# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

# GUIDANCE EXECUTIVE (GE)

## Review of TA185; Trabectedin for the treatment of advanced metastatic soft tissue sarcoma

This guidance was issued in February 2010.

The review date for this guidance is February 2013.

### 1. Recommendation

The guidance should be transferred to the 'static guidance list'. That we consult on this proposal.

### 2. Original remit(s)

To appraise the clinical and cost effectiveness of trabectedin within its licensed indication for the treatment of advanced metastatic soft tissue sarcoma.

### 3. Current guidance

1.1 Trabectedin is recommended as a treatment option for people with advanced soft tissue sarcoma if:

- treatment with anthracyclines and ifosfamide has failed **or**
- they are intolerant of or have contraindications for treatment with anthracyclines and ifosfamide

**and**

- the acquisition cost of trabectedin for treatment needed after the fifth cycle is met by the manufacturer

### 4. Rationale[1]

As no changes to the marketing authorisation or costs are known, and no changes to the evidence base have emerged or are expected, it is proposed that TA185 be transferred to the 'static guidance list'.

[1] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

## 5. Implications for other guidance producing programmes

There is no proposed or ongoing guidance development that overlaps with this review proposal.

## 6. New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from January 2009 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

## *7.* Summary of evidence and implications for review

Since the publication of TA185 in February 2010, no further NICE Technology Appraisals have been published for the treatment of advanced soft tissue sarcoma. TA185 compared trabectedin with best supportive care. No new interventions or comparators have come to market since the original guidance was issued.

Trabectedin has a UK marketing authorisation for the treatment of patients with advanced soft tissue sarcoma after failure of anthracyclines and ifosfamide or who are unsuited to receive these agents. The marketing authorisation was granted under 'exceptional circumstances'. The summary of product characteristics (SPC) states that 'efficacy data are based mainly on liposarcoma and leiomyosarcoma patients'.

[redacted]

TA185 remains the sole guidance for advanced soft tissue sarcoma. The list price of trabectedin has not changed since the publication of TA185 (that is, £363.00 for a 250-microgram vial and £1366.00 for a 1-mg vial).

The clinical evidence for TA185 was derived primarily from STS-201, a phase II randomised trial of two dosing regimens of trabectedin in patients with locally advanced or metastatic soft tissue sarcoma in whom the disease had relapsed or become refractory after treatment with at least one anthracycline and ifosfamide, given either in combination or in sequence.

Since the publication of TA185, no additional trial-based evidence on the use of trabectedin in advanced soft tissue sarcoma has been produced. One paper relating to the pivotal STS-201 study was accepted for publication during TA185, and therefore was not used as a source of clinical efficacy data for the appraisal (Demetri et al., 2009a). A longer-term follow-up study of STS-201 also confirmed the advantage of trabectedin at its licensed dosage, in terms of median time-to-progression and overall survival (Demetri et al., 2009b). The conclusions in these studies are in-line with what was presented in the manufacturer's submission and

support the original recommendation in TA185 and do not increase the evidence base for decision making about the use of trabectedin in advanced soft tissue sarcoma. A phase 2 study of trabectedin for previously treated patients with soft tissue sarcoma, excluding L-type sarcomas, who are not expected to benefit from currently available therapeutic options but who may benefit from trabectedin is due for completion in December 2012. However, it is not expected that the results of this study will lead to changes in the licensed indication for trabectedin or affect the recommendation in TA185.

Based on the available evidence and above information presented, it is proposed that TA185 be transferred to the 'static guidance list'.

## 8. Implementation

A submission from implementation is included in Appendix 3. The use of trabectedin in hospitals in England increased from 2008-09 after its UK marketing authorisation was granted in September 2007 with another sharp increase in February 2010 to over £600,000 per month following the publication of NICE technology appraisal guidance 185. Between September 2010 and January 2012 the use of trabectedin has varied between £350,000 and £450,000 per month. According to the Hospital Pharmacy Audit Index, monthly costs were approximately £350,000. It should be noted that trabectedin, in combination with pegylated liposomal doxorubicin hydrochloride (PLDH), also has a marketing authorisation for the treatment of patients with relapsed platinum-sensitive ovarian cancer. Therefore, it is not possible to assess the impact of NICE guidance on trabectedin and the treatment of advanced soft tissue sarcoma separately.

## 9. Equality issues

No equalities issues were raised when the scope for NICE technology appraisal guidance 185 was developed, or during the course of the appraisal.

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**Contributors to this paper:**

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# Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

| **Options** | **Consequence** | **Selected – 'Yes/No'** |
|---|---|---|
| A review of the guidance should be planned into the appraisal work programme. | A review of the appraisal will be planned into the NICE's work programme. | No |
| The decision to review the guidance should be deferred to [specify date or trial]. | NICE will reconsider whether a review is necessary at the specified date. | No |
| A review of the guidance should be combined with a review of a related technology appraisal. | A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology. | No |
| A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. | A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology. | No |
| The guidance should be incorporated into an on-going clinical guideline. | The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review.<br>This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal. | No |
| The guidance should be updated in an on-going clinical guideline. | Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn.<br>Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation). | No |

| Options | Consequence | Selected – 'Yes/No' |
|---|---|---|
| The guidance should be transferred to the 'static guidance list'. | The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review. | Yes |

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise
- There is evidence of unjustified variation across the country in access to a treatment
- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed
- The treatment is excluded from the Payment by Results tariff

v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

# Appendix 2 – supporting information

## Relevant Institute work

*Published*

Mifamurtide for the treatment of osteosarcoma. TA235. Published: October 2011. Review: November 2013.

Improving outcomes for people with sarcoma. Cancer service guidance, CSG Sarcoma. Published: March 2006.

*In progress*

None

*Referred - QSs and CGs*

Sarcoma - new quality standard topic referred to NICE in March 2012.

*Suspended/terminated*

Ridaforolimus for the maintenance treatment of metastatic soft tissue or bone sarcoma [ID415]. Suspended: May 2012. *The manufacturer of ridaforolimus has informed NICE that they will not provide an evidence submission for this appraisal.*

## Details of changes to the indications of the technology

| Indication considered in original appraisal | Proposed indication (for this appraisal) |
|---|---|
| Trabectedin has a UK marketing authorisation for the treatment of patients with advanced soft tissue sarcoma after failure of anthracyclines and ifosfamide or who are unsuited to receive these agents. The marketing authorisation was granted under 'exceptional circumstances'. The summary of product characteristics (SPC) states that 'efficacy data are based mainly on liposarcoma and leiomyosarcoma patients'.<br><br>The acquisition cost of trabectedin is £363.00 for a 250-microgram vial and £1366.00 for a 1-mg (1000-microgram) vial (excluding VAT; 'British national formulary' [BNF] edition 58). | Yondelis is indicated for the treatment of adult patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients.<br>Source: SPC (August 2012)<br><br>[redacted]<br><br>No change to the costs.<br>250-microgram vial = £363.00<br>1-mg vial = £1366.00<br>Source: BNF (October 2012) |

## Details of new products

| Drug (manufacturer) | Details (phase of development, expected launch date, ) |
|---|---|
| Trabectedin (PharmaMar)<br>First line treatment of advanced / metastatic translocation-related soft tissue sarcoma | [redacted] |
| Eribulin mesylate (Eisai)<br>Soft tissue sarcoma - metastatic disease, 3rd line | Phase 3 clinical trial<br>[redacted] |
| Ombrabulin (Sanofi Aventis)<br>Soft tissue sarcoma - 2nd line + cisplatin | Phase 3 clinical trial<br>[redacted] |
| Pazopanib (GSK)<br>Soft tissue sarcoma - 2nd line + cisplatin | Launched August 2012 |
| Palifosfamide (Ziopharm)<br>1st line, in combination with doxorubicin | Phase 3 clinical trial<br>[redacted] |
| TH-302 (Merck) | Phase 3 clinical trials<br>[redacted] |
| Cixutumumab (Eli Lilly) | Phase 2 clinical trials<br>[redacted] |

## Registered and unpublished trials

| Trial name and registration number | Details |
|---|---|
| A Study to Provide Access to Trabectedin in Patients With Non L-type Soft Tissue Sarcoma Who Have Persistent or Recurrent Disease and Who Are Not Expected to Benefit From Currently Available Standard of Care Treatment<br>NCT00210665 | A Multicenter, Open-Label Single-Arm Study of YONDELIS (Trabectedin) for Subjects With Locally Advanced or Metastatic Soft Tissue Sarcoma Excluding Leiomyosarcoma and Liposarcoma Who Have Relapsed or Are Refractory to Standard of Care Treatment<br>Enrolment: 3000<br>Estimated completion: December 2012 |

| Trial name and registration number | Details |
|---|---|
| A Study of Trabectedin or Dacarbazine for the Treatment of Patients With Advanced Liposarcoma or Leiomyosarcoma<br>NCT01343277 | Purpose: to evaluate whether overall survival for the trabectedin group is superior to the dacarbazine group for patients with advanced L-sarcoma.<br>Randomized, open label, parallel assignment<br>Enrolment: 570<br>Estimated completion: July 2014 |
| A Study of the Safety and Effectiveness of Trabetedin Versus Doxorubicin-based Chemotherapy in Patients With Translocation-Related Sarcomas<br>NCT00796120 | A Randomized, Multicenter, Phase III Trial of Trabectedin (Yondelis) Versus Doxorubicin-based Chemotherapy as First-Line Therapy in Patients With Translocation-Related Sarcomas<br>Enrolment: 80<br>Estimated completion: July 2011 |
| Continuing vs Intermittent Trabectedin-regimen in Patients With Advanced Soft Tissue Sarcoma Experiencing Response or Stable Disease After the 6th Cycle (T-DIS)<br>NCT01303094 | Phase II Randomized Trial to Evaluate Two Strategies: Continuing Versus Intermittent (Drug-holiday) Trabectedin-regimen in Patients With Advanced Soft Tissue Sarcoma Experiencing Response or Stable Disease After the Sixth Cycle<br>Enrolment: 50<br>Estimated completion: February 2017 |

## Additional information

SMC does not recommend trabectedin (Yondelis) for advanced soft tissue sarcoma (11 July 2011)

British Sarcoma Group (2010) Guidelines for the Management of Soft Tissue Sarcomas

## References

Demetri GD, et al. (2009a) Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: results of a randomized phase II study of two different schedules. *Journal of Clinical Oncology* 27 (25): 4188-4196.

Demetri GD, et al. (2009b) Long-term results of a randomized phase II study of trabectedin by two different dose and schedule regimens in patients with advanced liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide. *Journal of Clinical Oncology* 27 (15 SUPPL.1): 10509.

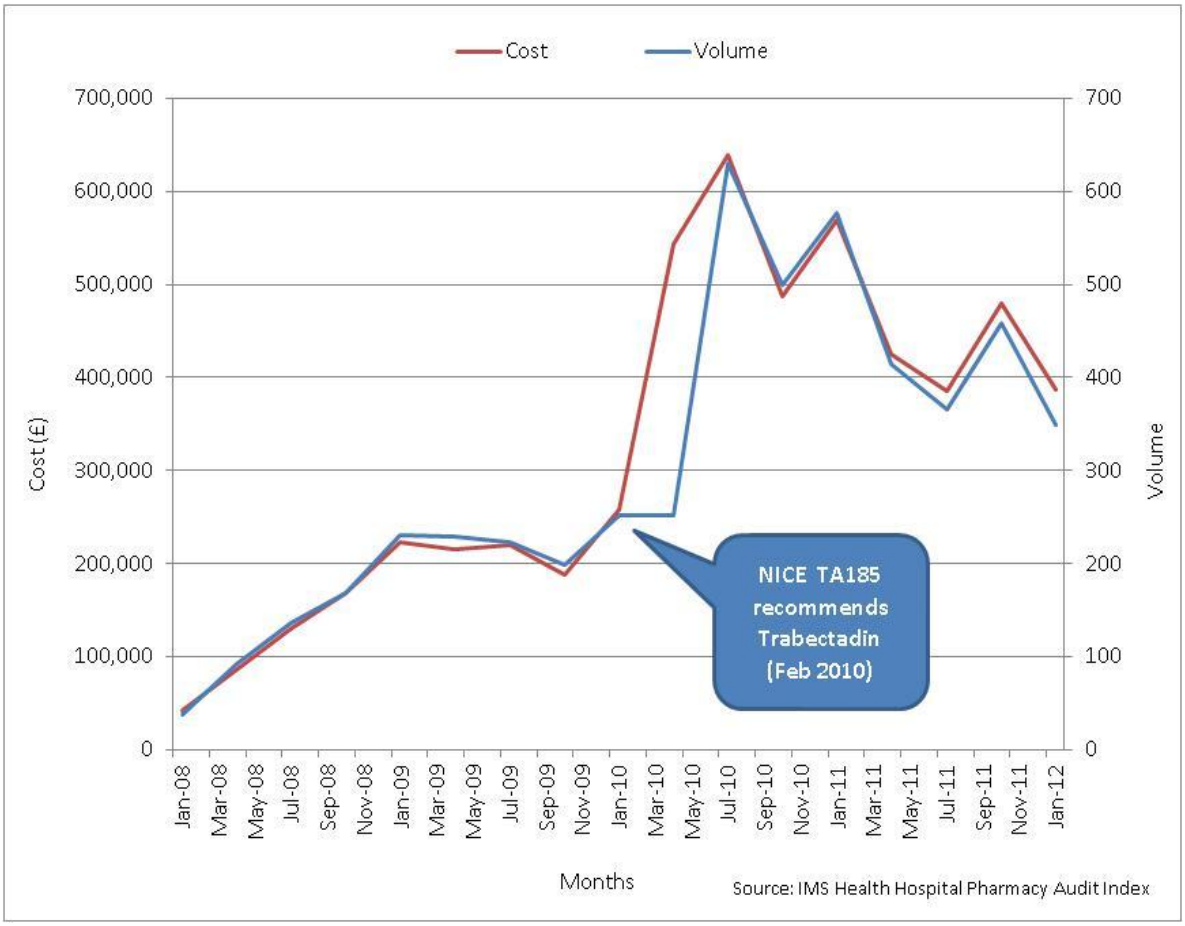
# Appendix 3 – Implementation submission

## 1 Routine healthcare activity data

### 1.1 Hospital Pharmacy Audit Index data

This section presents Hospital Pharmacy Audit Index data on the Net Ingredient Cost (NIC) and volume of Trabectedin prescribed and dispensed in hospitals in England between January 2008 and March 2012.

**Figure 1 Cost and volume of Trabectedin prescribed and dispensed in hospitals in England between January 2008 and March 2012.**




## 2 Implementation studies from published literature

Information is taken from the uptake database (ERNIE) website.

*Nothing to add at this time.*

## 3 Qualitative input from the field team

The implementation field team have recorded the following feedback in relation to this guidance:

*Nothing to add at this time.*

# 4 Appendix A: Healthcare activity data definitions

*IMS HEALTH Hospital Pharmacy Audit Index (IMS HPAI)*

IMS HEALTH collects information from pharmacies in hospital trusts in the UK. The section of this database relating to England is available for monitoring the overall usage in drugs appraised by NICE. The IMS HPAI database is based on issues of medicines recorded on hospital pharmacy systems. Issues refer to all medicines supplied from hospital pharmacies: to wards; departments; clinics; theatres; satellite sites and to patients in outpatient clinics and on discharge.

***Measures of prescribing***

Volume: The HPAI database measures volume in packs and a drug may be available in different pack sizes and pack sizes can vary between medicines.

Cost: Estimated costs are also calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost.

Costs based on the drug tariff provide a degree of standardization allowing comparisons of prescribing data from different sources to be made. The costs stated in this report do not represent the true price paid by the NHS on medicines. The estimated costs are used as a proxy for utilization and are not suitable for financial planning.

***Data limitations***

IMS HPAI data do not link to demographic or to diagnosis information on patients. Therefore, it cannot be used to provide prescribing information on age and sex or for prescribing of specific conditions where the same drug is licensed for more than one indication.