NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance
Published: 23 January 2013

www.nice.org.uk/guidance/ta272

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Vinflunine is not recommended within its marketing authorisation for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract that has progressed after treatment with platinum-based chemotherapy.

1.2 People currently receiving vinflunine that is not recommended according to section 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop.

2 The technology

2.1 Vinflunine (Javlor, Pierre Fabre) is a chemotherapeutic agent belonging to the vinca-alkaloid class of drugs. Vinflunine has a marketing authorisation for use as 'monotherapy for the treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen'. The summary of product characteristics (SPC) notes that vinflunine has not been studied in patients with a performance status of 2 or more.

2.2 According to the SPC, common undesirable effects associated with vinflunine include haematological disorders (neutropenia and anaemia), gastrointestinal disorders (constipation, nausea, stomatitis, vomiting, abdominal pain and diarrhoea), and general disorders (asthenia or fatigue). For full details of side effects and contraindications, see the SPC.

2.3 The SPC states that the recommended dosage of vinflunine is 320 mg/m^2 as a 20-minute intravenous infusion every 3 weeks. The SPC also states that in patients with a World Health Organization (WHO) and Eastern Cooperative Oncology Group (ECOG) performance status of 1 or of 0 who have had pelvic irradiation, treatment should be started at a dose of 280 mg/m^2; in the absence of any haematological toxicity during the first cycle causing treatment delay or dose reduction, the dosage can be increased to 320 mg/m^2 every 3 weeks for the subsequent cycles. The SPC states that monitoring of complete blood counts should be conducted before each treatment cycle, and that oral hydration and laxatives should be given during each cycle. Vinflunine is available in 50 mg and 250 mg vials, costing £212.50 and £1,062.50 respectively (excluding VAT; BNF edition 64). The acquisition cost of vinflunine for an entire course of treatment is £9,817.50, assuming an average of 4.2 cycles, a dose of 287 mg/m^2 and a body surface area of 1.85 m^2 (see section 3.10). Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee considered evidence submitted by the manufacturer of vinflunine and a review of this submission by the Evidence Review Group (ERG).

3.1 The main evidence for the clinical effectiveness of vinflunine was from 1 open-label, phase 3, randomised controlled trial (study 302, the registration trial) that compared vinflunine plus best supportive care with best supportive care alone in patients with advanced or metastatic transitional cell carcinoma of the urothelial tract whose disease had progressed after platinum-based chemotherapy. Results from 2 open-label, single-arm, phase 2 studies (study 202 and CA001) were also provided. The manufacturer's submission highlighted issues around using best supportive care alone as the control arm in study 302. In particular, patients had to be fit enough to receive chemotherapy but willing to accept randomisation to best supportive care. The manufacturer stated that patients in the trial had a poorer prognosis, as indicated by the high percentage (approximately 74%) of patients with visceral involvement in both groups in the trial. The manufacturer also highlighted that there is currently no standard chemotherapy regimen for patients with advanced transitional cell carcinoma of the urothelial tract whose disease has progressed after a prior platinum-containing chemotherapy, and there is a lack of trial evidence of survival advantage from chemotherapy in this clinical situation. Therefore, no standard active treatments were available to use as a control, and best supportive care was considered the most appropriate comparator for vinflunine.

3.2 Patients were included in study 302 if they had progressive disease after at least 2 cycles of platinum-based first-line chemotherapy (or after 1 cycle if there was clear evidence of disease progression at this point), an ECOG performance status of 0 or 1, and an estimated life expectancy of at least 12 weeks. Previous systemic chemotherapy must have been stopped at least 30 days before randomisation. Patients were excluded if they had received more than 1 previous systemic chemotherapy for advanced or metastatic disease, or if they had been treated with neoadjuvant or adjuvant chemotherapy. Patients were randomised on a 2:1 basis to vinflunine plus best supportive care (hereafter called the vinflunine arm) or best supportive care alone (hereafter called the best supportive care arm). Patients in the vinflunine arm initially received 320 mg/m^2

every 21 days via infusion, but the protocol was subsequently amended to allow a lower starting dose (280 mg/m^2) in patients at greater risk of haematological toxicity. Best supportive care included palliative radiotherapy, antibiotics, analgesics, corticosteroids and blood transfusions.

3.3 A total of 370 patients were enrolled into the study (253 in the vinflunine arm and 117 in the best supportive care arm). The median age of study participants was 64 years, and 79% were male. Most baseline characteristics were similar across the 2 treatment arms. However, a greater proportion of patients in the vinflunine arm had an ECOG performance status of 1 compared with the best supportive care arm (72% and 62% respectively) although this difference was not statistically significant. Cisplatin was the most common first-line platinum treatment and had been received by more patients in the best supportive care arm than in the vinflunine arm (73% and 65% respectively), although this difference was not statistically significant. More patients in the vinflunine arm than in the best supportive care arm had received carboplatin as first-line platinum treatment (30% and 20% respectively; p=0.044).

3.4 Study results were provided for 4 study populations, only 2 of which are presented here: the intention-to-treat (ITT) population, which included all randomised patients, and the 'eligible ITT population'. The latter excluded 13 patients who were found, upon retrospective review of the patient inclusion criteria, not to have progressive disease at the time of entry into the study, and who therefore should not have been randomised (4 patients in the vinflunine arm and 9 in the best supportive care arm; 3 of the 4 excluded patients in the vinflunine arm and 6 of the 9 excluded patients in the best supportive care arm were also ineligible because they had received neoadjuvant or adjuvant chemotherapy). The primary outcome of study 302 was median overall survival. For the ITT population, this was 6.9 months in the vinflunine arm compared with 4.6 months in the best supportive care arm (hazard ratio [HR] 0.88, 95% confidence interval [CI] 0.69 to 1.12, p=0.2868). A pre-planned multivariate analysis, adjusting for a number of prognostic factors (performance status, visceral invasion, alkaline phosphatase, haemoglobin and prior pelvic irradiation), showed a statistically significant overall survival benefit for vinflunine (HR 0.77, 95% CI 0.61 to 0.98, p=0.036). For the eligible ITT population, median overall survival was 6.9 months in the vinflunine arm and 4.3 months in the best supportive care arm (HR 0.78, 95% CI 0.61 to 0.99, p=0.0403). An extended

multivariate analysis was also done, adjusting for the same prognostic factors outlined above plus additional baseline characteristics such as age, sex and disease stage at diagnosis. This analysis also showed a statistically significant overall survival benefit for vinflunine (HR 0.68, 95% CI 0.52 to 0.88, p=0.0035).

3.5 Progression-free survival for the ITT population was 3.0 months in the vinflunine arm compared with 1.5 months in the best supportive care arm (HR 0.68, 95% CI 0.54 to 0.86, p=0.0012). In the vinflunine arm, 46.5% of patients had stable disease after second-line treatment, 44.9% had progressive disease, and 8.6% had a partial or complete response. In the best supportive care arm, 27% of patients had stable disease, 73% had progressive disease, and none had a partial or complete response. These outcomes were not reported for the eligible ITT population. After disease progression, 29% of patients in the vinflunine arm and 34% of patients in the best supportive care arm received palliative chemotherapy; 60% of these re-treated patients received multi-agent chemotherapy.

3.6 Quality of life was assessed using the cancer-specific European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire. This was done at study entry and at the end of cycles 1, 2, 4 and 6 for both arms. There were no statistically significant differences in overall EORTC QLQ-C30 global health status score between the 2 arms (p=0.658).

3.7 In the 2 phase 2, single-arm trials (study 202 and CA001), vinflunine was given every 21 days at a dose of 320 or 280 mg/m^2. In study 202 (n=58), the overall response rate (partial or complete response) was 18%, median progression-free survival was 3 months (95% CI 2.4 to 3.8 months) and median overall survival was 6.6 months (95% CI 4.8 to 7.6 months). In CA001 (n=151), the overall response rate was 14.6% (95% CI 9.4% to 21.2%), median progression-free survival was 2.8 months (95% CI 2.6 to 3.8 months) and median overall survival was 7.9 months (95% CI 6.7 to 9.7 months).

3.8 The most common adverse events (any grade) associated with vinflunine across the 3 phase 2 and phase 3 studies (n=450) were constipation (55%), nausea (41%), infusion-site reactions (28%), stomatitis or mucositis (27%) and vomiting (27%). Overall, there were 6 deaths related to treatment (1.3%), of which 4 were a result of myelotoxicity. Four treatment-related deaths occurred in the vinflunine

arm of study 302. Grade 3 or 4 toxicities relating to neutropenia, anaemia and constipation occurred in 50%, 19% and 16% respectively of patients in the vinflunine arm of study 302, compared with 1%, 8% and 1% of patients respectively in the best supportive care arm. Febrile neutropenia occurred in 6% of patients receiving vinflunine (none in the best supportive care arm).

3.9 The manufacturer submitted an economic analysis comparing vinflunine plus best supportive care with best supportive care alone. The manufacturer's model was similar to a Markov cohort model in that it included 3 health states: pre-progression, post-progression and dead. The model calculated the proportion of patients expected to be in each health state, based on the estimated survival curves for the eligible ITT population from study 302. The model assumed that treatment is administered in cycles of 21 days until disease progression, major toxicity or other reason for treatment discontinuation, or death (if occurring before progression). All patients are assumed to be in a pre-progression health state at model entry (baseline). Patients who experience disease progression are assumed to stop treatment with vinflunine and remain in the post-progression state until death. The cycle length of the model was 1 day and the time horizon was 5 years.

3.10 Costs of vinflunine were based on the mean dose (287 mg/m^2), the mean body surface area (1.85 m^2) and the mean number of treatment cycles (4.2) in study 302. Other treatment costs included administration for intravenous infusion every 21 days in an outpatient setting, complete blood count before drug administration and constipation prophylaxis. Drug wastage was assumed to be zero in the base-case analysis. The total per-patient cost of treatment with vinflunine included in the model was £10,207. Costs for 3 common adverse events were included in the model: constipation (£39; based on 1 GP consultation and 1 pack of laxatives), febrile neutropenia resulting in hospitalisation (£3,538; NHS HRG [healthcare resource group] costs) and abdominal pain resulting in hospitalisation (£557; NHS HRG costs).

3.11 Costs for best supportive care were calculated for the pre-progression and post-progression health states. For the pre-progression health state, best supportive care included: home visits by a GP, community nurse, health home visitor and dietician, an oncologist follow-up visit (assumed to be the same for each treatment group) and palliative radiation therapy (which differed by treatment

group). For the post-progression health state, best supportive care included home visits by a GP, community nurse, health home visitor and dietician, a non-consultant oncologist follow-up visit, hospice care, pain medication (assumed to be the same for each treatment group), and palliative radiation therapy and palliative chemotherapy (which differed by treatment group).

3.12 The pre-progression utility values used in the manufacturer's submission were based on responses to 1 item from the EORTC QLQ-C30 questionnaire used in study 302, which asked patients to rate their overall quality of life in the previous week. Responses were transformed to health-state utilities using a published regression model relating this measure to utility values from a time-trade-off analysis in a sample of US cancer patients and their relatives. Post-progression utility values were taken from a study reporting EQ-5D values in 1270 terminally ill cancer patients with painful bone metastases or poor-prognosis non-small-cell lung cancer. Disutility values associated with treatment-related adverse events were not included in the model.

3.13 In the manufacturer's base case, the incremental cost-effectiveness ratio (ICER) for vinflunine plus best supportive care compared with best supportive care alone was £100,144 per quality-adjusted life year (QALY) gained (incremental cost of £13,071 and incremental benefit of 0.131 QALYs). The manufacturer's deterministic sensitivity analyses showed that vial price and pre-progression utility values had the greatest impact on the base-case ICER. When a vial price of £0 was used, the ICER was £27,478 per QALY gained. When a pre-progression utility of 0.4 was used (instead of 0.65), the ICER was £133,094 per QALY gained. The ICER was also sensitive to assumptions about the number of vinflunine treatment cycles (£70,233 per QALY gained when 3 cycles were costed) and vial wastage (£121,095 per QALY gained when wastage was accounted for). The manufacturer's probabilistic sensitivity analysis suggested that vinflunine had a 6% probability of being cost effective at a threshold of £30,000 per QALY gained when compared with best supportive care alone.

3.14 The ERG considered the modelling approach and model structure used by the manufacturer to be appropriate and reasonable; however, it commented on a number of areas of uncertainty. The ERG stated that the modelled population reflected that of the pivotal trial (study 302) but may not be representative of the majority of patients whose disease progresses after first-line therapy. This was

because patients who had received prior neoadjuvant or adjuvant platinum-based chemotherapy had been excluded from the trial. The ERG commented that best supportive care may not be the most appropriate comparator because alternative second-line treatments are available in UK clinical practice. However, the ERG noted that best supportive care was the comparator specified in the scope for the appraisal, and that there are no randomised controlled trials of relevant comparators for the population of interest. The ERG stated that data from the ITT population of study 302 may have been a more appropriate basis for the economic model than the data from the eligible ITT population that were used by the manufacturer. It also stated that the utility values used did not fit with the preferred NICE reference case, and that there is considerable uncertainty around these estimates because standard methods were not used. The ERG also compared the overall survival curve for vinflunine used in the manufacturer's economic model with that obtained using Kaplan–Meier estimates. It concluded that the most realistic results were those obtained using the Kaplan–Meier estimates, although it noted that the choice of survival curve did not have a significant impact on the cost effectiveness of vinflunine in the manufacturer's sensitivity analysis.

3.15 The ERG conducted an exploratory analysis using the confidence intervals around the modelled estimates of overall survival and progression-free survival. This resulted in ICERs ranging from £87,871 to £117,938 per QALY gained. In a separate exploratory analysis the ERG used estimates of progression-free survival and overall survival from the ITT population of study 302 (rather than the eligible ITT population) and corrected an error in the manufacturer's model in which the vinflunine vial cost was entered incorrectly. The resulting ICER was £99,792 per QALY gained when the manufacturer's method of estimating survival was used, and £126,422 per QALY gained when Kaplan–Meier estimates based on trial data for the ITT population were used.

3.16 Full details of all the evidence are in the manufacturer's submission and the ERG report.

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of vinflunine, having considered evidence on the nature of transitional cell carcinoma of the urothelial tract and the value placed on the benefits of vinflunine by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.2 The Committee considered current UK practice for the treatment of patients with advanced or metastatic transitional cell carcinoma of the urothelial tract. It heard from clinical specialists that patients with localised muscle-invasive disease who are fit enough usually undergo either radical surgery (frequently preceded by neoadjuvant chemotherapy) or radical radiotherapy with concurrent chemotherapy. For patients whose disease progresses after radical treatment, platinum-based chemotherapy may be given to improve survival and quality of life. The clinical specialists stated that there is currently no standard treatment for patients whose disease relapses after first-line chemotherapy for advanced disease and who are fit enough to receive further treatment, although a number of agents may be used. They commented that there is general agreement that this patient group can benefit from second-line treatment, particularly if their disease has shown a good response to previous chemotherapy, and therefore would not usually receive palliative care alone. The clinical specialists stated that there was no comparative evidence on the use of any agents for the second-line chemotherapy of advanced or metastatic transitional cell carcinoma of the urothelial tract and that studies in this setting would be welcomed. 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.

Clinical effectiveness

4.3 The Committee considered the clinical evidence on the use of vinflunine for the second-line chemotherapy of patients with advanced or metastatic transitional cell carcinoma of the urothelial tract. It noted there was only 1 randomised clinical trial (study 302), and that this compared vinflunine with best supportive care alone. The Committee was aware that best supportive care was the only comparator listed in the scope for the appraisal. It was also aware that there are no proven standard agents for second-line chemotherapy (see section 4.2). For these reasons, the Committee concluded that best supportive care was the appropriate comparator for vinflunine.

4.4 The Committee discussed whether the population in study 302 was representative of patients with advanced or metastatic transitional cell carcinoma of the urothelial tract who would receive vinflunine in UK clinical practice. It heard from the clinical specialists that the study population was younger, fitter and had better renal 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 chemotherapy, adjuvant chemotherapy and concurrent chemotherapy and radiotherapy are all 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 2 lines of treatment (that is, neoadjuvant chemotherapy, adjuvant chemotherapy or concurrent chemotherapy and radiotherapy, plus first-line palliative chemotherapy). Finally, the Committee noted that the manufacturer considered the trial population to be only people with a poor prognosis. The Committee understood that this was because 74% of people in the trial had visceral involvement, and because it was unlikely that people with a better prognosis would be willing to be randomised to a trial in which one of the treatment options was best supportive care. The Committee noted that the marketing authorisation for vinflunine is for all patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen. The manufacturer was invited to submit further evidence for vinflunine in the whole licensed patient population compared with best supportive care, but no data were submitted for the

Committee to consider. The Committee considered whether the evidence from study 302 might be generalisable to the full licensed population. It was mindful of clinical specialists' comments regarding the differences in the characteristics and treatment pathway of patients in the trial compared with patients in UK clinical practice. The Committee was not persuaded that the evidence for the effectiveness of vinflunine would be generalisable to the whole population who might receive vinflunine in UK clinical practice, compared with best supportive care. However, the Committee was aware that study 302 was the only available evidence on which a decision could be based. The Committee concluded that the nature and availability of the evidence base would result in significant uncertainty regarding the effectiveness of vinflunine for the whole licensed population compared with best supportive care.

4.5 The Committee discussed the results of study 302. It noted that vinflunine was associated with improved progression-free survival and a higher disease control rate (defined as the percentage of patients with a complete response, a partial response or stable disease) compared with best supportive care alone. 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 Committee was aware that the difference between the 2 analyses resulted from the exclusion of 13 patients from the ITT analysis because they had not been shown to have progressive disease after prior therapy. 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. 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 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.

4.6 The Committee discussed the most common adverse events associated with vinflunine, namely constipation, anaemia, stomatitis and infusion-site reactions. It noted that grade 3 or 4 constipation occurred in 16% of patients receiving

vinflunine. It was aware that grade 4 constipation can lead to intestinal obstruction or acute abdominal distension requiring hospitalisation. The Committee also noted the 6% incidence of febrile neutropenia in the vinflunine arm of the study. The clinical specialists stated that the safety profile of second-line chemotherapy in this setting needed to be predictable, acceptable to patients and manageable, and that they had concerns about vinflunine in this regard. The Committee concluded that there were concerns about the tolerability of vinflunine.

Cost effectiveness

4.7 The Committee reviewed the economic model submitted by the manufacturer and the ERG's critique of the model. The Committee was aware that the costs for the intravenous administration of vinflunine included in the manufacturer's model were based on out-of-date NHS HRG figures which were lower than current estimates. The Committee considered the manufacturer's lack of inclusion of vial wastage in the model to be inappropriate because of the small number of patients who would be treated with vinflunine at any one centre and time. The Committee concluded that the costs of treatment with vinflunine had been underestimated in the manufacturer's model.

4.8 The Committee discussed the utility values used in the manufacturer's model. It noted that different methods of estimating utilities were used for the post-progression and pre-progression health states. It noted that the utility for the post-progression health state was taken from a study of patients with lung cancer. The pre-progression utility was based on answers to 1 of the 30 questions in the EORTC questionnaire, which asked patients to rate their overall quality of life during the past week. The questionnaire was administered at the end of each treatment cycle. The Committee noted clinical specialist opinion that quality of life varies considerably between 2 consecutive clinic visits. It therefore considered that this question may have to be interpreted with caution because a patient's quality of life in the last week of a treatment cycle may not reflect their quality of life for the whole period before disease progression. It also noted that established algorithms for mapping EORTC responses to EQ-5D exist but were not used by the manufacturer. The Committee noted that neither utility used in the economic model conformed to the preferred NICE reference case and

concluded that the lack of appropriate utility data contributed to uncertainty in the model.

4.9 The Committee discussed the data on clinical effectiveness used in the model. It was aware that various hazard ratios of overall survival had been reported depending on the population analysed and the type of analysis used (multivariate analysis or extended multivariate analysis). The Committee noted that the modelled hazard ratios were based on the multivariate analysis of the results for the eligible ITT population and that these results were more favourable for vinflunine than those obtained from the ITT population. The Committee had previously concluded (see section 4.5) that the results from the ITT population were the most appropriate for this appraisal. It therefore concluded that the survival benefit of vinflunine compared with best supportive care alone was likely to be overestimated in the manufacturer's model.

4.10 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 costs for grade 3 and 4 constipation, and considered that these were likely to be significantly higher than the cost for constipation used in the model (£39).

4.11 The Committee discussed the manufacturer's base-case ICER of £100,100 per QALY gained (incremental cost of £13,100 and incremental QALYs of 0.131). It noted that in the manufacturer's sensitivity analyses the inclusion of vial wastage and the use of a lower pre-progression utility value increased the ICER significantly from the base case (to £121,100 and £133,100 per QALY gained respectively). It also noted that in the ERG's exploratory analysis, based on Kaplan–Meier estimates of survival from the ITT population rather than the eligible ITT population, the ICER was £126,400 per QALY gained. The Committee considered the most plausible ICER to be above £120,000 per QALY gained. It further considered that additional uncertainties around the costs of adverse events and the modelling of survival data would increase the ICER.

4.12 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the

following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- The treatment is licensed or otherwise indicated for small patient populations.

  In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of the extension to life are robust and the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.13 The Committee considered that the life expectancy of patients with advanced or metastatic transitional cell carcinoma of the urothelial tract whose disease has progressed after first-line chemotherapy is usually less than 6 months. It discussed the number of UK patients for whom vinflunine is licensed, estimated by the manufacturer to be about 800 to 1,500, and concluded that this could be considered a small patient population. The Committee discussed the extension to life offered by vinflunine in the study populations. In the manufacturer's model, the overall survival benefit of vinflunine was 3.2 months. However, the overall survival benefit based on the trial results was 2.3 months in the ITT population (not statistically significant) and 2.6 months in the eligible ITT population. 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 (above £120,000 per QALY gained) was substantially higher than would normally be considered cost effective. The Committee was mindful of the limitations of the evidence base for vinflunine in the whole licensed population of patients who may receive treatment with vinflunine in UK clinical practice compared with best supportive care. However, the Committee was conscious of uncertainty in the overall survival results for vinflunine from the available evidence (see section 4.5), and the exceptionally

high ICER which was based on this evidence. On balance, the Committee did not consider it plausible that additional evidence, even if available, would demonstrate the magnitude of survival gain which would be required to bring the cost effectiveness of vinflunine to a level considered an acceptable use of NHS resources. Therefore, 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.

5 Recommendations for further research

5.1 The Committee noted the need for research on second-line treatments for transitional cell carcinoma of the urothelial tract. It noted that the vinflunine studies were the only studies in patients with transitional cell carcinoma of the urothelial tract whose disease had progressed after platinum-based chemotherapy. The Committee noted the lack of evidence for the relative effectiveness of treatment options at this stage in the pathway of care. It recommended that studies be undertaken to investigate the relative safety and efficacy of second-line treatments for transitional cell carcinoma of the urothelial tract, particularly randomised controlled trials.

6 Appraisal Committee members and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Darren Ashcroft
Professor of Pharmacoepidemiology, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Dr Matthew Bradley
Value Demonstration Director, AstraZeneca

Dr Brian Buckley
Lay member

Professor Usha Chakravarthy
Professor of Ophthalmology and Vision Sciences, Queen's University of Belfast

Professor Peter Clark (Chair)
Consultant Medical Oncologist, Clatterbridge Centre for Oncology

Dr Ian Davidson
Lecturer in Rehabilitation, University of Manchester

Dr Martin Duerden
Assistant Medical Director, Betsi Cadwaladr University Health Board

Dr Alexander Dyker
Consultant Physician, Wolfson Unit of Clinical Pharmacology, University of Newcastle

Gillian Ells
Prescribing Advisor, NHS Sussex Downs and Weald

Dr Jon Fear
Consultant in Public Health Medicine, Head of Healthcare Effectiveness NHS Leeds

Paula Ghaneh
Senior Lecturer and Honorary Consultant, University of Liverpool

Niru Goenka
Consultant Physician, Countess of Chester NHS Foundation Trust

Dr Susan Griffin
Research Fellow, Centre for Health Economics, University of York

Professor Carol Haigh
Professor in Nursing, Manchester Metropolitan University

Alison Hawdale
Lay member

Professor Peter Jones
Emeritus Professor of Statistics, Keele University

Dr Vincent Kirkbride
Consultant Neonatologist, Regional Neonatal Intensive Care Unit, Sheffield

Dr Rachel Lewis
Doctoral Researcher, Manchester Business School

Dr Anne McCune
Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

Professor Jonathan Michaels (Vice Chair)
Professor of Vascular Surgery, University of Sheffield

Dr Neil Milner
General Medical Practitioner, Tramways Medical Centre

Professor Femi Oyebode
Professor of Psychiatry and Consultant Psychiatrist, The National Centre for Mental Health

Dr John Radford
Director of Public Health, Rotherham Primary Care Trust

Dr Phillip Rutledge
GP and Consultant in Medicines Management, NHS Lothian

Dr Brian Shine
Consultant Chemical Pathologist, John Radcliffe Hospital

Dr Murray D Smith
Associate Professor in Social Research in Medicines and Health, University of Nottingham

Paddy Storrie
Lay member

Dr Cathryn Thomas
GP and Associate Professor, University of Birmingham

Charles Waddicor
Chief Executive, NHS Berkshire

Mike Wallace
Health Economics and Reimbursement Director, Johnson & Johnson Medical Ltd

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Mary Hughes
Technical Lead

Joanne Holden
Technical Adviser

Rebecca Pye
Project Manager

7 Sources of evidence considered by the Committee

The Evidence Review Group (ERG) report for this appraisal was prepared by Southampton Technology Assessments Centre:

- Cooper K, Frampton G, Mendes D, Bryant J, Vinflunine for the second line treatment of transitional cell carcinoma of the urothelial tract, September 2010

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Manufacturers or sponsors were also invited to make written submissions. Professional or specialist and patient or carer groups, and other consultees, had the opportunity to give their expert views. Manufacturers or sponsors, professional or specialist and patient or carer groups, and other consultees, also have the opportunity to appeal against the final appraisal determination.

Manufacturers or sponsors:

- Pierre Fabre

Professional or specialist and patient or carer groups:

- Macmillan Cancer Support
- British Uro-oncology Group (BUG)
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians, Medical Oncology Joint Special Committee
- United Kingdom Oncology Nursing Society

Other consultees:

- NHS Bury

- Department of Health
- NHS Norfolk
- Welsh Assembly Government

Commentator organisations (did not provide written evidence and without the right of appeal):

- British National Formulary
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- NHS Quality Improvement Scotland
- Institute of Cancer Research
- Southampton Health Technology Assessment Centre
- National Institute for Health Research Health Technology Assessment Programme

The following individuals were selected from clinical specialist nominations from the non-manufacturer consultees and commentators. They gave their expert personal view on vinflunine by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Alison Birtle, Consultant Clinical Oncologist, Royal Preston Hospital, nominated by British Uro-oncology Group – clinical specialist
- Dr John Chester, Honorary Consultant in Medical Oncology, Leeds Institute of Molecular Medicine, nominated by Royal College of Physicians – clinical specialist
- Dr Tony Elliott, Consultant Clinical Oncologist, The Christie Hospital, nominated by Royal College of Physicians – clinical specialist

Representatives from the following manufacturer attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Pierre Fabre

ISBN: 978-1-4731-6731-5