Scottish Medicines Consortium

lapatinib, 250mg film-coated tablets (Tyverb®) No. (526/09)
GlaxoSmithKline

09 January 2009

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

lapatinib (Tyverb®) is not recommended for use within NHS Scotland, in combination with capecitabine, for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress ErbB2 (HER2) and who have progressive disease following prior therapy including anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting.

In a randomised open-label study the median time to progression for lapatinib plus capecitabine was significantly longer than for capecitabine monotherapy. There was no significant difference in overall survival.

The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC and, in addition, the justification of the treatment's cost in relation to its health benefits was not sufficient.

The licence holder has indicated their intention to resubmit.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

In combination with capecitabine, for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress ErbB2 (HER2). Patients should have progressive disease following prior therapy, which must include anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting.

Dosing information

Lapatinib 1250mg (i.e. five tablets) once daily continuously (at least one hour before, or at least one hour after food).

The recommended dose of capecitabine is 2000mg/m^2/day taken in 2 doses 12 hours apart on days 1 - 14 in a 21 day cycle. Capecitabine should be taken with food or within 30 minutes after food.

Lapatinib should only be initiated by a physician experienced in the administration of anti-cancer agents.

Product availability date

12 June 2008

Summary of evidence on comparative efficacy

Lapatinib is an orally administered tyrosine kinase inhibitor that selectively targets both the human epidermal growth factor receptor type 1 (ErbB1) and ErbB2 (also known as EGFR and HER2 respectively) receptors.

Efficacy is based on one phase III randomised, open-label, multi-centre, parallel-group trial which evaluated lapatinib plus capecitabine versus capecitabine alone in adult women with advanced or metastatic breast cancer and over-expression of ErbB2 who had progressed after receiving prior therapy which included anthracyclines, taxanes and trastuzumab (administered for at least 6 weeks in the locally advanced/metastatic setting, but may also have been given in the adjuvant setting). Patients received either lapatinib 1,250mg once daily on a continuous basis plus capecitabine 2,000mg/m^2/day on days 1 to 14 of a 21-day treatment cycle or capecitabine 2,500mg/m^2/day alone on days 1 to 14 of a 21-day treatment cycle.

The primary endpoint was time to progression (TTP), defined as the interval between the date of randomisation and the earliest date of either disease progression or death due to breast cancer as assessed by the Independent Radiological Review Committee (IRC) under blinded conditions. Secondary endpoints included: overall survival (OS), defined as the time from randomisation until death due to any cause; progression-free survival (PFS), defined as the time from randomisation until the first documented sign of disease progression or death due to any cause; and overall response rate (ORR), defined as the percentage of subjects achieving either a complete response or partial response. Changes in quality of life were assessed relative to baseline using the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire and the Euro QOL (EQ-5D) questionnaire.

The intention-to-treat (ITT) population comprised all randomised subjects and was used for the analyses of all efficacy endpoint data. For endpoints that determined percentage of responders, subjects with unknown or missing response data were treated as non-responders. A total sample size of 528 patients was planned based on 90% power to detect a 50% increase in median TTP (from an estimated 3 months in the group receiving

capecitabine monotherapy to 4.5 months in the group receiving lapatinib plus capecitabine) and statistical power of 80% to detect a 30% increase in median survival (from 8 months in the monotherapy group to 10.4 months in the combination group).

After a planned interim analysis the independent data monitoring committee unanimously recommended that, for ethical reasons, study enrolment be halted based on the clinically meaningful, statistically significant advantage in TTP for the lapatinib plus capecitabine arm versus capecitabine alone. At termination of enrolment on 3 April 2006, a total of 399 patients (lapatinib plus capecitabine n=198; capecitabine n=201) were enrolled in the study.

Patients in the lapatinib plus capecitabine group had a significantly longer TTP compared with the capecitabine monotherapy group. The median TTP was 27.1 weeks and 18.6 weeks in the lapatinib plus capecitabine and capecitabine groups respectively (Hazard Ratio [HR] 0.57, 95% confidence interval 0.43 to 0.77). Secondary endpoints are reported in the table below. Differences were significant for progression free survival and overall response rate only.

Table 1: Results of secondary endpoints for the pivotal trial (3 April 2006 cut-off except for overall survival, 28 September 2007 cut-off) in the ITT population (assessed by the Independent Radiological Review Committee)

Outcome Measure	lapatinib plus capecitabine (n=198)	capecitabine (n=201)	Hazard Ratio (95% CI)
Median overall survival (weeks) *	74.0	65.9	0.9 (0.71 to 1.12)
Median progression free survival (weeks)	27.1	17.6	0.55 (0.41 to 0.74)
Overall response rate (CR or PR) (%)	23.7	13.9	Odds ratio: 1.9 (1.1 to 3.4)

CR=complete response, PR=partial response, CI=confidence interval.
* n=36 of 39 patients on capecitabine monotherapy at the 3 April 2006 cut-off crossed over to receive lapatinib in addition to capecitabine (for analysis were included in group originally assigned).

The incidence of brain metastases as the site of first progression was examined by an exploratory post-hoc analysis. Significantly fewer patients in the lapatinib plus capecitabine group (4/198 [2%]) developed Central Nervous System (CNS) metastases as the first site of relapse than in the capecitabine monotherapy group (13/201 [6%]).

There were no significant differences between groups in relation to quality of life data assessed by FACT-B and EQ-5D although slightly more favourable results were observed for the combination arm.

Summary of evidence on comparative safety

In the study 87% and 82% of patients in the lapatinib plus capecitabine and capecitabine monotherapy arms respectively had adverse events deemed by the investigator to be treatment-related. Treatment-related diarrhoea and rash were more commonly reported in the lapatinib plus capecitabine arm (60% [119/198] and 25% [49/198) versus the capecitabine monotherapy arm (37% [71/191] and 12% [23/191]). The summary of product characteristics (SPC) for lapatinib recommends proactive management of diarrhoea with anti-diarrhoeal agents. The numbers of patients reporting palmar-plantar erythrodysaethesia were similar in the two groups.

The incidence of serious adverse events and adverse events leading to study discontinuation were similar between groups. There were no deaths considered related to treatment in the lapatinib plus capecitabine arm and three deaths in the capecitabine monotherapy arm considered related to treatment.

Seven patients (3.5%) in the lapatinib plus capecitabine arm and two (1%) patients in the capecitabine monotherapy arm experienced a decreased left ventricular ejection fraction (LVEF) during the study. In the lapatinib plus capecitabine group, all cases were considered to be related to treatment and LVEF returned normal on follow-up assessment. Five of the seven events in this group were classified as serious adverse events and five were asymptomatic (grade 2 or less). Both events in the monotherapy group were considered unrelated to treatment. No patients in either arm experienced an interstitial pneumonia or pnemonitis event although the SPC includes this under special warnings and precautions for use.

Hepatobiliary events (predominantly elevated transaminases and/or bilirubin) were reported commonly in the study. More subjects in the lapatinib plus capecitabine group (50/182 [27%]) had an increase in post-screening total bilirubin values compared with the capecitabine monotherapy group (28/170 [16%]). Analysis of hepatic events in a combined dataset of clinical trials and post-marketing data led the European Medicines Agency (EMEA) to conclude that the data is suggestive of a drug-related effect.

Summary of clinical effectiveness issues

Efficacy is based on one randomised open-label study that was terminated early, recruiting 76% of the planned 528 patients. The choice of primary endpoint (TTP) was criticised by the EMEA who commented that generally, when survival is expected to be short and if there are no evidence-based next-line therapies available, confirmatory studies should be designed to show a survival benefit. The pivotal study was designed to demonstrate a survival benefit but as a secondary endpoint. In addition, survival analyses may be confounded by crossover as well as patients' exposure to subsequent treatments. At study termination 36 of 39 patients in the capecitabine monotherapy arm crossed over to the lapatinib plus capecitabine arm. In addition the EMEA noted that 277 patients (141 treated with lapatinib plus capecitabine and 136 treated with capecitabine monotherapy) received 'next-line' anti-cancer therapy. Treatments included trastuzumab-containing regimens (monotherapy or in combination with vinorelbine, gemcitabine, capecitabine, taxanes, bevacizumab or cisplatin), which were received by 26% and 21% of patients randomised to lapatinib plus capecitabine and capecitabine monotherapy, respectively. However the EMEA commented that crossover to lapatinib appeared unlikely to constitute a major confounding factor and that no bias related to next line therapies was identified.

From the study, the addition of lapatinib to capecitabine increased median TTP by 8.5 weeks compared with capecitabine monotherapy. However, the EMEA considered the IRC assessment as likely to overestimate the difference between study arms in terms of TTP due to non-confirmation of investigator-assessed events of progression and absence of follow-up imaging. They noted that a reasonable estimate of HR was around 0.7 and a difference in median TTP of 6 to 8 weeks.

A conditional marketing authorisation has been granted by the EMEA and this is reviewed annually. The EMEA has requested data from further survival analyses as well as an additional phase III randomised trial to evaluate the decreased incidence of brain metastases as a site of relapse with appropriate lapatinib-containing versus trastuzumab-containing arms.

Although more favourable results were seen for the lapatinib plus capecitabine arm versus capecitabine monotherapy in terms of quality of life measures, these differences were not statistically significant. However lapatinib and capecitabine are administered orally, and compared with parenteral treatments, their use may allow changes to service delivery that have individual patient or organisational benefits.

Only a small number of patients with brain metastases were recruited to the study (23/399 [5.8%]) and this may not reflect the numbers of patients in clinical practice with brain metastases who are eligible for treatment with lapatanib.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis using a survival modelling approach (similar to a Markov model) to assess the cost-effectiveness of lapatinib plus capecitabine in the licensed patient population. Comparators included: capecitabine monotherapy; trastuzumab plus capecitabine; trastuzumab plus vinorelbine; vinorelbine monotherapy and trastuzumab monotherapy. The model included progression-free and post-progression health states. Clinical data came from the study that compared lapatinib plus capecitabine to capecitabine monotherapy, as well as an indirect comparison with trastuzumab-containing regimes. Quality Adjusted Life Years (QALYs) were reported for health benefits, based on utility data collected in the pivotal study for health status up to progression and a previous research study for utilities post-progression. Costs included the medicine and its administration; while costs of breast cancer care were considered they were assumed to be the same across groups. A time horizon of five years was adopted.

The manufacturer stated that lapatinib plus capecitabine was not cost-effective when compared with capecitabine monotherapy or vinorelbine monotherapy, with ICERs of £93,825 and £78,503 respectively, based on net costs of £14,015 and £11,726 and QALY gains of 0.15 and 0.17 respectively. In the manufacturer's submission, lapatinib –plus capecitabine was estimated to be cost-effective compared to trastuzumab monotherapy (£24,227 per QALY based on a gain of 0.03 QALYs and net cost of £638), trastuzumab plus capecitabine (a gain of 0.03 QALYs and saving of £1,075) and trastuzumab plus vinorelbine (a gain of 0.03 QALYs and a saving of £3,582).

The manufacturer accepted that the comparisons with capecitabine and vinorelbine monotherapies did not achieve conventional cost-effectiveness criteria; however, in their analysis, lapatinib plus capecitabine appeared to be a cost-effective alternative to trastuzumab. This analysis suffered from several weaknesses:

(i) The off-label use of trastuzumab in this setting has not been evaluated by SMC. Consequently there is considerable uncertainty around the incremental cost per QALY of continued trastuzumab use after disease progression.

(ii) The manufacturer's claim of cost-effectiveness is dependent on the validity of the assumptions in the baseline scenario:
   - Exclusion of adverse event costs
   - Assumptions about dosing, frequency of use and wastage of trastuzumab which when changed made a critical difference to the conclusions

   The manufacturer's sensitivity analysis suggested that the cost per QALY results were sensitive to these assumptions and it is possible that when these assumptions are altered to reflect current trastuzumab use in Scotland then lapatinib plus capecitabine would be less cost-effective. Additional analysis to assess a scenario

that accounted for the combined effect of these issues resulted in a cost per QALY of £35,736.

(iii) There were some weaknesses in the clinical data:

- Indirect comparison – as the submission recognised there was limited evidence available. The clinical study of trastuzumab had several problems when used as an indirect comparison – for example, recruitment stopped early, which may affect the median values used, and the present submission had to digitise data from graphs
- Uncertainties in the modelling – a number of assumptions were required and the modelled prediction of PFS did not correspond closely to observed data, causing concern about the uncertainty in the results
- The need to make assumptions about survival benefits of trastuzumab and the assumption that trastuzumab monotherapy has the same effectiveness as trastuzumab plus capecitabine.

The manufacturer's sensitivity analysis presented made some changes to clinical assumptions but these did not cover the full range of uncertainty. Overall the cost of the treatment in relation to its health benefits was not justified.

Summary of patient and public involvement

A Patient Interest Group Submission was made jointly by Breakthrough Breast Cancer, Breast Cancer Campaign and Breast Cancer Care.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network guideline, *Management of breast cancer in women,* was published in December 2005. The need for an update is currently being considered.

The National Institute for Health and Clinical Excellence (NICE) has issued technology appraisals; No 62 - *Guidance on the use of capecitabine for the treatment of locally advanced or metastatic breast cancer* (May 2003); No 54 - *The use of vinorelbine for the treatment of advanced breast cancer* (December 2002); and No. 34 - *Guidance on the use of trastuzumab (Herceptin) for the treatment of advanced breast cancer* (March 2002). NICE is expected to publish the clinical guideline; *Advanced breast cancer - diagnosis and treatment*, in February 2009.

Additional information: previous SMC advice

In the absence of a submission from the holder of the marketing authorisation, the Scottish Medicines Consortium (SMC) issued advice in July 2007: trastuzumab (Herceptin) in combination with an aromatase inhibitor is not recommended for metastatic breast cancer. The holder of the marketing authorisation has not made a submission to SMC regarding this product in this indication. As a result we cannot recommend its use within NHSScotland.

Following an abbreviated submission the Scottish Medicines Consortium (SMC) issued advice in August 2007: vinorelbine capsule (Navelbine®) is accepted for restricted use within NHS Scotland for treatment of advanced breast cancer stage III and IV relapsing after, or refractory to, an anthracycline-containing regimen. It is restricted to use by specialist oncologists as an alternative to the intravenous formulation of vinorelbine where vinorelbine

is considered to be appropriate. It is more expensive than the intravenous formulation of vinorelbine. However, its use may allow changes to service delivery that have individual patient or organisational benefits.

Following a full submission the Scottish Medicines Consortium (SMC) issued advice in March 2003: capecitabine (Xeloda) is recommended for restricted use within NHS Scotland. Capecitabine is recommended for use in Scotland by oncologists with appropriate expertise in treating locally advanced/metastatic breast cancer. It is an orally active treatment which has improved outcomes both as monotherapy in those previously treated with an anthracycline and a taxane, and in combination with docetaxel in those previously treated with an anthracycline.

Additional information: comparators

Capecitabine, capecitabine plus trastuzumab, vinorelbine plus trastuzumab, and less commonly vinorelbine alone and trastuzumab alone are used in the treatment of advanced or metastatic breast cancer.

Cost of relevant comparators

Drug	Dose regimen	Cost per 3 weeks (£)	Cost for 24 weeks (£)
Lapatinib + capecitabine	**lapatininb 1250mg once daily capecitabine 2000mg/m^2 * days 1 to 14 in a 21 day cycle**	**1,458**	**11,634**
Trastuzumab + vinorelbine**	trastuzumab 2mg/kg weekly vinorelbine 25-30 mg/m^2 weekly	1,731	13,851
Trastuzumab + capecitabine**	trastuzumab 2mg/kg weekly capecitabine 2500mg/m^2 days 1 to 14 in a 21 day cycle	1,532	12,158
Trastuzumab	trastuzumab 2mg/kg weekly	1,222	9,778
Vinorelbine	vinorelbine 25-30 mg/m^2 weekly	up to 509	up to 4,073
Capecitabine	capecitabine 2500mg/m^2 days 1 to 14 in a 21 day cycle	310	2,478

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 27 October 2008.Costs are based on a body surface area of 1.8m^2 and a weight of 70kg.
*Unlicensed dose and not licensed for use in combination with lapatinib.
** Unlicensed combinations.
Trastuzumab licence does not cover its use in combination with capecitabine or vinorelbine or its continued use following progression.

Additional information: budget impact

The manufacturer presented two scenarios estimating the potential NHS budget impact. Firstly, lapatinib plus capecitabine was assumed to replace all other therapies proportionately. This resulted in an estimated annual budget impact of approximately £90k in year 1, rising to £625k in year 5 on the basis of 17 patients in year 1 and 84 patients in year 5. In the second scenario, it was assumed that only 10% of trastuzumab-based regimens would be replaced by lapatinib plus capecitabine. This resulted in an estimated annual medicines budget saving of £15k in years 1 and 2, rising to a net cost of £80k in year

5 on the basis of 10 patients in year 1 and 36 patients in year 5. No estimates of the medicines budget impact alone were presented.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 15 December 2008.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission.

Geyer CE, Forster J, Lindquist D et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006; 355(26): 2733-43.

Cameron D, Casey M, Press M, et al. A phase III randomised comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on tratsuzumab: updated efficacy and biomarker analyses. Breast Cancer Res Treat 2008; epub ahead of print publication.

European Medicines Evaluation Agency (EMEA). Assessment Report for Tyverb (lapatinib). Document Reference: EMEA/302222/2008.

GlaxoSmithKline Clinical Study Report EGF100151: A phase III randomised, open-label, multicenter study comparing GW572016 and capecitabine (Xeloda) versus capecitabine in women with refractory advanced or metastatic breast cancer (03 April 2006 data cut-off).