Pierre Fabre

24 March 2011

[redacted]

Chair, Appeal Committee
National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
London WC1V 6NA

Dear [redacted]

Re: Final Appraisal Determination – Vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract.

Pierre Fabre Ltd would like to appeal against the Final Appraisal Determination for the above mentioned technology appraisal on the following grounds:

Ground 1: The Institute has failed to act fairly

1.1 In formulating Guidance, the Institute has been unfair by applying inconsistent data quality standards from the manufacturer and commentators on perceived current practice.

The data submission from the manufacturer conformed to the Appraisal Scope. It was based on a randomised phase III clinical trial conducted to GCP that has been published in a prestigious peer reviewed journal (JCO) and subjected to very detailed scrutiny by the Competent Authority (EMEA, MHRA) before granting a Marketing Authorisation. These data were further scrutinised by the EAU and ESMO before adoption of vinflunine into pan-European treatment guidelines by these organisations (evidence rated 1b). Vinflunine is the only treatment licensed for this indication.

In the course of this Appraisal, the ERG and other commentators have claimed an existing 2nd line chemotherapy treatment service for these patients in the NHS (unspecified chemotherapy agents). This assertion is inconsistent with the Scope but has had a major effect on the conduct and outcome of this appraisal process, being cited extensively in the Summary of Appraisal Committee's key conclusions:

Current practice (4.2)
The technology (proposed benefits) (4.2)
The technology (position in pathway) (4.5)
Evidence (Availability, nature and quality of evidence) (4.3)
Evidence (relevance to general clinical practice) (4.4)

The opinions stated about alternative chemotherapy have been variously reported in the FAD as anecdotal, or from small, often single institution, phase II studies of selected patients and that considerable publication bias was likely to exist. No evidence for an alternative existing treatment service (references, publications or data) was provided to the manufacturer and it is not known if any evidence was provided for the Committee to scrutinise.

Comments on the relative toxicity of treatment to the Committee can only be speculative as the total cumulative base of direct clinical experience with vinflunine in bladder cancer available to the ERG and the Committee was only one patient from an early phase II study in 2001. Objective assessment of relative toxicity was not performed. The toxicity of other classes of agents proposed to the Committee as alternative treatment (platinum or taxanes based) is considerable, especially neutropenia and associated sepsis with the taxanes, and both types of drug require extensive pre-medication programmes [1,2].

The De Facto assumption of an existing clinical service receives significant prominence in the ERG, ACD and FAD, is inconsistent with the Scope, is not substantiated with evidence and has had a significant detrimental effect on the conduct and outcome of this Appraisal Process.

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This is unfair.

1.2 The Institute has not been consistent or fair in the economic evaluation of new treatment for patients with urothelial cancer that relapse after prior chemotherapy.

To comply with the Scope for this Appraisal, the manufacturer's economic submission was built to describe a completely new clinical service for a previously unmet clinical need, replacing supportive care as the current NHS standard of care for selected patients. No existing costs for other alternative chemotherapy could be used to offset "new" treatment in the economic model. So in addition to the acquisition cost, vinflunine had to bear the additional cost of specialist consultations and follow-up with the oncologist, the cost of cytotoxic reconstitution, cytotoxic administration (chemotherapy suite time and specialist nurse resource), the management of treatment toxicity and all care cost associated with these patients living longer. Through the model, this total cost of treatment (£13,071) was amplified to £100,100 as the calculated cost per QALY.

To highlight the unique obstacle these associated treatment costs represent for the development of the first new treatments for previously untreatable cancer, the £30,000 cost-effectiveness threshold for NICE could only be achieved if the drug cost was reduced to £0, as stated in the FAD. The further amplification of the comparative cost of vinflunine v BSC by the ERG, reaching £126,000 per QALY, effectively means that the drug cost would have to be less than zero in order to reach the normal £30,000 cost-effectiveness threshold.

The conclusion of this economic modelling v BSC can only be that additional survival for patients relapsing after prior platinum chemotherapy is not cost effective and these patients should only receive supportive care until they die. Further research to extend survival with chemotherapy will be futile.

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However, the de facto recommendation to allow treatment with unlicensed, unsubstantiated 2nd line chemotherapy to continue was not subjected to the same economic comparison with BSC. If this approach is applied even-handedly to the alternative chemotherapy suggested in the clinical section, it would also appear to be impossible for these other agents to reach the normal cost effectiveness threshold.

The Committee has applied different standards for economic assessment of treatment.

This is unfair.

Summary

The clinical evidence for vinflunine has been significantly undermined by the frequent reference to the availability of alternative treatment at this stage of this disease. No other agents have been licensed for this treatment and no treatment guidelines had previously informed the Company, EMEA or NICE during drug development, registration or the Appraisal Scoping Process.

The evidence considered by the committee regarding an existing clinical service for NHS patients was not consistent with the Scope and did not meet the quality standard for evidence normally applied by NICE. Unsubstantiated opinion significantly affected the outcome of this appraisal and the manufacturer was denied an opportunity to scrutinise or respond to the data from which these opinions were formed.

While the clinical evidence for vinflunine was severely undermined by speculation of an existing clinical service with platinum based or taxane based treatment, the ERG did not adjust the economic analysis to be consistent with this approach. As a new cancer treatment for a previously unmet clinical need, vinflunine was assigned all the associated cost of specialist treatment and extended survival, projecting the total cost above £120,000 compared to BSC, requiring a price less that £0 to be cost effective in a model.

No such economic consideration was applied to the continued use of alternative, un-licensed chemotherapy. This is unfair.

The purpose of developing new cancer treatment for a previously unmet clinical need is to improve outcomes. Currently, around 5,000 people die with this disease every year and fewer than 300 appear to have access to chemotherapy to extend life. Vinflunine is an opportunity to improve the treatment service in the NHS.

Interpretation of these data is hard and it is very easy to inappropriately undermine confidence by including unsubstantiated comments and opinions.

We hope that NICE will reconsider the evidence more fairly and would welcome an oral appeal to state our concerns.

[redacted]

Managing Director

References

1. Summary of product characteristics for cisplatin. Available at www.**medicines**.org.uk
2. Summary of Product Characteristics for docetaxel. Available at www.**medicines**.org.uk

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