All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Docetaxel (Taxotere®) for locally advanced squamous cell carcinoma of the head and neck

Sanofi-Aventis

Advice No: 1008

Recommendation of AWMSG

Docetaxel (Taxotere®) is recommended for restricted use within NHS Wales in combination with cisplatin and 5-fluorouracil (5-FU) for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).

Docetaxel (Taxotere®) should be restricted for use as an induction treatment for patients of good performance status (0 or 1) anticipated to be receiving chemo-radiotherapy.

Docetaxel (Taxotere®) is not suitable for shared care within NHS Wales.

This report should be cited as:

1.0 RECOMMENDATION OF AWMSG

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Friday, 13th May 2008

The recommendation of AWMSG is:

Docetaxel (Taxotere®) is recommended for restricted use within NHS Wales in combination with cisplatin and 5-fluorouracil (5-FU) for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).

Docetaxel (Taxotere®) should be restricted for use as an induction treatment for patients of good performance status (0 or 1) anticipated to be receiving chemo-radiotherapy.

Docetaxel (Taxotere®) is not suitable for shared care within NHS Wales.

2.0 PRODUCT DETAILS:

2.1 Licensed indication:
Docetaxel (Taxotere®) in combination with cisplatin and 5-fluorouracil (5-FU) is indicated for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN)[1].

2.2 Dosing:
Dosing depends on whether the docetaxel regimen is being used as induction chemotherapy for subsequent radiotherapy (RT) or concurrent chemo-radiotherapy (CRT)[1]:

Induction chemotherapy followed by CRT
For the induction treatment of patients with locally advanced SCCHN, the recommended dose of docetaxel is 75 mg/m^2 as a 1 hour intravenous infusion on day 1, followed by cisplatin 100 mg/m^2 administered as a 30-minute to 3 hour infusion, followed by 5-FU 1,000 mg/m^2/day as a continuous infusion from day 1 to day 4. This regimen is administered every 3 weeks for 3 cycles.

Induction chemotherapy followed by RT
For the induction treatment of inoperable locally advanced SCCHN, the recommended dose of docetaxel is 75 mg/m^2 as a 1 hour infusion followed by cisplatin 75 mg/m^2 over 1 hour, on day one, followed by 5-FU as a continuous infusion at 750 mg/m^2 per day for five days. This regimen is administered every 3 weeks for 4 cycles.

2.3 Market authorisation date: Variation to licence application approved by EMEA 23rd November 2007[2]. This variation removed the word “inoperable” from the above licensed indication[3].

2.4 UK Launch date: Docetaxel was already marketed for other indications.

3.0 DECISION CONTEXT:

SCCHN includes: cancer of lip and oral cavity; oro-, naso- and hypo-pharyngeal cancer; laryngeal cancer; and cancer of paranasal sinus and nasal cavity. It is potentially curable when diagnosed at an early stage, but most patients present with advanced loco-regional disease, defined as either stage III or stage IV disease. Prognosis has remained poor for this group of patients. Between 50% and 60% will develop loco-regional recurrence within 2 years, and 20% to 30% will develop distant metastases[3]. The 5-year survival rate has been estimated as 40–67%, depending on site and stage of the cancer[4].

Currently, CRT is the standard treatment for locally-advanced SCCHN[4]. Induction therapy involves the use of chemotherapy before patients receive CRT (or RT), with the aim of shrinking the primary tumour and reducing the risk of development of distant metastases. Several induction chemotherapy trials have been conducted with different drugs and schedules, with mixed results. A meta-analysis showed a small survival benefit with cisplatin plus 5-FU (PF) induction chemotherapy, which has become *a* standard regimen for patients with locally advanced head and neck cancer[3]. However, a

recent SIGN guideline, which was issued before the results of docetaxel trials TAX 324 and TAX 323 were fully published, did not recommend the routine use of induction chemotherapy[5].

Docetaxel is a taxane antineoplastic agent, which is also licensed for the treatment of several other types of cancer. The company submission anticipates that docetaxel plus cisplatin and 5-FU (TPF) would become the standard induction therapy regimen if approved[2]. However, the extent to which patients in clinical practice would be suitable for induction therapy with TPF rather than PF is unclear; the TAX 324 and TAX 323 clinical trials involved relatively young patients with good performance status (PS), which may differ from many patients in clinical practice.

4.0 EXECUTIVE SUMMARY:

4.1 Review of the evidence on clinical effectiveness

The licensed indication for docetaxel in SCCHN is supported by two phase III trials (TAX 323 and TAX 324). TAX 324 would seem to provide the most relevant data as this assessed the use of the docetaxel-containing induction therapy regimen (TPF) prior to CRT, which is the standard treatment for locally advanced SCCHN. TPF induction therapy was associated with consistent and significant improvements in key outcomes of overall survival, progression free survival and response compared with the standard cisplatin and 5-FU (PF) induction therapy in the trial populations. Quality of life and function measures also favoured TPF in TAX 323. There were no new safety concerns with the docetaxel regimens evident from TAX 324 and TAX 323, but TPF induction therapy was associated with a higher incidence of haematological adverse events and febrile neutropenia compared with PF induction therapy, despite the use of prophylactic antibiotics.

4.2 Review of the evidence on cost-effectiveness

A cost utility analysis based on a Markov model was presented in the company submission. This compared TPF against PF as induction therapy prior to CRT. Patient-level efficacy and safety data from TAX 324 was used in the model, supplemented with quality of life data from TAX 323 and resource use estimates derived from a range of other sources.

The model was not provided by the company and the outputs cannot be verified. It is reported that the model predicts an incremental cost per quality adjusted life year (QALY) gained with TPF compared with PF of £1,832.

5.0 LIMITATIONS OF DECISION CONTEXT:

- Trials were conducted in relatively young patients with good PS (0 or 1). These patients may have a better prognosis and respond better to induction treatment than many patients seen in clinical practice.
- Patients included in the studies had good renal, hepatic and bone marrow functions. There is little information on the use of docetaxel in SCCHN patients with impaired renal, hepatic or bone marrow function, which may be a significant consideration in elderly patients.

- The licensed indications for docetaxel include its use as induction chemotherapy prior to CRT or RT. The economic model relates only to the use of docetaxel as induction chemotherapy prior to CRT.
- Information received from the Welsh consultants referred to in this report whilst useful, form part of the company submission and are not a result of the AWMSG process. The recommendation is based on medical expert opinion independently obtained by WMP.

6.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY:

6.1 Clinical efficacy:

The company submission describes two phase III studies of the addition of docetaxel to cisplatin + 5-FU as induction treatment followed by RT (TAX 323) and CRT (TAX 324)[2]. TAX 323 was the phase III study used to support the first licensed indication for docetaxel for the treatment of SCCHN. This study included only patients with locally advanced, unresectable cancer, and the original licensed indication was for the treatment of inoperable locally advanced SCCHN. TAX 324 was conducted in patients with inoperable SCCHN (on the basis that their tumour was technically unresectable, or had a low probability of surgical cure or in who the tumour could be resected but organ preservation was an aim) and was used to broaden the licensed indication in SCCHN, which is now for the treatment of locally advanced SCCHN (the word inoperable has been removed)[3].

6.1.1 TAX 324 study: induction chemotherapy prior to CRT[3,6]

This was an open-label, phase III trial in 501 adult patients with stage III or IV SCCHN and PS 0 or 1. Patients were randomised (1:1) to receive a maximum of three 3-week cycles of induction therapy as below:

Docetaxel arm (TPF): docetaxel 75 mg/m^2 as a 1-hour IV infusion on day 1, followed by cisplatin 100 mg/m^2 administered as a 30-minute to 3-hour infusion on day 1, followed by 5-FU 1000 mg/m^2/day as a continuous infusion from day 1 to day 4. In addition, these patients received prophylactic ciprofloxacin 500mg twice a day for 10 days starting on day 5 of each cycle, to cover neutrophil nadir and reduce the rates of neutropenic sepsis, plus dexamethasone 16 mg/day in divided doses for 3 days starting 1 day prior to docetaxel administration, to prevent hypersensitivity reactions and reduce or delay fluid retention[2,3].

Control arm (PF): cisplatin 100mg/m^2 as IV infusion over 30-minutes to 3-hours, followed by 5-FU 1000mg/m^2 per day by continuous 24-hour IV infusion for 5 days[3].

All patients in both arms received prophylactic anti-emetic agents (e.g. ondansetron or granisetron) before and after cisplatin administration.

All patients who did not experience disease progression then began CRT within 3–8 weeks of the start of the last cycle of induction therapy. Carboplatin was given weekly (dose was calculated by the area under the curve (AUC) estimate of Calvert formula, and for the first dose the AUC was 1.5) as a 1-hour infusion for a maximum of 7 doses during RT. The RT dose to the site of the tumour was 70–74 Gray, given in 2 Gray/day fractions continuously 5 days/week for a maximum of 12 weeks[2].

The primary endpoint was overall survival (OS), measured from the date of randomisation to the date of death in the intention to treat population. Secondary endpoints were progression-free survival (PFS), time to treatment failure (TTF) and overall response rate (ORR), which comprised complete response (CR) plus partial response (PR). Other categories of response were no change (NC) and progressive disease (PD) (see Appendix 1, Table 1A for definitions). In addition, quality of life and function was assessed, along with pain intensity and analgesic consumption.

Results for the primary efficacy analysis of TAX 324

The patients were followed until death or study completion, up to 2 years after the randomisation of the last patient. Median follow-up achieved was 42 months. 5.9% of the TPF and 5.7% of the PF groups had been lost to follow up.

Table 1. OS in TAX 324[3]

	TPF (n=255)	**PF (n=246)**
Median OS (months) in ITT population		
	70.6 (95 %CI 49.0 to NA)	30.1 (95% CI 20.9 to 51.5)
	HR 0.70 (95% CI 0.54 to 0.90), p=0.0058	
OS rates		
1-year	80.0% (95% CI 75.0 to 84.9)	69.9% (64.1 to 75.7)
2-year	67.3% (95% CI 61.5 to 73.2)	54.5% (95% CI 48.2 to 60.8)
3-year	62.1% (95% CI 55.9 to 68.2)	48.1% (95% CI 41.7 to 54.5)

At the cut off point, 40.8% of the TPF group and 52.8% of the PF group had died.
In the whole ITT population, median OS was significantly longer with TPF than with PF, (see Table 1). Among patients with resectable tumours who were candidates for organ preservation, median OS was not reached in the TPF group, but in the PF group median OS was 42 months (hazard ratio [HR] 0.52, 95% CI, 0.32 to 0.84, p=0.007)[3]. In patients with unresectable tumours, median survival was longer in the TPF group than the PF group (41 months versus 21) but this was not statistically significantly different (HR 0.68, 95% CI 0.45 to 1.01, p=0.06). There was no significant difference in median OS when analysed by tumour site, but the median OS in patients with oropharyngeal cancer had not been reached in either group[6].

Results for secondary efficacy analyses of TAX 324

PFS was significantly longer in the TPF group than in the PF group (35.5 months versus 13.1 months, HR 0.71, 95% CI 0.56 to 0.90, p=0.004). Median TTP was also longer in the TPF group (20.5 months versus 10.8 months, HR=0.74, 95% CI 0.59 to 0.93, p=0.0102). There was no significant difference between treatment groups for the endpoints of ORR (CR + PR) or CR when measured either at the end of induction therapy and/or at the end of CRT.

Quality of life assessment using Functional Assessment of Cancer Therapy Head and Neck (FACT-HN) tool showed no difference between groups. The Performance Status Scale for Head and Neck (PSS-HN) scale was only sufficiently completed during the induction therapy phase of treatment, and this also indicated no significant differences between treatment groups in subscales of “eating in public”, “normalcy of diet” or “understandability of speech” when scores were adjusted for multiple testing. Completion of the pain intensity rating scale was also low during follow up, and results available for

the induction therapy phase indicate no significant difference between treatment groups. Analgesic consumption fluctuated during the course of treatment but was similar in both treatment groups[3].

6.1.2 Supporting studies

6.1.2.1 TAX 323 study: induction chemotherapy prior to RT[7,8]

This was an open-label, phase III trial in 358 adult patients with stage III or IV SCCHN and PS 0 or 1. Patients were randomised (1:1) to receive a maximum of four 3-week cycles of induction therapy as below:

Docetaxel arm (TPF): docetaxel 75 mg/m^2 as a 1-hour IV infusion on day 1, followed by cisplatin 75 mg/m^2 administered as 1-hour infusion on day 1, followed by 5-FU 750 mg/m^2/day as a continuous infusion from day 1 to day 5. In addition, these patients received prophylactic ciprofloxacin 500mg twice a day for 10 days starting on day 5 of each cycle, plus dexamethasone 16 mg/day in divided doses for 3 days starting 1 day prior to docetaxel administration during each cycle.

Control arm (PF): cisplatin 100mg/m^2 as IV infusion over 1 hour on day 1, followed by 5-FU 1000mg/m^2 per day by continuous 24-hour IV infusion on days 1 to 5.

All patients in both arms received prophylactic anti-emetic agents (e.g. ondansetron or granisetron) before and after cisplatin administration[8].

All patients who did not experience disease progression then began RT within 4–7 weeks of completion of induction therapy. The RT dose to the site of the tumour was 66–74 Gray, depending on whether it was given as a conventional fractionated or as an accelerated/hyperfractionated regimen. RT was delivered on 5 days per week for 7 weeks. Neck dissection was considered for all patients before radiotherapy and 3 months after the completion of radiotherapy[8].

The primary endpoint was PFS, calculated from the point of randomisation to progression, relapse, or death, whichever occurred first, in the ITT population[7]. Secondary endpoints included OS, ORR, and duration of overall response. In addition, quality of life and function, along with pain intensity were assessed[2].

Results for the primary efficacy analysis of TAX 323

The patients were followed until death or study completion up to 12 months after the recruitment period. Median follow-up achieved was 33.7 months, and at the cut off date, 61.0% and 71.3% in the TPF and PF treatment groups, respectively, had died. The proportion of patients lost to follow-up was similar in the 2 treatment groups (3.9% overall)[8].

The primary efficacy analysis was the comparison of the PFS in the ITT population based on a Cox proportional hazards model. TPF induction treatment was associated with a 30% reduction in risk of progression and death compared with PF treatment (HR 0.70, 95% CI 0.55 to 0.89, p=0.0042). Median PFS was significantly longer with TPF than PF (11.4 months versus 8.3 months; p=0.0073). This represented a 28% reduction in the risk of progression (HR 0.72, 95% CI 0.57 to 0.92). The results on the primary endpoint were similar whether non-tumour related deaths or further therapies were used as the censoring event[8].

Results for secondary efficacy analyses of TAX 323
All secondary endpoint results consistently favoured TPF over PF treatment.

OS was regarded as the main secondary endpoint. Median time to death was significantly longer in the TPF treatment group than in the PF treatment group (18.6 months versus 14.5 months, HR 0.72, 95% CI 0.56 to 0.93, p=0.0128). Survival rates at 3 years were estimated as 37.9% for TPF and 26.3% for PF.

ORR (CR + PR) was significantly improved with TPF compared with PF treatment, both after the induction chemotherapy phase (67.8% versus 53.6%, p=0.006) and after RT (72.3% versus 58.6%, p=0.006). CR was only significantly different between groups after RT (33.3% versus 19.9%, p=0.004). Surgery (neck dissection) was undertaken more frequently in the TPF group than the PF group (25.9% versus 14.9%) but had little influence on the response rates obtained. Median duration of overall response was higher in the TPF treatment group than in the PF treatment group (15.7 months versus 11.7 months, HR 0.72, 95% CI 0.52 to 0.99, p=0.0457)[8].

The results of quality of life assessments (using QLQ C-30 self administered questionnaire, a cancer-specific quality of life instrument) and function (measured using PSS-HN) were consistently in favour of TPF. However, pain intensity measures were comparable between both treatment groups[2]. No analgesic consumption data are provided.

Points to note from TAX 324 and TAX 323

- In TAX 324, 80.5% of those who started induction therapy with TPF and 75.7% of those who started induction therapy with PF went on to start CRT[3]. In TAX 323, 74.7% and 68.5%, respectively, went on to start RT[8].
- TAX 324 was used to support the broader licensed indication for docetaxel (removal of the word “inoperable” from the licensed indication). All patients in this trial had inoperable cancer, and in around two-thirds of cases the cancer was inoperable due to being technically unresectable or unlikely to result in surgical cure. The remaining one-third of cases had resectable tumours but opted for organ preservation as they did not want to lose their voice [8].
- In TAX 324, carboplatin at a weekly dose calculated by the AUC estimate of Calvert formula was used alongside RT. A recent guideline from the Scottish Intercollegiate Guidelines Network (SIGN) recommends cisplatin as the agent of choice in concurrent CRT[5], and the EPAR for Taxotere® considers that the CRT regimen in TAX 324 was suboptimal, stating that more intensive chemotherapy is usually used for a CRT-based regimen (e.g. cisplatin 100 mg/m^2)[3].
- Treatment with TPF was associated with fewer deaths within 30 days of study treatment and fewer deaths due to infections compared to treatment with PF. The routine antibiotic prophylaxis in the TPF group may account for this difference[3,8].
- In contrast to TAX 324, TAX 323 demonstrated significant improvements in quality of life and function with TPF compared with PF treatment. This may be due to the degree of completion of the assessment tools, which appeared higher at the end of TAX 323 than at the end of TAX 324.
- OS rates, median OS, PFS rates, median PFS, and ORR were all greater in both treatment arms of TAX 324 than in TAX 323[3,8].

6.2 Safety[3,6,7]:

There were no new safety concerns with the docetaxel regimens evident from TAX 324 and TAX 323. The adverse event profiles were similar in the two trials and, as TAX 324 is considered the main study, only safety data related to TAX 324 are discussed here.

Almost all patients experienced at least one treatment-emergent adverse event (TEAE) during the induction chemotherapy phase. The TPF and PF treatment groups were similar for most TEAEs related to study treatment (all grades), the most frequent being nausea (75.7% versus 78.2%), alopecia (67.7% versus 43.2%), stomatitis (64.5% versus 67.1%), lethargy (58.6% versus 51.0%), and vomiting (56.2% versus 60.9%).

Grade 3 or 4 TEAEs were generally similar between groups. Diarrhoea (6.8% versus 3.3%) and esophagitis/dysphagia/odynophagia (12.0% versus 7.4%) occurred more frequently in the TPF group, and stomatitis (20.7% versus 27.2%) and lethargy (4.0% versus 9.9%) were more frequent in the PF group.

Grade 3 or 4 neutropenia was more frequent in the TPF group than in the PF group (83.5% versus 56.0%). Despite the fact that 97.2% of patients in the TPF group received prophylactic antibiotics compared with 28.0% in the PF group, the incidence of febrile neutropenia (12.1% versus 6.6%) and neutropenic infection (11.7% versus 8.3%) was greater in the TPF group than the PF group. One patient in the TPF treatment group and one in the PF treatment group died due to neutropenic infection. Other Grade 3 or 4 haematological effects that occurred more frequently with TPF than PF treatment were anaemia (12.4% versus 9.5%) and leucopenia (54.2% versus 23.5%).

Serious adverse events related to treatment occurred in 36.7% of patients in the TPF group and 29.6% in the PF group during induction chemotherapy. The most frequent were fever in the absence of infection (15.1% versus 8.6%), granulocytes (6.8% versus 2.1%), stomatitis (6.0% versus 8.6%), and vomiting (5.6% versus 4.5%).

During CRT, serious adverse events occurred in 12.4% of patients in the TPF group and 16.8% in the PF group. Stomatitis occurred in 3.0% of the TPF group and 6.0% of the PF group, and esophagitis/dysphagia/odynophagia in 2.0% and 5.4%, respectively.

There were fewer patients with one or more cycle delays in the TPF group than the PF group (29.1% versus 64.6%). Haematological toxicity was the most common cause of this in the PF treatment group (44.4%, compared to 4.4% in the TPF group). Dose reduction occurred at least once in 21.9% of patients in the TPF group and 25.9% of patients in the PF group, mainly due to non-hematological toxicities (14.7% versus 19.8%). Discontinuation of study treatment due to adverse events occurred in 10.2% of TPF patients and in 8.5% of PF patients. Deaths within 30 days of last study treatment from non-malignant cause (i.e., due to “toxicity” or “other”) were more frequent in the PF treatment group (4.9%) than in the TPF treatment group (1.6%).

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES:

7.1 Comparator medications:
When induction therapy is used, a regimen of cisplatin and 5-FU (PF) is usually employed[3].

7.2 Comparative effectiveness issues:
In newly diagnosed SCCHN patients with locally advanced and unresectable disease, or those where organ preservation is being pursued, CRT is usually preferred over RT alone[5]. TAX 324 may therefore be more relevant to clinical practice than TAX 323. However, the patient populations in TAX 324 and TAX 323 were relatively young (median age 56 years and 53 years in TAX 324 and TAX 323, respectively). Data from other studies indicate that the relative reduction in risk of death is age dependent; it is greatest in patients under 60 years and lowest in those aged over 70 years[5]. The patients in these trials therefore may have had a better prognosis than many patients seen in clinical practice. Furthermore, the majority of patients (53.5% and 50.6%) had a PS of 0[3,8]. These patients may have a better prognosis and respond better to induction treatment than many patients seen in clinical practice.

The use of induction chemotherapy prior to CRT (or RT) has been described as controversial[3]. Several induction chemotherapy trials have been conducted with different drugs and schedules, with mixed results. A meta-analysis showed a small survival benefit with PF induction chemotherapy, which has become *a* standard regimen for patients with locally advanced head and neck cancer[3]. However, a recent SIGN guideline, which was issued before the results of TAX 324 and TAX 323 were fully published, did not recommend the *routine* use of induction chemotherapy[5].

TPF induction therapy was associated with consistent improvements in key outcomes of OS, PFS and response compared with PF induction therapy in the trial populations. Quality of life and function measures also favoured TPF in TAX 323, but not in TAX 324 (although this may be due to lower completion of assessment tools in TAX 324). There were no new safety concerns with the docetaxel regimens evident from TAX 324 and TAX 323, but TPF induction therapy was associated with a higher incidence of febrile neutropenia compared with PF induction therapy, despite the significantly greater use of prophylactic antibiotics. This is a potentially life threatening complication that requires isolation in hospital.

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE:

8.1 Overview of the key economic issues for AWMSG to consider
The key economic issue for AWMSG to consider is whether any additional benefits offered by the use of docetaxel in addition to cisplatin and 5-FU justify any associated increase in costs over the use of cisplatin and 5-FU alone when used as induction chemotherapy in patients with locally advanced SCCHN.

8.2 Review of published evidence on cost-effectiveness
Standard literature searches conducted by WMP have not identified any relevant published evidence on the cost-effectiveness of docetaxel in the treatment of SCCHN.

8.3 Review of the company's submission on cost-effectiveness

8.3.1 Description and critique of the company's submission

The company's submission describes a cost-utility analysis of TPF compared with PF induction therapy prior to CRT in patients with locally advanced SCCHN. A Markov model has been constructed based on four health states: stable state; response state (combines CR and PR); progressive state; and death. All patients are assumed to start in the stable state where they are permitted to remain or transition directly to the response or progressive state (but not death). Patients in the response state may remain there or transit to progressive state (but not death). Those who transit to the progressive state may remain there or transit to the state of death[2].

A 3-step pathway is assumed in the model and a Markov cycle length of 3 weeks has been used to coincide with the induction chemotherapy cycle length. At the start, a patient in the model receives three cycles of chemotherapy at three week intervals (Step 1). If a patient moves to either "response" or remains in "stable" state, CRT is given (Step 2), whereas if a patient moves to the "progressive" state, then surgery is performed. A patient, who receives CRT during Step 2 and remains in the "stable" state or moves to the "progressive" state, undergoes surgery (Step 3). A patient who receives CRT during Step 2 and moves to "response" state does not receive any further treatment. A patient in the "progressive" state who received surgery in Step 2 receives RT in Step 3. After the three treatment steps, a patient is followed until death. All patients in the stable and progressive states receive palliative chemotherapy in the long term[2].

Patient-level data from TAX 324 has been used to derive the transition probabilities, and additional analyses of the TAX 324 data have been conducted to determine the proportion of patients in each health state at the end of the induction chemotherapy phase, CRT, surgery and follow up[2].

There are some limitations with the model in terms of the extent of incorporation of adverse events and the associated disutility and costs. The model has not been provided, so the outputs cannot be verified.

8.3.2 Population

The phase III trial TAX 324 has been used to provide patient-level data for the model[3,6]. Patients in TAX 324 meet the licensed indication for docetaxel in SCCHN and the company submission states that Welsh oncologists have verified that these patients are representative of Welsh patients[2]. However, patients in TAX 324 were relatively young, and had good performance status. These factors may mean that these patients had a better prognosis and potential to benefit from induction chemotherapy than many patients seen in clinical practice (see section 7.2).

8.3.3 Perspective and time horizon

The model considers direct health-related costs from the perspective of NHS Wales. A lifetime time horizon (30 years) is used in the base case analysis[2].

8.3.4 Comparator

The cisplatin and 5-FU (PF) regimen is an appropriate comparator in this setting (see section 7).

8.3.5 Clinical inputs

8.3.5.1 Efficacy data

Patient level data from TAX 324 was used to derive transition probabilities between the four health states. The data had to be adjusted to account for the 3-week cycle length. In addition, in TAX 324 patients could have died at any time point, whereas the model only allows patients in the progressive state to die. Therefore, the clinical trial data was reportedly adjusted by adding the proportion of patients who moved directly from a stable or response state to death to those patients who moved to a progressive state[2].

The transition probabilities are provided, but it is not possible to verify these from the data available. Within each treatment arm, it would appear that the transition probabilities have been assumed to be the same for those who received CRT during Step 2 and those who received Surgery during Step 2. Given that those who received surgery during Step 2 had experienced progression, whereas those who received CRT had remained stable or had responded to induction chemotherapy, it is uncertain how reliable this assumption would be. Similarly, in Step 3, the transition probabilities are assumed to be the same irrespective of whether patients received surgery following CRT or RT following surgery[2].

8.3.5.2 Adverse events

The model only includes those adverse events that are considered to be cost-drivers (see 8.3.6.2). Welsh consultants agreed which adverse events would be appropriate to include in the model. Adverse event rates were reportedly adjusted to account for the cycle length, and were applied to the proportion of patients receiving induction chemotherapy and CRT during a particular Markov cycle. The adverse event rates were assumed to remain the same during any cycle (i.e. no change in rates over time and no impact on disease progression and survival)[2]. It is unclear how reliable this approach is, as adverse events can lead to delays in treatment cycles and dose reductions (see section 6.2).

Only costs are included in the model, as it is assumed that any disutility associated with adverse events is accounted for in the global quality of life assessments that were used to derive utility scores[2] (see 8.3.5.3).

8.3.5.3 Utility weights

TAX 324 and TAX 323 assessed quality of life in patients using self administered questionnaires. However, in TAX 324 the completion of the questionnaires was low during the study and the company submission considers that the data derived in this study are not robust. In TAX 323, completion of the questionnaire (QLQ-C30) was more complete and the results from this study have been used to derive utility weights for patients receiving TPF and PF.

There are some differences in the TAX 323 and TAX 324 studies that may impact on the quality of life scores and utility achieved. The TAX 323 study used lower doses of cisplatin and 5-FU in the TPF arm than in TAX 324, and the patients received four cycles of induction chemotherapy rather than three. This may have had an impact on patients' experiences of treatment, and the side effects they experienced with the TPF treatment regimen relative to the PF regimen. As global quality of life has been used to derive utility values (i.e. specific utility decrements are not applied to the adverse events included in the model), this is a potentially important consideration. The side effect profiles were similar in TAX 323 and Tax 324 (see 6.2 above), but the actual incidence of important adverse events differed. For example, in TAX 324 the incidence of grade 3 or 4 neutropenia during induction chemotherapy was 83.5% for TPF and 56.0% for PF, compared with 76.9% and 52.5%, respectively, in TAX 323. The incidence rates

of febrile neutropenia also differed (12.1% versus 6.6% in TAX 324; 5.2% versus 2.8% in TAX 323)[3,6,7]. In addition, following induction chemotherapy, patients in TAX 323 were intended to receive RT alone, whereas patients in TAX 324 were to receive RT plus carboplatin (CRT). Patients' experiences during this phase of treatment may also have differed between the two studies.

The QLQ-C30 global health scores from TAX 323 have been mapped to EQ-5D index scores. This was done on the basis that a published study conducted in patients with liver metastases found the responsiveness of EQ-5D index to be equal to QLQ-C30 global health scores[9]. The EQ-5D and QLQ-C30 scores from patients with liver metastases were assessed at baseline, 0.5 months, 3 months and 6 months following liver surgery in the published study. For the company submission, these have been mapped and a regression equation derived. The QLQ-C30 scores from TAX 323 have then been inputted to the regression equation to derive the associated EQ-5D-derived utility scores for patients in stable, response and progressive states.

8.3.6 Healthcare resource utilisation and cost

Health care resource use was not collected in TAX 324. Several sources have been used to derive the associated resource use including: a cost-effectiveness analysis of photodynamic therapy compared with palliative surgery and chemotherapy in head and neck cancer that was published in 2004[10]; the NICE clinical cancer services guidance on head and neck cancer issued in 2004[11]; a health technology assessment (HTA) of treatment for ovarian cancer published in 2006[12]; and the opinions of three English consultants experienced in the management of SCCHN and a clinical pharmacist[2]. Unit costs have been applied to the items of resource use using standard published sources where available, and the total costs of the three Steps of the treatment pathway that are modelled have been estimated. It is not specifically stated that all costs have been inflated to current prices, and it seems that some of the adverse event costs assumed in the model are at 2006 prices.

8.3.6.1 Drug costs

TPF and PF drug acquisition costs are based on the doses used in TAX 324. The TPF arm also received prophylactic antibiotics, which are costed in the model. A body surface area of 1.75m^2 has been assumed and drug costs calculated based on prices in the Monthly Index of Medical Specialities and British National Formulary. Dose reductions or treatment delays appear not to have been considered in the model. It is assumed that vial wastage is minimal. Anti-emetic treatment costs are not included as these agents were received by both treatment groups and are assumed to cancel each other out.

8.3.6.2 CRT, RT and surgery costs

The costs of radiation therapy are derived from a published paper that provided cost estimates in 1989. The company submission assumes the lowest cost per fraction estimated in this paper (£22.21 in 1989 prices) for the base case analysis, yet the published paper indicates that cost per fraction has been estimated between £22.21 and £38.46 (in 1989 prices)[13]. A supplementary sensitivity analysis has been performed using the higher cost.

8.3.6.3 Long-term costs

It was assumed that almost all patients in the stable and progressive states would receive palliative chemotherapy in the long term. Other costs include clinical nurse specialists, dietitians, language and speech therapists.

8.3.6.4 Adverse events

Only those adverse events that are considered cost-drivers are included in the model. These included the costs of grade 3 or 4 neutropenia, febrile neutropenia, diarrhoea, stomatitis, anaemia, nausea, thrombocytopenia and fever in the absence of infection. The source of the costings for these adverse events (with exception of febrile neutropenia) is reported to be the HTA in ovarian cancer [Main et al. 2006]. The incidence of these adverse events in TAX 324 was greater in the TPF group than in the PF group (see section 6.2). It is not possible to verify the probabilities of these events that have been used in the model.

8.3.7 Discounting

All costs and outcomes were discounted at 3.5% in the base case analysis, which is the preferred discount rate. Sensitivity analysis explores discount rates of 0% and 6%[2].

8.3.8 Results

8.3.8.1 Base case analysis:

The model predicts the incremental cost per quality adjusted life year (QALY) gained with TPF compared with PF to be £1832. This is based on an incremental cost of £3824 and a gain of 2.08 QALYs.

8.3.9 Sensitivity analysis

8.3.9.1 One-way (univariate) sensitivity analyses

Various scenarios have been tested in one-way sensitivity analyses, including: varying the discount rates between 0% and 6%; varying the assumed cost of the treatment of febrile neutropenia between £2000 and £5000; and adjusting the time horizon from life time (30 years) to 10 years and 5 years. The model was sensitive only to the time horizon, which increased the incremental cost per QALY gained to £2,760 and £5,332 for a 10-year and 5-year time horizon, respectively.

8.3.9.2 Multivariate sensitivity analysis

A scenario was modelled to represent an increase in the number of complications. Increasing the number of blood and biochemistry tests used during induction chemotherapy, RT and surgery, and increasing the number of days in hospital due to complications had little effect on the model outputs. This scenario analysis is of limited informative value as it does not consider potential changes in other resource use associated with treating the complications, and it does not consider any impact on the QALYs gained.

8.3.9.3 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was conducted, which is reported to have involved running 1,000 simulations using different input values in the range of 2.5th and 97.5th percentile of the lifetime outcomes and costs. Further details are not provided but this analysis indicates that there is a 95% probability that the docetaxel-based induction therapy regimen is cost effective compared to standard induction therapy at a willingness to pay of £20,000/QALY.

8.4 Review of evidence on budget impact:

8.4.1 Description and critique of the company's submission

The company's submission states that the budget impact analysis considers the use of the docetaxel-based induction therapy regimen in patients with SCCHN. The submission states that Welsh consultants have confirmed that in routine care, locally advanced SCCHN patients who are fit enough for chemotherapy are likely to be treated with induction chemotherapy followed

by CRT. However, it appears from the data provided by the three Welsh consultants that the number of patients expected to be eligible for treatment with TPF is composed of those who receive PF induction therapy followed by CRT or RT.

The EPAR for Taxotere® suggests that SCHNN includes cancer of lip and oral cavity; oro-, naso- and hypo-pharyngeal cancer; laryngeal cancer; and cancer of paranasal sinus and nasal cavity[3]. However, the company submission excludes cancer of the nasopharynx, lip and salivary glands[2].

8.4.2 Perspective and time horizon

The perspective adopted by the budget impact analysis is that of NHS Wales, with a five-year time horizon.

8.4.3 Data sources

8.4.3.1 Incident cases

Welsh Cancer Intelligence and Surveillance Unit data[14] suggests that the incidence of head and neck cancers over the period 2001 to 2005 has remained relatively stable. It is therefore assumed that the incidence of SCCHN over the next five years will remain relatively stable.

Excluding cancer of the nasopharynx, lip and salivary glands, the company submission states the average incidence (over the last five years) of head and neck cancer is 351 patients in Wales. The company submission states that 10% of these are adenocarcinomas and the remainder are squamous cell carcinomas. Therefore 90% of the 351 cases of head and neck cancer (316 cases) are estimated to be SCCHN. Three Welsh consultants are reported to have estimated that around 50% of these 316 patients (158 patients) would have locally advanced disease (Stage III or IV) and be eligible for treatment. Collectively, these consultants estimate that around 14% of these patients currently receive PF induction chemotherapy followed by CRT or RT in clinical practice, which equates to 22 patients per year in Wales[2]. It should be noted that other published reviews estimate that between a quarter and a third of chemotherapy-treated locally advanced SCCHN patients receive induction therapy in the UK[4]. However, the extent to which these patients would be suitable for induction therapy with TPF rather than PF is unclear; the TAX 324 and 323 clinical trials involved relatively young patients with good PS, which may differ from many patients in clinical practice.

The budget impact analysis does not suggest that there will be an increase in the overall number of patients eligible for treatment as a result of the introduction of docetaxel in this indication.

8.4.3.2 Prevalent cases

As induction therapy is given for less than a year, it is assumed that 22 patients each year receive induction therapy. See section 8.4.3.1.

8.4.3.3 Rates of adoption

The company submission anticipates that the uptake of TPF will be 75% in 2008, 80% in 2009 and 85% thereafter to 2012. This would be equivalent to 17 patients receiving TPF in 2008, 18 patients in 2009 and 19 patients in each subsequent year.

8.4.3.4 Costs and resource use

TPF induction therapy is given for three cycles. The model considers the costs of TPF and PF as calculated per cycle of treatment for the cost-utility mode (£1276 and £205, respectively).

The doses of TPF and PF are those used in TAX 324 and an average patient's body surface area is assumed to be 1.75m^2. The TPF regimen includes the cost of prophylactic antibiotics and dexamethasone. These costs relate only to the costs of the induction therapy and no other costs or resource use are considered.

8.4.4 Results

Based on the above assumptions of patient number and anticipated uptake, the net resource impact of the introduction of docetaxel to the induction treatment regimen is estimated as £52,193 in 2008, £55,673 in 2009, and £59,152 in each of the subsequent years to 2012.

8.4.5 Sensitivity analysis

No sensitivity analyses have been conducted.

9.0 ADDITIONAL INFORMATION:

9.1 Guidance and audit requirements:

- Docetaxel would not be suitable for a shared-care agreement. Treatment, monitoring and supervision should be retained under specialist care.

9.2 Related guidance:

- The Scottish Intercollegiate Guidelines Network issued guidance on the diagnosis and treatment of cancer of the head and neck in November 2006. This stated that neoadjuvant (induction) chemotherapy was not routinely recommended in oral, laryngeal and oropharyngeal cancer. This guideline was issued before the results of TAX 323 and TAX 324 were fully published[5].

9.3 Previous AWMSG/NICE advice:

- The then National Institute for Clinical Excellence (NICE) issued cancer services guidance for head and neck cancer in November 2004. This made recommendations on the provision of cancer services and briefly reviewed the evidence that was available at that time[11].

9.4 Ongoing studies

There are no additional study data anticipated in the next 6–12 months[2].

9.5 Patient Interest Group information

A patient interest group submission by The Rarer Cancers Forum was provided to AWMSG members.

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Appendix 1. Additional Clinical Information

Table 1A. Definitions of response categories in TAX 234[2]

Complete Response (CR):	Disappearance of all known disease.
Partial Response (PR):	In case of bidimensionally measurable disease, decrease by at least 50% of the sum of the products of the largest perpendicular diameters of all measurable lesions. For unidimensionally measurable disease, decrease by at least 50% in the sum of the largest diameters of all lesions. It was not necessary for all lesions to have regressed to qualify for PR, but no lesion should have progressed and no new lesion should have appeared. Serial evidence of appreciable change documented by radiography or photography was to be obtained and was to be available for subsequent review. The assessment was to be objective.
No change (NC):	For bidimensionally measurable disease, <50% decrease and <25% increase in the sum of the products of the largest perpendicular diameters of all measurable lesions observed at least 6 weeks after start of treatment. For unidimensionally measurable disease, <50% decrease and <25% increase in the sum of the diameter of all lesions observed at least 6 weeks after start of treatment. No new lesions should have appeared.
Progressive disease (PD):	>25% increase in the size of at least 1 bidimensionally or unidimensionally measurable lesion (in comparison with the measurements at nadir) or appearance of a new lesion. The occurrence of pleural effusion or ascites was also considered as PD if this was substantiated by positive cytology. Pathological fracture or collapse of bone were not necessarily evidence of disease progression. Patients could be assigned to the progression category 6 weeks after entering the study. If progression was observed before this, the patient was considered to have "early progression."