Bayer HealthCare
Bayer Schering Pharma

3rd December 2009

Dear Andrew

Notice of Appeal

Thank you for the Final Appraisal Determination (FAD) regarding Nexavar® (sorafenib) for advanced hepatocellular carcinoma. Bayer are disappointed that, despite the evidence provided and patient access scheme agreed with the Department of Health, the Committee has not recommended the use of Nexavar in these patients, in whom prognosis is poor and no other treatment options are available.

In accordance with the procedure set out in the email and the "Guidance for Appellants", Bayer wishes to appeal the conclusions set out in the FAD.

Background

Hepatocellular carcinoma ("HCC") is the most common form of primary liver cancer, accounting for about 80% - 90% of liver cancer cases.[1] It is the third most common cause of cancer related death worldwide and most prevalent in Asia and Africa; unlike most other cancers, the incidence of HCC is rising in western societies.[2] The primary risk factor for HCC is cirrhosis, commonly due to hepatitis B, hepatitis C or alcohol.[3]

The prognosis for patients with HCC is poor. In patients who receive no active treatment, average life expectancy is 4 to 6 months from diagnosis.[3] In many cases HCC produces few specific symptoms until the condition is advanced and, in less than 30% of patients is a diagnosis made in the early stages of the disease, when liver tumours are considered more amenable to curative resection, transplantation or localised embolisation or ablation. In approximately 25% - 35% of cases, systemic therapy is the only active treatment option.[4]

The treatment options for patients unsuitable for surgical or loco-regional treatments, are very limited. Nexavar, authorised for HCC by the European Commission in 2007, has orphan drug status and is the only medicinal product licensed for this indication in the EU. It has shown substantial benefits in the clinical trial programme, extending median overall survival from 34.4 weeks to 46.3 weeks, with a hazard ratio of 0.69 (a 30.7% reduction in the hazard (risk of death) over placebo).[5] In the context of this background information regarding Nexavar, demonstrating the high clinical need of patients with HCC, the innovative nature of the technology and the substantial benefits associated with treatment, in the areas identified below, Bayer does not believe the approach followed in this appraisal and the conclusions of the Appraisal Committee as set out in the FAD are fair, consistent with NICE's procedures or soundly based on the evidence for Nexavar.

Bayer appeals on the ground that the Institute has failed to act fairly and in accordance with its published procedures as set out in the Institute's Guide to the Technology Appraisal Process, as more fully described below.

1.1 The Appraisal Committee has failed to explain why it has changed its conclusions with respect to the modelling of overall survival following Nexavar treatment, in the absence of new data regarding this effect.

The principal RCT investigating the effects of Nexavar in HCC is the SHARP study[5], comparing Nexavar plus best standard care with placebo plus best standard care in 602 patients with HCC. The blinded phase of the SHARP study was stopped early when an interim analysis confirmed superior survival in the Nexavar arm (46.3 weeks (95% CI 40.9 to 57.9)) as compared with the placebo arm (34.4 weeks (95% CI 29.4 to 39.4)). Due to the unblinding in the trial, because of the significant survival benefit shown by Nexavar, final survival analysis was undertaken at this time and therefore it was necessary to extrapolate the survival results, through modelling, to a lifetime horizon for the full study cohort.

Bayer used a log-normal distribution curve to extrapolate overall survival on the basis that this best satisfied the Akaike Information Criterion (a measure of the goodness of fit of an estimated statistical model). Using this survival curve, Bayer produced an incremental cost effectiveness ratio (ICER) of £64,754 per QALY gained, in association with Nexavar treatment.

In the first ACD, the Committee considered the approach to modelling of survival and concluded that, while alternative statistical models could be used, the log-normal extrapolation was likely to produce the most reliable results: "*The Committee noted that although the log-normal curve was the best fit for most of the trial data, alternatives also fitted the data well and the main differences were in the shape of the curves beyond the available trial data and at the tail where an alternative model fit was better. The Committee concluded that overall there was considerable uncertainty in extrapolating the data and that the base-case lognormal extrapolation probably produced the most robust ICER for sorafenib*" (Section 4.8 first ACD).

However, when considering use of Nexavar in accordance with the supplementary advice on end of life treatments, the Committee concluded that, while it "*was satisfied that the population and Sorafenib met the criteria for an appraisal of life extending end of life treatment and that the evidence presented was supported by robust data*" (paragraph 4.11), "*the magnitude of additional weight that would need to be assigned to the original QALY benefits in this patient group for the cost effectiveness of the drug to fall within the current threshold range would be too great, even if the base case was accepted*" (paragraph 4.12).

Bayer is committed to ensuring UK patients with this poor prognosis disease have access to this innovative and effective medicine. In order to provide value for money and reduce the financial burden of Nexavar to the NHS, we therefore proposed a patient access scheme taking into consideration the Committee's discussions and conclusions outlined in the first ACD. This reduced the ICER associated with Nexavar to £51,900 per QALY, a figure consistent with other cancer treatments recommended by NICE under the supplementary advice on end of life treatments.

However, after reviewing the patient access scheme in the second ACD, the Committee seemingly changed their conclusion regarding the modelling of survival, in particular their view that the log-normal curve produced the "*most robust ICER*" for Nexavar. The second ACD

therefore stated "*the Committee noted that although the log-normal curve was the best fit amongst these overall and for the early trial data, alternatives also fitted the data well; the main differences were in the shape of the curves at the tail of the distribution where, for example, a Weibull curve with a heavier tail was the better fit. The Committee concluded that both curve fits were reasonable*" (section 4.9). Despite the base case lifetime economic model clearly showing that most incremental life years (75%) are gained within 5 years and 94% within 10 years (i.e. it is most important to place emphasis on fitting earlier parts of survival curves), the Committee concluded alternative fits that place increased weight on the tail (such as the Weibull) should be considered, commenting that "*the Weibull extrapolation of survival data produced an ICER, which was substantially higher than the base-case*". The second ACD did not include the earlier statement that the log-normal curve produced the most robust ICER.

In its response to the second ACD, Bayer provided substantial data explaining why, based on the Akaike Information Criterion and the Bayesian Information Criterion, the log-normal model provided a better fit than a Weibull distribution. However, when the FAD was issued, the Committee continued to maintain that "*although the log-normal curve provided a slightly better fit to the observed data, it could not be accepted as the definitive function to extrapolate beyond the data.*" (paragraph 4.9).

Bayer is aware of no new information available to the Appraisal Committee, to justify a change in its view expressed in the first ACD, that the log-normal extrapolation probably produced the most robust ICER for Nexavar. The only situation that has changed during this period is Bayer's efforts to make Nexavar available to NHS patients by setting up a patient access scheme which brought the ICER value for Nexavar within the range recommended by NICE in other similar cases. This scheme had no impact on the estimate of overall survival. In view of the substantial weight placed on the potential effect of using a Weibull distribution, fairness requires that the Appraisal Committee should explain why its emphasis has changed following the first ACD and why it has placed such reliance on the Weibull curve, in view of the accepted position that the log-normal curve fits the data for Nexavar more closely.

1.2 The Institute has acted in a non transparent and unfair manner by not stating the degree to which they considered evidence received during the appraisal regarding appropriate survival extrapolation methods

Following the Committee's shift in position in relation to its interpretation of appropriate survival curves to extrapolate the data for Nexavar, Bayer provided the Institute with further substantial confirmatory evidence that supported the appropriateness of the log-normal curve over the Weibull in extrapolating overall survival. This evidence was based on patient level data of 3,280 patients followed for up to 32 years compared to the non patient level data used by the ERG based on only up to 496 patients for a maximum of up to 6 years.

The FAD provides no explanation for the consideration of these data by the Committee and, based on a comparison of the wording in the second ACD with the FAD, it would appear that this information has not been taken into account at all. The data submitted by Bayer in relation to the superior reliability of the log-normal curve in this case are important and failure by the Institute to consider such information or alternatively to show how these data were taken into account, when discussing the uncertainty surrounding the extrapolation of survival data and the resulting ICER, is unfair.

1.3 Insufficient time was allowed for consideration of the response to consultation by the Appraisal Committee in this case

The third meeting of the Appraisal Committee to consider Nexavar in the treatment of HCC took place on 14 October 2009, commencing at 10am. The meeting first considered the appraisals of rituximab for the treatment of relapsed/refractory chronic lymphocytic leukaemia and then dasatinib and nilotinib for chronic myeloid leukaemia; these discussions took up almost the entirety of the meeting. The consideration of Nexavar did not commence until approximately 4.40 and the open session of the meeting concluded at around 4.50. The further discussion of the Appraisal Committee in closed session lasted no more than a further 10 minutes. Therefore the Committee gave less than 20 minutes consideration to the results of consultation on the second ACD, including the substantial new data submitted by Bayer in relation to extrapolation of survival from the SHARP trial.

A fundamental part of a fair consultation is that the responses received following the consultation exercise must be conscientiously considered and taken into account before a decision is finalised. In this case however the time allowed for consideration of Nexavar at the meeting on 14 October 2009 was plainly inadequate and did not allow for any real review or discussion of the products of consultation. The appraisal of Nexavar has therefore fallen short of a fair procedure and Bayer believes that this deficiency has resulted in the conclusion that the product should not be recommended.

1.4 In reaching its recommendation, the Institute has failed to place adequate weight on innovation and has therefore acted unfairly and not fulfilled its obligations to the Secretary of State in considering the long term benefits to the NHS of innovation

Nexavar is the first product to demonstrate benefit compared to placebo in the treatment of HCC in over 30 years of research [5] and over 75 randomised controlled trials [6] and represents a significant step-change in treatment for patients with an exceptionally poor prognosis. Nexavar therefore forms part of standard therapy for patients with HCC in other EU countries, including France, Germany, Spain and Italy.

The Secretary of State has directed the Institute to have regard to the potential for long term benefits to the NHS of innovation when fulfilling its functions.[7] In their consultation response[8] to Sir Ian Kennedy's independent report on valuing innovation[9], that recommended that the Institute should incorporate explicit consideration of other benefits, the Institute stated that they expect their Committees to take account of matters that have not been adequately captured in the estimates of gains in health-related quality of life. Specifically regarding innovation, the Institute recommended that, where there is a "step change", the Committee "*will be expected to demonstrate either that the product's identified innovative characteristics have been taken into account in the QALY calculation (in other words, that their impact on health related quality of life has been fully captured) or, if not how it has separately evaluated them and what their impact is (if at all) on its judgement of the most plausible ICER.*" The Institute's own Citizen's Council Report on Innovation further supports that explicit reference should be made to how innovation has been taken into account.[10]

Furthermore, the Institute has stated that it will "cooperate fully in implementing the Office of Life Science's Blueprint", which also includes the Innovation Pass for rare diseases.[11] This Blueprint states "it is vital that the NHS values and uses cost-effective innovations" (2.1) and that "the adoption and uptake of new medicines and technologies in the NHS is variable and in some

cases, far behind that of other European countries" (2 8). In particular, the Institute and the Department of Health are actioned to adopt measures to ensure the NHS leads the way in the uptake of groundbreaking and cost-effective medicines and technologies.

The requirement to take account of the benefits of innovation is explicitly stated in the Institute's supplementary advice on end-of-life treatments[12]: "*In addition, the Institute has taken account of its responsibility to recognise the potential for long term benefits to the NHS of innovation. In this context, it considers it appropriate for its Appraisal Committees to have regard to the importance of supporting the development of innovative treatments that are anticipated to be licensed for small groups of patients who have an incurable illness*".

On any view, Nexavar represents a highly innovative technology and a real development in the treatment of HCC. However, despite NICE's stated commitment to supporting innovation in the NHS as demonstrated by the statements referenced above, the Committee has seemingly failed adequately to take into account the innovative nature and step-change significance of Nexavar in the treatment of advanced HCC. Importantly, the FAD does not explain how the Appraisal Committee has taken the support of innovation into account when assessing Nexavar for the treatment of HCC.

1.5 In reaching its recommendation, the Institute has failed to take into account the follow up research programme offered by Bayer as part of the Patient Access Scheme (PAS) which would address any residual uncertainty regarding survival, and has therefore acted unfairly

It has been acknowledged in the Office of Life Sciences Blueprint, the Kennedy Report, and by the Institute, that there may be uncertainty in assessing the effects (for example overall survival) for patients receiving new innovative products, shortly after product launch, primarily due to limited availability of information at this early stage. There are various reasons why information may be limited, including rarity of the disease, regulatory requirements (for example, primary endpoint may be time to progression rather than overall survival) and cases where, as with Nexavar, the demonstrated benefits of treatment mean that continuance of a double blind trial is unethical.

Bayer has explained why it believes that the uncertainty in relation to the effects of Nexavar is small. However the only way in which such uncertainty may be eliminated is through investigating treatment clinical practice. In these circumstances the Bayer research programme offered as part of the PAS provided the Institute an opportunity to recommend Nexavar for a fixed time period, whilst any uncertainty around the survival prediction could be confirmed in practice. Therefore, in addition to every fourth pack free, the PAS also provided the NHS with a Bayer-funded research programme which would collect data to form the basis for subsequent review by NICE.

However, despite the clear benefits of this research programme, and the fact that it represents the only way in which information may be obtained to reduce any uncertainty regarding the cost-effectiveness of Nexavar, the FAD gives no explanation as to how this benefit of the PAS has been taken into account by the Appraisal Committee. In fact, the absence of any reference to the Bayer research programme, raises a strong inference that it has been disregarded by the Committee in appraising Nexavar and considering whether, in the context of the clinical need of patients with HCC and NICE's commitment to supporting innovation in the NHS, the product should be recommended to treat NHS patients.

1.6 The Institute has acted unfairly by not accounting for the degree of clinical need of patients under consideration as directed by the Secretary of State.

Nexavar is a highly innovative product indicated for a small patient population with a high clinical need. In over 30 years of investigation, Nexavar is the first product to show benefit compared to placebo in over 75 randomised controlled trials.[5] [6] Patients diagnosed with advanced HCC have a uniformly dismal prognosis[13]; Nexavar is the only therapeutic option with evidence of efficacy and the benefits in this patient population are substantial.

While the Secretary of State's Directions to NICE[7] require the Appraisal Committee to take account of the clinical need of patients with the disease under consideration, there is no indication in the FAD that the Committee placed adequate weight on the desperate circumstances of patients with advanced HCC and the absence of any alternative active treatment options. If the Committee placed any weight on such matters, this is unexplained and lacks transparency.

The clinical need of patients with advanced HCC is clearly very great; their prognosis is grim and their disease is complex and resistant to treatment, as demonstrated by the fact that, despite investigation of many other products, Nexavar is the first to show benefit in this condition. While Bayer does not believe there is substantial uncertainty surrounding the assessment of cost-effectiveness, the fact that there will only be up to 600 patients in England and Wales eligible for Nexavar means that the opportunity costs of uncertainty will be significantly lower than those for more common conditions, in any event. This therefore needs to be balanced against the fact that the effect of the preliminary guidance in the FAD is that patients suffering from advanced HCC will be deprived of any active treatment for their condition

The FAD however provides no explanation as to how the Appraisal Committee has weighed the clinical need of patients against these other factors in reaching its view that Nexavar should not be recommended.

1.7 **The Appraisal Committee's approach to the difference between independent and investigator assessments of time to disease progression in the SHARP trial is inappropriate and unfair**

A secondary outcome in the SHARP trial[5] was time to radiological disease progression (TTP). TTP was assessed by both independent assessors (the primary assessment) and by SHARP investigators. The results of the study showed that median time to disease progression was extended by 11.7 weeks according to the independent assessors and by 5.1 weeks according to the SHARP investigators.

The patient access scheme for Nexavar established by Bayer provides that patients discontinue treatment at disease progression as determined by their treating doctors. Therefore, at paragraph 4.13 of the FAD, the Appraisal Committee noted concerns by the ERG in relation to differences between independent assessments of TTP in the SHARP trial and those assessments conducted by investigators, in circumstances where a greater TTP could mean that a patient would continue on treatment for a longer period. The Appraisal Committee referred to an analysis by the ERG that the base-case ICER would increase to £76,000 per QALY gained (not including the patient access scheme) when using the independent assessment of TTP.

Bayer believes that the approach of the Appraisal Committee to the assessment of TTP is unfair. Firstly, in describing the uncertainty associated with measurement of TTP, the Appraisal Committee has omitted to record an ICER that takes account of the patient access scheme for

Nexavar, and has therefore over estimated the potential implication of a difference in measurement of TTP. Furthermore, the Appraisal Committee has seemingly failed to recognise that the assessment of TTP by investigators in the SHARP trial most closely reflects the assessments by treating physicians that will determine discontinuation of treatment in clinical practice and that the concern of the ERG is of peripheral relevance at most.

1 8 **The Appraisal Committee has not explained its conclusion that the magnitude of additional weight that would need to be assigned to the original QALY benefits would be too great for the product to be cost-effective.**

At paragraph 4.16 of the FAD the Appraisal Committee considers the cost-effectiveness of Nexavar in the context of NICE's supplementary advice on end of life treatments and concludes "*that the magnitude of additional weight that would need to be assigned to the original QALY benefits in this patient group for the cost effectiveness of the drug to fall within the current threshold range would be too great*".

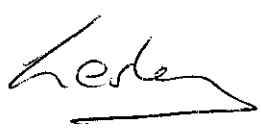
Adopting the log-normal extrapolation of survival, that the Appraisal Committee has previously accepted is probably the most robust (paragraph 4.8 of the first ACD), the Committee calculates the ICER for Nexavar as £52,600 (paragraph 4.15 of the FAD). This value is wholly consistent with those for other technologies recommended by NICE for the treatment of other cancers, under the supplementary advice on end-of-life treatments (e.g. lenalidomide for multiple myeloma and sunitinib for renal cell carcinoma). In this situation, the Committee is required to explain its conclusion that, in contrast to other cancer treatments, the additional weight to be attached to the QALY value for Nexavar, for it to fall within the current threshold range, would be too great. The current wording of the FAD provides no explanation of the approach followed by the Committee and Bayer is therefore unable either to understand the reasoning of the Committee or to respond to it.

Summary

While we recognise that NICE has difficult decisions to make, the preliminary recommendation goes completely against UK HCC treatment guidelines[14], and current Government strategies[15] to bring cancer outcomes in line with Europe and promote the NHS as an innovation champion.[11]

We ask the Appeal Panel to consider the above points and that the recommendation is reconsidered in light of these issues. The preliminary recommendations, if implemented without amendment, will leave no treatment options for the small number of patients with advanced HCC, where surgical or locoregional therapies have failed or are not suitable.

Yours sincerely



Lesley Gilmour

References

1. Wilson J. Liver cancer on the rise. *Ann Intern Med* 2005;**142**(12 pt 1):1029-1032

2. Ryder SD. Guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults. *Gut* 2003;**52 Suppl 3**:iii1-iii8.

3. National Institute for Health and Clinical Excellence. Hepatocellular carcinoma (advanced and metastatic) - sorafenib (first line): final scope. 2008.

4. Bayer plc. Data on File: BayerSchering HCC Advisory Board (October 2007). 2007.

5. Llovet JM, Ricci S, *et al*. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;**359**(4):378-390

6. Lopez PM, Villanueva A and Llovet JM. Systematic review: evidence-based management of hepatocellular carcinoma--an updated analysis of randomized controlled trials. *Aliment Pharmacol Ther* 2006;**23**(11):1535-1547.

7. Secretary of State for Health. Directions and Consolidating Directions to the National Institute for Health and Clinical Excellence (31 March 2005). 2005

8. National Institute for Health and Clinical Excellence. Response to Sir Ian Kennedy's Report: Appraising the Value of Innovation. 2009.

9. Kennedy I. Appraising the value of innovation and other benefits - a short study for NICE. 2009.

10. National Institute for Health and Clinical Excellence. Citizens Council report: innovation. 2009.

11. Office for Life Sciences. Life Sciences Blueprint (July 2009). 2009.

12. National Institute for Health and Clinical Excellence. Supplementary advice to the Appraisal Committees: Appraising life-extending, end of life treatments. 2009

13. American Cancer Society. Liver Cancer – Detailed Guide. http://www.cancer.org/docroot/CRI/CRI_2_3x.asp?dt=25 Accessed 8th November 2007. 2007

14. Ryder SD. UK Guidelines for the management of suspected hepatocellular carcinoma (HCC) in adults iii1-iii8. 2009.

15. Richards M. Cancer Reform Strategy. 2007