its marketing authorisation. The final scope issued by NICE stated that the population should be women with advanced, metastatic or

recurrent breast cancer that overexpresses the HER2 receptor who have had previous therapy that includes trastuzumab. The outcomes stated in the manufacturer's definition of the decision problem were time to progression (primary end point), progression-free survival, response rates, overall survival, health-related quality of life and adverse effects.

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 (PSA) were undertaken by the ERG. The cost-effectiveness acceptability curves for capecitabine monotherapy and lapatinib plus capecitabine from the ERG's PSA are shown in *Figure 1*.

Results

Summary of submitted clinical evidence

The main evidence in the submission came from one multicentre, multinational, open-label randomised controlled trial (RCT), EGF100151. Interim analyses from the trial were published in 2006, but the evidence in the report was from a later time point. These later data were expected to be published in June 2007,[8] but had not been published when the ERG report and this summary were written.

Median time to progression was longer in the lapatinib plus capecitabine arm than in the capecitabine monotherapy arm [27.1 weeks (95% CI 17.4 to 49.4) versus 18.6 weeks (95% CI 9.1 to 36.9)], although the CIs overlapped. The hazard ratio reported in the manufacturer's submission was 0.57 (95% CI 0.43 to 0.77; $p = 0.00013$).

Median overall survival was very similar between the two groups [67.7 weeks (95% CI 58.9 to 91.6) versus 66.6 weeks (95% CI 49.1 to 75.0) for lapatinib plus capecitabine versus capecitabine monotherapy respectively)]. The hazard ratio was 0.78 (95% CI 0.55 to 1.12; $p = 0.177$).

Median progression-free survival was statistically significantly longer in the lapatinib plus capecitabine group than in the capecitabine monotherapy group [27.1 weeks (95% CI 24.1 to 36.9) versus 17.6 weeks (95% CI 13.3 to 20.1); hazard ratio 0.55 (95% CI 0.41 to 0.74); $p = 0.000033$].

Summary of submitted cost-effectiveness evidence

The cost-effectiveness analysis used survival modelling methodology to estimate progression-free and overall survival for patients with HER2-positive advanced/metastatic breast cancer who had relapsed following treatment with an anthracycline, a taxane and trastuzumab. The incremental costs and consequences of treatment with lapatinib plus capecitabine were estimated relative to each of five different comparator regimes. Comparators were capecitabine monotherapy, vinorelbine monotherapy, trastuzumab monotherapy, trastuzumab plus capecitabine and trastuzumab plus vinorelbine.

The model was generally internally consistent and appropriate to metastatic breast cancer in terms of structural assumptions, although it used a different approach from previous economic evaluations of treatments for metastatic breast cancer.[9–13] The cost-effectiveness analysis generally conformed to the NICE reference case and the scope/decision problem.

Treatment effects for lapatinib plus capecitabine and capecitabine monotherapy were derived from direct clinical trial evidence. In the absence of data on the effectiveness of vinorelbine monotherapy, it was assumed to be identical to that of capecitabine monotherapy. The effectiveness of trastuzumab-containing regimes was based on pooling of data on time to disease progression, which was used in an unadjusted indirect comparison.

Utilities for preprogression survival were based on responses to the EuroQol 5 dimensions (EQ-5D) questionnaire in the EGF100151 trial. There were substantial missing data for the quality of life assessment in the trial. The utility reduction

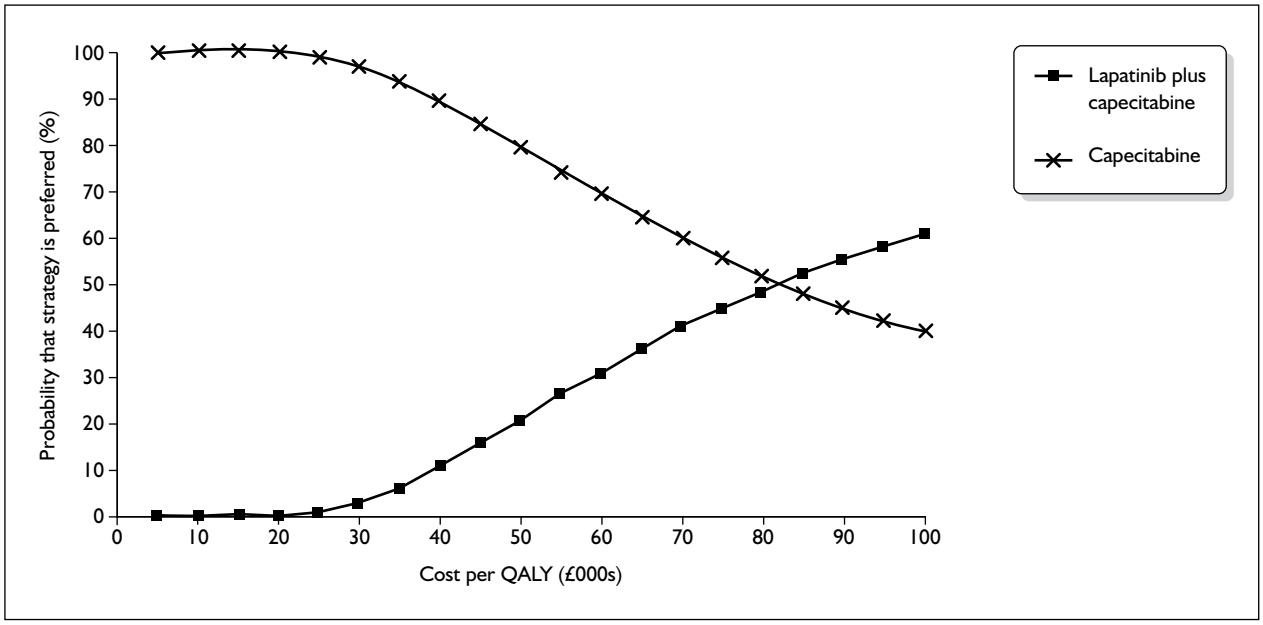

FIGURE 1 *Cost-effectiveness acceptability curves for capecitabine monotherapy and lapatinib plus capecitabine from the ERG's probabilistic sensitivity analysis. QALY, quality-adjusted life-year.*

following disease progression was based on a published study,[14] which reported general population valuations of disease progression and the impact of treatment-related adverse events.

The base-case incremental cost-effectiveness ratios (ICERs) for lapatinib plus capecitabine compared with capecitabine monotherapy or vinorelbine monotherapy were higher than would conventionally be considered cost-effective. When compared with trastuzumab-containing regimes, lapatinib plus capecitabine dominated (i.e. gave improved outcome at lower cost).

Sensitivity analyses reported in the manufacturer's submission and undertaken by the ERG showed that the ICER for lapatinib plus capecitabine compared with capecitabine monotherapy or vinorelbine monotherapy was robust to variation in assumptions. In all sensitivity analyses the ICERs remained higher than would conventionally be considered cost-effective. ICERs for trastuzumab-containing regimes were highly sensitive to assumptions over the frequency of treatment (weekly or three-weekly), the distribution of weight and body surface area of patients receiving treatment, and wastage for infusional regimes.

Commentary on the robustness of submitted evidence

Strengths

The manufacturer's submission was well written and presented a clear description of the evidence base. The manufacturer conducted a systematic review for this appraisal and searched all relevant databases using appropriate search strategies.

The identified RCT EGF100151 appeared to be of reasonable methodological quality, although enrolment was terminated before the required sample size had been met.

The economic model presented with the manufacturer's submission used an appropriate approach for the disease area and given the available data.

Weaknesses

There was some deviation from the scope issued by NICE in terms of the timing of previous lines of therapy, and of comparator treatments.

Only one relevant RCT was identified by the manufacturer's systematic review and the evidence base for lapatinib plus capecitabine in the manufacturer's submission was largely based on this one trial. Early termination of enrolment meant that there was insufficient power to detect a statistically significant difference in mean overall survival.

The trastuzumab studies pooled for an indirect comparison contained a variety of treatment regimens. None of the studies contained a capecitabine monotherapy arm and so it was not possible for the manufacturer to perform an adjusted indirect comparison.[15] The manufacturer therefore used a methodologically weaker unadjusted indirect comparison. The resulting pooled mean of median time to progression values for trastuzumab may not be a reliable estimate and should therefore be treated with caution.

There was no evidence in the manufacturer's submission of a systematic search for model parameters, in particular cost inputs and utilities.

Conclusions

Areas of uncertainty

Trastuzumab monotherapy was included as a comparator. Consultation with clinical advisors suggested that trastuzumab is used beyond progression in combination with chemotherapy agents in some primary care trusts, but not others. Clinical advisors indicated that trastuzumab monotherapy is unlikely to be continued beyond disease progression.

The manufacturer's submission included a post hoc subgroup analysis of patients with brain metastases. It is likely that this is underpowered and so it should be treated with caution.

There was a lack of robust and reliable evidence on the effectiveness of the majority of comparators included in the economic model (vinorelbine monotherapy and all of the trastuzumab-containing regimes).

There was uncertainty over the pattern of treatment with trastuzumab if it is continued beyond disease progression, in particular whether treatment is weekly or three-weekly. This had a large effect on the cost-effectiveness of lapatinib plus capecitabine.

Key issues

The included trial was not powered to detect a statistically significant difference in overall survival between lapatinib plus capecitabine and capecitabine monotherapy.

There was a general lack of evidence on the effectiveness of comparators included in the economic model. A lack of evidence on other key parameters (such as dose adjustments) meant that there was a great deal of uncertainty and model outputs need to be interpreted in the light of that uncertainty.

Summary of NICE guidance issued as a result of the STA

At the time of writing, NICE were still considering the available evidence for this appraisal.

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Infliximab for the treatment of ulcerative colitis

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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 infliximab for moderately to severely active ulcerative colitis (UC) based upon a review of the manufacturer's submission to the National Institute for Health and Clinical Excellent (NICE) as part of the single technology appraisal (STA) process. The submission indicated that the efficacy of infliximab (5 mg/kg) had been demonstrated in terms of higher response rates and a sustained response in health-related quality of life. For the cost-effectiveness analysis, the manufacturer built a Markov model to compare infliximab with standard care. It estimated the incremental cost per quality-adjusted life-year (QALY) gained was between £25,044 and £33,866 depending on the strategy used. The ERG report generally agreed with the evidence on effectiveness of infliximab for subacute exacerbations of UC. However, there were several areas of uncertainty, of which the interpretation of the importance of the quality of life changes in the subacute situation and the assessment of the adequacy of the evidence of effectiveness of infliximab in the acute hospital-based situation were considered pre-eminent by the ERG. This challenged the estimates of cost-effectiveness offered and suggested that there should be a separate assessment of infliximab for acute exacerbations of moderately to severely active UC. The summary of the NICE guidance issued in April 2008 as a result of the STA states that: infliximab is not recommended for the treatment of subacute manifestations of moderately to severely active UC.

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

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.[1] 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 infliximab for ulcerative colitis (UC).[2] This STA was subsequently split into two parts, infliximab for subacute manifestations of UC and infliximab for acute exacerbations of UC. The latter is the subject of a separate STA and report (08/37/01).

Description of the underlying health problem

Ulcerative colitis is a chronic condition in which there is inflammation of the mucosa of the large intestine. The incidence of UC is approximately 10–20 per 100,000 per year with a reported prevalence of 100–200 per 100,000 in the UK.

The symptoms of UC vary according to the extent and severity of the inflammation. The classic symptom of UC is bloody diarrhoea. Associated symptoms of colicky abdominal pain, urgency or tenesmus may be present. Mildly active UC is defined as less than four bowel movements daily. Moderately active UC is defined as more than four bowel movements daily, but when the patient is not systemically ill. Severe UC is defined as an attack in which the patient has more than six bowel movements daily and is systemically ill as shown by tachycardia, fever and anaemia. Fulminant disease correlates with more than 10 bowel movements daily, continuous bleeding, toxicity, abdominal tenderness and distension, blood transfusion requirement and colonic dilatation (expansion).

In UC the severity of the symptoms fluctuates unpredictably over time with intervals of remission or reduced symptoms. Approximately 50% of patients with UC have a relapse in any year. A significant minority have frequently relapsing or chronic continuous disease. In total, 25% of patients with severe UC are admitted to an inpatient setting with flares of UC that are not responding to steroids. An estimated 20–30% of patients with pancolitis (disease affecting the entire colon) will require colectomy.

The British Society of Gastroenterology published guidelines for the treatment of UC in 2004. The main recommendations for the medical management of active left-sided or extensive UC are treatment with oral aminosalicylates or corticosteroids. In active distal UC (i.e. colitis confined to the rectum, or rectum and sigmoid colon) treatment options include topical mesalazine, or topical corticosteroids combined with oral mesalazine, or systemic corticosteroids. When in remission patients with UC should normally receive maintenance therapy with aminosalicylates, azathioprine or mercaptopurine to reduce the risk of relapse. Patients frequently receive combination therapies. Severe UC should be managed jointly by a gastroenterologist in conjunction with a colorectal surgeon.

Infliximab (Remicade®, Schering-Plough) is a chimeric monoclonal antibody that binds with high affinity to tumour necrosis factor (TNF)-α, thereby neutralising its activity. It is administered by intravenous infusion and is licensed for use in rheumatoid arthritis, active Crohn's disease, psoriasis, psoriatic arthritis and ankylosing spondylitis as well as in UC.

Infliximab is licensed for moderately to severely active UC in patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine or azathioprine, or who are intolerant to or who have medical contraindications to such therapies.

Scope of the ERG report

The purpose of the ERG report is to comment on the validity of the manufacturer's submission on the technology of interest. The scope for this submission and hence the scope for the ERG report was to appraise the clinical effectiveness and cost-effectiveness of infliximab for moderately to severely active UC.

The population considered was adults with moderately to severely active UC who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine or azathioprine, or who are intolerant to or who have medical contraindications to such therapies. The intervention was infliximab.

The standard comparators to be considered included standard care [which may include conventional therapy with a combination of 5-aminosalicylic acid (5-ASA) compounds, corticosteroids and immunomodulators (azathioprine or 6-mercaptopurine)], ciclosporin and surgery.

The outcome measures to be considered included health-related quality of life, survival, measures of disease activity, rates of and duration of response, relapse and remission, rates of hospitalisation, reduction in use of corticosteroids, rates of surgical intervention and adverse effects of treatment.

For the economic analysis the reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life-year (QALY). The time horizon should be long enough to allow reasonable estimation of expected costs (including adverse events if applicable) and benefits for each of the two clinical situations. Costs were considered from an NHS and personal social services perspective.

When evidence permitted, the appraisal of infliximab for moderate to severely active UC was to identify patient subgroups for whom the technology was most appropriate and to consider the length of treatment required when patients have responded to infliximab. Guidance was only to be issued in accordance with the summary of product characteristics.

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.

Specific steps undertaken by the ERG included:

- discussion of the nature of the problem with a clinical expert
- reanalysis of the nature of the underlying clinical question
- rerunning searches indicated to have been carried out to inform the manufacturer's submission
- extending searches, particularly for ongoing trials
- a formal critical appraisal of the systematic review underpinning the manufacturer's submission, and a related Cochrane review
- reappraisal and checking of data abstraction on two key included studies
- detailed checking of company reports (commercial-in-confidence data) of the pivotal trials
- rerunning of meta-analyses, correcting errors in the submission
- checking the consistency of the effectiveness estimates emerging from the systematic review with the parameters used in the economic model
- rerunning of the economic model supplied by the company
- correction of an error in the reporting of the results of the economic model
- additional sensitivity analyses within the limits of the facilities of the submitted model.

The work was carried out between 20 May 2007 and 22 July 2007. Members of the ERG team attended and advised the meetings of the NICE appraisal committee where this guidance was discussed on 22 August 2007 and 20 November 2007.

Results

Summary of submitted clinical evidence

The submission attempted to systematically review the randomised controlled trial (RCT) evidence comparing infliximab with placebo. It used an existing Cochrane review as its starting point. The submission identified no new RCTs and included five RCTs, reported in four articles, which are well recognised. Three RCTs consider the subacute, outpatient application of infliximab and two consider the acute, hospital-based application, which is argued to be 'off-label' use.

The submission highlighted that the efficacy of infliximab at a dose of 5 mg/kg has been demonstrated, particularly by two large RCTs [ACT (Active Ulcerative Colitis Trial) I and II] in terms of higher response rates and a sustained response in health-related quality of life. Infliximab was well tolerated.

Summary of submitted cost-effectiveness evidence

No published economic evaluations of infliximab in UC were identified and so the cost-effectiveness work focused almost entirely on the de novo model and economic evaluation undertaken by the manufacturer. A Markov model was built to compare two treatment strategies, infliximab versus standard care, in terms of costs and QALYs. The patient group modelled had moderately to severely active UC and included patients 'who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA (6-mercaptopurine or azathioprine respectively), or who are intolerant to or have medical contraindications for such therapies'. The main submission only considered patients in this category (although the manufacturer's clarification response included results for patients who were more severe, for whom surgery is the comparator considered). The modelling was undertaken, in part, using data from the ACT trials.

The model followed a cohort of patients with moderate or severe UC from entry through to 10 years, with patients being tracked as they moved between the nine states in the model. The cycle length was 8 weeks. The disease states in the model were defined as remission (Mayo score 0–2), mild (Mayo score 3–5) and moderate/severe (Mayo score 6–12).

Two separate treatment strategies were evaluated, which differ in the assumption made about continuation of infliximab therapy. Strategy A modelled the continuation of infliximab in treatment responders who achieved and maintained remission or mild health states. In contrast, strategy B considered a narrower therapy continuation group defined as responders who achieve and maintain remission. The results of the economic analyses indicated that the incremental cost per QALY gained was £33,866 for strategy A and £25,044 for strategy B.

Commentary on the robustness of submitted evidence

Strengths

The submission comprehensively ascertained all of the available RCTs comparing infliximab with placebo. This is in agreement with other reviews in the field. Helpful additional information on the key included RCTs was made available when requested.

The submission reported a de novo model-based economic evaluation that considered the cost-effectiveness of infliximab in UC. The use of a Markov model is appropriate as the disease is characterised by progression over time and so a modelling approach that can deal with transition between states and the timing of events is required. The main transition probability inputs were derived from two relevant trials, the ACT trials, and many of the other inputs and parameters were based on appropriate data. Probabilistic sensitivity analysis (PSA) and one-way sensitivity analyses were performed.

Weaknesses

The review was generally poorly reported. The conduct of the review was at best adequate and there were some important deficiencies. For instance, several data abstraction errors were identified. Also the summary of the results of the included studies lacked clarity and the meta-analyses attempted were incorrect. In the analysis the submission failed to clearly separate the results relating to subacute applications of infliximab from the acute applications in hospital.

Despite the errors in the review of clinical evidence offered in the submission the ERG's own summary suggests that portrayal of the effectiveness evidence in the manufacturer's submission remains reasonably faithful. Infliximab is effective in increasing clinical response, remission and mucosal healing and in improving health-related quality of life in moderate to severe UC in the outpatient setting.

In terms of the submitted evidence on cost-effectiveness there are serious concerns in relation to the appropriateness of the policy question being addressed and a judgement is required as to whether this question is the question of most interest to NICE. The manufacturer's analysis considered the use of infliximab in patients with moderate to severe UC compared with standard care including 5-ASA compounds, corticosteroids and immunomodulators (azathioprine or 6-mercaptopurine). However, the scope indicated that the question of interest for NICE was the use of infliximab in patients who have had an inadequate response to conventional therapy for whom the comparator technologies include surgery or ciclosporin.

The manufacturer chose not to make use of the health utility data available from the ACT trials,

but rather commission a new cross-sectional study to gather new health utility data. Given that much of the input data for the model were taken from the ACT trials, this decision is surprising and requires justification.

The model had a time horizon of 10 years for the base case, but the longest follow-up in the ACT trials was 54 weeks. Thus, the transition probabilities were derived from trial data up to 54 weeks and were assumed to remain constant through to 10 years.

The PSA was undertaken in a very partial manner, with distributions placed around selected parameters only. Errors in the interpretation of the PSA and calculation of the cost-effectiveness acceptability curve were identified.

Conclusions

The key areas of uncertainty identified were:

- There is evidence on the effectiveness of infliximab in the acute hospital-based setting in terms of response and avoidance of surgery; however, the results are primarily based on one small study, even though the effect on colectomy rates is highly statistically significant.
- The evidence on colectomy and ostomy rates in the subacute setting is unclear, and indeed there are some inconsistencies between different reports of hospitalisation rates from ACT I and II.
- In ACT I and II, although the statistical significance of the differences in change in quality of life with infliximab compared with placebo are clear, the importance of these changes to the patient is less easy to define, an issue with a key bearing on the interpretation of the cost-effectiveness component of the submission.
- In common with all newly introduced drugs the long-term safety of infliximab needs to be established, particularly with respect to the risk of malignancy.
- The definition of the policy question and, depending on the answer to this question, the appropriate trials from which to be drawing data.
- A key driver of the model results is the utility data and so a judgement on the most appropriate source of utility data is required.
- The robustness of the assumption concerning long-term follow-up to 10 years, given that this is based on trial data to 54 weeks.

Of these, the interpretation of the importance of the quality of life changes in the subacute situation and the assessment of the adequacy of the evidence of effectiveness of infliximab in the acute hospital-based situation were considered pre-eminent by the ERG.

Summary of NICE guidance issued as a result of the STA

At the time of writing, the guidance document issued by NICE in April 2008 states that:

Infliximab is not recommended for the treatment of subacute manifestations of moderately to severely active ulcerative colitis.

For the purposes of this guidance, a subacute manifestation of moderately to severely active ulcerative colitis is defined as disease that would normally be managed in an outpatient setting and that does not require hospitalisation or the consideration of urgent surgical intervention.

Key references

1. National Institute for Health and Clinical Excellence. *Guide to the single technology (STA) process*. 19 September 2006. URL: www.nice.org.uk/page.aspx?o=STAprocessguide.

2. Hyde C, Bryan S, Juarez-Garcia A, Andronis L. *Infliximab for ulcerative colitis*. Birmingham: West Midlands Health Technology Assessment Collaboration, University of Birmingham; July 2007. URL: www.nice.org.uk/nicemedia/pdf/UlcerativeColitisEvidenceReviewGroupReport.pdf. Accessed 1 November 2008.

Rimonabant for the treatment of overweight and obese people

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Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical and cost-effectiveness of rimonabant for the treatment of obese or overweight patients based upon a review of the manufacturer's submission to the National Centre for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The submission's main evidence came from four randomised controlled trials. Rimonabant resulted in a significantly greater benefit than placebo for all primary weight loss outcomes. At 1 year, rimonabant had a statistically significant beneficial effect on systolic blood pressure, high-density lipoprotein cholesterol, triglycerides and fasting plasma glucose in diabetics and non-diabetics, and glycosylated haemoglobin in diabetics. Improvements were maintained over 2 years with rimonabant; withdrawal of rimonabant at 1 year resulted in a reduction in weight loss until there was no difference from placebo at 2 years. Psychiatric adverse events were experienced by 26% and 14% of rimonabant and placebo patients respectively; figures for symptoms of depression were 9% and 5% respectively. Pairwise comparisons of orlistat, sibutramine and rimonabant showed beneficial effects of rimonabant over orlistat and sibutramine for weight loss outcomes; however, response hurdles imposed on orlistat or sibutramine in clinical practice may not have been applied in the orlistat and sibutramine trials. The manufacturer's Markov cohort model evaluated rimonabant versus orlistat, sibutramine and diet

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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).

and exercise alone for three base-case populations. The incremental cost-effectiveness ratio (ICER) of rimonabant varied from £10,534–£13,236 per quality-adjusted life-year (QALY) versus diet and exercise, to £8977–£12,138 per QALY versus orlistat, to £1463–£3908 per QALY versus sibutramine. In subgroup analysis there was a wider variation in the ICER estimates although none exceeded £20,000 per QALY. The ICER of rimonabant remained under £20,000 per QALY in reanalyses by the manufacturer and the ERG, with the results sensitive to the source of health-related quality of life (HRQoL) benefits in the model. Four treatment strategies were modelled in comparisons of rimonabant versus diet and exercise alone and orlistat and sibutramine in which rimonabant was continued only in patients achieving 5% weight loss at 3, 6, 9 or 12 months. In pairwise comparisons rimonabant remained below a threshold of £30,000 per QALY in 70% of the comparisons reported. The results were most sensitive to the decrement applied to depression and the costs of screening for depression. In conclusion, areas of uncertainty remain in relation to the clinical effectiveness and cost-effectiveness of rimonabant, for example lack of evidence on long-term outcomes and the effect of rimonabant on cardiovascular events, developing diabetes and mortality, and lack of data on the HRQoL benefits associated with rimonabant. The lack of response hurdles applied to sibutramine and orlistat means that the comparator strategies were not considered by the ERG to reflect their respective product licenses or current NHS use. The NICE guidance issued as a result of the STA states that rimonabant is recommended as an adjunct to diet and exercise for adults who are obese or overweight and who have had an inadequate response to, are intolerant of or are contraindicated to orlistat and sibutramine.

Introduction

The National Institute for Health Research Health Technology Assessment (NIHR HTA) programme supports the National Institute for Health and Clinical Excellence (NICE) by funding independent academic input to NICE technology appraisal activities. 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 (Sanofi-Aventis).[1] 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 to NICE. 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 rimonabant for the treatment of overweight and obese patients,[2] which was submitted on 5 October 2007 to NICE, with a subsequent submission of a commentary on 24 January 2008.

In October 2008, the European Medicines Agency (EMEA), based on new evidence that became available from postmarketing surveillance studies following the NICE appraisal of rimonabant, concluded that the balance of risks and benefits no longer supported the use of rimonabant and the drug was withdrawn from use. It should therefore be noted that this report is based only on evidence available to NICE at the time of its appraisal of rimonabant and does not include any further evidence that informed the EMEA's decision on withdrawal.

Description of the underlying health problem

Obesity is a chronic condition which is associated with a number of conditions such as type 2 diabetes that have a significant impact on morbidity and quality of life and reduce life expectancy. There are currently several options for the treatment of overweight and obese patients, including lifestyle changes, drug treatments and bariatric surgery. According to NICE guidelines, the initial treatments of choice for overweight and obese patients are multicomponent interventions that include behavioural change strategies to promote physical activity and improve eating habits.

Three drugs are currently used in practice to treat obesity: orlistat (Xenical®, Roche), sibutramine (Reductil®, Abbott) and rimonabant (Accomplia®). Orlistat is a specific and long-acting inhibitor of the enzyme lipase, which results in the inability to hydrolyse dietary fat in the form of triglycerides into absorbable free fatty acids

and monoglycerides, therefore preventing fat absorption. The net price per 84-cap pack is £33.58, with an approximate annual cost of £438. Sibutramine produces secondary and primary amine metabolites that inhibit noradrenaline, serotonin and dopamine reuptake, which in turn suppresses appetite by producing a feeling of satiety. The net price per 28-cap pack of 10 mg is £36.90. The net price per 28-cap pack of 15 mg is £43.65. The approximate annual cost is £481 for 10 mg and £569 for 15 mg. Rimonabant is a selective CB1 cannabinoid receptor antagonist and acts by decreasing appetite. The net price per 28-tab pack is £44.00, with an approximate annual cost of £574.

The manufacturer's submission to NICE stated that, since the introduction of rimonabant until the end of June 2007, approximately 32,500 patients have been prescribed rimonabant in England and Wales, accounting for 16.4% of prescription initiations for obesity treatments during that period. Patients with comorbidities accounted for a large majority of rimonabant prescriptions.

Concerns have been raised relating to the licensing of rimonabant, both in the UK and in the USA. In January 2007, the Scottish Medicines Consortium decided that the economic case for prescribing rimonabant had not been demonstrated and therefore did not recommend its use within NHS Scotland as an adjunct to diet and exercise for the treatment of obese or overweight patients. The US Food and Drugs Administration (FDA) also did not recommend a license for rimonabant in the USA because of the risk of psychiatric adverse events, particularly the incidence of suicidality and suicidal ideation. The safety profile of rimonabant was reviewed by the EMEA and its use in patients with ongoing major depressive illness and/or ongoing antidepressive treatment is now precluded.

Scope of the ERG report

The ERG report presented a critical evaluation of the manufacturer's submission (Sanofi-Aventis), which evaluated the evidence for the clinical effectiveness, safety, tolerability and cost-effectiveness of rimonabant in its licensed indication as an adjunct to diet and exercise, relative to other licensed antiobesity drugs (orlistat and sibutramine) and diet and exercise alone.

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. In addition, the ERG:

- Generated tables from data provided in the body of the original and clarification submissions, and the appendices of the original submission, in order to present a clear summary of the relative and absolute weight effects of rimonabant at 1 year.
- Repeated the meta-analyses for the primary weight loss outcomes [except for body mass index (BMI) as insufficient data were provided] including all four RIO trials (Rimonabant In Obesity).
- Compared the results for orlistat and sibutramine included in the submission with those presented in the NICE guidelines[3] because of concerns about how representative of the general literature the trials of orlistat and sibutramine included in the submission were.
- Conducted additional analyses to provide further insight into the potential impact on the cost-effectiveness estimates of key issues and uncertainties identified during the structured critique of the manufacturer's submission.
- Conducted additional analyses to clarify the relative importance of the independent effect of BMI on utilities compared with the impact of the other risk factors on cardiovascular disease (CVD) and diabetes event rates in the incremental cost-effectiveness ratio (ICER) estimates.

Results

Summary of submitted clinical evidence

Effectiveness of rimonabant

The evaluation of the efficacy of rimonabant focused primarily on the results of four Sanofi-Aventis-sponsored randomised control trials (RCTs): (RIO-Europe[4], RIO-North America[5], RIO-Diabetes[6] and RIO-Lipids[7]). Two further trials were cited but did not contribute to the main meta-analyses [SERENADE (Study Evaluating Rimonabant Efficacy in drug-NAive DiabEtic patients) and REBA (Riminobant Eating Behaviour Assessment study)]. Data from two unpublished studies were used to inform the analysis of adverse effects (EFC5745 and ACT3801).

Rimonabant resulted in a significantly greater benefit than placebo in terms of all primary weight loss outcomes:

- change in weight (kg): non-diabetics: weighted mean difference (WMD) –4.91 [95% confidence interval (CI) –5.35 to –4.48]; diabetics: WMD –3.90 (95% CI –4.57 to –3.23)
- proportion of patients losing 5% body weight: non-diabetics: relative risk (RR) 2.61 (95% CI 2.32 to 2.95); diabetics: RR 3.41 (95% CI 2.58 to 4.50)
- proportion of patients losing 10% body weight: non-diabetics: RR 3.48 (95% CI 2.84 to 4.27); diabetics: RR 8.07 (95% CI 3.37 to 17.46)
- change in waist circumference (cm): non-diabetics: WMD –4.01 (95% CI –4.50 to –3.53); diabetics: WMD –3.30 (95% CI –4.17 to –2.43)
- BMI (kg/m^2): non-diabetics: WMD –1.76 (95% CI –1.92 to –1.60); diabetics: WMD –3.90 (95% CI –4.57 to –3.23); for any baseline BMI, the average weight loss beyond that which can be achieved with diet and exercise over a 1-year period is around 5 kg, with a fall in BMI of 1.7 kg/m^2.

The ERG generated pooled estimates using data from all four of the RIO trials. The results for the change in weight and the proportion who achieved 5% weight loss are shown in *Figures 1* and *2* respectively. These analyses show that the a priori decision by the manufacturer to pool data for diabetics and non-diabetics separately was justified statistically as well as clinically. However, although the mean weight loss and placebo-subtracted reduction in BMI in the RIO-Diabetes trial were slightly lower than in the other RIO trials, the other primary outcomes did not indicate any materially different treatment effect in this population.

Two of the RIO trials (RIO-North America, RIO-Lipids) reported significantly greater reductions in body weight in patients achieving at least 5% weight loss with rimonabant than with placebo. None of the trials reported significantly greater reductions in body weight in patients achieving at least 10% weight loss with rimonabant, or in waist circumference in patients achieving at least 5% or 10% weight loss with rimonabant compared with placebo.

At 1 year, rimonabant had a statistically significant beneficial effect on systolic blood pressure, high-density lipoprotein cholesterol, triglycerides and fasting plasma glucose in both diabetic and non-diabetic patients, and glycosylated haemoglobin (Hb_{A1c}) in diabetic patients. Weight loss and improvements in associated cardiovascular and diabetes risk factors were maintained over 2 years when rimonabant was continued; however, the relative benefit over placebo was lower in year 2. Following withdrawal of rimonabant treatment at 1 year, there was a gradual reduction in the rate of weight loss until there was no difference from placebo at 2 years.

In total, 13 adverse events were identified by the manufacturer as being associated with rimonabant at a rate of ≥ 2%, and at a rate of ≥ 1% greater than placebo (*Table 1*). Some form of psychiatric adverse event was experienced by 26% of patients receiving 20 mg rimonabant across the four RIO trials, compared with 14% of patients receiving placebo. Symptoms of depression were reported in 9% of patients taking 20 mg rimonabant compared with 5% of patients taking placebo. These rates were broken down further, with the most commonly reported psychiatric adverse events as stated in the FDA briefing shown in *Table 2*.[8]

Two separate instruments were used to evaluate the effect of rimonabant on health-related quality of life (HRQoL). One was the obesity-specific Impact of Weight on Quality of Life-Lite (IWQOL-Lite) and the other the generic Medical Outcomes Study Short Form-36 (SF-36). Rimonabant provided benefits in some areas of HRQoL, particularly physical functioning, but was associated with a significant deterioration in mental health.

On request, the manufacturer provided analyses of responder and non-responder data for 3, 6, 9 and 12 months. These analyses were based on patients with complete weight measurements for months 3, 6 and 9. Data at 12 months were based on an intention-to-treat (ITT) analysis using last observation carried forward (LOCF). For rimonabant-treated patients, responders lost more weight than non-responders. Comparison of the 12-month response data based on the LOCF and completer analysis indicates the use of the completer analysis is likely to result in higher response rates than the LOCF approach (e.g. 49.3% using LOCF compared with 64.4% using a completer analysis for one of the two populations considered, 49.4% versus 56% for the other).

In addition, the manufacturer provided an assessment of the diagnostic value of predicting a

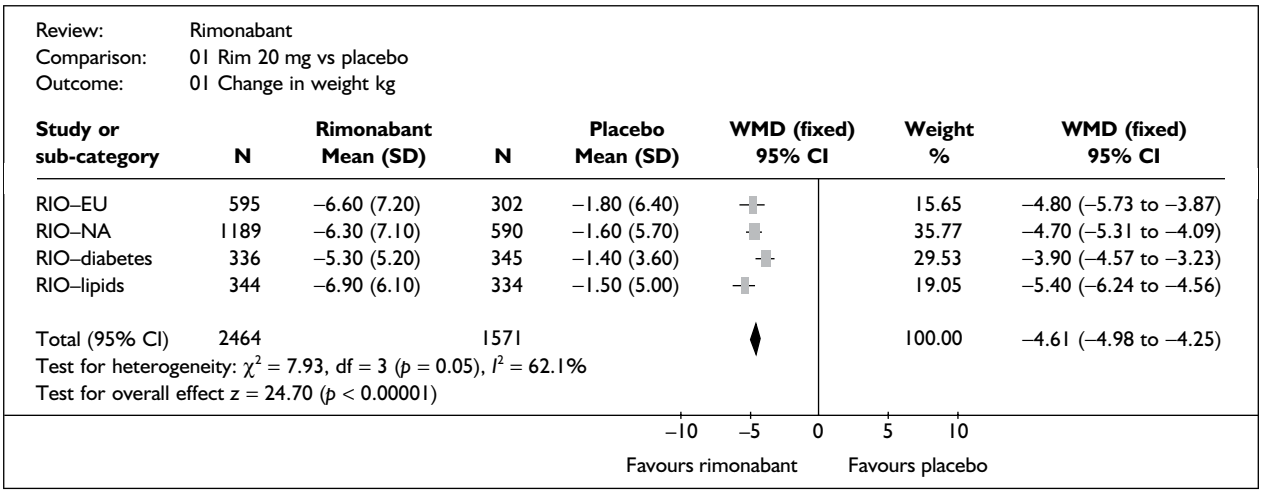

FIGURE 1 *Meta-analyses for change in weight (kg) from baseline to 1 year (intention to treat data) (ERG generated). CI, confidence interval; SD, standard deviation; WMD, weighted mean difference.*

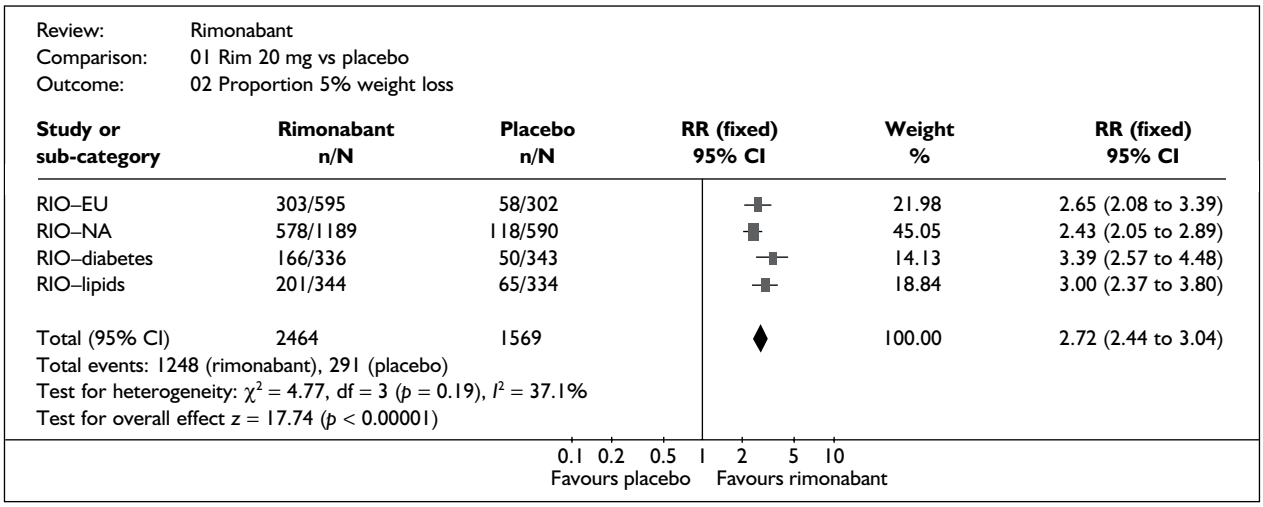

FIGURE 2 *Proportion of patients achieving 5% weight loss. CI, confidence interval; RR, relative risk.*

1-year response at earlier time points by calculating the sensitivity and specificity of these time points. At 3 months sensitivity was 0.57 and specificity 0.89; sensitivity increased at 6 and 9 months (0.85 and 0.91 respectively) and specificity remained high (0.80 and 0.81 respectively).

Comparison of rimonabant with orlistat and sibutramine

In the absence of head-to-head trials, the manufacturer provided tabulated comparisons between the placebo-subtracted results for orlistat, sibutramine and rimonabant. On request, pairwise comparisons between rimonabant and sibutramine and orlistat were provided for the primary outcomes. These pairwise comparisons showed a significant increase in the number of patients achieving 5% weight loss with rimonabant compared with sibutramine in the non-diabetic population. In addition, rimonabant compared favourably with orlistat in terms of body weight (non-diabetics, diabetics and dyslipidaemics); waist circumference (non-diabetics and dyslipidaemics); change in BMI (non-diabetics); patients who achieved 5% weight loss (non-diabetics and diabetics); and patients who achieved 10% weight loss (non-diabetics and diabetics). There was no comparison of adverse events or HRQoL between rimonabant and orlistat or sibutramine.

Summary of submitted cost-effectiveness evidence

Only one previously published study reporting on the cost-effectiveness of rimonabant was identified. This study evaluated the cost-effectiveness of rimonabant compared with diet and exercise

TABLE 1 *The proportion of patients experiencing adverse events at a rate of ≥ 2% in the rimonabant group and ≥ 1% more than in the placebo group; results are pooled from seven trials for the 1-year data (the four RIO trials, REBA, EFC5745 and ACT3801) and two trials for the 2-year data (RIO-North America and RIO-Europe)*

	Year 1	
	Rimonabant (*n* = 2742)	**Placebo (*n* = 2474)**
Any event	86.3	81.4
Nausea	13.6	4.7
Diarrhoea	7.7	5.8
Vomiting	4.7	2.3
Dizziness	7.3	4.1
Anxiety	5.9	2.1
Insomnia	5.8	3.4
Mood alterations with depressive symptoms	4.7	2.8
Depressive disorders	3.9	1.7
Influenza	10.3	9.1
Asthenia/fatigue	6.1	4.4
Gastroenteritis	4.5	3.5
Contusion	3.1	1.1
Hot flush	2	0.8

TABLE 2 *The number (%) of patients experiencing psychiatric symptoms across the four RIO trials as reported in the US Food and Drugs Administration briefing document*[8]

	20 mg rimonabant	**Placebo**
Any psychiatric adverse event	569 (26.2)	226 (14.1)
Anxiety	131 (6.02)	40 (2.50)
Insomnia	118 (5.42)	53 (3.31)
Depressed mood	83 (3.81)	45 (2.81)
Depression	74 (3.40)	23 (1.44)
Irritability	1.93%	0.56%
Stress	38 (1.75)	28 (1.75)
Nervousness	31 (1.42)	5 (0.31)
Depressive symptoms	23 (1.06)	12 (0.75)
Sleep disorder	21 (0.97)	7 (0.44)
Nightmare	21 (0.97)	3 (0.19)

alone. No published studies were identified that had compared rimonabant with other licensed antiobesity drugs.

The manufacturer's submission was based on a de novo economic evaluation of rimonabant compared with orlistat, sibutramine and diet and exercise alone. Separate models were presented based on a Markov cohort model and a patient-level approach using discrete event simulation. The main submission focused on the Markov cohort model.

The Markov model evaluated the following treatment comparisons: (1) lifetime rimonabant plus diet and exercise versus lifetime diet and exercise alone; (2) lifetime rimonabant plus diet and exercise versus lifetime orlistat plus diet and exercise; and (3) 1-year rimonabant plus diet and exercise versus 1-year sibutramine plus diet and exercise. The results of the economic evaluation were presented for three base-case populations: (1) overweight or obese patients with treated type 2 diabetes (diabetic group); (2) overweight or obese patients with dyslipidaemia, not treated with a statin and without type 2 diabetes (dyslipidaemic

group); and (3) obese patients with or without comorbidities (obese group). A number of additional subgroups were considered as part of the sensitivity analysis.

In the absence of direct head-to-head RCT data for the alternative strategies, indirect approaches were employed to assess the relative effectiveness of each treatment strategy in terms of its impact on a number of established risk factors for CVD and diabetes. A series of published risk equations was used to translate changes in these risk factors to a reduced risk of CVD and, in patients without diabetes, to a reduced risk of developing diabetes. The effect of the treatments on BMI was also assumed independently to influence HRQoL beyond that attributed to the effect on CVD and diabetes risks. These approaches were used as the basis for estimating quality-adjusted life-years (QALYs) over a lifetime time horizon. Costs were based on the drug acquisition and monitoring costs, adverse events and the costs of CVD and diabetes. Costs and QALYs were compared and ICERs of rimonabant estimated when appropriate. The robustness of the results was assessed using deterministic and probabilistic sensitivity analyses.

Across the base-case populations, the ICER of rimonabant varied from £10,534 to £13,236 per QALY versus diet and exercise, from £8977 to £12,138 per QALY versus orlistat and from £1463 to £3908 per QALY versus sibutramine. In the additional subgroups considered there was a wider variation in the ICER estimates; however, none of the individual pairwise ICERs for rimonabant exceeded £20,000 per QALY in any of the subgroups. The ICER estimates across the majority of the sensitivity analyses were broadly consistent with the base-case results.

The ERG considered that the original submission contained a number of important uncertainties and issues which potentially compromised the validity of the model results. A number of these issues were addressed by the manufacturer as part of their response to the ERG's points for clarification. The ERG identified a number of remaining issues related to the manufacturer's response and several of these were subsequently addressed with additional analyses conducted by the ERG. The ICER of rimonabant remained relatively robust throughout the reanalyses by the manufacturer and the ERG (< £20,000 per QALY), although the results did appear to be sensitive to the source of HRQoL benefits assumed in the model, with markedly less favourable ICER estimates using data from the RIO trials. However, the ERG considered that several important caveats and uncertainties remained.

On request, the manufacturer provided comparisons of rimonabant versus diet and exercise alone and orlistat and sibutramine; in each analysis, four treatment strategies were modelled in which treatment with rimonabant was continued only in patients achieving 5% weight loss at 3, 6, 9 or 12 months. Further modifications to the model included: discontinuation of treatment when a patient returned to their original weight while on treatment; a disutility for depressive adverse events associated with rimonabant; inclusion of costs of screening/monitoring for depression for patients treated with rimonabant; and long-term deterioration of efficacy of all treatments after 1 year.

Compared with diet and exercise alone, the response hurdles for rimonabant of between 6 and 9 months were demonstrated to be more cost-effective than a response hurdle of 3 months in the analyses of overweight or obese patients with diabetes and obese patients with or without risk factors. When compared with orlistat and sibutramine, the ICER of rimonabant employing a 6-month response hurdle was £30,743 per QALY compared with a 3-month response hurdle for sibutramine for overweight or obese patients with diabetes, and £23,644 per QALY for obese patients with or without risk factors.

Pairwise comparisons were presented, showing the upper and lower ICERs for rimonabant versus the three comparators. Rimonabant was reported to remain below a threshold of £30,000 per QALY in 70% of the pairwise comparisons reported. The results appeared most sensitive to the decrement applied to depression and the costs of screening for depression.

Commentary on the robustness of submitted evidence

Strengths

The manufacturer's submission presented a clear overview of the four major trials (RIO trials[4–7]) conducted with rimonabant in overweight or obese patients with data for up to 2 years. The submission also included a comparison with the appropriate comparators orlistat and sibutramine.

The manufacturer used appropriate criteria to assess the quality of the RIO trials, although

the ERG noted some discrepancies between the assessments provided in the submission and the information available in published trial reports. The ERG assumes that the manufacturer had access to the full trial reports.

The manufacturer's submission was considered to comprise the most relevant source of cost-effectiveness evidence relating to the use of rimonabant. The ERG identified a number of strengths in the manufacturer's cost-effectiveness analysis. The overall model structure, approaches to estimating long-term costs and outcomes (expressed using QALYs), the time horizon employed and the approach to handling parameter uncertainty were all consistent with the NICE reference case for cost-effectiveness analysis. The ERG also noted that the manufacturer had compared rimonabant against other licensed antiobesity drugs as well as against diet and exercise alone. A broad range of sensitivity analyses was also undertaken to explore alternative assumptions. Variation in the cost-effectiveness estimates for rimonabant was considered in a number of different patient subgroups. The ERG also felt that the validation approaches employed by the company (including presenting the results of a separate discrete event simulation) were a relative strength of the submission. Finally, the ERG felt that the manufacturer had attempted to address a number of areas of uncertainty identified by the ERG in their response to the points for clarification.

In general, the ERG felt that the revised submission provided by the manufacturer had adequately addressed the main clarification points raised. The ERG noted that several of the assumptions employed by the manufacturer to address these points were conservative towards rimonabant; however, a more limited range of subgroups was considered in the resubmission – data on overweight and obese patients with risk factors other than diabetes were omitted.

Weaknesses

The four included trials may not be generalisable to the UK population, both in terms of baseline BMI and the differences in lifestyle, diet and attitudes towards alcohol consumption and exercise between the UK and the USA and other European countries. Furthermore, the diabetic patients included in the manufacturer's submission did not include insulin-dependant diabetics and so may not be generalisable to the broader diabetic population.

The comparison of the effects of rimonabant with those of orlistat and sibutramine on weight loss outcomes is uncertain given the differences in diet and exercise that might have been employed across the different trials. There was no comparison of 2-year data between rimonabant and orlistat. There are differences in the licensing of rimonabant compared with that of orlistat and sibutramine; orlistat and sibutramine are subject to response 'hurdles' in practice that may not be applied in trials and therefore any additional benefit of rimonabant over orlistat or sibutramine may be overestimated and may not be apparent in normal clinical practice.

Overall, the ERG found the presentation of the data unclear, particularly that for orlistat and sibutramine. The ERG has concerns over how representative of the general literature the trials of orlistat and sibutramine in the submission are, and how objectively the data have been used.

The ERG identified a number of potential weaknesses in the manufacturer's cost-effectiveness analysis. The most significant was considered to be the lack of response hurdles applied to sibutramine and orlistat, such that the comparator strategies were not considered by the ERG to reflect their respective product licenses or current NHS use. Although this issue was partially addressed by the manufacturer in the response to the ERG points for clarification, the ERG did not consider that this aspect had been robustly considered by the manufacturer and hence it represents a major limitation. The revised submission by the manufacturer addressed this issue further. However, there remained potential inconsistency in the approaches used to estimate the response rates for the alternative time points representing continuation hurdles for rimonabant; at 3, 6, and 9 months completer data were used and at 12 months LOCF was used. Although the ERG recognises that the manufacturer presented a more consistent approach as part of their clarification, the ERG considers that the full ITT LOCF would represent a more conservative approach and that the current analyses may overstate the response rates at 3, 6 and 9 months. In addition, there was a lack of conditional response data for sibutramine and orlistat (the change in individual risk factors for responders and non-responders) resulting in the use of different approaches to estimate the cost-effectiveness of rimonabant versus diet and exercise alone (patient-level data from the RIO trials) and versus orlistat and sibutramine [applying the average change in risk factors reported for the active treatments (regardless of response status) to

responders, and the average change in risk factors for diet and exercise to non-responders].

The ERG also considered the manufacturer's approach to evaluating HRQoL benefits to be subject to a number of important uncertainties. The ERG considered that the manufacturer's reliance on external utility estimates, as opposed to the HRQoL data reported in the RIO trials, was a potential weakness. Indeed, the HRQoL benefits associated with rimonabant remain highly uncertain and need more detailed investigation by the manufacturer.

Conclusions

Key issues

The adequacy of the cost-effectiveness modelling and assumptions regarding strategies utilising response hurdles for rimonabant and comparator treatments is a key concern. Also, the use of external evidence on the HRQoL impact of BMI independent of longer-term clinical events rather than estimates from the trials, and the choice of this external evidence, are key issues.

The lack of evidence on the effect of rimonabant on 'hard' end points, such as CVD, diabetes and mortality, is a major limitation. Data are also lacking on the effectiveness and safety of rimonabant beyond 2 years. In addition, the appropriateness of incorporating the link between BMI reductions and a lower risk of diabetes and CVD and the choice of evidence to inform this link are questionable.

There are concerns over the psychiatric morbidity associated with rimonabant and, given the lack of long-term data, the cumulative data on less common side-effects are uncertain. The generalisability to the UK overweight and obese population is uncertain, particularly in the broader diabetic population as there are no data on the effectiveness or safety of rimonabant in insulin-dependant diabetics.

Areas of uncertainty

Areas of uncertainty remain in relation to the clinical effectiveness and safety of rimonabant. A major area where data are lacking relates to the long-term outcomes, with no effectiveness or safety data presented for rimonabant beyond 2 years and limited data available beyond 1 year. Also, the manufacturer has identified no direct evidence for the effect of rimonabant on hard clinical end points, such as cardiovascular events, developing diabetes and mortality. The manufacturer states that results from an ongoing trial, CRESCENDO (Comprehensive Rimonabant Evaluation Study of Cardiovascular Endpoints and Outcomes), which is evaluating the effect of rimonabant on cardiovascular morbidity and mortality, are expected to be available in 2011.

Given the lack of head-to-head comparisons between rimonabant and orlistat or sibutramine with all three drugs given as per license, it is unclear whether the pairwise comparisons between rimonabant and orlistat and sibutramine, presented in the clarification submission, will reflect that seen in clinical practice; response hurdles imposed on orlistat or sibutramine in clinical practice may not have been applied in the orlistat and sibutramine trials.

With respect to cost-effectiveness, a number of issues and uncertainties were addressed by the manufacturer in their response to the ERG's points for clarification. Some remaining issues relating to the manufacturer's response were subsequently addressed with additional analyses conducted by the ERG and a revised submission by the manufacturer. However, some caveats and uncertainties remain with respect to the modelling of the comparator technologies and the HRQoL benefits associated with rimonabant.

Summary of NICE guidance issued as a result of the STA

The guidance issued by NICE in March 2008 states that:

Rimonabant, within its licensed indications, is recommended as an adjunct to diet and exercise for adults who are obese or overweight and who have had an inadequate response to, are intolerant of or are contraindicated to orlistat and sibutramine.

Rimonabant treatment should be continued beyond 6 months only if the person has lost at least 5% of their initial body weight since starting rimonabant treatment.

Rimonabant treatment should be discontinued if a person returns to their original weight while on rimonabant treatment.

Rimonabant treatment should not be continued for longer than 2 years without a formal clinical assessment and discussion of the individual risks and benefits with the person receiving treatment.

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Telbivudine for the treatment of chronic hepatitis B infection

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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 telbivudine for the treatment of chronic hepatitis B (CHB) in adults 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 one randomised controlled trial (RCT) (GLOBE) of reasonable methodological quality comparing telbivudine with lamivudine. One other RCT that appeared to meet the inclusion criteria was excluded from the submission. For the primary outcome of therapeutic response telbivudine was statistically superior to lamivudine at weeks 52 and 104 for hepatitis B e antigen (HBeAg)-positive patients, and at week 104 for HBeAg-negative patients. There were statistically significant differences in favour of telbivudine for some secondary outcomes at 2 years including hepatitis B virus (HBV) DNA reduction, HBV DNA non-detectability and alanine aminotransferase normalisation though not for HBeAg-positive patients. In HBeAg-positive patients there was no significant difference between treatment groups for HBeAg loss or seroconversion at any time point. The incidence of adverse events was similar between treatments. Two RCTs comparing entecavir with lamivudine were included in the indirect comparison; however, this was poorly conducted and the results should be treated with caution. The manufacturer developed two economic models to determine the cost-effectiveness of telbivudine. Evidence on the efficacy of telbivudine and lamivudine was taken from the GLOBE trial; efficacy of adefovir was

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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).

based on assumption. There was a lack of critical assessment and assurance of the quality of the data used to populate the models. The manufacturer concluded that telbivudine is a cost-effective option compared with lamivudine using evidence from the viral load model [HBeAg-positive patients/HBeAg-negative patients: mean incremental cost £19,087/£49,003, mean quality-adjusted life-year (QALY) gain 1.30/4.67, incremental cost-effectiveness ratio (ICER) £14,665/£10,497 per QALY]. Resubmitted results after a request for clarification by the ERG gave less favourable ICERs (HBeAg-positive patients/HBeAg-negative patients: mean incremental cost £23,983/£41,910, mean QALY gain 1.56/2.07, ICER £15,377/£20,256 per QALY). The manufacturer concluded that telbivudine is a cost-effective option (on its own or followed by adefovir) for patients who have developed resistance to first-line telbivudine treatment; however, the presentation of the results was not ideal. In conclusion, although telbivudine was statistically superior to lamivudine for most antiviral outcomes, the difference was not clinically significant; in addition, the cost-effectiveness evidence for telbivudine presented in the manufacturer's submission was limited. The NICE guidance issued as a result of the STA states that telbivudine is not recommended for the treatment of chronic hepatitis B and that people currently receiving telbivudine should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

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.[1] 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 the clinical effectiveness and cost-effectiveness of telbivudine for the treatment of chronic hepatitis B (CHB) in adults.

Description of the underlying health problem

Hepatitis B is an infectious disease of the liver caused by the hepatitis B virus (HBV). The majority of people who are infected as adults recover spontaneously, but around 5% develop CHB, defined as viraemia and hepatic inflammation for more than 6 months.[2] If not successfully treated it can lead to progressive liver damage, including cirrhosis, hepatocellular carcinoma (HCC) and death. Patients with CHB may be hepatitis B e antigen (HBeAg) positive or HBeAg negative, depending on the presence or absence of the 'e' antigen.

The Department of Health[2] and the British Liver Trust[3] estimate that the prevalence of CHB in the UK is approximately 150,000–200,000, with around 7000 estimated new cases every year (mostly from immigration of established HBV carriers). However, the Hepatitis B Foundation[4] recently estimated that prevalence may have increased to 325,000, and it is thought likely to increase further as a consequence of increasing rates of immigration of people from countries with a high CHB prevalence.

The main goal of antiviral therapy is to suppress the level of the virus (HBV DNA) for a prolonged period of time to reduce the risk of disease progression and HCC, and also to improve long-term outcomes. HBV DNA is one of the key markers of disease management, as well as HBeAg seroconversion, alanine aminotransferase (ALT) levels and, over the longer term, histological response.

Scope of the ERG report

The ERG critically evaluated the evidence submission from Novartis for the use of telbivudine for the treatment of CHB, in accordance with the licensed indication. Telbivudine is a synthetic thymidine nucleoside analogue that inhibits HBV DNA polymerase and thus HBV replication. It is licensed for the treatment of CHB in adult patients with compensated liver disease and evidence of viral replication, persistently elevated serum

ALT levels and histological evidence of active inflammation and/or fibrosis.

The outcomes stated in the manufacturer's definition of the decision problem were HBV DNA virological response, seroconversion rate, histological improvement, biochemical response, viral resistance, time to treatment failure, survival, health-related quality of life and adverse effects.

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 (*Figures 1* and *2*) were undertaken by the ERG.

Results

Summary of submitted clinical evidence

The manufacturer's submission presented clinical evidence for telbivudine in patients with compensated CHB based on one multicentre, international, double-blind randomised controlled trial (RCT) (the GLOBE trial).[5] This was the pivotal registration trial for telbivudine. The trial compared telbivudine with lamivudine in patients with HBeAg-positive and HBeAg-negative CHB for 104 weeks. The 2-year data presented throughout the manufacturer's submission are unpublished, although publications of earlier results from the GLOBE trial are available.

For the primary outcome of therapeutic response (suppression of HBV DNA < 5 log copies/ml plus either clearance of detectable HBeAg or ALT normalisation) telbivudine was statistically superior to lamivudine at weeks 52 and 104 for HBeAg-positive patients, and at week 104 for HBeAg-negative patients.

In terms of secondary outcomes there were statistically significant differences in favour of telbivudine for HBV DNA reduction, HBV DNA non-detectability, ALT normalisation (although not for HBeAg-negative patients), virological breakthrough and HBV resistance at 2 years. In HBeAg-positive patients there was no significant difference between treatment groups for HBeAg loss or seroconversion at any time point. There were no significant differences in histological response or change in fibrosis score at 1 year, with the exception of histological improvement in HBeAg-positive patients, which was greater in telbivudine patients than in lamivudine patients. In terms of adverse events there appeared to be no difference between treatments.

In the elevated ALT subset analysis of the HBeAg-positive subgroup, telbivudine was statistically superior to lamivudine for most outcomes. In the ethnicity subgroup analysis, telbivudine was significantly more favourable than lamivudine in Asian patients, but there were no statistically significant differences between treatments for HBeAg-positive Caucasian patients and few differences for HBeAg-negative Caucasian patients.

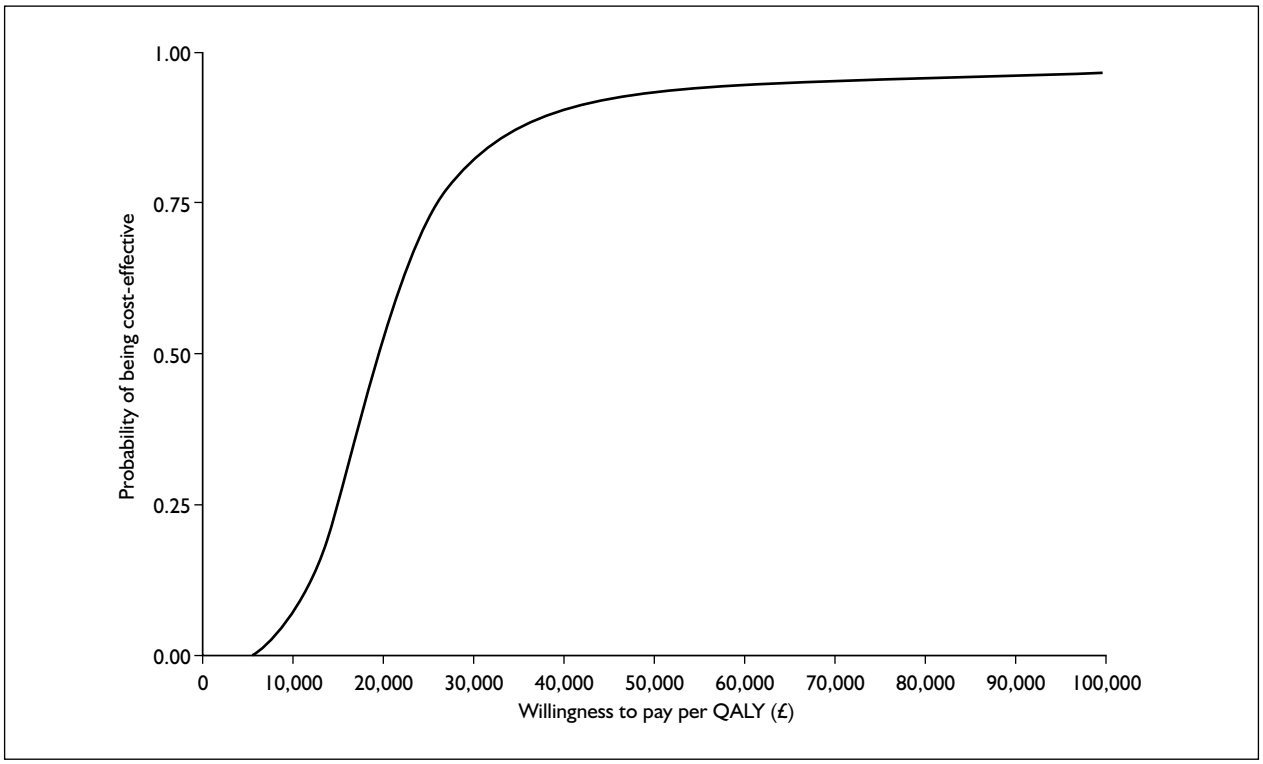
Two RCTs comparing entecavir with lamivudine were included in the indirect comparison, one in HBeAg-positive patients[6] and one in HBeAg-negative patients.[7] In the indirect comparison of telbivudine and entecavir, the manufacturer's submission reported that there were no statistically significant differences for any efficacy outcome.

Summary of submitted cost-effectiveness evidence

The manufacturer's submission presented evidence on the cost-effectiveness of telbivudine using two economic models, referred to as the viral load and seroconversion models. Evidence on the efficacy of telbivudine and lamivudine, in terms of reducing viral load, the probability of normalising ALT and HBeAg seroconversion, was taken from the GLOBE trial for a subgroup of patients with ALT levels ≥ two times the upper limit of normal (ULN). The benefit of these outcomes is that they are associated with reduced probability of progression to advanced liver disease. Efficacy of adefovir was based on assumption.

The viral load model, the manufacturer's preferred approach, stratified response to treatment and

(a)



(b)

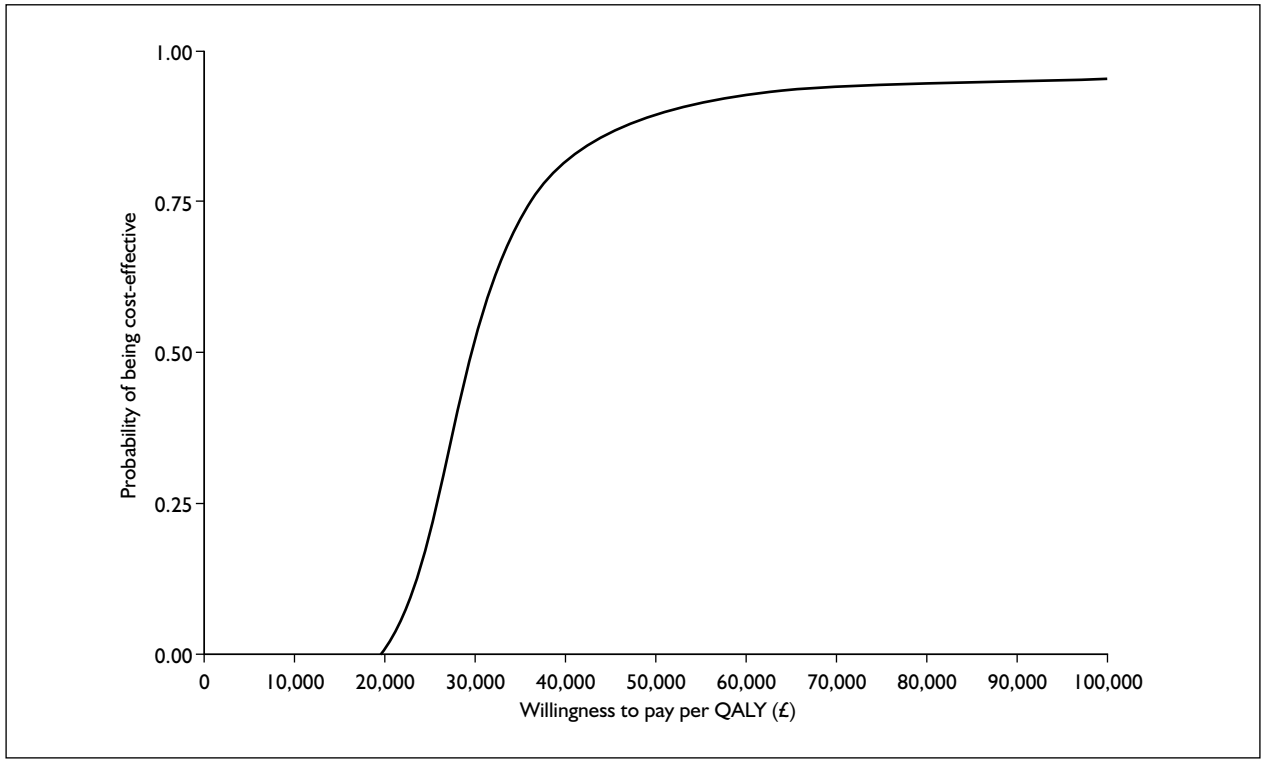


FIGURE 1 *CEACs from ERG probabilistic analysis using viral load model. a, CEAC for telbivudine compared with lamivudine (HBeAg-positive cohort – prior =0); b, CEAC for telbivudine compared with lamivudine (HBeAg-negative cohort – prior = 0). CEAC, cost-effectiveness acceptability curve; ERG, evidence review group; HBeAg, hepatitis B e antigen; QALY, quality-adjusted life-year.*

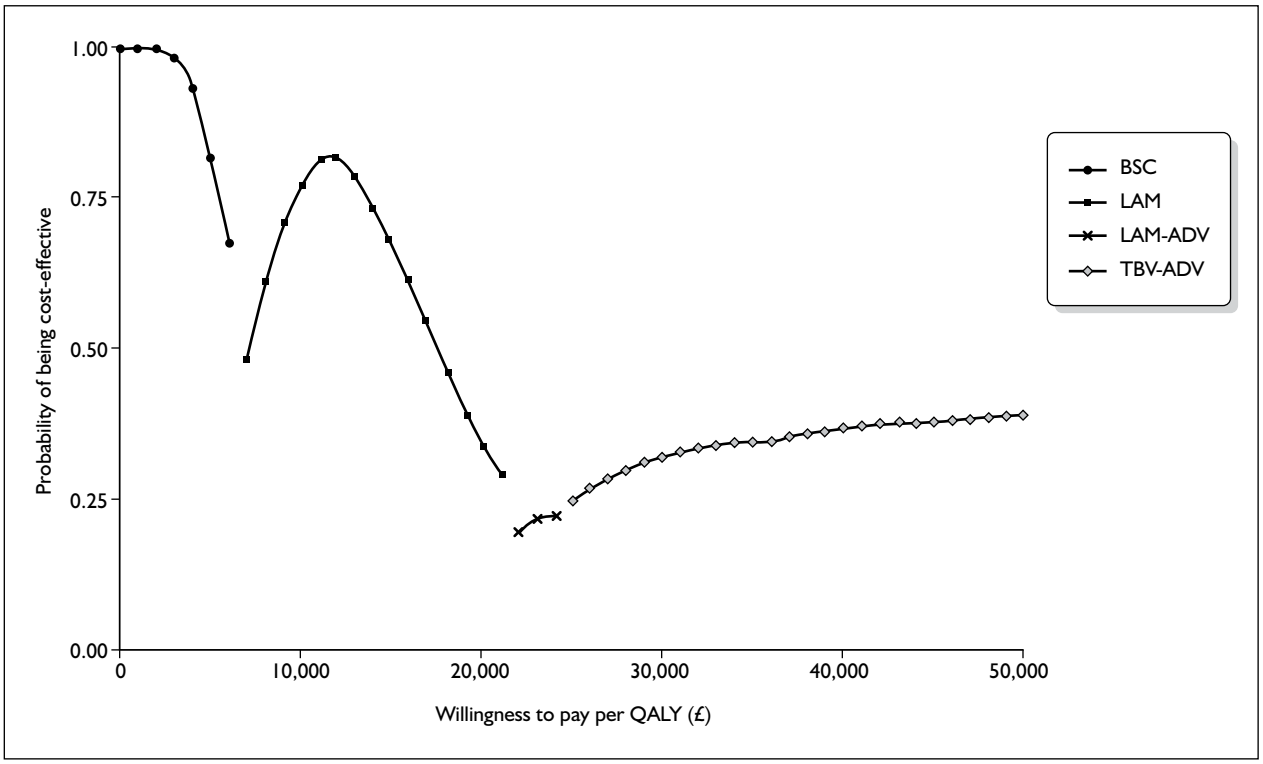


FIGURE 2 *Cost-effectiveness frontier from seroconversion model (ERG's probabilistic sensitivity analysis). BSC, best supportive care; ERG, evidence review group; LAM, lamivudine; LAM→ADV; lamivudine followed by adefovir; QALY, quality-adjusted life-year;TBV→ADV, telbivudine followed by adefovir.*

the development of resistance by five viral load levels and regarded reducing viral load as a key determinant of disease progression. This model is relevant both to patients with HBeAg-positive CHB and to those with HBeAg-negative CHB. The viral load model incorporated a multivariate risk model to derive transition probabilities for the development of progressive liver disease based on viral load levels, the probability of ALT normalisation and HBeAg serological status (for HBeAg-positive patients). Two versions of the viral load model were submitted. The first used the observed proportion of patients moving between states to estimate transition probabilities (referred to as 'zero prior'). In the second model an arbitrary value of 0.5 was added to all numerators and denominators (referred to as '0.5 prior').

The seroconversion model was an attempt to replicate the model used in a recent NICE assessment[2] and was structured with HBeAg seroconversion as the key determinant of disease progression. By definition this model is relevant only to patients with HBeAg-positive CHB.

Both models adopted a lifetime horizon and extrapolated lifetime costs and quality-adjusted life-years (QALYs) for patients treated with telbivudine and each of the included comparators. Incremental cost-effectiveness ratios (ICERs) were estimated against different comparators (depending on the model used) in the manufacturer's submission. The comparator in the viral load model was lamivudine, whereas in the seroconversion model there were multiple competing interventions (lamivudine, telbivudine and adefovir alone or in sequence as well as best supportive care). All ICERs in the seroconversion model were calculated relative to best supportive care.

The manufacturer's submission concluded that telbivudine is a cost-effective option compared with lamivudine using evidence from the viral load model (mean incremental cost of £19,087, mean QALY gain of 1.30 with an ICER of £14,665 per QALY gained for HBeAg-positive patients and mean incremental cost of £49,003, mean QALY gain of 4.67 with an ICER of £10,497 per QALY gained for HBeAg-negative patients). In response to a request for clarification from the ERG the manufacturer noted that there were errors in the models originally submitted and therefore in the results reported in the submission. Resubmitted results gave less favourable ICERs, particularly for HBeAg-negative patients (mean incremental cost of £23,983, mean QALY gain of 1.56 with an ICER of £15,377 per QALY gained for HBeAg-positive patients and mean incremental cost of £41,910,

mean QALY gain of 2.07 with an ICER of £20,256 per QALY gained for HBeAg-negative patients).

The manufacturer's submission concluded that telbivudine is a cost-effective option – on its own or followed by adefovir – for patients who have developed resistance to first-line telbivudine treatment. The manufacturer's submission reported ICERs for seven treatment strategies relative to best supportive care. This is not an ideal presentation of the results of competing treatment strategies. The ERG derived appropriate comparisons, based on the manufacturer's results, using the cost-effectiveness frontier, estimating ICERs of £7887, £19,680 and £24,277 per QALY gained for lamivudine, telbivudine and telbivudine followed by adefovir respectively. The sequence of treatment options implied is problematic as the strategy of using telbivudine followed by adefovir (for patients who develop resistance to telbivudine) is not accessible to patients who have lamivudine as their first-line treatment. To provide the treatment strategy of telbivudine followed by adefovir (which yields the greatest QALY gain of all of the strategies in the seroconversion model and which is optimal at a willingness to pay greater than £25,000 per QALY) telbivudine must be available as a first-line treatment.

Commentary on the robustness of submitted evidence

Strengths

The manufacturer conducted a systematic search for clinical effectiveness studies of telbivudine. It appears unlikely that any additional trials would have met the inclusion criteria had the search been widened to include other databases.

The GLOBE trial appears to be of reasonable methodological quality (with some limitations) and measured a range of outcomes that are as appropriate and clinically relevant as possible, although health-related quality of life was not reported. On the whole, the manufacturer's submission appears to represent an unbiased estimate of the antiviral treatment effect of telbivudine based on the results of one trial.

The methods adopted for the economic evaluation of telbivudine were broadly consistent with those adopted for previous evaluations of antiviral treatment of CHB, including the recent NICE assessment of adefovir and pegylated interferon.[2]

Weaknesses

The manufacturer's submission did not include all of the comparators specified in the scope.

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. Further high-quality RCT evidence for the effectiveness of telbivudine in the patient group meeting the licensed indication would be beneficial.

Literature searches were poorly documented, lacking clarity and transparency throughout. Search filters were extremely precise at the expense of sensitivity. The processes undertaken by the manufacturer for data extraction and applying quality criteria to the GLOBE trial were not detailed and no formal quality assessment was undertaken on the comparator trials. These factors limit the robustness of the systematic review. In addition, one RCT[8] that appeared to meet the inclusion criteria was excluded from the submission.

The indirect comparison with entecavir was poorly conducted and should be treated with caution. It was reported as a visual comparison and then as a statistical comparison, which the manufacturer deemed invalid. An inadequate description of the methodology was provided and the conclusions are based largely on a visual comparison of efficacy outcomes.

The economic models used data from a subgroup of patients in the GLOBE study and these data were not presented in detail in the clinical evidence section of the manufacturer's submission. No information was given on the baseline characteristics of the subgroup of patients with ALT levels ≥ two times the ULN.

In the cost-effectiveness section of the submission the manufacturer paid insufficient attention to appraising the data used to populate the economic models. Denominators used for calculation of some transition probabilities appear inconsistent and some input values (e.g. resistance rates calculated using data reported in appendices) are substantially lower than those reported for all patients in the GLOBE study. These discrepancies were not discussed in the submission.

The electronic models submitted are complex and highly reliant on Visual Basic programming to

produce any analyses. There is a large amount of reprocessing of data within the models that was not clearly documented or readily apparent to the user.

There was little discussion in the manufacturer's submission of uncertainty around the mean estimates reported as the base case for both the viral load and seroconversion models. The NICE guide to methods of technology appraisal describes confidence ellipses and scatter plots on the cost-effectiveness plane and cost-effectiveness acceptability curves as the most appropriate ways of presenting uncertainty in probabilistic sensitivity analysis. These were not presented for all comparisons and were submitted in appendices, without commentary, rather than in the main body of the report.

Conclusions

Areas of uncertainty

The results of the key efficacy outcomes were broken down by HBeAg status, study treatment and (1) race/ethnicity or (2) ALT levels. It is not clear whether the GLOBE study was powered to detect differences in these subgroups. Without confidence intervals and standard deviations in the reporting of the results it is not possible to ascertain how much variance there was among the subgroups/patients.

The rates of viral resistance to entecavir were not reported in the manufacturer's submission and therefore do not allow for a comparison with the resistance rates for telbivudine.

The adjustments to the Cox proportional hazards models used to estimate the probability of developing compensated cirrhosis and HCC were inadequately reported as was the process of recalibration. These values enter the viral model deterministically – there is no assessment of parameter uncertainty for the risk models used in the viral model, nor of the methodological uncertainty around the adjustment or recalibration.

The lack of quality assurance of input data for both models introduces uncertainty – the impact of the prior value (zero or 0.5) on the model outcomes suggests that sparsity of data may be a problem, particularly for the model of HBeAg-negative patients. This is not surprising, given that data on around 250 patients were stratified across viral load levels, ALT and serological status. The manufacturer's submission contained no discussion of alternative modelling strategies that might reduce the impact of sparsity of data nor did it clearly indicate which input variables were most affected by differences in prior values.

Key issues

Although telbivudine was statistically superior to lamivudine for most antiviral outcomes, the difference was not clinically significant, having an effectiveness advantage of only about 2% in patients treated between the two drugs. Viral breakthrough (> 1 log increase over nadir) for telbivudine was 28.6% at 2 years; although this is significantly lower than that for lamivudine (45.5%), the ERG's clinical advisor asserts that it is still high in clinical terms.

The conclusions from the indirect comparison were based largely on a visual comparison of efficacy outcomes and a statistical indirect comparison, which the manufacturer's submission states was not considered valid in the absence of any meta-analyses. Telbivudine seems to have approximately the same efficacy as entecavir for viral suppression, but markedly higher rates of viral resistance (as per the rates for entecavir reported in the published trials).

The exclusion of entecavir from all of the economic models and the restricted comparison included in the viral load model – telbivudine versus lamivudine, with no follow-up antiviral treatments – means that the cost-effectiveness evidence for telbivudine presented in the manufacturer's submission is limited. Lack of critical assessment and assurance of the quality of the data used to populate the model (apparent inconsistencies and incomplete data for lamivudine and telbivudine from the GLOBE trial along with the absence of systematic searches for evidence on the comparative effectiveness of adefovir) further limits the evidence reported in the manufacturer's submission.

Summary of NICE guidance issued as a result of the STA

NICE guidance, published August 2008,[9] states that:

1.1 Telbivudine is not recommended for the treatment of chronic hepatitis B.

1.2 People currently receiving telbivudine should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

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Entecavir for the treatment of chronic hepatitis B infection

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Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical and cost-effectiveness of entecavir for the treatment of chronic hepatitis B (CHB) in adults 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 five randomised controlled trials (RCTs), of good methodological quality and measuring a range of clinically relevant outcomes, comparing entecavir with lamivudine. After 1 year of treatment entecavir was statistically superior to lamivudine in terms of the proportion of patients achieving hepatitis B virus (HBV) DNA suppression, alanine aminotransferase (ALT) normalisation and histological improvement, but not in terms of the proportion of patients achieving hepatitis B e antigen (HBeAg) seroconversion. The incidence of adverse or serious adverse events was similar for both treatments. The results of the manufacturer's mixed treatment comparison (MTC) model to compare entecavir with the comparator drugs in nucleoside-naive patients were considered to be uncertain because of concerns over its conduct and reporting. For the economic evaluation the manufacturer constructed two Markov state transition models, one in HBeAg-positive and one in HBeAg-negative patients. The modelling approach was considered reasonable subject to some uncertainties and concerns over some of the structural assumptions. In HBeAg-positive patients the base-case incremental cost-effectiveness ratios (ICER) for entecavir compared with lamivudine and pegylated interferon alpha-2a were £14,329 and £8403 per quality-adjusted life-

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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).

year (QALY) respectively. Entecavir was dominated by telbivudine. In HBeAg-negative patients the base-case ICERs for entecavir compared with lamivudine, pegylated interferon alpha-2a and telbivudine were £13,208, £7511 and £6907 per QALY respectively. In HBeAg-positive lamivudine-refractory patients entecavir dominated adefovir added to lamivudine. In one-way deterministic sensitivity analysis on all key input parameters for entecavir compared with lamivudine in nucleoside-naive patients, ICERs generally remained under £30,000 per QALY. In probabilistic sensitivity analysis in nucleoside-naive HBeAg-positive patients the probability of the ICER for entecavir being below £20,000 per QALY was 57%, 82% and 45% compared with lamivudine, pegylated interferon alpha-2a and telbivudine respectively. In nucleoside-naive HBeAg-negative patients the probabilities were 90%, 100% and 96% respectively. The manufacturer's lifetime treatment scenario for HBeAg-negative patients and the ERG's 20-year treatment scenario for HBeAg-positive patients increased the ICERs, particularly in the latter case. Amending the HBeAg-negative model so that patients with compensated cirrhosis would also receive lifetime treatment gave probabilities of entecavir being cost-effective at a willingness to pay of £20,000 and £30,000 of 4% and 40% respectively. The NICE guidance issued in August 2008 as a result of the STA states that entecavir is recommended as an option for the treatment of people with chronic HBeAg-positive or HBeAg-negative hepatitis B in whom antiviral treatment is indicated.

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.[1] 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 entecavir for the treatment of chronic hepatitis B (CHB).

Description of the underlying health problem

Hepatitis B is an infectious disease of the liver caused by the hepatitis B virus (HBV). It is transmitted through blood-to-blood contact (e.g. through sharing of blood-contaminated needles by drug users) and sexual contact. It is also transmitted vertically from mother to infant during or soon after birth. Infected individuals develop an acute infection, which may or may not result in symptoms. The majority of those infected during adulthood make a full recovery and acquire immunity from future infection. Only about 2–10% of infected adults will develop CHB, defined as viraemia and hepatic inflammation that persists for more than 6 months after acute infection with HBV. In contrast, almost 100% of infected neonates and about 50% of infected young children will develop CHB if infected with HBV.

Active infection can be described as HBeAg positive or HBeAg negative according to whether hepatitis B 'e' antigen (HBeAg) is secreted. HBeAg is an indicator of viral replication, although some variant forms of the virus do not express HBeAg. The response to treatment and rates of progression differ between the two forms. People can be infected with the so-called HBeAg-negative form of the virus initially, or the viral mutation can emerge later in the course of infection in people initially infected with the HBeAg-positive form of the virus. Chronic infection with mutant strains of HBV that do not produce the 'e' antigen (i.e. HBeAg negative) is associated with a fluctuating course and a poor prognosis.

The Department of Health estimates that about 180,000 people in the UK have CHB. There are about 7700 new cases of CHB each year. Of these, around 300 people were infected within the UK; the remainder (mainly immigrants to the UK) were infected abroad, generally in areas of high prevalence where the virus is frequently transmitted from mother to child.

The progression to cirrhosis occurs at an annual rate of 2–5.5%, with a cumulative 5-year rate of progression of 8–20% in HBeAg-positive CHB and an annual rate of 8–10% in HBeAg-negative CHB.

Scope of the ERG report

The ERG critically evaluated the evidence submission from Bristol Myers Squibb on the use of entecavir for the treatment of CHB. Entecavir has a marketing authorisation in the UK for the treatment of chronic HBV infection in adults with compensated liver disease and evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.

The population considered in the scope was adults with CHB according to the licensed indication. Patient subgroups included those with HBeAg-positive and HBeAg-negative CHB and those who are treatment (nucleoside analogue) naive or refractory to lamivudine (e.g. those with persistent viraemia and/or genotypical resistance). Patients with coinfections were excluded in accordance with the scope. The intervention was entecavir alone in the treatment of CHB.

Comparators included the nucleoside analogues lamivudine and telbivudine; the nucleotide analogue adefovir dipivoxil; and the immune modifiers interferon alpha-2a and -2b and pegylated interferon alpha-2a.

Outcomes included HBeAg/HBsAg seroconversion rate, virological response (HBV DNA), histological improvement (liver inflammation and fibrosis), biochemical response (e.g. ALT levels), development of viral resistance and adverse events. Outcomes included in the scope and decision problem, but not reported in the submission include time to treatment failure, survival (unless within the context of adverse events) 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 were undertaken by the ERG.

Results

Summary of submitted clinical evidence

The manufacturer's systematic review included five randomised controlled trials (RCTs), all of which compared entecavir with lamivudine. Three of the trials were conducted in nucleoside-naive patients (one in HBeAg-positive patients, one in HBeAg-negative patients and one in a mixed HBeAg-positive and HBeAg-negative status group). The other two were conducted in lamivudine-refractory patients (one in HBeAg-positive patients, the other in a mixed HBeAg-positive and HBeAg-negative status group). Outcome data were reported for up to 1 year of treatment, and for a subset of patients who did not achieve a complete response and who continued treatment in year 2. Cumulative proportions of all patients ever attaining a treatment response up to 2 years were also presented. Some of the patients from the RCTs have entered long-term observational extension studies, with treatment continuing for up to 5 years; however, fully published data are not yet available.

After 1 year of treatment entecavir was statistically superior to lamivudine in terms of the proportion of patients achieving HBV DNA suppression, ALT normalisation and histological improvement. There was no statistically significant difference between the treatments in the proportion of patients achieving HBeAg seroconversion (HBeAg-positive patients only, by definition). Most of the entecavir-treated patients did not have any detectable resistance-associated substitutions at 1 year of treatment. The proportions of patients with any adverse events or serious adverse events were similar for entecavir and lamivudine. The proportions of patients who withdrew during the first year because of adverse events were similar for entecavir and lamivudine except in one trial in which significantly more lamivudine patients withdrew. The number of deaths during treatment was low (< 1% in all cases).

The manufacturer also constructed a mixed treatment comparison (MTC) model to compare entecavir with the comparator drugs in nucleoside-naive patients. An MTC was not considered possible in lamivudine-refractory patients because

of lack of evidence. The results of the MTC generally accord with the results of the RCTs in that, with the exception of HBeAg seroconversion, entecavir was superior to lamivudine across outcomes. The MTC suggests that entecavir is either significantly better or equivalent to the other comparators, depending on the outcome measure and the time point.

Summary of submitted cost-effectiveness evidence

The manufacturer's economic evaluation comprised a systematic review of economic evaluations of CHB treatments and a cost–utility analysis based on a de novo economic model.

Two Markov state transition models were constructed, one in HBeAg-positive patients and one in HBeAg-negative patients. The models estimated progression to 14 health states (15 in the HBeAg-negative model) representative of progressive CHB-related liver disease (e.g. compensated and decompensated cirrhosis, hepatocellular carcinoma). The models had a lifetime horizon and a cycle length of 1 year.

In HBeAg-positive and -negative nucleoside-naive patients, the models compared entecavir with lamivudine, pegylated interferon alpha-2a and telbivudine. Treatment lasted for 2 years in HBeAg-positive patients and 5 years in HBeAg-negative patients (with the exception of pegylated interferon alpha-2a, which was given for only 1 year). In HBeAg-positive patients who were refractory to lamivudine, entecavir was compared with adefovir added to lamivudine for 2 years. Response to treatment was defined by HBeAg seroconversion and undetectable HBV DNA.

In HBeAg-positive patients the base-case incremental cost-effectiveness ratio (ICER) for entecavir compared with lamivudine was £14,329 per quality-adjusted life-year (QALY). Compared with pegylated interferon alpha-2a the ICER was £8403 per QALY. Entecavir was associated with the same number of QALYs as telbivudine, but at a slightly higher total cost and was therefore dominated. In HBeAg-negative patients the base-case ICERs for entecavir compared with lamivudine, pegylated interferon alpha-2a and telbivudine were £13,208, £7511 and £6907 per QALY respectively. In HBeAg-positive lamivudine-refractory patients entecavir dominated adefovir added to lamivudine.

One-way deterministic sensitivity analysis for entecavir compared with lamivudine on all key input parameters, and performed for nucleoside-naive patients, showed that the results were most sensitive to the baseline transition probabilities from CHB to seroconversion (spontaneous seroconversion) and active cirrhosis, the baseline transition probability from active cirrhosis to decompensated cirrhosis, baseline cirrhosis risk and treatment effects. ICERs generally remained under £30,000 per QALY.

The probabilistic sensitivity analysis in nucleoside-naive HBeAg-positive patients showed that the probability of the ICER for entecavir being below £20,000 per QALY was 57% compared with lamivudine, 82% compared with pegylated interferon alpha-2a and 45% compared with telbivudine. In nucleoside-naive HBeAg-negative patients the probabilities were 90%, 100% and 96% respectively.

The manufacturer included a lifetime treatment scenario in HBeAg-negative patients and the ERG included a scenario of up to 20 years treatment for HBeAg-positive patients. The ICERs increased as a consequence, particularly in the latter case.

The ERG updated the sensitivity analyses with utilities and drug costs varied by ± 20%. The model for HBeAg-positive patients was most sensitive to changes in response and CHB utility rates and the transition probabilities from CHB to compensated cirrhosis and CHB to seroconversion. The model for HBeAg-negative patients was most sensitive to changes in the response rates and resistance utility and the transition probabilities between compensated cirrhosis and decompensated cirrhosis and between CHB treatment and compensated cirrhosis.

The ERG conducted a probabilistic sensitivity analysis using wider uncertainty around the utilities (± 10%) and drug costs (± 20%) than presented in the manufacturer's submission. In the HBeAg-positive model, patients with CHB were treated for 2 years with entecavir, lamivudine or telbivudine, but it was considered more appropriate for them to be treated for longer. The ERG attempted to run the HBeAg-positive model for a longer duration but the results were inconsistent with those from the deterministic scenario analyses.

The ERG ran the HBeAg-negative model for a lifetime treatment duration. The model was

amended so that patients with compensated cirrhosis would also receive treatment, lasting until they developed decompensated cirrhosis, hepatocellular carcinoma or died. As can be seen from *Figure 1* the probability of entecavir being cost-effective at a willingness to pay of £20,000 and £30,000 was 4% and 40% respectively.

Commentary on the robustness of submitted evidence

Strengths

The manufacturer conducted a systematic search for clinical effectiveness and cost-effectiveness studies of entecavir. It appears unlikely that the searches missed any additional trials that would have met the inclusion criteria.

The five entecavir RCTs identified were of generally good methodological quality and measured a range of outcomes that are appropriate and clinically relevant, although health-related quality of life was not reported. Overall, the manufacturer's submission presents an unbiased estimate of the efficacy of entecavir versus lamivudine, based on the results of the five RCTs.

Overall, the manufacturer's economic evaluation accords with the decision problem and the NICE reference case. The approach to modelling was generally considered reasonable and the model was judged to be internally and externally consistent, subject to some uncertainties (see Conclusions).

Disease progression pathways assumed in the economic models were generally consistent with the natural history of CHB, although there were some concerns about some of the structural assumptions (see Conclusions).

Weaknesses

The MTC suffers from certain limitations in conduct and reporting, including small numbers of studies/single studies in some networks, no assessment or discussion of heterogeneity and no reporting of criteria for judging statistical significance or equivalence.

Conclusions

Areas of uncertainty

Given the concerns about the conduct and reporting of the MTC the ERG considers its results to be uncertain. This limits any conclusions that can be drawn regarding the comparative efficacy of entecavir and telbivudine and entecavir and pegylated interferon alpha-2a in nucleoside-naive patients (notwithstanding the head-to-head RCT evidence comparing entecavir with lamivudine).

There is relatively limited clinical effectiveness and cost-effectiveness evidence for entecavir in

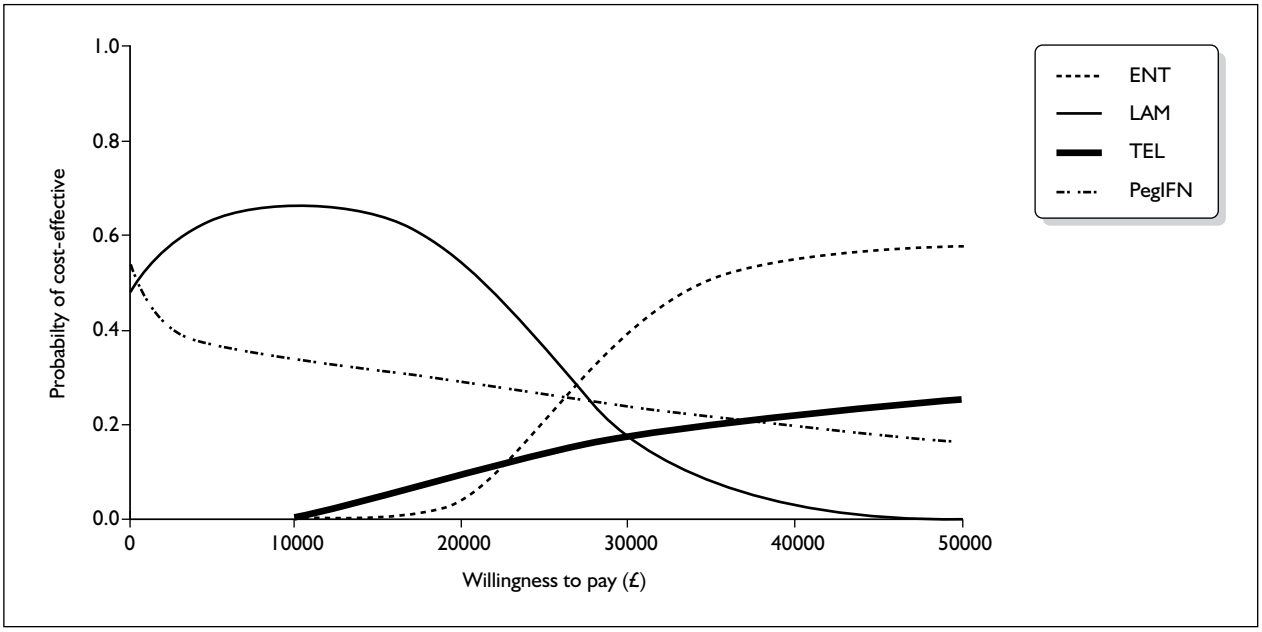

FIGURE 1 *Cost effectiveness acceptability curves for entecavir, lamivudine, telbivudine and pegylated interferon for the HBeAg-negative model. ENT, entecavir; LAM, lamivudine; PEG IFN, pegylated interferon alpha; TEL, telbivudine.*

lamivudine-refractory patients. Head-to-head RCT evidence is available for entecavir versus ongoing lamivudine but only in HBeAg-positive patients. Smaller RCTs have been published comparing switching to adefovir versus adding adefovir to ongoing lamivudine, but these have not been compared in a statistical indirect comparison to entecavir. The manufacturer presented cost-effectiveness estimates only for HBeAg- positive, not HBeAg-negative, lamivudine-refractory patients.

Structural assumptions in both the HBeAg-positive and HBeAg-negative disease models precluded the patients with response from directly entering the active/compensated cirrhosis health state. The rationale for this assumption was not clear and it is not possible to estimate the impact of these structural assumptions.

Treatment of CHB in many patients will be longer than the 2 and 5 years assumed in the HBeAg-positive and HBeAg-negative disease models respectively. However, there is a paucity of published clinical effectiveness data from RCTs beyond the second year of treatment [long-term observational studies (up to 5 years) are in progress]. Increasing the treatment duration in scenario analysis resulted in higher ICERs.

No data were presented in the submission on the efficacy and safety of entecavir in combination with other licensed agents.

Contrary to the assumptions in the manufacturer's economic evaluation, a certain proportion of CHB patients will first present with compensated cirrhosis. Moreover, it is unlikely that treatment will be terminated once patients progress to the active cirrhosis stage of disease. Changing these assumptions to reflect a more realistic scenario increased the ICER for entecavir compared with lamivudine.

Summary of NICE guidance issued as a result of the STA

The Final Appraisal Determination issued by NICE in June 2008 states that:

Entecavir, within its marketing authorisation, is recommended as an option for the treatment of people with chronic HBeAg-positive or HBeAg-negative hepatitis B in whom antiviral treatment is indicated.

Key references

1. National Institute for Health and Clinical Excellence. *Guide to the single technology (STA) process*. 19 September 2006. URL: www.nice.org.uk/page.aspx?o=STAprocessguide.

Febuxostat for the treatment of hyperuricaemia in people with gout: a single technology appraisal

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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 febuxostat for the management of hyperuricaemia in patients with gout 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 randomised controlled trials comparing the efficacy and safety of febuxostat with allopurinol. The trials were of reasonable methodological quality and measured a clinically relevant range of outcomes. A pooled clinical efficacy analysis showed that a daily dose of 80 mg or 120 mg of febuxostat was significantly more effective than fixed-dose allopurinol (300/100 mg/day) at lowering serum uric acid (sUA) levels to therapeutic targets (< 6 mg/dl); however, a large percentage of febuxostat patients did not achieve the primary end point and the fixed-dose allopurinol regimen may have introduced bias. There were no differences between treatments in more clinically important outcomes such as gout flares and tophi resolution after 52 weeks of treatment. No subgroup analyses were conducted for patients with renal impairment, non-responders to allopurinol or patients with severe disease. Supplementary data from a 2-year open-label extension study were also provided, but were difficult to interpret and poorly reported. The incidence of adverse events was similar between treatments, although more febuxostat recipients discontinued treatment prematurely. A decision tree model was

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developed to determine the cost-effectiveness of febuxostat. The scope was limited to the comparison of continual febuxostat treatment with continual allopurinol treatment. Switching between treatments or withdrawing treatment in patients whose sUA levels had not decreased was not permitted. The model predicted a cost-effectiveness of £16,324 [95% confidence interval (CI) £6281 to £239,928] per quality-adjusted life-year (QALY) gained for febuxostat compared with allopurinol after 2 years of treatment. The incremental cost per QALY was below £20,000 in 63% of the simulations undertaken. Changes in the time horizon did not materially affect the results. The ERG believes that the modelling structure employed was not appropriate to estimate the cost-effectiveness of febuxostat within a treatment algorithm. In addition, there were concerns about the methodology used for collecting data on key model inputs. Given these reservations the cost-effectiveness of febuxostat could not be determined. The guidance issued by NICE in August 2008 as a result of the STA states that febuxostat is recommended as an option for the management of chronic hyperuricaemia in gout only for people who are intolerant of allopurinol or for whom allopurinol is contraindicated.

Introduction

The National Institute of 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.[1,2] 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 manufacturer's 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 febuxostat for the management of hyperuricaemia in patients with gout.[3]

Description of the underlying health problem

Gout is a metabolic disorder that causes acute, intermittent and painful attacks of arthritis in the joints of the foot (especially the big toe), knee, hand and wrist. Gout occurs when there is a sudden onset of inflammation as a result of excess uric acid (crystals of monosodium urate) in the blood (hyperuricaemia) and tissues. Urate crystals deposited in and around joints and tissue are known as tophi,[4] which can cause significant pain.

The incidence of gout has been estimated to range from 11.9 to 18.0 cases per 10,000 patient-years.[5] Incidence is affected by both age and gender, with men aged from 65 to 84 years having an incidence rate approximately 60 times greater than that in women aged below 45 years.[5] The overall prevalence of gout in the UK has been estimated at 1.4%,[5,6] with this value being 7.3% among men aged from 65 to 75 years.[5]

Scope of the ERG report

The objective of the appraisal was to assess the clinical effectiveness and cost-effectiveness of febuxostat for the management of hyperuricaemia in adults with gout in whom urate deposition has already occurred (including a history or presence of tophus and/or gouty arthritis). The comparators included: allopurinol, alternative standard care (including sulphinpyrazone, benzbromarone, probenecid or a combination of these) for adults unresponsive to or with hypersensitivity to allopurinol, and allopurinol (dose adjusted according to glomerular filtration rate), benzbromarone or a combination of these for adults with renal impairment. The outcomes measured included surrogate [serum uric acid levels (sUA)] and clinical outcomes (gout flares, reduction in tophi size), tolerance and health-related quality of life.

The main evidence presented in support of the clinical effectiveness of febuxostat was based on two head-to-head, phase III, randomised controlled trials [the Febuxostat Allopurinol Controlled Trial (FACT) study[7] and the Allopurinol and Placebo-controlled Efficacy study of febuXostat (APEX) trial[8]] comparing the efficacy and safety of febuxostat with fixed-dose allopurinol. The manufacturer did not present comparisons with alternative comparators (such as sulphinpyrazone,

benzbromarone, probenecid or a combination of these) for adults unresponsive to, or intolerant of, allopurinol or with renal impairment.

The scope of the manufacturer's cost-effectiveness submission was limited to the comparison of continual febuxostat treatment with continual allopurinol treatment. Switching between treatments was not permitted, nor was there the possibility of withdrawing treatment in patients whose sUA levels had not decreased. Although the dosage level of febuxostat was allowed to vary, increasing from 80 mg daily to 120 mg daily in patients not initially responding to treatment, the dose of allopurinol was assumed fixed at 300 mg per day. Costs were considered from an NHS and personal social services perspective. Cost-effectiveness was expressed in terms of incremental cost per quality-adjusted life-year (QALY) gained, with a time horizon of 2 years used for the base-case results.

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. A narrative critique of the submitted evidence was presented. The economic model submitted by the manufacturer was regarded as inappropriate to assess the decision problem.

Results

Summary of submitted clinical evidence

A pooled (not meta-analysed) clinical efficacy analysis of two head-to-head, multiarm, randomised, double-blind, controlled trials (52-week FACT study[7] and 28-week APEX trial[8]) comparing the efficacy and safety of febuxostat with fixed-dose allopurinol in 1689 patients with hyperuricaemia (sUA levels ≥ 8 mg/dl) and gout showed that febuxostat (80 mg/day and 120 mg/day) was significantly more effective than fixed-dose allopurinol (300/100 mg/day) at reducing sUA levels to < 6 mg/dl. However, a large percentage of patients on febuxostat did not achieve the primary end point and the fixed-dose regimen employed for allopurinol patients may have introduced bias.

Despite the significantly greater effect on sUA levels with febuxostat (including mean percentage reduction from baseline) than with allopurinol, there were generally no differences between treatments in more clinically important outcomes such as gout flares and tophi resolution (secondary end points).

A post hoc subgroup analysis showed that febuxostat was more effective than allopurinol in decreasing sUA levels to < 6 mg/dl in patients with baseline sUA concentrations of < 9 mg/dl, between 9 and 10 mg/dl and > 10 mg/dl. In addition, significantly more febuxostat recipients than fixed-dose allopurinol recipients achieved a reduction in sUA levels to therapeutic targets (< 5 mg/dl). No subgroup analyses were conducted for patients with renal impairment, non-responders to allopurinol or patients with severe disease.

Supplementary data from an ongoing, long-term, open-label extension study (EXCEL – fEbuXostat/allopurinol Comparative Extension Long-term study) of the two head-to-head trials showed that more patients on febuxostat (80 mg/day and 120 mg/day) than on fixed-dose allopurinol (300/100 mg/day) remained on initial treatment after more than 24 months of follow-up, and the number of tophi and gout flares were reduced over time in these patients. However, these data need to be interpreted with caution as the manufacturer's submission does not provide statistical analysis of event rates over time or data on withdrawals because of gout flares, adverse events or non-response.

Although the adverse event profile was similar in those receiving febuxostat compared with those receiving allopurinol, more febuxostat recipients discontinued treatment prematurely [the statistical analysis comparing the rates of discontinuation between the treatment groups was not reported in the manufacturer's submission or in the requested supplementary data; however, the primary published peer-reviewed clinical paper for the FACT study reports that the rates of discontinuation were significantly higher in febuxostat recipients ($p < 0.04$) than in those receiving allopurinol]. Reasons for withdrawal included gout flares and adverse events such as liver function test abnormalities.

Summary of submitted cost-effectiveness evidence

A decision tree model was developed in Microsoft EXCEL. The model subdivided patients into four mutually exclusive categories of sUA levels, which were related to both the expected number of gout flares and the underlying utility of a patient. Two

identical cohorts of men and women entered the model with an assumed baseline sUA acid level of ≥ 8 mg/dl. One cohort was assumed to receive 80 mg/day of febuxostat treatment, increased to 120 mg/day in those patients who did not adequately respond; the remaining cohort was assumed to receive 300 mg/day of allopurinol. The primary analysis was for a period of 2 years; however, sensitivity analyses were undertaken using different time periods.

The manufacturer's submission predicted a cost-effectiveness of £16,324 (95% CI £6281 to £239,928) per QALY gained for febuxostat compared with allopurinol after 2 years of treatment. The incremental cost per QALY was below £20,000 in 63% of the simulations undertaken. Changes in the time horizon did not materially affect the results.

Commentary on the robustness of submitted evidence

The manufacturer conducted an adequate systematic search for clinical effectiveness and cost-effectiveness studies of febuxostat for the treatment of gout. It appears unlikely that any additional trials would have met the inclusion criteria had the search been widened to include other databases. The processes undertaken by the manufacturer for screening studies, data extraction and applying quality criteria to included studies are not explicitly clear in the submission. These factors limit the robustness of the systematic review.

The two identified trials, which represent the main clinical efficacy evidence, were of reasonable methodological quality (with some limitations) and measured a range of outcomes that are as appropriate and clinically relevant as possible. Although a simple pooled analysis of the individual patient level data from the two head-to-head trials was undertaken by the manufacturer, the methods for this type of data pooling were not explicitly 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. A meta-analysis undertaken by the ERG showed that the methodology used by the manufacturer to synthesise the data was unlikely to alter the conclusions on efficacy.

The ERG considered the modelling structure inappropriate. Given the nature of the disease and the interventions it was deemed likely that a treatment algorithm that started all patients on the relatively inexpensive allopurinol and which treated those who did not respond with the more expensive febuxostat would be more cost-effective than the strategies evaluated in the submission. The ERG requested that the following analysis be undertaken at a minimum: allopurinol – febuxostat – no treatment; febuxostat – allopurinol – no treatment; allopurinol – no treatment and febuxostat – no treatment; however, the manufacturer did not comply with this request.

Even overlooking the inappropriateness of the model structure there were a number of errors within the analyses presented. For example, the price of allopurinol was incorrect and the price of febuxostat was altered within the probabilistic sensitivity analyses. Reanalyses were not undertaken by the manufacturer despite these issues being raised.

The ERG has serious concerns regarding the data selected to estimate the relationship between sUA levels and the number of gout flares expected. A large portion of the data collected to develop this linkage was excluded (accounting for 51% of all patients and 77% of UK patients), and the ERG was not convinced by the arguments provided to exclude these data.

The ERG has additional serious concerns about the interpretation of the multivariate analyses. It is indicated that there is no significant association between sUA levels and the number of gout flares reported within the data set used. This analysis has apparently been overlooked in favour of a bivariate analysis that does not include other confounders. Note that, although no statistically significant relationship was found within this data set, this does not mean that such a relationship does not exist, as indicated in clinical guidelines.

The ERG noted that the chronic utility gain associated with reduced sUA levels was a key driver in the cost per QALY gained ratio. It was noted that the relationship between sUA level and chronic utility had been modelled assuming a linear relationship. The evidence for this assumption was uncertain and not clearly established.

The ERG noted that the derivation of the disutility associated with a gout flare came from data that did

not appear internally consistent, with some people giving greater utility to a health state associated with a gout flare than to one without such a flare.

The ERG further noted that the dose of allopurinol was assumed to be fixed, whereas guidelines allow for the upwards titration of this dose. Although the manufacturer reported that the dose of allopurinol commonly used was 300 mg/day, this does not represent best practice, which allows for doses of 900 mg/day of allopurinol.

Conclusions

The clinical evidence, based on a simple pooled analysis of the patient level data from two randomised controlled trials, showed that a daily dose of 80 mg or 120 mg of febuxostat was significantly more efficacious than allopurinol at the commonly used fixed daily dose of 300 mg in lowering sUA levels to therapeutic targets (< 6 mg/dl). However, a large percentage of patients on febuxostat did not achieve the primary end point and the fixed-dose regimen employed for allopurinol patients may have introduced bias. In general, there were no differences between treatments in more clinically important outcomes such as gout flares and tophi resolution after 52 weeks of treatment. No subgroup analyses were conducted for patients with renal impairment, non-responders to allopurinol or patients with severe disease. Supplementary data from a 2-year open-label extension study were also provided, but were difficult to interpret (no statistical analysis undertaken) and poorly reported.

The ERG believes that the modelling structure employed was not appropriate to estimate the cost-effectiveness of febuxostat within a treatment algorithm. In addition, there were concerns about the methodology used for collecting data on key model inputs. Given these reservations the cost-effectiveness of febuxostat could not be determined.

Key issues

The head-to-head trials presented in the manufacturer's submission directly compared febuxostat with fixed-dose allopurinol. However, gout management guidelines and the allopurinol summary of product characteristics generally recommend dose titration of allopurinol according to therapeutic targets (usual maintenance dose in mild conditions 100–200 mg/day, in moderately severe conditions 300–600 mg/day, in severe conditions 700–900 mg/day). Nevertheless, the manufacturer's submission and our clinical advisors suggest that dose escalation is rarely used by most clinicians in clinical practice.

Although measures such as gout flares and tophi resolution were secondary outcomes, these are more clinically important. Randomised controlled trial evidence shows that even though more febuxostat recipients achieved the recommended biochemical goal (< 6 mg/dl) this did not translate into an advantage over allopurinol in clinically important outcomes.

As previously described, the ERG has serious concerns regarding the model structure (and choice of treatment algorithms compared) and the robustness of key parameters within the model.

Areas of uncertainty

There is uncertainty around the clinical effectiveness and cost-effectiveness of febuxostat in comparison to other relevant treatments (including sulphinpyrazone, benzbromarone, probenecid or a combination of these) for adults unresponsive to, or intolerant of, allopurinol or with renal impairment. In addition, long-term efficacy and safety data are limited on febuxostat and there is uncertainty around the relationship between sUA levels and the expected number of gout flares.

The incremental costs per QALY of sequential approaches of treatment are uncertain as these approaches have not been modelled. The inclusion of sequential treatments is likely to produce a more cost-effective solution than allowing only one treatment for the duration of the model. Moreover, there is uncertainty in the relationship between sUA levels and underlying patient utility.

Summary of NICE guidance issued as a result of the STA

The appraisal consultation document issued by NICE in May 2008 stated that:

Febuxostat is not recommended for the management of chronic hyperuricaemia in people with gout.

The manufacturer appealed against the preliminary decision and produced additional evidence not contained in the STA submission that compared febuxostat with no treatment. This evidence was not formally critiqued by the ERG.

In August 2008 the final appraisal determination was released with the guidance that febuxostat, within its marketing authorisation, is recommended as an option for the management of chronic hyperuricaemia in gout only for people who are intolerant of allopurinol or for whom allopurinol is contraindicated.

Intolerance of allopurinol was defined as:

> adverse effects that are sufficiently severe to warrant its discontinuation, or to prevent full dose escalation for optimal effectiveness as appropriate within its marketing authorisation.

At the time of writing the manufacturer was appealing this decision.

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Rivaroxaban for the prevention of venous thromboembolism: 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 rivaroxaban for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery 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 four randomised controlled trials (RCTs) comparing rivaroxaban with enoxaparin [RECORD (Regulation of Coagulation in Orthopedic surgery to pRevent Deep venous thrombosis and pulmonary embolism) 1–4] and three comparing dabigatran with enoxaparin [RE-NOVATE (the prevention of venous thromboembolism after total hip replacement trial), RE-MODEL (the prevention of venous thromboembolism after total knee replacement trial) and RE-MOBILIZE (the prevention of venous thromboembolism after total knee arthroplasty trial)]. The evidence from the four RECORD trials indicates that rivaroxaban had superior efficacy over enoxaparin after total hip replacement (THR) and total knee replacement (TKR). For the composite primary outcome of any deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE) and death from all causes the relative risk reductions were 70–79% in THR and 31–49% in TKR. Rivaroxaban also had superior efficacy over enoxaparin for the secondary outcome major VTE. Rivaroxaban was not inferior to enoxaparin on the safety outcome of major bleeding. After the correction of some errors found by the ERG, the manufacturer's economic model represented a reasonable model

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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).

of patients receiving prophylaxis for THR or TKR. In the base-case analyses rivaroxaban dominated both enoxaparin and dabigatran. The incremental costs saved and quality-adjusted life-years (QALYs) gained were small (below £200 and 0.005, respectively, per person). Analyses were conducted sampling from the distributions observed from the RCTs. When all parameters were sampled rivaroxaban dominated enoxaparin in all scenarios except for two, in which enoxaparin produced more QALYs than rivaroxaban and had an incremental cost per QALY gained of £5000 and £8000 respectively. Rivaroxaban dominated dabigatran when RECORD 1 and RECORD 2, individually or pooled, were compared with RE-NOVATE and when all four rivaroxaban RCTs pooled were compared with all three dabigatran RCTs. Dabigatran dominated rivaroxaban comparing RECORD 4 with RE-MODEL and RE-MOBILIZE, and was more cost-effective than rivaroxaban comparing RECORD 3 (incremental cost per QALY gained of rivaroxaban compared with dabigatran of £123,000) or RECORD 3 and RECORD 4 pooled (incremental cost per QALY gained of dabigatran compared with rivaroxaban of £400) with RE-MODEL and RE-MOBILIZE. In conclusion, the evidence indicates that rivaroxaban is not inferior to enoxaparin in terms of the primary and secondary outcomes. The submission presents a reasonable estimation of the cost-effectiveness of rivaroxaban compared with enoxaparin and dabigatran, although the uncertainty in the decision has been underestimated. The results are particularly sensitive to any assumed difference in the number of fatal PEs, but the ERG does not believe there is sufficient evidence to support a difference between interventions. The NICE guidance issued as a result of the STA states that: riveroxaban, within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective THR or elective TKB.

Introduction

The National Institute of 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.[1] 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 rivaroxaban for the prevention of venous thromboembolism (VTE),[2] which followed a manufacturer's submission by Bayer Schering Pharma.[3]

Description of the underlying health problem

The manufacturer's submission reported that there are approximately 25,000 deaths each year in England due to VTE. This figure includes not only those undergoing surgery but also those admitted to hospital for the medical care of serious illnesses and will overestimate deaths associated with total hip and knee replacement.[3]

Scope of the ERG report

The manufacturer's submission reported on the clinical and cost-effectiveness of rivaroxaban (Xarelto®) for the prevention of VTE in adult patients undergoing elective hip or knee replacement surgery. The recommended dose of rivaroxaban is 10 mg taken orally once daily. The duration of treatment recommended in the summary of product characteristics depends on the type of orthopaedic surgery. Patients undergoing total hip replacement (THR) have a recommended treatment duration of 5 weeks; this value is 2 weeks for total knee replacement (TKR). The acquisition cost of rivaroxaban reported in the manufacturer's submission was £4.50 per day.

The manufacturer's submission considered enoxaparin, a low-molecular-weight heparin (LMWH), as the most relevant comparator, as reflected in the scope. A weighted comparison against all LMWHs was presented as a sensitivity analysis assuming equal efficacy between all LMWHs. Indirect comparisons with dabigatran

(which NICE has recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective THR or elective TKR[4]) were undertaken. The majority of outcome measures identified in the scope [mortality, incidence of symptomatic and asymptomatic VTE, pulmonary embolism (PE)], and safety outcomes (bleeding events), were reported. However, outcomes relating to knee and hip joints, although identified in the scope, were not reported.

Clinical data on effectiveness were taken from four randomised controlled trials (RCTs) of rivaroxaban compared with enoxaparin [RECORD (Regulation of Coagulation in Orthopedic surgery to pRevent Deep venous thrombosis and pulmonary embolism) 1–4[5–8]] and from three RCTs of dabigatran compared with enoxaparin [RE-NOVATE (the prevention of venous thromboembolism after total hip replacement trial),[9] RE-MODEL(the prevention of venous thromboembolism after total knee replacement trial)[10] and RE-MOBILIZE (the prevention of venous thromboembolism after total knee arthroplasty trial)[11]].

The manufacturer submitted a model in Microsoft EXCEL. The model was divided into a prophylaxis stage (a period of 35 days for THR and 12 days for TKR), a postprophylaxis stage (until 3 months after surgery) and a long-term complication stage (assumed to end when a patient died or became 101 years of age). The initial two stages were assessed using a decision trees, whereas the third phase was divided into a 5-year period, in which VTE, post-thrombotic syndrome (PTS) or death could occur, followed by a duration in which only transitions to death were allowed. The base case in the manufacturer's submission assumed that only those parameters that were statistically significantly different would be varied between rivaroxaban and the comparator. Additional analyses requested by the ERG used all variables regardless of statistical significance.

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 searches performed by the manufacturer were examined by the ERG and found to be satisfactory. Repeat searches were performed by the ERG and no additional relevant trials were identified. The ERG is confident that all relevant studies were included in the manufacturer's submission and details of ongoing trials that are likely to be reporting additional evidence within 12 months were reported. The inclusion/exclusion criteria appeared to be appropriate; they included appropriate detail and a rationale for the inclusion and exclusion criteria was provided. The reasons provided for excluding studies were all justified.

The manufacturer's submission reported on efforts to ensure blinding but did not report if any of these studies assessed the success of blinding, as required by point 11 on the Consolodated Standards of Reporting Trials (CONSORT) checklist (www.consort-statement.org/). The view of the ERG is that such assessments were not undertaken.

The manufacturer's submission answered the questions suggested by NICE for validity assessment. The ERG assessed the validity of the three published trials (RECORD 1, RECORD 2 and RECORD 3) and the trial information for RECORD 4. This was found to be satisfactory and of adequate methodological quality.

The manufacturer's submission used the modified intention-to-treat (MITT) population in the analyses of the trials. The MITT population was defined as the number of patients who were: (1) valid for safety analysis; (2) had the appropriate surgery; and (3) had an adequate assessment of thromboembolism. The ERG judged this to be an appropriate approach.

The manufacturer's submission contained a series of meta-analyses. Each comparison was conducted initially using a fixed-effects model, with a random-effects model performed if heterogeneity was observed between studies. Theoretically this approach is incorrect as a decision on the most appropriate model should be made before analysis, but this methodology did not materially affect the conclusions.

The deterministic results produced by the model matched those reported in the manufacturer's submission. The results from probabilistic sensitivity analyses were not checked because the ERG found errors within the model. These errors were identified by a thorough, although not exhaustive, review of the model structure and internal logic and the responsiveness of the results to changes in parameter values.

Results

Summary of submitted clinical evidence

In RECORD 1, 3 and 4, rivaroxaban was demonstrated to have superior efficacy over enoxaparin after THR and TKR. RECORD 2 also demonstrated superiority comparing 35 days of rivaroxaban with 12–14 days of enoxaparin. Based on the composite primary end point of any deep vein thrombosis (DVT), non-fatal PE and death from all causes the relative risk reductions were 70–79% in THR and 31–49% in TKR. Rivaroxaban was also demonstrated to have superior efficacy over enoxaparin in RECORD 1, 2 and 3 for the secondary end point of major VTE. Superior efficacy was also shown for the symptomatic VTE end point in RECORD 2 and RECORD 3.

There were no adverse events that were significantly different between rivaroxaban and enoxaparin. Major bleeding occurred more frequently in patients on rivaroxaban. Individually there was no statistically significant difference in major bleed rates between patients receiving rivaroxaban and those receiving enoxaparin, although all point estimates favoured enoxaparin treatment. On meta-analysing all four RCTs, the results remained non-significant in a fixed-effects model ($p = 0.697$). The point estimate favoured enoxaparin rather than rivaroxaban (relative risk 1.8516, 95% CI 0.9434 to 3.6340). Clinical evidence, where not commercial-in-confidence, is presented in Chapter 6 of the manufacturer's submission.

The indirect comparison with dabigatran was marked as commercial-in-confidence in the manufacturer's submission.

Summary of submitted cost-effectiveness evidence

In the base-case analyses rivaroxaban was shown to dominate [i.e. produce more quality-adjusted life-years (QALYs) at a lower cost] both enoxaparin and dabigatran. The incremental costs saved and QALYs gained were small (typically below £200 and 0.005, respectively, per person).

Analyses were conducted sampling from the distributions observed from the RCTs (or indirect comparison with dabigatran) regardless of statistical significance. These results were firmly driven by the assumed impact on fatal PE. Unfortunately this parameter was excluded within the probabilistic sensitivity analyses, which rendered the uncertainty generated in the remaining parameters as largely redundant. Using RECORD 4 alone, enoxaparin produced more QALYs than rivaroxaban and had an incremental cost per QALY gained of approximately £5000; using the pooled results this value was approximately £8000. These results imply that enoxaparin was more cost-effective than rivaroxaban in both of these scenarios using current recommended thresholds.[12]

When dabigatran was used as the comparator, rivaroxaban dominated dabigatran when RECORD 1 individually, RECORD 2 individually or the pooled results from RECORD 1 and RECORD 2 were compared with RENOVATE and when all four rivaroxaban RCTs pooled were compared with all three dabigatran RCTs. Dabigatran dominated rivaroxaban using RECORD 4 compared with RE-MODEL and RE-MOBILIZE, and was more cost-effective than rivaroxaban using RECORD 3 compared with RE-MODEL and RE-MOBILIZE (an incremental cost per QALY gained of rivaroxaban compared with dabigatran of approximately £123,000) and when RECORD 3 and RECORD 4 were pooled and compared with RE-MODEL and RE-MOBILIZE (an incremental cost per QALY gained of dabigatran compared with rivaroxaban of approximately £400).

Commentary on the robustness of submitted evidence

Appropriate analyses and comparisons were included in the manufacturer's submission. Data on the final primary outcome measure (all-cause mortality) were not presented or meta-analysed. The ERG have inferred that this was due to no additional deaths bar fatal PE, the data for which were presented as commercial-in-confidence. The ERG has no concerns with the methodology used for the evidence syntheses. The reporting and interpretation of the safety data were good.

Following dialogue iterations with the ERG team, the resultant EXCEL file was a reasonable model of patients receiving prophylaxis for THR or TKR. The iterations were needed to amend errors found by the ERG, which included incorrect use of standard errors, probabilities becoming negative and some cells being incorrectly cleared.

The probabilistic sensitivity analyses did not capture all of the uncertainty present within the decision. The number of total VTEs for rivaroxaban is assumed to equal the rates observed

in the appropriate RCT(s). For both rivaroxaban and the comparator the proportions of total VTEs that are symptomatic, non-fatal and fatal are fixed at the rates observed in the appropriate RCTs. These are relatively small numbers. For example, in RECORD 1 there were 18 VTEs of which four were non-fatal PE; fixing the proportion of non-fatal PEs to 0.22 (4/18) of the total VTEs will result in considerable uncertainty being excluded compared with a more appropriate approach of sampling this value from a beta distribution. The long-term effects of major bleeding, in particular those that are intracranial, were excluded from the model, although the manufacturer subsequently conducted an external calculation which showed that this omission did not markedly affect the results for the comparison with enoxaparin. The ERG conducted a similar calculation for the comparison with dabigatran, with similar conclusions.

Following the postprophylaxis stage of the model all VTE events are assumed to be DVT. This is conservative and will be unfavourable to the intervention that has the lowest number of VTEs, which is generally rivaroxaban.

The utility of a patient was set to that of a 50-year-old and does not decline as the simulated patient ages. This will favour the intervention that has the greater estimated number of patients alive following the postprophylaxis stage. The manufacturer conducted additional analyses to assess the impact of altering the underlying utility, with only a minor reduction in the incremental QALYs gained associated with rivaroxaban. The manufacturer concluded that the inaccuracy introduced by not altering the utility will be small. The ERG agrees with this conclusion.

Conclusions

The manufacturer's search strategy was adequately reported and the submission appears to contain all of the relevant head-to-head RCTs. The outcomes selected were relevant and appropriate, although joint outcomes, included in the final scope issued by NICE, were excluded as none of the trials reported this.

Processes and validation of study screening and data extraction appear to be appropriate. Statistical methods were explicitly described for the meta-analyses and indirect comparisons and all relevant analyses were performed, although reporting of the results of these analyses were limited because of the omission of conclusions or plots to aid interpretation. The manufacturer's submission appears to contain an unbiased estimate of the treatment effect of rivaroxaban in relation to the relevant outcomes and the comparator enoxaparin. Overall the evidence from the four RECORD trials in the manufacturer's submission indicates that rivaroxaban 10 mg once daily is not inferior to the comparator enoxaparin in terms of the total VTE and all-cause mortality, symptomatic VTE, non-fatal PE and fatal PE. Rivaroxaban was also indicated not to be inferior to the comparator on the safety outcome of major bleeding.

The ERG believes that, following iterations with the ERG, the manufacturer's submission represents a reasonable estimation of the cost-effectiveness of rivaroxaban compared with enoxaparin and dabigatran, although the uncertainty in the decision has been underestimated. This is important as the costs and QALYs accrued by all interventions were similar and the incremental differences reported were small, typically below £200 and 0.005, respectively, per person.

The ERG notes that the results are particularly sensitive to any assumed difference in the number of fatal PEs, but does not believe that there is sufficient evidence to support a difference between interventions.

Summary of NICE guidance issued as a result of the STA

The guidance states that:

Rivaroxaban, within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective THR or elective TKB.

Key references

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Cetuximab for the treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck

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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 cetuximab for recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN) 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 a single reasonably high-quality randomised controlled trial (RCT) [EXTREME (Erbitux in First-Line Treatment of Recurrent or Metastatic Head and Neck Cancer); $n = 442$] comparing cetuximab plus chemotherapy (CTX) with CTX alone. Cetuximab plus CTX had significant effects compared with CTX alone on the primary outcome of overall survival (10.1 versus 7.4 months respectively) and the secondary outcomes of progression-free survival (PFS) (5.6 versus 3.3 months), best overall response to therapy (35.6% versus 19.5%), disease control rate (81.1% versus 60%) and time-to-treatment failure (4.8 versus 3.0 months), but not on duration of response (5.6 months versus 4.7 months). No safety issues with cetuximab arose beyond those already previously documented. The manufacturer developed a two-arm state-transition Markov model to evaluate the cost-effectiveness of cetuximab plus CTX versus CTX alone, using clinical data from the EXTREME trial. The ERG recalculated the base-case cost-effectiveness results taking changes in parameters and assumptions into account. Subgroup and threshold analyses were also explored. The manufacturer reported

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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).

an incremental cost-effectiveness ratio (ICER) of £121,367 per quality-adjusted life-year (QALY) gained and an incremental cost per life-year gained of £92,226. Univariate sensitivity analysis showed that varying the cost of day-case infusion and the utility values in the stable/response health state of the cetuximab plus CTX arm had the greatest impact on the ICER. Probabilistic sensitivity analysis illustrated that cetuximab plus CTX is unlikely to be cost-effective for patients with recurrent and/or metastatic SCCHN, even at what would usually be considered very high levels of willingness to pay for an additional QALY. With regard to the economic model the appropriateness and reliability of parametric survival projection beyond the duration of trial data could not be fully explored because of lack of information. The ERG also questioned the appropriateness of economic modelling in this STA as evidence is available only from a single RCT. In conclusion, the ERG considers that patients with metastatic SCCHN were not shown to receive a significant survival benefit from cetuximab plus CTX compared with CTX alone and that even setting a lower price for cetuximab would not strengthen the manufacturer's case for cost-effectiveness.

Introduction

The National Institute of 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.[1] 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 cetuximab for recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN).[2]

Description of the underlying health problem

The term head and neck cancer covers a wide variety of different cancers [30 different International Classification of Diseases (ICD) codes] occurring in the tissues of the head and neck. As a group they account for over 8000 cancer registrations in England and Wales.[3] Around 90% of head and neck cancers are squamous cell. SCCHN most commonly arises in the oral cavity, pharynx and larynx.[3] The number of registrations for these subgroups was 5833 in England in 2005[4] and 446 in Wales in 2006,[5] with a ratio of male to female cases of approximately 70:30.

There is no standard treatment for all patients with recurrent or metastatic disease; guidelines recommend the tailoring of therapy to the individual patient.[3,6] In some patients the tumour may still be amenable to surgery or radiotherapy with curative intent; however, in patients with metastatic disease or who have previously received radiotherapy for the initial tumour, this may not be possible. For this group of patients palliative CTX is the mainstay of treatment if they are able to tolerate it. The most commonly used chemotherapeutic treatments for recurrent and/or metastatic SCCHN include methotrexate, bleomycin, 5-fluorouracil (5-FU) and platinum compounds. The prognosis for recurrent and/or metastatic SCCHN subjects is poor with a median survival time of only 6–9 months.

Scope of the ERG report

The ERG report presents the results of the assessment of the manufacturer (Merck Serono) evidence submission regarding the use of cetuximab with platinum-based CTX (cisplatin plus fluorouracil or carboplatin plus fluorouracil) compared with platinum-based CTX alone for the first-line treatment of recurrent and/or metastatic SCCHN. The report includes an assessment of both the clinical effectiveness and cost-effectiveness evidence submitted by the manufacturer. The primary clinical outcome measure was overall survival (OS), with secondary outcomes of progression-free survival (PFS), response to therapy, safety and quality of life (QoL). The cost-effectiveness measures were incremental cost-effectiveness ratio (ICER) and incremental cost per life-year (LY) gained.

Cetuximab (Erbitux®) is a monoclonal antibody that inhibits the action of the epidermal growth factor receptor (EGFR), which is highly expressed in nearly all SCCHN tumours. Whilst the ERG report was in progress, a positive opinion from the European Medicines Agency (EMEA) Committee for Medicinal Products for Human Use (CHMP) to extend the use of cetuximab to include the treatment of patients with recurrent and/or metastatic SCCHN in combination with platinum-based CTX was issued. Final approval was given by the EMEA after the submission of the ERG report. Neither the EMEA nor NICE limited the indication to first-line use; this limitation was imposed by the manufacturer.

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 evaluated the quality of the manufacturer's clinical effectiveness review. Searches conducted by the manufacturer were assessed for completeness and the single trial put forward as evidence of effectiveness was critically appraised using a standard tool (CASP[7] – Critical Appraisal Skills Programme). With regard to cost-effectiveness evidence, the ERG assessed the manufacturer's searches for completeness, critically appraised the submitted economic model using a standard assessment tool (Drummond and Jefferson[8]) and conducted a detailed evaluation of the model. The ERG recalculated the base-case cost-effectiveness results taking changes in parameters and assumptions into account, for example revised drug costs, mid-cycle correction, overall PFS utility value. Subgroup and threshold analyses were also explored by the ERG.

Results

Summary of submitted clinical evidence

The clinical effectiveness evidence described in the manufacturer's submission was derived from a single phase III open-label randomised controlled trial (RCT) that compared the use of cetuximab plus CTX with CTX alone. The EXTREME (Erbitux in First-Line Treatment of Recurrent or Metastatic Head and Neck Cancer) trial was conducted in 80 centres within 17 European countries and included 442 patients. The results of the EXTREME trial showed significant effects of cetuximab plus CTX compared with CTX alone on the primary outcome of OS (10.1 months versus 7.4 months respectively). There was also a significant effect of cetuximab plus CTX compared with CTX alone on the secondary end points of median PFS (5.6 months versus 3.3 months), best overall response to therapy (35.6% versus 19.5%), disease control rate (81.1% versus 60%) and median time-to-treatment failure (TTF) (4.8 months versus 3.0 months). No significant difference was noted in the median duration of response between the cetuximab plus CTX and CTX alone groups (5.6 months versus 4.7 months). The results are summarised in *Table 1*. The QoL data described were very limited; the manufacturer states that there was no difference in QoL between the two treatment groups. No safety issues related to cetuximab arose beyond those already previously documented.

Summary of submitted cost-effectiveness evidence

In the absence of UK-based economic evaluations, the manufacturer conducted a de novo economic evaluation. A two-arm state-transition Markov model was developed to evaluate the cost-effectiveness of cetuximab plus CTX compared with CTX alone. The clinical data used in the economic evaluation were generated from the EXTREME trial. Although the economic evaluation was trial based there was also a modelling component with regard to the extrapolation of health effects beyond the period of the trial (24 months). The economic evaluation adopted a lifetime horizon for the consideration of costs and benefits and the perspective is that of the UK NHS and personal social services.

The manufacturer reported an ICER of £121,367 per quality-adjusted life-year (QALY) gained and an incremental cost per LY gained of £92,226. In addition to the main results, ICERs for selected subgroups were also presented. Univariate sensitivity analysis showed that varying (1) the cost of day-case infusion and (2) the utility values in the stable/response health state of the cetuximab plus CTX arm had the greatest impact on the ICER. Probabilistic sensitivity analysis illustrated that cetuximab plus CTX is unlikely to be cost-effective for patients with recurrent and/or metastatic SCCHN, even at what would usually be considered very high levels of willingness to pay for an additional QALY.

TABLE 1 *Key results of the EXTREME trial*

Outcome	Cetuximab plus CTX (*n* = 222)	CTX (*n* = 220)	Hazard ratio (HR)/ odds ratio (OR)	*p*-value
Primary				
OS (months), median (95% CI)	10.1 (8.6–11.2)	7.4 (6.4–8.3)	HR 0.797 (0.644–0.986)	0.00362[a]
Secondary				
PFS (months), median (95% CI)[a]	5.6 (5.0–6.0)	3.3 (2.9–4.3)	HR 0.538 (0.431–0.672)	< 0.001
Best overall response	35.6% (29.3–42.3)	19.5% (14.5–25.4)	OR 2.326 (1.504–3.600)	< 0.001[b]
Disease control rate (95% CI)[c]	81% (75.3–86.0)	60% (53.2–66.5)	OR 2.881 (1.870–4.441)	< 0.001[d]
Time to treatment failure (months) (95% CI)[a]	4.8 (4.0–5.6)	3.0 (2.8–3.4)	HR 0.59 (0.48–0.73)	< 0.001[b]
Duration of response (months) (95% CI)[e]	5.6 (4.7–6.0)	4.7 (3.6–5.9)	HR 0.76 (0.50–1.17)	0.21[b]

CI, confidence interval; CTX, chemotherapy; OS, overall survival; PFS, progression-free survival.
p-values, hazard ratios and odds ratios are stratified according to receipt or non-receipt of previous chemotherapy and Karnofsky Performance Status at randomisation.

a Number of months estimated using Kaplan–Meier method.
b *p*-value calculated using the log-rank test.
c Disease control includes complete response, partial response and stable disease.
d *p*-value calculated using Cochrane–Mantel–Haenszel test.
e Data on duration of response were available for 62 patients in the cetuximab group and 36 patients in the CTX alone group; data on disease progression in these patients were available at the time of analysis. The number of months was estimated using the Kaplan–Meier method.

The manufacturer argued that the assessment of QoL associated with the use of cetuximab plus CTX may misrepresent the real health gain for patients with recurrent and/or metastatic SCCHN. The manufacturer would prefer that other indicators of benefit (e.g. socioeconomic status) are taken into account.

Commentary on the robustness of submitted evidence

The manufacturer cited evidence from a reasonably high-quality trial (EXTREME) of the clinical benefit of cetuximab plus CTX compared with CTX alone. The trial was well designed, used robust randomisation techniques and was suitably powered to show differences between the treatment groups. Appropriate exploratory subgroup analyses were carried out and statistical reporting was generally good.

However, the clinical effectiveness evidence was based only on this single trial, which was open label and relied on the unblinded assessment of clinical outcomes. Despite designing the trial to include a comprehensive analysis of QoL, very limited QoL data were collected and reported.

The manufacturer provided clinical evidence to support the use of cetuximab as a first-line treatment for patients with recurrent and/or metastatic SCCHN; hence, there is no discussion of the costs and benefits of second-line treatment options for this patient group. Neither the final scope issued by NICE nor the EMEA CHMP positive opinion limits the use of cetuximab to first-line treatment only.

The ERG was confident that neither model assumptions nor parameter values were likely to introduce sufficient uncertainty to allow cetuximab plus CTX to be cost-effective for this group of patients. A number of key issues and parameters in the economic model did not seem to be justified. The results of the ERG's threshold analysis indicate that cetuximab plus CTX may not be cost-effective at any price according to current NICE guidance. The ERG identified a number of different areas in the economic model in which it was appropriate to correct or revise model assumptions, which taken together increased the size of the ICER (*Table 2*).

Conclusions

The EXTREME trial demonstrated the superior clinical effectiveness of cetuximab plus CTX over CTX alone. However, whether or not the patients in the EXTREME trial are sufficiently similar (in terms of age and Karnofsky Performance Status) to patients in England and Wales with recurrent and/or metastatic SCCHN who require treatment

TABLE 2 *ERG modifications to manufacturer's economic model*

Model/amendment	Incremental costs	Incremental survival	Incremental QALYs	Incremental cost/LY gained	Incremental cost/QALY gained
Base case	£17,286	0.1874	0.1424	£92,226	£121,367
Mid-cycle correction	£16,185 (–£1101)	0.1874	0.1414 (–0.0011)	£86,353 (–£5873)	£114,484 (–£6884)
Limit to 24 months	£16,760 (–£526)	0.1318 (–0.0556)	0.1134 (–0.0290)	£127,149 (+£34,923)	£147,817 (+£26,449)
Overall PFS utility value	£17,286	0.1874	0.1240 (–0.0184)	£92,226	£139,390 (+£18,023)
Adverse event utility adjustment	£17,286	0.1874	0.1443 (+0.0019)	£92,226	£119,808 (–£1560)
Revised drug costs	£20,441 (+£3155)	0.1874	0.1424	£109,059 (+£16,833)	£143,519 (+£22,152)
100% cisplatin use	£17,332 (+£46)	0.1874	0.1424	£92,473 (+£247)	£121,692 (+£325)
Cetuximab dose adjustment	£17,404 (+£118)	0.1874	0.1424	£92,858 (+£632)	£122,199 (+£831)
Cisplatin dose adjustment	£17,259 (–£27)	0.1874	0.1424	£92,081 (–£145)	£121,177 (–£191)
Rebase unit costs	£18,852 (+£1566)	0.1874	0.1424	£100,580 (+£8354)	£132,361 (+£10,993)
Revised discounting	£17,283 (–£3)	0.1873(–0.0002)	0.1423 (–0.0001)	£92,297 (+£71)	£121,437 (+£69)
Base case + all changes – full life	£20,932 (+£3646)	0.1873 (–0.0002)	0.1259 (–0.0166)	£111,784 (+£19,558)	£166,307 (+£44,939)
Base case + all changes – 24 months	£20,331 (+£3045)	0.1317 (–0.0558)	0.0976 (–0.0449)	£154,420 (+£62,194)	£208,266 (+£86,899)

LY, life-year; PFS, progression-free survival; QALY(s), quality-adjusted life-year(s).
Numbers in parentheses indicate the change relative to the base case.

is uncertain. There is also no clinical evidence available to demonstrate the effectiveness of cetuximab plus CTX in patients who are not cetuximab naive. Finally, the ERG considered that patients with metastatic SCCHN were not shown to receive a significant survival benefit from cetuximab plus CTX compared with CTX alone.

With regards to the economic model, some questions over the appropriateness and reliability of parametric survival projection beyond the duration of trial data could not be fully explored by the ERG because of lack of information; in particular, the appropriateness of employing Weibull modelling for all patient groups may benefit from further examination. The ERG also questioned the appropriateness of economic modelling in this STA as many health economists would prefer to carry out direct evaluation of trial data when evidence is available only from a single RCT.

The cost per QALY figures reported in the manufacturer's submission were high (in excess of £100,000 per QALY gained). Both the original model submitted by the manufacturer and the model corrected/adjusted by the ERG yielded ICERs that far exceed accepted values. Given the high cost of cetuximab plus CTX and the marginal health benefits gained in comparison to CTX, discussion of further economic issues within NICE's current acceptability range (from £20,000 to £30,000 per QALY) seemed unnecessary. The ERG concluded that even setting a lower price for cetuximab would not strengthen the manufacturer's case for cost-effectiveness.

Summary of NICE guidance issued as a result of the STA

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

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Ustekinumab for the treatment of moderate to severe psoriasis

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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 ustekinumab for the treatment of moderate to severe 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 main evidence came from three randomised controlled trials (RCTs), of reasonable methodological quality and measuring a range of clinically relevant outcomes. Higher proportions of participants treated with ustekinumab (45 mg and 90 mg) than with placebo or etanercept achieved an improvement on the Psoriasis Area and Severity Index (PASI) of at least 75% (PASI 75) after 12 weeks. There were also statistically significant differences in favour of ustekinumab over placebo for PASI 50 and PASI 90 results, and for ustekinumab over etanercept for PASI 90 results. A weight-based subgroup dosing analysis for each trial was presented, but the methodology was poorly described and no statistical analysis to support the chosen weight threshold was presented. The manufacturer carried out a mixed treatment comparison (MTC); however, the appropriateness of some of the methodological aspects of the MTC is uncertain. The incidence of adverse events was similar between groups at 12 weeks and withdrawals due to adverse events were low and less frequent in the ustekinumab than in the placebo or etanercept groups; however, statistical comparisons were not reported. The manufacturer's economic model of treatments for psoriasis compared ustekinumab with other biological therapies. The

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model used a reasonable approach; however, it is not clear whether the clinical effectiveness estimates from the subgroup analysis, used in the base-case analysis, were methodologically appropriate. The base-case incremental cost-effectiveness ratio for ustekinumab versus supportive care was £29,587 per quality-adjusted life-year (QALY). In one-way sensitivity analysis the model was most sensitive to the number of hospital days associated with supportive care, the cost estimate for intermittent etanercept 25 mg and the utility scores used. In the ERG's scenario analysis the model was most sensitive to the price of ustekinumab 90 mg, the proportion of patients with baseline weight > 100 kg and the relative risk of intermittent versus continuous etanercept 25 mg. In the ERG's probabilistic sensitivity analysis ustekinumab had the highest probability of being cost-effective at conventional NICE thresholds, assuming the same price for the 45-mg and 90-mg doses; however, doubling the price of ustekinumab 90 mg resulted in ustekinumab no longer dominating the comparators. In conclusion, the clinical effectiveness and cost-effectiveness of ustekinumab in relation to other drugs in this class is uncertain. Provisional NICE guidance issued as a result of the STA states that ustekinumab is recommended as a treatment option for adults with plaque psoriasis when a number of criteria are met. Final guidance is anticipated in September 2009.

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.[1] 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 ustekinumab for the treatment of psoriasis.

Description of the underlying health problem

Psoriasis is a chronic systemic inflammatory skin disease. The most common form of psoriasis is chronic plaque psoriasis. This is characterised by exacerbations of thickened, erythematous, scaly patches of skin that can occur at any skin site but commonly appear on the elbows, knees, scalp and trunk. Estimates suggest that psoriasis affects approximately 2% of the population in the UK.[2] Psoriasis is associated with a significant negative impact on heath-related quality of life.

The severity of psoriasis is determined by several factors and can vary from mild, through to moderate and severe. A number of different criteria are available for determining the severity of psoriasis. 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[3] 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. Severe psoriasis is generally accepted as a PASI ≥ 10 when combined with a DLQI > 10[2] or, if taken alone, a PASI > 12.[4] Moderate psoriasis is generally defined as a PASI between 7 and 12.[4]

Scope of the ERG report

The ERG critically evaluated the evidence submission from Janssen-Cilag on the use of ustekinumab for the treatment of moderate to severe plaque psoriasis.

Ustekinumab is a fully human monoclonal antibody. The licensed indication for ustekinumab for injection is for the treatment of adults with moderate to severe chronic plaque psoriasis who have had an inadequate response to or who have a contraindication to or who are intolerant to other systemic therapies.

The outcomes stated in the manufacturer's definition of the decision problem were measures of severity of psoriasis, remission rate, relapse 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. One-way sensitivity analyses, scenario analyses and a probabilistic sensitivity analysis were undertaken by the ERG.

Results

Summary of submitted clinical evidence

The main evidence on efficacy in the submission came from three randomised controlled trials (RCTs), two comparing ustekinumab with placebo and one comparing ustekinumab with etanercept. One further RCT contributed to the evidence on adverse events.

Higher proportions of participants treated with ustekinumab (at both the 45-mg and 90-mg doses) than with placebo (two trials) or etanercept (one trial) achieved an improvement on the PASI of at least 75% (PASI 75) after 12 weeks. No statistical comparisons between the two ustekinumab doses were presented for any of the trials. There were also statistically significant differences in favour of ustekinumab (at both the 45-mg and 90-mg doses) over placebo for the proportion of participants achieving a PASI 50 and a PASI 90 (two trials), but again no statistical comparisons between the two ustekinumab doses were presented. In the trial comparing ustekinumab with etanercept, PASI 50 results appeared to be similar across the three treatment groups (45 mg ustekinumab, 90 mg ustekinumab and etanercept), but no statistical comparison of these data was presented. In contrast, both doses of ustekinumab led to statistically significantly higher proportions of participants achieving a PASI 90 than was observed in the etanercept group.

The manufacturer's submission also presented PASI 75 data from a weight-based subgroup dosing analysis for each of the three included trials, but the methodological description of these analyses was limited and no statistical analysis to support the chosen weight threshold was presented.

The manufacturer's submission did not present a narrative or quantitative synthesis of the data from the three included trials except as part of a mixed treatment comparison (MTC). The MTC was conducted using data from the ustekinumab trials in two ways, either all participants as randomised or subgroups of participants from the dose by weight analysis noted above. The result from the all participant analysis MTC for treatment with 45 mg ustekinumab was a mean probability of achieving a PASI 75 response to treatment of 69%, with a different result obtained from the weight-based ustekinumab analysis MTC. For the 90-mg ustekinumab dose the all participant analysis MTC resulted in a mean probability of achieving a PASI 75 response to treatment of 74%; again, a different result was obtained from the weight-based ustekinumab analysis MTC. For the PASI 75 MTC outcome the probability of response was greatest for infliximab, and the probability of response with ustekinumab was greater than those of the other comparators, except for infliximab.

For the reported secondary outcomes there were statistically significant differences in favour of ustekinumab over placebo and etanercept in the Physician's Global Assessment score, and in favour of ustekinumab over placebo in the DLQI. The DLQI outcome was not reported for the ustekinumab versus etanercept trial. The incidence of adverse events appeared to be similar in the treatment and placebo arms at 12 weeks although this was not statistically tested. Withdrawals due to adverse events were low and appeared to occur less often in the ustekinumab groups than in either the placebo or the etanercept groups, although a statistical comparison was not reported in the manufacturer's submission.

Summary of submitted cost-effectiveness evidence

The manufacturer's economic evaluation included a review of the published economic literature on therapies used for psoriasis and a report of an economic evaluation undertaken for the NICE STA process, which included a cost-effectiveness model of treatments for psoriasis comparing ustekinumab with other biological therapies. The analysis estimated the number of individuals who responded to treatment at each time interval, the mean length of time that an individual

would respond to treatment and the utility gains associated with this response. The model was based closely on the model reported in Woolacott and colleagues.[3]

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

The evidence-based treatment effectiveness was reported in terms of the probability of achieving a specified PASI response with each of the treatment alternatives and supportive care by the end of the trial period. Evidence was synthesised from a variety of trials for ustekinumab and the comparators using an MTC model. In the base-case analysis it was assumed that those under a weight of 100 kg (80% of patients in base case) received 45 mg ustekinumab whereas those over 100 kg (20% of patients) received 90 mg ustekinumab. The manufacturer's submission proposed a patient access scheme (PAS) providing ustekinumab 90 mg at an equivalent cost to ustekinumab 45 mg and the model assumed these costs in the base case.

Patients who achieved improvements in PASI score were assigned an associated improvement in quality of life (a utility gain), with higher responses associated with larger improvements in quality of life. Two approaches were used to achieve this task. In the first the observed patient-level changes in DLQI were used as surrogate outcomes in the statistical modelling that related the PASI scores to utility gains assessed using the EuroQol 5 dimension (EQ-5D) questionnaire. The EQ-5D utility values derived from the DLQI were used in the base-case analysis. In the second approach the observed patient-level Short Form-36 (SF-36) scores were converted into Short Form-6D (SF-6D) utility values and aggregated according to the PASI response categories. The SF-6D utility estimates were used in the sensitivity analysis.

The base-case incremental cost-effectiveness ratio for ustekinumab compared with supportive care for patients with severe psoriasis was £29,587 per quality-adjusted life-year (QALY). The one-way sensitivity analysis reported in the manufacturer's submission shows that the model was most sensitive to the number of hospital days associated with supportive care, the estimate of the cost of dosing for intermittent etanercept 25 mg and the use of SF-6D utility scores instead of EQ-5D utility scores (with SF-6D utility scores associated with a much higher cost-effectiveness ratio for ustekinumab in comparison to supportive care then the cost-effectiveness ratio estimated in the base-case analysis).

Scenario analyses were presented in the manufacturer's submission that compared outcomes from the model when the efficacy estimates came from (1) the MTC subgroup data in which the ustekinumab dose regimen depends on the baseline weight and (2) the all patients according to their randomisation outcome. Scenario analysis conducted by the ERG showed that the model was most sensitive to the assumptions about the price of ustekinumab 90 mg, the proportion of patients with baseline weight > 100 kg and the relative risk of intermittent etanercept 25 mg in comparison to continuous etanercept 25 mg.

The ERG amended the manufacturer's probabilistic sensitivity analysis to include distributions for parameters not previously included in the model. *Figure 1* shows the cost-effectiveness acceptability curve assuming the same price for the 45-mg and 90-mg doses of ustekinumab. According to these results ustekinumab has the highest probability of being cost-effective at conventional NICE thresholds, whereas all other biologics have a zero probability of being cost-effective. The probability of ustekinumab being cost-effective at thresholds of £20,000 and £30,000 per QALY is 10% and 47% respectively.

Commentary on the robustness of submitted evidence

Strengths

The manufacturer conducted a systematic search for clinical effectiveness and cost-effectiveness studies of ustekinumab. It appears unlikely that the searches missed any additional trials that would have met the inclusion criteria.

The three key ustekinumab trials identified and systematically reviewed 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 ustekinumab at 12 weeks based on the results of two placebo-controlled trials and one trial comparing ustekinumab with etanercept.

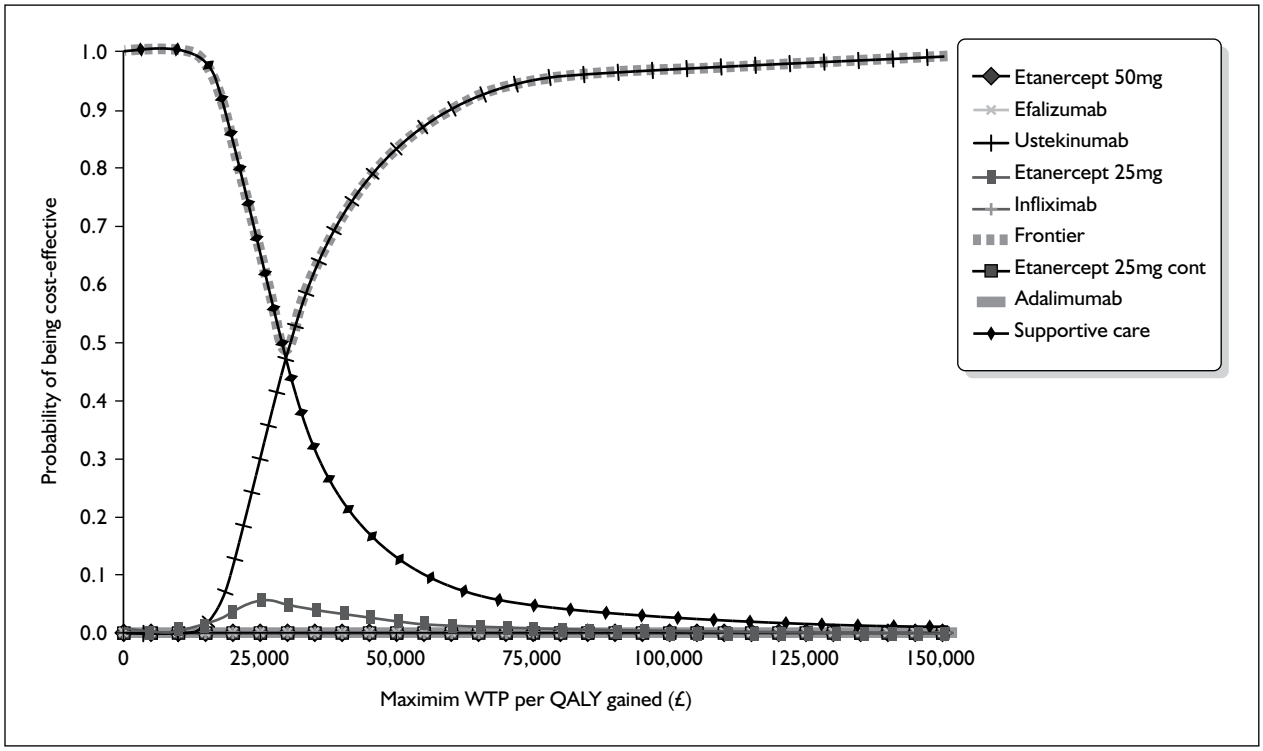

FIGURE 1 *ERG analysis of the cost-effectiveness acceptability curve for biologics in the base case. QALY, quality-adjusted life-year; WTP, willingness to pay.*

The economic model presented in the manufacturer's submission used a reasonable approach.

Weaknesses

There is a lack of information regarding the methodology used for the subgroup analysis and it was therefore difficult for the ERG to determine whether the methods used were appropriate and whether the subgroup analysis supports the weight-based categorisation presented. These clinical effectiveness estimates of the subgroup data were used in the base-case analysis of the modelled economic evaluation of ustekinumab presented in the manufacturer's submission.

Conclusions

Areas of uncertainty

The reliability of the estimates of clinical effectiveness derived from subgroups of participants receiving differential weight-based dosing is uncertain. In addition, the impact on MTC outcomes of using a fixed-effect model rather than a random-effects model (which was used by the assessment group who developed the original MTC) is unclear.

The clinical effectiveness and cost-effectiveness of ustekinumab in relation to other drugs in the class is uncertain. A number of factors contribute to this uncertainty, including the two points above but also the assumption about the proportion of patients with baseline weight > 100 kg and the assumptions about the relative risk of intermittent etanercept 25 mg in comparison to continuous etanercept 25 mg.

It is not clear whether the estimates from the subgroup analysis, which were used in the base-case analysis in the manufacturer's submission, were methodologically appropriate. The choice of utility estimates used for the cost-effectiveness analysis has a major impact on the estimated cost-effectiveness of ustekinumab.

Key issues

Two of the trials of ustekinumab efficacy presented by the manufacturer were placebo-controlled trials. There was also one head-to-head RCT that directly compared ustekinumab with etanercept 50 mg. No studies were identified that directly compared ustekinumab with the other possible comparators included within the STA.

The manufacturer's submission did not present the results of the subgroup analysis according to NICE methodological guidance and therefore the ERG was unable to determine whether the weight-based categorisation used in the cost-effectiveness analysis was justified.

Although the manufacturers carried out an MTC, the effectiveness of ustekinumab in relation to other drugs of this type remains unclear because of uncertainties about the appropriateness of some of the methodological aspects of the MTC.

All of the economic outcomes in the manufacturer's submission were conditional on the price of ustekinumab 90 mg as indicated in the PAS. Doubling the price of ustekinumab 90 mg resulted in ustekinumab no longer dominating the comparators at a cost-effectiveness threshold of £20,000–30,000 per QALY.

Summary of NICE guidance issued as a result of the STA

The NICE guidance issued as a result of the STA states that ustekinumab is recommended as a treatment option for adults with plaque psoriasis when the following criteria are met:

- The disease is severe, as defined by a total Psoriasis Area Severity Index (PASI) score of 10 or more and a Dermatology Life Quality Index (DLQI) score of more than 10.
- The psoriasis has not responded to standard systemic therapies, includingciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation), or the person is intolerant of or has a contraindication to these treatments.
- The manufacturer provides the 90 mg dose (2 × 45 mg vials) for people who weigh more than 100 kg at the same total cost as for a single 45 mg vial.

Ustekinumab treatment should be stopped in people whose psoriasis has not responded adequately by 16 weeks after starting treatment. 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 5-point reduction in the DLQI score from when treatment started.

When using the DLQI, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties, that could affect the responses to the DLQI and make any adjustments they consider appropriate.

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We look forward to hearing from you.

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