Pierre Fabre

22 November 2012

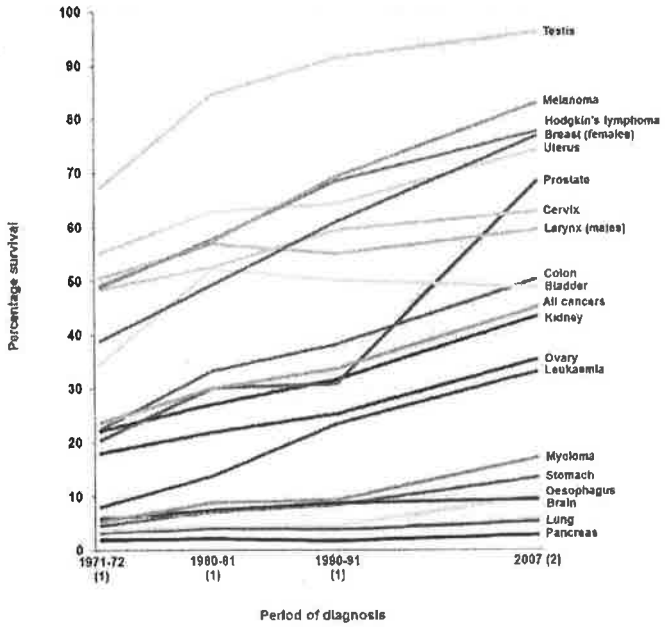
Chair, Appeal Committee
National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
London WC1V 6NA

Dear

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

Let me first remind you of the UK Scorecard for managing bladder cancer, courtesy of Cancer Research UK and published on their website at http://www.cancerresearchuk.org/cancer-info/cancerstats/survival/latestrates/

Figure 1.2: Ten year relative survival (%), adults (15-99 years), selected cancers, England and Wales: survival trends for selected cancers 1971-2007



Pierre Fabre Ltd, Hyde Abbey House, 23 Hyde Street, Winchester, Hampshire, SO23 7DR Tel: -44- (0)1962 874400 Fax: -44- (0)1962 844014 E-Mail: contactus@pierre-fabre.co.uk
Pierre Fabre Medicament, 45 place Abel-Gance, 92654 Boulogne Cedex, France
Registered Office: One Fleet Place, London, EC4M 7WS. Registered No. 986736 England

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Exceptional, is it not? Every picture tells a story.

In defence of the urology / oncology specialists that manage bladder cancer, it should be noted that they have made tremendous progress in renal, testis and prostate cancer where we now have multiple lines of treatment following the development and adoption of new treatment tools. We obviously have the skill sets to sort out bladder cancer, we just need the tools.

The Appraisal Committee should be recognised for their work on this Appraisal which has brought this survival trend into the public eye and triggering renewed interest in the needs of patients at all stages of this disease. It is relevant to note that NICE have further developed this programme and started a full Clinical Guideline process on the diagnosis and management of Bladder Cancer. The Final Scope has been published.

The manufacturer is an active participant in this process. We needed new treatment to tackle this deteriorating survival trend and these accept that these must be developed using robust scientific principles. The pivotal clinical trial (302) is recognised and acknowledged as a bold and brave study that has defined a new standard of activity and survival. Vinflunine is the first medicine to demonstrate robust evidence for a survival advantage in bladder cancer for nearly 30 years and it has done so when used on its own and in very late stage disease – the most difficult area to attempt to show a survival gain. But we did it, we got registration and it was rapidly adopted into European treatment guidelines.

We had a high expectation that this technology would be appraised fairly by NICE and welcomed as the UK scorecard indicates an urgent need to bring new treatment to the clinic. New drugs from phase III trials also provide validated controls for future randomised trials and provide a strong base to attract even more research.

It should be highlighted that a number of older drugs have been available for a decade or two but have, so far, never previously impressed investigators with their activity in bladder cancer – not even enough to merit progression to a phase III clinical trial. An extended range of treatment would be an advantage in the clinic but it is not unreasonable for us to

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expect that NICE would apply the same robust scientific, evidence and economic principles fairly to all proposed treatments, new or old.

But they have not, so instead of providing an opportunity to align activity of multiple organisations with a common purpose of improving survival in bladder cancer, NICE have again thrown friends into the bear pit of an Appeal to slug it out while patients perish.

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

Ground one: The Institute has failed to act fairly.
Ground three: The Institute has exceeded its powers.

Ground 1: The Institute has failed to act fairly

1.1 In formulating Guidance, the Institute has been unfair by not responding to the findings of the previous Appeal Hearing and has continued to apply inconsistent data quality standards.

The visible response to the previous Appeal Hearing is limited to the simple deletion of the specific paragraphs or sentences highlighted by the Appeal Panel without attempting to change existing bias in the analysis or offer any further clarification. This is very disappointing.

In the previous Appeal (Ground 1.1(b,d)) it was clear that no evidence for any alternative existing 2nd line treatment service was considered by the panel and yet multiple references to such a treatment persist throughout this FAD (4.2, 4.3, 4.4 and the summary).

Vinflunine is the only treatment that has been specifically developed in this indication and used to generate robust data to an accepted quality standard and has been granted a Marketing Authorisation for use in this indication. Yet in this evidenced-based appraisal process, "other" 2nd line chemotherapy still take

precedence and remain the implied standard of care. No attempt has been made to justify or even identify what alternative treatment could be considered by clinicians in their attempts to improve outcomes.

The Committee has not responded to direct requests from the manufacturer to share or confirm any information relating to alternatives to Vinflunine in bladder cancer.

This has severely disadvantaged the manufacturer in this process and we have been denied any opportunity to offer a perspective on the unsupported opinion expressed by the Committee.

This is unfair on patients, clinicians as well as the manufacturer.

1.2 The Institute has been unfair in the economic evaluation of vinflunine for patients with urothelial cancer that relapse after prior chemotherapy.

In the context of the deteriorating survival trend in bladder cancer it is actually very encouraging that NICE support the clinical need for 2nd line chemotherapy throughout this FAD. Extending the treatment options will also stimulate earlier identification of relapse and referral. Treating patients with a lower burden of disease increases the chance of gaining control of the disease and enhancing survival further. It is also highly encouraging that 2nd line chemotherapy has been included in the Final Scope for the Clinical Guideline. It is just unfortunate that the choice of chemotherapy is not evidence based.

An obstacle to the use of Vinflunine as the recommended treatment is the perceived cost of Vinflunine compared to BSC. In the economic model, the cost of using chemotherapy – consultation with the doctor, blood tests, chemo suite time, pharmacy time, outpatient cost and side effect management is additional to the cost of the drug. In this case, the cost of Vinflunine is estimated to be £9,817 (2.3)

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and the total incremental cost is £13,071 (3.13) thereby estimating the "fixed" cost of using this chemotherapy to be £3,254.

If "other" chemotherapy is already being used in routine clinical practice, the fixed cost of using Vinflunine would be pre-existing. The incremental cost of a Vinflunine based service would then be reduced by about £3,254 and the cost of the drug that Vinflunine was replacing. This would reduce the incremental cost of a Vinflunine based service by about 25%. Obviously we would need to build this model and would need to know that it would be acceptable to NICE when we did.

The NCRN have recently opened a randomised phase II clinical trial for 2nd line bladder cancer (Trial number CRUKE/11/021, PLUTO) using weekly paclitaxel as the control arm. Paclitaxel has been available in the UK since 1994 and although the clinical evidence in bladder cancer is of generally poor quality and contradictory, it is an old drug and relatively inexpensive to buy. However, the fixed cost of using weekly chemotherapy can be expected to be roughly three times greater than the cost of using Vinflunine (used once every 3 weeks) as the chemo suite, pharmacy and outpatients are all used every week. If the fixed cost of weekly paclitaxel was approaching £10,000, the incremental cost of Vinflunine rapidly diminishes and the use of Vinflunine could easily become cost effective.

It is known that the NCRN were developing this clinical trial (CRUKE/11/021) at the time of this appraisal process. It is inconceivable that the Appraisal Committee were not aware of this trial and that weekly paclitaxel was being used as the control arm as key members of the NCRN Bladder Cancer Group were present at the meeting.

The manufacturer has requested clarification about the identity of the "Other" 2nd line chemotherapy in the FAD and specifically asked if we could use weekly paclitaxel to develop an economic model to adjust for pre-existing fixed costs of using alternative chemotherapy. We have had no response to our requests and have been denied any opportunity to model the cost of the alternative 2nd line treatments that feature in the FAD.

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This is unfair.

Ground 3: The Institute has exceeded its powers

3.1 The Institute has exceeded its powers by reviewing decisions made by the EMEA and MHRA and drawing different conclusions despite not having the data available or the qualifications to so do.

The clinical dossier submitted to the Competent Authority for registration (26,726 pages) was sufficiently detailed to allow appropriate scrutiny and analysis of the efficacy of Vinflunine in bladder cancer. The Competent Authority allocated the appropriate time, resource and expertise to explore this matter fully before reaching their conclusion and granting the Marketing Authorisation for Vinflunine on behalf of all member states.

The "Eligible ITT" analysis arose from this process as the Competent Authority could see that there were a number of patients in study 302 that were clearly not within the agreed target study population because they did not have progressive disease. Despite the number being relatively small (13), the distortion of the statistical analysis was significant because the relative numbers were different in each arm (8% v 2% (section 4.5)) and the expected survival of patients that did not have progressive disease is dramatically longer than the target population for this study (13 months v 4.3 months). All other survival targets, + 2 months (which is 50% longer than that expected with BSC) and the multivariate analysis were met or exceeded. Only the ITT result was an anomaly due to the much greater survival and imbalance in the number of ineligible patients in each arm – a factor that is purely down to chance.

The Eligible ITT analysis was conducted after the data base lock and strictly according to recognised, valid, scientific principles and closely scrutinised by the Competent Authority (MHRA for the EMEA). The eligible ITT is accepted by the Competent Authority and other European Guideline groups as an accurate result from this study. The survival gain is significant and did form the basis for registration in all member states.

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The completed template for the Manufacturer's submission to NICE is 122 pages. Clearly, this could never contain all of the clinical data used in the assessment by the Competent Authority. It was our understanding that NICE did not have the resources needed to replicate the detailed analysis already done by the EMEA, hence only a summary was required. It was expected that NICE would respect and adopt the expert analysis and conclusions made by the EMEA regarding the efficacy of vinflunine and the validity of the eligible ITT analysis.

It remains a surprise that the Appraisal Committee felt qualified to discard this detailed analysis without requesting access to the full data set and repeating the analysis performed by the Competent Authority. They did not have the resources required to repeat this analysis and did not request the detailed data on which the EMEA had based their decisions.

In choosing to discard the opinion and conclusions made by the EMEA, we feel that NICE has exceeded its powers.

Summary

The cancer survival trend for bladder cancer in the UK is terrible and we desperately need new treatments in the clinic to stimulate management and kick start further research.

Vinflunine was tested in a brave and bold study that delivered the target survival gain and extended MS by 60% compared to BSC. It is the first drug to demonstrate a survival gain in advanced or metastatic disease for 30 years and should be made available for clinical use.

The first Appraisal was determined to be unfair but little attempt has been made to address the problems identified and this old Appraisal has now been effectively bullied through with no meaningful change. The manufacturer has attempted to engage with NICE and requested clarification on several points but none has been issued.

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

Managing Director

Pierre Fabre Ltd, Hyde Abbey House, 23 Hyde Street, Winchester, Hampshire, SO23 7DR Tel: -44- (0)1962 874400 Fax: -44- (0)1962 844014 E-Mail: conlaclus@pierre-fabre.co.uk
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