NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

HEALTH TECHNOLOGY APPRAISAL

APPEAL HEARING

Advice on vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract

Decision of the Appeal Panel

Introduction

1. An appeal panel was convened on 23rd May 2011 to consider an appeal against the Institute's Final Appraisal Determination (FAD), to the NHS, on the use of vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract.

2. The appeal panel consisted of Dr Maggie Helliwell, Chair of the panel, Ms Mercy Jeyasingham, Non-Executive Director of NICE, Dr Frank McKenna, NHS representative, Dr Mercia Page, industry representative, and Mr Peter Sanders, lay representative.

3. Ms Mercy Jeyasingham declared that she is evaluating lung cancer information for Macmillan Cancer Support, an organisation who is a consultee for this appraisal. No objection was made to Ms Jeyasingham's participation in the appeal. The Chair of the panel made a decision that this could not be thought to create a concern about the ability of Ms Jeyasingham to participate in the hearing objectively. None of the other members of the Appeal Panel had any interest to declare.

4. The panel considered an appeal submitted by Pierre Fabre.

5. Mr Martin Grange of Pierre Fabre and Professor Roger James, a clinical oncologist, represented the appellant.

6. In addition the following individuals involved in the appraisal were present and available to answer questions from the appeal panel - Professor Peter Clark, Committee Chair, Mr Meindert Boysen, NICE Programme Director, Ms Joanne Holden, Technical advisor and Mr Christian Griffiths, Technical Lead**.**

7. All of the above declared no conflicts of interest.

8. The Institute's legal adviser Ms Eleanor Tunnicliffe from Beachcroft LLP was in attendance as the legal representative to the Panel.

9. Under the Institute's appeal procedures members of the public are admitted to appeal hearings and several members of the public were present at this appeal.

10. There are three grounds under which an appeal can be lodged:

    - The Institute has failed to act fairly
    - The Institute has formulated guidance which cannot reasonably be justified in the light of the evidence submitted
    - The Institute has exceeded its powers

11. The Chair of the Appeal Committee (Dr Maggie Helliwell) in preliminary correspondence had confirmed that the appellant, Pierre Fabre, had potentially valid grounds of appeal under Ground 1 that "The Institute has failed to act fairly" as follows:

    1.1(b) That in the course of the appraisal vinflunine has been compared with (unlicensed) second line chemotherapy agents in a way that is inconsistent with the scope for the appraisal.

    1.1(d) That no evidence for an alternative existing treatment service was provided to the manufacturer and it is not known if any evidence was provided for the Committee to scrutinise.

    1.2(a) That the Institute has been inconsistent in recognising in the FAD that there are possible alternative (unlicensed) treatments to vinflunine but relying on economic modelling that compares vinflunine to best supportive care rather than these treatments.

    1.2(c) That the FAD amounts to a de facto recommendation of unlicensed second line treatments but these have not been subjected to the same economic comparison with best supportive care as vinflunine.

12. The Panel were made aware in documentary evidence that vinflunine is a vinca alkaloid chemotherapeutic agent manufactured by Pierre Fabre. It is administered by intravenous infusion and acts as a typical tubulin antagonist. Vinflunine is licensed in the UK as monotherapy for the treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelium after failure of a prior platinum-containing chemotherapy regimen i.e. as second-line treatment for this patient group.

13. The appraisal that is the subject of the current appeal has prepared advice to the NHS on the use of vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract.

14. Before the Appeal Panel inquired into the detailed complaints, the following made preliminary statements: Mr Martin Grange on behalf of the appellant and Professor Peter Clark on behalf of the appraisal committee.

Appeal Ground 1: The Institute has failed to act fairly

15. In his introductory remarks Mr Martin Grange explained that he had participated in the scoping exercise for the appraisal. Following publication of the final scope, which stated that the comparators to which vinflunine should be compared were *"best supportive care defined as palliative radiotherapy, blood transfusion, analgesia, and symptomatic care"*, Pierre Fabre had prepared a submission setting out the benefits of vinflunine compared with best supportive care ("BSC").

16. He was therefore concerned that the Evidence Review Group (ERG) in their submission had commented that BSC might not be the most appropriate comparator because alternative second-line treatments are available in UK clinical practice for patients with a better prognosis. Mr Grange expressed concern that this was mentioned several times in the FAD with the implication that the appraisal committee had considered comparison with comparators not included in the scope. Pierre Fabre therefore felt disenfranchised by the appraisal process through this change in the scope.

17. Mr Grange considered that no evidence relating to alternative second-line treatments had been presented to the appraisal committee and as the alternative treatments were not properly defined there was no basis for comparing any of them to vinflunine.

18. In addition Mr Grange considered that this interfered with the assessment by the ERG and led to an unfair economic evaluation of treatment with vinflunine.

19. Mr Grange also argued that the FAD as written implied a de facto recommendation of unlicensed treatments for metastatic transitional cell carcinoma through recognising the use of the alternative treatments.

20. Professor Clark for the appraisal committee stated that the benefits of palliative chemotherapy for this condition were modest and there needed to be a balance between a potential benefit to some patients compared with toxicity to all patients who were treated. There also had to be a balance between clinical

effectiveness against cost effectiveness. Professor Clark explained how the Committee understood both the technology and the clinical setting and drew conclusions about vinflunine's potential place in the care pathway. The Committee considered that this place in the pathway was central to determining the health economic evaluation of vinflunine. From the trial evidence submitted by the manufacturer it was considered that the evaluable patients were close to death and therefore the role of vinflunine was as an active palliative treatment for patients who were close to death. Vinflunine was compared with best supportive care in these patients. Professor Clark made it clear the appraisal did not undertake any other assessment of vinflunine treatment other than comparison with best supportive care. Professor Clark also said that several national cancer groups had described the appraisal to have been a rigorous process.

21. The hearing then considered each appeal point in turn.

Appeal Ground 1.1(b): That in the course of the appraisal vinflunine has been compared with (unlicensed) second line chemotherapy agents in a way that is inconsistent with the scope for the appraisal.

22. In relation to Ground 1.1(b) the Panel asked Professor Clark whether the Committee was clear on the scope for the appraisal. The Panel noted that the scope defined the patient population as "*adults with advanced or metastatic TCC of urothelial tract after failure of prior platinum-containing chemotherapy*" and the comparator as BSC. Professor Clark explained that the Committee were fully aware of the scope and he had chaired the scoping meeting. He described how the Committee first had to understand the role of vinflunine in the care pathway. The Committee had heard evidence from clinical specialists that patients may undergo a range of treatment and there was general agreement that there is no standard treatment for those who relapse after first-line chemotherapy. However, the experts considered that currently patients with a better prognosis following relapse would usually receive (unlicensed) second-line treatment rather than moving straight to palliative care. Those with a poor prognosis following relapse would usually only receive palliative care.

23. The main evidence for the clinical effectiveness of vinflunine was from study 302. In study 302 the prognosis of the patients was typically poor - only a few months of expected survival. These were the patients willing to enter the trial. The manufacturer therefore tested vinflunine in an extreme end of life setting where patients were closer to the end of life and broadly would not be offered other treatment. The Committee considered that in this setting it was inappropriate to compare vinflunine with other treatment and felt the appropriate comparison was with BSC as described in the scope.

24. The Panel then enquired whether the Committee considered that through stipulating a comparator of BSC the scope implied that only patients with a poor prognosis should be considered for treatment with vinflunine. Professor Clark thought that the scope was not clear about this.

25. For the Committee, Mr Boysen accepted that the scope did not necessarily define the patient group as being patients with a poor prognosis and agreed that the Evidence Review Group did raise the possibility of comparing vinflunine with other treatment. He explained that the ERG evidence was only part of that which is given to the Committee and it did not dictate the approach that the Committee should take. The Committee had discussed where vinflunine fits in the care pathway and had agreed with the manufacturer that it should be used in patients with a poor prognosis.

26. The Panel then asked the appellant whether the Committee's understanding of the manufacturer's position was correct. Mr Grange considered that this interpretation of their position was incorrect and that Pierre Fabre wished the Committee to appraise vinflunine for all patients whose disease had progressed following platinum-based chemotherapy – not just those with a poor prognosis. As there was not any standard treatment to compare vinflunine to in a clinical trial, Pierre Fabre had undertaken a trial against BSC in poor prognosis patients as an initial study. The Committee had misinterpreted that data as relating to the position of vinflunine in the pathway.

27. The Panel asked whether the Committee considered that there was an apparent change in the scope because of the last sentence in 4.5 of the FAD which reads "*The committee therefore considered that best supportive care was the appropriate comparator for patients presenting with advanced or metastatic disease who may not benefit from other currently used second-line chemotherapy regimens*." The Panel noted that this paragraph describes a smaller group of patients - those with a poor prognosis - than that described in the scope - which encompasses all patients relapsing after first-line treatment, regardless of prognosis.

28. Professor Clark replied that clinical specialists had given anecdotal evidence that vinflunine would probably be used third-line (i.e. after treatment with platinum-based chemotherapy and further chemotherapy) in patients with a better prognosis but nevertheless the Committee had not compared vinflunine with other treatment. Professor Clark also described how there was not an established standard of treatment for patients with a better prognosis with which to compare vinflunine. Professor Clark accepted that paragraph 4.5 in the FAD did clarify a population that was not defined in the scope.

29. For the Committee Mr Boysen considered that the scope could have been improved had the population been described more accurately but it was his opinion that because the comparator was BSC this implied that the scope was to evaluate patients with a poor prognosis.

30. The Panel then asked the Committee to comment on paragraph 4.7 of the FAD, which stated that the Committee had heard from clinical specialists that other second-line treatment was well tolerated but the Committee had concerns about the toxicity of vinflunine. Professor Clark stated that the Committee did have concerns regarding the toxicity of vinflunine, particularly related to severe constipation, but the Committee did not receive comparative evidence comparing the toxicity of vinflunine with other treatment.

31. The Panel then asked the appellant to describe what they considered to be the most optimistic survival data and the most optimistic health economic evaluation. Mr Grange informed the Panel that in the clinical trial vinflunine increased survival by an average of 2.6 months and that the most optimistic ICER may be as low as £87,000 per QALY.

32. The Committee were invited to make any further comment in relation to point 1.1(b) of the appellant's appeal. In response Professor Clark explained that the FAD was written in order to try and bring clarity to this clinical area and that any clinical opinion that led to comparison of vinflunine with other drugs was discarded because clinical opinion was that vinflunine was not used when other second line treatment was an option.

33. For the Committee Mr Boysen stated that in his opinion the FAD did follow the scope and that a table had been introduced to clarify key statements of the conclusion. In this table of key statements there is no indication that the Committee had addressed any perceived change in the scope. He also emphasised that there was no evidence for the outcome in patients with a better prognosis treated with vinflunine.

34. For the appellant Professor James emphasised that the patients in the 302 study had a poor prognosis but that in the FAD the Committee appeared to be unclear about an appropriate comparator. Mr Grange also emphasised that the EMEA had licensed vinflunine for the treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelium after failure of a prior platinum-containing chemotherapy regimen on the basis of evidence from the 302 study and that the 302 trial with vinflunine is the first randomised trial of chemotherapy in this treatment area.

35. For the Committee Professor Clark considered that patient performance as an entry criterion to the trial was not a good indicator of prognosis noting that

although apparently fit, 84% of patients relapsed within six months of chemotherapy. The patient population had a high visceral involvement of disease indicating their poor prognosis. Professor James for the appellant disagreed and considered that patient performance was a good indicator of prognosis.

36. In summary, Professor Clark explained that the Committee felt it was important to consider where vinflunine sat in the pathway and that although the setting of complex chemotherapy needed to be better understood, the scope of this technology was correct. For the appellant, Mr Grange explained that the manufacturer had presented data superimposed on an area of chaos and that this structured approach would lead to an improvement in patient outcome. He stated that they embraced the Health Technology Assessment process but had felt sidelined. For the appellant, Professor James also wanted to emphasise that there was no evidence for vinflunine to be used any differently than any other second-line drug treatment.

37. In considering the evidence the Panel reviewed the scope and noted that Professor Clark had chaired the scoping workshop. The Panel considered the comments made by Professor Clark explaining the purpose of the FAD in attempting to clarify the patient pathway and the potential role of vinflunine in the pathway. The Panel also considered the key statements made in the summary table at the end of the FAD. However, the Panel noted that Professor Clark had accepted that the scope population was further defined by the Committee in the course of the appraisal as referring to poor prognosis patients. It was apparent that the Committee had concentrated on the poor prognosis group when drafting the FAD.

38. The Panel considered that the Committee had narrowed the patient population from that which was described in the scope. It understood that this was because the Committee considered there was only published evidence of treatment in the poor prognosis patient population. Provided a committee at least initially considers all of the patients within a scope, it is not unfair subsequently only to concentrate on or make recommendations for a subsection of patients, if the evidence available makes this unavoidable. That would amount to a response to the evidence base rather than a redefinition of the scope. However, the Panel considered that in this case the initial broader consideration was defective and because the Committee only considered a more selective patient population, the opportunity was lost to the manufacturer to discuss vinflunine treatment in a wider population. Although the Committee discussed treatments of the wider population to a degree the Panel concluded that final sentence of 4.5 in the FAD reflected a redefinition of the scope rather than a response to a lack of evidence. In addition the comparison of vinflunine to comparators not mentioned in the scope, in particular at paragraph 4.7 where

side effects of vinflunine and other second-line treatments are compared, was unfair. The manufacturer was not given an opportunity to make submissions on the performance of vinflunine compared to other second-line treatments as it was not aware this comparison was being drawn.

39. The Panel considered that one of the basic tenets of fairness was that those participating in consultations should understand the basis on which a decision is to be made. The basis for this appraisal – on which the manufacturer based its submissions – was set out in the scope. In view of the redefinition of the patient population and the comparison of vinflunine with unlicensed second line treatments contrary to the scope, the Panel considered that the Institute had failed to act fairly and Ground 1.1(b) was upheld.

Appeal Ground 1.1(d): That no evidence for an alternative existing treatment service was provided to the manufacturer and it is not known if any evidence was provided for the committee to scrutinise.

40. The Panel considered that Pierre Fabre had explained this point when discussing 1.1(b) and invited the Committee to respond. Professor Clark drew attention to the manufacturer's submission where other chemotherapeutic treatment was described in relation to current treatment options. Professor Clark particularly drew attention to comments in section 2 of the manufacturer's submission describing how a variety of drugs have been adopted into local practice (p16-17) and also in section 7 (p114) where assumptions were made on other treatment options.

41. In response Mr Grange for the appellant emphasised that there was not an established treatment pathway for this disease and there was no published data that could be used to compare vinflunine with other treatment. It was also unfair to draw a comparison between vinflunine and other treatment that had not been properly described.

42. In considering this point, the Panel considered the descriptive evidence submitted by the manufacturer of other treatment options and also considered the Committee's consideration of other treatment as expressed in the FAD. The Panel considered that this point was a subsidiary argument to 1.1(b). The Panel considered it was unfair to the manufacturer for vinflunine to be compared with comparators outside the scope. The manufacturer had not directed its submissions to such comparisons. Ground 1.1(d) was upheld.

Appeal Ground 1.2(a) That the Institute has been inconsistent in recognising in the FAD that there are possible alternative (unlicensed) treatments to vinflunine but relying on economic modelling that compares vinflunine to best supportive care rather than these treatments.

43. The Panel invited the Appellant to expand this point. In response Mr Grange explained how he considered the manufacturer was at a disadvantage if vinflunine treatment costs were compared to the costs of BSC rather than of another treatment. It was inevitable that costs of any treatment would appear to be high when compared to BSC. Mr Grange explained that because of having BSC as the comparator, the cost of vinflunine would need to be zero for the cost effectiveness to be within the range acceptable to the Institute. Mr Grange therefore considered that it was unfair to limit the health economic assessment of vinflunine to comparison with BSC while comparing the clinical benefit with other treatment.

44. In response Professor Clark explained that the Committee had some sympathy with the manufacturer's point but that the value of the ICERs for this technology were very high. Professor Clark commented on the effect of simple corrections being made to the analysis, for example, with a correction for vial wastage, the ICER increased to approximately £120,000 per QALY. Professor Clark described how the Committee was aware that the most optimistic ICER for vinflunine was much higher than could be considered to be cost effective. As survival gains were small and less than three months the Committee were unable to apply the end of life criteria for this technology.

45. In considering this point, the Panel understood the manufacturer's argument to be that the Committee had compared vinflunine to other active treatments for clinical effectiveness but not for cost effectiveness. The Panel were also aware that the scope was clear that the comparison was to be between vinflunine and BSC. The health economic evaluation was consistent with this. The Panel noted that the evaluation led to ICERs that were very high and that the manufacturer's most optimistic ICER was £87,000. The Panel considered that this appeal point did not relate to the cost effectiveness figures produced by the evaluation but to the fairness of the process. The Panel did not consider that the manufacturer was disadvantaged in preparing its submissions on the evaluation of cost effectiveness as it was explicit in the scope that the comparator for vinflunine would be BSC (and, indeed, other appeal grounds had complained that the consideration of other comparators was unfair). It was therefore not an unfair process for the cost effectiveness analysis to be undertaken as described in the scope. The inconsistency in approach between the clinical effectiveness section and the cost effectiveness section should be resolved by bringing the clinical section in line with the cost effectiveness

section and only comparing vinflunine with BSC in both. Ground 1.2(a) was dismissed.

Appeal Ground 1.2(c) That the FAD amounts to a de facto recommendation of unlicensed second line treatments but these have not been subjected to the same economic comparison with best supportive care as vinflunine.

46. The appellant was invited to explain this point. Mr Grange stated that the FAD was written as though there was a floating assumption that there is other second-line treatment available for this patient group. However, Mr Grange explained that there is no established treatment pathway for this group of patients and there was also no clinical trial evidence for other treatment. Nevertheless, the FAD by not approving vinflunine was recommending the continuation of other unproven unlicensed treatment for this patient group.

47. Professor Clark for the Committee stated that they were aware of the current care pathway for patients who had failed initial chemotherapy but that the subject of the appraisal was an evaluation of vinflunine and not of other treatment. Professor Clark emphasised that the appraisal process was not to develop a guideline and that the FAD did not make any recommendation for treatment other than that for vinflunine.

48. In considering this final point the Panel was aware that the appraisal of vinflunine is a single technology appraisal rather than an appraisal of any non-licensed comparator treatment. It was therefore not possible to make any recommendation on the use of other treatment. The Panel took account of the references to other treatment in the FAD but did not believe that the FAD made any recommendation of other treatment. The Panel did not consider that it was factually correct to describe any failure to recommend vinflunine as amounting to a promotion of an unlicensed comparator. Ground 1.2(c) was therefore dismissed.

Appeal Ground 2: The Institute has formulated guidance which cannot be reasonably justified in the light of the evidence submitted

49. There was no appeal under this ground.

Appeal Ground 3: The Institute has exceeded its powers

50. There was no appeal under this ground.

Conclusion and effect of the Panel's decision

51. The Panel therefore upholds the appeal on the grounds that the Institute has failed to act fairly in relation to points 1.1(b) and 1.1(d). The appeal is dismissed on all other grounds.

52. The appraisal is remitted to the Committee who must now take all reasonable steps to address the findings of the Panel. The Panel considers that the Committee needs to ensure that the conduct of the appraisal is consistent with the scope. In particular the FAD must reflect the fact that the scope sets out that the task of the Committee is to produce guidance in relation to all patients in the patient population, not just those with a poor prognosis, and under the scope the comparator is BSC.

53. If the Committee considers all of the patients within the scope and concludes that the evidence base is such that it is not possible to produce robust guidance for the whole patient population, the Committee should state that fact, with reasons.

54. The Panel anticipates that as a result of this appeal the Committee will reconsider its guidance. In so doing it must consider the whole patient population, although as noted above it will be a matter for the Committee whether or not it is possible to make recommendations for the whole or a subset of that population. The manufacturer should be given an appropriate opportunity to engage with this reconsideration. Consultees will be able to appeal against the contents of any new FAD in the usual way. However, appeal points already dealt with in this appeal will not be reconsidered. This appeal decision may be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made promptly and within three months of the publication of this decision.