Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House (8th floor) 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman Professor Kenneth R Paterson
NHS SCOTLAND

trabectedin, 250 microgram, 1mg powder for concentrate for solution for infusion (Yondelis®) SMC No. (634/10)

PharmaMar S.A. Ltd.

06 August 2010

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

trabectedin (Yondelis) is not recommended for use within NHS Scotland.

Indication under review: Trabectedin in combination with pegylated liposomal doxorubicin (PLD) is indicated for the treatment of patients with relapsed platinum-sensitive ovarian cancer.

In an open-label randomised controlled study trabectedin in combination with PLD was significantly superior to PLD monotherapy in terms of progression free survival. There was a significant difference in an exploratory interim analysis of overall survival in the sub-group of patients with partially platinum-sensitive disease.

The manufacturer's justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC and in addition, the manufacturer did not present a sufficiently robust economic case to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Trabectedin in combination with pegylated liposomal doxorubicin (PLD) is indicated for the treatment of patients with relapsed platinum-sensitive ovarian cancer.

Dosing Information

Trabectedin is administered every three weeks as a 3-hour infusion at a dose of 1.1 mg/m^2, immediately after PLD 30 mg/m^2. All patients must receive corticosteroids (e.g. 20 mg of dexamethasone intravenously 30 minutes prior to PLD) not only as anti-emetic prophylaxis, but also because it appears to provide hepatoprotective effects. Additional anti-emetics may be administered as needed.

Trabectedin must be administered under the supervision of a physician experienced in the use of chemotherapy. Its use should be confined to qualified oncologists or other health professionals specialised in the administration of cytotoxics.

Product availability date

28 October 2009. This product has orphan drug status for this indication.

Summary of evidence on comparative efficacy

The submitting company has requested that the Scottish Medicines Consortium consider the use of this product in a sub-population of the licensed indication, namely patients with partially platinum sensitive disease (i.e. platinum free interval [PFI] of 6 to 12 months), as an alternative to pegylated liposomal doxorubicin (PLD) monotherapy.

One phase III open-label, multi-centre randomised study designed to investigate the efficacy and safety of trabectedin in combination with PLD versus PLD monotherapy has been conducted in women 18 years and over with histologically confirmed epithelial ovarian, fallopian tube or primary peritoneal carcinoma. Patients were recruited if they had received only one prior platinum based chemotherapy regimen and experienced persistence, recurrence or progression including platinum-resistant (PFI < 6 months) and platinum sensitive disease (PFI ≥ 6 months) patients. Patients were required to have disease measurable by Response Evaluation Criteria in Solid Tumors (RECIST), an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2, and to satisfy haematological and hepatic function criteria.

Patients were randomised to treatment with dexamethasone 20mg (or equivalent) intravenous (iv) infusion followed 30 minutes later by PLD 30mg/m^2 as a 1.5 hour iv infusion, immediately followed by trabectedin 1.1mg/m^2 as a 3 hour iv infusion via a central venous catheter (every 3 weeks) or PLD 50mg/m^2 as a 1.5 hour iv infusion (every 4 weeks). Randomisation was stratified by ECOG PS (0 or 1 versus 2) and platinum sensitivity (sensitive versus resistant). Treatment was continued until disease progression or confirmation of complete response and could continue for two or more cycles beyond complete response. The use of colony-stimulating factors was permitted after cycle one in accordance with American Society of Clinical Oncology (ASCO) guidelines and additional anti-emetics were permitted at the investigator's discretion. The primary endpoint was progression free survival (PFS), defined as the time from randomisation to disease progression or death. Independent radiology review

was based on disease progression by radiological evaluation alone using RECIST. Secondary endpoints included overall survival (OS), overall response rate (ORR), defined as a response maintained ≥ 4 weeks by RECIST, and duration of response (calculated from date of first documentation of response to date of disease progression or death due to disease progression).

A total of 672 patients were randomised and 328 and 317 patients in the trabectedin/PLD and PLD monotherapy arms respectively were included in the analysis of PFS. At the clinical cut-off (15 May 2008), there were 389 PFS events based on independent radiology review. Overall, treatment with trabectedin/PLD resulted in a 21% risk reduction for PFS compared with PLD monotherapy (hazard ratio [HR] 0.79; 95% confidence interval [CI], 0.65 to 0.96; p=0.0190). The median PFS was 7.3 months for trabectedin/PLD and 5.8 months for PLD monotherapy. In the subgroup of patients with platinum-sensitive disease (licensed population, n=417) the trabectedin/PLD combination also improved PFS compared with PLD alone (9.2 versus 7.5 months; HR 0.73; 95% CI, 0.56 to 0.95; p=0.017). Trabectedin/PLD also improved PFS compared with PLD alone in patients with partially platinum-sensitive disease (target population in submission, n=208): 7.4 versus 5.5 months; HR = 0.65; 95% CI, 0.45 to 0.92; p=0.0152.

Updated (31 May 2009 cut-off) *ad hoc* interim OS data were presented to the European Medicines Agency (EMA). Four hundred and nineteen deaths (trabectedin/PLD, 204; PLD, 215) had occurred which represented 81% of the 520 death events required for the pre-specified final OS analysis. OS results for the whole population, platinum-sensitive population and partially platinum-sensitive population (exploratory) are included in the table below.

Table: Median overall survival for trabectedin/PLD and PLD in the pivotal study (31/5/09 cut-off)

Endpoint	**Trabectedin/PLD**		**PLD monotherapy**		**Hazard Ratio (95% CI), p-value**
	n	**months**	**N**	**months**	
Overall survival (whole population)	337	22.4	335	19.5	0.85 (0.70 to 1.03), 0.0920
Overall survival (platinum-sensitive population)	218	27.0	212	24.3	0.82 (0.63 to 1.06), 0.1259
Overall survival (partially platinum-sensitive population)	123	23.0	90	17.1	0.59 (0.42 to 0.82), 0.0015

In the overall population, the objective response rate (ORR with trabectedin/PLD was significantly higher than with PLD monotherapy (28% [93/337] versus 19% [63/335]); Odds Ratio 1.65, p=0.008. For the platinum-sensitive population (licensed indication) the ORR was (35% [77/218] versus 23% [48/212); p=0.0042 for trabectedin/PLD and PLD monotherapy respectively. For the partially platinum-sensitive population (target population in submission): ORR with trabectedin/PLD (33%) was significantly higher than that with PLD (15%); p=0.0041. In the overall population, the median response duration was 7.9 months (95% CI 7.4 to 9.2) for trabectedin/PLD and 7.7 months (95% CI 6.5 to 9.0) for PLD; HR 0.95, 95% CI 0.62 to 1.46. There were no significant differences between the treatment arms for any of the pre-specified quality of life scales measured.

Summary of evidence on comparative safety

Drug related treatment emergent adverse events (TEAE) were experienced by >99% (332/333) and 95% (312/330) of patients in the trabectedin/PLD and PLD arms respectively. TEAE that lead to treatment discontinuation occurred in 23% (78/333) and 15% (50/330) of patients and these were considered to be drug-related in 17% (57/333) and 9% (31/330) of patients respectively. Gastrointestinal adverse events were the most commonly reported and overall were similar between groups (89% versus 83%). However, nausea (74% versus 42%) and vomiting (56% versus 30%) were more common in the trabectedin/PLD group and stomatitis (20% versus 33%) was more frequent in the PLD monotherapy group as was hand-foot syndrome (24% versus 54%).

Neutropenia (77% versus 38%), leukopenia (48% versus 26%), anaemia (48% versus 25%) and thrombocytopenia (36% versus 8%) were more common in the trabectedin/PLD group compared to PLD alone. Colony stimulating factors were used more frequently in the trabectedin/PLD arm (42% of patients/26% of cycles) than in the PLD alone arm (17% of patients/8% of cycles).

Rises in alanine aminotransferase, aspartate aminotransferase and blood alkaline phosphatase occurred more frequently in the trabectedin/PLD group. The Summary of Product Characteristics notes that rhabdomyolysis has been uncommonly reported, usually in association with myelotoxicity, severe liver function test abnormalities and/or renal or multiorgan failure. There were seven reported cases of non-fatal congestive heart failure-related diagnoses, irrespective of causality (one in the PLD arm and six in the trabectedin/PLD arm).

Deaths associated with adverse events occurred in five patients on trabectedin/PLD (three of which were considered drug-related) and one patient on PLD.

Summary of clinical effectiveness issues

The submitting company has requested that the Scottish Medicines Consortium consider the use of this product in a sub-population of the licensed indication; patients with partially platinum sensitive disease (i.e. PFI of 6 to 12 months) as an alternative to PLD monotherapy.

In the whole population a significant difference in PFS of 1.5 months in favour of the trabectedin/PLD combination has been demonstrated and this difference increased to 1.9 months in the subgroup of patients with partially platinum-sensitive disease (i.e. target population proposed in manufacturer's submission). For the whole population immature OS data indicated that survival was numerically longer for the trabectedin/PLD combination and the difference significantly longer in the subgroup of patients with partially platinum-sensitive disease only. There were no differences in quality of life between the two groups.

However, the pivotal study included patients with platinum-resistant (PFI<6 months) and platinum-sensitive (PFI ≥ 6 months) disease. Therefore only sub-group analyses support the use of trabectedin in combination with PLD for the licensed indication and proposed target sub-population and the study may not have sufficient power for these analyses. There are other limitations with respect to the clinical data. Evaluation bias may be present whereby PFS is

determined to be shorter in the control arm as an artefact, because patients may be more inclined to report symptoms and physicians follow-up on these earlier. The use of PFS as a surrogate for OS in recurrent ovarian cancer has also been questioned. The assessment of mature OS data (final analysis due to take place in mid-2011) may be advisable before assuming that PFS translates into a beneficial OS for the trabectedin/PLD combination.

Following disease progression, a similar proportion of patients in each arm received subsequent treatments for ovarian cancer (69% versus 72%) which included platinum compounds (41% versus 49%), taxanes (24% versus 21%), pyrimidine analogues (21% versus 28%) and others (19% versus 21%) in the trabectedin/PLD and PLD monotherapy arms respectively.

The only direct comparative evidence is versus PLD monotherapy. However, other treatment options are available for patients with partially platinum-sensitive disease, including paclitaxel plus carboplatin or cisplatin, weekly paclitaxel monotherapy (in platinum allergic patients) and topotecan monotherapy (in platinum allergic patients in whom monotherapy with PLD or paclitaxel is inappropriate). Therefore comparative efficacy versus treatments other than PLD monotherapy is not known.

It is strongly recommended that trabectedin be administered by central venous catheter and this may not be usual practice in the treatment of patients with recurrent ovarian cancer. In addition hepatic and haematological function should be monitored prior to initiation of trabectedin and prior to re-treatment and certain criteria need to be met. In the pivotal study colony stimulating factors (CSFs) could be prescribed (according to ASCO guidelines) and were given in 42% of patients receiving trabectedin/PLD. In patients recruited to the study from European countries only 26% of patients in the trabectedin/PLD arm received CSFs. The addition of CSFs may be necessary for a proportion of patients treated with trabectedin/PLD, however, the number of patients in Scotland who may require this is not known.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis of adding trabectedin to PLD monotherapy in patients partially sensitive to platinum chemotherapy (i.e patients who previously responded for between 6 and 12 months to platinum treatment). The manufacturer specifically requested that trabectedin be considered for this sub-group within the full licence and provided an economics case that was confined to this role. The general modelling approach used was based on a previous National Institute for Health and Clinical Excellence (NICE) Multiple Technology Appraisal Report (TAR) of medicines for ovarian cancer. Clinical data, dosing assumptions and utilities were taken from the main clinical study. A lifetime time horizon for the analysis was adopted. Utility values were estimated based of EQ-5D values assessed during the clinical trial and these indicated that trabectedin/PLDH patients had higher utility scores for stable and progressive disease compared to PLDH patients.

The manufacturer estimated the additional cost per patient would be £16,325 and the quality adjusted life year (QALY) gain 0.37, to give an additional cost per QALY gained of £44,237, based on the independent radiologist's assessment of when progression occurred.

There were several important problems with the case made:

- The manufacturer extrapolated observed trial data using an exponential functional form. While this is certainly a valid option to consider, other functional forms may arguably have provided a better fit to the data and the use of these increased the cost-effectiveness ratios.
- In general, because the model was based on a previous analysis, there were some difficulties in terms of transparency in the handling of data and thus this approach may have been unhelpful. For example, the manufacturer was unable to supply an economic model with discounted costs and benefits; while this is unlikely to make a major difference to the results this is a basic requirement of a submission as laid out in the SMC's guidance to manufacturers.
- The analysis used utility values from the trial and these indicated better quality of life for patients on trabectedin for stable disease than for PLD monotherapy on stable disease, despite the potentially increased side effect profile associated with the drug, and this may lack some face validity. The manufacturer was unable to offer any explanation for this and although the differences were small they appeared counter-intuitive. By contrast, the utility values from the NICE TAR on which the model was based assumed a common value across treatments for each disease state. The submission did not make any specific allowance for adverse events.
- The dose of PLD monotherapy used in the comparator arm of the trial was higher than the dose Scottish experts report is used in clinical practice (50mg/m^2 in the trial, 40mg/m^2 in practice). Experts report this is intended to reduce side-effects. The manufacturer selected this dose on the basis that it was the approved dose for monotherapy. The impact of this on the cost per QALY was unclear. This would increase the net cost of trabectedin because there are less savings on PLD and it would also reduce adverse events in the monotherapy arm. However, 40mg/m^2 may be less effective than 50mg/m^2 so the overall impact is uncertain.

Given these issues and the relatively high base case estimate of cost-effectiveness, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline number 75; Epithelial ovarian cancer; a national clinical guideline in October 2003. For relapsed disease they note:

- Chemotherapy for recurrent ovarian cancer should be regarded as palliative in intent and should be reserved for symptomatic recurrence of disease.
- Symptomatic platinum-sensitive cancer recurrence can be treated with further platinum and paclitaxel.

A consultation regarding updating the guideline is ongoing.

NICE issued technology appraisal guidance 91; Paclitaxel, pegylated liposomal doxorubicin hydrochloride and topotecan for second-line or subsequent treatment of advanced ovarian cancer (review) in May 2005. The following recommendations are made:

- Paclitaxel in combination with a platinum-based compound (carboplatin or cisplatin) is recommended as an option for the second-line (or subsequent) treatment of women with platinum-sensitive or partially platinum-sensitive advanced ovarian cancer, except in women who are allergic to platinum-based compounds.
- Single-agent paclitaxel is recommended as an option for the second-line (or subsequent) treatment of women with platinum-refractory or platinum-resistant advanced ovarian cancer, and for women who are allergic to platinum based compounds.
- Pegylated liposomal doxorubicin hydrochloride is recommended as an option for the second-line (or subsequent) treatment of women with partially platinum-sensitive, platinum-resistant or platinum-refractory advanced ovarian cancer, and for women who are allergic to platinum-based compounds.
- Topotecan is recommended as an option for second-line (or subsequent) treatment only for those women with platinum-refractory or platinum-resistant advanced ovarian cancer, or those who are allergic to platinum-based compounds, for whom PLDH and single-agent paclitaxel are considered inappropriate.
- Within these recommendations, the choice of treatment for second-line (or subsequent) chemotherapy should be made after discussion between the responsible clinician and the patient about the risks and benefits of the options.

Additional information: comparators

NICE recommend paclitaxel plus carboplatin or cisplatin, paclitaxel (weekly) monotherapy, PLD monotherapy and topotecan monotherapy in patients with relapsed platinum-sensitive or partially platinum-sensitive ovarian cancer.

Cost of relevant comparators

Drug	Dose Regimen	Cost per cycle (£)	Cost per 6 cycles (£)
trabectedin + pegylated liposomal doxorubicin (PLD)	**trabectedin 1.1 mg/m^2 iv PLD 30 mg/m^2 iv every 3 weeks**	**3,474**	**20,844**
pegylated liposomal doxorubicin monotherapy	PLD 50 mg/m^2 iv every 4 weeks	1,484	8,904
topotecan monotherapy	topotecan 1.5 mg/m^2 for 5 days iv every 3 weeks	1,453	8,718
paclitaxel + carboplatin	paclitaxel 175 mg/m^2 (over 3 hours) iv carboplatin area under curve (AUC) 5 iv every 3 weeks	881	5,286

paclitaxel + cisplatin	paclitaxel 175 mg/m^2 (over 3 hours) or 135mg/m^2 (over 24 hours) iv cisplatin 75mg/m^2 iv every 3 weeks	676 to 743	4,056 to 4,458
paclitaxel monotherapy	paclitaxel 175 mg/m^2 iv every 3 weeks	668	4,008

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 31 May 2010, MIMs (May 2010) and BNF edition 59 (March 2010). iv=intravenous
Costs based on a body surface area of 1.8m^2 and GFR of 105ml/min (for carboplatin) and do not include cost of pre-medications (e.g. corticosteroids, diphenhydramine), anti-emetics or colony stimulating factors.

Additional information: budget impact

The manufacturer's estimate of the net budget impact was £23k per year. This included administration costs; while these were similar per cycle, adding trabectedin was assumed to result in at least one more cycle of treatment, hence the medicines budget impact would be slightly lower. The manufacturer estimated that of around 90 partially platinum sensitive patients per year, 3 would currently receive PLD monotherapy, and only 2 of whom would receive concurrent trabectedin in future. SMC clinical experts have indicated that the eligible patient population would be significantly greater than the manufacturer's estimates.

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

Monk BJ, Herzog T, Kaye S et al. Trabectedin plus Pegylated Liposomal Doxorubicin in Recurrent Ovarian Cancer. Journal of Clinical Oncology 2010 published ahead of print on June 1 2010 as 10.1200/JCO.2009.45.4037.

The European Medicines Agency (EMA). European Public Assessment Report trabectedin (Yondelis®), 28th October 2009. EMEA/640507/2009 www.ema.europa.eu

Cannistra S. Evaluating new regimens in recurrent ovarian cancer: how much evidence is good enough?. Journal of Clinical Oncology. 2010: published ahead of print on June 1 2010 as 10.1200/JCO.2010.29.7077.

This assessment is based on data submitted by the applicant company up to and including 16 July 2010.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.