National Institute for Health and Clinical Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Vinflunine for the treatment of transitional cell carcinoma of the urothelial tract

ERG Review of Accuracy from Pierre Fabre

8/10/10

Issue 1 2.2 Critique of manufacturer's overview

Description of problem	Description of proposed amendment	Justification for amendment
The statement of clinical advice creates an impression that "most" patients are offered further chemotherapy. We are unaware of any UK or European guidelines or any commissioning policies for treatment at this stage of the disease prior to the registration of vinflunine. This existing statement undermines confidence in the clinical development programme, registration strategy and NICE Scope without proposing any evidence to support. It simply creates a circular argument that nobody can move on from.	Clinical advice to the ERG confirmed that there is no standard second line therapy for patients with advanced TCCU after failure of prior platinum-containing chemotherapy and that there is variation in practice. Some patients receive second line treatment with repeated use of first line chemotherapy or with taxanes.	If we accept wide inter- and intra-hospital variation we need a bigger sample of clinical opinion. We propose wording that acknowledges that some patients are not abandoned by their oncologist at relapse and are treated with subsequent chemotherapy. But we would remove "most" as this implies structured, logical and consistent patient access and we do not think we are there yet.

Issue 2 2.3.6 Subgroups

Description of problem	Description of proposed amendment	Justification for amendment
The patient population selected for Study 302 had substantial representation of all known or anticipated prognostic factors. 74% visceral involvement, 72% PS 1, 75% > 2 organs involved, 82% relapse within 6 months. The multivariate analysis indicated that all these groups benefitted from treatment.	Delete comment or replace with: Multivariate analysis indicated that subgroups of patients with known or suspected prognostic factors received benefit from active treatment.	This document will be used by commissioners to formulate a treatment policy. The previous wording could lead to subgroups of patients being excluded from these policies.

Issue 3 3.2 Systematic review

Description of problem	Description of proposed amendment	Justification for amendment
Some missing evidence in the MS: "no details are given for any of the processes used in the systematic review"	An overview only of the systematic review was provided by PF in the MS. Due to space constraints it was not possible to include all of the detail. As highlighted by the ERG the quality was good and the risk of error was low.	Highlighting this will give confidence to any reader that the review was carried out thoroughly but is under reported in the MS for the sake of brevity

Issue 4 3.1.2.1 Identified studies Para 4, sentence 3.

Description of problem	Description of proposed amendment	Justification for amendment
The ERG report that cisplatin or carbo were used "alone" as prior treatment in the RCT. This is incorrect. Platinum based chemotherapy was used but only the platinum component is reported. You may also like to know that the reporting of ethnicity is not permitted under French anti-discrimination legislation – even in clinical trial reports.	.....64.8% of the vinflunine plus BSC group and 72.6% of the BSC-only group received cisplatin-based chemotherapy..... ,whilst 29.6% and 19.7% respectively had received carboplatin-based chemotherapy which.....etc.	To avoid a mis-conception that single agent platinum was used as prior chemotherapy. You may choose to delete the comment on ethnicity as this could create a false impression that data was deliberately withheld from the MS.

Issue 5 3.1.3 Table 1: Manufacturer and ERG assessment of trial quality

Description of problem	Description of proposed amendment	Justification for amendment
Item 1, ERG Response "Unclear"	Yes: The following parameters were used in order to generate the randomisation lists of the study 302 : - Permuted randomisation by block of size 6 as the	To reassure the reader that this clinical research was performed to GCP and high standards of research practice were

	number of patients expected by centre was 5 at the time of the writing of the protocol, - Treatment arms : Vinflunine + Best Supportive Care versus Best Supportive Care, - A ratio of 2:1 (i.e 2 patients receiving Vinflunine + Best Supportive Care and 1 patient receiving Best Supportive Care, - Two factors of stratification : centre and refractory status : for each centre, two lists were prepared, one for the refractory patients and one for non refractory patients. The randomisation was performed using “Block Stratified Randomization” for Windows Version 5.0 developed by Steven Piantadosi, M.D., Ph.D, Director of Oncology Biostatistics of the Johns Hopkins Oncology Center. The computer program used to generate sheets makes permuted block stratified assignments with user selected block size. The pseudorandom number generator is a linear congruential algorithm of Park and Miller with Bays-Durham shuffling. It has a period of over 2 billion (Press WH et al. Numerical Recipes in C. Cambridge *University Press, 1992, p 280).*	maintained throughout.

Issue 6 3.1.3 Table 1: Manufacturer and ERG assessment of trial quality

Description of problem	Description of proposed amendment	Justification for amendment
Item 2, Was the allocation adequately concealed? ERG Response “Unclear”	Yes: Concealment of the allocated process : In order to ensure concealment of the allocation process, a **centralised randomisation by fax**, at Pierre Fabre headquarters, was used. For all patients enrolled, the treatment allocation was done only after receiving information	To reassure the reader that this clinical research was performed to GCP and high standards of research practice were maintained throughout.

	that the patient was eligible and had consented to the clinical trial. The process was the following : Once written consent had been signed by the patient and eligibility assessed, an investigator could request randomisation of a patient in the study. The investigator requested randomisation by sending, by fax, the following information to Pierre Fabre headquarters : - The Baseline Randomisation Form, - The Baseline Eligibility Form, - The Baseline Prior Diagnosis Form, - The Baseline Prior Treatment Forms, and, - The Baseline Tumour assessment Forms. The listed pages had to be duly completed by the investigator apart from the patient number the refractory status and treatment allocation section of the Baseline Randomisation Form. When receiving a randomisation fax , the people responsible at Pierre Fabre headquarters transmitted for review to the Clinical Study Manager. While validating the inclusion, the Clinical Study Manager completed the strata information on the Baseline Randomisation Form (Refractory status). Once the inclusion had been validated by the Clinical Study Manager, the people in charge of the centralised randomisation at Pierre Fabre assigned a patient number. Each patient received a six digit number. The first two digits identify the country, the third and fourth corresponded to the centre and the last two digits, the patient within the strata.	

	The people in charge of randomisation at Pierre Fabre identified the list (kept in the Biometric Department locked cupboards) corresponding to the centre and the strata reported on the Baseline Randomisation Form and assigned the treatment corresponding to the rank in the randomisation list. Then he/she reported the treatment arm and the date of randomisation on the Baseline Randomisation Form. The Access software was used for all studies not using a minimisation procedure in order to record the randomised patients. A copy of the Access spreadsheet was forwarded to the investigator's centre and the original Access spreadsheet was filed in a study folder in the Biometry Department. <u>Concealment through sequence generation :</u> In order to ensure concealment through the sequence generation a permuted block design with a block size of 6 for each centre and each stratum of the statification factor "Refractory status" was chosen as the number of patients expected by centre was 5 at the time of writing the protocol. As no information was given in the protocol and the Informed Consent Form, investigators and patients were ignorant of the block size used in order to be unable to predict the next allocated treatment in the centre and the stratum. The clinical team (Clinical Research Associates, Study clinical manager) and the study data manager/statisticians were also ignorant of the block size. Only one internal independent statistician who generated the lists was aware of the size of the block.	

Issue 7 3.1.3 Table 1: Manufacturer and ERG assessment of trial quality

Description of problem	Description of proposed amendment	Justification for amendment
Item 3, Were the groups similar at the outset of the study in terms of prognostic factors, e.g. severity of disease? ERG Response “Unclear”	Yes: The treatment groups are similar in terms of prognostic factors distribution, with the exception of PS, presenting a 10% difference disfavoring VFL arm. The PS is known to be an important prognostic factor of OS for the patients with TCCU. In order to consider the prognostic factors, a multivariate analysis of overall survival using a Cox proportional hazard model was planned in the SAP. The identified prognostic factors were the following: alkaline phosphatase, haemoglobin, presence of visceral metastases, performance status, radiotherapy of the pelvis (Bajorin, JCO 1999). This analysis showed a significant VFL treatment effect (HR=0.77, p=0.0360) and a clear impact of PS on the analysis of OS (HR=0.48, p<0.0001). In order to reinforce the assertion that the imbalance in PS altered the primary analysis of OS, a post hoc Cox proportional hazard model including Arm and PS only, is presented below. In this analysis, the effect of PS is taken into account for the evaluation of the treatment effect on OS: Arm : HR(95% CI)=0.78 (0.61-0.99) p=0.0453 PS : HR(95% CI)=0.44 (0.34-0.57) p<0.0001 A non significant difference in distribution of PS (p=0.071) across arms does not necessarily imply that this difference does not have an impact on OS. With a HR=0.44 (p<0.0001), the impact of PS on OS is clear.	To reassure the reader that this clinical research was performed to GCP and high standards of research practice were maintained throughout.

Issue 8 3.1.3 Table 1: Manufacturer and ERG assessment of trial quality

Description of problem	Description of proposed amendment	Justification for amendment
Item 4, Were the care providers, participants and outcome assessors blind to the treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)? ERG Response "Unclear"	Appropriate: Response was confirmed by the Independent Review Committee (IRC). To minimise bias from the analysis, the IRC were blinded from treatment allocation. Cytotoxic chemotherapy agents are associated with significant side-effects and may require support medications and vigilance for signs and symptoms of infection. It is not possible or ethical to blind care providers and participants from their allocation and it is an open-label study.	To reassure the reader that this clinical research was performed to GCP and high standards of research practice were maintained throughout.

Issue 9 3.1.3 Table 1: Manufacturer and ERG assessment of trial quality

Description of problem	Description of proposed amendment	Justification for amendment
Item 5, Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for? ERG Response "Unclear"	There were no unexpected imbalances in the drop-outs between the treatment groups. Indeed, the imbalance observed in the discontinuation due to AE (20.9% vs. 6.0%) was expected given that no chemotherapy was administered in the control arm. Regarding progressive disease (PD) leading to drop-out, the distribution should be compared by pooling the patients withdrawing due to PD and patients that discontinued due to death for PD, as in both cases the main reason for drop-out is PD. Furthermore, the duration of treatment was planned to be 18 weeks in the BSC arm, then the drop-outs should be compared within this period, given that no discontinuation due to PD can be observed in the BSC group after that period. The rates of patients who discontinued study within 18 weeks for progression or death due to progression were balanced,	To reassure the reader that this clinical research was performed to GCP and high standards of research practice were maintained throughout.

	with rates of 46% and 43% for VFL+BSC and BSC arms, respectively. Of note, 11% of patients in VFL arm discontinued study for PD, or death due to PD, after 18 weeks of treatment.	

Issue 10 3.1.3 Table 1: Manufacturer and ERG assessment of trial quality

Description of problem	Description of proposed amendment	Justification for amendment
Item 7, Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data? ERG Response "Unclear"	An ITT analysis was presented. The eligible ITT analysis, excluding 13 non-eligible patients was also presented. This population excludes patients with major deviations at baseline and represents the targeted population to receive the proposed treatment, thus it is a more appropriate population to estimate the effect of vinflunine on OS. The method used to deal with missing data is the multiple imputation approach proposed by Raghunathan[1]. Raghunathan TE., Lepkowski JM., Van Hoewyk J. and Solenberger P. A multivariate technique for multiply imputing missing values using a sequence of regression models, Survey Methodology, 27: 85-95, June 2001.	To reassure the reader that this clinical research was performed to GCP and high standards of research practice were maintained throughout.

Issue 11 3.1.5 Description and critique of the manufacturer's approach to trial statistics paragraph 2

Description of problem	Description of proposed amendment	Justification for amendment
The Competent Authority, in possession of the complete efficacy and methodology, granted a marketing authorisation for vinflunine, accepting the eligible ITT analysis as a fair and accurate	The primary endpoint (2 months overall survival advantage of VFL over BSC) reached statistical significance in the eligible ITT population (p=0.0403, HR (95% CI): 0.78 (0.61, 0.99)) but not in the ITT population due to the inclusion of 13 patients who did not correspond to the study population and especially	This would provide sufficient information to reassure the ERG that adequate attention has been made to their concerns and provide a basis for a consistent conclusion with the Competent Authority.

representation of efficacy in this patient population. The ERG has had only a summary of these data and has made a conclusion that conflicts with that of the Competent Authority. Such conflicting conclusions are unhelpful to subsequent readers as they have less access to the data and less resource with which to analyse it. The solution seems to be to provide appropriate additional detail and a suitable reference to the analysis performed by the Competent Authority so that the ERG can confirm the conclusion of the EMEA in granting a marketing authorisation.	to the survival hypothesis of the study. The intention-to-treat principle implies that the primary analysis should include all randomised subjects. However, as stated in the ICH E9 guideline (ICH E9, section 5.2.1), there are a limited number of circumstances that might lead to excluding randomised subjects from the full analysis set including the failure to satisfy major entry criteria (eligibility violations). Subjects who fail to satisfy an entry criterion may be excluded from the analysis without the possibility of introducing bias under the following circumstances: (i) the entry criterion was measured prior to randomisation; (ii) the detection of the relevant eligibility violations can be made completely objectively; (iii) all subjects receive equal scrutiny for eligibility violations; (iv) all detected violations of the particular entry criterion are excluded. As regard to the 4 major criteria definition[1] and the application of a blind review to determine the non eligible patients, all circumstances given above are satisfied. As a consequence, the eligible population did preserve the intention-to-treat principle, and this analysis was still a comparison of randomised groups as the violations could not be as a result of treatment. The ERG report considers that the eligible analysis may not be valid due to the breaking of randomization. From a methodological standpoint, it could be argued that the exclusion of the 13 non eligible patients from the ITT population results in non-respect of the randomisation scheme, from which potential biases may arise. Possible imbalances in	It is crucial that reviewers understand that the analysis of the eligible ITT population was statistically valid. The explanation provided establishes that the concern of the ERG about breaking randomisation was taken into consideration and did not invalidate the analysis or conclusion. This is consistent with the conclusion drawn by the competent authority (CHMP/EMA) in granting MA for vinflunine

	the patients' characteristics between the treatment groups in the eligible population may result from these exclusions. In order to verify that the potential imbalances in prognostic factors arising from the exclusion of patients did not challenge the treatment effect on overall survival, an extended multivariate Cox analysis adjusted on 16 covariates (initial prognostic factors and baseline characteristics) has been conducted in the eligible population. This analysis showed a significant impact of the treatment on OS (p= 0.0035) when adjusting its effect on potential confounding covariates. Thus, the potential imbalances in prognostic factors induced by the exclusion of the 13 non eligible patients did not challenge the treatment effect in the eligible population. As a conclusion, the eligible population respects the ITT principle described in the ICH guideline E9, and potential biases arising from patient exclusions have been ruled out. 1: no progression after 1st line chemotherapy; no evidence of advanced disease at baseline; 1st line non platinum containing regimen; more than one line of chemotherapy for advanced disease The process for identifying these ineligible patients was reviewed in the CHMP Report page 56. EMEA/CHMP/370293/2009 The primary analysis performed in the ITT population was affected by the higher proportion of non eligible patients in the BSC arm (9 non eligible patients for BSC vs. 4 for VFL + BSC). Ineligible patients included patients with no progression to first line platinum-containing chemotherapy for advanced disease	

	(12 out of 13 patients) or patients with no advanced or metastatic histologically proven TCCU. This is consistent with the longer survival observed in these patients. Importantly, non eligible patients were identified using a blinded review before database lock, and all analyses were performed after the database lock (30th March 2007). These patients are not representative of the population targeted by the protocol (advanced TCCU that has failed prior platinum-containing regimen).	

Issue 12 3.1.4 Description and critique of manufacturer's outcome selection

Description of problem	Description of proposed amendment	Justification for amendment
Inconsistency in reporting of response rates in the MS. The statement in the MS was directed at the phase III RCT data set where there is no comparable published data with which to compare. We would again highlight that the patient population in the RCT represented an extreme test of efficacy and the impact on survival in this difficult group was the most interesting result. Response rates were the primary objective in the two phase II trials and are reported in the MS. The current wording could wrongly undermine confidence in the manufacturer's disclosure of information and transparency. We would highlight that the MS is 122	Revise text of sentence 2.	To prevent creating a false impression that the MS has attempted to withhold or pervert the transparent flow of information

pages (empty template is 76 pages). We must be careful not to drill into details that could not possible exist in such a brief summary/ overview of efficacy, safety and economics. Where possible, the MS has directed the reader to detailed reviews from reliable third parties e.g. EMEA/CHMP or JCO to reassure the ERG that rigorous evaluation has been properly conducted.		

Issue 13 3.3.5 Summary of Adverse events paragraph 2

Description of problem	Description of proposed amendment	Justification for amendment
Only the clinical toxicity is reported in table B28 on page 64 of the MS. The haematological toxicity is reported in Table B29 on page 65. The reference to the most common adverse events with vinflunine is taken from the discussion in the EMEA/CHMP report page 79. The complete discussion of adverse events is on page 59-81 of this report.	The MS and the CHMP report state that the most frequently observed adverse events with vinflunine were neutropenia, anaemia, constipation and fatigue/asthenia as shown on Table B28 and B29 of the MS. Evidence from the RCT alone indicates that the occurrence of fatigue/asthenia is similar in both arms of this study suggesting that is a consequence of the underlying disease.	Greater accuracy.

Issue 14 3.3.5 Summary of Adverse events paragraph 5

Description of problem	Description of proposed amendment	Justification for amendment
The ERG expresses uncertainty about the impact of adverse events associated with VFL. In the MS, the adverse event profile is considered to be reasonable but this does not concur with clinical information received by the ERG. A more detailed review is accessible in the EMEA/CHMP/370293/2009 page 59-81 with the quoted statement on page 79.	**The main toxicities of VFL were neutropenia (79.6% of the 450 TCCU patients), anaemia (92.8%), constipation (54.9%) and asthenia/fatigue (55.3%), all these AEs being class effects of the vinca alkaloids.** Grade 3/4 **neutropenia** occurred in 54.6% of the patients. This AE is a well known class effect of the vinca alkaloids and its incidence is in the range observed with other members of this class of compounds such as vinorelbine or even lower as compared with topotecan, a registered drug utilized today in daily practice in similar clinical situations like ovary or SCLC 2nd line post platinum containing regimen. Neutropenia did not frequently lead to major clinical consequences; febrile neutropenia and infection with severe neutropenia occurred in 6.7% and 4.2% of the patients respectively and grade 4 infection with severe neutropenia was rare (1.1%). Out of the 450 TCCU patients, four (<1%) died, 2 due to severe infection with severe neutropenia (patient 202-130102 and patient 001-13-124), one due to febrile neutropenia (patient 202-130601) and one due to pancytopenia (patient 302-520503). This patient was exposed to major protocol violations as the administration of VFL dose should have been reduced as per protocol for cycle 2 and 3 due to the severe neutropenia reported at the 1st cycle. **Anaemia** was already common at baseline (47% of the patients). Seventeen percent (17.3%) of the TCCU patients experienced grade 3/4 anaemia; in the phase III, 19.1% of the	The ERG require a more explicit statement of the adverse event profile to formulate a robust analysis that will properly inform subsequent readers.

	patients treated with VFL presented severe anaemia as compared with 8.1% in the BSC. Anaemia was in all cases reversible and manageable. A clear relationship has been shown between the occurrence of anaemia and asthenia/fatigue on study, the incidence of asthenia/fatigue increasing with the grade of anaemia : - when anaemia is grade 1, asthenia/fatigue occurred in 3.2% of the patients - when anaemia is grade 2, asthenia/fatigue occurred in 6.7% of the patients - when anaemia is grade 3, asthenia/fatigue occurred in 14.1% of the patients - when anaemia is grade 4, asthenia/fatigue occurred in 21.4% of the patients It is important to mention that in the pivotal phase III trial, due to patient selection, dose adjustement and selective use of G-CSF the myelotoxicity and its clinical consequences decreased overtime. Grade 3/4 neutropenia and febrile neutropenia were observed in 34.6% (154 pts) and 3.8% (17 pts) during course 1 as compared with 24.5% (53 pts) and 0.9% (2 pts) during course 4 respectively. **Grade 3/4 asthenia/fatigue** occurred in 15.8% of the TCCU patients with rare grade 4 (0.7%). Of note, in the BSC group, severe asthenia/fatigue occurred in 17.9% of the patients which illustrates that the disease itself had a significant impact on the worsening of the general condition of the patients. This supports the suggestion that VFL chemotherapy has no apparent major deleterious effect on the treated patients for these AEs. The incidence of asthenia/fatigue on study seems to also depends on the PS at baseline, PS $\geq$ 1 patients displaying more asthenia/fatigue on study (10.4% versus 5.3% of the patients with PS=0).	

	Constipation, a well-known side effect of vinca alkaloids, was the most common gastrointestinal disorder observed in patients treated with VFL. Grade 3/4 events occurred in 15.3% of patients (69 pts) and grade 4 events were reported in 2 patients (0.4%),were alleviated by symptomatic measures (enema, laxatives) and did not recur when dose adjustment was performed. No cumulative effect was observed for constipation as related grade 3/4 constipation decreased from cycle 1 (10%) to cycle 3 (median of treatment) (2%). Constipation is of short duration lasting between 1 and 3 days in 41% of the cycles where constipation occurred and between 4 and 7 days in 39%. Constipation is associated with a relative absence of major clinical consequences: few patients withdrew due to constipation (2.3% of TCCU patients); the apparent discrepancy between the rate of Grade 3/4 and the very low rate of discontinuation, is probably related to the definition of the grade 3 and its relatively simple way of resolution (manual evacuation or enema). Besides, 35/450 patients were hospitalised due to constipation (40 events), about 50% of the patients were hospitalised when presenting only with a grade 2 constipation (18/40). All the 40 events of constipation resolved and the median time to recovery was 5 days either after laxative treatments (osmotics and/or stimulants and/or enema) or without any specific treatment. **Both dose reduction and laxatives contributed to decrease the incidence of constipation.** 1) Use of laxatives - Patients treated with laxatives are the patients who were treated from day1 to at least day 5 of the cycle with laxatives as proposed in the protocol (osmotics or stimulants or enema). Although 47.6% of patients (214 pts out of 450)	

	received laxatives as prophylactic treatment, it was shown, only in opioids receiving patients, a substantial decrease in the global and Grade 3/4 incidences of constipation per cycle (all Grades: from 43% to 33%, Grade 3/4: from 8% to 5%). Therefore it is wise to recommend the use of laxatives to alleviate the risk of constipation especially in patients presenting with 1 or more of the following conditions: chronic or refractory constipation, Grade≥1 constipation experienced after a previous VFL administration, extensive abdominal surgery, peritoneal carcinomatosis, abdominal tumour masses and concomitant treatment with opioids. - Besides, it should be noted that when patients experienced constipation, most of them resolved when treated by laxatives. As a matter of fact, among the 40 events of constipation requiring hospitalization, all resolved, 33 of them were treated by laxatives with or without enema. No patient underwent any surgery. Out of 78 cases of grade 3/4 constipation (76 grade 3 and 2 grade 4), all but 1 were treated by laxatives and resolved in a median time of 2 days. Most of the constipation were treated by enema (58/78) and/or osmotics (35/78) and/or stimulants (11/78). Few constipation required dose reduction (27/78) or treatment discontinuation (6/78) and thus patients had the benefit to pursue their treatment at the initial VFL dose. Overall, it was shown that all cases of constipations resolved in a short timeframe when treated with laxatives demonstrating that constipation observed with VFL is manageable by appropriate measures (laxatives and/or enema). 2) Dose reduction - The dose reduction of VFL as recommended by the	

	protocol in case of constipation (grade 2 lasting ≥ 5 days or ≥ 3 of any duration) was implemented in only 10.5% of patients which allowed to substantially reduce the incidence of further Grade 3/4 constipation and this, whether or not a concomitant laxative treatment (grade 3/4 downgraded from 42% to 1% and 37% to 7% respectively). It is interesting to note that dose reduction also decreased constipation in patients taking opioids during cycles. Finally, among the patients having presented a reduction due to a constipation grade 3/4, only 19% of them presented a second episode of grade 3 constipation after the dose reduction. All together, constipation Grade 3/4 was observed in 15.3% of patients and 4.2% of cycles. The rapid resolution of this AE combined with the implementation of specific and adapted measures (prophylactic treatments of constipation and dose reduction for further cycles) makes constipation an AE which remains manageable, reversible and do not translate to an unacceptable morbidity. **Infusion site reactions** Infusion site reactions were reported in 27.6% of TCCU patients. Among those, only 2 patients had grade 3 reactions with pain symptoms but without necrosis. Of note, 3 TCCU patients experienced extravasation following vinflunine dosing. All these events were reversible. **Overall** ➢ The main and most frequent AEs of VFL were neutropenia, anaemia, constipation and asthenia/fatigue. ➢ The main dose limiting toxicity is neutropenia. Of note per protocol in all the studies the prophylactic treatment with granulocyte colony stimulating factors (G-CSF) might be	

	used only in case of previous febrile neutropenia, which might have increased the incidence and severity of neutropenia. Neutropenia and anaemia are familiar AEs for physicians in the field of oncology and may be managed by a variety of medical measures such as G-CSF, and blood transfusions. In all cases a close monitoring of haematological parameters is required during treatment. ➢ Constipation is common but rapidly reversible and non cumulative. When prophylactic treatment with laxative is administered or dose adjustments are implemented as recommended by the protocol, the rate of constipation is reduced. Therefore it is wise to recommend the use of laxatives from Day 1 to Day 5 or Day 7 of VFL administration to alleviate the risk of constipation especially in patients presenting with 1 or more of the following conditions: chronic or refractory constipation, Grade≥1 constipation experienced in a previous VFL administration, extensive abdominal surgery, peritoneal carcinomatosis, abdominal tumour masses and concomitant treatment with opioids. The curative treatment with laxatives allowed to resolve all cases of constipation and as such constipation is manageable by laxatives. ➢ No cumulative toxicities were apparent in patients with TCCU receiving VFL. In general the toxicities induced by VFL were transient and manageable. These particular features of VFL allowed prolonged duration of treatment in a substantial number of patients (the median number of cycles is 3 and treatment has been administered up to 21 cycles). ➢ Globally in this population of 2nd line advanced/metastatic TCCU patients resistant or refractory to a prior platinum containing regimen, the safety profile of VFL is predictable, acceptable and manageable by appropriate measures and dose modifications leading to a low rate of discontinuation	

	and treatment related deaths. Notably, many of the AEs commonly induced by cytotoxic chemotherapy which are unpleasant to patients such as alopecia, skin /nail toxicity, and which are potentially dose limiting, debilitating and/or life threatening such as diarrhoea, neurotoxicity, pulmonary toxicity, and hepatic toxicity, are not characteristic of VFL therapy. Finally, VFL does not induce renal toxicity, which is a significant advantage in this population where patients often present with renal impairment at baseline. In summary VFL has a well-characterised safety profile and is generally well-accepted by patients. This is particularly important in this setting where all patients had undergone extensive prior therapy (surgery and/or radiotherapy and polychemotherapy).	

Issue 15 3.3.5 Summary of Adverse events paragraph 5, final sentence

Description of problem	Description of proposed amendment	Justification for amendment
The ERG raises concern regarding the additional cost of managing extravasation. Extravasation results from a mechanical breach of the vein by the infusion needle. In association with a class 1 vesicant (e.g. vincristine, vinblastine, vindesine, vinorelbine (except oral vinorelbine) vinflunine, doxorubicin, epirubicin,	Revise text	Class 1 vesicants are in daily use in most specialist units and the cost of staff training and direct management of this risk is already included within the administration tariff for chemotherapy.

paclitaxel), extravasation requires prompt action to prevent subsequent soft tissue damage. Specialist chemotherapy nurses are routinely trained in the management of extravasation and appropriate administration techniques to minimise occurrence. Class 1 vesicants are in common, routine use. The relative risk of extravasation with vinca alkaloids (all) is estimated in the NPSA Rapid Response Report 2008 (supplementary information page 7) as 0.027%. Unlike other vinca alkaloids which are given weekly, vinflunine is administered once every 3 weeks and the total patient exposure to this risk is relatively lower than with other vincas. Given the routine handling of class 1 vesicants in every chemotherapy unit, it was reasonably assumed that the management of this risk would be included within the chemotherapy administration cost and would not require us to calculate an additional, supplementary cost.		

Issue 16 3.5 Summary paragraph 1, 2, 3

Description of problem	Description of proposed amendment	Justification for amendment
The ERG may wish to revise the text if it can be satisfied that the eligible ITT is a fair and reasonable assessment of the efficacy	Revise text	More accurately describe the efficacy of vinflunine and support the decision of the EMEA to grant a marketing Authorisation.

of vinflunine in the patient population from the response in Issue 11 and by reference to the CHMP analysis.		

Issue 17 4.2.1 Critical appraisal of the economic evaluation methods, Table 7

Description of problem	Description of proposed amendment	Justification for amendment
Item 4: Is the correct comparator used? The ERG raises a question mark that unfairly creates doubt in the mind of the reader. The Comparator used is consistent with the NICE Scope and the registration strategy accepted by the EMEA. The comparator is consistent with UK and European management guidelines available prior to the approval of vinflunine for this indication.	Remove the final sentence.	The chosen comparator is consistent with the NICE Scope, treatment guidelines available at this time and the registration strategy with the EMEA.

Issue 18 4.2.1 Critical appraisal of the economic evaluation methods, Table 7

Description of problem	Description of proposed amendment	Justification for amendment
The ERG may wish to revise this text if satisfied with answers to Issue 11.	Revise text	Consistency within the report

Issue 19 4.3.2.1 Patient Group.

Description of problem	Description of proposed amendment	Justification for amendment
The ERG may wish to revise this text if satisfied with issue 17	Revise text	Consistency within the report

Issue 20 4.3.2.2 Clinical effectiveness, paragraph 1

Description of problem	Description of proposed amendment	Justification for amendment
The ERG may wish to revise this text if satisfied with issue 17	Revise text	Consistency within the report

Issue 21 4.3.2.2 Clinical effectiveness, paragraph 2

Description of problem	Description of proposed amendment	Justification for amendment
The ERG requests an explanation of how the Grambsch and Thereau test was conducted. A separate document " A validation of the Grambsch and Therneau test.doc" is attached	Review of text	Additional explanation supplied as requested.

Issue 22 4.3.4.1 One-way sensitivity analysis (DSA), paragraph 2

Description of problem	Description of proposed amendment	Justification for amendment
The ERG expresses concern that some of the values chosen were unrealistic, such as zero cost for vinflunine. The ERG has already noted that the manufacturer has developed a reasonable model. If the efficacy described by the EMEA is also recognised by the ERG from earlier responses, vinflunine is a useful and active drug – even in the extreme test of study 302 population. SO the big question is how can the economic analysis go so wrong? This indication is a previously unmet clinical need with no recognised standard treatment. Without existing, known treatments costs, we have nothing to offset the cost of anything new. Furthermore, as there is no real world data on the NHS resources these patients actually consume, we have had to make broad assumptions on community and hospital resource use (4.3.2.4) and apply	Propose the final sentence to read: The ERG recognises that calculations using an assumption of zero cost for vinflunine highlight the difficulty of introducing new treatments for previously unmet clinical need towards the end of life.	We then have a basis to agree some prospective data collection and resource implications of new cancer drugs for previously unmet clinical need in small tumour groups.

this equally to both arms and pre-and post progression. The result is that a new treatment is effectively penalised with the assumed cost of extended survival. Dialling in £0 for the cost of vinflunine in this reasonable model is our attempt to highlight the impossible dilemma we face when trying to bring forward a new treatment. If this were 2nd line NSCLC, we would already have the cost of docetaxel and some new drugs have been approved on the basis of equivalent survival and equivalent cost. The situation for a previously unmet clinical need is approaching impossible and we must have a sensible discussion about how this can be improved or we will never make any progress.		

Issue 23 4.3.6 Summary of uncertainties and issues, point 1 & 2

Description of problem	Description of proposed amendment	Justification for amendment
The first point is a “Catch 22”. We hope the responses to previous issues and reference to the detailed analysis performed by the EMEA/CHMP will satisfy	Revise text	We also have to consider the cancer service we want in the next 10 years. Drugs that demonstrate efficacy in the extreme test of BSC often yield significant long term survival when used earlier and in combined modality, e.g. vinorelbine in NSCLC, oxaliplatin in

the ERG that vinflunine has demonstrated a survival advantage in an extreme test of efficacy.		colorectal cancer and docetaxel in breast cancer. Unless we establish early clinical confidence in the first, end of life indication, we will never progress to curative options and more good drugs will be wasted. We have an excellent opportunity to introduce new drugs more effectively through the new cancer drug fund and associated data collection

Issue 24 Executive Summary page 6-9

Description of problem	Description of proposed amendment	Justification for amendment
Consider revising text following review of issues raised.	Revise Text	Consistency within the report.

Issue 25

Description of problem	Description of proposed amendment	Justification for amendment

Issue 26

Description of problem	Description of proposed amendment	Justification for amendment