National Institute for Health and Clinical Excellence

Single Health Technology Appraisal (STA)

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

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	RCN	No comments	Comment noted.
	Pierre Fabre	There is currently no recognised therapy for patients with advanced or metastatic TCCU after failure of a platinum-containing regimen. The licensed indication for this novel technology represents an unmet clinical need. We prefer that this fact should be recognised by the remit as it has significant implications for the suitability of comparators.	Comment noted. Following consultation the draft remit has been updated to state: 'To appraise the clinical and cost effectiveness of vinflunine for the second line treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of prior platinum-containing chemotherapy'.
	RCP	Effective 2nd line chemotherapy in urothelial TCC is certainly an area of unmet clinical need. The vinflunine phase2 data is similar to that of many other agents. A single phase 3 trial of vinflunine vs best supportive care has been performed. This shows modest quality of life and survival benefits for the eligible population (after excluding ineligible patients with major protocol violation and patients who did not receive vinflunine after randomisation), though not the intention to treat population (likely to be more representative of the patients we would treat clinically). Multivariate analysis of prognostic factors specified a priori strengthened the significance of the survival benefit.	Comment noted. The scope forms the framework for the appraisal and does not normally include detail about the available evidence. Consultees are invited to submit a statement in which they may provide any information they think relevant to the appraisal.

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		Problems: Some difficulty here with the control arm and patient selection. Standard of care for post-platinum progression in the UK for fit patients is 2nd line chemotherapy (often taxane-containing) and the decision to enter a patient into this study (containing a BSC control arm) suggests that this population may have been considered unfit for existing 2nd line regimens (though ~30% went on to have other chemo in both groups). It may not therefore be representative of the group who we consider fit for 2nd line chemo (to whom vinflunine would be indicated if NICE appraisal is positive).	
Wording	RCN	No comments	Comment noted
	Pierre Fabre	Adult patients with advanced or metastatic transitional cell carcinoma of the urotheilal tract who have failed a platinum-containing regimen have an unmet clinical need. Vinfunine is now licensed in this indication and the remit is to appraise its clinical and cost effectiveness in this end-of-life setting	Comment noted. Following consultation the draft remit has been updated to state: 'To appraise the clinical and cost effectiveness of vinflunine monotherapy for the second line treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of prior platinum-containing chemotherapy'. The scope forms the framework for the appraisal. End of life considerations will be taken into account by the Appraisal Committee if appropriate.
	RCP	Yes	Comment noted

Section	Consultees	Comments	Action
Timing Issues	RCN	No comments	Comment noted
	Pierre Fabre	No comments	Comment noted
	RCP	Timescale of meetings appropriate	Comment noted
Additional comments on the draft remit	RCN	No comments	Comment noted
	Pierre Fabre	No comments	Comment noted
	RCP	Vinflunine may become the comparator arm for future 2nd line trials.	Comment noted

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	RCN	In the 3rd paragraph of the "background" section, it is not clear whether carboplatin is added to gemcitabine or whether it is given as a single agent.	Comment noted. The background section of the scope has been updated following consultation.
	Pierre Fabre	We suggest inserting the following at the end of the third paragraph of Background after the sentence: " Chemotherapy such as gemcitabine and paclitaxel in combination may also be used". It is estimated that 30-40% patients subsequently relapse after surgery +/- radiotherapy +/- chemotherapy with metastatic spread of disease from the primary site(s) and receive first line (or repeated) chemotherapy with the agents listed above (2040-3060 patients in England and Wales). Treatment for advanced metastatic disease is palliative and further relapse is common. It is estimated that 40-50% of these patients are too fit to abandon from further treatment and will be candidates for 2nd line treatment (816-1530 patients). Expert opinion is that these may currently be over estimates. There are currently no other agents licensed in the UK for second line treatment of TCC.	Comments noted. The background section of the scope has been updated following consultation.

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	RCP	1st sentence of "Background" - cancer not cancers. 3rd paragraph of "Background" - The summary of chemotherapy in urothelial TCC needs amending. It should specify neoadjuvant, adjuvant and first line metastatic indications. Cis/Gem and Carbo/Gem are by far most common in all indications and should reflect this. Paclitaxel is not licensed for this indication. e.g. Patients with advanced TCC that has invaded the bladder wall or spread to the lymph nodes may receive treatment with surgery (radical cystectomy) and/or radiotherapy. Chemotherapy may be given before (neoadjuvant) or after (adjuvant) surgery/radiotherapy in an attempt to improve cure rates. If the urothelial cancer is too advanced for surgery/radiotherapy or has recurred after these treatments, chemotherapy can be used to improve quality of life and survival. The most common first line chemotherapies in this setting are cisplatin/gemcitabine and carboplatin/gemcitabine. Combinations of methotrexate, vinblastine, doxorubicin and cisplatin [MVAC]; or gemcitabine and paclitaxel may also be used. There are currently no agents specifically licensed in the UK for second line treatment of TCC.	Comments noted. The background section of the scope has been updated following consultation.
	Pierre Fabre	The statement "...acts as a typical tubulin antagonist" is not accurate. Vinflunine was generated using an innovative chemical approach which resulted in a novel vinca-derived chemotherapeutic agent with some unique features. One such feature is the contrast between the relatively low and reversible tubulin binding affinity and the high level of tumour cell cytotoxicity.This antitumour activity, demonstrated in in vitro and in vivo screening models, is higher than that seen in earlier generations of vinca alkaloids while having a more favourable tolerability profile. It has a wide therapeutic index; suppression of microtubule dynamicity and spindle formation resulting in apoptotic cell death involves different pathways at different concentrations. Additionally, vinflunine has anti-angiogenic and anti-vascular properties and is a less potent inducer of Pgp-mediated resistance than the earlier generation vincas. In summary, the therapeutic doses achievable with vinflunine, being orders of magnitude greater than earlier generation vincas, while maintaining a favourable safety profile underpins its	Comments noted. The background section of the scope has been updated following consultation.

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		potential in difficult-to-treat tumours.	
	RCP	Yes	Comment noted.
	Pierre Fabre	This is accurate but at present the only options many such patients are offered are symptom-specific containment procedures. These are often delivered by a range of health care professionals creating the potential for delays. In some cases, chemotherapy which is unproven in this setting is used to contain symptoms by tackling the underlying disease. The availabilty of vinflunine with its favourable safety profile compared to some other cytotoxics is likely to increase the number of patients for whom meaningful life-prolonging treatment is an option, without significantly impacting on quality of life as compared to supportive care alone.	Comment noted.
	RCP	See above re: appropriateness	Comment noted.
Comparators	RCN	No comments	Comment noted
	Pierre Fabre	The only controlled data (phase III) available is "best" supportive care as defined by the trial protocol. This was essentially symptom-driven palliation according to local procedures and was not designed to achieve life-extending outcomes. In NHS practice it is understood that a proportion of patients too fit to abandon after failure of first-line chemotherapy. Such patients may receive second-line chemotherapy with other cytotoxics unlicensed in this indication. Therefore, in terms of a cost comparator, considering supportive care alone excludes the costs of any unlicensed chemotherapy for patients progressing after first line. Inevitably this will under-estimate the the true costs currently incurred of managing patients who fall within the licensed indication for vinflunine. Vinflunine extended survival to an acceptable and credible level to achieve regulatory approval from the competant authority. A further difficulty in the assessment of cost effectiveness of this treatment will be that the associated cost of longer survival (excluding the cost of vinflunine and its administration) will be associated only with the treatment arm. The QALY calculation and the impact of "utility" scores will further exacerbate this attributed cost inbalance	Comment noted. The scope forms the framework for the appraisal. Manufacturer consultees are invited to submit evidence for this appraisal. For information about end of life considerations please refer to NICEs supplementary advice (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp).

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		of extending survival.	
	RCP	As above: no currently licensed agents for 2nd line therapy. For fit patients, standard therapy is 2nd line chemotherapy. For patients considered unfit for chemo, BSC is an acceptable control arm.	Comment noted. It was established at the scoping workshop that best supportive care was the only appropriate comparator for this appraisal.
Outcomes	RCN	No comments	Comment noted.
	Pierre Fabre	We suggest replacing response rate with disease control rate.	Comment noted. Consultees at the scoping workshop agreed that it was appropriate for response rate to remain in the scope.
	RCP	Yes	Comment noted.
Economic analysis	RCN	No comments	Comment noted.
	Pierre Fabre	As discussed above, improved survival is the primary goal in cancer research and the development of new treatments for previously unmet clinical need. If, through the process of economic analysis, the indirect cost of extended survival is attributed only to the active treatment, achieving cost effectiveness becomes very difficult. The effect of the utility score in this end-of-life setting will amplify this discrepency further.	Comment noted. Consultees are invited to submit evidence for this appraisal. For information about end of life considerations please refer to NICEs supplementary advice (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp).
	RCP	Median survival time short	Comment noted.

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Equality and Diversity	RCN	No comments	Comment noted.
	Pierre Fabre	The incidence of bladder cancer in 'poorer' socioeconomic groups is higher, most likely due to the impact of smoking and industrial exposure to carcinogens. We note that the one year survival rates in other cancers vary markedly between different demographic groups. Therefore, it is important to ensure that the technology is equitably available to all socioeconomic groups.	Comment noted.
	RCP	No issues	Comment noted.
Other considerations	RCN	No comments	Comment noted.
	Pierre Fabre	The introduction of new technologies for unmet clinical needs is intended to improve the overall health of the population. Therefore, it is useful to reflect on the effect that the introduction of new treatments has had on management in other end-of-life situations. For example, the introduction of the taxanes, gemcitabine and vinorelbine for the management of NSCLC (TAG No 26), has led to a significant improvement in the speed of diagnosis and referral of lung cancer patients. This has further improved the management and outcomes of this patient population. The survival gain seen with vinflunine in 2nd line TCCU is at least comparable to that seen in NSCLC in the 1990s. By analogy with NSCLC, it can be argued that the adoption of vinflunine into the management of TCCU is likely to streamline the patient pathway and result in further improvements in outcome. Therefore, the long-term benefits of introducing new treatments for unmet clinical needs will be underestimated by trial data alone. It might be useful to compare the cost to achieve the survival gains obtained with vinflunine in TCCU with the costs of drugs for other tumours that provided similar survival gains at adoption. For example the inflation-adjusted cost of paclitaxel introduced in 1994 for ovarian and lung cancers.	Comment noted. Consultees are invited to submit evidence for this appraisal. For information about end of life considerations please refer to NICEs supplementary advice (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp).
	RCP	Toxicity presumably appraised in clinical effectiveness	Comment noted.
Questions for consultation	RCN	Best Supportive Care is symptom control and can include palliative radiotherapy, blood transfusion, analgesia, bisphosphonates.	Comment noted. The comparators section of the

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			scope has been updated following consultation to provide a definition of BSC.
	Pierre Fabre	See our comments for 'Comparators' Supportive care as defined for the phase III trial was according to institutional standards and is inevitably inconsistent being symptom-driven without addressing the underlying disease. It included radiotherapy, antibiotics, analgesics, steroids and transfusions. In normal practice further lines of chemotherapy are sometimes given in attempts to restrain the disease.	Comment noted. The comparators section of the scope has been updated following consultation to provide a definition of BSC.
	RCP	No comments	Comment noted.
Additional comments on the draft scope.	RCN	No comments	Comment noted.
	Pierre Fabre	We believe that it is important to audit the outcomes (efficacy, safety and QoL) of the use of innovative new techologies over time. This would reveal important information about outcomes achievable in the 'real world' (ie outside of clinical trial settings) and give an indication of how experience with their use may improve outcomes (as in the example of NSCLC cited above). When patients receive symptom control-driven care they often re-enter the health care system at different points according to the symptomatic need. The availability of a new therapy aimed at controlling the underlying disease can redfine the treatment pathway by unifying the point of re-entry such that best practice, patient experience and outcomes are improved.	Comment noted. NICE sets a review date for the appraisal based on the available evidence for the technology, and knowledge of when ongoing research will be reported. Please note the questions regarding innovation in the letter of invitation to participate.
	RCP	No comments	Comment noted

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope:

Marie Curie Cancer Care
NHS QIS
Research Institute of the Care of Older People (RICE)
MHRA

National Public Health Service for Wales (now Public Health Wales NHS Trust)
Macmillan Cancer Support