NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA183; Topotecan for the treatment of recurrent and stage IVB cervical cancer

This guidance was issued in October 2009.

The review date for this guidance is September 2012.

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 topotecan within its licensed indications for the treatment of recurrent and stage IVB carcinoma of the cervix.

3. Current guidance

1.1 Topotecan in combination with cisplatin is recommended as a treatment option for women with recurrent or stage IVB cervical cancer only if they have not previously received cisplatin.

1.2 Women who have previously received cisplatin and are currently being treated with topotecan in combination with cisplatin for recurrent and stage IVB cervical cancer should have the option to continue their therapy until they and their clinicians consider it appropriate to stop

4. Rationale[1]

There are no clinical studies that are directly relevant to the decision problem for TA183 that have reported or are ongoing. Since the publication of TA183, the patent for topotecan has expired, with cheaper generic formulations now on the market. Results from a recently published cost-effectiveness analysis suggest that the reduction in the acquisition cost is not likely to have an impact on the existing recommendation for women who have previously received cisplatin. In summary, there is no significant new evidence that is likely to lead to a change in the recommendations, and no relevant ongoing studies, therefore it is appropriate that the guidance be transferred to the static 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 December 2008 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

Technology appraisal no. 183 'Topotecan for the treatment of recurrent and stage IVB cervical cancer' recommends topotecan as a treatment option in combination with cisplatin for women with recurrent or stage IVB cervical cancer who have not had cisplatin (cisplatin naïve). This is a subset of the licensed population (see Appendix 2 for a description of the licensed population).

Since the guidance was published, the marketing authorisation for topotecan for cervical cancer has not changed and no new comparators have come to market.

Clinical effectiveness evidence

The Committee had considered direct and indirect evidence from randomised controlled trials (RCTs) to compare the clinical effectiveness of topotecan plus cisplatin with platinum-based single and combination chemotherapy regimens in the licensed population and in a subpopulation which consisted of women who had not received prior cisplatin therapy.

The literature search for this review proposal did not identify any new or ongoing RCTs directly relevant to the decision problem for TA183.

Cost-effectiveness evidence

It is noteworthy that topotecan's patent has expired following appraisal, which has led to the introduction of cheaper generic formulations (see Appendix 2 for prices before and after patent expiry). The Committee was satisfied that topotecan in combination with cisplatin was a cost-effective use of NHS resources for cisplatin-naive women. This implies that the subsequent cost reduction of topotecan has made it even more cost-effective for cisplatin-naive women. However, topotecan may or may not have become cost-effective for the wider licensed population.

The Committee did not recommend topotecan plus cisplatin for the 'licensed population' (all women with cervical cancer that has recurred after radiotherapy, and

whose disease has spread beyond the cervix) based on trial data for both, women who had previously received cisplatin, and women who had no prior cisplatin treatment. The economic analysis based on the trial data suggested that paclitaxel plus cisplatin dominated topotecan plus cisplatin in the licensed population. The literature search for this review identified a model-based cost-effectiveness study that had compared topotecan plus cisplatin with cisplatin monotherapy and cisplatin plus paclitaxel in women with advanced, persistent, or recurrent cervical cancer (Geisler et al., 2012). The modelling had used the same trial data that had been considered by the Committee and it was largely comparable to the modelling undertaken for the appraisal. Results found that topotecan plus cisplatin was dominated by the other treatment regimens. Sensitivity analysis was conducted and it suggested that topotecan plus cisplatin would remain not a cost-effective use of NHS resources even when topotecan was given for free because the costs associated with the complications would still make the regimen expensive. The findings of the study are in line with the Committee's recommendation with regard to the licensed population and suggest that the reduced cost of generic topotecan is unlikely to render topotecan plus cisplatin cost-effective in the licensed population.

The literature search did not identify any new cost-effectiveness evidence that relates to women who had no prior cisplatin treatment.

In conclusion, no new evidence has been identified that is likely to lead to a change in the recommendations of the original guidance.

8. Implementation

A submission from Implementation is included in Appendix 3.

Topotecan is licensed for multiple indications and it would be difficult to single out the uptake of topotecan for cervical cancer from figures 1 and 2 in Appendix 3.

Richards (2010) discusses the impact of NICE guidance on clinical practice in a general context and does not provide implementation data that would be relevant for this review.

9. Equality issues

The Committee discussed the higher prevalence of cervical cancer among women living in the most socioeconomically deprived areas, as outlined by the patient expert statements. It also discussed comments received during consultation on the appraisal consultation document. The Committee noted that a negative recommendation for topotecan in combination with cisplatin for the group of women with prior exposure to cisplatin does not impact particularly on any group protected by the equalities legislation. In addition, given the uncertainty about whether topotecan in combination with cisplatin is more clinically effective than other combination therapies for the treatment of cervical cancer in women with prior exposure to cisplatin, and the availability of alternative treatment options, the committee was satisfied that its recommendation was consistent with NICE's obligations under the equalities legislation and the requirement for fairness.

GE paper sign off: Helen Knight, 16/08/12

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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. 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. 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

None

In progress

None

Referred - QSs and CGs

None

Suspended/terminated

None

Details of changes to the indications of the technology

Indication considered in original appraisal	Proposed indication (for this appraisal)
Topotecan in combination with cisplatin has a marketing authorisation for patients with carcinoma of the cervix recurrent after radiotherapy and for patients with stage IVB disease. The summary of product characteristics (SPC) states that patients with prior exposure to cisplatin require a sustained treatment-free interval to justify treatment with topotecan in combination with cisplatin	No change Topotecan in combination with cisplatin is indicated for patients with carcinoma of the cervix recurrent after radiotherapy and for patients with Stage IVB disease. Patients with prior exposure to cisplatin require a sustained treatment free interval to justify treatment with the combination. Generic topotecan is now available. Potactasol (generic topotecan, Actavis) was approved in January 2011. Sources: EPAR, SPC (Feb 2012).

Details of new products

None

Registered and unpublished trials

Trial name and registration number	Details
Study on Paclitaxel Plus Topotecan in Comparison With Topotecan Plus Cisplatin in Recurrent or Persistent Cervical Carcinoma (AGO-Zervix-1) NCT01405235	A Prospective, Randomized Phase III Study to Compare the Effects of Paclitaxel and Topotecan to Those of Cisplatin and Topotecan for Treatment of Patients With Recurrent and Persistent Cervical Cancer Status: ongoing, due for completion January 2015 Enrolment: 312
Paclitaxel and Cisplatin or Topotecan With or Without Bevacizumab in Treating Patients With Stage IVB, Recurrent, or Persistent Cervical Cancer NCT00803062	A Randomized Phase III Trial of Cisplatin Plus Paclitaxel With and Without NCI-Supplied Bevacizumab (NSC #704865, IND #7921) Versus the Non-Platinum Doublet, Topotecan Plus Paclitaxel, With and Without NCI-Supplied Bevacizumab, In Stage IVB, Recurrent or Persistent Carcinoma of the Cervix Status: recruiting Enrolment: 450
Topotecan, Cisplatin and Bevacizumab for Recurrent/Persistent Cervical Cancer NCT00548418	Phase II Trial of Topotecan, Cisplatin and Bevacizumab for Recurrent/Persistent Cervical Cancer Status: due for completion March 2012 Enrolment: 30
Carboplatin and Topotecan in Treating Patients With Relapsed or Metastatic Cervical Cancer NCT00807079	Phase I/II Study of Carboplatin in Association With Weekly Oral Topotecan in Patients With Metastatic or Recurrent Cervical Cancer Status: completed May 2011 Enrolment: 56
Veliparib, Topotecan Hydrochloride, and Filgrastim or Pegfilgrastim in Treating Patients With Persistent or Recurrent Cervical Cancer NCT01266447	A Phase II Evaluation of ABT-888 (IND# 77840, NCI Supplied Agent: ABT-888, NSC #737664), Topotecan (NSC #609699) and Filgrastim or Pegfilgrastim in the Treatment of Persistent or Recurrent Squamous or Non-Squamous Cell Carcinoma of the Cervix Status: recruiting Enrolment: 60 Completion: November 2016

Additional information

Price - as quoted in TA183

The acquisition cost of topotecan is £97.65 for a 1-mg vial or £290.62 for a 4-mg vial (excluding VAT; 'British national formulary' [BNF] edition 57). The acquisition cost of cisplatin is £24.50 for a 50-mg vial or £50.22 for a 100-mg vial (excluding VAT; BNF edition 57).

Price - current

Topotecan (Non-proprietary)

Concentrate for intravenous infusion, topotecan (as hydrochloride) 1 mg/mL, net price 1-mL vial = £87.88, 4-mL vial = £261.55; Intravenous infusion, powder for reconstitution, topotecan (as hydrochloride), net price 1-mg vial = £97.00, 4-mg vial = £290.00 [BNF63, March 2012]

Hycamtin (GSK)

Intravenous infusion, powder for reconstitution, topotecan (as hydrochloride), net price 1-mg vial = £97.65; 4-mg vial = £290.62 [BNF63, March 2012]

Cisplatin (Non-proprietary)

Injection, cisplatin 1 mg/mL, net price 10-mL vial = £5.85, 50-mL vial = £24.50, 100-mL vial = £50.22; Injection, powder for reconstitution, cisplatin, net price 50-mg vial = £17.00 [BNF63, March 2012]

References

Faustino C, Afonso N, Sousa B et al. (2009) **Cisplatin plus topotecan in advanced/recurrent cervical cancer - Experience from a single institution**. *European Journal of Cancer*, Supplement. Conference: Joint ECCO 15 – 34th ESMO Multidisciplinary Congress Berlin Germany. 7(2-3): 462.

Geisler J, Apoian A, Labarge D et al. (2012) **Treatment of advanced or recurrent cervical cancer with cisplatin or cisplatin containing regimens: A cost effective analysis**. *Gynecologic Oncology.* Conference: 43rd Annual Meeting of the Society of Gynecologic Oncology Austin, TX United States*.* 125: S15.

Richards, M (2010) **Extent and causes of international variation in drug usage: A report for the Secretary of State for Health by Professor Sir Mike Richards CBE**. Department of Health.

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 topotecan prescribed and dispensed in hospitals in England between July 2000 and March 2012.

Figures 1 and 2 below show the publication dates of all NICE guidance that recommends the use of topotecan. These data need to be used with caution as there is more than one indication for its use.

Figure 1 Volume of topotecan prescribed and dispensed in hospitals in England

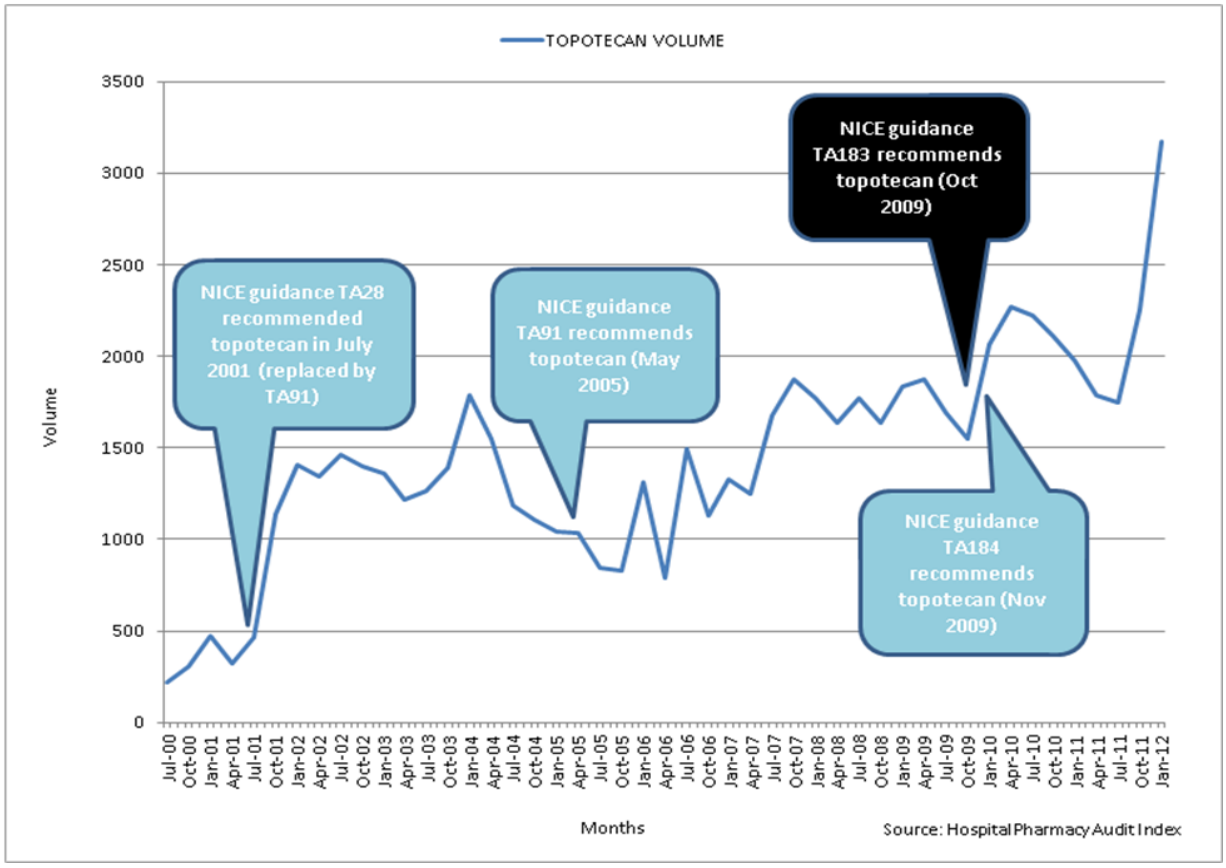
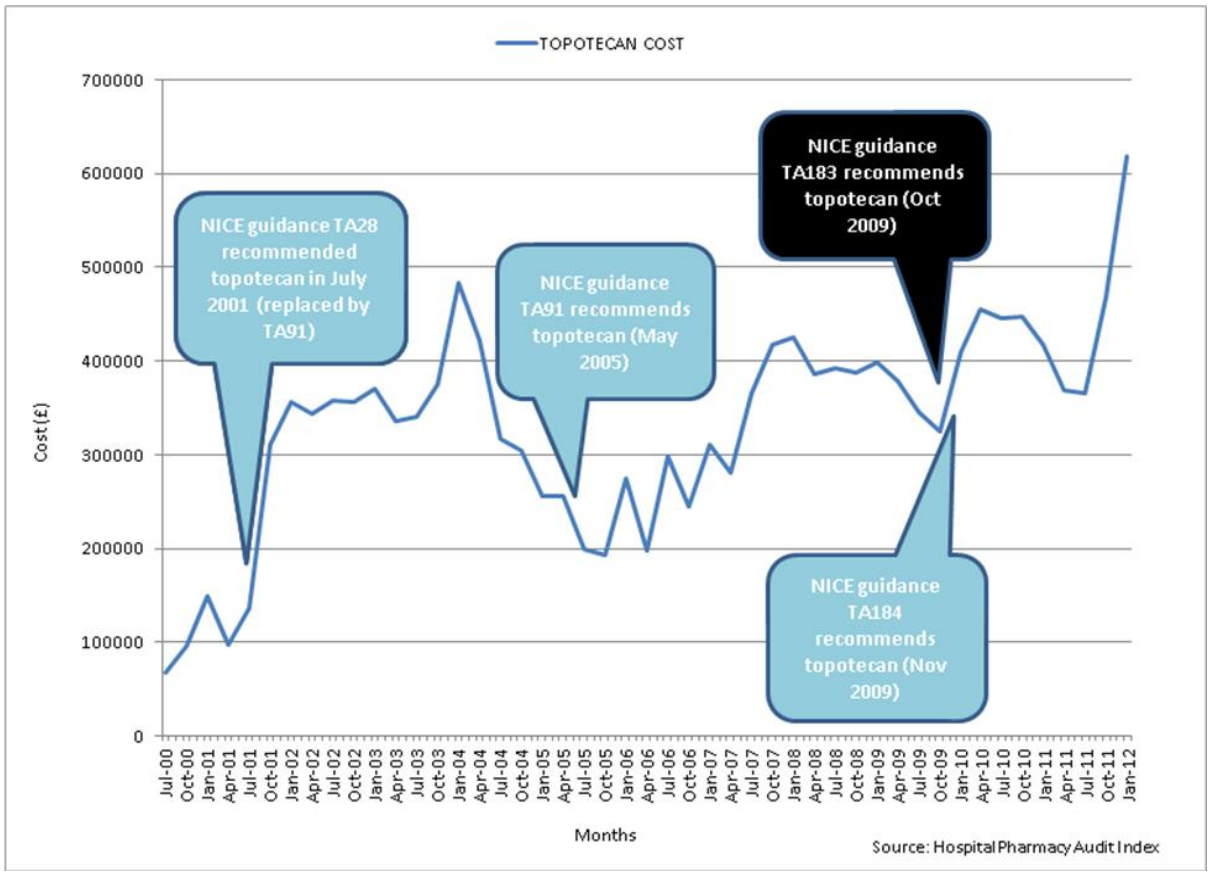


Figure 2 Net ingredient cost of topotecan prescribed and dispensed in hospitals in England



2 Implementation studies from published literature

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

2.1 All Wales Medicines Strategy Group (2011) Monitoring of AWMSG recommendations

This paper covers medicines that have been recommended by the All Wales Medicines Strategy Group (AWMSG) for use in NHS Wales. Five of these medicines, Adalimumab, Teriparatide, Topotecan Hydrochloride, Bortezomib and Docetaxel are also covered by a NICE Technology Appraisal. The report includes hospital and homecare usage data for three of these drugs, Adalimumab, Teriparatide, Topotecan Hydrochloride.

2.2 Richards, M (2010) **Extent and causes of international variation in drug usage: A report for the Secretary of State for Health by Professor Sir Mike Richards CBE**

This report looks at medicines usage between countries, using IMS Health data. The WHO defined daily dose or the maximum or prescribed daily dose was used to measure usage. Results rank the UK relative to other countries usage and present calculations showing how close or otherwise the UK is to the average use across groups of other countries. It should be noted that countries other than the UK would not be expected to adhere to NICE guidance making comparisons between countries not possible.

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.

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.