NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

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

> This briefing presents the key issues arising from the manufacturer's submission, Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that this briefing is a summary of the information available and should be read with the full supporting documents.

The manufacturer was asked to provide:

- clarification of the inclusion and exclusion criteria for the literature review

- levels of statistical significance for differences in baseline characteristics between the study arms of the pivotal clinical trial

- clarification of primary and secondary outcomes in the trial

- a rationale for and clarification of the methodology and analyses in the pivotal clinical trial (such as information about the censoring method, and the reason for the superiority hypothesis)

- an explanation for discrepancies in the clinical trial data reported in the submission and in the primary publication of the trial results

- clarification of the population modelled in cost-effectiveness analyses (with regard to response to prior treatment)

- an explanation for discrepancies between the hazard ratios that were modelled and those presented in the clinical effectiveness section of the submission

- a description of the methodology used to calculate some costs in the model.

Licensed indication

In September 2009 vinflunine (Javlor, Pierre Fabre) received a marketing

authorisation for use as 'monotherapy for the treatment of adult patients with

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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.

Key issues for consideration

Clinical effectiveness

- The manufacturer's submission compares vinflunine with best supportive care (BSC) only. Should alternative second-line therapies have been included as comparators? (Note: this was not specified in the scope.)
- Is there sufficient evidence that vinflunine plus BSC has superior clinical efficacy to BSC alone?
- Is the population of the pivotal clinical trial (study 302) representative of patients with transitional cell carcinoma of the urothelial tract (TCCU) who progress to second-line treatment in the UK?

Cost effectiveness

- The economic model was based on the eligible intention-to-treat (ITT) population of the pivotal trial (which excludes 13 patients who were randomised but did not meet inclusion criteria). Is this appropriate?
- Are the costs of adverse events included in the economic analysis appropriate?
- Is it appropriate to assume no vial wastage as in the manufacturer's base-case analysis?
- Were the methods used to generate pre-progression and post-progression utilities appropriate?
- The results of the economic analysis demonstrate that vinflunine is not a cost-effective treatment compared with BSC (with an incremental cost-effectiveness ratio [ICER] of approximately £100,000 per quality-adjusted life year [QALY] gained).

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- Does the Committee consider that vinflunine for TCCU should be considered within the context of NICE's supplementary advice on 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?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	Adults with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen	As per scope
Intervention	Chemotherapy	As per scope
Comparators	No alternative treatment (best supportive care [BSC])	As per scope
Outcomes	Overall survival, progression-free survival, response rates, adverse effects of treatment, quality of life	As per scope; however, response rates were not included because there are no comparative data on this outcome for this end-of-life population
Economic evaluation	Cost–utility analysis from an NHS and PSS (personal social services) perspective	As per scope

1.2 Evidence Review Group comments

1.2.1 Population

The ERG stated that the population described in the decision problem is appropriate for the UK NHS.

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1.2.2   Intervention

The ERG considered that the description of the intervention in the decision problem is appropriate for the NHS.

1.2.3   Comparators

The main comparator in the decision problem is BSC, and the manufacturer's submission reports that there is no standard therapy for patients with advanced TCCU after failure of prior platinum-containing chemotherapy. The ERG noted that alternative chemotherapies are available in practice, because TCCU is a chemo-sensitive cancer. However, there are no randomised controlled trials (RCTs) of such treatments as second-line therapies.

1.2.4   Outcomes

The ERG stated that the outcomes included in the decision problem are appropriate and clinically meaningful to patients.

1.2.5   Economic evaluation

The ERG commented that the economic evaluation in the decision problem appears to be appropriate, but that the inclusion of alternative second-line therapies as comparators would be more appropriate (although it noted that these were not specified in the scope).

1.2.6   Subgroups

The ERG commented that clinical advice suggests that subgroups for performance status and visceral status could have been considered.

1.2.7   Special considerations

The ERG noted that end-of-life considerations are discussed in the manufacturer's submission, and the manufacturer proposes that vinflunine should be used to pilot the Innovation Pass/New Cancer Drug Fund.

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1.3 Statements from professional/patient groups and nominated experts

NICE received statements from the British Uro-Oncology Group, the Royal College of Pathologists and the Royal College of Physicians (NCRI/RCP/RCR/ACP/JCCO).

The clinical specialists commented that the most commonly used first-line chemotherapies for TCCU are cisplatin or carboplatin in combination with gemcitabine. They also commented that there is currently no consensus or standard treatment for patients whose disease has progressed after first-line treatment, and that clinical practice varies across the UK. For patients with poor performance status, best supportive care with symptom control and palliative radiotherapy is the standard of care. For patients who have had a good response to first-line treatment with a long disease-free interval (at least 6 to12 months), the first-line treatment may be repeated. Other options include an alternative platinum-based regimen such as methotrexate, vinblastine, adriamycin (doxorubicin) and cisplatin (MVAC), platinum/taxane combinations, single-agent gemcitabine, or single-agent taxanes.

The clinical specialists stated that vinflunine is likely to be delivered only in a specialist oncology chemotherapy clinic because it is given by intravenous infusion and has the potential to cause damage to surrounding soft tissue at the injection site. The delivery of this treatment is unlikely to require additional NHS resources.

The clinical specialists pointed out that there is an unmet need for patients who are fit enough to receive second-line treatment for TCCU. They commented that the main disadvantage of vinflunine is its toxicity, whereas other second-line treatment options are well tolerated and appear to result in similar response rates.

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2 Clinical effectiveness evidence

2.1 *Clinical effectiveness in the manufacturer's submission*

The key evidence for the clinical effectiveness of vinflunine comes from one phase III RCT comparing vinflunine plus BSC with BSC alone in patients with advanced or metastatic TCCU whose disease has progressed after platinum-based chemotherapy (study 302). Results from two open-label, single-arm, phase II studies (study 202 and CA001) were also provided to support the RCT evidence.

2.1.1 Study 302

Patients were included if they had progressive disease after at least two cycles of platinum-based first-line chemotherapy (or after one cycle if there was clear evidence of disease progression at this point), an Eastern Cooperative Oncology Group (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 one previous systemic chemotherapy.

Patients were randomised on a 2:1 basis to vinflunine (320 mg/m^2 every 21 days via infusion) plus BSC (hereafter referred to as the 'vinflunine arm') or BSC alone (hereafter referred to as the 'BSC arm'). BSC included palliative radiotherapy, antibiotics, analgesics, corticosteroids and/or transfusions.

A total of 370 patients were enrolled into the study (253 in the vinflunine arm and 117 in the BSC arm). The median age of study participants was 64 years, and 79% were male. Most baseline characteristics were similar across the two treatment arms. However, a greater proportion of patients in the vinflunine arm (72%) had an ECOG performance status of 1 compared with the BSC arm (62%), although this difference was not statistically significant. Cisplatin

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was the most common first-line platinum treatment and more people in the BSC arm received this than in the vinflunine arm (73% and 65% respectively; this difference was not statistically significant). More people in the vinflunine arm than in the BSC arm received carboplatin as first-line platinum treatment (30% and 20% respectively; p = 0.044).

Results were provided for four study populations:

- The intention-to-treat (ITT) population: all randomised patients.
- The eligible ITT population: the ITT population minus 13 ineligible patients who did not meet the inclusion criteria at baseline and should not have been randomised (four patients in the vinflunine arm [2%] and nine patients in the BSC arm [8%]).
- The per-protocol population: eligible patients who received treatment.
- The total population evaluable for response: eligible patients who received a minimum of two cycles during 42 days of treatment.

For the purposes of this pre-meeting briefing document, only the results for the ITT and eligible ITT populations are described.

For the ITT population, median overall survival was 6.9 months in the vinflunine arm compared with 4.6 months in the BSC arm. The difference in overall survival between the groups was not statistically significant (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 BSC arm. This difference was statistically significant (HR 0.78, 95% CI 0.61 to 0.99, p = 0.0403). An extended multivariate analysis was conducted for this population which

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adjusted 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).

Secondary outcomes included progression-free survival, tumour response (complete response plus partial response), and disease control (complete response plus partial response plus stable disease). Progression-free survival for the ITT population was 3.0 months in the vinflunine arm compared with 1.5 months in the BSC arm (HR 0.68, 95% CI 0.54 to 0.86, p = 0.0012). The median duration of disease control for the ITT population was 5.7 months in the vinflunine arm and 4.2 months in the BSC arm (p = 0.0233). In the vinflunine arm, 47% of patients had stable disease after second-line treatment, 45% had progressive disease, 9% had a partial response and none had a complete response. In the BSC arm, 27% of patients had stable disease, 73% had progressive disease, and none had either a partial or a complete response (response rates were assessed in evaluable patients [73% in each study arm] by an independent review committee). Secondary outcomes for the eligible ITT group were not reported.

Quality of life was assessed using the cancer-specific European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire, at study entry and at the end of cycles 1, 2, 4, and 6 for the vinflunine arm, and at study entry and on days 21, 42, 84 and 126 for the BSC arm. There were no statistically significant differences in overall EORTC QLQ-C30 global health status score between the two groups (p = 0.658). More patients in the BSC arm than in the vinflunine arm received at least one palliative radiotherapy treatment (23% and 4% respectively). As stated in the ERG report, it is not known whether this was because of factors relating to patients' quality of life and clinical benefit or because the treating clinicians offered earlier palliative radiotherapy to patients who were not receiving any chemotherapy.

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2.1.2   Non-RCT evidence

Two phase II, multicentre, open-label, non-randomised, non-comparative trials of vinflunine in patients with TCCU after failure of a prior platinum-containing regimen were also included in the manufacturer's submission. In the two studies, which included 58 (study 202) and 151 patients (CA001), vinflunine was given every 21 days at a dose of 320 or 280 mg/m^2. In study 202 (median follow-up not reported), the overall response rate (partial or complete response) was 18% (nine patients); 25 patients (49%) had stable disease and 14 (27%) had progressive disease after treatment (three patients could not be evaluated for response and one patient died before treatment). The time to relapse was less than 3 months in 19 patients, 3 to 12 months in 24 patients and more than 12 months in eight patients. The median duration of response was 9.1 months (95% CI 4.2 to 15.0 months), 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 (median follow-up 11.9 months), the overall response rate was 14.6% (95% CI 9.4% to 21.2%). The median duration of response was 6 months (95% CI 5.4 to 9.5 months), 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).

2.1.3   Adverse events

Adverse events were presented for a total of 450 patients who received vinflunine across the three phase II and phase III studies. The most common adverse events (any grade) associated with vinflunine were constipation (55%), nausea (41%), infusion site reactions (28%), stomatitis/mucositis (27%) and vomiting (27%). Grade 3 or 4 adverse events occurred in 15% of patients, and two patients required withdrawal from treatment. Febrile neutropenia (any grade) occurred in 7% of patients and infection associated with severe neutropenia occurred in 5%. Overall, there were six deaths

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related to treatment (1.3%), of which four were related to myelotoxicity. Four deaths occurred in the vinflunine arm of study 302.

In study 302, the most common adverse events were neutropenia, anaemia and constipation. Grade 3 or 4 neutropenia occurred in 50% of patients in the vinflunine arm compared with 1% in the BSC arm. Grade 3 or 4 anaemia occurred in 19% of patients in the vinflunine arm and 8% in the BSC arm. Grade 3 or 4 constipation occurred in 8% of patients in the vinflunine arm and 1% in the BSC arm.

2.2 Evidence Review Group comments

The ERG concluded that the manufacturer's systematic review of clinical effectiveness studies was methodologically appropriate and that all relevant studies meeting the inclusion criteria have been identified. It noted that the inclusion and exclusion criteria were consistent with the final scope, except that the manufacturer did not include response rates as an outcome because there are 'no comparative data for response rate in this end of life population with a heavy tumour burden'.

The ERG noted that the evidence base for the clinical effectiveness of vinflunine is limited primarily to a single RCT of uncertain methodological quality. It commented that the populations and interventions in the two non-randomised studies are relevant to the decision problem; however, the primary outcome in these studies was response rates, which the manufacturer did not include in the decision problem because of a lack of comparative data.

The ERG noted the following limitations with study 302:

- Many aspects of study quality, such as adequacy of randomisation, allocation concealment and similarity of the study groups at baseline, were unclear, which meant that bias cannot be ruled out (see page 16 of the ERG report).

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- The study population may be more restrictive than patients with TCCU who proceed to second-line chemotherapy in UK clinical practice, because it included only patients with a performance status of 0 or 1 and excluded patients who had been given previous neoadjuvant or adjuvant chemotherapy.

- Results for several study populations were presented, and the analyses of both the ITT and eligible ITT populations have limitations. The ITT analysis included patients who should not have been randomised, and although the eligible ITT analysis excluded these patients, it may not be valid as it breaks randomisation. The ERG noted that the results of the conservative ITT analysis were not statistically significant and those of the eligible ITT analysis were. It concluded that the ITT analysis is probably the preferred analysis, despite giving a more conservative estimate of treatment effect.

- The BSC arm had a higher proportion of patients with a better performance status at baseline (although this difference was not statistically significant). The ERG noted that although this prognostic factor is accounted for in the multivariate analyses, it is not accounted for in univariate analyses.

- There are inconsistencies in the reporting of data both throughout the manufacturer's submission and between the manufacturer's submission and the published paper of the trial.

- Very little information was provided about the measurement of quality of life and clinical benefit.

Because of concerns about the validity of the methods of analysis of the trial data, and uncertainties about quality of life, clinical benefit and adverse events, the ERG concluded that it is unclear whether treatment with vinflunine is superior to BSC alone and that further work would be needed to clarify this.

The ERG commented that the clinical advice it received was not in agreement with the manufacturer's statement that the safety profile of vinflunine overall is predictable, acceptable and manageable by prophylactic and therapeutic measures. The clinical advice received by the ERG was that vinflunine does

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not have an acceptable safety profile and is not well tolerated by patients, especially in relation to constipation, which can be difficult to treat.

The ERG also commented that the manufacturer's submission does not mention the vesicant (tissue blistering) nature of vinflunine, which can result in patients suffering soft tissue damage at the site of infusion. When asked for clarification, the manufacturer stated that this issue was not discussed because of a lack of information about vinflunine (see appendix 1 of the ERG report).

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The manufacturer's modelling approach was described as a 'partitioned-survival' model. The model was similar to a Markov cohort model in that it included three health states: pre-progression, post-progression and dead. However, instead of transition probabilities governing movement between health states, the model calculated the proportion of patients that is expected to be in each health state, based on the estimated survival functions for progression-free survival and overall survival. The model assumes 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 and remain in the post-progression state (with palliative care only) until death (see pages 69 to 72 of the manufacturer's submission for further information). The model uses daily cycles with a 5-year time horizon. No subgroups were considered in the analysis.

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3.2 Clinical evidence

The risk of disease progression was based on results for the eligible ITT population of study 302. For the BSC arm, progression-free survival and overall survival from study 302 were extrapolated beyond the study period using a Weibull survival model. For the vinflunine arm, progression-free survival and overall survival were calculated by adjusting the modelled survival estimates in the BSC arm using the HR from study 302 (using a proportional hazards assumption). The modelled HRs for vinflunine compared with BSC were 0.47 for progression-free survival and 0.70 for overall survival.

3.3 Utilities

Health-related quality of life for the pre-progression health state was based on responses to the EORTC QLQ-C30 questionnaire used in study 302. A two-stage mapping process was used whereby responses to the item 'How would you rate your overall quality of life during the past week?' (scale of 0–100) were pooled across treatment groups and converted to a scale of 0 to 1. Next, responses were transformed to health-state utilities using a published regression model (see page 83 of the manufacturer's submission for further information). The modelled utility for the pre-progression state was 0.65.

Post-progression health-related quality of life was not available from study 302. Instead, the utility value for this health state was 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 (see page 87 of the manufacturer's submission). The modelled utility for the post-progression state was 0.25.

Disutilities associated with treatment-related adverse events were not included in the model.

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3.4 *Costs*

The following costs were included in the model (see pages 89 to 97 of the manufacturer's submission):

- treatment costs for vinflunine, including drug costs, administration, monitoring and prophylaxis for constipation
- adverse-event costs
- health state costs, including BSC and palliative treatment in the pre-progression and post-progression states.

3.4.1 Treatment costs

Treatment costs for vinflunine included drug costs (£1062.50 per 250 mg vial), administration costs for intravenous infusion every 21 days in an outpatient setting (£208 for the first cycle and £154 for subsequent cycles), monitoring costs for a complete blood count before drug administration (£3.18 per cycle) and prophylaxis for constipation (£0.70 per cycle).

Vinflunine doses 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. Drug wastage was assumed to be zero in the base-case analysis (vinflunine is available in 250 mg and 50 mg vials). Treatment continued until disease progression, patient refusal, discontinuation because of toxicity, or death (based on data from study 302).

The total per-patient cost of treatment with vinflunine included in the model was £10,207.

3.4.2 Adverse-event costs

Only costs for the most common grade 3 and 4 adverse events associated with vinflunine (as identified in the three vinflunine studies) were included in the model: constipation (£39, based on one GP consultation and one pack of laxatives), febrile neutropenia resulting in hospitalisation (£3538; NHS HRG

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[healthcare resource groups] costs) and abdominal pain resulting in hospitalisation (£557; NHS HRG costs). Fatigue and injection-site reactions were common adverse events but were assumed not to have any associated costs. Anaemia was one of the most common adverse events in study 302, but this was not included in the model. The incidence of adverse events in each treatment group was based on data from study 302.

The total per-patient costs of adverse events included in the model were £199 for the vinflunine group and £4 for the BSC group.

3.4.3   Health state costs

Costs for BSC in the pre-progression health state included: home visits by a GP, community nurse, health home visitor and dietician, and an oncologist follow-up visit. Costs for BSC in the post-progression health state included home visits by a GP, community nurse, health home visitor and dietician, a non-consultant-oncologist follow-up visit, hospice care and pain medication. BSC costs were assumed to be the same regardless of treatment group.

Costs for the pre-progression health state included palliative radiation therapy, with estimated incidence based on data from study 302. The cost and incidence of pre-progression palliative radiotherapy were higher for the BSC group.

Costs for the post-progression heath state included palliative radiation therapy (higher costs and incidence for vinflunine group) and palliative chemotherapy (higher costs and incidence for the BSC group).

The total per-patient costs of pre-progression BSC included in the model were £2423 for the vinflunine group and £1560 for the BSC group. The total per-patient costs of post-progression BSC included in the model were £8884 for the vinflunine group and £7078 for the BSC group.

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3.5 Results

In the manufacturer's base case, the incremental cost-effectiveness ratio (ICER) for vinflunine plus BSC compared with BSC alone was £100,144 per quality-adjusted life year (QALY) gained (incremental cost £13,071 and incremental benefit 0.131 QALYs).

In deterministic sensitivity analyses, the ICERs ranged from £27,478 to £133,094 per QALY gained (incremental costs and QALYs were not reported). The factors that had the largest impact on the base-case ICER were as follows:

- Vinflunine vial price: the base-case ICER decreased from £100,144 to £27,478 per QALY gained when a vial price of £0 was used (instead of £1063) and to £54,835 per QALY when a vial price of £400 was used.
- Utility for the pre-progression health state: the base-case ICER increased to £133,094 per QALY using a utility of 0.4 (instead of 0.65) and decreased to £76,054 per QALY using a utility of 0.7.
- Number of cycles of vinflunine treatment: the base-case ICER decreased to £70,233 per QALY when the model included three cycles of vinflunine instead of 4.2 (the mean number of cycles in study 302).
- Vinflunine vial wastage: the base-case ICER increased to £121,095 per QALY when vial wastage was accounted for. The base case assumed zero vial wastage (that is, drug costs were based on the actual mean dose rather the number of vials needed to obtain that dose).

Two scenario analyses were conducted around estimates of clinical benefit (page 106 of the manufacturer's submission): the first used trial-based Kaplan–Meier estimates of overall survival and progression-free survival over the duration of the trial (2.4 years) and the second used modelled data based on a Gamma survival function (extrapolated over 5 years). These alternative estimation methods for survival did not significantly alter the base-case ICER

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(the resulting ICERs were £104,751 and £103,370 per QALY gained respectively).

In probabilistic sensitivity analyses, the probability that vinflunine is cost effective at a threshold of £30,000 per QALY was 6%.

3.6   End of life

The manufacturer proposed that vinflunine should be considered in the context of NICE's end-of-life supplementary advice for the following reasons:

- The treatment is indicated for patients with a short life expectancy: the median survival of the population indicated for vinflunine (adult patients with advanced or metastatic TCCU after failure of a prior platinum-containing regimen) rarely exceeds 3 to 6 months.

- The treatment offers an extension to life (the supplementary advice states that this should normally be at least an additional 3 months). In the eligible ITT population of study 302, vinflunine demonstrated a 2.6-month survival benefit over BSC (6.9 months vs 4.3 months; $p = 0.04$). The value for incremental life years gained in the economic model (for the eligible ITT population) was 3.2 months. (Note: in the ITT population, the survival benefit for vinflunine was 2.3 months; 6.9 months vs 4.6 months, $p = 0.287$).

- The treatment is licensed for small populations: the manufacturer estimates that 2000–3000 patients in the UK (30–40% of patients with metastatic bladder cancer) receive first-line chemotherapy, of whom 800–1500 (40–50%) will be eligible for second-line treatment.

In line with NICE's end-of-life supplementary advice, the manufacturer provided estimates of:

- the impact of giving greater weight to QALYs achieved in the later stages of terminal diseases, using the assumption that the extended survival period

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is experienced at the full quality of life anticipated for a healthy person of the same age and

- the magnitude of the additional weight that would need to be assigned to the QALY benefits in this patient group for the cost effectiveness of the technology to fall within the current threshold range.

The manufacturer conducted additional analyses using a post-progression utility of 0.79 based on the trial-based, gender-weighted average of the UK population norms for the EQ-5D among healthy people of the same age (a post-progression utility of 0.25 was used in the manufacturer's base case). The manufacturer stated that this resulted in a more favourable ICER of £61,890 per QALY gained (compared with the base-case ICER of £100,144 per QALY). Using this revised ICER, the manufacturer calculated that the incremental QALY gain that would need to be assigned for vinflunine to be effective at the £30,000 threshold is 2.06 (that is, £61,890/£30,000).

3.7 Evidence Review Group comments

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 modelled population reflected that of the pivotal trial, but may not be representative of the majority of patients whose disease progresses after first-line therapy (because of the exclusion of patients who had received prior neoadjuvant or adjuvant platinum-based chemotherapy).
- The economic model uses BSC as a comparator, but this does not reflect usual UK clinical practice. A more appropriate comparator would have been alternative second-line treatments (although the ERG noted that this was not specified in the scope and there are no RCTs of relevant comparators for the population of interest).
- The economic model was based on the eligible ITT analysis, but the ITT analysis may have been more appropriate.

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- The ERG compared the overall survival curves used in the economic model with those obtained using an alternative method (using Kaplan–Meier trial data) for consistency (see page 38 of the ERG report). It concluded that the most realistic results were those using the Kaplan–Meier trial data. However, the ERG noted that the choice of alternative survival curves does not have a significant impact on the base-case results (ICERs obtained using different modelling methods ranged from £100,000 to £105,000 per QALY gained).

- The utility values do not fit with the NICE reference case, and there is considerable uncertainty around these estimates because standard methods were not used. The ERG suggested two alternative approaches to deriving EQ-5D utility values from EORTC QLQ-C30 scores (see page 33 of the ERG report).

3.7.1 Additional work undertaken by the ERG

The ERG conducted an additional sensitivity analysis to explore the impact of using different estimates of clinical benefit. The analysis used the CIs around the modelled HRs for overall survival and progression-free survival (see page 41 of the ERG report). The resulting ICERs ranged from £87,871 to £117,938 per QALY gained (compared with £100,144 per QALY in the manufacturer's base case).

The ERG undertook a scenario analysis using the estimates of progression-free survival and overall survival from the ITT population, rather than those from the eligible ITT population (as used in the manufacturer's base case). In the same analysis, the ERG corrected an error in the manufacturer's model in which the vinflunine vial cost was entered as £854 instead of £1062. The resulting ICER was £99,792 per QALY gained, compared with £100,144 per QALY in the manufacturer's base case. The ERG noted that this decrease in ICER was counterintuitive, since the HRs from the ITT population were more conservative than those from the eligible ITT population, but this was because

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of the method used to model survival in the manufacturer's base case. The ERG commented that a more intuitive result was obtained when Kaplan–Meier trial data were used to estimate progression-free survival and overall survival, in which case the ICER increased to £126,422 per QALY gained.

In probabilistic sensitivity analysis undertaken by the ERG, the probability that vinflunine is cost effective at a threshold of £30,000 per QALY was 3% (compared with 6% in the manufacturer's submission).

4 Equalities issues

No equalities issues were identified during the scoping of this topic or in the manufacturer's submission.

5 Authors

Sally Gallaugher and Joanne Holden, with input from the Lead Team (Brian Shine and Carol Haigh).

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Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

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

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

B   Submissions or statements were received from the following organisations:

I   Manufacturer/sponsor:

- Pierre Fabre Ltd

II   Professional/specialist, patient/carer and other groups:

- British Uro-Oncology Group
- Royal College of Pathologists
- Royal College of Physicians (NCRI/RCP/RCR/ACP/JCCO)