Pierre Fabre Response to the NICE ACD

Vinflunine for TCCU

14 December 2010

Criteria for comments:

- Has all the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?
- Are there any equality-related issues that need special consideration and are not covered in the appraisal consultation document?

Pierre Fabre will elect to comment on the grounds highlighted in Blue.

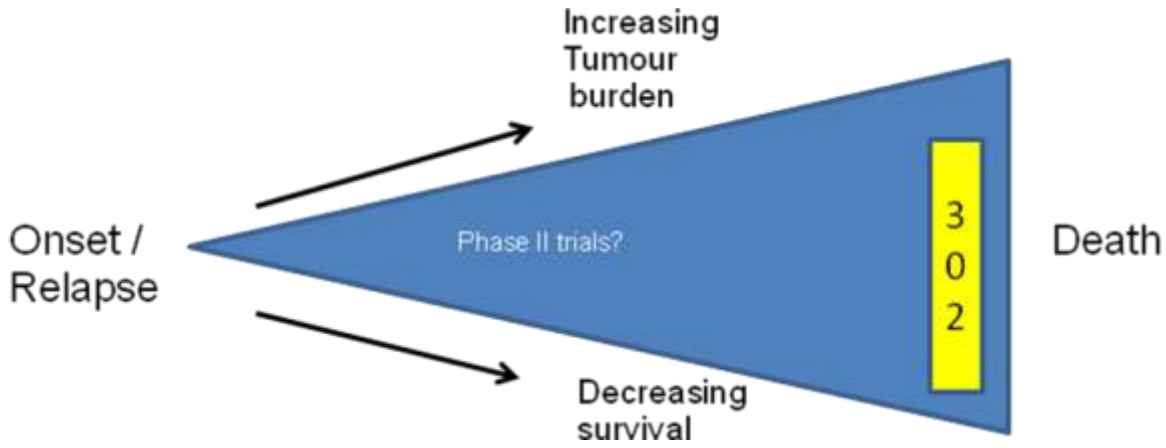
Pierre Fabre would like to express their optimism that a continued dialogue with NICE will allow a greater understanding of the clinical evidence presented in the ACD from the manufacturers submission for vinflunine in Transitional Cell Carcinoma of the Urothelial tract (TCCU) and yield guidance that will form the basis of treatment and commissioning policies to improve patient access to treatment and provide a solid platform for further research in this disease. Patients in the UK already appear to have less access to treatment at this stage of disease compared to other European countries and a clear treatment policy is urgently required.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The suitability of the patient population recruited to the phase III study for vinflunine as a means of describing the improved survival and the appropriateness of BSC as the control arm requires clarification.

The study 302 patient population was defined to allow researchers to report the effect of vinflunine in a scientific approach that could be reproduced in future clinical trials. As noted in the ACD, randomisation to BSC has significant implications regarding the patient population willing to enter this clinical trial. Patients were fit for chemotherapy but willing to accept a randomisation to forgo active treatment for their underlying cancer and the inevitable consequence this brings. Randomisation to BSC therefore attracts patients in a late stage of their cancer journey where survival is short, the burden and extent of disease is high and the available time for drugs to have an effect is short (See Figure 1). This is a patient population with a dreadful prognosis and an expected survival time of only 4 months.

Figure 1



Inclusion and exclusion criteria were set to minimise variability that is otherwise present in such a diverse population so that the clinical effects can be clearly observed. The prognosis

for patients in study 302 (4 months expected survival) was dreadful, despite being of PS 0-1. Deteriorating PS is associated with shortening survival and inclusion of patients with PS $\geq$ 2 would be unfair on participants. Potential inclusion of patients that did not have progressive disease or patients that had prior chemotherapy only as neo-adjuvant or adjuvant would have allowed patients to enter that were further to the left in Figure 1. These patients are expected to survive for longer (as observed in the patients that did not have progressive disease, median survival 13 months). This was not the patient group defined for study 302 and had to be excluded for clear, methodological reasons.

The resulting patient profile confirm that patients had very extensive disease (76% $\geq$ 2 organs involved, 74% visceral involvement) and aggressive disease with 84% having relapsed from first line platinum containing chemotherapy within 6 months or during treatment, making them unsuitable for any re-challenge with platinum treatment. Median survival of 4.3 months in the control arm is very short ("dreadful"), confirming the poor prognosis of patients with this burden of disease.

The patient population in study 302 was dreadfully sick and was at the extreme edge of scientific evaluation. These inclusion/exclusion criteria did not confer any advantage for vinflunine in this trial.

Prior to Study 302, there was no evidence that any chemotherapy agents would improve survival compared to BSC (current NHS standard of care). Study 302 has provided a clearly defined and reproducible patient population and demonstrated a significant survival advantage in an extremely sick patient population. This was a very tough environment in which to test a new drug and exceeding the planned 2 month improvement in median survival in this group of patients is remarkable.

Eligible ITT analysis

We would like to highlight that the statement made in section 4.6 of the ACD that "...results from the ITT population were the most appropriate basis for its deliberations because randomisation had not been broken..." is incorrect. The review of all patients conformed to ICH E9 :

(i) the entry criterion was measured prior to randomisation;

(ii) the detection of the relevant eligibility violations can be made completely objectively;

(iii) all subjects receive equal scrutiny for eligibility violations;

(iv) all detected violations of the particular entry criterion are excluded)

The randomisation was not broken as the violations were not a result of treatment. The OS analysis conducted in the eligible population is a comparison of randomised groups.

Furthermore, non eligible patients were identified using a blinded review before data base lock and all analyses were performed after data base lock.

The eligible population did preserve the ITT principle and is considered as the full analysis set.

The reason that these patients were ineligible was that they did not have progressive disease and this was a fundamental entry criteria for the scientific reasons discussed above. The median survival of the intended patient population was 4 months while the survival of ineligible patients (those without progressive disease) was 13 months, three times longer than the targeted patient group. We would highlight that the exclusion of ineligible patients did not enhance or change the survival of the treatment group. This adjustment corrects a statistical anomaly in the control (BSC) arm caused by a combined effect of 3 x longer survival, 4 x greater number of ineligible patients in the control arm (8% v 1.6%), contrary to an intended 1:2 randomisation. ICH E9 was defined to manage this situation and was properly conducted in a blinded review.

This procedure has been submitted to the EMA and a scientific discussion with the statistical experts allows us to use the Eligible Population. All these data were used to obtain the market authorisation across Europe.

The eligible ITT is a justified and scientific analysis that most accurately describes the impact of vinflunine in this target patient population and its exclusion by the ERG and committee is perverse.

Existing 2nd Line Treatment Service in the NHS

The ACD suggests that there is an existing 2nd line chemotherapy service for NHS patients and that BSC may not have been the most appropriate comparator from which to assess the survival gain with vinflunine. An analysis of the current treatment service for TCCU patients has been documented and discussed through this NICE process and treatment rates can be compared to the clinical need (incidence and mortality). Cancer registry data, the Manufacturer's submission, ERG, expert groups NCRI/RCP/RCR/ACP/JCCO and discussion in the Committee meeting defined the current situation as follows:

	Number of patients	Patients per million population	% of Incidence	Source
Incidence	10,681	194		SW Cancer registry
Mortality	4,949	90	46%	SW Cancer registry
1st line treatment	1,375	25	13%	NCRI, RCP,RCR, ACP, JCCO
2nd line treatment	297	5	2.8%	Discussion at NICE Committee

The estimated number of patients estimated to receive first line chemotherapy by the manufacturer (1,485) was consistent with the expert group (25 patients per million population = 1,375 patients for England and Wales (pop est. 55 million)).

The estimated number of patients treated 2nd line in the manufacturer's submission (742 per year, 13.5 per million) was based on wider European perspective and the Committee, ERG and clinical experts considered this manufacturers estimate to overstate the 2nd line treatment rate "..not by an order of magnitude, but by a factor of 2 or 3 fold", i.e. around 300 patients per year in the whole of England and Wales. This represents 2.8% of the annual incidence and means that only 6% of the 4,949 patients that die from this disease every year have access to 2nd line chemotherapy.

Such a high mortality and relatively low use of life-extending chemotherapy suggests that BSC is the current NHS standard of care for the vast majority of patients. Despite several small phase II trial results using a range of other drugs, there has been no phase III evidence from which to agree clinical guidelines for 2nd line chemotherapy for the NHS.

This may also explain why the clinical experts report that patients have a poor performance status when eventually diagnosed with relapse. When patient management is symptom driven (BSC) there is no clinical advantage to the formal diagnosis of relapse. The introduction of active chemotherapy for a previously unmet clinical need introduces a degree of urgency and purpose for the diagnosis of relapse (e.g. as seen in NSCLC).

Having identified an unmet clinical need with associated high mortality and the first evidence of survival benefit using chemotherapy, it appears that an institute dedicated to clinical excellence should have structured guidance for new and active treatment for patients with TCCU. The adoption of vinflunine in France and Germany already corresponds to 17.5 and 10.6 patients per million population, raising the risk of future survival differences between the NHS and European patients emerging over time.

Economic Evaluation

The economic model produced by the manufacturer has been built to a satisfactory academic standard but could only be populated with estimates of possible resource consumption for a patient population similar to that recruited into Study 302. As, discussed earlier, this was a defined patient population with a prognosis and survival that was towards the "dreadful" side of the expected prognostic range. The planned survival gain in this population was achieved but the additional cost of treatment is amplified to a level that currently places it out of reach for the practising clinician.

The limitations of economic modelling for this patient population with an unmet clinical need were highlighted by dialling in £0 as the cost of vinflunine in the model. The resulting estimated cost of survival was very close to the economic threshold. Based only on this economic approach, it would be impossible to find any treatment that can extend survival for these patients and progress and further research will halt. It is unreasonable to condemn patients to management with BSC because our economic tools are under-developed for previously unmet clinical needs.

This is a small number of patients where research has yielded very few developments. We have, for the first time, evidence of significant survival gain that provides a foundation for

clinical and commissioning guidelines. We know from other tumour types that this will stimulate diagnosis and referral, create care pathways, earlier diagnosis of relapse, PS or stage migration and result in longer survival than that seen in the early trials. This is an active drug which should not be rejected on the basis of economic modelling. Some way to make this available and measure the economic impact should be agreed.

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

The ACD analysed the current NHS clinical service provision for 2nd line chemotherapy for TCCU. Around 4949 patients per year will die from this disease and only around 300 will have access to chemotherapy (6% of mortality rate, 5 patients per million population). The majority of NHS patients are currently managed with BSC and there are no current clinical or commissioning guidelines for managing NHS patients with TCCU at this stage of disease.

Vinflunine is the first treatment approach to demonstrate a survival advantage, even in an extreme patient population at the end of life. This drug is active, prolongs survival and adoption into clinical guidelines will provide the solid foundation for further research, improved diagnostic urgency and will stimulate the overall management at this stage of disease. With nearly five thousand deaths per year there are significant improvements in outcome possible by implementing what we already know about vinflunine, uniformly across the selected NHS population.

Are there any equality-related issues that need special consideration and are not covered in the appraisal consultation document?

The major equality issue that arises from this ACD relates to relative access that NHS patients have compared to elsewhere in Europe. The European Association of Urology Guidelines, 2010 edition; Stenzl et al 2010 have been updated to include vinflunine and implemented elsewhere in Europe.