NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Appeal Hearing

Bevacizumab (first-line, sorafenib (first and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma.

1. An Appeal Panel was convened on 13 July 2009 to consider an appeal against the Institute's Final Appraisal Determination (FAD) to the NHS, on bevacizumab (first-line, sorafenib (first and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma.

2. The Appeal Panel ("the Panel") consisted of Mr Jonathan Tross (non-executive director of the Institute and chair of the Panel), Dr Margaret Helliwell (non-executive director of the Institute), Mr Peter Sanders (lay representative), Dr Frank McKenna (NHS representative) and Mr Robert Donnelly (industry representative). All members stated they had no interest to declare in respect of the appeal under consideration. Mr Stephen Hocking (Beachcroft) was in attendance as a legal adviser to the Panel.

3. The Panel considered appeals submitted by four appellants "the Appellants".

- The James Whale Fund for Kidney Cancer, represented at the hearing by Mr Nick Turkentine, Dr Thomas Powles, and Ms Jane Thompson.
- Macmillan Cancer Support and the Rarer Cancers Forum, represented at the hearing by Ms Stella Pendleton, Professor Robert Wagstaff, Mr David Cook, and Ms Helen Rainbow.

- Roche Products Limited, represented at the hearing by Dr Paul Catchpole, Dr Adela Williams, Dr Michelle Dawson, and Mr Douglas Millar.
- Wyeth Pharmaceuticals, represented at the hearing by Dr Vignesh Rajah, Mr Garth Baxter, Ms Boyka Stoykova, and Mr Michael Varcoe-Cocks.

4. In addition the following individuals involved in the appraisal were present and available to answer questions from the Panel: Professor Andrew Stevens (chair of the Appraisal Committee), Dr Carole Longson, Dr Peter Clark, Mr Meindert Boysen, and Ms Rebecca Trowman.

5. There are three grounds on which an appeal can be lodged:

1. Ground 1.The Institute has failed to act fairly and in accordance with the published procedures as set out in the Institute's Guide to the Technology Appraisal Process;

2. Ground 2. The Institute has prepared guidance that is perverse in light of the evidence submitted;

3. Ground 3. The Institute has exceeded its legal powers.

6. The chair of the Appeals Committee (Dr Margaret Helliwell), in preliminary correspondence, had confirmed that the appellants had potentially valid grounds of appeal in relation to the following grounds:

- James Whale Fund for Kidney Cancer in respect of Ground 2.

- Macmillan Cancer Support and the Rarer Cancers Forum in respect of Grounds 1 and 2.

- Roche Products Limited in respect of Grounds 1, 2 and 3.

- Wyeth Pharmaceuticals in respect of Ground 1 and 2.

7. The Final Appraisal Determination ("the FAD") considered at this Appeal provides guidance on bevacizumab (first-line, sorafenib (first and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma.

8. The Panel grouped the hearing in relation to the technologies being appraised, taking each ground accepted for appeal in turn as follows:

- Bevacizumab, hearing points from Roche products Ltd (Grounds 1, 2 and 3), Macmillan Cancer Support and the Rarer Cancers Forum (Grounds 1 and 2), and James Whale Fund for Kidney Cancer (Ground 2).

- Temsirolimus, hearing points from Wyeth Pharmaceuticals and the James Whale Fund for Kidney Cancer (Grounds 1 and 2).

- Sunitinib, hearing points from the James Whale Fund for Kidney Cancer (Ground 2).

- Sorafenib, hearing points from the James Whale Fund for Kidney Cancer (Ground 2).

9. Introducing the proceedings the Panel’s Chair noted that the appeal proceedings would tend to be dominated by technical issues. That did not detract from recognition of the serious nature of the condition and its impact on the patients and their families. In introduction, he also observed that the arguments on the different grounds of appeal tended to overlap. He would reflect that in the way he managed the proceedings, allowing overlap but not straight repetition.

10. Macmillan Cancer Support, the Rarer Cancer Forum, and the James Whale Fund for Kidney Cancer declared that they had received a number of grants from pharmaceutical companies for educational and other purposes.

Bevacizumab.

Ground 1. The Institute has failed to act fairly and in accordance with its published procedures.

11. In respect of Ground 1 the following arguments were advanced:

12. Roche Products Ltd appealed on three Ground 1 points.

1. The decision of the Appraisal Committee is improperly based on the overall affordability of treatments for renal cell cancer.
2. The Appraisal Committee's interpretation of the Supplementary Advice on appraising life extending end of life treatments lacks transparency and is unfair.
3. The basis for the Appraisal Committee's conclusions with regard to the tolerability of bevacizumab plus interferon alpha are unclear.

13. Macmillan Cancer Support and the Rarer Cancers Forum appealed under this point, arguing that the supplementary advice on end of life medicines had been unfairly and wrongly applied.

14. Introducing their appeal Dr. Catchpole explained that bevacizumab was an innovative drug, first in its class; which had been a long time in development and was now standard in use outside the UK. Within the UK it was not available on the NHS. Renal cell carcinoma was difficult to treat; there was an unmet medical need for those with the condition whose prognosis was poor. Roche had considered that the product would appear to meet the criteria set out in the

supplementary advice issued by the Institute, ‘Appraising life-extending, end of life treatments (‘the supplementary advice’) and were disappointed that it had not followed sunitinib to approval.

15. For the Appraisal Committee, Professor Stevens in an opening statement on the products covered by the FAD stressed that they had been very mindful of the severity of renal cell carcinoma and that the current standard treatment using interferon alpha had unpleasant side effects. None of the products being appraised would meet the normal threshold range for approval of £20,000-30,000 per QALY. The issue for the Committee was not affordability, but the opportunity cost of recommending a treatment. The supplementary advice enabled the Committee to recognise the value of innovation in small groups where extra months’ life may have special value for those affected. They had been able, applying the criteria, to give approval to sunitinib for first line treatment in a previous FAD. They were not able to do so for the products covered by this FAD.

16. On the fairness points 1 and 2 set out in paragraph 10, Dr Williams and Dr Dawson for the appellant argued three matters:

1. The purpose of the supplementary advice was to address a perceived failure in NICE's standard methodology, that it did not fully capture the value of life extension at the end of life. The small population criterion in the supplementary advice could only be a proxy for affordability. Consideration of affordability was outside NICE’s remit, and was irrelevant and/or improper. Basing the fourth criterion in the supplementary advice on a small population could only have the purpose of limiting the overall cost of the drug to the NHS and was therefore concerned with affordability rather than clinical or cost effectiveness.

2. The criterion was unfairly unclear. First, there was no guidance as to what was meant by a "small" population. Second, taking the cumulative

population covered by licences for the product when considering for the purposes of this appraisal whether the product met the small population criterion in the supplementary advice lacked transparency and was unfair. Each licence application entailed significant development costs. The original draft of the advice issued for consultation referred to a population of 7,000. No number was given in the final advice. That left open how the population should be judged, and in particular how cumulation should be applied, including over what jurisdiction. Was it in the UK, the EU, or worldwide? Cumulation acted as a disincentive to seek licences for rarer cancers. Furthermore it was relevant that bevacizumab had not been approved by NICE in respect of any of its licensed indications in the UK. In practice, it was not available for any of its indications, so it was unfair to cumulate across these populations.

3. The conclusion in regard to the tolerability of bevacizumab in combination with interferon alpha as set out in paragraph 4.3.8 of the FAD was unclear. An assumption had been made on high toxicity of the product when clinical trials suggest that overall the tolerability of bevacizumab and interferon alpha appears at least no worse than that of sunitinib which had been approved for first-line treatment in a previous FAD. The way that the Committee had considered disutility related to toxicity and side effects of treatment was unclear. There appeared to be expert evidence that had been taken into account, but the company's trial data should have been preferred.

17. Macmillan Cancer Support and the Rarers Cancer Forum expressed support for point 2 above but reserved their further comments to Ground 2 (perversity).

18. The Panel questioned Dr Carole Longson on the purpose and interpretation of the supplementary advice issued by the Institute. She explained that the Institute had two broad aims, outlined in the Consultation Document on the draft

advice. First , whether the benefits from end of life extension for conditions such as that covered by the FAD were undervalued in the normal criteria for assessing a cost per QALY. That was reflected in the supplementary guidance by giving the Committee the ability to attribute a higher value to life in these circumstances. Second, whether sufficient regard has been given to recognition of the desirability of developing new treatments in smaller disease areas. It was accepted that, in respect of treatments for small groups of patients, higher prices, and therefore reduced cost effectiveness, were more likely to be justified given the need to recoup costs of development of the product from more limited licences. That argument weakened as the potential total population of a product increased; hence the criterion of taking account of the cumulative population covered by a succession of the product's licences for different indications. Criterion four of the advice subsequently issued was intended to recognise the long–term benefits to the NHS of innovation in these circumstances.

19. For the Committee, Professor Stevens stated that they had understood and applied the policy in relation to evaluation of benefits and cumulation of licensed populations for particular products, which they were directed to follow. In the FAD they had accepted the principle that the population affected by advanced and/or metastasic renal cell carcinoma in itself met the small population criterion; they were however bound by the cumulation criterion as it applied to bevacizumab.

20. The Panel asked Dr Longson to consider two drugs for the same indication, A and B, each of equal cost effectiveness, where A is already licensed for a number of indications and B has only one licence for a small population. Dr Longson confirmed her understanding of the supplementary advice was that A could not be considered under its extension to the normal criteria to be applied, whereas B could be. This was, she said, to encourage the development of treatments for small populations.

21. The Panel also asked Dr Longson to consider the situation of a drug which was favourably appraised under the supplementary advice, but which had been granted marketing authorisations for more indications when it came to be reappraised. Dr Longson stated that her understanding was that it would be necessary to take account of the larger cumulative population on the normal review of the guidance.

22. The panel asked the Appellant whether its complaint was that the criterion would be unfair (and/or unlawful) if the purpose behind it was to address affordability, or if the criterion would be unfair (and/or unlawful) regardless of purpose, if the effect was to address affordability. The appellant confirmed that its argument was that there was an invalid purpose here, and that it was not arguing that some collateral effect on affordability, without more, made the criterion unfair or unlawful.

23. On the third point of appeal (toxicity) under this ground, Professor Stevens explained that the evidence is clear on the adverse effects and toxicity of interferon alpha. However, that had not impacted on the assessment. The calculation applied to bevacizumab used in combination with interferon alpha had used the same utility value as had been applied to sunitinib in the previous FAD. The ICER had not been revised downward to take account of the adverse effects, so it was not the case that the product had been discriminated against on this ground; rather the issue had been ignored in the calculation. However there was some evidence of higher adverse events from use in combination. There were more drop outs in the combined use trial than in the control arm. He noted that Sunitinib was administered orally; Bevacizumab was administered by intravenous infusion; interferon alpha by subcutaneous injection. Dr Peter Clark highlighted that fatigue and anorexia were significant side effects of the use of interferon alpha.

24. For the company Dr Dawson stated that the increased adverse effects reported in the combined use trial essentially reflected the longer use of the combined treatment compared to the control treatment. The company did not dispute the final calculation of the ICER of £53,820 for bevacizumab as used compared to its comparator. However it felt it was unfair to describe this as the "lowest possible" ICER.

Ground 2 The Institute has prepared a FAD that is perverse in the light of the evidence submitted.

25. Roche Products Ltd considered that the conclusions reached regarding the side effect profile of bevacizumab plus interferon alpha were inappropriate given the evidence that has been presented to the Appraisal Committee. The arguments advanced in relation to ground 1 also applied to this ground.

26. Macmillan Cancer Support and the Rarer Cancers Forum argued that the supplementary advice had been applied in a perverse way. For the two organizations Professor Wagstaff argued that cumulation was perverse in light of the criterion that second and subsequent licences for a product should be treated on their merits. This was because the effect of cumulation will militate against seeking a licence for a rare condition where an indication for a more common cancer had already been granted. That did not amount to considering second and subsequent licences on their independent merits. The normal evaluation would apply as a result of cumulation, although the population affected by the subsequent indication would otherwise qualify for more favourable consideration under the supplementary advice. Bevacizumab was a particularly hard case in that none of its licensed applications had been recommended by NICE for use in the NHS. Mr. Cook added personal testimony highlighting the grave impact on patients such as him of denial of effective treatment. He highlighted the stress of applying to a PCT for exceptional approval to be given a drug that had not been

approved by NICE. He considered the side effect issue had been overstated since side effects could be managed.

27. The James Whale Fund for Kidney Cancer supported the appeal on this point endorsing the points made on behalf of Macmillan Cancer Support and the Rarer Cancers Forum. Mr Turkentine argued that a licensed drug that might help patients was being denied. The arguments on fatigue had been overstated. Dr Powles added his view that the advice had been perversely applied to bevacizumab. He considered that bevacizumab had a role to play in the treatment of renal cell carcinoma. He observed that, under the advice, if sunitinib had received its first licence for a common cancer then the cumulation criterion meant it would not have been approved for use for advanced and/or metastatic renal cell carcinoma. Ms Thompson added her personal testimony in support of the appeal and the points made by Mr Cook, adding that the effect of the guidance would be to deny her second-line treatment as the condition progressed.

Ground 3 The Institute has exceeded its legal powers.

28. Roche Products Ltd asked that the Appeal Panel consider their points from Ground 1 in relation to the negative decision of the Appraisal Committee regarding bevacizumab being improperly based on overall affordability under Ground 3 also. Dr Williams said that the company had initially welcomed the purpose of the draft advice. However, she considered that the attempt to link the application to small populations, excluding the more common cancers, is legally flawed without a direction from the Secretary of State

Conclusions of the Panel.

29. The Panel considered the grounds of appeal in turn.

30. They noted more generally that the issues turned on the legality and fairness and reasonableness of the application of the supplementary advice. It had been accepted by all sides that the population affected by advanced and renal cell carcinoma in itself met the small population criterion, leaving to one side the purpose and effect of cumulation for a series of licences. It followed that, but for cumulation, bevacizumab would have fallen for consideration within the supplemental guidance, although it did not seem possible to say from that that it would have been recommended for use. It was clear that bevacizumab (and the other products covered by the FAD) showed clinical benefits. However the remit of the Institute is to look beyond this to assess cost effectiveness; that is, looking at the case for the use of resources on this treatment as against other calls on NHS resources.

31. Equally, it was clear and not disputed that, under the normal threshold range for cost effectiveness (that is leaving aside the supplementary advice), none of the products covered by the FAD would qualify for recommendation. The supplementary advice adds a basis, as governed by the criteria, for recommendation by the Committee of a product as an exception to the application of the normal "thresholds". It permits and encourages a positive use of discretion where otherwise a recommendation would very probably be denied. Further, though there were differences of view on the details of the cost effectiveness calculations for individual products, these were within a sufficiently small range that the issues did not turn on the precise assessed values themselves in the FAD. What was at issue was the legality and fairness of the supplemental advice itself and the fairness and reasonableness of its application to the products assessed in the FAD.

Ground 1.

32. On fairness and compliance with the published procedures, it was clear to the Panel that the Committee had understood and applied the supplementary advice issued by the Institute. The Panel found that intention of the advice was twofold: to place a higher value on life extension in certain circumstances, and to support innovation. That was apparent both from Dr Longson's comments, and from the contemporaneous consultation documents when the guidance was being created.

33. As regards the small population criterion per se, the Panel's view was that the purpose of that criterion was to direct the advice to supporting innovation, which was within the Institute's remit, and that the criterion was a permissible means to achieve that end. The Panel noted that more favourable treatment for drugs used in small populations was not a wholly new concept, in that, for example, special consideration is given to orphan drugs in the licensing context. Although the small population criterion was not the same as orphan drug status, it appeared that the reasoning behind it was similar.

34. The Panel noted Roche's fair concession that, if the purpose behind the criterion was fair and lawful, it would not argue that the criterion was nevertheless unlawful if it had some effect on affordability. The Panel did not therefore need to consider whether the effect of the criterion in practice included an effect on affordability.

35. The Panel rejected the complaint that the criterion was unfairly vague. Consistently with its conclusion in the lapatinib appeal, the Panel would have pointed out the drawbacks of any hard edged threshold in any event. Although it was not possible to put an exact numerical value on when a population would no longer be considered "small", the Panel did not believe this lead to any unfairness, as the broad concept was clear, and would become clearer as the

supplemental guidance is applied in different appraisals. In any event, the point was not a live one in this appeal as the Committee had agreed that this patient population was "small".

36. The Panel turned to the question of cumulation. The instruction to the Committee to apply a cumulative assessment of populations where a product had a number of licences was clear, as further explained by the Institute at the hearing. That approach was permissible, in as much as the Institute had given a rational explanation for the connection between a small cumulative population and the need for more favourable treatment to encourage innovation. The instruction had been applied correctly by the Committee. The Panel noted the apparent inconsistency highlighted by Macmillan Cancer Support and the Rarer Cancers Forum but considered that the three sentences in paragraph 3.2 of the supplementary advice were separate and needed to be applied to the assessment of products individually. In light of the purpose behind the small population criterion, it was not inconsistent to state both that a licence would be considered on its merits, and that the relevant population for the small population criterion is the total population for whom a product is licensed. The two were separate criteria.

37. It was appropriate under the advice to cumulate the populations in terms of the potential population covered by licences for different indications rather than on the basis of actual or recommended use. Further, the Panel did not accept the argument that bevacizumab plus immunotherapy was a different treatment to bevacizumab plus chemotherapy such that the two populations should not be cumulated. It was not consistent with the intent of the advice to subdivide different licences for a product depending on what other products were given in combination therapy, even where the licence in question may only be for combination therapy.

38. However the Panel considered as a point of clarification that the calculation of cumulative population should reflect only the population covered by the licensed indications in the territories where NICE guidance had formal effect (that is, England and Wales). Although there was a suggestion that a world wide population might be considered, and in the panel's view that would be an incorrect application of the guidance, there was no evidence that this had been done in this case.

39. It was clear further clear from the material in the FAD (paragraphs 4.3.6 , 4.3.7 and 4.3.8) that the issue of side effects had as a matter of fair process been considered appropriately by the Committee . The Panel noted , consistently with the judgement in R ota Servier v NICE, that it was not necessary to give detailed reasons within an FAD for judgements such as this, both because the FAD was intended to be guidance, and because the reader was to be taken to be technically well informed.

40. The Panel therefore dismissed the appeals by Roche Products Limited, Macmillan Cancer Support, the Rarer Cancers Forum and the James Whale Cancer Fund on this ground.

Ground 2.

41. On perversity, the Panel is concerned with whether the Committee could reasonably have reached the conclusion it did on the basis of the evidence before it, rather than to reconsider the substance of the issues and/or substitute its judgment for that of the Committee. The Panel concluded that the Committee had reasonably reached its conclusions in the light of the evidence and the advice directing its consideration. The Panel recognised and understood the comments made by the appellants on the perverse implications, as they saw it, of the policy, in particular the application of cumulation of populations licensed for a range of indications for a particular product. However, that is essentially a matter

for the Institute to consider as they review the impact and effect of the supplementary advice; the Committee can not be held to be unreasonable in applying the policy as intended. Furthermore, some of the more challenging scenarios, for example the situation where a drug is reappraised having gained additional licences, were hypothetical for this appeal.

42. The Panel further concluded that the issue of side effects had been reasonably considered by the Committee. They noted that the product had not been discriminated against as the same utility value had been applied as in a previous assessment and the issue of side effects had not been further taken into account in calculating the ICER of £53,820, considered the lowest plausible ICER estimate. The Panel noted the dispute between Roche and the Committee as to whether this was merely a reasonable ICER, or the lowest possible ICER, but did not consider this dispute could amount to perversity on the part of the Committee. Accordingly, the Panel dismissed the appeals from Roche Products Limited, Macmillan Cancer Support, the Rarer Cancers Forum, and the James Whale Cancer Fund on this ground.

Ground 3.

43. It is common ground that it is not within its remit for the Institute to appraise treatments on the grounds of affordability. The Panel noted that the advice enables the application in certain circumstances of a positive exercise of judgement in agreeing an exception to the normal criteria for recommendation of medicines in respect of life extending treatments for small groups of patients. They noted the statement of purpose in the consultation document issued in 2008 on the draft supplementary advice, in particular the rationale for the small population criterion, as set out in paragraph 1.3 of the consultation document.

44. The purpose of the advice, as being to recognize the longer term benefit for the NHS of innovation in cases where higher prices may be justified by the

smaller groups to which the products apply, was re-iterated at the hearing by the Institute (paragraph 18 above). They noted that the effect of the argument advanced on this point at the appeal, if accepted, may be to negate the supplementary advice previously welcomed by the appellants. Given the stated purpose in the consultation document, the final issued advice, and the explanation at the hearing as linked to recognising the value of innovation, the Panel did not consider that the advice's reference to small populations was importing affordability criteria into the appraisal process beyond the Institute's remit.

45. The Panel also considered whether the advice itself might be unlawful as being unreasonable in the legal sense, particularly in light of some of the scenarios explored around cumulation. The Panel concluded the advice was not unreasonable. Cumulation itself was rationally related to a relevant concern, the promotion of innovation. There would always be difficult issues around the boundaries of any criterion. Care would be needed in borderline cases to avoid results which might individually be unreasonable, but the possibility of such cases did not of itself render the criterion or the advice per se unreasonable. The effect of the cumulation requirement was to restrict the scope of the supplementary advice, such that there would be some life extending medicines which would not fall within it (although it did not follow that they could not be recommended in the usual way). However it was open to the Institute to require that a treatment should both be life extending and (in effect) be innovative before it benefited from the supplementary advice.

46. Accordingly the appeal by Roche Products Limited on this ground was dismissed.

Temsirolimus.

47. Introducing the appeal**,** Dr Rajah for Wyeth stated that the sole indication for temsirolimus was the first line treatment of a small sub-group of advanced renal cell carcinoma patients with at least three poor prognosis factors. This covered only about 390 patients in England and Wales. It is the only technology demonstrating a survival benefit in such patients, of 3.6 months on average. The effect of the FAD is therefore to deny access for a group of patients to an effective treatment.

Ground 1. The Institute has failed to act fairly and in accordance with its published procedures.

48. Under this heading Wyeth Pharmaceuticals raised three points.

1. Inconsistent use of economic models in decision making.
2. Failure to consider the size of the patient population.
3. Failure to consider the degree of clinical need.

49. For the company Mr. Baxter commented at the hearing.

1. It was unfair that the Committee had not used the assessment group model applied to other products when assessing the cost effectiveness of temsirolimus. Instead the company's model had been used. While the model captures the QALY benefit of the product principally derived from the maintenance of patients in progression free survival the model underestimates the overall survival advantage. In particular the befits from the Wyeth model was constrained by the three year time horizon compared to the ten years used in the other models.

2. The Committee should have given explicit consideration to the very small size of the population -390 - when considering the use of temsirolimus. As a treatment for an ultra orphan condition Wyeth had been disappointed the product had been included in the appraisal at all. They recognised no direction had been given to the Institute that ultra orphan products should be appraised differently, but they considered that an extra end of life weighting premium should have been applied to the product.

50. For the Appraisal Committee Professor Stevens explained that they were concerned to choose the best model for the assessment. In the case of this product that was not the assessment group model. He observed that the original assessment group model had been further tailored to the individual products following comments and was not the same in practice for all the other products. Therefore the argument of inconsistency was weak. Whichever model was applied to temsirolimus, the resultant ICER was high; beyond what could reasonably be approved in terms of the extra weighting needed to be applied to extension of life, compared to other use of NHS resources. On the technicalities of the model, Professor Stevens explained that the model did not split between progression free survival and overall survival so that had not affected the outcome. He further said that the benefits of the product accrued overwhelmingly within a three year time horizon. Further, the assessment report had considered the effect of a three year versus a ten year model horizon.

51. Professor Stevens explained the process the Committee had gone through in assessing the ICER under supplementary guidance criteria. They had considered what is the extra value of a life that would be needed to justify recommendation compared to that assessed for other groups of patients in the NHS? Is the extra value multiplier needed to bridge the gap between the assessment and the normal upper end of the threshold (£30,000) justified in terms of recommendation, taking account of the opportunity cost of use of this product compared to treatments for other groups of patients who may also be facing

terminal or distressing diseases? The analysis of temsirolimus implied a multiplier well above that applied normally to other products appraised. It compared to the multiplier of approximately 1.6 times accepted for sunitinib in the circumstances set out in that appraisal. While not taking that as a general threshold, the committee could not justify the degree of extra weighting that would be needed here in order to give a positive recommendation.

Ground 2 The Institute has prepared a FAD that is perverse in the light of the evidence submitted.

52. Under this ground Wyeth Pharmaceuticals argued there had been inconsistent use of economic models in decision making. By taking account of the severity and rareness of the disease and the sub-group it would have been reasonable to approve the use of temsirolimus. The additional weight needed was not very great, of the order of 2.03-2.12.

53. The James Whale Fund for Kidney Cancer supported the appeal under Ground 2 arguing that the decision of the Committee denied a proven active drug for a small patient group lacking other therapeutic options.

54. For the Committee Professor Stevens stated that the additional weight needed was 3-4. The Committee found that the base ICERS for temsirolimus were of the order of £90-100,000. The weighting needed was simply too high, having in mind the opportunity cost to other patients.

The Conclusion of the Panel.

55. The Panel considered the two grounds in turn.

Ground 1

56. The Panel considered it was unlikely as a general rule to be unfair to use an assessment model developed by the manufacturer of the product. In this case they noted that the results of different models were not that dissimilar and for the reasons explained in paragraph 50 they did not consider its application to temsirolimus unfairly disadvantaged the manufacturer. They noted the point on the very small number of patients affected. However, there was no separate process for ultra orphan products, so the Committee had of necessity to use the normal assessment approach, as modified by the supplementary guidance, when evaluating the product. They further noted that the very small number reflected a sub group (those with three poor prognosis factors) within a larger group (those with advanced and/or metastatic renal cell carcinoma) rather than a fully separate disease population. The Panel dismissed the appeal on this ground.

Ground 2

57. The committee noted and understood the arguments on the particular circumstances of the small number of patients who might benefit from temsirolimus. However, even if the manufacturer's estimates were accepted, they could not conclude that the judgement by the Committee – that the multiplier that would need to be accepted for the value for life for this sub-group compared to that applied to others looking to the NHS for treatment was above that on which approval could be given - was unreasonable, recognizing the cost effectiveness remit of the Institute. Accordingly the Committee dismissed the appeal on this ground.

Ground 3

58. There were no points of appeal in respect of temsirolimus under this ground.

59. The appeal panel of its own motion asked the appellants whether any of the patient population for temsirolimus should be considered to be disabled, over and above the disabilities inherent in the population of renal cell cancer patients generally, and if so whether there were any points the panel should have in mind in that regard. The appellants were not in a position to answer that question at the hearing, and so the panel agreed to receive any submissions in writing by close of business on 15 July. Submissions on this point were made by Wyeth by letter dated 16 July 2009 and were considered by the panel.

60. In its letter of 16 July Wyeth observed that:

- 80% of the patient population for temsirolimus (with a poor prognosis) needed some help with self care and were not capable of normal activity or work;
- only 40% of the patient population of sunitinib (with a good to intermediate prognosis) were restricted in their ability to perform physically strenuous activity; the remaining 60% were able to carry on all pre-disease activities without restriction.

Wyeth submitted that this difference meant that patients with a poor prognosis should be treated as a differently disabled group to those with a good or moderate prognosis, and that any less favourable treatment of the poor prognosis group compared to the good/moderate prognosis group could be considered discriminatory and unlawful under the Disability Discrimination Act 1995 (the DDA).

61. On considering Wyeth's submissions, the panel concluded that patients with a poor prognosis should not be treated as having a separate category of disability to those with a good or moderate prognosis. Regrettably, all patients with advanced and/or metastatic renal cell carcinoma were disabled and were likely to move into the poor prognosis group as time progressed unless some

other illness or event intervened as their condition deteriorated. Those with a good/moderate prognosis would become those with a poor prognosis and the likelihood was that patients in both groups would die of the disease. The panel did not think that patients in the poor prognosis group were sufficiently different from those in the good or moderate prognosis group to justify being treated as having a different disability.

62. In case there was any disagreement about the panel's conclusions on this point, the panel went on to consider whether the Committee had complied with its obligations under the DDA if it was assumed that the two patient groups were two categories of disabled persons for the purposes of the DDA.

63. Wyeth's submissions centred on the argument that the quality of life questionnaire used to calculate QALYs in relation to all patients underestimated the value of the extension to life to patients at the end of life and that the closer a patient was to the end of life the greater this effect was. As poor prognosis patients were closer to the end of life than good or moderate prognosis patients, this practice discriminated unfairly against the poor prognosis group. Wyeth went on to argue that the supplementary advice was designed to address this imbalance, but as the Committee had not applied it properly, the discriminatory impact remained.

64. The panel was conscious of its duties under the DDA and in particular its duty to consider treating disabled persons more favourably. It noted that the supplementary advice itself was a more favourable treatment of patients at the end of life compared to those not at the end of life. As the Committee had considered that advice, it had clearly considered more favourable treatment. Bearing in mind its conclusion at paragraph 57 above, the panel was satisfied that the Committee’s conclusions under that advice were justified. The panel further noted its decision in the lapatinib appeal that the amount of life extension required by the supplementary advice was not to be varied relative to the overall

life expectancy of the patients in question. There was no sanction for this in the policy itself. Furthermore, such an approach would have the result of placing ever increasing value on shorter and shorter periods of extension, depending on how close to a patient's probable death the extension was obtained. Although it was understandable that patients and their carers might feel that this was correct, it was not a logical position from a broader NHS perspective.

65. Accordingly the Committee dismissed the appeal on this ground.

Sunitinib

66. No points of appeal were admitted in respect of this technology under Grounds 1 and 3.

Ground 2 The Institute has prepared a FAD that is perverse in the light of the evidence submitted.

67. Under this ground the James Whale Fund for Kidney Cancer argued that although there were no phase three RCTs to support the use of sunitinib in second line treatment, there were reports and anecdotal evidence to support such use, and second line treatment is included in UK, EAU and NCCN guidelines.

The Conclusion of the Panel

68. The Panel is aware that the committee does not assume clinical or cost effectiveness in the absence of what it considered to be sufficient evidence. The Panel will intervene only if the Committee acts perversely. Typically, the weight and persuasiveness to be assigned to evidence is a matter for the Committee. There are no grounds to conclude that the Committee's view of the evidence in this case was perverse.

Sorafenib

69. No points of appeal were admitted in respect of this technology under Grounds 1 and 3.

Ground 2 The Institute has prepared a FAD that is perverse in the light of the evidence submitted.

70. Under this ground the James Whale Fund for Kidney Cancer argued that it was unreasonable to deny this treatment to patients unsuitable for interferon alpha. The Committee had rejected evidence of the clinical effect of sorafenib illogically and perversely.

71. For the Committee Professor Stevens explained that, on the evidence available, the most plausible ICER for sorafenib compared to best supportive care for people in whom immunotherapy had failed was £65,900 per QALY gained. This was over double the value of the upper end of the normal threshold range. It was not for the Committee to set the price of products but clearly the cost effectiveness calculations reflected the price set by the company. At the resultant cost per QALY, requiring a multiplier over twice that normally applied for approval, the Committee could not justify approval.

The Conclusion of the Panel

72. The Panel noted that the Committee can only appraise the evidence that is before it and give it due weight. They noted in passing that the manufacturer had not appealed against the decision. Given the premium required to give a positive answer, the Panel could not hold that the decision of the Committee in not accepting a multiplier over twice that normally accepted was unreasonable.

Conclusion and effect of the Appeal Panel’s decision

73. All of the appeals brought are dismissed.

74. There is no possibility of further appeal within the Institute against this decision of the Panel. However, the decision of the Panel may be challenged by an interested party through an application to the High Court for permission to apply for judicial review. Any such application must be made promptly and in any event within three months of this decision or the issuing of the Guidance.