

**NATIONAL INSTITUTE FOR HEALTH AND CARE  
EXCELLENCE**

**Final appraisal determination**

**Topotecan, pegylated liposomal  
doxorubicin hydrochloride, paclitaxel,  
trabectedin and gemcitabine for treating  
recurrent ovarian cancer (including reviews  
of technology appraisal guidance 91 and  
222)**

**1 Guidance**

- 1.1 Paclitaxel in combination with platinum or as monotherapy is recommended within its marketing authorisation as an option for treating recurrent ovarian cancer.
- 1.2 Pegylated liposomal doxorubicin hydrochloride (PLDH) as monotherapy is recommended within its marketing authorisation as an option for treating recurrent ovarian cancer.
- 1.3 PLDH in combination with platinum is recommended as an option for treating recurrent ovarian cancer.<sup>1,2</sup>

---

<sup>1</sup> At the time of publication (December 2014), PLDH in combination with platinum did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

<sup>2</sup> The use of PLDH (Caelyx) in combination with platinum is outside the terms of the marketing authorisation for Caelyx. Consequently the statutory funding requirement does not apply to this recommendation. NICE received a remit to appraise this combination under Regulation 5 of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#).

1.4 The following are not recommended within their marketing authorisations for treating the first recurrence of platinum-sensitive ovarian cancer:

- gemcitabine in combination with carboplatin
- trabectedin in combination with PLDH
- topotecan.

The Appraisal Committee was unable to make recommendations on the use of these technologies for treating platinum-sensitive ovarian cancer beyond the first recurrence.

1.5 Topotecan is not recommended within its marketing authorisation for treating recurrent platinum-resistant or platinum-refractory ovarian cancer.

1.6 People currently receiving treatment initiated within the NHS with gemcitabine in combination with carboplatin, trabectedin in combination with PLDH, or topotecan that is not recommended for them by NICE in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

## **2 Clinical need and practice**

2.1 Ovarian cancer is a common gynaecological cancer which represents a group of different tumours arising from diverse types of ovarian tissue. The most common type arises from epithelial cells (the outside layer of cells), and can often spread 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 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.

- 2.2 Recurrent ovarian cancer may be categorised according to the response to first-line platinum chemotherapy as follows: platinum-sensitive (disease that responds to first-line platinum-based therapy but relapses after 6 months or more,– can be further subdivided into partially platinum-sensitive disease that relapses between 6 and 12 months and fully platinum sensitive disease that relapses after 12 months or more); platinum-resistant (disease that relapses within 6 months of completion of initial platinum-based chemotherapy); and platinum-refractory (disease that does not respond to initial platinum-based chemotherapy). However, the 'partially platinum-sensitive' and 'platinum-resistant' categories should not necessarily be defined rigidly.
- 2.3 Ovarian cancer predominantly occurs in older women, with over 80% of cases being diagnosed in women over 50 years. In 2010, around 7000 new cases of ovarian cancer were diagnosed and there were approximately 4300 deaths from ovarian cancer in the UK. The overall 5-year survival rate for ovarian cancer is approximately 43%. Although a significant percentage of women have ovarian cancer that responds to initial chemotherapy, between 55% and 75% relapse within 2 years of completing treatment with chemotherapy.
- 2.4 Fear of recurrence and subsequent treatment, particularly for women with platinum-refractory disease, has an emotional impact. Recurrence of disease is associated with poorer prognosis and treatment options are limited. Treatment for recurrent ovarian cancer is also likely to diminish a woman's physical and emotional wellbeing to a point where they can no longer work, or need ongoing support with day-to-day activities. In NICE technology appraisal guidance 91 (to be replaced by the recommendations in this final appraisal determination), the recommended options for the second-line (or subsequent) treatment of women with platinum-

sensitive or partially platinum-sensitive advanced ovarian cancer were paclitaxel in combination with a platinum-based compound (carboplatin or cisplatin), or PLDH for partially platinum-sensitive ovarian cancer and for women allergic to platinum-based compounds. The recommended second-line (or subsequent) treatment options for women with platinum-resistant or platinum-refractory ovarian cancer, and for women allergic to platinum based compounds, were single-agent paclitaxel, PLDH, or topotecan for women for whom PLDH and paclitaxel were considered inappropriate. NICE technology appraisal guidance 222 (also to be replaced by the recommendations in this final appraisal determination) did not recommend trabectedin in combination with PLDH for treating relapsed platinum-sensitive ovarian cancer.

### **3 The technologies**

#### ***Gemcitabine***

- 3.1 Gemcitabine (various manufacturers) is a chemotherapeutic agent that inhibits DNA synthesis. It is a nucleoside analogue with antitumour activity against a number of solid tumours. Gemcitabine, in combination with carboplatin, has a UK marketing authorisation for the treatment of 'patients with locally advanced or metastatic epithelial ovarian carcinoma, in combination with carboplatin, in patients with relapsed disease following a recurrence-free interval of at least 6 months after platinum-based, first-line therapy'.
- 3.2 Gemcitabine is administered by intravenous infusion. The recommended dosage is 1000 mg/m<sup>2</sup> of body surface area administered on days 1 and 8 of each 21-day cycle. After gemcitabine, carboplatin is given on day 1 consistent with a target area under curve of 4.0 mg/mlxmin. The summary of product characteristics lists the following as the most common adverse

reactions associated with gemcitabine treatment: leukopenia, thrombocytopenia, anaemia, dyspnoea, vomiting, nausea, elevation of liver transaminases and alkaline phosphatase, allergic skin rash, alopecia, haematuria, mild proteinuria, influenza-like symptoms and oedema/peripheral oedema.

- 3.3 Gemcitabine is available in 200 mg and 1 gram vials at net prices of £32.55 and £162.76 respectively (excluding VAT; 'British national formulary' [BNF] edition 65). The Assessment Group estimated that the cost of a course of treatment of gemcitabine 1000 mg/m<sup>2</sup> (based on an average body surface area of 1.71m<sup>2</sup>) on day 1 and 8 of every 21 days, plus carboplatin given on day 1, is £706. Costs may vary in different settings because of negotiated procurement discounts.

### ***Paclitaxel***

- 3.4 Paclitaxel (various manufacturers) is a cytotoxic anticancer drug that belongs to the taxane group of drugs. Taxanes prevent the formation of mitotic spindles, interfering with the process of cell division and resulting in cell death. Paclitaxel has a UK marketing authorisation 'for the treatment of metastatic carcinoma of the ovary after failure of standard, platinum containing therapy'.
- 3.5 Paclitaxel is administered by intravenous infusion. The recommended dosage is 175 mg/m<sup>2</sup> of body surface area administered over a period of 3 hours, with a 3-week interval between treatment cycles. Paclitaxel has also been evaluated in randomised controlled trials with a weekly interval between treatment cycles, and this is in line with clinical practice for the treatment of platinum-refractory or -resistant recurrent ovarian cancer. The summary of product characteristics lists the following as the most common adverse reactions associated with paclitaxel treatment: infection, myelosuppression, neutropenia, anaemia,

thrombocytopenia, leukopenia, bleeding, mild hypersensitivity reactions, neurotoxicity, hypotension, diarrhoea, vomiting, nausea, mucositis, alopecia, arthralgia and myalgia.

- 3.6 Paclitaxel is available in 5 ml, 16 ml, 25 ml and 50 ml vials at net prices of £66.85, £200.35, £300.52 and £601.03 respectively (excluding VAT; BNF edition 65). The Assessment Group estimated that the cost of a course of 3-weekly treatment with paclitaxel 175 mg/m<sup>2</sup> (based on an average body surface area of 1.71m<sup>2</sup>) for 18 weeks is £638. The cost of weekly treatment with paclitaxel 80 mg/m<sup>2</sup> for 18 weeks is £306. However, the weekly dose is currently unlicensed. Costs may vary in different settings because of negotiated procurement discounts.

### ***Pegylated liposomal doxorubicin hydrochloride***

- 3.7 Pegylated liposomal doxorubicin hydrochloride (Caelyx, Jansen-Cilag; PLDH) is an anthracycline – a group of cytotoxic antibiotics that inhibit DNA synthesis. They also interact with cell membranes, altering their function and generating cytotoxic chemicals. PLDH has a UK marketing authorisation for the treatment of advanced ovarian cancer in women for whom a first-line platinum-based chemotherapy regimen has failed. It has been studied in combination with carboplatin for the treatment of platinum sensitive ovarian cancer but this combination does not have a marketing authorisation.
- 3.8 PLDH is administered by intravenous infusion. The recommended dosage is 50 mg/m<sup>2</sup> of body surface area once every 4 weeks for as long as the disease does not progress and the patient continues to tolerate treatment. Combination treatment at lower doses has been studied in clinical trials. The summary of product characteristics lists the following as the most common adverse reactions associated with treatment with PLDH: anorexia, nausea,

stomatitis, vomiting, palmar–plantar erythrodysesthesia, alopecia, rash, asthenia, fatigue and mucositis.

- 3.9 PLDH is available in 10 ml and 25 ml vials at net prices of £360.25 and £712.49 respectively (excluding VAT; BNF edition 65). The Assessment Group estimated that the cost of a course of treatment of PLDH 40 mg/m<sup>2</sup> (based on an average body surface area of 1.71m<sup>2</sup>) on day 1 of every 28-day cycle is £1211. Costs may vary in different settings because of negotiated procurement discounts.

### ***Topotecan***

- 3.10 Topotecan (various manufacturers) is a naturally derived chemotherapeutic agent that prevents DNA replication in cancer cells. It has a UK marketing authorisation for the treatment of women with 'metastatic carcinoma of the ovary after failure of first-line or subsequent chemotherapy'. The recommended dosage is 1.5 mg/m<sup>2</sup> of body surface area per day, administered by intravenous infusion over 30 minutes daily for 5 consecutive days, with 3 weeks between each course. If well tolerated, treatment may continue until disease progression. The summary of product characteristics lists the following as the most common adverse reactions associated with treatment with topotecan: febrile neutropenia, neutropenia, thrombocytopenia, anaemia, leukopenia, nausea, vomiting and diarrhoea, constipation, abdominal pain, mucositis, alopecia, anorexia, infection, pyrexia, asthenia and fatigue.
- 3.11 Topotecan is available in 1 mg and 4 mg vials at net prices of £97.65 and £290.62 respectively (excluding VAT; BNF edition 65). The Assessment Group estimated that the cost of a course of treatment of topotecan 1.5 mg/m<sup>2</sup> (based on an average body surface area of 1.71m<sup>2</sup>) on days 1–5 every 21-day cycle is £1305.

Costs may vary in different settings because of negotiated procurement discounts.

### ***Trabectedin***

- 3.12 Trabectedin (Yondelis, PharmaMar) is an anticancer agent that binds to the minor groove of the DNA and bends the helix to the major groove, which disrupts the cell cycle. It has a UK marketing authorisation, in combination with PLDH, for the treatment of women 'with relapsed platinum-sensitive ovarian cancer'. The recommended dosage is 1.1 mg/m<sup>2</sup> of body surface area, immediately after PLDH 30 mg/m<sup>2</sup>, administered every 3 weeks as a 3-hour infusion. The summary of product characteristics lists the following as the most common adverse reactions associated with treatment with trabectedin: neutropenia; thrombocytopenia; anaemia; leukopenia; anorexia; headache; vomiting; constipation; hyperbilirubinemia; fatigue; increases in alanine aminotransferase, aspartate aminotransferase, blood alkaline phosphatase, gamma-glutamyltransferase, blood creatine phosphokinase, and blood creatinine; and decrease in blood albumin.
- 3.13 Trabectedin is available in 250-microgram and 1-mg vials at net prices of £363.00 and £1366.00 respectively (excluding VAT; BNF edition 65). The Assessment Group estimated that the cost of 5 cycles of treatment of trabectedin 1.1 mg/m<sup>2</sup> (based on an average body surface area of 1.71m<sup>2</sup>) and PLDH 30 mg/m<sup>2</sup> on day 1 of every 21-day cycle is £18,394.
- 3.14 The manufacturer of trabectedin has agreed a patient access scheme with the Department of Health. The scheme will apply to patients who need more than 5 cycles of trabectedin plus PLDH; when an order is received for a patient on cycle 6 onwards, the manufacturer will authorise an appropriate rebate. Rebates will be in the form of either an adjustment to the invoice (free stock) or, if



preferred, by credit note. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

## 4 Evidence and interpretation

The Appraisal Committee (section 8) considered evidence from a number of sources (section 9).

### 4.1 *Clinical effectiveness*

4.1.1 The Assessment Group carried out a systematic review and identified 16 randomised controlled trials, evaluating 14 different pairwise comparisons that met the inclusion criteria. Eleven of these trials were open label, and the masking technique was unclear in the remaining studies. The size of the trial populations ranged from 61 to 976 patients. The interventions in the trials were paclitaxel (6 trials), pegylated liposomal doxorubicin hydrochloride (PLDH; 5 trials), topotecan (3 trials), gemcitabine (1 trial) and trabectedin (1 trial). The Assessment Group stated that 5 of these trials evaluated the interventions and comparators within their licensed indications, dosage and routes of administration. The remaining 11 trials included dosages or routes of administration different from the relevant marketing authorisations. The population in 9 of the 16 trials was restricted to women experiencing their first recurrence. This included the main trials available for gemcitabine plus carboplatin and trabectedin plus PLDH, and 3 of the 4 trials for topotecan. One trial comparing weekly topotecan with 3-weekly topotecan included women with platinum resistance who were experiencing subsequent recurrences. The Assessment Group stated that in general the trials were well designed and conducted. It expressed some concerns about the difference in baseline characteristics between trials, that masking and independent reviewer assessment in some trials was unclear, that some trials

were not sufficiently powered to detect differences in overall survival and progression-free survival, and that the results of some trials may have been confounded because patients crossed over between the intervention and control groups.

4.1.2 The Assessment Group determined that it was appropriate to analyse the results from patients with platinum-sensitive disease and patients with platinum-resistant or -refractory disease separately. Patients with platinum allergy were assumed to have the same probability of response to therapy as patients without an allergy for the same non-platinum treatments, and therefore treatments for patients with platinum allergy were not analysed separately. The Assessment Group stated that there were insufficient data for most comparisons to carry out a standard pairwise meta-analysis. Consequently, a series of network meta-analyses were conducted for platinum-sensitive disease, and platinum-resistant or -refractory disease using a Bayesian Markov Chain Monte Carlo simulation. In the absence of individual patient data, the network meta-analysis synthesised data on relative treatment effect from the whole study populations.

4.1.3 For patients with platinum-sensitive disease, it was not possible to construct a complete network based on the trials identified, and therefore it was necessary to generate 2 discrete networks. Platinum-sensitive network 1 evaluated platinum-based treatments and platinum-sensitive network 2 evaluated non-platinum-based treatments. The Assessment Group emphasised that these networks cannot be compared directly. For trials not limited to patients with platinum-sensitive, -resistant or -refractory disease, results for the full trial population were presented, but the Assessment Group stated that these results were not synthesised in a network meta-analysis because, in practice, patients with platinum-sensitive, -resistant or -refractory disease would not

receive the same range of treatments and therefore the results of this analysis would not be clinically meaningful.

4.1.4 In general, the Assessment Group stated that treatment groups within trials were well matched. Some differences in baseline characteristics between trials were identified, in particular with respect to length of the platinum-free interval, number of previous lines of chemotherapy and the method used to diagnose recurrence. However, the Assessment Group considered that the magnitude of these differences was unlikely to affect estimates of the relative effect of treatment and the trials were sufficiently clinically homogeneous to compare the clinical effectiveness of treatments. The Assessment Group clarified that the assessment of clinical homogeneity was limited to platinum-sensitive network 1, which evaluated platinum-based therapies. For this network, the Assessment Group considered that as a result of the imbalance in Eastern Cooperative Oncology Group (ECOG) status at baseline, the treatment effect associated with platinum may have been underestimated. Baseline characteristics were not reported for subgroups, and therefore an assessment of clinical heterogeneity was not possible for platinum-sensitive network 2 evaluating non-platinum-based regimens, or for platinum-resistant or -refractory groups, because both were informed by subgroup analyses. The Assessment Group also expressed concern that the subgroup data may not have been sufficiently powered to detect differences in overall survival or progression-free survival. In addition, it was noted that statistical assessment of heterogeneity was not possible for either network, primarily because of the low number of trials identified.

4.1.5 The Assessment Group specified that unadjusted hazard ratios were used for progression-free survival and overall survival in the network meta-analysis. It acknowledged that adjusting for baseline

characteristics may be important because certain characteristics are considered to influence prognosis. However, in the absence of a consistent dataset for all comparisons, the Assessment Group did not consider it appropriate to analyse a blend of unadjusted and adjusted hazard ratios.

### **Progression-free survival**

- 4.1.6 For platinum-sensitive network 1 evaluating platinum-based regimens, the Assessment Group included 5 trials evaluating progression-free survival in the network meta-analysis. Results from the network meta-analysis found that paclitaxel plus carboplatin, gemcitabine plus carboplatin, and PLDH plus carboplatin statistically significantly improved progression-free survival compared with platinum alone with hazard ratios of 0.73 (95% confidence interval [CI] 0.64 to 0.84), 0.71 (95% CI 0.57 to 0.90) and 0.59 (95% 0.50 to 0.71) respectively. PLDH plus carboplatin was found to be statistically significantly more effective at prolonging progression-free survival than paclitaxel plus carboplatin (HR=0.81, 95% CI 0.71 to 0.92). No other statistically significant differences were identified between platinum-combination regimens.
- 4.1.7 For the platinum-sensitive network 2 evaluating non-platinum-based regimens, the Assessment Group included 3 trials evaluating progression-free survival in the network meta-analysis. Results found that trabectedin plus PLDH statistically significantly improved progression-free survival compared with PLDH alone, paclitaxel alone and topotecan alone, with hazard ratios of 0.73 (95% CI 0.56 to 0.94), 0.44 (95% CI 0.26 to 0.82) and 0.55 (95% CI 0.38 to 0.82) respectively. No statistically significant differences were identified among the monotherapies evaluated (that is, PLDH, topotecan, and paclitaxel).

- 4.1.8 For the platinum-resistant or platinum-refractory ovarian cancer group, the Assessment Group included 3 trials evaluating progression-free survival for inclusion in the network meta-analysis. The Assessment Group also highlighted that trabectedin plus PLDH is outside of the scope for this subgroup, and although the data were included in the network to capture all the available evidence, they were not included in the economic analysis. Results from the network meta-analysis found no statistically significant differences in progression-free survival between PLDH, paclitaxel and topotecan alone, and these results were in line with results from the individual trials.
- 4.1.9 For the fully platinum-sensitive ovarian cancer subgroup, the Assessment Group stated that although 3 trials (OVA-301, ICON4/AGO-OVAR, and a study by Pfisterer et al.) included subgroups with fully platinum-sensitive ovarian cancer, only the OVA-301 trial reported data, so it was not possible to perform an indirect comparison. In addition, 4 trials (OVA-301, CALYPSO, ICON4/AGO-OVAR and the study by Pfisterer et al.) included subgroups with partially platinum-sensitive recurrent ovarian cancer, but only the OVA-301 and CALYPSO trials reported data, and as they did not contain a common comparator it was not possible to make an indirect comparison. The OVA-301 trial reported a statistically significant improvement in progression-free survival with trabectedin plus PLDH compared with PLDH alone (HR=0.65, 95% CI 0.45 to 0.92; p=0.015). The CALYPSO trial reported a statistically significant improvement in progression-free survival with PLDH plus carboplatin compared with paclitaxel plus carboplatin (HR=0.73, 95% CI 0.58 to 0.90; p=0.004).

**Overall survival**

- 4.1.10 For platinum-sensitive network 1 evaluating platinum-based regimens, the Assessment Group included 6 trials evaluating overall survival in the network meta-analysis. Results indicated that PLDH plus carboplatin statistically significantly improved overall survival compared with platinum therapy alone (HR=0.79, 95% CI 0.64 to 0.97). Paclitaxel plus carboplatin was also found to statistically significantly improve overall survival compared with platinum alone (HR=0.77, 95% CI 0.66 to 0.91). No other statistically significant differences in overall survival were identified between platinum-combination regimens.
- 4.1.11 For platinum-sensitive network 2 evaluating non-platinum-based regimens, the Assessment Group included 4 trials evaluating overall survival in the network meta-analysis. Results indicated that PLDH alone statistically significantly improved overall survival compared with topotecan alone (HR=0.73, 95% CI 0.56 to 0.97). Trabectedin plus PLDH was also found to statistically significantly improve overall survival compared with topotecan alone (HR=0.60, 95% CI 0.43 to 0.86). No other statistically significant differences were identified between platinum-combination regimens.
- 4.1.12 For the platinum-resistant or platinum-refractory ovarian cancer group, the Assessment Group included 4 trials evaluating overall survival in the network meta-analysis. The Assessment Group stated that trabectedin plus PLDH is outside of the scope for this subgroup and although the data were included in the network to capture all the available evidence, the data were not included in the economic analysis. Results from the network meta-analysis found no statistically significant differences in overall survival among the treatments evaluated. This was in line with results from the individual trials.

- 4.1.13 For the fully platinum-sensitive ovarian cancer group, the Assessment Group identified 4 trials evaluating overall survival. The Assessment Group stated that it was not possible to perform a network meta-analysis because only 2 of the trials reported the necessary data for analysis and these trials did not have a common comparator.
- 4.1.14 For the partially platinum-sensitive ovarian cancer group, the Assessment Group identified the same 4 trials evaluating overall survival. As before, the Assessment Group constructed 2 networks. Network 1, evaluating platinum-based regimens, included only 1 trial (CALYPSO). No statistically significant difference in overall survival was identified for PLDH plus carboplatin compared with paclitaxel plus carboplatin in this trial. For network 2, evaluating non-platinum-based regimens, results indicated that trabectedin plus PLDH statistically significantly improved overall survival compared with PLDH alone (HR=0.84, 95% CI 0.667 to 1.032). Trabectedin plus PLDH was also found to statistically significantly improve overall survival compared with topotecan alone (HR=0.60, 95% CI 0.43 to 0.86).

### **Quality of life**

- 4.1.15 Of the 16 trials identified, 10 reported data on quality of life. The most commonly used scale in the trials was the EORTC QLQ-C30 questionnaire. However, the Assessment Group reported that there were considerable differences in the level of reporting of results, the questionnaires used to evaluate quality of life, and the time points for evaluation. Broadly, improvements in quality of life were identified for PLDH plus platinum compared with paclitaxel plus platinum; paclitaxel compared with oxaliplatin; and trabectedin plus PLDH compared with PLDH alone, in a subgroup of patients with partially platinum-sensitive ovarian cancer.

## Adverse reactions

4.1.16 The Assessment Group stated that the most frequently reported adverse reactions in the trials reflected those listed in the individual summaries of product characteristics. Consequently, based on advice from clinical experts, the Assessment Group limited its network meta-analyses to the following severe grade 3–4 adverse events, which it considered to be the most problematic: allergic reaction, alopecia, anaemia, fatigue, febrile neutropenia, nausea/vomiting and neuropathy. In many cases a network meta-analysis was not possible due to lack of available data. The majority of results, supplemented by the individual trial results when a network meta-analysis was not possible, indicated that the likelihoods of adverse events were not statistically significantly different across treatment regimens. However, in some instances, chemotherapies were estimated as having statistically significantly lower risks of 1 or more adverse events but significantly higher risks of other adverse events. For example, when compared with paclitaxel plus platinum, PLDH plus platinum was associated with statistically significantly lower risks of allergic reaction and alopecia but statistically significantly higher risks of anaemia and nausea/vomiting. Overall, no chemotherapy was consistently associated with either a lower risk or a higher risk of the adverse events assessed.

## 4.2 **Cost effectiveness**

### **Manufacturer's model – trabectedin**

4.2.1 The manufacturer of trabectedin submitted cost-effectiveness evidence as part of its submission. The manufacturer developed a decision analytical model comparing trabectedin plus PLDH with PLDH alone in patients with recurrent platinum-sensitive ovarian cancer for whom platinum-based chemotherapy was not suitable



because of allergy or intolerance or because they have partially platinum-sensitive disease. The cohort only had 1 previous platinum-based chemotherapy regimen, and experienced recurrence or progression.

- 4.2.2 The structure was identical to the model developed for NICE technology appraisal guidance 91; disease was classified into 3 distinct periods: stable disease, progressive disease, and death.
- 4.2.3 The manufacturer stated that because the OVA-301 trial was not powered for subgroup analysis within the platinum-sensitive group, data for the entire platinum-sensitive population were considered appropriate for the cost-effectiveness analyses. The manufacturer fitted 5 parametric survival distributions, adjusting for potential covariates. Based on the Weibull distributions, the mean progression-free survival for trabectedin plus PLDH and PLDH alone was 11.26 and 8.25 months respectively. Based on the log-logistic distributions, the mean overall survival for trabectedin plus PLDH and PLDH alone was 44.69 and 34.97 months respectively.
- 4.2.4 The manufacturer's base-case deterministic results, incorporating the patient access scheme for trabectedin, indicated incremental costs of £13,397 and incremental QALYs of 0.49 for trabectedin plus PLDH compared with PLDH alone, resulting in an incremental cost-effectiveness ratio (ICER) of £27,573 per QALY gained. The corresponding probabilistic results indicated an ICER of £27,761 per QALY gained, and the ICER was most sensitive to the estimate of overall survival. Scenario analyses indicated that the results were also sensitive to the adjustment of the platinum-free interval as an explanatory variable and alternative survival distributions for progression-free survival and overall survival.

4.2.5 The manufacturer argued that trabectedin was eligible for consideration under the end-of-life criteria. It stated that trabectedin plus PLDH was indicated for women with a life expectancy of less than 2 years without treatment: for patients treated with PLDH alone, median overall survival in the platinum-sensitive and partially platinum-sensitive populations was 24.1 months and 16.4 months respectively. Accounting for the imbalance in platinum-free interval and other prognostic factors in the platinum-sensitive population reduced the median to 19.4 months. For women with platinum-sensitive and partially platinum-sensitive recurrent ovarian cancer, trabectedin treatment increased median survival (after correction of prognostic factors including progression-free interval) by 4 months, and the estimated mean survival suggested this extension of life could be in excess of 9 months. The manufacturer also estimated that trabectedin would be indicated for approximately 500 women with relapsed platinum-sensitive ovarian cancer in 2014.

#### **Assessment Group's model**

4.2.6 The Assessment Group conducted a systematic review and stated that no cost-effectiveness analyses including the full range of interventions and comparators were available in the literature. It noted that the majority of analyses available were based on the model developed for NICE technology appraisal guidance 91. The Assessment Group considered that this model structure, also adopted by the manufacturer for trabectedin, was the most appropriate for the decision problem, and therefore used it to develop a de novo model. The model had a lifetime time horizon, which was set as 15 years because at this point over 99.9% of patients in the model would have died. In NICE technology appraisal guidance 91, and other models based on it, the time spent in each health state was based on the estimated mean time to progression (time spent in the stable disease health state) and

mean time to death (time spent in the progressed disease health state, after subtracting time spent in the stable disease health state). The Assessment Group incorporated a similar methodology to estimate the proportion of patients in each health state, but full survival curves rather than mean estimates were derived from the clinical data for each therapy. The Assessment Group stated that this would appropriately capture time in the economic model, and facilitate the assignment of costs, utilities and discounting.

4.2.7 The NICE scope for this appraisal specified that the interventions of interest for women with platinum-sensitive ovarian cancer were paclitaxel alone or paclitaxel plus platinum chemotherapy, PLDH alone or PLDH plus platinum chemotherapy, gemcitabine plus carboplatin, trabectedin plus PLDH, and topotecan. The Assessment group explained that although all interventions specified in the scope were considered, 2 independent networks were constructed evaluating platinum and non-platinum-based regimens, and therefore interventions were not simultaneously compared with each other.

4.2.8 The populations with platinum-sensitive disease and platinum-resistant or -refractory disease were modelled separately and there was no explicit analysis of the full population. The Assessment Group explained that this was because separation of the results by platinum sensitivity is more clinically relevant because the platinum-free interval was a key prognostic factor, as confirmed by experts, and this approach was also in line with the data available to inform the analysis. The Assessment Group stated that data for women with fully or partially platinum-sensitive disease was insufficient, so these groups were considered in sensitivity rather than base-case analyses. The Assessment Group considered that response to non-platinum-based therapies would be expected to be consistent between patients with or without an allergy or intolerance to

platinum-based therapy. Therefore, the platinum-allergic subgroup was included in platinum-sensitive network 2 and platinum-resistant and platinum-refractory subgroups.

4.2.9 The Assessment Group noted 3 main concerns with the use of data from the network meta-analyses in the model. First, due to lack of individual patient data, the network meta-analyses synthesised data from the whole trial population. Individual patient data would have allowed for differences in baseline characteristics within and between trials to be incorporated. In addition, as discussed in section 4.1.6, unadjusted hazard ratios were incorporated, which could include potential bias. Second, using hazard ratios based on the literature assumes proportional hazards; that is, the relative treatment effects captured by the hazard ratios hold true across all time points. However, log-cumulative hazard plots indicated that this assumption may not be appropriate. The Assessment Group highlighted that when the relative hazard decreases over time for both progression-free survival and overall survival, the model was likely to overestimate the relative benefit of treatment and vice versa. Third, it was noted that several of the included trials allowed for crossover, which could have confounded overall survival data. The Assessment Group was unable to assess the degree of crossover bias because of a lack of individual patient data and because none of the trials described the crossover treatment.

4.2.10 The Assessment Group included grade 3 and 4 adverse events associated with significant costs in the base-case analysis – allergic reaction, anaemia, febrile neutropenia, nausea and vomiting. The relative likelihood of an adverse event associated with each therapy was estimated from the network meta-analysis. Adverse events were not analysed by population because of a lack of data; instead, adverse event data from any population (platinum sensitive or platinum resistant/refractory) were included in the

analysis, therefore assuming that the likelihood of an adverse reaction is independent of the platinum-free interval. Inconsistent reporting between trials led to differences in the networks of treatments available to assess the relative effect of treatment on each adverse event. Consequently, estimates of the impact of treatment on the rates of adverse events were not available for all treatments for all adverse events. Although it was possible to estimate the possibility of each adverse event for the baseline treatment in each network, odds ratios and expert opinion were used to estimate probabilities for the remainder.

- 4.2.11 The Assessment Group conducted a systematic review and identified 22 studies measuring health-related quality of life. It was noted that the utility values based on the OVA-301 trial were most relevant, because EQ-5D utility values in the recurrent ovarian cancer population for the health states needed for the economic model were reported, and were based on a large sample of patients (n=600). The manufacturer clarified that these utilities were derived from the platinum-sensitive population (n=400). The mean estimates of utility in the stable and progressive disease health states were estimated to be 0.718 and 0.649 respectively. These estimates were used in NICE technology appraisal guidance 222, and were identical to the EQ-5D data identified by the Assessment Group from the systematic review of the literature. Disutilities associated with adverse events were not included in the base-case analysis because the estimates identified were based on small samples. This was also to avoid double counting, because the effect of adverse events on quality of life associated with trabectedin plus PLDH and PLDH alone were already included in health state EQ-5D estimates from NICE technology appraisal guidance 222. This was explored in sensitivity analyses.

- 4.2.12 The Assessment Group model included costs associated with the technologies, administration costs, health state-related costs and adverse event costs. Chemotherapy costs per cycle were estimated using drug costs in the 'British national formulary' (BNF) and regimens as per the summaries of product characteristics (see section 3), with verification and amendment from clinical experts. The costs of adverse events in the model were £111 for paclitaxel, £78 for paclitaxel plus platinum, £69 for PLDH alone, £97 for PLDH plus platinum, £172 for gemcitabine plus carboplatin, £198 for trabectedin plus PLDH and £200 for topotecan.
- 4.2.13 The model assumed that treatments would be administered as infusions in a hospital, and associated administration costs were included in the model: £533 for 3-weekly paclitaxel plus carboplatin, £501 for weekly paclitaxel, £551 for PLDH, £665 for PLDH plus carboplatin, £1155 for gemcitabine plus carboplatin, £665 for trabectedin plus PLDH and £2789 for topotecan. For the base-case analyses, it was assumed that no vial sharing would occur.

***Results of network 1 – platinum-based regimens in platinum-sensitive disease***

- 4.2.14 Both deterministic and probabilistic results indicated that PLDH plus platinum was strictly dominated by (that is, it was more costly and less effective than) paclitaxel plus platinum. Similarly, gemcitabine plus carboplatin was extendedly dominated by paclitaxel plus platinum (that is, its ICER was higher than that of the next, more effective, option when compared with platinum). Therefore, PLDH plus platinum and gemcitabine plus carboplatin were excluded, leaving paclitaxel plus platinum compared with platinum alone as the only relevant comparison for this network. For this comparison, the deterministic ICER was estimated as £24,361 per QALY gained; paclitaxel plus platinum was associated

with an estimated incremental cost of £5694 and an additional 0.23 quality-adjusted life years (QALYs) when compared with platinum alone. The probabilistic ICER for paclitaxel plus platinum compared with platinum alone was £24,539 per QALY gained. The Assessment Group also estimated an ICER of £114,410 per QALY gained for gemcitabine plus carboplatin compared with platinum alone and an ICER of £30,188 per QALY gained for PLDH plus platinum compared with platinum alone.

4.2.15 One-way sensitivity analyses on various model parameters indicated that the comparisons of paclitaxel plus platinum, and PLDH plus platinum, when compared with platinum alone, were most sensitive to the relative effect of treatment on overall survival. For example:

- When the lower bounds of the hazard ratio for survival for gemcitabine plus carboplatin compared with paclitaxel plus platinum was used, the ICER for gemcitabine plus carboplatin compared with platinum alone was £23,578 per QALY gained. However when the upper bound was used, gemcitabine plus carboplatin was dominated.
- When the hazard ratio for survival for platinum alone compared with paclitaxel plus platinum was used, gemcitabine plus carboplatin was dominated by platinum alone. When the lower bound of the hazard ratio for survival for gemcitabine plus carboplatin compared with paclitaxel plus platinum was used, paclitaxel plus platinum was less costly and less effective than gemcitabine plus carboplatin. When the upper bound was used, the ICER was £8719 per QALY gained.
- When the lower bound of the hazard ratio for survival for PLDH plus platinum compared with paclitaxel plus platinum was used, the ICER for PLDH plus platinum compared with paclitaxel plus platinum was £20,672 per QALY gained. When the upper bound

was used, PLDH plus platinum was less costly and less effective than paclitaxel plus platinum.

The Assessment Group stated that the impact of other parameters, such as the relative effect of treatment on progression-free survival and the utility value associated with each health state, were relatively minimal.

- 4.2.16 Probabilistic sensitivity analyses indicated that at a maximum acceptable ICER of £20,000 per QALY gained, the probabilities of paclitaxel plus platinum or PLDH plus platinum being considered cost effective compared with platinum alone were 13% and 3% respectively. Furthermore, PLDH plus platinum was estimated to be almost as likely to result in greater costs and QALYs as to be dominated by paclitaxel plus platinum. The Assessment Group highlighted that the costs and QALYs accumulated by the addition of paclitaxel or PLDH to platinum therapy were similar, producing cost-effectiveness estimates that were sensitive to minor changes in parameter estimates.

***Results of network 2 – non-platinum-based regimens in platinum-sensitive disease***

- 4.2.17 Base-case results (deterministic and probabilistic) indicated that topotecan was dominated by PLDH. Topotecan was therefore removed from the analysis and the relevant fully incremental comparisons of PLDH compared with paclitaxel and trabectedin plus PLDH compared with PLDH alone were presented. When compared with paclitaxel, PLDH was associated with an incremental cost of approximately £3900 and approximately 0.16 additional QALYs. This resulted in ICERs of £23,733 and £25,931 per QALY gained in the deterministic and probabilistic analyses, respectively. When compared with PLDH alone, trabectedin plus PLDH was associated with an incremental cost of approximately



£13,000 and 0.16 additional QALYs. The resulting ICERs for trabectedin plus PLDH compared with PLDH alone were £85,212 and £81,353 per QALY gained in the deterministic and probabilistic analyses respectively.

4.2.18 The Assessment Group undertook a series of one-way sensitivity analyses on various model parameters. In network 1, the cost-effectiveness estimates for all 3 comparisons (PLDH compared with paclitaxel, trabectedin plus PLDH compared with paclitaxel, and trabectedin plus PLDH compared with PLDH alone) were most sensitive to the relative effect of treatment on overall survival:

- When the lower bound of the hazard ratio for overall survival for paclitaxel compared with PLDH was used, PLDH dominated paclitaxel, but when the upper bound was used the ICER for PLDH compared with paclitaxel was £15,900 per QALY gained.
- When the lower bound of the hazard ratio for survival for trabectedin plus PLDH compared with PLDH alone was used, the ICER for trabectedin plus PLDH compared with PLDH alone was £44,266 per QALY gained. When the upper bound was used, trabectedin plus PLDH dominated PLDH alone.
- When the lower bound of the hazard ratio for overall survival for trabectedin plus PLDH compared with PLDH alone was used, the ICER for trabectedin plus PLDH compared with topotecan was £18,437 per QALY gained. When the upper bound was used, the ICER was £30,754 per QALY gained.
- When the lower bound of the hazard ratio for survival for topotecan compared with PLDH was used, the ICER for trabectedin plus PLDH compared with topotecan was £35,482 per QALY gained. When the upper bound was used, the ICER was £18,478 per QALY gained.

4.2.19 The Assessment Group undertook a series of scenario analyses and noted that the base-case results were robust in the majority of the scenarios modelled, with the exception of increasing the dosage of PLDH from 40 mg/m<sup>2</sup> to 50 mg/m<sup>2</sup> body surface area. This increased the ICER for PLDH compared with paclitaxel from £23,733 to £31,222 per QALY gained. The Assessment Group stated that apart from this scenario, the ICER remained below £30,000 per QALY gained and highlighted that topotecan was dominated by trabectedin plus PLDH in every scenario. The Assessment Group also carried out an exploratory scenario analysis using clinical-effectiveness data from the manufacturer of trabectedin's submission for a head-to-head comparison of trabectedin plus PLDH compared with PLDH alone. This resulted in an ICER of £35,646 per QALY gained, compared with ICERs of £85,212 and £27,573 estimated by the Assessment Group's and the manufacturer's base-case analyses respectively. The Assessment Group stated that this difference was predominantly a consequence of using adjusted clinical-effectiveness data, and acknowledged that adjustment of clinical-effectiveness data for key prognostic factors was likely to result in more accurate estimates of progression-free survival and overall survival.

***Results of network 3 – platinum-resistant and platinum-refractory group***

4.2.20 The Assessment group explained that data for paclitaxel plus platinum were not available from the literature for women with platinum-resistant or -refractory ovarian cancer, so this intervention was not included in the base-case analysis. Base-case results (deterministic and probabilistic) indicated that paclitaxel was dominated by PLDH alone. Paclitaxel was associated with an incremental cost of £901 and 0.022 fewer QALYs. Therefore, topotecan compared with PLDH was the only comparison considered in the final cost-effectiveness analysis. Topotecan plus

PLDH was associated with an incremental cost of approximately £7000 and 0.02 additional QALYs. The resulting ICERs for topotecan plus PLDH compared with PLDH alone were £449,553 and £324,188 per QALY gained in the deterministic and probabilistic analyses respectively.

4.2.21 As with platinum-sensitive networks 1 and 2, the cost-effectiveness results were most sensitive to the relative effect of treatment on overall survival:

- When the lower bound of the hazard ratio for overall survival for paclitaxel compared with PLDH was used, the ICER for paclitaxel compared with PLDH was £17,904 per QALY gained. When the upper bound was used, paclitaxel was less costly and less effective.
- For the incremental comparison of topotecan with paclitaxel, when the lower bound of the hazard ratio for overall survival for topotecan compared with PLDH was used, the ICER was £39,903 per QALY gained. When the upper bound was used, topotecan dominated paclitaxel.
- When the lower bound of the hazard ratio for overall survival for paclitaxel compared with PLDH was used, topotecan dominated paclitaxel. When the upper bound was used, the ICER for topotecan compared with paclitaxel was £39,485 per QALY gained.

4.2.22 The Assessment Group undertook a series of scenario analyses and noted that the base-case results were robust in the majority of the scenarios modelled. It highlighted that the ICER for topotecan compared with PLDH ranged from £374,963 to £503,885 per QALY gained across the scenarios. Paclitaxel was dominated in all scenarios except when the cost associated with a 50 mg/m<sup>2</sup> dose of PLDH was used and paclitaxel became the least costly

treatment, resulting in an ICER of £10,480 per QALY gained for PLDH compared with paclitaxel.

### 4.3 ***Consideration of the evidence***

- 4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of topotecan, PLDH, paclitaxel, trabectedin and gemcitabine, having considered evidence on the nature of recurrent ovarian cancer and the value placed on the benefits of these technologies by women with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.
- 4.3.2 The Committee heard from clinical specialists that women with recurrent ovarian cancer can experience several relapses after initial treatment with platinum-based chemotherapy, and it was very important to have a range of treatment options available at each relapse. The clinical specialists stated that treatment is tailored to individuals, taking into account factors such as previous treatment, and the potential for developing platinum resistance. The patient experts stated that there is no screening programme for ovarian cancer and disease is usually identified at an advanced stage. They highlighted the emotional impact of developing recurrent ovarian cancer, particularly emphasising the fear of further recurrence and the great importance of progression-free survival to patients' wellbeing. They also highlighted the psychological benefit of having a range of treatment options available. The clinical specialists stated that ovarian cancer is increasingly seen as a group of diseases, that histological subtype plays an important role in how the disease responds to particular treatments, and that many treatments are not very effective in the rarer histological subtypes. Therefore, a range of chemotherapy agents is needed until more targeted therapies become available. The Committee

heard that approximately 70% of people with ovarian cancer have serous adenocarcinoma, and this was not expected to vary significantly across the trials included in the review. The Committee concluded that progression-free survival was an important outcome measure and noted that availability of a range of treatment options is valuable for treating recurrent ovarian cancer.

- 4.3.3 The Committee discussed current clinical practice for treating recurrent ovarian cancer. The Committee heard from the clinical specialists that the Assessment Group's approach of presenting results separately for women with platinum-sensitive disease and platinum-resistant or platinum-refractory disease was appropriate. The Committee heard that the majority of patients in clinical practice had platinum-sensitive disease at first recurrence, but this proportion would decline at each subsequent recurrence. The clinical specialists stated that standard treatment for women with platinum-sensitive disease, including those with partially platinum-sensitive disease, was platinum-combination chemotherapy. The clinical specialists pointed out that the platinum-resistant and platinum-refractory group was heterogeneous because it included women whose disease may never have responded to platinum as well as women whose disease developed resistance over time. The Committee noted that no trials had taken this into account. The Committee heard from the clinical specialists that only a small proportion of women were allergic to a particular platinum agent such as carboplatin, and that these women were either offered an alternative platinum agent (cisplatin) or non-platinum regimens. Desensitisation could also be carried out. The Committee considered the Assessment Group's assumption that women with a platinum allergy would have the same probability of response to non-platinum regimens as women without an allergy to be

appropriate. The Committee concluded that the Assessment Group's approach to the decision problem was appropriate.

- 4.3.4 The clinical specialists stated that weekly paclitaxel, rather than the licensed 3-weekly paclitaxel, was established clinical practice for treating platinum-refractory or platinum-resistant disease. However, the licensed 3-weekly regimen was more often used for women with platinum-sensitive disease. The Committee was aware that the trials used 3-weekly paclitaxel. The Committee also heard that in practice PLDH monotherapy is usually initiated at a lower than that specified in the licence. It was also aware that PLDH was used at dose of 30 mg/m<sup>2</sup>, which is lower than the licensed dose, in clinical trials of PLDH in combination with carboplatin.
- 4.3.5 The Committee discussed the indications in the marketing authorisations for the treatments being appraised. It noted that the marketing authorisations for trabectedin and gemcitabine restricted their use to women with platinum-sensitive disease. The Committee considered that, although the wording in the marketing authorisations varied, they did not restrict the treatments being appraised to specific recurrences.
- 4.3.6 The Committee discussed the clinical-effectiveness evidence available, focusing on results from the Assessment Group's network meta-analyses. The Committee noted the following:
- For women with platinum-sensitive disease who had platinum-based treatment, paclitaxel, PLDH and gemcitabine (all plus carboplatin) statistically significantly improved progression-free survival compared with platinum alone. For overall survival, PLDH and paclitaxel (both plus carboplatin) gave statistically significant improvements compared with platinum alone, but there was no statistically significant overall survival benefit from

gemcitabine plus carboplatin compared with platinum alone. The Committee questioned the possible reasons why the progression-free survival benefit seen with gemcitabine plus carboplatin did not translate into an overall survival benefit in the trial or network meta-analyses as it did for PLDH and paclitaxel. The clinical specialists cautioned that it is difficult to show overall survival benefits because multiple lines of treatment have a confounding effect. However, they also stated that because of the lack of overall survival benefit in the trial, in some centres gemcitabine is given only when paclitaxel plus platinum and PLDH plus platinum are unsuitable.

- For women with platinum-sensitive disease who could not receive platinum-based treatment, trabectedin plus PLDH statistically significantly improved progression-free survival compared with PLDH alone, paclitaxel alone and topotecan alone. In addition, for overall survival, both PLDH monotherapy and trabectedin plus PLDH were associated with statistically significant improvements compared with topotecan.
- For women with platinum-resistant or -refractory disease, no statistically significant differences between PLDH, paclitaxel and topotecan were identified for progression-free survival or overall survival.

4.3.7 The Committee discussed the limitations of the analysis, particularly the differences in baseline characteristics between trials, uncertainty about whether trials were adequately powered to detect differences in overall survival and progression-free survival, and concerns about confounding because of crossover. However, the Committee also heard from the clinical specialists that the results of the network meta-analyses were broadly in line with those expected from both the trial data and experience in clinical practice. The Committee acknowledged that the analyses had

methodological limitations and that some assumptions had to be accepted. However, it noted that they had been constructed using hazard ratios from peer reviewed publications, and represented a distillation and systematic analysis of the same body of evidence that is used by clinicians and patients when deciding between the various treatments. The Committee expressed disappointment with the quality and breadth of the trial evidence, and also with some of the trial design and reporting, but on balance agreed that the Assessment Group's approach was reasonable given the data available, and accepted the clinical-effectiveness results from the network meta-analyses. It concluded that for women with platinum-sensitive disease, paclitaxel, gemcitabine and PLDH (all plus carboplatin) improved progression-free survival compared with platinum alone and that PLDH and paclitaxel (both plus carboplatin) also improved overall survival. It also concluded that trabectedin plus PLDH improved progression-free survival compared with PLDH, paclitaxel and topotecan (all given alone), and that there was evidence that PLDH alone and trabectedin plus PLDH increased overall survival compared with topotecan. Finally, it accepted that for women with platinum-resistant or platinum-refractory disease, there were no statistically significant differences in progression-free and overall survival between PLDH, paclitaxel and topotecan.

- 4.3.8 The Committee discussed the cost-effectiveness analyses conducted by the Assessment Group. It considered the cost-effectiveness results based on network 1 for women with platinum-sensitive recurrent ovarian cancer receiving platinum-based chemotherapy, and noted that the fully incremental deterministic results indicated that paclitaxel plus platinum was the most cost-effective treatment, with an ICER of £24,400 per QALY gained compared with platinum alone. The Committee also noted that



although PLDH plus platinum was dominated by paclitaxel plus platinum and was therefore excluded from the fully incremental analysis, the costs and QALYs were very similar to those of paclitaxel plus platinum, and the ICER for PLDH plus platinum compared with platinum alone was approximately £30,200 per QALY gained. The Committee concluded that paclitaxel plus platinum was the most cost-effective option for women with recurrent platinum-sensitive ovarian cancer but that PLDH plus platinum could also be considered a cost-effective alternative.

- 4.3.9 The Committee discussed the cost-effectiveness results for gemcitabine plus carboplatin based on network 1. It noted that gemcitabine plus carboplatin was extendedly dominated and was therefore excluded from the incremental analysis including all the treatment options. It also noted that the cost-effectiveness estimates based on the network 1 meta-analysis showed that gemcitabine plus carboplatin resulted in an ICER compared with platinum alone of £114,000 per QALY gained. The Committee noted that the results of the economic model based on the network 1 meta-analysis showed that gemcitabine plus carboplatin produced fewer QALY gains, representing less clinical benefit than paclitaxel plus platinum and PLDH plus platinum. The Committee considered that this was primarily because of the lack of overall survival benefit demonstrated with gemcitabine plus carboplatin in the Pfisterer trial. The Committee noted that this trial was powered to detect a statistically significant difference in progression-free survival between treatments but not to detect a statistically significant difference in overall survival. It also noted statements from one of the clinical specialists that the trial took place at a time when few post-progression therapies were available, and that overall survival has since improved because patients are now offered multiple lines of therapy. The Committee noted that

extended follow-up data from the Pfisterer trial were not available. However if multiple lines of follow-on therapies had been given, although this could have increased the overall survival in both arms, confounding from subsequent lines of therapy might make the comparison between gemcitabine plus platinum and platinum alone even less reliable than reported in the Pfisterer trial. The Committee acknowledged that any gain in progression-free survival was important to patients, but was satisfied that the benefits of treatment on progression-free survival had been adequately captured in the model. The Committee concluded that the Pfisterer trial was the only relevant randomised controlled trial of gemcitabine plus platinum compared with platinum. It was of reasonable size, properly conducted, and was appropriate for decision-making as part of the network 1 meta-analysis and had not shown a statistically significant improvement in overall survival unlike the combinations of paclitaxel and PLDH with platinum.

4.3.10 Although the Committee was satisfied that the network meta-analysis was suitable for decision-making, it noted that the clinical evidence for gemcitabine plus platinum that informed the cost-effectiveness analysis only included women with a first recurrence of ovarian cancer, at which stage paclitaxel plus platinum or PLDH plus platinum would be alternative treatment options. The Committee acknowledged that the sensitivity analysis around overall survival estimates indicated a high degree of uncertainty, and it concluded that gemcitabine could not be considered a cost-effective use of NHS resources for treating a first recurrence of platinum-sensitive ovarian cancer.

4.3.11 The Committee heard from the clinical specialists that patients with ovarian cancer often had multiple lines of treatment, and that it was important to have a wide range of treatments available for use in future recurrences. The Committee noted that there was no

evidence included in the assessment report on the clinical effectiveness of gemcitabine for recurrences after the first. It noted that the marketing authorisation for gemcitabine did not explicitly limit it to first recurrence. Although the Committee accepted the results of the network meta-analysis, it considered that it could not assume that identical results for relative clinical effectiveness would be found in women who had a second or subsequent recurrence. The Committee concluded that it could not make any recommendation about the clinical or cost effectiveness of gemcitabine beyond the first recurrence of platinum-sensitive ovarian cancer, and that clinicians should take this into account when considering gemcitabine plus carboplatin as a treatment option.

4.3.12 The Committee discussed the cost-effectiveness results based on network 2 in women with platinum-sensitive disease receiving non-platinum-based treatments. The Committee noted that the ICER for PLDH monotherapy compared with paclitaxel monotherapy was approximately £23,700 per QALY gained. It also noted the Assessment Group's comments that the costs and QALYs associated with paclitaxel were similar to those of PLDH. The Committee concluded that paclitaxel and PLDH could be recommended for use in the NHS for women with platinum-sensitive disease for whom platinum-based treatment was unsuitable.

4.3.13 In network 2, topotecan produced the fewest QALYs compared with PLDH monotherapy, trabectedin plus PLDH, and paclitaxel. However, it was associated with higher costs than both PLDH and paclitaxel monotherapy and was therefore dominated and excluded from the fully incremental analysis. The Committee agreed that in the network meta-analysis topotecan had not been demonstrated to be cost effective for the treatment of platinum-sensitive ovarian

cancer in women unable to take platinum and that this remained the case in the sensitivity analyses. It understood that having a range of treatment options was desirable, although topotecan was not widely used in clinical practice. However, the Committee also acknowledged that the bulk of the evidence for topotecan in the context of platinum-sensitive disease was for women with a first recurrence. The Committee concluded that topotecan is not a cost-effective use of NHS resources for a first recurrence, but was unable to make a recommendation for the use of topotecan in platinum-sensitive disease beyond the first recurrence.

4.3.14 The Committee carefully considered the cost-effectiveness results for trabectedin plus PLDH compared with PLDH alone, and the comments received from the manufacturer of trabectedin during consultation on the appraisal consultation document. The Committee noted that the Assessment Group's ICER for trabectedin plus PLDH compared with PLDH alone was over £85,200 per QALY gained. However, it accepted the manufacturer's comment that the Assessment Group had overestimated the cost of a course of trabectedin and PLDH, and underestimated the cost of a course of PLDH alone, because it had based its calculations on a lower dose than the one specified in the marketing authorisation. The Committee accepted that correcting this reduced the ICER for trabectedin plus PLDH compared with PLDH alone to £77,000 per QALY gained, as calculated using the network meta-analysis for network 2.

4.3.15 The Committee understood that the manufacturer's economic evaluation, which used clinical-effectiveness data obtained from the OVA-301 trial, had been retrospectively adjusted for the following potential covariates: imbalances between arms in the platinum-free interval (considered to be a major prognostic indicator), Eastern Cooperative Oncology Group (ECOG) status, and the antigen

CA125. It noted that the resulting ICER using the manufacturer's model was £27,600 per QALY gained, and that this was substantially lower than the Assessment Group's base-case ICER of £77,000 per QALY gained. The new base-case ICER was also substantially lower than the ICER previously estimated by the manufacturer (over £94,800 per QALY gained [without the patient access scheme], using OVA-301 data) in NICE technology appraisal guidance 222. The Committee noted that the Assessment Group also performed an analysis incorporating these adjusted results into its model, which gave an ICER of £35,000 per QALY gained, and that this fell to £33,000 per QALY gained after corrections to the costs had been made (see section 4.2.18). The Committee heard from the manufacturer that the substantial reduction in the ICER since NICE technology appraisal guidance 222 was predominantly because of the post-hoc adjustment for imbalances in the platinum-free interval, and that pre-specified adjustments to ECOG status and CA125 had less of an effect. The Committee heard from the manufacturer that the results were also partly influenced by the choice of modelling distributions, which had changed from exponential distributions in NICE technology appraisal guidance 222 to Weibull and log logistic distributions in the current appraisal because more mature overall survival data were available. The Committee accepted the views of the Assessment Group that the manufacturer had used the best-fitting distributions in its model. However, the Committee was concerned that the log logistic extrapolation resulted in 2% of women in the treatment arm being alive after 15 years, which it considered was likely to be optimistic for women with recurrent advanced ovarian cancer.

4.3.16 The Committee carefully considered the manufacturer's adjustment of the treatment effects, noting that this increased the non-

statistically significant overall survival benefit for the platinum-sensitive subgroup in the trial from 2.9 months to 4.3 months and made this benefit statistically significant. The Committee considered the manufacturer's consultation comment that the NICE Decision Support Unit [guidance for survival analyses](#) recommends 'adjusting for the characteristics of the patients included in the clinical trial of interest – thus correcting for any patient population differences which may be present between different clinical trials'. However, it understood from the Assessment Group that the focus of the Decision Support Unit guidance is on head-to-head comparisons in which patient-level data are available and where evidence synthesis between trials is not required. Guidance on adjustment of dissimilar trial level data to create a homogeneous network for which there is only a single trial informing each head-to-head comparison is not available. The Committee concluded that it was not required to accept the suggested post hoc adjustments of the trial data.

- 4.3.17 The Committee also considered the manufacturer's concerns that the conclusions around retrospective adjustment of treatment effects in the appraisal consultation document were inconsistent with those made in NICE technology appraisal guidance 222. The Committee was aware that the Evidence Review Group for NICE technology appraisal guidance 222 had accepted an adjustment for CA125, and so the Committee asked what the ICER would have been if the manufacturer had adjusted for CA125 alone in the current appraisal. The manufacturer indicated that this analysis was not available, but that CA125 adjustment did not have a major effect on the ICER. The Committee also noted that the Appraisal Committee for NICE technology appraisal guidance 222 had not made an explicit judgement about the validity of the retrospective adjustment of CA125, but had favoured the Evidence Review

Group's analysis because it used data from the fully platinum-sensitive population rather than from a post hoc partially sensitive subgroup as in the manufacturer's submission. The Committee concluded that it would have given consideration to a retrospective adjustment for CA125 for consistency with NICE technology appraisal guidance 222, had it been supplied by the manufacturer, but that this did not oblige the Committee to accept additional retrospective adjustments.

4.3.18 The Committee examined the assumption underpinning the adjustment for platinum-free interval that response to future therapy would be better the longer the platinum-free interval. The Committee questioned whether this applied only to further platinum therapy. One of the clinical specialists indicated that the platinum-free interval was important, subject to ongoing research, and that a longer platinum-free interval may be associated with a better response to non-platinum therapies as well. However, no trials have yet provided evidence to support this hypothesis for PLDH.

4.3.19 The Committee also considered the manufacturer's approach to carrying out the retrospective analysis. It was concerned that the platinum-free interval was treated as a continuous rather than a categorical variable. It expressed concerns that this had not been done for any other trials, and questioned the accuracy with which the platinum-free interval could be assessed as a continuous variable, because assessments are made at set intervals, and a precise date of progression would not be known. The Committee also questioned why the platinum-free interval had not been a stratification factor at randomisation (except for with the platinum-sensitive and platinum-resistant groups) if it was critical to the interpretation of the trial results. The manufacturer responded that the platinum-free interval was not considered as important a prognostic indicator at the time of the trial. It acknowledged that it

had not included it in its submission for the whole platinum-sensitive population for NICE technology appraisal guidance 222, but was of the opinion that it should now be retrospectively adjusted for. The Committee agreed that the platinum-free interval, as an important prognostic factor, should be considered carefully in the design and pre-specified analyses of future ovarian cancer trials. However, the Committee was concerned that retrospective adjustment for the platinum-free interval as a continuous variable is currently an unvalidated post-hoc approach in ovarian cancer trials, and was not sufficiently reliable as a basis for estimating effectiveness.

- 4.3.20 The Committee also evaluated the impact of the retrospective adjustments suggested by the manufacturer. Using the manufacturer's adjusted results, and its new model, there was a calculated mean overall survival benefit of 9.7 months for trabectedin plus PLDH compared with PLDH alone. This contrasted with a mean 2.9 months overall survival gain as calculated by the Assessment Group. The Committee did not consider a 9.7 month overall survival gain to be plausible, given that no statistically significant overall survival benefit was demonstrated in OVA-301. It also noted that the mean progression-free survival gain as calculated by the manufacturer was only 3 months. This would imply that more than twice as much benefit was gained after progression, when patients had stopped taking the drug, as when they were receiving it before progression. The Committee considered that the manufacturer's modelled overall survival benefit lacked credibility, and that this cast further doubt on the validity of the adjustment of treatment effects that had been introduced since the manufacturer's previous analyses presented for NICE technology appraisal guidance 222.



- 4.3.21 The Committee agreed that the Assessment Group's ICER of £77,000 per QALY gained, based on the unadjusted results, was a more plausible estimate of the cost effectiveness of trabectedin plus PLDH compared with PLDH alone than the manufacturer's, and that this was not within the range usually considered a cost-effective use of NHS resources. The Committee noted however that OVA-301 included only women with a first recurrence of ovarian cancer, and no clinical-effectiveness evidence for trabectedin was available for subsequent recurrences. The Committee therefore concluded that trabectedin plus PLDH could not be considered a cost-effective use of NHS resources for treating a first recurrence of platinum-sensitive ovarian cancer. It further concluded that it could not make any recommendation about the clinical or cost effectiveness of trabectedin plus PLDH in later recurrences, and that clinicians should take this into account when considering trabectedin plus PLDH as a treatment option.
- 4.3.22 The Committee then discussed network 3 and the cost-effectiveness results for paclitaxel, PLDH and topotecan, all given as monotherapy for women with platinum-refractory or platinum-resistant disease. In the comparison between PLDH and paclitaxel, the Committee noted that paclitaxel was dominated by PLDH and therefore excluded from the incremental analysis. However, the Committee noted the clinical specialists' opinion that paclitaxel was considered standard care in this setting, and that the costs and QALYS associated with paclitaxel were similar to those of PLDH (£900 difference in total costs and 0.022 difference in QALYs). The Committee noted that the incremental ICER for topotecan compared with PLDH was approximately £450,000 per QALY gained and remained above £50,000 per QALY gained in the sensitivity analyses. The Committee also noted the previous comments from the clinical specialists that topotecan is rarely used

in clinical practice for platinum-resistant disease because of low response rates. The Committee therefore concluded that PLDH and paclitaxel could be recommended for use, but that topotecan could not be considered a cost-effective use of NHS resources, for treating platinum-resistant or -refractory ovarian cancer.

4.3.23 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of people with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- The treatment is licensed or otherwise indicated for small patient populations.

In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of the extension to life are robust and the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.3.24 The Committee was aware that the manufacturer of trabectedin had stated that using the adjusted trial results, the median life expectancy in the platinum-sensitive population was 19.4 months, and a gain in median life expectancy of 4 months was estimated with trabectedin for the platinum-sensitive and partially platinum-sensitive populations. However, the Committee did not accept that the adjusted trial results were sufficiently reliable as a basis for

estimating effectiveness (see sections 4.3.17–4.3.21) and noted that estimates from OVA-301 discussed in NICE technology appraisal guidance 222 continued to be relevant. The Committee noted that the median overall survival for people treated with PLDH in the entire platinum-sensitive population was more than 24 months, and that the overall survival gain was less than 3 months and not statistically significant. The Committee concluded that trabectedin in combination with PLDH did not fulfil the criteria for being a life-extending, end-of-life treatment and that, even if it had met the criteria, the cost-effectiveness estimates (see section 4.3.22) remained outside the range usually considered a cost-effective use of NHS resources.

***Summary of Appraisal Committee’s key conclusions***

<b>TAXXX</b>	<b>Appraisal title: Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer (including reviews of technology appraisal guidance 91 and 222)</b>	<b>Section</b>
<b>Key conclusion</b>		
<p>Paclitaxel in combination with platinum or as monotherapy is recommended within its marketing authorisation as an option for treating recurrent ovarian cancer.</p> <p>Pegylated liposomal doxorubicin hydrochloride (PLDH) is recommended within its marketing authorisation as an option for treating recurrent ovarian cancer.</p> <p>PLDH in combination with platinum is recommended as an option for treating recurrent ovarian cancer.</p>		1.1 to 1.5

<p>The following are not recommended within their marketing authorisations for treating the first recurrence of platinum-sensitive ovarian cancer:</p> <ul style="list-style-type: none"> <li>• gemcitabine in combination with carboplatin</li> <li>• trabectedin in combination with PLDH</li> <li>• topotecan.</li> </ul> <p>The Appraisal Committee was unable to make recommendations on the use of these technologies for treating platinum-sensitive ovarian cancer beyond the first recurrence.</p> <p>Topotecan is not recommended within its marketing authorisation for treating recurrent platinum-resistant or platinum-refractory ovarian cancer.</p> <p>The Committee concluded that paclitaxel plus platinum was the most cost-effective option for women with recurrent platinum-sensitive ovarian cancer but that PLDH plus platinum could also be considered cost effective, noting that the dose of PLDH used in the clinical studies in combination with platinum was lower than that specified in the marketing authorisation.</p> <p>The Committee was aware that the cost-effectiveness estimates based on the network 1 meta-analysis showed that gemcitabine plus carboplatin resulted in an ICER compared with platinum alone of £114,000 per QALY gained, which could not be considered a cost-effective use of NHS resources. Although the Committee accepted the results of the network meta-analysis, it noted that the clinical evidence for gemcitabine plus platinum that informed the cost-effectiveness analysis only included women with a first recurrence of ovarian cancer, at which stage paclitaxel plus platinum or PLDH plus platinum would be alternative treatment</p>	<p>4.3.8</p> <p>4.3.9 to 4.3.11</p>
--	-------------------------------------

<p>options. It considered that it could not assume that identical results for relative clinical effectiveness would be found in women who had a second or subsequent recurrence. The Committee concluded that it could not make any recommendation about the clinical or cost effectiveness of gemcitabine beyond the first recurrence of platinum sensitive ovarian cancer.</p>	<p>4.3.12 to 4.3.14</p>
<p>The Committee noted that the ICER for PLDH monotherapy compared with paclitaxel monotherapy was approximately £23,700 per QALY gained. It also noted the Assessment Group's comments that the costs and QALYs associated with paclitaxel were similar to those of PLDH. Topotecan produced the fewest QALYs compared with PLDH monotherapy, trabectedin plus PLDH, and paclitaxel but was associated with higher costs than both PLDH and paclitaxel monotherapy. The Committee concluded that paclitaxel and PLDH could be recommended for use in the NHS for women with platinum-sensitive disease for whom platinum-based treatment was unsuitable, but topotecan had not been demonstrated to be cost effective for the treatment of platinum-sensitive ovarian cancer in women unable to take platinum and that this remained the case in the sensitivity analyses.</p>	<p>4.3.12</p>
<p>The Committee agreed that the Assessment Group's ICER of £77,000 per QALY gained, based on the unadjusted results, was a more plausible estimate of the cost effectiveness of trabectedin plus PLDH compared with PLDH alone than the manufacturer's and that this was not within the range usually considered a cost-effective use of NHS resources.</p>	<p>4.3.22</p>
<p>The Committee discussed the cost-effectiveness results for paclitaxel, PLDH and topotecan, all given as monotherapy for platinum-refractory or platinum-resistant disease. In the comparison between PLDH and paclitaxel, the Committee noted that the costs</p>	

<p>and QALYS associated with paclitaxel were similar to those of PLDH (£900 difference in total costs and 0.022 difference in QALYs). The Committee noted that the incremental ICER for topotecan compared with PLDH was approximately £450,000 per QALY gained and remained above £50,000 per QALY gained in the sensitivity analyses. The Committee concluded that PLDH and paclitaxel could be recommended for use, but that topotecan could not be considered a cost-effective use of NHS resources, for treating platinum-resistant or -refractory ovarian cancer.</p>		
<p><b>Current practice</b></p>		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>The Committee heard from clinical specialists that women with recurrent ovarian cancer can experience several relapses after initial treatment with platinum-based chemotherapy, and it was very important to have a range of treatment options available at each relapse.</p> <p>The Committee heard that standard treatment for women with platinum-sensitive disease, including those with partially platinum-sensitive disease, was platinum-combination chemotherapy and that paclitaxel was used for treating platinum-refractory or platinum-resistant disease. The Committee heard from the clinical specialists that only a small proportion of women were allergic to a particular platinum agent such as carboplatin, and that these women were either offered an alternative platinum agent</p>	<p>4.3.2 to 4.3.4</p>

	(cisplatin) or non-platinum regimens.	
<b>The technology</b>		
Proposed benefits of the technology  How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	Not applicable.	
What is the position of the treatment in the pathway of care for the condition?	The clinical specialists stated that treatment is tailored to individuals, taking into account factors such as previous treatment, and the potential for developing platinum resistance.	4.3.2
Adverse reactions	The results of the Assessment Group's network meta-analyses found that overall, none of the treatments were consistently associated with either a lower or a higher risk of adverse events.	4.1.16
<b>Evidence for clinical effectiveness</b>		
Availability, nature and quality of evidence	The Committee expressed disappointment with the quality and breadth of the trial evidence, and also with some of the trial design and reporting, but on balance concluded that the Assessment Group's approach was reasonable given the data	4.3.7

	available, and accepted the clinical-effectiveness results from the network meta-analyses.	
Relevance to general clinical practice in the NHS	<p>The Committee agreed that the Assessment Group's approach of presenting results separately for women with platinum-sensitive disease and platinum-resistant or platinum-refractory disease was appropriate.</p> <p>The clinical specialists stated that weekly paclitaxel, rather than the licensed 3-weekly paclitaxel, was established clinical practice for treating platinum-refractory or platinum-resistant disease. However the licensed 3 weekly regimen was more often used for those with platinum-sensitive disease. The Committee was aware that the trials used 3-weekly paclitaxel. The Committee also heard that in practice PLDH is usually initiated at a lower dose than that specified in the licence. It was also aware that PLDH was used at dose of 30 mg/m<sup>2</sup>, which is lower than the licensed dose, in clinical trials of PLDH in combination with carboplatin.</p>	<p>4.3.3</p> <p>4.3.4</p>
Uncertainties generated by the evidence	The Committee discussed the limitations of the network meta-analyses, particularly the differences in baseline characteristics between trials, uncertainty around whether trials were adequately powered to detect differences in overall survival and progression-free survival, and concerns about confounding because of crossover.	4.3.7



	The Committee acknowledged that the analyses had methodological limitations and that some assumptions had to be accepted.	
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	None were identified.	
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee concluded that for women with platinum-sensitive disease, paclitaxel, gemcitabine and PLDH (all plus carboplatin) improved progression-free survival compared with platinum alone and that PLDH and paclitaxel (both plus carboplatin) also improved overall survival. It also concluded that trabectedin plus PLDH improved progression-free survival compared with PLDH, paclitaxel and topotecan (all given alone), and that there was evidence that PLDH alone and trabectedin plus PLDH increased overall survival compared with topotecan. Finally, it accepted that for women with platinum-resistant or platinum-refractory disease, there were no statistically significant differences in progression-free and overall survival between PLDH, paclitaxel and topotecan.	4.3.7

<p><b>For reviews (except rapid reviews):</b> How has the new clinical evidence that has emerged since the original appraisals (TA91 and TA222) influenced the current (preliminary) recommendations?</p>	<p>Topotecan is no longer recommended for second-line (or subsequent) treatment for 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.</p>	
<p><b>Evidence for cost effectiveness</b></p>		
<p>Availability and nature of evidence</p>	<p>The manufacturer of trabectedin submitted cost-effectiveness evidence as part of its submission.</p> <p>The Assessment group developed a de novo model.</p>	<p>4.2.1 4.2.6</p>
<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>Uncertainty around estimates generated by the Assessment Group’s network meta-analyses which were incorporated in the model. The Committee noted that no evidence was available for gemcitabine plus carboplatin, topotecan and trabectedin plus PLDH for treating 2nd and subsequent recurrences of ovarian cancer in women with platinum-sensitive disease. The recommendations were therefore limited to a first recurrence of ovarian cancer and did not stop clinicians and patients from considering</p>	<p>4.3.7</p>

	these treatments for second or subsequent recurrences of platinum-sensitive ovarian cancer.	
Incorporation of health-related quality-of-life benefits and utility values  Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The Committee did not draw any specific conclusions about the health-related quality-of-life benefits and utility values.	4.2.11
Are there specific groups of women for whom the technology is particularly cost effective?	None were identified.	
What are the key drivers of cost effectiveness?	The ICER estimates were most sensitive to the relative effect of treatment on overall survival.	4.2.15 4.2.18 4.2.21
Most likely cost-effectiveness	For women with platinum-sensitive recurrent ovarian cancer, the Committee agreed that:	4.3.8 to 4.3.14

<p>estimate (given as an ICER)</p>	<ul style="list-style-type: none"> <li>• the ICER for paclitaxel plus PLDH compared with platinum alone was approximately £24,400 per QALY gained</li> <li>• PLDH plus platinum was dominated by paclitaxel plus platinum in the fully incremental analysis but the Committee accepted that the ICER for PLDH plus platinum compared with platinum alone was approximately £30,200 per QALY gained and it could also be considered cost-effective for women who cannot receive platinum treatment, the ICER for PLDH monotherapy compared with paclitaxel monotherapy was approximately £23,700 per QALY gained</li> <li>• gemcitabine plus carboplatin was extendedly dominated and excluded from the fully incremental analysis. The Committee also agreed that the ICER for gemcitabine plus carboplatin compared with platinum alone was £114,000 per QALY gained</li> <li>• the ICER for trabectedin plus PLDH compared with PLDH alone was likely to be over £77,00 per QALY gained</li> <li>• topotecan was dominated and excluded from the fully incremental analysis.</li> </ul> <p>For women with platinum-resistant or refractory ovarian cancer. The Committee</p>	
------------------------------------	--	--

	<p>accepted that:</p> <ul style="list-style-type: none"> <li>the ICER for topotecan compared with PLDH was approximately £450,000 per QALY gained</li> <li>paclitaxel was dominated by PLDH, but the Committee noted that the costs and QALYS associated with paclitaxel are similar to those of PLDH and concluded that both could be considered cost-effective.</li> </ul>	
<p><b>For reviews (except rapid reviews):</b></p> <p>How has the new cost-effectiveness evidence that has emerged since the original appraisals (TA91 and TA222) influenced the current (preliminary) recommendations?</p>	<p>For women with platinum-refractory or platinum-resistant disease, or who are allergic to platinum-based compounds, for whom PLDH and single-agent paclitaxel are considered inappropriate, topotecan is now not considered to be a cost-effective use of NHS resources.</p>	
<p><b>Additional factors taken into account</b></p>		
<p>Patient access schemes (PPRS)</p>	<p>A patient access scheme for trabectedin was submitted.</p>	<p>3.14</p>
<p>End-of-life considerations</p>	<p>The Committee concluded that trabectedin in combination with PLDH did not fulfil the criteria for being a life-extending, end-of-life</p>	<p>4.3.24</p>

	treatment.	
Equalities considerations and social value judgements	Not applicable.	

## 5 Implementation

- 5.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 5.2 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has recurrent ovarian cancer and the doctor responsible for their care thinks that paclitaxel or pegylated liposomal doxorubicin hydrochloride (PLDH) is the right treatment, they should be available for use, in line with NICE’s recommendations.
- 5.3 NICE has developed tools [[link to www.nice.org.uk/guidance/TAXXX](#)] to help organisations put this guidance into practice (listed below). [**NICE to amend list as needed at time of publication**]
- Slides highlighting key messages for local discussion.
  - Costing template and report to estimate the national and local savings and costs associated with implementation.

- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

## 6 Related NICE guidance

Details are correct at the time of publication. Further information is available on the [NICE website](#).

### Published

- [Trabectedin for the treatment of relapsed ovarian cancer](#). NICE technology appraisal guidance 222 (2011).
- [Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for the treatment of advanced ovarian cancer](#) NICE technology appraisal guidance 91 (2005).
- [Ovarian cancer: the recognition and initial management of ovarian cancer](#). NICE clinical guideline 122 (2011).

### Under development

- Vintafolide in combination with pegylated liposomal doxorubicin hydrochloride for treating folate-receptor-positive platinum-resistant ovarian cancer. NICE technology appraisal guidance (publication date to be confirmed).

## 7 Review of guidance

- 7.1 The guidance on this technology will be considered for review 3 years after publication. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Jane Adam  
Chair, Appraisal Committee  
December 2014



## **8 Appraisal Committee members, guideline representatives and NICE project team**

### **8.1 *Appraisal Committee members***

The Appraisal Committees are standing advisory committees of NICE. 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. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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.

#### **Dr Jane Adam (Chair)**

Department of Diagnostic Radiology, St George's Hospital, London

#### **Professor Iain Squire (Vice-Chair)**

Consultant Physician, University Hospitals of Leicester

#### **Dr Graham Ash**

Consultant in General Adult Psychiatry, Lancashire Care NHS Foundation Trust

#### **Professor Thanos Athanasiou**

Professor of Cardiovascular Sciences and Cardiac Surgery, Imperial College London; Consultant Cardiothoracic Surgeon, Imperial College Healthcare NHS Trust

**Dr Simon Bond**

Senior Statistician, Cambridge Clinical Trials Unit

**Dr Jeremy Braybrooke**

Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

**Dr Gerardine Bryant**

GP, Swadlincote, Derbyshire

**Professor Aileen Clarke**

Professor of Public Health & Health Services Research, University of Warwick

**Mr Andrew England**

Lecturer in Medical Imaging, NIHR Fellow, University of Liverpool Dr Brian Hawkins

Chief Pharmacist, Cwm Taf Health Board, South Wales

**Dr Peter Heywood**

Consultant Neurologist, Frenchay Hospital, Bristol

**Dr Ian Lewin**

Consultant Endocrinologist, North Devon District Hospital

**Mr Terence Lewis**

Lay Member

**Dr Louise Longworth**

Reader in Health Economics, HERG, Brunel University

**Dr Anne McCune**

Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

**Professor John McMurray**

Professor of Medical Cardiology, University of Glasgow

**Dr Alec Miners**

Lecturer in Health Economics, London School of Hygiene and Tropical  
Medicine

**Dr Mohit Misra**

GP, Queen Elizabeth Hospital, London

**Ms Sarah Parry**

CNS Paediatric Pain Management, Bristol Royal Hospital for Children

**Dr Ann Richardson**

Lay Member

**Ms Ellen Rule**

Programme Director, NHS Bristol

**Dr Sharon Saint Lamont**

Head of Quality and Innovation, North East Strategic Health Authority

**Mr Stephen Sharp**

Senior Statistician, MRC Epidemiology Unit

**Dr Brain Shine**

Consultant Chemical Pathologist, John Radcliffe Hospital

**Dr Peter Sims**

GP, Devon

**Mr Cliff Snelling**

Lay Member

**Mr David Thomson**

Lay Member

**Dr Olivia Wu**

Reader in Health Economics, University of Glasgow

## 8.2 *NICE project team*

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

### **Helen Tucker**

Technical Lead

### **Raisa Sidhu and Zoe Charles**

Technical Advisers

### **Bijal Joshi**

Project Manager

## 9 Sources of evidence considered by the Committee

A. The assessment report for this appraisal was prepared by BMJ-TAG:

- Edwards SJ, Barton S, Thurgar E et al. Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for the treatment of recurrent ovarian cancer: A Multiple Technology Appraisal. BMJ-TAG, London, July 2013.

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I, II and III were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I. Manufacturers/sponsors:

- Eli Lilly (gemcitabine)
- GlaxoSmithKline (topotecan)
- Jansen-Cilag (pegylated liposomal doxorubicin hydrochloride)
- PharmaMar (trabectedin)

II. Professional/expert and patient/carer groups:

- Ovacome
- Ovarian Cancer Action
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- Target Ovarian Cancer

III. Other consultees:

- Department of Health
- Welsh Government

IV. Commentator organisations (without the right of appeal):

- BMJ-TAG
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Health Improvement Scotland
- Merck Sharp & Dohme (vintafolide)
- National Collaborating Centre for Cancer
- National Institute for Health Research Health Technology Assessment Programme
- Pfizer (cisplatin)
- Roche Products (bevacizumab)

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for the treatment of recurrent ovarian cancer by attending Committee discussions and/or providing written evidence to the Committee.

- Professor Charlie Gourley, Professor and Honorary Consultant in Medical Oncology, nominated by organisation representing Healthcare Improvement Scotland – clinical expert (attended first discussion only)
- Professor Jonathan A Ledermann, Professor of Medical Oncology, UCL Cancer Institute & Clinical Director Cancer Services UCL Hospitals, London, nominated by organisation representing Royal College of Physicians – clinical expert
- Mrs Tilean Clarke, Professional Support Manager, nominated by organisation representing Target Ovarian Cancer – patient expert
- Ms Wendy Fisher, Retired University Lecturer, nominated by organisation representing Ovarian Cancer Action – patient expert

D. Representatives from the following manufacturer attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- PharmaMar