National Institute for Health and Clinical Excellence

Trabectedin for the treatment of advanced metastatic soft tissue sarcoma

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	PharmaMar	The estimated number of patients potentially considered for treatment for metastatic soft tissue sarcoma in England and Wales after failure of an anthracycline and ifosfamide is likely to be around 150 per annum, of whom only a fraction will receive therapy with trabectedin. The expected cost per patient treated is around £15,000. In these circumstances we suggest that the use of trabectedin in metastatic soft tissue sarcoma is unlikely to impact significantly on NHS or other societal resources. No studies conducted to date have compared trabectedin to other active agents or to best supportive care in metastatic soft tissue sarcoma. No quality of life data were collected in any trabectedin study, and a literature review did not identify any quality of life data in metastatic soft tissue sarcoma There is therefore limited evidence on which to base the appraisal. The majority of patients with metastatic soft tissue sarcoma will be managed at a small number of highly specialised centres by doctors who are experts in the management of metastatic soft tissue sarcoma. Variation in practice and inappropriate use of the technology are therefore unlikely. We suggest that a NICE technology appraisal of trabectedin for treatment for metastatic soft tissue sarcoma at this time is unlikely to add value for the NHS. Ongoing research is addressing the potential use of trabectedin in ovarian cancer, which has higher prevalence and more extensive data available, and a regulatory submission is anticipated in late 2008. We suggest that deferring consideration of trabectedin until evidence is available for the ovarian cancer indication may be more likely to result in guidance which is helpful to the NHS in England and Wales.	Comment noted. These issues were considered by the topic selection panel and the referral oversight group. The Department of Health have referred this technology to be appraised by NICE.
	RCPath	This is a highly appropriate study.	Comment noted.

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	RCP	Yes	Comment noted.
	ICR	Yes	Comment noted.
	Rarer Cancers Forum	It is surprising that NICE are undertaking this appraisal as this is an ultra - orphan drug with approximately 179 patients needing this therapy a year. We wonder why NICE is wasting taxpayer's money on this exercise. A PCT may only have one patient a year	Comment noted. These issues were considered by the topic selection panel and the referral oversight group. The Department of Health have referred this technology to be appraised by NICE.

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	Sarcoma UK	The Cancer Reform Strategy states: “In future the default position for all new cancer drugs and significant new licensed indications will be that they will be referred to NICE, providing that NICE agrees that there is a sufficient patient population and evidence base on which to carry out an appraisal and that there is not a more appropriate alternative mechanism for appraisal." Sarcoma is an extremely rare condition and the numbers of patients who could potentially benefit from trabectedin are small (<200). Given the rarity of sarcoma, a decision by NICE to appraise trabectedin would seem to go against the spirit of this announcement. Trabectedin is an extreme orphan medicine. It is questionable whether appraising it would be an effective use of NICE’s resources. Because of the small patient numbers involved, it is likely that the cost impact of approving trabectedin will be relatively low (c£3 million for the whole United Kingdom), negating the need for a lengthy and costly appraisal process. Trabectedin represents a breakthrough treatment for advanced sarcoma and has attracted a great deal of support from the clinical and patient community. Because improvements in sarcoma treatment have been few and far between trabectedin has the potential to fill a genuine unmet health need. Trabectedin is licensed for use in patients with advanced sarcoma where other treatments have failed or are inappropriate. As such, it offers a new option for patients who might otherwise have exhausted their options for active treatment.	Comments noted. These issues were considered by the topic selection panel and the referral oversight group. The Department of Health have referred this technology to be appraised by NICE.
Wording	PharmaMar	The wording of the remit appears appropriate.	Comment noted.
	RCPath	The wording has been simplified for a lay readership. Some descriptions of the technology are therefore less precise than might otherwise be the case.	Comment noted.
	RCP	Our concern here is that median duration of benefit may be inappropriate since some patients, a sizeable subset, experience prolonged disease stabilisation.	Comment noted. If evidence allows, subgroups will be considered.

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	ICR	I don't know how cost effectiveness is calculated my concern here is that median duration of benefit may be inappropriate since some patients, a sizeable subset, experience prolonged disease stabilisation.	Comment noted. If evidence allows, subgroups will be considered.
	Rarer Cancers Forum	We do not think that enough emphasis is made on the fact that this drug meets unmet need This is the first new drug available for STS for more than 20 years and most other countries are delighted that a therapy can help a small group of patients who have until now had no treatments if they have failed at surgery and first line chemotherapy	Comment noted.
	Sarcoma UK	GIST (gastrointestinal stromal tumour) is a soft tissue sarcoma. It is inappropriate for this appraisal to include GIST as no trial data exist. The wording should therefore be amended to specifically exclude it.	Comment noted. The background section of the scope has been amended, this issue has also been included within the other considerations section.
Timing Issues	PharmaMar	Notwithstanding the comments made in regards to the appropriateness of the appraisal, the suggested timing presents no difficulties. With respect to the timing of the scoping workshop, however, this clashes with the major international oncology meeting of 2008. The 44th ASCO Annual Meeting takes place in Chicago from 30 May-3rd June and the vast majority of physicians will fly out by the 29th. Given that this is a highly specialised area, there are only a small number of physicians who treat this rare disease and we believe that it could be inappropriate to proceed with this key Scoping Workshop in the absence of such specialists. With this in mind we should be grateful if NICE would reschedule the date for the Scoping Workshop to allow all interested parties to attend to ensure a more effective and relevant workshop .	Comment noted.

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	RCP	The drug was granted a product licence in September and currently access to the drug is determined on an individual basis by PCTs leading to "post-code prescribing".	Comment noted.
	ICR	The drug was granted a product licence in September and currently access to the drug is determined on an individual basis by PCTs leading to "post-code prescribing".	Comment noted.
	Rarer Cancers Forum	Patients are being denied this drug by PCTs even though it has not had NICE guidance so it important to sort out this issue urgently.	Comment noted.
	Sarcoma UK	An approvals process is needed urgently as differential approaches by PCTs to this new treatment are already apparent, leading to inconsistent (and inappropriate) funding decisions.	Comment noted.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	PharmaMar	Complete surgical resection of the metastases is only feasible in a small minority of cases, systemic chemotherapy being the main treatment modality for STS patients with metastatic disease. Despite available chemotherapy, the prognosis for these patients is very poor, with an estimated median survival of 8-12 months from the start of first-line cytotoxic therapy.	Comments noted. The background section of the scope has been amended.
	RCPath	Acceptable	Comment noted.
	RCP	The stomach is a rare site for leiomyosarcoma. Uterus is not uncommon, otherwise they can arise anywhere in the body, retroperitoneum, inferior vena cava, limbs, etc. The commonest sarcoma in the stomach is gastrointestinal stromal tumour. The incidence of sarcoma is generally underestimated and a figure closer to 1800-2000 per annum is probably more accurate for the UK. Otherwise reasonable.	Comments noted. The background section of the scope has been amended.
	ICR	Reasonable	Comment noted.
	Rarer Cancers Forum	This does not focus on the issue of meeting unmet need with an ultra orphan therapy	Comment noted. This is not an issue that would be covered by the scope document.
	Sarcoma UK	The Background is incomplete and factually inaccurate. Suggest: Soft tissue sarcomas (STS) are a heterogeneous group of cancers which develop from cells in the soft, supporting tissues in the body including muscle, fat and blood vessels. Most cases (about 55%) are on extremities (legs/arms) while about 15% are in the head and neck area. STS also develop on the trunk, in the abdomen and in the retroperitoneum sometimes associated with specific organs such as the womb (uterus). It affects people of all ages. Soft tissue sarcoma has a UK incidence of around 2000 cases a year making up less than 1% of all cancers. However gastrointestinal stromal tumour (GIST) accounts for approximately 700 of these, leaving about 1300 cases relevant to this proposed appraisal. It is estimated that each year 600 to 700 UK patients develop advanced metastatic STS. Overall 5-year survival is	Comments noted. The background section of the scope has been amended.

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		about 55% while for some subtypes of STS it can be up to 90%. Five-year survival with metastatic disease is around 10 to15% of those affected. There are many types of STS, two of the commoner being leiomyosarcoma (which is associated with smooth muscle) and liposarcoma (which develops from fat cells). Distinguishing between STS histological subtypes is important for their clinical management. The primary treatment is surgery, which can be a cure. There is no valid adjuvant therapy. Owing to delayed diagnosis many patients are metastatic at diagnosis. For others the histological subtype makes metastasis certain, or most probable. Grade, location and size of tumour are prognostic for metastasis with all sarcomas. Where metastasis occurs surgical intervention is possible for some patients. This may be supported by radiotherapy and chemotherapy. Metastectomy is currently the principle factor in long term survival for advanced patients. If surgical intervention is not appropriate chemotherapy is the only available treatment. The standard chemotherapies for metastatic STS are doxorubicin (usually administered as an out-patient) and high dose ifosfamide (given as an in-patient). They may be delivered in combination. Certain histological subtypes respond to other treatments and some STS do not respond to any of the standard treatments. Two year survival based on treatment with chemotherapy alone is <3% of those treated.	
The technology/ intervention	PharmaMar	Yes, the draft scope accurately describes trabectedin and its use in treating patients who have failed other active chemotherapies.	Comment noted.
	RCPath	As far as I can judge.	Comment noted.

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	RCP	We disagree with the description of trabectedin in the draft scope. This is a DNA minor groove binder. It is not an alkylating agent in the usually accepted sense of the term, i.e. this usually refers to bifunctional cross-linking agents that cause DNA damage leading to apoptosis through this mechanism. It does however produce adducts that cannot be repaired in the usual way and as such the presence of absence of DNA repair proteins appears to be important in its mechanism of drug-induced cell death. It produces a conformational change in DNA and interferes with the binding of transcription factors, resulting in inhibition of downstream gene expression. The latter may be particularly important in the activity against certain sarcomas, e.g. myxoid liposarcoma, which is driven by specific chromosomal translocations.	Comments noted. The technology section of the scope has been amended.
	ICR	Yes	Comment noted.
	Rarer Cancers Forum	Yes	Comment noted.
	Sarcoma UK	Yes	Comment noted.
Population	PharmaMar	Yes, the draft scope accurately describes the use of trabectedin in those patients who are willing and able to continue systemic chemotherapy having undergone disease progression following failure of both ifosfamide and an anthracycline.	Comment noted.
	RCPath	Data relating to different primary sarcomas should be considered separately, as well as combined as a single cohort.	Comment noted.
	RCP	Subgroup - as mentioned above, myxoid liposarcoma appears to be particularly susceptible to treatment with this agent, otherwise the population is as described and one would not wish to restrict the drug to this disease.	Comment noted. The scope has been amended accordingly.
	ICR	Subgroup - as mentioned above, myxoid liposarcoma appears to be particularly susceptible to treatment with this agent, otherwise the population is as described and one would not wish to restrict the drug to this disease.	Comment noted. The scope has been amended accordingly.

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	Rarer Cancers Forum	This population is so small there is no way it can be subdivided	Comment noted. Discussions during the scoping workshop suggested that subgroups should be considered where evidence allows.
	Sarcoma UK	The population is a diverse group which it is inappropriate to consider as suffering from a single disease. However we are only just beginning to understand some of the crucial differences between sarcomas and even if we did have full biological knowledge we lack the range of treatments to address those differences. Any appraisal should therefore consider both the whole population as a single treatment group and the fact that there are multiple subgroups within that population, mostly defined by histology, some of which are not yet defined but will be in coming months/years. There is also a teenage and young adult community where the distinction between paediatric sarcoma and adult sarcoma is blurred. Trabectedin may be appropriate to this group of patients but owing to very small numbers there are no data and formal trials are unlikely.	Comment noted. Discussions during the scoping workshop suggested that subgroups should be considered where evidence allows. Discussions at the scoping workshop indicated that while certain sarcomas that are more frequent in the paediatric population are managed differently (rhabdomyosarcomas), other histological types are managed in the same manner as similar tumours in adults. NICE can only issue guidance in line with the marketing authorisation of the technology.

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Comparators	PharmaMar	Yondelis is indicated for treatment of patients after failure of both standard treatments (anthracyclines and ifosfamide). The main trial of trabectedin in metastatic STS was a randomised trial comparing two dose schedules of trabectedin. No comparative study against BSC or other active chemotherapy agents has been conducted. No other chemotherapies are licensed at this stage for treatment of relapsed STS after failure of standard therapies. Furthermore, there are no data available to support an indirect comparison as no placebo / best supportive care comparison data are available. Instead, the regulatory submission included an indirect comparison, using an analysis against relevant data from the EORTC database. It would be expected that an economic evaluation performed in preparation for a NICE STA would require a similar approach despite the requirements underlying the NICE reference case. The type of chemotherapies administered is likely to vary widely from one patient to another. With BSC defined in a way that acknowledges these factors, BSC would seem an appropriate comparator.	Comments noted. BSC was agreed to be the appropriate comparator at the scoping workshop.
	RCPath	Outside the scope of a pathologist to answer.	Comment noted.
	RCP	Yes, alternatives at this stage are likely to be experimental, apart from individual tumour types that are treated differently such as angiosarcoma. The combination of gemcitabine + docetaxel is also active against leiomyosarcoma.	Comment noted. BSC was decided to be the most appropriate comparator at the scoping workshop.
	ICR	Yes, alternatives at this stage are likely to be experimental, apart from individual tumour types that are treated differently such as angiosarcoma. The combination of gemcitabine + docetaxel is also active against leiomyosarcoma.	Comment noted. BSC was decided to be the most appropriate comparator at the scoping workshop.
	Rarer Cancers Forum	There is no approved therapy for the treatment of patients with advanced or metatatic STS This is the only treatment that is available as noted below we will be asking for the cost effectiveness model for best supportive care so that the comparator is fair and open	Comment noted. BSC was decided to be the most appropriate comparator at the scoping workshop.

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	Sarcoma UK	Best supportive care is the only treatment option having failed doxorubicin/ifosfamide, except for one or two exceptions. It is the appropriate comparator.	Comment noted. BSC was decided to be the most appropriate comparator at the scoping workshop.
Outcomes	PharmaMar	The primary endpoint in the randomised trial was time to progression (TTP). Secondary endpoints included progression-free survival (PFS), overall survival (OS), response rate (RR) and safety. Health related quality of life was not collected in the pivotal trial. Moreover, given the small patient population (as evidenced by the orphan drug status of trabectedin), a review of the literature identified no alternative quality of life data in patients with metastatic soft tissue sarcoma.	Comment noted. The outcomes in the draft scope were discussed at the scoping workshop and remain unchanged.
	RCPath	Yes	Comment noted.
	RCP	Yes	Comment noted.
	ICR	Yes	Comment noted.
	Rarer Cancers Forum	The most important outcome is that patients are given a chance of survival. The results of studies show that the therapy arrests tumour growth in 50% of patients and gives statistically significant extention of time to tumour progression as well as tumour free survival. This is the reson why we have a NHS to give to patients at the time of need	Comment noted.
	Sarcoma UK	Disease stability (within the context of overall clinical benefit) is an important measure of response and should be specifically included.	It was accepted that disease stability was an important outcome in clinical practice and is included in the outcomes section of the scope (as subtype of response outcome).

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Economic analysis	PharmaMar	As discussed above, while a cost-utility analysis would be desirable to ensure that the value for money of trabectedin could be assessed against that of other health care interventions, there are no data available to undertake such an analysis in such a way that could reliably assist decision-makers. The reference case proposed is appropriate, however, with respect to the time horizon. The patient population of interest has a short life expectancy from the point of treatment with trabectedin. An economic evaluation of trabectedin in this population would need to capture both costs and health outcomes over the remainder of the patient's lifetime. The cost perspective proposed is appropriate to capture those costs Relevant from the NHS perspective.	Comment noted. The appraisal would need to be based on the available evidence noting any areas of uncertainty. A lifetime horizon would be the most appropriate for terminal illnesses.
	RCPath	QALY is an appropriate measure.	Comment noted.
	Rarer Cancers Forum	This if it has to be done needs to be fast and quick and meanwhile patients a small group of patients are being denied this drug.	Comment noted.
	Sarcoma UK	This is an ultra orphan disease and trabectedin is an innovative treatment awarded orphan status because of its promise in treating it. It is recognised that orphan treatments carry a higher cost than treatments for more common conditions. Even so, the financial impact of approval for the NHS is limited because of the low numbers of patients. These facts mean that it will be inappropriate for the £30,000 QALY to be used as a factor in the economic analysis.	Comment noted.
Other considerations	PharmaMar	The draft scope's comments regarding the components of best supportive care are of utmost importance. Any economic evaluation of trabectedin in this indication would need to acknowledge the fact that chemotherapy use does continue for a substantial proportion of patients following failure of anthracyclines and ifosfamide.	Comment noted.
	Rarer Cancers Forum	We will be demanding to see the final best supportive care model if one is used as comparator and check this against best practice agreed by clinicians. It occurs to us that best supportive care in many instances can be more expensive over a period	Comment noted.

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Questions for consultation	PharmaMar	PharmaMar are of the opinion that a Single Technology Appraisal is the only relevant mechanism by which to appraise trabectedin in this patient population, should NICE wish to proceed. With respect to the way in which BSC is defined, the comments made in response to the questions above are relevant. That is, BSC should include the possibility of further chemotherapy for a proportion of patients despite the fact that these treatments have not been clearly shown to be active or that they are not currently reimbursed by the NHS. Discussions held with clinicians to date indicate that approximately one-third of patients will seek further chemotherapy in the UK, though the estimates vary widely. Additionally, the accepted definition of BSC would need to include other inpatient stays, treatment of adverse events, terminal care, diagnostic tests and other non-chemotherapy drugs.	Comment noted. At the scoping workshop it was agreed that if this appraisal is referred a STA would be appropriate.
	RCPath	Outcomes should be derived for subgroups (e.g. defined by grade) and maybe even for different tumours (defined pathologically). This may not yield statistically significant data, but could allow the cohort analyses to be more considered should trend defined, disease specific anomalies be removed.	Comments noted. At the scoping workshop it was agreed that all STSs types (excluding certain defined tumours) should all be considered together but that if evidence allows sub-groups will be considered.

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	Sarcoma UK	Which process would be most suiutable for appraising this technology ? We have expressed our surprise that NICE is considering an appraisal of the clinical and cost effectiveness of trabectedin in view of the workload it faces, the new demands placed on it by the Cancer Reform Strategy, and the potential for approval by other means indicated in the Cancer Reform Strategy. We also note the comments made by NICE to the Commons Health Select Committee about appraisal of rare diseases and remarks made by Sir Michael Rawlings in various for a about the standards which should apply in such circumstances. We are unclear as to the exact standards that will apply to an appraisal of an ultra-orphan treatment-condition pairing such as trabectedin-sts and would wish to have that clarified. Specifically we would expect to see removal of the £30,000 QALY, clear statements about validity of data from non-randomised studies, and open support for orphan situation, in line with that of the European Commission, EMEA and MHRA. If it is decided that an appraisal is inappropriate, whether because of patient numbers or for any other reason, we wish to have it clearly stated what "alternative mechanism for appraisal" (using the words of the Cancer Reform Strategy) will be employed. In the absence of a full NICE Appraisal we expect to see guidance to the NHS published which supports the present licence and any future licence modifications for trabectedin for soft tissue sarcoma, with the full implementation requirements of NICE Technology Appraisal Guidance.	Comments noted. These issues were considered by the topic selection panel and the referral oversight group. The Department of Health have referred this technology to be appraised by NICE.
Additional	RCN	The draft remit and the draft scope seem appropriate.	Comment noted.

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comments on the draft scope.	RCP	1. Ifosfamide is currently always given as an inpatient treatment for sarcoma as far as we are aware (usually 3 to 5 nights) 2. Trabectidin may well have particular activity against certain sub-types of STS such as myxoid liposarcoma and myxoid leiomyosarcoma. 3. Unlike other cytotoxic chemotherapy the practice is usually to continue treatment with trabectidin until there is evidence of progression and this may mean over a year on therapy. The drug is well tolerated. 4. Central venous access is required for trabectidin usually. It is given as a 24 hour infusion (this also usually means an inpatient stay	Comments noted. Consideration to include a continuation rule of trabectedin with stable disease was discussed at the scoping workshop and is included in the other considerations section of the scope.
	ICR	The stomach is a rare site for leiomyosarcoma. Uterus is not uncommon, otherwise they can arise anywhere in the body, retroperitoneum, inferior vena cava, limbs, etc. The commonest sarcoma in the stomach is gastrointestinal stromal tumour. The incidence of sarcoma is generally underestimated and a figure closer to 1800-2000 per annum is probably more accurate for the UK. I would take issue with the description of trabectedin in the draft scope. This is a DNA minor groove binder. It is not an alkylating agent in the usually accepted sense of the term, i.e. this usually refers to bifunctional cross-linking agents that cause DNA damage leading to apoptosis through this mechanism. It does however produce adducts that cannot be repaired in the usual way and as such the presence of absence of DNA repair proteins appears to be important in its mechanism of drug-induced cell death. It produces a conformational change in DNA and interferes with the binding of transcription factors, resulting in inhibition of downstream gene expression. The latter may be particularly important in the activity against certain sarcomas, e.g. myxoid liposarcoma, which is driven by specific chromosomal translocations.	Comments noted. The scope has been amended accordingly.
	Rarer Cancers Forum	Yet again we would ask NICE to give us the accuracy of references surely you have them and do not make up the material. This is standard good professional practice.	Comment noted. NICE documents do not contain references; changes have been made to the scope following consultation.

Comment 4: Regulatory issues

Section	Consultees	Comments	Action
Remit			
Current or proposed marketing authorisation	PharmaMar	For the treatment of patients with advanced soft tissue sarcomas, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma.	Comments noted.

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

Macmillan Cancer Support

Welsh Assembly Government

Marie Curie Cancer Care

NHS Quality Improvement Scotland

Royal College of Anaesthetists

Royal Pharmaceutical Society