NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for the treatment of recurrent ovarian cancer (including review of technology appraisal no. 91 and technology appraisal no. 222)

Draft scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine within their licensed indications for the treatment of recurrent ovarian cancer.

Background

Ovarian cancer is a common gynaecological which represents a group of different tumours that arise from diverse types of tissue contained within the ovary. The most common type of ovarian cancer arises from epithelial cells (the outside layer of cells) on the surface of the ovary. Ovarian cancer often spreads from the ovary to any surface within the abdominal cavity including the fallopian tubes and peritoneal cavity. Symptoms of ovarian cancer tend to be non-specific and are widely experienced among the general population. These include persistent pelvic and abdominal pain, abdominal bloating, urinary frequency or urgency, loss of appetite, and abnormal or postmenopausal bleeding. Most women are diagnosed with advanced stage disease.

Ovarian cancer mainly affects women who have had their menopause, with the highest rates of incidence in the age group of 65 and above. Approximately 6900 new cases of ovarian cancer are diagnosed annually in the UK, with 4600 deaths from the disease each year. The outcome of ovarian cancer is generally poor, with an overall 5-year survival rate of less than 35%.

Although a significant percentage of women with ovarian cancer respond to initial chemotherapy, between 55% and 75% of women whose tumours respond to first-line therapy relapse within 2 years of completing treatment. Recurrent ovarian cancer may be classified according to the duration of response to first-line platinum-based chemotherapy into platinum-sensitive, when the cancer responds to initial chemotherapy but recurs 6 months or more after completion of the regimen and platinum-resistant, when the cancer recurs within 6 months of completion of initial chemotherapy. Ovarian cancer may also not respond to first-line platinum-based chemotherapy at all, in which case it is termed platinum-refractory. Platinum-sensitive ovarian cancer is sometimes further divided into fully platinum-sensitive (when the

recurrence-free interval is 12 months or more) and partially platinum-sensitive (when the interval is between 6 and 12 months).

Treatment of recurrent ovarian cancer aims to control the disease as long as possible. Platinum chemotherapy as single agent or in combination with paclitaxel, pegylated liposomal doxorubicin hydrochloride or gemcitabine is often used in women with platinum-sensitive ovarian cancer. For cancers that did not respond well to first-line platinum-based chemotherapy, paclitaxel, pegylated liposomal doxorubicin hydrochloride or topotecan may be offered.

The technologies

Paclitaxel (various manufacturers) is a cytotoxic anticancer drug that belongs to the taxane group of drugs, which prevent the formation of mitotic spindles thus interfering with the process of cell division and resulting in cell death. Paclitaxel is licensed for the second-line treatment of metastatic ovarian cancer after failure of standard platinum-containing therapy.

Pegylated liposomal doxorubicin hydrochloride (Caelyx, Jansen-Cilag) belongs to the class of drugs known as anthracyclines, which is a group of cytotoxic antibiotics that have antineoplastic activity. Anthracyclines intercalate with DNA, and so inhibit its synthesis. They also interact with cell membranes thereby altering their function and generating cytotoxic chemical species. Pegylated liposomal doxorubicin hydrochloride is licensed for the treatment of advanced ovarian cancer in women for whom a first-line platinum-based chemotherapy regimen has failed.

Topotecan (various manufacturers) is a naturally-derived chemotherapeutic agent. It prevents DNA replication in cancer cells by inhibiting the enzyme topoisomerase I. Topotecan is licensed for the treatment of women with metastatic cancer of the ovary after failure of first-line or subsequent chemotherapy.

Trabectedin (Yondelis, PharmaMar) is a synthetic, marine-derived anticancer agent that binds to the minor groove of the DNA and as a result bends the helix to the major groove, which results in perturbation of the cell cycle. Trabectedin, in combination with pegylated liposomal doxorubicin hydrochloride, has a marketing authorisation for the treatment of women with recurrent platinum-sensitive ovarian cancer.

Gemcitabine (various manufacturers) is a chemotherapeutic agent that exerts its action by inhibiting DNA synthesis. It is a nucleoside analogue with anti-tumour activity against a number of solid tumours. Gemcitabine, in combination with carboplatin, has a marketing authorisation for the treatment of locally advanced or metastatic epithelial ovarian cancer in women with recurrent platinum-sensitive cancer after first-line platinum-based therapy.

Intervention(s)	For people with platinum-sensitive ovarian cancer: • paclitaxel as monotherapy or in platinum-containing chemotherapy • pegylated liposomal doxorubicin hydrochloride as monotherapy or in platinum-containing chemotherapy • gemcitabine in combination with carboplatin • trabectedin in combination with pegylated liposomal doxorubicin hydrochloride • topotecan monotherapy. For people with platinum-resistant or platinum-refractory ovarian cancer: • paclitaxel monotherapy • pegylated liposomal doxorubicin hydrochloride monotherapy • topotecan monotherapy.
Population(s)	People with ovarian cancer that has recurred after first-line (or subsequent) platinum-based chemotherapy or is refractory to platinum-based chemotherapy.
Comparators	For people with platinum-sensitive ovarian cancer: • the interventions listed above in comparison with each other • bevacizumab in platinum-containing chemotherapy (subject to NICE appraisal) • single-agent platinum chemotherapy. For people with platinum-resistant or platinum-refractory ovarian cancer: • the interventions listed above in comparison with each other • etoposide • best supportive care.

Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation.

Related NICE recommendations	Related Technology Appraisals: Technology Appraisal No. 55, Jan 2003, 'Review of the clinical effectiveness and cost effectiveness of paclitaxel for ovarian cancer'. Review date TBC. Technology Appraisal No. 91, May 2005, 'Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for the treatment of advanced ovarian cancer'. Review date Aug 2012. Technology Appraisal No. 222, Apr 2011, 'Trabectedin for the treatment of relapsed ovarian cancer'. To be reviewed with TA91. Technology Appraisal in Preparation, 'Bevacizumab in combination with paclitaxel and carboplatin for the first-line treatment of ovarian cancer.' Earliest anticipated date of publication Apr 2013. Technology Appraisal in Preparation, 'Bevacizumab for the treatment of recurrent advanced ovarian cancer'. Earliest anticipated date of publication Jun 2013. Proposed Technology Appraisal, 'Vintafolide in combination with pegylated liposomal doxorubicin hydrochloride for the treatment of folate-receptor-positive platinum-resistant ovarian cancer'. Publication TBC. Related Guidelines: Clinical Guideline No. 122, Apr 2011, 'The recognition and initial management of ovarian cancer'. Related Quality Standards: Published Quality Standard, 'Ovarian cancer'.

Questions for consultation

NICE intends to appraise vintafolide in combination with pegylated liposomal doxorubicin hydrochloride for the treatment of folate-receptor-positive platinum-resistant ovarian cancer as a single technology appraisal. Would it be more appropriate to include vintafolide in combination with pegylated liposomal doxorubicin hydrochloride in this review?

Have the most appropriate comparators been included in the scope?

- Is bevacizumab a relevant comparator for people with platinum-resistant or platinum-refractory ovarian cancer? If so, in which regimens would it be used?
- Is it appropriate to include 'best supportive care' as a comparator for people with platinum-resistant or platinum-refractory ovarian cancer? If so, how should 'best supportive care' be defined?

Are there any subgroups of people in whom the technologies are expected to be more clinically effective and cost effective or other groups that should be examined separately?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine are licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technologies;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider that the use of the technologies can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.