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**Paclitaxel, pegylated
liposomal doxorubicin
hydrochloride and
topotecan for second-line
or subsequent treatment of
advanced ovarian cancer**

**Review of Technology Appraisal
Guidance 28, 45 and 55**

Technology Appraisal Guidance 91

Paclitaxel, pegylated liposomal doxorubicin hydrochloride and topotecan for second-line or subsequent treatment of advanced ovarian cancer

Ordering information

You can download the following documents from www.nice.org.uk/TA091

- The full guidance for this technology appraisal (this document).
- A quick reference guide, which has been distributed to health professionals working in the NHS in England.
- Information for people with advanced ovarian cancer, their families and carers, and the public.
- The assessment report – details of all the studies that were looked at.

For printed copies of the quick reference guide or information for the public, phone the NHS Response Line on 0870 1555 455 and quote:

- N0872 (quick reference guide)
- N0873 (information for the public).

This guidance is written in the following context

This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Health professionals are expected to take it fully into account when exercising their clinical judgement. The guidance does not, however, override the individual responsibility of health professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

National Institute for Health and Clinical Excellence

MidCity Place
71 High Holborn
London
WC1V 6NA

www.nice.org.uk

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This guidance will replace the following guidance issued by the Institute:

- Ovarian cancer – topotecan; *Technology Appraisal Guidance* no. 28 (2001)
- Ovarian cancer (advanced) – pegylated liposomal doxorubicin hydrochloride; *Technology Appraisal Guidance* no. 45 (2002)

This guidance replaces recommendations 1.3, 1.4 and 1.5 on the second-line treatment of advanced ovarian cancer in the following guidance.

- Ovarian cancer – paclitaxel (review); *Technology Appraisal Guidance* no. 55 (2003)

The recommendations for first-line therapy in *Technology Appraisal Guidance* no. 55 are not affected by this guidance.

The review has resulted in a number of changes in the nature of the recommendations from the original appraisal:

- Topotecan is now only recommended for the treatment of women with platinum-refractory or platinum-resistant ovarian cancer if PLDH and paclitaxel are considered unsuitable.
- Paclitaxel in combination with platinum-based therapy is now recommended as a treatment option for women whose disease relapses after 6 months of first-line platinum-based therapy.
- Within these recommendations, women who have received paclitaxel as part of their first-line treatment may receive paclitaxel as part of their second-line (or subsequent) treatment.
- PLDH is now recommended as a treatment option for women whose disease does not respond to, and those women whose disease relapses within 12 months from, initial platinum-based therapy.

1 Guidance

This guidance applies only to paclitaxel, pegylated liposomal doxorubicin hydrochloride (PLDH) and topotecan.

For the purposes of this guidance, the following definitions are used:

- platinum-sensitive ovarian cancer: disease that responds to first-line platinum-based therapy but relapses 12 months or more after completion of initial platinum-based chemotherapy
- partially platinum-sensitive ovarian cancer: disease that responds to first-line platinum-based therapy but relapses between 6 and 12 months after completion of initial platinum-based chemotherapy
- platinum-resistant ovarian cancer: disease that relapses within 6 months of completion of initial platinum-based chemotherapy
- platinum-refractory ovarian cancer: disease that does not respond to initial platinum-based chemotherapy.

1.1 Paclitaxel in combination with a platinum-based compound (carboplatin or cisplatin) is recommended as an option for the second-line (or subsequent) treatment of women with platinum-sensitive or partially platinum-sensitive advanced ovarian cancer, except in women who are allergic to platinum-based compounds.

1.2 Single-agent paclitaxel is recommended as an option for the second-line (or subsequent) treatment of women with platinum-refractory or platinum-resistant advanced ovarian cancer, and for women who are allergic to platinum-based compounds.

1.3 PLDH is recommended as an option for the second-line (or subsequent) treatment of women with partially platinum-sensitive, platinum-resistant or

platinum-refractory advanced ovarian cancer, and for women who are allergic to platinum-based compounds.

- 1.4 Topotecan is recommended as an option for second-line (or subsequent) treatment only for those women with platinum-refractory or platinum-resistant advanced ovarian cancer, or those who are allergic to platinum-based compounds, for whom PLDH and single-agent paclitaxel are considered inappropriate.
- 1.5 Within these recommendations, the choice of treatment for second-line (or subsequent) chemotherapy should be made after discussion between the responsible clinician and the patient about the risks and benefits of the options.

2 Clinical need and practice

- 2.1 Ovarian cancer is the fourth most common cause of cancer mortality in women and resulted in over 4000 deaths in England and Wales in 2002. The age-standardised incidence per 100,000 women in 2000 was 17.9 in England and 20.6 in Wales. The total number of new cases in England and Wales registered in 2000 was close to 6000. The 5-year survival rate is approximately 30%.
- 2.2 Around 80% of ovarian cancers occur in women over the age of 50 years. Between 5% and 10% of cases occur in women with mutations in the genes BRCA1 and BRCA2 or who carry the hereditary non-polyposis colorectal cancer (HNPCC) gene. Other factors suspected to be associated with an increased risk of ovarian cancer include an early age at menarche, a late menopause, infertility, and the use of drug treatments to increase fertility.
- 2.3 Ovarian cancer is staged surgically according to the International Federation of Gynaecologists and Obstetricians criteria, whereby stage I describes tumours confined to the ovaries, stage II describes tumours that have extended to the pelvis, stage III describes tumours that have spread beyond

the pelvis and/or involve the lymph nodes and stage IV describes disease where distant metastasis is detectable. Ovarian cancer is often asymptomatic in the early stages and over 75% of cases are diagnosed with advanced disease, that is stage III or stage IV disease.

- 2.4 Surgery is usually the first intervention used to treat the disease. However, in most women complete removal of the tumour is not possible. Radiotherapy is of limited effectiveness and has adverse effects on other abdominal organs.
- 2.5 For the majority of patients first-line chemotherapy consists of platinum-based therapy alone or in combination with paclitaxel (where the platinum agent is either carboplatin or cisplatin).
- 2.6 Between 55% and 75% of women whose tumours respond to first-line therapy relapse within 2 years of completing treatment. Second-line chemotherapy is palliative and aims to reduce symptoms and prolong survival. Response to initial first-line therapy and time to relapse are predictive of response to second and subsequent courses of treatment with platinum-based therapy.
- 2.7 The treatment-free interval (time between the end of first-line chemotherapy and the start of second-line chemotherapy) has been widely adopted to stratify patients into three groups.
 - Disease that does not respond to first-line therapy (platinum-refractory disease).
 - Disease that responds to first-line therapy but relapses within 6 months of completion of initial platinum-based therapy (platinum-resistant disease).
 - Disease that responds to first-line therapy but relapses 6 months or more after completion of initial platinum-based therapy (platinum-sensitive disease).

It is recognised that these categories are not absolute and that the boundary between platinum-sensitive and platinum-resistant disease is blurred. In particular, platinum-sensitive disease may be further stratified into two subgroups: disease that relapses after 12 months of completion of initial platinum-based therapy; and disease that relapses between 6 and 12 months after completion of initial platinum-based therapy.

- 2.8 Currently, it is usual to re-challenge patients who have platinum-sensitive disease with a platinum compound. Non-platinum-based regimens are usually used for women with platinum-refractory or platinum-resistant disease.
- 2.9 Ovarian tumours eventually develop multi-drug resistance. However, some women may achieve long remissions with each line of chemotherapy and survive for up to 10 years with repeated treatments. Women who have platinum-refractory disease after two or three lines of treatment are unlikely to respond to further chemotherapy.

3 The technologies

3.1 Paclitaxel

3.1.1 Paclitaxel (Bristol-Myers Squibb and IVAX Pharmaceuticals) is a cytotoxic anticancer drug and belongs to the taxane group of drugs, which prevent the formation of mitotic spindles, interfering with the process of cell division and resulting in cell death.

3.1.2 Paclitaxel under the brand name of Taxol (Bristol-Myers Squibb) has the following licensed indications for ovarian cancer in the UK:

- first-line treatment of ovarian cancer in combination with cisplatin (a platinum drug) in people with advanced disease or with residual disease after initial surgical treatment
- metastatic ovarian cancer where standard platinum-containing therapy (cisplatin or carboplatin) has failed.

- 3.1.3 Paclitaxel under the brand name of Paxene (IVAX Pharmaceuticals) is licensed only for the treatment of people with metastatic carcinoma of the ovary after failure of platinum-containing combination therapy without taxanes.
- 3.1.4 The Summary of Product Characteristics states that the recommended dose for second-line chemotherapy with paclitaxel is 175 mg per square metre of patient's body surface area, in a 3-hour intravenous infusion at 3-weekly intervals.
- 3.1.5 Contraindications include pregnancy and breastfeeding, severe hypersensitivity to the drug and baseline neutrophils $< 1500/\text{mm}^3$. Adverse effects include severe hypersensitivity reactions (routine premedication with a corticosteroid, an antihistamine and a histamine H_2 -receptor antagonist is recommended to prevent this), myelosuppression, peripheral neuropathy, cardiac conduction defects with arrhythmias, alopecia, muscle and joint pain, nausea and vomiting. For full details of adverse effects and contraindications, see the Summary of Product Characteristics.
- 3.1.6 The acquisition costs of paclitaxel are £347.82 (Bristol-Myers Squibb) for a 16.7-ml vial (6 mg/ml) (excluding VAT; *British National Formulary* 49th edition) and £374 (IVAX) per 100 mg (*Pharmaceutical Journal*, 29th May 2004). For a woman with a body surface area of 1.7 square metres the acquisition cost is £1033 per cycle (based on the price of Taxol, and excluding premedication and VAT). This assumes that no wastage of the drug occurs. The overall acquisition cost depends on the number of cycles per patient undertaken. Costs may vary in different settings because of negotiated procurement discounts.

3.2 Pegylated liposomal doxorubicin hydrochloride

- 3.2.1 PLDH (Schering-Plough) is doxorubicin hydrochloride encapsulated in pegylated liposomes, and belongs to the class of drugs known as anthracyclines, a group of cytotoxic antibiotics that have potent antineoplastic

activity. Anthracyclines intercalate with DNA, and so inhibit DNA synthesis. They also interact with cell membranes thereby altering their functions and generating hydrogen peroxide and hydroxy radicals, which are highly destructive to cells.

- 3.2.2 PLDH is licensed for the treatment of advanced ovarian cancer in women for whom a first-line platinum-based chemotherapy regimen has failed.
- 3.2.3 PLDH is administered intravenously at a dose of 50 mg per square metre of patient's body surface area, once every 4 weeks for as long as the disease does not progress and the person continues to tolerate treatment.
- 3.2.4 Contraindications include breastfeeding and a history of hypersensitivity to the drug. Based on clinical experience, patients with poor performance status tend to have a lower response rate, while those with extensive abdominal tumour deposits leading to bowel obstruction are less likely to benefit from treatment. The principal treatment-related adverse effects are palmar–plantar erythrodysesthesia (PPE [intense, often painful reddening of the hands and feet]) and stomatitis (ulceration of the mouth). The Summary of Product Characteristics recommends that all people receiving PLDH routinely undergo frequent electrocardiogram monitoring. For full details of adverse effects and contraindications, see the Summary of Product Characteristics.
- 3.2.5 The acquisition cost of PLDH is £411.30 for a 10-ml vial (excluding VAT; *British National Formulary* 49th edition). For a woman with a body surface area of 1.7 square metres, the acquisition cost is £1383 per cycle (excluding premedication and VAT). This assumes that no wastage of the drug occurs. The overall acquisition cost depends on the number of cycles per patient undertaken. Costs may vary in different settings because of negotiated procurement discounts.

3.3 Topotecan

- 3.3.1 Topotecan (GlaxoSmithKline; GSK) is derived from the oriental tree *Camptotheca acuminata*. It prevents DNA replication in cancer cells by inhibiting the enzyme topoisomerase I.
- 3.3.2 Topotecan is licensed in the UK for the treatment of women with metastatic carcinoma of the ovary after the failure of first-line or subsequent therapy.
- 3.3.3 The Summary of Product Characteristics states that the recommended initial dose of topotecan is 1.5 mg per square metre of the patient's body surface area per day, administered by intravenous infusion over 30 minutes daily for 5 consecutive days, with a 3-week interval between the start of each course. If well tolerated, treatment may continue until disease progression occurs.
- 3.3.4 Contraindications include pregnancy and breastfeeding, a history of severe hypersensitivity to the drug, and severe bone-marrow depression before the first course of treatment. The Summary of Product Characteristics states that topotecan is not recommended in people with severe renal or hepatic impairment, and that patients with poor performance status have a lower response rate and an increased incidence of complications such as fever and infection. In addition (based on clinical experience), those with extensive abdominal tumour deposits leading to bowel obstruction are less likely to benefit from treatment. Adverse effects include dose-limiting myelosuppression (a decrease in the ability of bone marrow to produce blood cells), gastro-intestinal effects, asthenia (lack of strength or energy), alopecia (hair loss) and anorexia (loss of appetite). For full details of adverse effects and contraindications, see the Summary of Product Characteristics.
- 3.3.5 The acquisition cost of topotecan is £97.65 per 1-mg vial and £290.62 per 4-mg vial (excluding VAT; *British National Formulary* 49th edition). For a woman with a body surface area of 1.7 square metres the acquisition cost of topotecan is £926 per cycle (excluding premedication and VAT). This assumes that a 4-mg vial is used and no wastage of the drug occurs. The

overall acquisition cost depends on the number of cycles per patient undertaken. Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (see Appendix A) considered evidence from a number of sources (see Appendix B).

4.1 Clinical effectiveness

4.1.1 Five randomised controlled trials (RCTs) were identified in which the interventions under consideration were used within their licensed indications.

The five studies compared:

- PLDH with topotecan
- topotecan with single-agent paclitaxel
- PLDH with single-agent paclitaxel
- platinum monotherapy with platinum and paclitaxel combination therapy
- a combination (CAP; consisting of cyclophosphamide, doxorubicin and cisplatin) with single-agent paclitaxel.

All of the studies involved women with disease that did not respond to and/or that recurred after platinum-based chemotherapy.

PLDH vs topotecan

4.1.2 The RCT that compared PLDH with topotecan included 474 participants. Most (73%) had been previously treated with platinum and taxanes. At long-term follow-up, 87% of participants had died. Overall median survival was 63 weeks for patients treated with PLDH and 60 weeks for patients treated with topotecan (hazard ratio [HR] = 1.22; 95% confidence interval [CI], 1.00 to 1.48). The 3-year survival rate in the PLDH group was 20.2% (95% CI, 14.9 to 25.5), compared with 13.2% (95% CI, 8.8 to 17.7) for topotecan-treated participants. There were no statistically significant differences in median progression-free survival (16 weeks for PLDH vs 17 weeks for topotecan;

HR = 1.12; 95% CI, 0.93 to 1.35) or in response rates (total response rates: 19.7% for PLDH [95% CI, 14.6 to 24.7] vs 17% for topotecan [95% CI, 12.2 to 21.8]).

- 4.1.3 The survival benefit associated with PLDH was most pronounced in platinum-sensitive participants (46% of the trial population), among whom the median survival time was statistically significantly higher in the PLDH arm compared with the topotecan arm (108 weeks for PLDH vs 70 weeks for topotecan; HR = 1.43; 95% CI, 1.07 to 1.92). No statistically significant treatment-related differences in median survival were shown for the group defined as platinum-refractory (54% of the trial population), which included women with platinum-resistant and platinum-refractory disease (38 weeks vs 42 weeks for PLDH and topotecan, respectively; HR = 1.07; 95% CI, 0.82 to 1.39). There were no statistically significant differences between treatment groups for progression-free survival and response rates when the results were analysed according to baseline platinum sensitivity.
- 4.1.4 For quality of life, assessed at 12 weeks using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), the only statistically significant difference was that more participants receiving topotecan had a stable or improved pain score (relative risk [RR] = 1.26; 95% CI, 1.08 to 1.50). However, less than 50% of participants completed the questionnaire at this time. A quality-adjusted survival analysis (Q-TwiST [Quality-adjusted Time without Symptoms and Toxicity]) was also undertaken to compare the periods of time during which participants experienced no symptoms and no toxicity. This showed a statistically significant difference favouring PLDH (difference = 1.14 months; 95% CI, 0.46 to 1.82).
- 4.1.5 The relative risk of suffering a grade 3 event (that is, a severe adverse event) with PLDH was statistically significantly higher for mucous membrane disorder, stomatitis, PPE and rash, but there were no statistically significantly higher risks associated with any type of grade 4 event (that is, a life-

threatening or disabling adverse event). For topotecan, the relative risk of experiencing a grade 4 event was statistically significantly higher for fever (RR = 10.17; 95% CI, 1.00 to 105.11), anaemia (RR = 10.17; 95% CI, 1.70 to 61.42), leucopenia (RR = 12.20; 95% CI, 4.07 to 37.04), neutropenia (RR = 14.85; 95% CI, 8.18 to 27.36) and thrombocytopenia (RR = 13.56; 95% CI, 4.54 to 41.00). The pattern of grade 3 events for topotecan was similar to that observed for grade 4 events.

Topotecan vs single-agent paclitaxel

- 4.1.6 The RCT that compared topotecan with single-agent paclitaxel included 235 patients (all of whom were taxane naive). At long-term follow-up (4 years after randomisation), no statistically significant differences between treatment groups were reported, other than in median time to response, which favoured single-agent paclitaxel (6 weeks vs 9 weeks, $p = 0.041$ [95% CIs not given]). Median survival times were 63 weeks (95% CI, 47 to 72) and 53 weeks (95% CI, 42 to 69) for the topotecan and single-agent paclitaxel arms, respectively. Median time to progression was 19 weeks (95% CI, 12 to 24) for topotecan and 15 weeks (95% CI, 12 to 18) for single-agent paclitaxel. No data on quality of life were presented.
- 4.1.7 There were no statistically significant differences between treatment groups when the results were analysed according to baseline platinum sensitivity. Median survival times in the topotecan and single-agent paclitaxel groups, respectively, were 28 weeks and 40 weeks in participants with platinum-refractory disease, 72 weeks and 35 weeks in those with platinum-resistant disease and 63 weeks and 85 weeks in those with platinum-sensitive disease.
- 4.1.8 Grade 3 and grade 4 haematological toxicities (leucopenia, neutropenia, thrombocytopenia and anaemia) occurred more often in the topotecan arm compared with the single-agent paclitaxel arm. This was statistically significant in all categories other than grade 4 anaemia. The only exception was grade 3 neutropenia, which was statistically significantly higher in the single-agent paclitaxel group. Non-haematological grade 3 and grade 4

adverse events that were reported more commonly in the topotecan group were nausea (9.8% vs 1.8%), vomiting (9.9% vs 2.7%), constipation (5.4% vs 0%), abdominal pain (5.4% vs 3.5%), asthenia (5.4% vs 3.5%), fatigue (8.0% vs 6.1%), fever/infection (0.9% vs 0%), diarrhoea (6.3% vs 0.9%) and dyspnoea (6.3% vs 5.3%), whilst those reported more commonly for single-agent paclitaxel were arthralgia (2.6% vs 0.9%), myalgia (2.6% vs 0%), skeletal pain (5.3% vs 0%) and alopecia (all grades – 93.0% vs 75.9%).

4.1.9 Participants whose best response was stable disease after six courses of treatment could be removed from the study or switched to the alternative therapy (61 participants crossed over to topotecan and 49 to single-agent paclitaxel). There were no statistically significant differences in efficacy from the initiation of crossover therapy (median survival was 40 weeks and 48 weeks for participants treated third-line with topotecan and single-agent paclitaxel, respectively), and the toxicity profiles for the treatment groups were similar to those recorded in the randomised study.

PLDH vs single-agent paclitaxel

4.1.10 The RCT that compared PLDH with single-agent paclitaxel aimed to include 438 (taxane-naive) patients, but only 216 patients were randomised and the study was terminated prematurely. Data were reported for survival and adverse events only. No statistically significant differences in median survival between treatment groups were reported (47 weeks in the PLDH group vs 56 weeks in the single-agent paclitaxel group; HR = 0.931; 95% CI, 0.70 to 1.23). Grade 3 toxicities that occurred statistically significantly less frequently in the single-agent paclitaxel group relative to the PDLH group were PPE (RR = 0.03; 95% CI, 0.003 to 0.30), stomatitis (RR = 0.091; 95% CI, 0.02 to 0.53) and dyspnoea (RR = 0.17; 95% CI, 0.03 to 1.03). Alopecia was the only grade 3 toxicity that occurred statistically significantly more frequently in the single-agent paclitaxel group (RR = 6.67; 95% CI, 2.20 to 20.66). The incidence of grade 4 adverse events was relatively low in both treatment groups.

Platinum monotherapy vs paclitaxel and platinum combination therapy

- 4.1.11 The RCT that compared paclitaxel and platinum combination therapy with platinum monotherapy included 802 participants with platinum-sensitive disease, 75% of whom had a treatment-free interval greater than 12 months and 43% of whom had received taxanes as part of their first-line treatment. The platinum agent used in the majority of cases was carboplatin. The trial was coordinated in three countries (Italy, Germany and the UK) and the study protocols differed slightly between these countries.
- 4.1.12 At a median follow-up of 42 months, 66% of participants had died. There was a statistically significant difference in median survival (29 months vs 24 months) for participants receiving paclitaxel and platinum combination therapy and platinum monotherapy, respectively (HR = 0.82; 95% CI, 0.69 to 0.97). A statistically significant difference in median progression-free survival favouring the paclitaxel and platinum combination therapy arm was also found (12 months vs 9 months; HR = 0.76; 95% CI, 0.66 to 0.89). There were no statistically significant differences in response rate between the two arms. Subgroup analyses based on previous exposure to taxanes, coordinating country, age and time since last chemotherapy cycle showed no statistically significant differences in outcomes between treatment groups.
- 4.1.13 For quality of life, assessed using the EORTC QLQ-C30 questionnaire, there were no statistically significant differences in eight of nine symptom scales in the first 6 months. Nausea and/or vomiting were statistically significantly worse in the platinum monotherapy group, but this difference lasted for the first 15 weeks of treatment only.
- 4.1.14 The relative risk of experiencing a grade 2 to 4 neurological event was statistically significantly higher among participants receiving paclitaxel and platinum combination therapy (RR = 19.1; 95% CI, 7.4 to 49.9), as was the relative risk of experiencing alopecia (RR = 3.5; 95% CI, 2.9 to 4.2). By contrast, fewer women in the platinum combination therapy arm experienced haematological adverse events (RR = 0.6; 95% CI, 0.52 to 0.75). The

incidence of nausea and/or vomiting was also slightly less in this group (RR = 0.9; 95% CI, 0.7 to 1.0).

Single-agent paclitaxel vs cyclophosphamide, doxorubicin and cisplatin (CAP)

- 4.1.15 The RCT that compared single-agent paclitaxel with CAP included 97 (taxane-naive) patients whose disease had progressed or recurred more than 12 months after the end of the previous treatment. At a median follow-up of 49 months, by which time 57% of the CAP group and 72% of the single-agent paclitaxel group had died, median survival times were higher in the CAP treatment group than in the single-agent paclitaxel group (34.7 months vs 25.8 months; HR, adjusted for differences in residual tumour, length of treatment-free interval and age = 0.58; 95% CI, 0.34 to 0.98). The median progression-free interval was also higher in the CAP treatment group (15.7 months vs 9 months; adjusted HR = 0.60; 95% CI, 0.37 to 0.97). There were no statistically significant differences in response rate. Quality of life was not assessed.
- 4.1.16 Participants who did not respond to their randomised treatment were crossed over to the alternative treatment arm. Of the 23 participants who crossed over to single-agent paclitaxel, five (22%) achieved a complete or partial response, compared with 14 of the 30 participants (46%) who switched to CAP.
- 4.1.17 Single-agent paclitaxel was associated with statistically significantly less grade 3 and grade 4 leucopenia (RR = 0.13; 95% CI, 0.03 to 0.45), neutropenia (RR = 0.35; 95% CI, 0.15 to 0.78) and thrombocytopenia (RR = 0.08; 95% CI, 0.01 to 0.81), and with statistically significantly less grade 2 and grade 3 nausea and/or vomiting (RR = 0.33; 95% CI, 0.17 to 0.64). Participants in the single-agent paclitaxel arm did however experience statistically significantly more alopecia (RR = 1.46; 95% CI, 1.15 to 1.95), myalgia (RR = 4.50; 95% CI, 1.18 to 17.91) and allergic reactions (RR = 7.00; 95% CI, 1.19 to 42.86).

Other RCTs

4.1.18 A further four RCTs were identified in which at least one of the comparators was used outside of its licensed indications. One study compared single-agent paclitaxel with oxaliplatin in 86 taxane-naive participants and found the median overall survival was 37 weeks in the paclitaxel arm and 42 weeks in the oxaliplatin arm. A second study of single-agent paclitaxel compared weekly administration with administration every 3 weeks in 208 taxane-naive participants and found no statistically significant differences in efficacy, However, the planned number of participants was not recruited to this study. The third study compared two doses of single-agent paclitaxel (175 mg and 250 mg per square metre of patient's body surface area) in 372 taxane-naive participants and found a significantly higher response rate in the higher dose arm but no statistically significant differences in overall survival or progression-free survival. In the fourth study, which compared intravenous topotecan with oral topotecan in 266 participants, survival was lower in the oral topotecan arm (51 weeks vs 58 weeks) but no statistically significant differences were observed for any other efficacy outcome.

Evidence from clinical and patient experts

4.1.19 The Committee heard from the clinical experts that the mainstay of ovarian cancer chemotherapy is a platinum-based compound (that is, either carboplatin or cisplatin). When the treatment-free interval after first-line platinum-based therapy exceeds 1 year, standard practice is to re-challenge patients with a platinum-based therapy. The clinical experts explained that, for women who relapse between 6 and 12 months after completion of platinum-based chemotherapy, there is a consensus that it is reasonable to re-treat with a platinum agent, although there remains some uncertainty as to the best strategy to adopt in this patient group. The experts also advised the Committee that platinum-based therapy is not a standard treatment for women with platinum-resistant or platinum-refractory disease, and is not used to treat women who are allergic to platinum. The experts commented that

alternatives to single-agent paclitaxel are usually considered for women with platinum-resistant or platinum-refractory disease who have previously received paclitaxel as part of first-line therapy.

4.1.20 The Committee heard from the clinical and patient experts that health-related quality of life with progressive disease is considerably worse than when the disease is stable. The experts also explained the importance of the different side-effect profiles of the different interventions. These could sometimes be so severe that patients might opt to avoid chemotherapy altogether. Furthermore, when treatments are used sequentially, persistent adverse effects from one previous treatment may necessitate a switch of therapy at the next stage.

4.1.21 The experts gave their views on a home-based administration service for topotecan. They informed the Committee that this was more acceptable to some patients as it reduced the frequency of hospital visits. However, they also explained that some women prefer administration of topotecan in a hospital setting, and, when topotecan is administered in the home, at least one visit to hospital for clinical assessment is still necessary.

4.2 Cost effectiveness

4.2.1 The Assessment Group identified three published economic evaluations that compared two or more of the technologies under review. In addition, three manufacturers each submitted an economic analysis, and the Assessment Group developed its own economic model.

Published studies

4.2.2 One published economic study used a cost-minimisation approach (that is, only the costs associated with treatment were compared, and health outcomes were assumed to be equivalent). This included an analysis from a UK health service perspective and used data from the short-term results of the RCT that compared PLDH and topotecan. The costs of drug acquisition, drug administration and the management of adverse events were included in

the analysis. Estimates of resource use were obtained from the trial data supplemented by expert opinion on the resources required to manage adverse events. The analysis used UK-based unit cost estimates for the year 2000 and included data from all patients (European and North American) in the trial. The study found that PLDH was significantly less costly than topotecan with a difference of £1620 (95% CI, £430 to £1910). The mean costs for topotecan and for PLDH were £9430 (95% CI, £8710 to £10,510) and £7810 (95% CI, £7170 to £8580), respectively.

- 4.2.3 Two other published papers reported the results of cost-minimisation analyses from Spanish and Italian health service perspectives. Both analyses found that PLDH was less costly than topotecan.

Manufacturers' analyses

- 4.2.4 GSK submitted details of a cost-minimisation analysis on the basis that topotecan had been shown to be at least as effective as PLDH in the early results of the RCT that compared the two treatments. In the analysis, the results from the published cost-minimisation analysis (described in Section 4.2.2) were recalculated after substituting the values of some resource-use items with data from an observational study carried out by GSK/Merck. This included changing the values for the drug doses, the number of cycles of therapy, and the frequency of neutropenic sepsis. Unlike the published analysis, GSK's analysis also included the costs associated with toxicity monitoring (chemical pathology, haematology and biochemistry tests) for all patients treated with topotecan, and the costs associated with cardiac monitoring (electrocardiogram [all patients], echocardiogram [two thirds of patients] and multiple gated acquisition [MUGA] scan [one third of patients]) for patients treated with PLDH. The observational study was based on 198 women receiving second-line or subsequent treatment at nine UK centres. The 92 women who received topotecan and were included in the study had fewer cycles and a lower dose of topotecan compared with the trial participants, and the 60 women who received PLDH also received fewer

cycles at a slightly lower dose compared with the trial participants. The proportion of women in the topotecan group who developed neutropenic sepsis was lower in the observational study than in the trial. All women who developed neutropenic sepsis were hospitalised, but compared with the clinical trials, a smaller proportion were treated with granulocyte colony stimulating factor (G-CSF).

- 4.2.5 The results of the GSK analysis suggested that the mean costs per patient were £7770 for topotecan and £8080 for PLDH. GSK also estimated that home administration of topotecan would save on average £2300 per patient for every four cycles of treatment. In order to test the robustness of the results, the Assessment Group conducted a sensitivity analysis around the number of cycles used in the GSK model. They found that the results were sensitive to changes in the assumptions about the number of cycles of therapy received. Recalculating the results using the mean number of cycles of second-line treatment from the observational study, rather than a weighted average of the number of cycles of second-line and subsequent therapy used in the GSK analysis, increased the costs of topotecan to £8330 and reduced the costs of PLDH to £6850.
- 4.2.6 Schering-Plough submitted details of a cost-minimisation analysis based on the long-term follow-up of the trial that compared topotecan and PLDH. The approach in this analysis was similar to the approach used in the published cost-minimisation analysis described in Section 4.2.2. The main difference between the analyses was that expert opinion was used to estimate the number and types of resources used to treat all adverse events. The results showed that the mean cost (with 95% CI) for topotecan was £12,610 (£11,510 to £13,710) compared with £9960 (£9070 to £10,850) for PLDH.
- 4.2.7 Bristol-Myers Squibb submitted the results of an economic model designed to estimate the cost per life year gained from treatment with paclitaxel/platinum combination therapy, single-agent paclitaxel, topotecan and PLDH. Three trials were used to estimate effectiveness in the model: the trial comparing

paclitaxel/platinum combination therapy with platinum monotherapy was used to estimate survival following paclitaxel/platinum combination therapy; early results from the trial comparing PLDH with topotecan were used to estimate survival following treatment with PLDH; and data from the trial comparing topotecan with single-agent paclitaxel were used to estimate survival following treatment with topotecan and single-agent paclitaxel. No adjustment was made to account for differences in the baseline characteristics of participants in the three trials. Survival was estimated up to 3 years. The calculation of costs included drug acquisition costs and the costs of administration. The costs associated with managing adverse events were excluded from the analysis.

- 4.2.8 Estimates of life-years gained, from the Bristol-Myers Squibb model, were 1.78 years for paclitaxel/platinum combination therapy, 1.34 years for topotecan, 1.27 years for single-agent paclitaxel, and 1.42 years for PLDH. The costs were £25,290 for paclitaxel/platinum combination therapy, £30,300 for topotecan therapy, £19,000 for single-agent paclitaxel and £26,990 for PLDH therapy. The results of the model suggested that paclitaxel/platinum combination therapy was both more effective and less costly than either PLDH or topotecan. The incremental cost per life-year gained from paclitaxel/platinum therapy relative to single-agent paclitaxel was £12,120.

Assessment Group's analyses

- 4.2.9 The Assessment Group developed a probabilistic economic model and used this to conduct two separate analyses: one for platinum-sensitive disease only and one for both platinum-sensitive and platinum-refractory/resistant disease.
- 4.2.10 The analysis for platinum-sensitive disease compared the cost effectiveness of topotecan, PLDH, single-agent paclitaxel, paclitaxel/platinum combination therapy, standard platinum therapy and CAP. Data from four trials were used to estimate the treatment effects: topotecan vs PLDH, topotecan vs single-agent paclitaxel, single-agent paclitaxel vs CAP, and platinum therapy vs paclitaxel/platinum combination therapy.

- 4.2.11 The analysis for both platinum-refractory/resistant disease and platinum-sensitive disease only compared the cost effectiveness of single-agent paclitaxel, topotecan and PLDH. It was based on the long-term effectiveness data from the RCT that compared topotecan and PLDH, and from the RCT that compared topotecan and single-agent paclitaxel. These trials included some platinum-sensitive patients and results were presented for the overall population and for patients with platinum-sensitive disease as well as separately for patients with platinum-refractory or platinum-resistant disease. A sensitivity analysis was conducted, which incorporated data from a third trial, the one that compared single-agent paclitaxel with PLDH (which was terminated prematurely).
- 4.2.12 In both analyses, health outcomes were estimated in terms of life years gained and quality-adjusted life years (QALYs). Utility weights, estimating the effect of the disease on health-related quality of life, were applied to the length of time spent with stable disease and progressive disease. The estimate of the health-related utility associated with stable disease was taken from a published study. As data were not available for the health-related utility associated with progressive disease, data from women with progressive breast cancer were used to estimate the difference between stable and progressive ovarian cancer. Data were not available to incorporate into the economic analyses the effect on quality of life of the toxicities associated with the drugs.
- 4.2.13 The Assessment Group's analyses included the costs of the study drugs, pre-medication, monitoring, drug administration and the costs associated with managing severe (grades 3 and 4) adverse events. The analysis of costs was confined to the initial treatment period only and discounting was not therefore applied. Prices for the year 2003–2004 were obtained from published sources and from the manufacturers' submissions. The costs associated with home administration of topotecan were also considered in a sensitivity analysis, which showed that topotecan administered at home was dominated by PLDH.

4.2.14 The Assessment Group's analysis for platinum-sensitive disease found that the numbers of QALYs for women with platinum-sensitive disease were 0.79 for single-agent paclitaxel, 0.80 for topotecan, 1.13 for PLDH, 1.28 for platinum therapy, 1.34 for CAP and 1.56 for paclitaxel/platinum combination therapy. Estimates of the cost of treatment were £6270 for single-agent paclitaxel, £11,280 for topotecan, £7660 for PLDH, £2880 for platinum monotherapy, £3990 for CAP and £8840 for paclitaxel/platinum combination therapy. Platinum monotherapy was less costly and more effective than single-agent paclitaxel, PLDH and topotecan. The incremental cost of a QALY gained from CAP compared with platinum therapy was £16,420 and the incremental cost of a QALY gained from paclitaxel/platinum combination therapy compared with CAP was £20,950. The Assessment Group noted that there was additional uncertainty around the results of this analysis because of the approach used to synthesise the data and the heterogeneity in the trial populations used to inform the analysis.

4.2.15 In the Assessment Group's analysis that included both platinum-refractory/resistant disease and platinum-sensitive disease, estimates of QALYs gained for the overall population were 0.59 for treatment with single-agent paclitaxel, 0.79 for treatment with PLDH and 0.66 for topotecan. The Assessment Group estimated survival by calculating the areas under the survival curves, and thus included data from all patients in the trials. This approach produced different results compared with median survival estimates in the trial that compared PLDH and topotecan because the survival curves crossed after the median survival estimate. The results showed that the costs were £6350 for single-agent paclitaxel, £7710 for PLDH and £11,390 for topotecan. The additional cost of a QALY gained from treatment with PLDH was £7030 compared with single-agent paclitaxel. The cost of PLDH, per QALY gained, was lower for patients with platinum-sensitive disease (£5780) and higher for those with platinum-resistant or platinum-refractory disease (£9560). Topotecan was more costly and less effective than PLDH in all groups of patients. A sensitivity analysis showed that incorporating data from

the trial comparing single-agent paclitaxel and PLDH increased the incremental cost per QALY gained from PLDH, compared with single-agent paclitaxel, to £20,620 in the overall study population. The Assessment Group advised the Committee of the results of an additional sensitivity analysis, which excluded the costs associated with the use of G-CSF to treat grade 4 neutropenic adverse events. The results showed that topotecan was dominated by PLDH, and that the additional cost of a QALY gained from treatment with PLDH was £7160 compared with single-agent paclitaxel.

4.3 Consideration of the evidence

4.3.1 The Committee reviewed the evidence available on the clinical and cost effectiveness of paclitaxel, PLDH and topotecan having considered evidence on the nature of the condition and the value placed by users on the benefits of these drugs from women with advanced ovarian cancer that has relapsed following first-line treatment, those who represent them, and clinical experts. It was also mindful of the need to ensure that its advice took account of the effective use of NHS resources.

4.3.2 The Committee considered the evidence from the clinical trials and the experts' testimonies that, in women with ovarian cancer, the response of the disease to second-line treatment is heavily influenced by the duration of the treatment-free interval after initial platinum-based therapy. The Committee concluded that it was appropriate to issue separate recommendations for the treatment of platinum-sensitive disease and for the treatment of platinum-refractory or platinum-resistant disease.

Platinum-sensitive disease

4.3.3 The Committee noted that standard clinical practice when the treatment-free interval after first-line platinum-based therapy exceeds 1 year is to re-challenge patients with chemotherapy that includes a platinum compound (that is, either carboplatin or cisplatin). The Committee also noted that there is uncertainty regarding the most appropriate treatment for women whose

disease relapses between 6 and 12 months after completion of previous chemotherapy. The clinical experts usually, but not invariably, considered it appropriate to re-challenge these patients with a platinum-based regimen. Thus the Committee decided to distinguish women whose treatment-free interval following initial platinum-based therapy is between 6 and 12 months (hereafter referred to as 'partially-platinum sensitive' disease).

- 4.3.4 Consideration was given to the clinical trials relevant to platinum-sensitive disease and to the economic models based on those trials (that is, the models provided by the Assessment Group and Bristol-Myers Squibb). The Committee noted that the model provided by Bristol-Myers Squibb incorporated no utility estimates, excluded the costs associated with managing adverse events, and did not adjust for differences in the treatment-free interval of participants when comparing survival between the trials, which could lead to bias in the results. The Committee considered that the Assessment Group's analysis for platinum-sensitive disease provided the most informative analysis, as it included the full range of comparators and adjusted for differences in health-related quality of life for the stable and progressive disease periods, which the clinical experts agreed was appropriate. It was acknowledged, however, that an important limitation of the analysis was that the differential toxicity profiles of the drugs were not reflected in the utility estimates, because of lack of data. The Committee was also mindful of the model's (unavoidable) use of indirect comparisons, particularly given the heterogeneity of the trial populations used to inform the analysis; in particular that platinum-sensitive disease was defined as relapse after 6 months or more after completion of first-line platinum therapy in most of the trials that included single-agent paclitaxel, PLDH and topotecan, whereas it was predominantly defined as relapse after 12 months or more after completion of first-line platinum therapy in the trials that included the platinum-based comparators.
- 4.3.5 Notwithstanding these caveats the Committee agreed that platinum and paclitaxel combination therapy was clinically effective and cost effective

relative to the other treatments considered. This was because the trial that compared paclitaxel and platinum combination therapy with platinum monotherapy in women with platinum-sensitive disease and partially platinum-sensitive disease, suggested a small but statistically significant survival benefit in favour of the combination therapy – even in those patients who had previously received paclitaxel. The Committee concluded that paclitaxel in combination with a platinum-based compound should be recommended as a treatment option for women with platinum-sensitive disease and women with partially platinum-sensitive disease.

4.3.6 The Committee considered the experts' testimonies that the adverse effects of paclitaxel may be severe and last several months. It accepted the evidence from the clinical and patient experts that the small benefit in survival associated with paclitaxel and platinum combination therapy compared with platinum-based therapy alone needs to be balanced against its increased toxicity. The Committee also recognised that paclitaxel and platinum combination therapy may not be appropriate for some women with platinum-sensitive disease who received paclitaxel as part of first-line therapy, because of the persistence of the adverse effects. It concluded that the decision to use paclitaxel and platinum combination therapy for the treatment of women with platinum-sensitive disease should be made following discussion of the potential risks and benefits of treatment between the woman and the responsible clinician.

4.3.7 The Committee considered the advice from the experts that a small proportion of women with advanced ovarian cancer are allergic to platinum. The Committee concluded that treatment with paclitaxel and platinum combination therapy would be unsuitable for these women.

4.3.8 The Committee considered the results of the Assessment Group's analysis in relation to single-agent paclitaxel, PLDH and topotecan for the treatment of platinum-sensitive advanced ovarian cancer. It noted the heterogeneity of the trials used in the analysis, and concluded that the benefits of PLDH may have

been underestimated relative to those for platinum monotherapy, paclitaxel/platinum combination therapy and CAP for women with partially platinum-sensitive disease. Although the benefits of topotecan and single-agent paclitaxel may also have been underestimated in these women, the Committee considered the model to reliably show that PLDH was cost-effective compared with single-agent paclitaxel and topotecan in women with platinum-sensitive disease. The Committee concluded that PLDH should be recommended as a treatment option for women with partially platinum-sensitive disease, but were not persuaded that topotecan or single-agent paclitaxel should be recommended for the treatment of partially platinum-sensitive disease.

Platinum-resistant and platinum-refractory disease

- 4.3.9 The Committee considered the evidence relating to the treatment of women with platinum-resistant or platinum-refractory disease. It noted that the majority of women receive paclitaxel in combination with platinum-based therapy as first-line therapy, and that alternatives to single-agent paclitaxel are usually considered in this group of patients with platinum-resistant or platinum-refractory disease.
- 4.3.10 The Committee considered the evidence on the cost effectiveness of topotecan, single-agent paclitaxel and PLDH administered as single-agent therapies in women with platinum-resistant or platinum-refractory disease (that is, the models provided by the Assessment Group, Bristol-Myers Squibb, GlaxoSmithKline, Schering-Plough and the published economic evaluations). The Committee considered that the Assessment Group's analysis of cost effectiveness was the most appropriate, as it considered all the relevant costs associated with treatment and an estimation of the impact of the disease on health-related quality of life.
- 4.3.11 The Committee considered the results of the Assessment Group's base-case economic analysis for patients with platinum-resistant or platinum-refractory disease, which showed that the additional cost of a QALY gained from PLDH

compared with single-agent paclitaxel is under £10,000. The Committee concluded that PLDH should be recommended as a treatment option for women with platinum-resistant or platinum-refractory disease. Given that the Assessment Group's economic model could not incorporate the impact of the different adverse events associated with the drugs on health-related quality of life, that the costs of PLDH and single-agent paclitaxel are similar, and that there is uncertainty regarding the relative effectiveness of PLDH and single-agent paclitaxel, the Committee concluded that it would be appropriate to recommend single-agent paclitaxel as a further treatment option in women with platinum-resistant or platinum-refractory disease.

4.3.12 The Committee discussed the results of the Assessment Group's economic model, and considered that topotecan was not cost effective compared with PLDH and single-agent paclitaxel. The Committee noted the need to administer topotecan over 5 consecutive days. It also considered the experts' views on a service to provide topotecan in the patient's home, which, despite increasing acceptability amongst some patients, still requires a visit to hospital for clinical assessment. The Committee considered comments from the manufacturer of topotecan that the home administration of topotecan could reduce the costs of topotecan by between £1780 and £2650 depending on the number of cycles of treatment. It noted that these estimates excluded the costs of home visits by a nurse and that home administration would not be appropriate for all women with advanced ovarian cancer. The Committee considered this potential reduction in the costs of administering topotecan alongside the cost estimates from the Assessment Group's analyses. It concluded that the potential cost savings from administering topotecan at the patient's home would not offset the difference in cost between PLDH and topotecan. It also noted that there was no evidence of the relative effectiveness of topotecan administered at home compared with administration in a hospital.

4.3.13 The Committee considered the costs included in the Assessment Group's economic analyses of treating adverse events associated with topotecan. It

noted that G-CSF was used to treat a smaller proportion of neutropenic events in the observational study submitted by the manufacturer of topotecan compared with the clinical trials of topotecan. The Committee considered the results of the Assessment Group's sensitivity analysis around the assumptions regarding the use of G-CSF to treat neutropenic events, and concluded that the cost-effectiveness estimates were robust to changes in these assumptions.

4.3.14 The Committee acknowledged the testimony from the patient and clinical experts that the associated toxicities of PLDH and single-agent paclitaxel would be unacceptable to some women. The Committee concluded that treatment with topotecan should only be recommended for women in whom PLDH and single-agent paclitaxel are considered inappropriate because they have previously been exposed to PLDH and single-agent paclitaxel, or if the impact of the adverse effects of treatment with these drugs is considered unacceptable.

Third-line and subsequent treatment

4.3.15 The Committee acknowledged the insufficient evidence on third-line and subsequent treatment of advanced ovarian cancer. However, on the basis of the evidence from the clinical experts, the Committee concluded that the same general principles used to determine appropriate second-line therapy should also apply to third-line and subsequent therapy.

Choice of treatment

4.3.16 Finally, the Committee agreed that, within the restrictions set out above, the choice of treatment for second-line or subsequent chemotherapy should be made after discussion between the responsible clinician and the patient about the risks and benefits of the options available.

5 Recommendations for further research

- 5.1 The Institute noted the lack of data on the health-related quality of life of women with ovarian cancer and recommends that these data are collected. The data collected should incorporate information on the quality of life of women in remission and of women with asymptomatic and symptomatic disease progression, and the effects of drug toxicities. Data collection should also include generic measures of health-related quality of life that are compatible with techniques for conducting economic evaluations.
- 5.2 The Institute noted the need for research on further platinum-based combinations. It also noted that a trial designed to consider the effectiveness of PLDH/platinum combination therapy is expected to start soon, and that research into other combinations would be worthwhile. The Institute recommended that such trials should also provide information on the effectiveness of treatments in women who relapse between 6 and 12 months from initial chemotherapy and should stratify patients accordingly.
- 5.3 The Institute recommends that a study be undertaken to investigate the effectiveness of single-agent non-platinum therapy compared with platinum alone or in combination with paclitaxel, as second-line treatments for patients with platinum-sensitive disease.
- 5.4 The Institute acknowledges that studies are being undertaken to investigate the effectiveness of platinum in combination with other agents in women with platinum-resistant or platinum-refractory disease.

6 Implications for the NHS

- 6.1 The estimated impact on NHS resources of the guidance is presented separately for platinum-sensitive disease and for platinum-resistant and platinum-refractory disease. The calculations assume that 6000 women are diagnosed with ovarian cancer each year and that, of the 75% of women who are estimated to receive first-line chemotherapy, 50% will have platinum-

sensitive disease and 25% will have platinum-resistant or platinum-refractory disease.

Platinum-sensitive disease

- 6.2 It is expected that the number of women who receive paclitaxel in combination with a platinum-based agent will increase overall, and that the number who receive platinum monotherapy will fall (paclitaxel was not previously recommended as a second-line treatment option for women who received it as part of first-line treatment). The Assessment Group estimated that the additional cost of paclitaxel in combination with a platinum agent is approximately £5970 per person compared with platinum monotherapy. It is not clear what proportion of women receive paclitaxel as part of their first-line therapy. However, assuming that 50% of women receive paclitaxel as part of first-line therapy, the additional annual cost to the NHS would be around £1.3 million if 20% of these women were to receive paclitaxel in combination with a platinum agent as second-line therapy. This estimate increases to £3.4 million and £5.4 million, if 50% and 80% of the women who receive paclitaxel as part of first-line treatment, respectively, were to receive this combination as second-line therapy. For a population of 100,000, the additional estimated annual cost would be in the region of £2600 to £10,200 (this assumes that local age and sex profiles reflect the national profile).
- 6.3 It is unclear how many women with partially platinum-sensitive disease will receive PLDH. The Assessment Group estimated the additional cost of treatment with PLDH to be slightly less than treatment with paclitaxel in combination with a platinum-based agent. The extent to which this will reduce the estimates presented in Section 6.2 will depend on the number of women who receive PLDH rather than paclitaxel in combination with a platinum-based agent.

Platinum-resistant and platinum-refractory disease

- 6.4 It is expected that fewer women with platinum-resistant or platinum-refractory disease will receive topotecan as a second-line treatment, and that more will receive PLDH. Although single-agent paclitaxel is recommended as a second-line treatment on an equal basis to PLDH, it is assumed that the number of women who receive paclitaxel would not change substantially, as the majority receive it as part of first-line therapy.
- 6.5 Given that the cost of treatment with topotecan is estimated to be £3680 more per person than the cost of treatment with PLDH, it is expected that the guidance will reduce the costs associated with the second-line treatment of platinum-resistant or platinum-refractory disease. However, no national data are available on the percentage of women with platinum-resistant or platinum-refractory ovarian cancer who currently receive topotecan and PLDH. It is also difficult to quantify with precision the number of women who would have previously received topotecan, but would now be considered appropriate candidates for treatment with PLDH as a result of the guidance.
- 6.6 Based on an assumption that 60% of women with platinum-resistant or platinum-refractory disease currently receive PLDH, and that 30% currently receive topotecan, the annual saving to the NHS would be around £1.2 million if 99% of women who would normally receive topotecan as a second-line treatment were to receive PLDH instead. This figure falls to £0.9 million if 75% of women were to receive PLDH instead of topotecan. For a population of 100,000, the estimated annual saving would therefore be in the region of £1800 to £2300 (this assumes that local prescribing patterns mirror national prescribing patterns).

Overall impact on NHS resources

- 6.7 On the basis of these separate estimates, the overall annual impact on NHS resources would be an additional cost of between £0.1 million and £4.4 million. These estimates relate to changes in the costs associated with

second-line treatment only, and do not take into account potential changes in the prices of the drugs under consideration.

7 Implementation and audit

7.1 Clinicians who care for women with ovarian cancer should review their current practice and policies to take account of the guidance set out in Section 1.

7.2 Local guidelines, protocols or care pathways that refer to the care of women with advanced ovarian cancer should incorporate the guidance.

7.3 To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in Appendix C.

7.3.1 A woman with advanced ovarian cancer that is platinum-sensitive or partially platinum-sensitive is offered paclitaxel in combination with a platinum-based compound as second-line (or subsequent) treatment option, unless she is allergic to platinum-based compounds.

7.3.2 A woman with advanced ovarian cancer that is platinum-refractory or platinum-resistant or a woman who is allergic to platinum-based compounds is offered single-agent paclitaxel as a second-line (or subsequent) treatment option.

7.3.3 A woman with advanced ovarian cancer that is partially platinum-sensitive, platinum-refractory or platinum-resistant or a woman who is allergic to platinum-based compounds is offered PLDH as a second-line (or subsequent) treatment option.

7.3.4 A woman with advanced ovarian cancer that is platinum-refractory or platinum-resistant, or a woman who is allergic to platinum-based compounds, and for whom PLDH and single-agent paclitaxel are considered inappropriate, is offered topotecan as a second-line (or subsequent) treatment option.

7.3.5 The responsible clinician and the woman discuss the risks and benefits of the options available before the choice of treatment for second-line (or subsequent) chemotherapy is made.

7.4 Local clinical audits on the management of ovarian cancer also could include measurement of compliance with accepted clinical guidelines or protocols or with the measures for the treatment of ovarian cancer that are suggested in *Guidance on commissioning cancer services: Improving outcomes in gynaecological cancers*.

8 Related guidance

This guidance replaces the following guidance issued by the Institute.

- Ovarian cancer – topotecan; *Technology Appraisal Guidance* no. 28 (2001)
- Ovarian cancer (advanced) – pegylated liposomal doxorubicin hydrochloride; *Technology Appraisal Guidance* no. 45 (2002)

This guidance replaces recommendations 1.3, 1.4 and 1.5 on the second-line treatment of advanced ovarian cancer in the following guidance.

- Ovarian cancer – paclitaxel (review); *Technology Appraisal Guidance* no. 55 (2003)

The recommendations for first-line therapy in *Technology Appraisal Guidance* no. 55 are not affected by this guidance.

9 Proposed date for review of guidance

9.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider any new evidence on the technology, in the form of an updated Assessment Report, and decide whether the technology should be referred to the Appraisal Committee for review.

9.2 The guidance on these technologies will be considered for review in February 2008.

Andrew Dillon
Chief Executive
May, 2005

A version of this guidance written for people with advanced ovarian cancer, their families and carers, and the public is available from the NHS Response Line (telephone 0870 1555 455 and quote reference number N0873). It is also available from the NICE website (www.nice.org.uk/TA091publicinfo).

Appendix A. Appraisal Committee members and NICE project team

A. Appraisal Committee members

NOTE The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The committee is split into three branches. In order to ensure consistency, the chair of each branch is also a member of a branch of which he is not chair. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Ms Julie Acred

Chief Executive, Derby Hospital, Southern Derbyshire Acute Hospitals NHS Trust

Dr Darren Ashcroft

Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical sciences,
University of Manchester

Professor David Barnett

Professor of Clinical Pharmacology, University of Leicester

Mr Brian Buckley

Vice Chairman, InContact

Dr Mark Chakravarty

Head of Government Affairs and NHS Policy, Procter and Gamble Pharmaceuticals (UK) Ltd, Egham, Surrey

Dr Peter I Clark

Honorary Chairman, Association of Cancer Physicians

Ms Donna Covey

Chief Executive, National Asthma Campaign

Dr Mike Davies

Consultant Physician, University Department of Medicine & Metabolism, Manchester Royal Infirmary

Mr Richard Devereaux-Phillips

Public Affairs and Reimbursement Manager, Medtronic Ltd

Professor Jack Dowie

Health Economist, London School of Hygiene

Professor Gary A Ford

Professor of Pharmacology of Old Age/Consultant Physician, Newcastle upon Tyne Hospitals NHS Trust

Dr Fergus Gleeson

Consultant Radiologist, The Churchill Hospital, Oxford

Professor Trisha Greenhalgh

Professor of Primary Health Care, University College London

Professor Peter Jones

Professor of Statistics & Dean Faculty of Natural Sciences, Keele University

Professor Robert Kerwin

Professor of Psychiatry and Clinical Pharmacology, Institute of Psychiatry, London

Ms Rachel Lewis

Staff Nurse (Nephrology) Hull Royal Infirmary

Professor Jonathan Michaels

Professor of Vascular Surgery, University of Sheffield

Dr Ruairidh Milne

Senior Lecturer in Public Health, National Coordinating Centre for Health Technology Assessment, University of Southampton

Dr Neil Milner

General Medical Practitioner, Sheffield

Dr Rubin Minhas

General Practitioner with a Special Interest in Coronary Heart Disease, Primary Care CHD Lead, Medway PCT & Swale PCT

Mr Miles Scott

Chief Executive, Harrogate Health Care NHS Trust

Professor Mark Sculpher

Professor of Health Economics, University of York

Dr Ken Stein

Senior Lecturer, Peninsula Technology Assessment Group (PenTAG), University of Exeter

Professor Andrew Stevens (Chair)

Professor of Public Health, University of Birmingham

B. NICE Project Team

Each appraisal of a technology is assigned to a Health Technology Analyst and a Technology Appraisal Project Manager within the Institute.

Louise Longworth and Zoe Charles

Technical Leads, NICE project team

Emily Marschke

Project Manager, NICE project team

Appendix B. Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by C Main, L Ginnelly, S Griffin, G Norman, M Barbieri, L Mather, D Stark, S Palmer, R Riemsma, University of York: *Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for second-line or subsequent treatment of advanced ovarian cancer*, September 2004.

B The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD). Consultee organisations are provided with the opportunity to appeal against the Final Appraisal Determination.

I Manufacturer/sponsors:

- Bristol-Myers Squibb
- GlaxoSmithKline
- IVAX Pharmaceuticals UK
- Schering-Plough

II Professional/specialist and patient/carer groups:

- British Gynaecological Cancer Society
- CancerBACUP
- Department of Health
- Helene Harris Memorial Trust
- Mid Sussex PCT
- Ovacome
- Royal College of Nursing
- Royal College of Obstetricians & Gynaecologists
- Royal College of Physicians
- Welsh Assembly Government

III Commentator organisations (without the right of appeal):

- British National Formulary
- NHS Quality Improvement Scotland
- Patients Association
- Purchasing and Supplies Agency

C The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on paclitaxel, pegylated liposomal doxorubicin hydrochloride and topotecan by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Ms Louise Bayne, Director, Ovacome, nominated by Ovacome
- Mrs Susan Dunning, nominated by Ovacome
- Professor Martin Gore, Consultant Medical Oncologist, Royal College of Physicians, nominated by Royal College of Physicians
- Dr Jonathan Ledermann, Reader in Oncology and Consultant in Oncology, Cancer Research UK and UCL Clinical Trials Centre, nominated by MRC Clinical Trials

Appendix C. Detail on criteria for audit of the use of paclitaxel, pegylated liposomal doxorubicin hydrochloride and topotecan for second-line or subsequent treatment of advanced ovarian cancer

Possible objectives for an audit

An audit could be carried out to ensure the appropriateness of the use of paclitaxel, pegylated liposomal doxorubicin hydrochloride and topotecan in women with advanced ovarian cancer.

Possible patients to be included in the audit

An audit could be carried out on women with advanced ovarian cancer who are seen in a reasonable time period for audit, for example, 6 months to 1 year. It may be useful to include women who were diagnosed and treated sufficiently long ago that relapse and second-line therapy may have occurred.

Measures that could be used as a basis for an audit

The measures that could be used in an audit of paclitaxel, pegylated liposomal doxorubicin hydrochloride and topotecan in women with advanced ovarian cancer are as follows. Alternative therapies (including standard platinum monotherapy) for the second-line or subsequent treatment of advanced ovarian cancer also may be included in the audit design; however, the measures provided below are limited to the treatments covered by this appraisal.

Criterion	Standard	Exception	Definition of terms
<p>1. A woman with advanced ovarian cancer that is platinum-sensitive or partially platinum-sensitive is offered paclitaxel in combination with a platinum-based compound as a second-line (or subsequent) treatment option</p>	<p>100% of women in the audit who have platinum-sensitive or partially platinum-sensitive advanced ovarian cancer</p>	<p>A. The woman has a contraindication to paclitaxel in combination with a platinum-based compound B. The woman is allergic to platinum-based compounds</p>	<p>‘Platinum-sensitive ovarian cancer’ means ovarian cancer that responds to first-line platinum-based therapy but relapses 12 months or more after completion of initial platinum-based chemotherapy. ‘Partially platinum-sensitive ovarian cancer’ means ovarian cancer that responds to first-line platinum-based therapy but relapses between 6 and 12 months after completion of initial platinum-based chemotherapy. ‘Platinum-based compound’ refers to carboplatin or cisplatin. For measures 1–4, clinicians will need to agree locally on how the offering of treatment options is documented for audit purposes. See the Summary of Product Characteristics for contraindications.</p>
<p>2. A woman with advanced ovarian cancer is offered single-agent paclitaxel as a second-line (or subsequent) treatment option in any of the following</p>	<p>100% of women in the audit who have platinum-refractory or platinum-resistant advanced</p>	<p>None</p>	<p>‘Platinum-refractory ovarian cancer’ means ovarian cancer that does not respond to initial platinum-based chemotherapy. ‘Platinum-resistant ovarian cancer’</p>

<p>situations:</p> <p>(a) The woman's cancer is platinum-refractory or</p> <p>(b) The woman's cancer is platinum-resistant or</p> <p>(c) The woman is allergic to platinum-based compounds</p>	<p>ovarian cancer or who are allergic to platinum-based compounds</p>		<p>means ovarian cancer that relapses within 6 months of completion of initial platinum-based chemotherapy.</p>
<p>3. A woman with advanced ovarian cancer is offered PLDH as a second-line (or subsequent) treatment option in any of the following situations:</p> <p>(a) The woman's cancer is partially platinum-sensitive or</p> <p>(b) The woman's cancer is platinum-refractory or</p> <p>(c) The woman's cancer is platinum-resistant or</p> <p>(d) The woman is allergic to platinum-based compounds</p>	<p>100% of women in the audit who have partially platinum-sensitive, platinum-refractory or platinum-resistant advanced ovarian cancer or who are allergic to platinum-based compounds</p>	<p>A. The woman has a contraindication to PLDH</p>	<p>See above for definitions of partially platinum-sensitive, platinum-refractory or platinum-resistant ovarian cancer. See the Summary of Product Characteristics for contraindications.</p>
<p>4. A woman with advanced ovarian cancer is offered topotecan as a second-line (or subsequent) treatment option in any of the following situations:</p> <p>(a) The woman's cancer is platinum-refractory and PLDH and single-agent paclitaxel are considered inappropriate or</p>	<p>100% of women in the audit who have platinum-refractory or platinum-resistant advanced ovarian cancer, or who are allergic to platinum-based compounds, and for whom</p>	<p>A. The woman has a contraindication to topotecan</p>	<p>'Considered inappropriate' refers to a woman who has been previously exposed to PLDH and single-agent paclitaxel or the impact of the adverse effects of treatment with these drugs is considered unacceptable. See the Summary of Product Characteristics for contraindications.</p>

<p>(b) The woman's cancer is platinum-resistant and PLDH and single-agent paclitaxel are considered inappropriate or</p> <p>(c) The woman is allergic to platinum-based compounds and PLDH and single-agent paclitaxel are considered inappropriate</p>	<p>PLDH and single-agent paclitaxel are considered inappropriate</p>		
<p>5. The responsible clinician and the woman discuss the risks and benefits of the options before the choice of treatment for second-line (or subsequent) chemotherapy is made</p>	<p>100% of women with advanced ovarian cancer</p>	<p>A. The woman declines participation in the discussion</p>	<p>'Discussion' could cover the side-effect profiles of the alternative therapies, the stage of the woman's disease and the disease-related performance status. Clinicians will need to agree locally on how the discussion will be documented, for audit purposes.</p>

Calculation of compliance

Compliance (%) with each measure described in the table above is calculated as follows.

$$\frac{\text{Number of patients whose care is consistent with the **crit**erion **plus** number of patients who meet any **exception** listed}{\text{Number of patients to whom the **measure** applies}} \times 100$$

Clinicians should review the findings of measurement, identify whether practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.