Ovarian cancer - topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for advanced recurrent disease only (Review of TA 91 & TA 222): appraisal consultation document

The Department of Health has asked the National Institute of Health and Care Excellence (NICE) to produce guidance on using topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine in the NHS in England and Wales. The Appraisal Committee has considered the evidence submitted and the views of non-manufacturer consultees and commentators, and clinical specialists and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 9) and the public. This document should be read along with the evidence base (the evaluation report).

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on these technologies. The recommendations in section 1 may change after consultation.

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine in the NHS in England and Wales.

For further details, see the Guides to the technology appraisal process.

The key dates for this appraisal are:

Closing date for comments: 18 October 2013

Second Appraisal Committee meeting: 6 November 2013

Details of membership of the Appraisal Committee are given in section 8, and a list of the sources of evidence used in the preparation of this document is given in section 9.

Note that this document is not NICE's final guidance on these technologies. The recommendations in section 1 may change after consultation.

1 Appraisal Committee's preliminary recommendations

1.1 Paclitaxel is recommended, within its marketing authorisation, as an option for treating recurrent ovarian cancer.

1.2 Pegylated liposomal doxorubicin hydrochloride (PLDH) is recommended, within its marketing authorisation, as an option for treating recurrent ovarian cancer.

1.3 Gemcitabine in combination with carboplatin is not recommended, within its marketing authorisation, for treating the first recurrence of platinum-sensitive ovarian cancer.

1.4 Trabectedin in combination with PLDH is not recommended, within its marketing authorisation, for treating the first recurrence of platinum-sensitive recurrent ovarian cancer.

1.5 Topotecan is not recommended, within its marketing authorisation, for treating the first recurrence of platinum-sensitive ovarian cancer.

1.6 Topotecan is not recommended, within its marketing authorisation, for treating platinum-resistant or refractory recurrent ovarian

cancer.

1.7 Women currently receiving gemcitabine in combination with carboplatin, topotecan, or trabectedin in combination with PLDH that is not recommended according to 1.3, 1.4, 1.5 and 1.6 should be able to continue treatment until they and their 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: fully platinum-sensitive (disease that responds to first-line platinum-based therapy but relapses after 12 months or more); partially platinum-sensitive (disease that responds to first-line platinum-based therapy but relapses between 6 and 12 months); 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.

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, plus 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/m² of body surface area administered on days 1 and 8 of each 21-day cycle. After gemcitabine, carboplatin will be given on day 1 consistent with a target area under curve of 4.0 mg/ml×min. 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 cost of a course of treatment of gemcitabine 1000 mg/m^2 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, which prevent the formation of mitotic spindles, thus 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/m² 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 at 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 cost of a course of 3-weekly treatment with paclitaxel 17 mg/m^2 for 18 weeks is £638. The cost of weekly treatment with paclitaxel 80 mg/m^2 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.

3.8 PLDH is administered by intravenous infusion. The recommended dosage is 50 mg/m² 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 cost of a course of treatment of PLDH 40 mg/m^2 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/m² 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 cost of a course of treatment of topotecan 1.5 mg/m^2 on days 1–5 every 21 day cycle is £1305.

Trabectedin

3.12 Trabectedin (Yondelis, PharmaMar) is an anticancer agent that binds to the minor groove of the DNA and as a result 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/m² of body surface area, immediately after PLDH 30 mg/m², 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 cost of a course of treatment of trabectedin 1.1 mg/m^2 and PLDH 30 mg/m^2 on day 1 of every 21 day cycle is £3679 (with patient access scheme included).

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 9) considered evidence from a number of sources (section 10).

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. Of these trials, 7 were phase III open label, 4 were phase II open label and the phase or 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 a 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 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 intervention and control group.

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-containing 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 the platinum-sensitive network 1 in which platinum-based therapies were identified. 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 the 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 any 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 the 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 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 are 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 and therefore it was not possible to perform an indirect comparison. No statistically significant differences were reported in the OVA-301 trial for progression-free survival. 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 the 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 the 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 reported 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 where 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 is associated with statistically significantly lower risks of allergic reaction and alopecia but statistically significantly higher risks of anaemia and nausea and 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 had received only 1 previous platinum-based chemotherapy regimen, and experienced recurrence or progression.

4.2.2 The structure was identical to the model developed within 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 post-hoc analysis of subgroups in 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 stated 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. In addition, for women with platinum-sensitive and partially platinum-sensitive recurrent ovarian cancer, median survival (after correction of prognostic factors including progression-free interval) showed an extension in life of 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; however, 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 are paclitaxel alone or plus platinum chemotherapy, PLDH alone or 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 population 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 the 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 where the relative hazard decreases over time for both progression-free survival and overall survival, the model is 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 due to lack of individual patient data and because none of the trials described further treatment received.

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 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 included in Trabectedin for the treatment of relapsed ovarian cancer (NICE technology appraisal guidance 222) from 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, and 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 based on drug costs in the British national formulary (BNF) and regimens as per the summaries of product characteristics with verification and amendment from clinical experts (see section 3). 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 carboplatin, and £200 for topotecan.

4.2.13 The model assumed that treatment regimens would be administered as an infusion in a hospital and associated administration costs were included in the model. The estimated administration costs in the model were £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 women with 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 presented an ICER of £114,410 per QALY gained for gemcitabine plus carboplatin 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 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 therapy 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 are similar, producing cost-effectiveness estimates that are sensitive to minor changes in parameter estimates.

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

4.2.17 Base-case results (deterministic and probabilistic) indicated that topotecan was strictly 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. When the upper bound of the hazard ratio for survival 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 but 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, but 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^2 to 50 mg/m^2 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 £35,363 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 – platinum-resistant and platinum-refractory group

4.2.20 For women with platinum-resistant or -refractory ovarian cancer, the Assessment group explained that data for paclitaxel plus platinum were not available from the literature and therefore this intervention was not included in the base-case analysis. Base-case results (deterministic and probabilistic) indicated that paclitaxel was dominated by PLDH alone. 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 £499,553 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 but 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 but 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 but 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 scenarios 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 across the scenarios. Paclitaxel was dominated in all scenarios except when the cost associated with a 50 mg/m^2 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, treatment options that may be reserved for any future recurrences, 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. The patient experts highlighted the emotional impact of developing recurrent ovarian cancer, particularly emphasising the fear of recurrence, and the importance of progression-free survival and the psychological benefit of having a range of treatment options available. The clinical specialists also 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 are needed until more targeted therapies become available. The Committee heard that approximately 70% of women 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 had a response 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 platinum and were either offered an alternative platinum agent (cisplatin) or non-platinum-containing 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 those with platinum-sensitive disease. The Committee was aware that the trials used 3-weekly paclitaxel. The Committee also heard that PLDH dose in practice was usually lower than in the licence, especially for combination therapy, to reduce the toxicity. However, the Committee noted that any recommendations needed to be in line with the respective marketing authorisations.

4.3.5 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 received 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 progression-free survival benefit with gemcitabine in combination with carboplatin did not translate into an overall survival benefit in the trial or network meta-analyses as it did for PLDH and paclitaxel, and the Committee questioned the potential reasons for this apparent discrepancy. The clinical specialists cautioned that it is difficult to show overall survival benefits because multiple lines of treatment have a compounding 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.

The Committee discussed the limitations of the analysis, 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. 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 the trial data and experience in clinical practice. The Committee acknowledged that the analyses had methodological limitations but, on balance, concluded that the Assessment Group's approach was reasonable given the data available and accepted the clinical-effectiveness results from the network meta-analyses.

4.3.6 The Committee then discussed the cost-effectiveness analyses conducted by the Assessment Group. It considered the cost-effectiveness results based on network 1, that is for women with platinum-sensitive recurrent ovarian cancer receiving

platinum-based chemotherapy, and considered that the fully incremental deterministic results indicated that paclitaxel plus platinum was the most cost-effective treatment with an ICER of £24,361 per QALY gained compared with platinum alone. The Committee also noted that although PLDH plus platinum was dominated by paclitaxel plus platinum and 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 in combination with platinum was the most cost-effective option for women with recurrent platinum-sensitive ovarian cancer, and that PLDH in combination with platinum could also be considered cost effective.

4.3.7 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 excluded from the fully incremental analysis. The Committee considered that this was linked to the lack of overall survival benefit demonstrated with gemcitabine plus carboplatin in the trial. The Committee acknowledged the value of several treatment options being available to patients. The Committee discussed whether gemcitabine plus carboplatin could be considered cost effective when compared with platinum alone in women for whom paclitaxel and PLDH were unsuitable. However, the Committee noted that in the incremental analysis the QALY gains for gemcitabine plus carboplatin compared with platinum alone were modest compared with those from the paclitaxel and PLDH combination therapies, and resulted in an ICER compared with platinum alone of £114,000 per QALY gained. The Committee acknowledged that the sensitivity analysis around overall survival estimates indicated a high degree of uncertainty. It also noted that the clinical evidence for gemcitabine plus platinum that informed the cost-effectiveness analysis included only women with a first recurrence of ovarian cancer for whom other choices of combination therapies would be available, and there was no evidence included in the Assessment Group's meta-analysis on the clinical effectiveness for subsequent recurrences. The Committee concluded that, on the basis of the clinical evidence available from the trial, the network meta-analysis, and the economic model, gemcitabine plus carboplatin could not be considered a cost-effective use of NHS resources for treating a first recurrence of platinum-sensitive ovarian cancer.

4.3.8 The Committee discussed the cost-effectiveness results based on network 2, that is 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. 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 Assessment Group's comments that the costs and QALYS associated with paclitaxel are similar to those of PLDH. It noted that topotecan produced fewer QALY gains than 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 also heard from the clinical specialists that topotecan is rarely used in clinical practice in this setting, with only anecdotal evidence on effectiveness in some cancer subtypes. The Committee noted that all 3 trials studying topotecan in women with platinum-sensitive disease included women with a first recurrence of ovarian cancer and evidence for those with subsequent recurrences in the platinum-sensitive setting was not available. The Committee concluded that topotecan could not be considered a cost-effective use of NHS resources for treating the first recurrence of platinum-sensitive ovarian cancer and that paclitaxel and PLDH could be recommended for use in the NHS for women with platinum-sensitive disease.

4.3.9 The Committee noted that the Assessment Group's ICER for trabectedin plus PLDH compared with PLDH alone was over £85,200 per QALY gained. The Committee acknowledged that the manufacturer's economic evaluation, which used clinical-effectiveness data obtained from the OVA-301 trial, had been retrospectively adjusted for potential covariates, primarily for imbalances in platinum-free interval between arms, and that the resulting ICER was £27,600 per QALY gained. The Committee was aware that the Assessment Group also performed an analysis incorporating these adjusted results, which yielded an ICER of £35,000 per QALY gained. The Committee carefully considered the manufacturer's post hoc adjustment of the treatment effects, which resulted in the non-statistically significant overall survival benefit reported for the platinum-sensitive population in the trial becoming statistically significant. The Committee agreed that adjustment of the treatment effect for imbalances in platinum-free interval (a major prognostic indicator) between treatment arms was a new concept and an interesting approach, and more precise stratification in respect of platinum-free interval might be considered in future trials. However, the Committee noted that this was an unvalidated retrospective approach in ovarian cancer trials. It also noted that the Assessment Group had incorporated unadjusted effect estimates for all the comparisons in the analyses, and without similar data being available from other trials for comparison it was not possible to accept the cost-effectiveness analyses based on these adjusted results. The Committee noted that the OVA-301 trial included only women with a first recurrence of ovarian cancer and no clinical effectiveness evidence for trabectedin was available for subsequent recurrences. The Committee concluded that trabectedin plus PLDH could not be considered a cost-effective uses of NHS resources for treating a first recurrence of platinum-sensitive ovarian cancer.

4.3.10 The Committee then discussed the cost-effectiveness results for topotecan for women with platinum-refractory or platinum-resistant disease. The incremental ICER for topotecan compared with PLDH was approximately £450,000 per QALY gained. The Committee also noted the previous comments from the clinical specialists that topotecan is rarely used in clinical practice because of low response rates. 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 Assessment Group's comments that the costs and QALYS associated with paclitaxel are similar to those of PLDH. The Committee therefore concluded that topotecan could not be considered a cost-effective use of NHS resources for treating platinum-resistant or -refractory ovarian cancer and PLDH and paclitaxel could be recommended for use in the NHS in women with platinum-resistant or -refractory recurrent ovarian cancer.

4.3.11 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.

4.3.12 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 population. However, the Committee noted that it could not accept estimates based on adjusted results for just one of the technologies being appraised (see section 4.3.6) and that estimates from the OVA-301 trial discussed in NICE technology appraisal guidance 222 would continue to be relevant. The Committee noted that the median overall survival for people treated with PLDH in the entire platinum-sensitive population was 24.3 months and the overall survival gain was less than 3 months. The Committee concluded that trabectedin in combination with PLDH did not fulfil the criteria for being a life-extending, end-of-life treatment.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title:	Section
Key conclusion		
Paclitaxel is recommended, within its marketing authorisation, as an option for treating recurrent ovarian cancer. Pegylated liposomal doxorubicin hydrochloride (PLDH) is recommended, within its marketing		1.1–1.6

authorisation, as an option for treating recurrent ovarian cancer. Gemcitabine in combination with carboplatin is not recommended, within its marketing authorisation, for treating the first recurrence of platinum-sensitive ovarian cancer. Trabectedin in combination with PLDH is not recommended, within its marketing authorisation, for treating the first recurrence of platinum-sensitive ovarian cancer. Topotecan is not recommended, within its marketing authorisation, for treating the first recurrence of platinum-sensitive ovarian cancer. Topotecan is not recommended, within its marketing authorisation, for treating platinum-resistant or refractory recurrent ovarian cancer.		
Current practice		
Clinical need of patients, including the availability of alternative treatments	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 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 that women who were allergic to platinum were either offered an alternative platinum agent such as cisplatin or non-platinum containing regimens or desensitisation could be carried out.	4.3.2 4.3.3
The technology		
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, treatment options that may be reserved for any future recurrences, and the potential for developing platinum resistance. Gemcitabine 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'. Paclitaxel has a UK marketing authorisation 'for the treatment of metastatic carcinoma of the ovary after failure of standard, platinum containing therapy'. 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. Topotecan has a UK marketing authorisation for the treatment of women with 'metastatic carcinoma of the ovary after failure of first-line or subsequent chemotherapy' Trabectedin has a UK marketing authorisation, in combination with PLDH, for the treatment of women 'with relapsed platinum-sensitive ovarian cancer'	4.3.2 3.1 3.4 3.7 3.10 3.12
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
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Assessment Group identified 16 randomised controlled trials that met the inclusion criteria, of which 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 a 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 (Sehouli et al.; n=90) comparing weekly topotecan with conventional topotecan included women with platinum-resistance experiencing subsequent recurrences. A series of network meta-analyses were conducted for platinum-sensitive disease, and platinum resistant or refractory disease. In the absence of individual patient data, the network meta-analysis synthesised summary measures of relative treatment effect data from the whole study populations. 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	4.1.1 4.1.2

	network 2 evaluated non-platinum-based treatments.	
Relevance to general clinical practice in the NHS	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. 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 PLDH dose in practice was usually lower than in the licence, especially for combination therapy, to reduce the toxicity. However, the Committee noted that any recommendations needed to be in line with the respective marketing authorisations. 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.	4.3.3 4.3.4 4.3.3
Uncertainties generated by the evidence	The Committee discussed the limitations of the analysis, 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. The Committee acknowledged that the analyses had methodological limitations but, on balance, concluded that the Assessment Group's approach was reasonable given the data available and accepted the clinical-effectiveness results from the network meta-analyses.	4.3.5
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 accepted the clinical-effectiveness results from the network meta-analyses.	4.3.5
For reviews (except rapid reviews): How has the new clinical evidence that has emerged since the original appraisals (TA91 and TA222) influenced the current (preliminary) recommendations?	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.	
Evidence for cost effectiveness		
Availability and nature of evidence	The manufacturer of trabectedin submitted cost-effectiveness evidence as part of its submission. The Assessment group developed a de novo model.	4.2.1 4.2.6
Uncertainties around and plausibility of assumptions and inputs in the economic model	Uncertainty around estimates generated by the Assessment Group's meta-analyses which were incorporated in the model. The Committee discussed the limitations of the analysis, particularly around 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. 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.	4.3.5 4.3.7 4.3.8 4.3.9
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 Assessment Group noted that the utility values included in Trabectedin for the treatment of relapsed ovarian cancer (NICE technology appraisal guidance 222) from 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. The mean estimates of utility in the stable and progressive disease health states were estimated to be 0.718 and 0.649 respectively.	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 estimate (given as an ICER)	For women with platinum-sensitive recurrent ovarian cancer, the Committee agreed that: · the ICER for paclitaxel plus PLDH compared with platinum alone was approximately £24,000 per QALY gained · 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 £30,000 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 £24,000 per QALY gained · 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 · the ICER for trabectedin plus PLDH compared with PLDH alone was likely to be over £85,000 per QALY gained · topotecan was dominated and excluded from the fully incremental analysis For women with platinum-resistant or refractory ovarian cancer. The Committee accepted that: · the ICER for topotecan compared with PLDH was approximately £450,000 per QALY gained · 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	4.3.6 to 4.3.10
For reviews (except rapid reviews): How has the new cost-effectiveness evidence that has emerged since the original appraisals (TA91 and TA222) influenced the current (preliminary) recommendations?	For platinum-refractory or platinum-resistant, or women 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.	
Additional factors taken into account		
Patient access schemes (PPRS)	A patient access scheme for trabectedin was submitted.	3.14
End-of-life considerations	The Committee concluded that trabectedin in combination with PLDH did not fulfil the criteria for being a life-extending, end-of-life treatment.	4.3.12
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 consultation. 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 Proposed date for review of guidance

7.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive in December 2016. NICE welcomes comment on this proposed date. 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
September 2013

8. Appraisal Committee members, guideline representatives and NICE project team

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 Jeremy Braybrooke
Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

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

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 Mohit Misra
GP, Queen Elizabeth Hospital, London

Dr Ann Richardson
Lay Member

Ms Ellen Rule
Programme Director, NHS Bristol

Mr Stephen Sharp
Senior Statistician, MRC Epidemiology Unit

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

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
Technical Adviser

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/specialist 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 specialist 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 the initial Committee discussion and/or providing written evidence to the Committee. They are invited to comment on the ACD.

- Professor Charlie Gourley, Professor and Honorary Consultant in Medical Oncology, nominated by organisation representing Healthcare Improvement Scotland – clinical specialist
- 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 specialist
- 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

E. 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

This page was last updated: **18 October 2013**

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