NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Pierre Fabre	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.	Comment noted. The Committee concluded that the extent of the clinical effectiveness of vinflunine compared with best supportive care had not been conclusively demonstrated because of the uncertainty in the overall survival results. See FAD section 4.2. The Committee concluded that vinflunine could not be considered a cost-effective use of NHS resources for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract that has progressed after treatment with platinum-based chemotherapy. See FAD section 4.14.
	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	Comments noted. The Committee was aware that although patients in study 302 were randomised to receive vinflunine plus best supportive care or best supportive care alone, many of the participants could have been eligible for chemotherapy according to current UK practice. Nevertheless, patients were prepared to pursue a policy of best supportive care in consultation with their clinicians. The committee noted that 30% of the patients in the study went on to receive chemotherapy after disease progression (section 4.5). The Committee heard from the clinical specialists that the study population was younger, fitter and had better renal

Consultee	Comment	Response
	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 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 > 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% > 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.	function than the general population of UK patients with advanced or metastatic transitional cell carcinoma of the urothelial tract. The Committee was also aware that neoadjuvant or adjuvant chemotherapy and concurrent chemoradiotherapy are used as part of radical treatment for localised muscle-invasive transitional cell carcinoma of the urothelial tract. The Committee noted that patients treated in this way had been excluded from study 302. The Committee heard from the clinical specialists that many patients in the UK who are eligible to receive second-line palliative chemotherapy will already have received two lines of treatment (that is, neoadjuvant or adjuvant chemotherapy or concurrent chemoradiotherapy plus first-line palliative chemotherapy). The Committee concluded that there was uncertainty about whether the results of study 302 are generalisable to the use of vinflunine as second-line chemotherapy in UK clinical practice. See FAD section 4.4

Consultee	Comment	Response
	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	Comment noted. The Committee considered that the results from the ITT population were the most appropriate basis for its deliberations because randomisation had not been broken (FAD section 4.6).

Consultee	Comment	Response
	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	Comment noted. The Committee was aware that best

Consultee	Comment	Response
	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)	supportive care was the only comparator listed in the scope for the appraisal. However, the Committee considered comments from the clinical specialists that a number of agents are used for the second-line chemotherapy of advanced or metastatic transitional cell carcinoma of the urothelial tract. The Committee therefore thought it possible that best supportive care could be a comparator for patients presenting with advanced or metastatic disease who may not benefit from currently used second-line chemotherapy regimens because they failed to respond or only had a short-lived response to first-line chemotherapy. See FAD section 4.5.
	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	The Committee was aware that the lack of research on second-line treatments for advanced or metastatic transitional cell carcinoma of the urothelial tract meant there was a significant unmet need for evidence on the treatment of patients whose disease has progressed after platinum-based chemotherapy. It welcomed study 302 as the first randomised controlled trial of a second-line treatment for advanced or metastatic transitional cell carcinoma of the urothelial tract. (FAD section 4.2). However, the Committee concluded that the extent of the clinical effectiveness of vinflunine compared with best supportive care had

Consultee	Comment	Response
	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	not been conclusively demonstrated because of the uncertainty in the overall survival results (FAD section 4.6) The reference case stipulates that decisions on the cost effectiveness of a new technology must include judgements on the implications for healthcare programmes for other patient groups that may be displaced by the adoption of the new technology. See Guide to the Methods of Technology Appraisal section 6.2.13.

Consultee	Comment	Response
	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	Comment noted. NICE has recognised the value of technologies that provide additional benefits to people with poor prognosis by issuing guidance on 'end of life' criteria (See also FAD section 4.14.) The Committee was not persuaded that an extension to life of at least 3 months had been proven, and therefore concluded that the end-of-life advice did not apply to this appraisal. The Committee further noted that even if the end-of-life considerations were taken into account, the most plausible ICER for vinflunine compared with best supportive care was substantially higher than would normally be considered cost effective.

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	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	The Committee welcomed study 302 as the first randomised controlled trial of a second-line treatment for advanced or metastatic transitional cell carcinoma of the urothelial tract. (FAD section 4.2). However, the Committee concluded that the extent of the clinical effectiveness of vinflunine compared with best supportive care had not been conclusively demonstrated because of the uncertainty in the overall survival results (FAD section 4.6). The Committee also noted the large incremental costs of £13,100 for 0.131 QALY gain (FAD section 4.12).
	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	Provision of healthcare and therefore decisions on access to treatments in England and Wales are based on national criteria, and under current equality legislation this is not an equalities issue under relevant equality legislation.

Consultee	Comment	Response
Action on bladder cancer	Thank you for the invitation to comment on the appraisal consultation document (ACD) on vinflunine for the treatment of transitional cell carcinoma of the urothelial tract. The ACD concludes that vinflunine is not recommended for use as second-line chemotherapy in bladder cancer – on the basis of a lack of a clear statistically significant survival benefit over 3 months and a predicted cost per QALY of £120,000. As a group our main concern is that there are numerous references in the document to 'alternative' second-line chemotherapy treatments used in the UK. However, because the main registration study was against best supportive care, these treatments are neither defined nor considered in the economic model. The committee acknowledges that this is the first agent with randomised controlled trial data in this setting yet accepts that it is common practice to offer second-line chemotherapy with agents that are unproven, unlicensed in this setting and have not been through any NICE appraisal themselves. When calculating the cost effectiveness of vinflunine, although it may seem reasonable to compare with best supportive care (BSC) as in the trial, in reality these patients are often given unproven chemotherapy which is likely to entail significant cost over that of BSC. The lack of a proven and approved second-line chemotherapy has led to diverse practice within the uro-oncology community. Patients with metastatic bladder cancer are disadvantaged by the lack of a second line treatment option. Study 302 is the first trial to show a survival benefit and we feel that vinflunine should be available for this relatively small group of patients	Comment noted. The Committee was aware that best supportive care was the only comparator listed in the scope for the appraisal. However, the Committee considered comments from the clinical specialists that a number of agents are used for the second-line chemotherapy of advanced or metastatic transitional cell carcinoma of the urothelial tract. It understood that the evidence base for these agents consisted of small, often single-institution, phase II studies of selected patients and that considerable publication bias was likely to exist. The Committee was also aware that although patients in study 302 were randomised to receive vinflunine plus best supportive care or best supportive care alone, the patient population was fit and many of the participants could have been eligible for chemotherapy according to current UK practice. Nevertheless, patients were prepared to pursue a policy of best supportive care in consultation with their clinicians. The Committee thought it possible that best supportive care could be a comparator for patients presenting with advanced or metastatic disease who may not benefit from currently used second-line chemotherapy regimens because their disease failed to respond or only had a short-lived response to first-line chemotherapy. See FAD section 4.5.

Consultee	Comment	Response
British Uro-oncology Group	We are pleased to comment on the appraisal consultation document (ACD) on vinflunine for the treatment of transitional cell carcinoma of the urothelial tract. The ACD states that vinflunine is not recommended for the indication – on the basis of a lack of a clear statistically significant survival benefit and a predicted cost per QALY of £120,000. It is a concern that there's frequent mention of 'alternative' second-line chemotherapy treatments used in the UK, but because the main registration study was against best supportive care, these treatments are neither defined nor considered in the economic model. An additional issue is that although second-line treatments are currently given in the UK, they are off-licence treatments. Vinflunine therefore is the only drug with a randomised controlled trial and licensed indication in this setting which was emphasised at the NICE appraisal.	Comment noted. The Committee was aware that best supportive care was the only comparator listed in the scope for the appraisal. However, the Committee considered comments from the clinical specialists that a number of agents are used for the second-line chemotherapy of advanced or metastatic transitional cell carcinoma of the urothelial tract. It understood that the evidence base for these agents consisted of small, often single-institution, phase II studies of selected patients and that considerable publication bias was likely to exist. The Committee was also aware that although patients in study 302 were randomised to receive vinflunine plus best supportive care or best supportive care alone, the patient population was fit and many of the participants could have been eligible for chemotherapy according to current UK practice. Nevertheless, patients were prepared to pursue a policy of best supportive care in consultation with their clinicians. The Committee thought it possible that best supportive care could be a comparator for patients presenting with advanced or metastatic disease who may not benefit from currently used second-line chemotherapy regimens because their disease failed to respond or only had a short-lived response to first-line chemotherapy. See FAD section 4.5. See FAD section 4.2. The Committee was aware that the lack of research on second-

Consultee	Comment	Response
	With the current financial climate, there is likely to be pressure to only use "licensed" drugs and so as vinflunine is licensed for this indication, despite the fact that it seems no better or worse than many of the other drugs used second line, it would at least be giveable on the basis of a drug licensed in this setting whereas purchasers may stop us using the other agents we may use currently	line treatments for advanced or metastatic transitional cell carcinoma of the urothelial tract meant there was a significant unmet need for evidence on the treatment of patients whose disease has progressed after platinum-based chemotherapy. It welcomed study 302 as the first randomised controlled trial of a second-line treatment for advanced or metastatic transitional cell carcinoma of the urothelial tract.
Royal college of Physicians and NCRI/RCP/RCR/ACP/JCCO	We believe that section 4 is largely a balanced account of the major points raised by the clinical experts present at the appraisal meeting. It also adequately covers the questions they answered. The only exception to this would be the portion of section 4.5, which states that 'vinflunine might be used more commonly as a third-line rather than a second-line treatment for advanced or metastatic transitional cell carcinoma of the urothelial tract. This is because patients whose disease relapses after a response to first-line platinum-based chemotherapy would usually receive a further platinum treatment before an alternative agent was tried'. We do not believe that the above statement is an adequate reflection of what was said at the meeting, nor what the UK oncology community would consider accurate. Vinflunine might well be considered a third-line choice, but more because there are other 2nd-line agents which we consider to have a therapeutic index which is as	Comment noted. The FAD has been amended to reflect this – see FAD section 4.5.

Consultee	Comment	Response
	good or better, rather than the desire to use another platinum-based regimen. Confusion may have arisen around this point due to the situation where metastatic relapse is a considerable time after platinum-based neoadjuvant chemotherapy, where one might be inclined to use 're-challenge' platinum as first-line therapy for advanced disease. The misleading statement is also repeated as one of the 'key conclusions' in the summary. On balance, we believe it would be worth correcting this. The statement in the summary of 4.4 (bottom of page 23) states that 'Most patients in the UK receive systemic chemotherapy with radical treatment'. This is incorrect and we strongly recommend that the word 'most' is replaced by the word 'many' (which is the word actually used in section 4.4 itself). One important point raised by our clinical experts (and also by the experts at the appraisal meeting) was that the 302 data are imperfect but, nonetheless, are the best data available at present. This receives a tangential mention at the end of Section 4.2 and a slightly more direct one in 6.1 (as correctly stated). It may be that this point should receive greater emphasis within the FAD	Comment noted. The FAD has been amended to reflect this – see FAD section 4.4. Comment noted.
NHS Norfolk	We would strongly agree with section 4.6 as the primary outcome of the pivotal trial was not significant: The Committee also noted that the difference in overall survival between the study arms was not statistically significant for the ITT population, but was significant for the eligible ITT population. The	Comments noted.

Consultee	Comment	Response
	Committee was aware that the difference between the two analyses resulted from the exclusion of 13 patients from the eligible ITT analysis. A greater proportion of ineligible patients came from the best supportive care arm than from the vinflunine arm (8% versus 2%) and this lowered the overall survival in the best supportive care arm in the eligible ITT analysis. The Committee considered that the results from the ITT population were the most appropriate basis for its deliberations because randomisation had not been broken and therefore the trial reflected what is likely to happen in clinical practice. It also noted that there were no significant differences in health-related quality of life between patients receiving vinflunine and those receiving best supportive care alone. The Committee concluded that the clinical effectiveness of vinflunine compared with best supportive care had not been conclusively demonstrated because of the uncertainty in the overall survival results We would also endorse the comments in 4.11: The Committee discussed the inclusion of adverse events in the model and noted that although the costs of adverse events were included, the disutility associated with them was not. It discussed the cost of grade 3 and 4 constipation and considered that it was likely to be significantly higher than that used in the model (£39). We believe that the treatment costs for adverse effects to be higher than that estimated – not just for constipation – but also for neutropenia, as it would appear that the HRG used to estimate the neutropenia costs does not take into account the excluded drug costs for the management of febrile neutropenia. Finally we would also query the acceptance that the number of people likely to require second line therapy as estimated by the manufacturer	Comment noted. The Committee discussed the number of UK patients for whom vinflunine is licensed, estimated by the manufacturer to be about 800–1500, and concluded that this could be considered a small patient population.

Consultee	Comment	Response
	(1500) is a small population (as per NICE end of life criteria). Nationally about 10,000 patients a year are diagnosed with this form of cancer (according to Horizon Scanning centre) with c.4000 deaths. It's likely therefore that more than 1500 cited by the manufacturer and this would need further clarification	

Comments received from clinical specialists and patient experts

None received