Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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Resubmission:

vinflunine (as ditartrate), 25mg/mL, concentrate for solution for infusion (Javlor®) SMC No. (686/11)

Pierre Fabre Limited

05 June 2015

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a resubmission considered under the end of life process.

vinflunine (Javlor®) is not recommended for use within NHS Scotland.

Indication under review: 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. Efficacy and safety of vinflunine have not been studied in patients with performance status ≥ 2.

Vinflunine plus best supportive care was associated with improved survival when compared with best supportive care alone in the second-line treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract in patients with good performance status.

The submitting company did not present a sufficiently robust economic analysis and in addition their justification of the treatment's cost in relation to its benefits was not sufficient to gain acceptance by SMC.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 13 July 2015

Indication

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.

Efficacy and safety of vinflunine have not been studied in patients with performance status ≥2.

Dosing Information

The recommended dose is 320mg/m^2 vinflunine as a 20 minute intravenous infusion every three weeks.

In case of WHO/ECOG performance status (PS) of 1 or PS of 0 and prior pelvic irradiation, the treatment should be started at the dose of 280mg/m^2. In the absence of any haematological toxicity during the first cycle causing treatment delay or dose reduction, the dose will be increased to 320mg/m^2 every three weeks for the subsequent cycles.

In order to prevent constipation, laxatives and dietary measures including oral hydration are recommended for five to seven days after each vinflunine administration.

Vinflunine treatment should be initiated under the responsibility of a physician qualified in the use of anticancer chemotherapy and is confined to units specialised in the administration of cytotoxic chemotherapy.

Product availability date

September 2010.
Vinflunine meets SMC criteria for an end-of-life medicine.

Summary of evidence on comparative efficacy

Vinflunine is a vinca alkaloid that binds to tubulin, inhibiting its polymerisation into microtubules, resulting in mitotic arrest and apoptosis.[1] Patients with locally advanced or metastatic transitional cell carcinoma of the urothelial tract (TCCU) are offered first-line cisplatin-based chemotherapy, or carboplatin if cisplatin is not suitable. Second-line options, determined by duration of response to first-line treatment, include re-challenge with first-line regimen, entry into clinical studies or paclitaxel therapy.[2-4]

One pivotal, phase III, open-label, multi-centre, randomised study compared vinflunine plus best supportive care (BSC) with BSC alone in patients with advanced TCCU.[5] Eligible patients had locally advanced or metastatic TCCU which had progressed on or after first-line platinum-containing chemotherapy, an Eastern Co-operative Oncology Group (ECOG) performance status of 0 or 1 and adequate haematologic, renal and hepatic function. Eligible patients could have received previous radiation provided it affected less than 30% of the bone marrow and was completed at least 30 days before randomisation.

Patients were randomised, with stratification for study site and refractoriness to previous platinum therapy (i.e. those with disease progression within the first two cycles of first-line chemotherapy), in a ratio of 2:1, to receive either vinflunine plus best supportive care (BSC) (n=253) or BSC alone (n=117). Initially the vinflunine dose was 320mg/m^2 every 21 days in all patients but was subsequently amended so that those with performance status of 1 or performance status of 0 and previous pelvic irradiation, received a dose of 280mg/m^2 for the first cycle, which was increased to 320mg/m^2 if no haematologic toxicities caused delay of treatment. BSC met local standards and could include palliative radiotherapy, antibiotics, analgesics, corticosteroids and transfusion. Vinflunine treatment was continued until there was documented progression, unacceptable toxicity or the patient refused treatment; BSC was continued until progression requiring systemic chemotherapy, unable to meet 3-weekly schedule, patient refused treatment or after 18 weeks. The median durations of therapy with vinflunine and BSC were 9.5 and 9.4 weeks respectively and second-line chemotherapy was used in 29% (73/253) and 34% (40/117) patients respectively.[5,6]

The primary endpoint was overall survival assessed in the intention to treat (ITT) population. After a median follow-up of 21.5 months in the vinflunine group and 22.3 months in the BSC group, and accrual of 307 events, median overall survival was 6.9 months and 4.6 months respectively, and the hazard ratio (HR) was 0.88 (95% confidence interval [CI]: 0.69 to 1.12), p=0.287. Results for the pre-specified, multivariate Cox analysis, which adjusted for prognostic factors, estimated for the treatment groups in the ITT population, a HR of 0.77 (95% CI: 0.61 to 0.98), p=0.036.[5]

After discovering that 13 patients (four patients in the vinflunine plus BSC group and nine patients in the BSC alone group) had clinically significant protocol violations at baseline (mainly no disease progression or use of neoadjuvant or adjuvant chemotherapy), a post hoc analysis of overall survival was performed excluding them from an “eligible” population (n=357 with 300 events). This found a significant survival benefit with vinflunine with median survival of 6.9 months and 4.3 months respectively, corresponding to an HR of 0.78 (0.61 to 0.99), p=0.040.[5]

An updated survival analysis was presented in which the median follow-up was 42 months in the vinflunine group and 45 months for BSC. At this point, 352 events had accrued, representing 95% of total study population. In the ITT population median overall survival was 6.9 months and 4.6 months in the vinflunine and BSC groups respectively. The associated hazard ratio was not statistically significant, HR=0.88 (95% CI: 0.70 to 1.10), p=0.261. In the “eligible” population, median overall survival was 6.9 and 4.3 months respectively, HR=0.78 (95% CI: 0.61 to 0.96), p=0.023.[7]

Secondary endpoints significantly favoured vinflunine and included progression-free survival (PFS) which, when assessed by the independent review committee (IRC) in the ITT population, the medians were 3.0 months in the vinflunine group and 1.5 months in the BSC group; HR=0.68 (95% CI: 0.54 to 0.86), p=0.0012. Disease control rate, which included complete and partial responses or stabilisation, was 41% (104/253) in vinflunine and 25% (29/117) in BSC patients when assessed by the IRC in the ITT population. The median duration of disease control was 5.7 months and 4.2 months respectively. The objective response rate was 8.6% (16/185) in ‘eligible’ vinflunine and 0/85 in ‘eligible’ BSC patients as assessed by the IRC. All responses were partial with a median duration of response of 7.4 months. There was no significant difference between the two treatment groups in the clinical benefit response rate, a composite outcome which included performance status, weight, pain index (McGill Pain Questionnaire), analgesic consumption and use of palliative radiotherapy. Significantly more

BSC patients received at least one palliative radiotherapy treatment than vinflunine patients (24% versus 4.0%).[5]

There was no significant difference between the two treatment groups in the change from baseline in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30.[6]

A number of non-comparative cohort studies conducted in various European countries provide observational data for using vinflunine in accordance with the European marketing authorisation.[8-13] Median overall survival in these cohorts ranged from 4.6 to 10.4 months.

Summary of evidence on comparative safety

The most frequently reported adverse events in the vinflunine group were neutropenia, anaemia, constipation and asthenia/fatigue. These events are characteristic of the vinca alkaloid agents. Vinflunine, like other vinca alkaloids, is a vesicant and can cause severe local tissue irritation and care must be taken to avoid extravasation.

During the pivotal study, the incidence of serious adverse events was 62% in the vinflunine group and 47% in the BSC group.[6] Neutropenia was more common in the vinflunine group (77% versus 2.7%), with grade 3 or 4 neutropenia reported in 50% and 0.9% of patients respectively. This led to febrile neutropenia in 6.0% (15/253) vinflunine patients, all at grade 3 or 4 severity, and subsequent discontinuation of study drug in one patient. No cases of febrile neutropenia were reported in the BSC group. Anaemia was reported in 93% (229/253) vinflunine and 61% (68/117) BSC patients, and fatigue or asthenia in 50% (124/253) and 61% (71/117) patients respectively.[5]

Constipation was more common in vinflunine treated patients (48% versus 25%), including grade 3 or 4 cases (16% versus 0.9%).[3] The summary of product characteristics (SPC) recommends the use of preventative measures with laxatives and dietary measures including oral hydration from day 1 to day 5 or 7 after each vinflunine infusion.[1]

The SPC also notes that cases of severe hyponatraemia, including cases of syndrome of inappropriate anti-diuretic hormone secretion, have been observed with vinflunine treatment. There have also been cases of posterior reversible encephalopathy syndrome (PRES) observed with vinflunine.[1]

Summary of clinical effectiveness issues

Vinflunine is the first drug to be licensed specifically for the second-line treatment of advanced or metastatic TCCU. Patients whose disease has progressed after or during prior platinum-containing chemotherapy have a poor prognosis, and median overall survival of approximately four months.[6] European clinical guidelines note that vinflunine is the only medicine to have demonstrated a survival advantage in this setting.[3,4] One of the options noted in the Scottish Cancer Networks' protocols for TCCU is weekly paclitaxel ("off-label" indication).[14] In a non-comparative phase II study of weekly paclitaxel conducted in 45 patients, median overall survival was 208 days.[15,4] Vinflunine meets SMC criteria for an end-of-life medicine.

Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, since there is no effective second line treatment available for this group of patients.

There are no active comparative data - the pivotal study used BSC as a comparator. Although there are no standard second-line agents, other chemotherapy options are used, many outwith their licensed indication, e.g. paclitaxel. In addition, as the study was conducted between 2003 and 2006, BSC given during the study may not reflect current practice.

Overall survival is a direct health outcome. When compared in the ITT population, there was no statistically significant difference between vinflunine and BSC. A significant difference was noted in the "eligible" population. There was an imbalance between the groups in the proportion of patients who were excluded from the "eligible" population, which broke the original study randomisation and may affect the results. However, since results in this "eligible" population were consistent with those from the multivariate analyses and analyses of secondary endpoints, the European Medicines Agency considered overall survival to be significantly different between the two groups.[6] An extension in the median overall survival of 2.6 months is modest, but in the context of a disease in which no other treatment at this stage has demonstrated an overall survival advantage,[3,4] this may be clinically significant.

Results of subgroup analyses according to prior cisplatin use demonstrated efficacy in patients with and without prior cisplatin, which was better in patients without prior cisplatin although patient numbers in this group were smaller (approximately 30% of eligible population).[6]

The study was of open-label design which may have allowed the introduction of bias into the reporting of subjective outcomes (e.g. health-related quality of life questionnaires). Vinflunine was not associated with any improvement or deterioration of health-related quality of life compared with BSC.

Study randomisation was stratified by study site and refractoriness to previous platinum treatment but not by performance status which is an important prognostic factor. There was a difference in the baseline performance status with more vinflunine patients having a performance status of 1 (72% versus 62%).[5] The pre-specified multivariate analysis adjusted for baseline differences, including performance status, and suggested a statistically significant survival advantage for vinflunine treatment.

Eligible patients had performance status of 0 or 1 and so efficacy and safety in patients with performance status of ≥2 is unknown. Many of the patients with advanced or metastatic TCCU having failed platinum based therapy are likely to have a poorer performance status than those treated in the study and may not be suitable for systemic chemotherapy.[6] The non-comparative observational studies provide limited evidence of the use of vinflunine in patients with ECOG performance status of 2.[8-13]

Current clinical guidelines advocate the use of neoadjuvant chemotherapy on the basis that cisplatin-containing combinations improve overall survival.[2-4] The pivotal study excluded patients who had received adjuvant or neoadjuvant chemotherapy; therefore, the clinical efficacy of vinflunine in patients who have received neoadjuvant chemotherapy is unclear.

Summary of patient and clinician engagement

A patient and clinician engagement (PACE) meeting with a patient group representative and a clinical specialist was held to consider the added value of vinflunine, as an end of life medicine, in the context of treatments currently available in NHS Scotland 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 key points expressed by the group were:

- Living with the symptoms of bladder cancer and the knowledge that their condition is terminal has a huge psychological impact on patients and their families. In addition, as patients have to give up work and have their family care for them, this can also cause significant financial hardship.

- Bladder cancer has had no new treatments for 30 years and to date there have been no licensed treatments available for this very small group of patients. This is the first medicine to show any survival benefit in an RCT in the second line setting.

- An improvement in overall survival is hugely important for patients and their families and PACE participants felt that any treatment that could delay progression and disease related symptoms could give patients more time with a better quality of life.

- Minimal impact on service delivery is anticipated as: the potential patient population in Scotland is very small; in the clinical trial, the median number of cycles was only four; and vinflunine is administered on a 3 weekly basis through out-patient clinics which may be easier for patients and their families rather than weekly attendance for off-label use of gemcitabine or paclitaxel.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis of vinflunine compared to paclitaxel in patients with advanced or metastatic TCCU after failure of a prior platinum-containing regimen. A standard 3 state Markov model (pre-progression, post progression and dead) was used with a lifetime time horizon consisting of 10 years. In scenario analysis a comparison was performed versus BSC.

The clinical data used in the model were ‘eligible’ patients from the pivotal phase III study of vinflunine versus placebo (i.e. excluding 13 patients in the ITT population who had protocol violations at baseline). The placebo arm provided the proxy for the comparison with BSC. For the primary comparison versus paclitaxel, the placebo arm data were also used, with a hazard ratio adjustment of 0.95 applied for both PFS and overall survival (OS) outcomes to reflect an assumption of marginally better outcomes for paclitaxel relative to BSC. The data from the pivotal study were mature, so observed Kaplan-Meier data were used in the economic analysis base case for PFS and OS outcomes. In scenario analysis, extrapolation of these outcomes was also performed by fitting a range of parametric functions.

Base case utility estimates for the pre- and post-progression disease states (0.76 and 0.71 respectively) were derived from the pivotal study based on a conversion of the EORTC-QLQ-C30 disease-specific questionnaire to utility scores via the EORTC-8D algorithm. In scenario analysis, the mean values estimated by treatment arm were applied, which were utilities of 0.75 and 0.78 pre-progression, and 0.68 and 0.74 post-progression for vinflunine and BSC treatment arms respectively.

Vinflunine and paclitaxel drug acquisition, IV administration and adverse event management costs were estimated, with dosing of vinflunine and paclitaxel based on mean body surface area from the pivotal study and the methods of moments calculation used to estimate the average number of vials used for each treatment. The costs of managing grade 3 and 4 adverse events reported in the vinflunine pivotal study were estimated (fatigue, constipation, abdominal pain, febrile neutropenia), with treatment setting and resource use estimates provided through expert clinical opinion. For the comparison with paclitaxel, the same adverse event incidence and costs as for vinflunine were assumed. Expert clinical opinion was also used to provide estimates of pre- and post-progression patient monitoring and tests, which were assumed to be the same in both disease stages. Terminal care costs were based on published estimates.

A Patient Access Scheme (PAS) was submitted by the company and was accepted by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS a simple discount was given on the list price of the medicine. With the PAS, for the comparison of vinflunine with paclitaxel the company estimated an incremental cost-effectiveness ratio (ICER) of £53,111 per quality-adjusted life-year (QALY) gained, based on an incremental cost of £7,960 and incremental life years of 0.22 (or 2.6 months) and incremental QALYs of 0.15 The cost difference was driven by the additional drug costs for vinflunine, with some additional cost for monitoring/disease management associated with longer survival, but a small reduction in administration costs estimated. The life years and QALY gains are predominantly associated with a longer duration of progression-free survival with vinflunine.

For the comparison against BSC, the estimated ICER was £79,586/QALY with PAS (incremental cost of £14,554, and incremental QALYs of 0.18).

Sensitivity and scenario analysis was performed, with the results most sensitive to the choice of base case utilities, varying the OS hazard ratio for paclitaxel to BSC, the choice of parametric function for extrapolation, and use of the full ITT population from the pivotal study. The probabilistic sensitivity analysis performed demonstrated approximate 25% and 0% probabilities of vinflunine (with PAS) being considered cost-effective versus paclitaxel and BSC respectively at the £50,000/QALY threshold.

In addition to ICERs that are above usual accepted thresholds for cost-effectiveness, the main issues with the economic analysis were as follows:

- The comparison with paclitaxel lacks robustness. An indirect comparison has not been performed, and the estimates of PFS and OS for paclitaxel relative to BSC are based on assumption. Scenario analysis assuming a HR of 0.9 results in an ICER of £64k/QALY with PAS, and a HR of 0.8 results in an ICER of £283k/QALY with PAS, whereas an assumed HR of 0.99 produces an estimated ICER of £46k/QALY. Hence, there is high uncertainty in the ICER for vinflunine versus paclitaxel.
- SMC clinical experts considered unlicensed weekly paclitaxel to be an option in better performance status patients, but also mentioned BSC as a relevant comparator, especially in poorer performance status patients. The comparison against BSC is

relatively robust as it is based directly on mature survival data for both vinflunine and BSC from the pivotal study. However, a limitation of the clinical data for this comparison is that only patients with good performance status (ECOG 0-1) were included in the pivotal study, whilst the patients most likely to receive BSC are those with poorer performance status.

- There is also uncertainty in the survival benefit of vinflunine associated with use of the ITT or eligible patient population. A weakness of the pivotal study is the breaking of randomisation and imbalance across treatment arms associated with excluding in the "eligible" patient population BSC patients who had relatively better survival outcomes. Using the full ITT population for the economic analysis resulted in significantly higher ICERs (with PAS £89k/QALY and £124k/QALY for the comparisons with paclitaxel and BSC respectively), and given the small survival gains estimated, this illustrates that the results are sensitive to small changes in the survival benefit associated with vinflunine.
- For the comparison with paclitaxel in the base case, no difference in disutility or costs associated with adverse events has been assumed, although no evidence has been provided to support this assumption. For the comparison with BSC, a scenario using the pivotal study treatment arm specific utilities by health state, which takes adverse event impact into account, resulted in an increased ICER of £97k/QALY with PAS.
- The methods by which time on treatment with vinflunine and paclitaxel has been estimated remains unclear following the response provided by the company to a question requesting clarification on this.

The Committee also considered the benefits of vinflunine in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion regarding the absence of other treatments of proven benefit was satisfied.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee was unable to accept vinflunine for use in NHS Scotland.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

A Patient Group submission was not made.

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) published guidance on the diagnosis and management of bladder cancer in February 2015.[2] With regard to second-line chemotherapy in patients with locally advanced or metastatic bladder cancer, vinflunine is not recommended for use within its licensed indication. This guidance follows the technology appraisal conducted by NICE in 2013. Chemotherapy regimens to be considered as options include:

Adequate renal function and otherwise physically fit (ECOG performance status 0 or 1)	**Cisplatin-based therapy is not suitable**
gemcitabine plus cisplatin	carboplatin plus paclitaxel
accelerated (high dose) MVAC with G-CSF	gemcitabine plus paclitaxel

The European Association of Urology recently updated its clinical guidance for bladder cancer.[3] Data regarding second-line chemotherapy are inconsistent, but recently prognostic factors have been defined (involvement of liver metastases, haemoglobin <10g/dL and ECOG performance status >0). It is considered reasonable to re-challenge patients previously sensitive to cisplatin, for whom progression has occurred at least 6 to 12 months following first-line chemotherapy with a cisplatin-based combination. In small phase II trials, response rates ranged between 0 and 28% following second-line treatment with paclitaxel (weekly), docetaxel, nab-paclitaxel, oxaliplatin, ifosamide, topotecan, pemetrexed, lapatinib, gefitinib and bortezomib. Excellent response rates have been demonstrated following second-line use of gemcitabine, however this medicine is given to most patients during first-line treatment. Response rates of 38 to 60% have been shown for paclitaxel/gemcitabine, varying according to patient selection. There have been no randomised phase III studies with an appropriate comparator, so the true value and overall survival benefit is unknown for the second-line combination of paclitaxel/gemcitabine. Objective response rates of 18% and disease control in 67% of vinflunine-treated patients have been documented. Recently, vinflunine plus BSC was compared with BSC alone in a phase III study of patients with metastatic disease who progressed following first-line combination chemotherapy with a platinum-containing regimen. The overall response rate was 8.6%, and a survival benefit was shown for vinflunine plus BSC compared with BSC alone. This was statistically significant in the eligible patient population, but not the ITT population. Since vinflunine is currently the only agent approved for second-line treatment of advanced or metastatic urothelial cancer, other treatment should only be given for this indication in a clinical trial setting.

The European Society of Medical Oncology (ESMO) also recently updated its guidance for the management of bladder cancer.[4] There is only one relevant phase III study in patients with metastatic disease who progressed following first-line combination chemotherapy with a platinum-containing regimen (the vinflunine pivotal study). Vinflunine is the only medicine approved for this indication in Europe and it is unknown whether other agents would have similar benefit used in this setting. Data from phase II studies of second-line treatment are highly variable and dependent on patients selected. Better response rates have been shown with combination chemotherapy compared with monotherapy, however only short progression free survival has been demonstrated with either. Adverse prognostic factors for survival (PS>0,

haemoglobin <10g/dL, liver metastasis) have recently been established for patients who have failed to respond to platinum-based chemotherapy. Second-line options suggested in the ESMO guidance depend upon the duration of response to the initial palliative chemotherapy regimen:

- Progression <12 months – 2nd-line chemotherapy
  1. Vinflunine
  2. Taxane based
  3. Clinical trial
- Progression >12 months
  1. Platinum-based re-challenge.

Additional information: comparators

Whilst there are no standard second-line therapies, other chemotherapeutic agents may be used including re-treatment with the first-line platinum-containing regimen if it produced an initial durable response. Other second-line options depend on first-line therapy and may include gemcitabine (plus cisplatin) or unlicensed use of taxanes (e.g. paclitaxel).

Cost of relevant comparators

Drug	Dose Regimen	Cost per cycle (£)	Cost per course (£)
vinflunine	**320mg/m^2 intravenous infusion every 3 weeks**	**2,550**	**7,650**
paclitaxel	**80mg/m^2 intravenous infusion on days 1, 8 and 15 of a 28-day cycle**	**902**	**2,705**

Cost from MIMS online on 25 February 2015. Cost based on body surface area of 1.8m^2 and three cycles per course. Paclitaxel dose based on phase II study.[15] The costs do not take any patient access schemes into consideration

Additional information: budget impact

The submitting company estimated there to be 153 patients in year 1 rising to 166 patients in year 5 eligible for treatment with vinflunine with an assumed uptake rate of 15% of patients in year 1 (23 patients), rising to 25% in year 5 (42 patients).

Without PAS, the submitting company estimated the gross medicines budget impact to be £419k in year 1 and £760k in year 5. It was assumed that there would be displacement of paclitaxel resulting in a net medicines budget impact of £363k in year 1 and £657k in year 5.

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References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Pierre Fabre Médicament. Javlor 25 mg/mL concentrate for solution for infusion. 2014 June 2014 [cited 10.02.2015]; Available from: https://www.medicines.org.uk
2. National Institute for Health and Care Excellence. Bladder Cancer: diagnosis and management. NICE guideline. 2015 [cited 25.02.2015]; Available from: www.nice.org.uk
3. Witjes JA, Comperat E, Cowan NC, De Santis M, Gakis G, Lebret T, *et al.* EAU guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2013 guidelines. European urology. 2014;65(4):778-92.
4. Bellmunt J, Orsola A, Leow JJ, Wiegel T, De Santis M, Horwich A. Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2014;25(suppl 3):iii40-iii8.
5. Bellmunt J, Theodore C, Demkov T, Komyakov B, Sengelov L, Daugaard G, *et al.* Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2009;27(27):4454-61.
6. European Medicines Agency. CHMP assessment report for Javlor. 2009 [cited October 2014]; Available from: http://www.ema.europa.eu.
7. Castellano D, Puente J, de Velasco G, Chirivella I, Lopez-Criado P, Mohedano N, *et al.* Safety and effectiveness of vinflunine in patients with metastatic transitional cell carcinoma of the urothelial tract after failure of one platinum-based systemic therapy in clinical practice. BMC cancer. 2014;14:779. Epub 2014/10/25.
8. Chirivella I, Grande E, López-Criado P, González-Grajera B, Fernandez O, Santander C, *et al.* Vinflunine (VFL) as second-line chemotherapy for patients with transitional cell carcinoma of the urothelium (TCCU): A multicenter retrospective study. Eur J Cancer. 2013;49(Suppl. 2), S671.
9. Hegele A, de Geeter P, Goebell P, Matz U, de Schultz W, Retz M. Vinflunine in routine practice for the treatment of advanced or metastatic urothelial cell carcinoma in Germany. Eur J Cancer. 2013;49 (Suppl. 2), S665.
10. Hegele A, Goebell P, Matz U, Neuhaus T. Monotherapy with intravenous vinflunine in patients with advanced or metastatic urothelial cancer after failure of a platinum-containing regimen: a retrospective analysis of German routine data. Urologia internationalis. 2014;92(2):174-9. Epub 2013/12/18.
11. Médioni J, Guillot A, Spaeth D, Di Palma M, Théodore C. Historical data in real life from patients treated by vinflunine for advanced or metastatic urothelial carcinoma: results. Eur J Cancer. 2013;49 (Suppl. 2), S647.
12. Holmsten K, Dohn LH, Jensen NV, Shah C-H, Pappot H, Ullen A. Vinflunine as second line chemotherapy for patients with metastatic urothelial cancer- A Nordic multi-center retrospective study. European Urology, Supplements. 2013;12(6):136-7.
13. Hussain SA, Ansari J, Huddart RA, Wylie J, Vilarino-Varela M, Faust G, *et al.* VICTOR: vinflunine (vin) in advanced metastatic transitional cell carcinoma of the urothelium (TCCU) – a retrospective analysis of use of vin in multicenter, real life setting as second-line chemotherapy (ChT) through freef charge programme (FOCP) for patients (pts) in the UK. J Clin Oncol 2015; 33 (suppl. 7): abstr 352.
14. SCAN. Edinburgh Cancer Centre: Clinical management guideline for bladder cancer. 06.08.2014 [cited 10.02.2015]; Available from: http://intranet.lothian.scot.nhs.uk/.

15. Joly F, Houede N, Noal S, Chevreau C, Priou F, Chinet-Charrot P*, et al.* Do patients with advanced urothelial carcinoma benefit from weekly paclitaxel chemotherapy? A GETUG phase II study. Clinical genitourinary cancer. 2009;7(2):E28-33.

This assessment is based on data submitted by the applicant company up to and including 09 April 2015.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.