Response to Appraisal Consultation Document on lapatinib in previously treated women with advanced or metastatic breast cancer

GlaxoSmithKline (11 November 2009)

Thank you for the opportunity to respond to the Appraisal Consultation Document for lapatinib (October 2009).

GlaxoSmithKline is extremely disappointed that the draft guidance does not recommend lapatinib for use in the NHS, despite consideration under the supplementary advice to Appraisal Committees on appraising end of life medicines (EoL guidance). The EoL guidance was specifically developed to help small numbers of patients, who have limited time to live, gain access to important new medicines. The additional data submitted by GSK in response to points upheld at the appeal in June 2009 demonstrated that lapatinib met all three of the criteria for consideration under the EoL guidance but the Appraisal Committee concluded that lapatinib is still not a cost-effective use of NHS resources despite GSK offering the Tyverb Patient Access Programme (TPAP), which allows NHS patients in the UK free access to lapatinib for the first three months of treatment.

Our comments on specific aspects of the ACD are structured below under the questions requested by NICE.

1. Do you consider that all of the relevant evidence has been taken into account?

GlaxoSmithKline considers that the ACD does take into account the relevant evidence.

2. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?

We welcome the Appraisal Committee's acknowledgement that the evidence presented by GSK suggests that treatment with lapatinib plus capecitabine may increase survival by around 3 months compared with capecitabine alone. However, the Committee expresses concern about the robustness of the overall survival estimates, in particular the adjustments made to take account of patients crossing from the capecitabine arm to the lapatinib combination arm following the early termination of study EGF100151. Whilst we agree that alternative methods of minimizing the impact of crossover effects might indeed be employed, we would argue that any statistical method will have inherent deficiencies. The Decision Support Unit's preference for the methods of Robins and Tsiatis (1991) and Branson and Whitehead (2002) is based on a study funded by NICE, which is unpublished and was therefore unavailable to GSK at the time of submission.

Several alternative approaches were explored and presented in GSK's submission of 25 August 2009. It should be noted that these were not bespoke analyses initiated for the purposes of the NICE post-appeal submission; rather, they were performed primarily to support the regulatory process for lapatinib which was ongoing in parallel. The method chosen by GSK as most representing the likely effects of lapatinib on overall survival for both regulatory and NICE purposes (Cox regression model considering cross-over as a time dependent covariate) was selected as it addresses

some specific issues associated with this type of dataset. The time dependent analysis models each patient in one of two states over time: the first state represents the arm to which the patient was randomized; the second state represents cross-over to lapatinib + capecitabine. This model reflects the time at which the patient changes from capecitabine treatment to treatment with the lapatinib/capecitabine combination. The hazard up to the time point of cross-over for patients in capecitabine group is due to monotherapy capecitabine. The hazard from the time the patient crosses over to lapatinib/capecitabine is due to the combination therapy. GSK believes that this method is appropriate since it accounts for the effects of capecitabine up to the point of cross-over, as well as for the effects of the lapatinib/capecitabine combination from that point for those patients who have crossed over.

Interestingly, the Decision Support Unit (DSU) reports that excluding switching patients from the analysis altogether gives relatively small biases in situations with a low proportion of switchers, but they do not give any indication of what is considered a low proportion. The number of patients who crossed over to the combination arm was 36 (out of 201 patients in the capecitabine arm (18%); around 9% of the study total), which we would argue is a relatively low proportion. The analysis which excluded these patients altogether yielded a median overall survival estimate of 4.3 months, which is well above the end of life criterion threshold of 3 months. The DSU also comments that the method of Branson & Whitehead is particularly robust in settings when a high proportion patients switched, which we believe is not the case in study EGF100151.

To summarise we support the Committee's conclusion that lapatinib combination treatment may improve survival by 3 months or more compared with capecitabine monotherapy, but believe that their interpretation of the estimates as lacking robustness should be reconsidered in the context of the above arguments.

3. Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

GSK does not consider that the provisional recommendations in the ACD constitute a suitable basis for guidance to the NHS.

Having concluded that the evidence presented by GSK suggests that treatment with lapatinib plus capecitabine may increase survival by around 3 months compared with capecitabine alone, the Appraisal Committee considered the cost effectiveness results for lapatinib in combination with capecitabine under the EoL guidance (results shown in Table 1 overleaf).

The Committee did not consider that the impact of increasing QALY weighting such that the increased survival is experienced at the quality of life expected of a healthy individual (effectively reducing the ICER from £59,441/QALY to £45,525/QALY) was acceptable.

Furthermore, the magnitude of additional weight (a factor of around 2) that would need to be assigned to the QALY benefits for the base-case ICER of £59,441/QALY to fall within the current threshold range was deemed by the Committee to be unacceptable, with the conclusion that lapatinib would not be a cost-effective use of NHS resources.

Table 1. Cost effectiveness results for lapatinib in combination with capecitabine versus capecitabine considered in the context of end of life guidance

Analysis	Incremental cost effectiveness ratio (ICER) £/QALY
Cost effectiveness including patient access scheme	£59,441
As above and assuming additional life years gained experienced at same utility (0.85) as healthy individual	£45,524

We are concerned that NICE's rejection of lapatinib as an option at this level of cost effectiveness fails to account fully for lapatinib's potential benefits and the setting in which it is currently indicated, especially in the context of other appraisals where similar levels of cost effectiveness have been accepted (NICE 2009a). We would also like to highlight a lack of transparency in the ACD regarding the specific reason/s why the estimated level of cost effectiveness of lapatinib in combination with capecitabine is unacceptable when considered under EoL guidance.

The basis of a decision regarding whether lapatinib constitutes an effective use of NHS resources must necessarily take into account a range of factors in addition to an estimate of its cost effectiveness against a single comparator at a fixed cost effectiveness threshold, e.g. the level of unmet medical need, current clinical practice, end of life considerations, degree of innovation, patient choice, route of administration. We welcome NICE and the Appraisal Committee's consideration of some of the wider issues associated with the treatment of this group of women who have few therapeutic options available to them other than continued trastuzumab, through the EoL guidance and ACD/FAD development processes. However, we are concerned that the selected issues have largely been considered in isolation, and might not individually constitute a justification for the approval of lapatinib, whereas if considered collectively they might lead to a different decision that better reflects the realities of the management of these women. GSK believes that there are several important and exceptional factors which should be taken into account collectively in making the decision as to whether the introduction of lapatinib is an appropriate use of NHS resources. These are outlined below:

Current management of relapsed HER2 positive breast cancer

Regardless of the probability that trastuzumab continued beyond progression is unlikely to be cost effective and therefore should be eliminated from consideration in an incremental cost effectiveness analysis, the reality is that trastuzumab will continue to be used to a degree in this clinical setting, based on the current body of evidence supporting continued HER2 (ErbB2) suppression as the basis of treatment in this setting. The cost effectiveness analysis underpinning the current appraisal consultation is restricted to a comparison with single agent capecitabine. Even if the use of trastuzumab beyond progression decreases as a result of NICE Clinical Guideline 81 (which recommends that treatment with trastuzumab should not be discontinued if disease progression is only within the central nervous system (CNS), but that it should be discontinued at the time of disease progression outside the CNS) its use is unlikely to be eradicated. The ICER of £59,441/QALY does not take into account any impact on cost effectiveness of the continued use of trastuzumab in this setting, some of which will be legitimate according to the guideline (patients with CNS progression). Nor is the impact of an all-oral regimen (in the context of continued trastuzumab use) captured in this figure. This ICER is therefore an over estimate of the true ICER for lapatinib plus capecitabine compared with routine

clinical practice (i.e. lapatinib treatment is likely to be more cost effective than it appears).

Potential for savings to the NHS

GSK has made lapatinib available via a patient access programme (the TPAP), designed to facilitate equitable patient access to treatment and to maximise value to the NHS by linking payment for lapatinib to clinical benefit. Under the terms of the TPAP the initial cost of lapatinib, up to a maximum of 12 weeks, is borne by GSK. The NHS only funds lapatinib for patients continuing to derive clinical benefit beyond 12 weeks.

The potential for any cost savings is especially pertinent in the context of treatment of women whose disease has progressed only in the brain, for whom continued trastuzumab-based therapy is advocated. For patients who would otherwise be treated with trastuzumab at a cost of £1,222 per 3-week cycle (6mg/kg 3-weekly for average weight woman of 59.5Kg), treatment with lapatinib (£1,206.45 per 3-week cycle) is marginally less costly at list price, but this saving is increased substantially under the terms of the TPAP whereby the NHS will pay for lapatinib only after 12 weeks (i.e. 4 cycles). Furthermore, as an orally-administered regimen, lapatinib plus capecitabine would also help to reduce pressure on hospital-administered IV cancer therapy service capacity as well as on pharmacy workload since there is no need for reconstitution prior to administration.

It may be of interest to note that to date 27 NHS Trusts have entered into contracts for TPAP, reflecting the clinical demand for lapatinib and recognising its potential value to the NHS.

Management of patients with disease progression in the central nervous system

NICE Clinical Guideline 81 on the diagnosis and treatment of advanced breast cancer recommends that treatment with trastuzumab should not be discontinued if disease progression is only within the central nervous system (CNS), but that it should be discontinued at the time of disease progression outside the CNS. Between 28% and 43% of patients receiving trastuzumab in the metastatic setting have been reported to relapse with brain metastases (Bendell 2003; Lin 2004). The continued use of trastuzumab beyond progression as advocated by the clinical guideline is therefore likely to be significant in the population eligible for lapatinib even if it is restricted to the particular sub-group of patients who have progressed only in the CNS.

Lapatinib represents the only licensed alternative to trastuzumab for patients who have progressed in the CNS whilst taking trastuzumab. There is good evidence to suggest that control of non-CNS disease by lapatinib is comparable to that afforded by trastuzumab (Gomez 2008, Vogel 2002). In addition, as lapatinib is a small molecule, it is able to cross the blood-brain-barrier and penetrate the CNS (Van den Abbeele 2006; Gril 2008) and there is evidence that it has activity in both treating (Lin 2008; Lin 2009) and reducing the incidence of brain metastases as a first site of relapse (Cameron 2008).

As highlighted in our submission on EoL considerations (25 August 09) in the Lapatinib Expanded Access Programme (LEAP), a sub-population of patients with progressive brain metastases following whole brain radiotherapy and trastuzumab within a UK cohort showed favourable response rates to lapatinib plus capecitabine

with times to disease progression identical to the whole cohort (Dr Stephen Johnston, personal communication).

There will be patients who have progressed in the CNS for whom treatment with trastuzumab is unacceptable or no longer desirable, especially if an oral alternative is available, e.g. those with difficult venous access, those who have received multiple lines of trastuzumab containing regimens or who would rather receive an all-oral combination. In these circumstances lapatinib would be a clinically appropriate and much less costly alternative to trastuzumab.

Additional considerations

Lapatinib plus capecitabine offers the convenience of an all-oral regimen which can be self-administered by the patient at home, reducing time spent in hospital and the expense and inconvenience of hospital attendance, when compared with intravenous therapies. The importance of being able to spend time outside of hospital with family and friends cannot be overestimated for these patients whose life expectancy is short. The current recommendation is inconsistent with NHS policy of patient choice and of care closer to home - both of which would be provided by lapatinib.

Lapatinib represents an innovative approach to cancer treatment for several reasons, including:

- Selective targeting of both the epidermal growth factor receptor 1 (EGFR, ErbB1) and HER2 (ErbB2) receptors;
- Small molecule which can bind intracellularly, and with the potential to cross the blood brain barrier unlike large monoclonal antibodies;
- Oral formulation.

Conclusion

For this very small group of relatively young women with terminal illness, the additional time without disease progression and the extension to survival afforded by lapatinib can be disproportionately valuable to them and their families. We believe that taking into account all the above points in their entirety, rather than each in isolation, lapatinib when considered under the end of life guidance is a valuable option for use on the NHS. Furthermore, as it is the only HER2-targeted option for those who have progressed on trastuzumab exclusively outside the brain we urge the Committee to consider lapatinib as an option for medicine for the eligible population, in view of its ‘end of life’ status.

At the very least with application of the TPAP, lapatinib represents an effective and much less costly clinically valuable alternative for those patients who have progressed in the brain and for whom intravenous trastuzumab, which is recommended as an appropriate treatment in the advanced breast cancer guideline, is no longer desirable. We suggest that NICE consider this sub-group specifically in the context of this consultation.

4. Are there any equality related issues that need special consideration that are not covered in the ACD?

We do not believe that there are equality related issues needing special consideration which have not been highlighted in previous submissions and consultations.

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