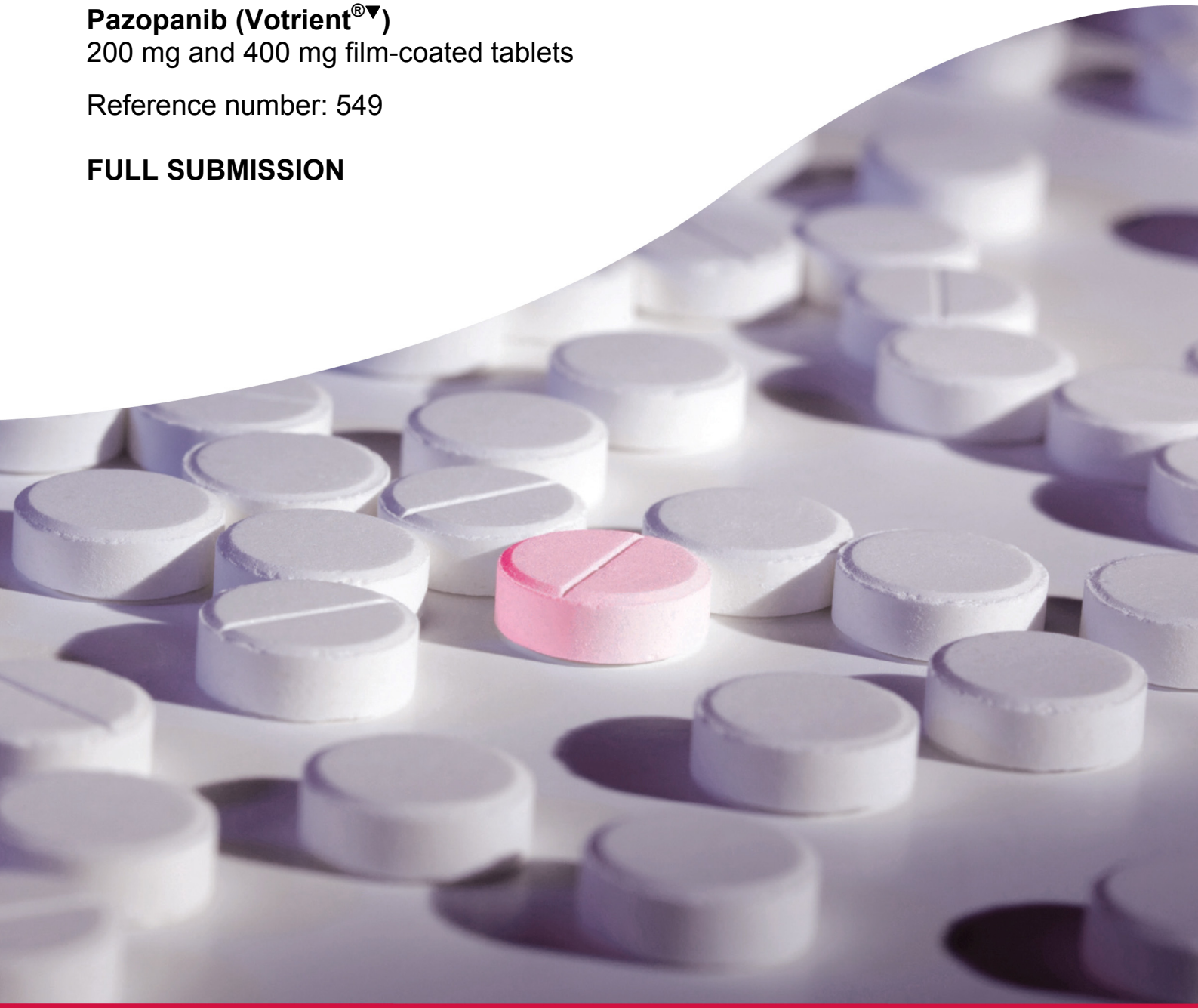
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Pazopanib (Votrient®▼)
200 mg and 400 mg film-coated tablets

Reference number: 549

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Pazopanib (Votrient®▼) 200 mg and 400 mg film-coated tablets

This assessment report is based on evidence submitted by GlaxoSmithKline on 24 October 2012[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Pazopanib (Votrient®▼) is indicated for the treatment of adult patients with selective subtypes of advanced soft tissue sarcoma (STS) who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo) adjuvant therapy. Efficacy and safety has only been established in certain STS histological tumour subtypes (see Section 5.1 of the Summary of Product Characteristics [SPC] for further information on specific tumour subtypes).
Dosing	The recommended dose of pazopanib is 800 mg once daily, taken without food, at least one hour before or two hours after a meal. Treatment should only be initiated by a physician experienced in the administration of anti-cancer agents. See SPC for further details[2].
Marketing authorisation date	3 August 2012[3] (licensed for renal cell carcinoma on 14 June 2010[2]).

2.0 DECISION CONTEXT

2.1 Background

Soft tissue sarcomas (STSs) are a heterogenous group of rare connective tissue cancers and represent less than 1% of all adult cancers[4]. The first line management of localised STS is usually surgery and for patients with locally advanced (unresectable) and metastatic STS conventional cytotoxic chemotherapy is widely used[5]. Metastatic disease occurs in 40–50% of STS patients and the median survival period from detection of metastasis is approximately 12 months[6].

According to British Sarcoma Group (BSG) guidelines anthracycline chemotherapy using doxorubicin[7] is the standard first line treatment for advanced STS. Ifosfamide is recommended for first line treatment if anthracyclines are contraindicated and is also an option for second line therapy. Additional second line medications include dacarbazine, trabectedin and gemcitabine/docetaxel[4].

Pazopanib is an orally administered multi-tyrosine kinase inhibitor of vascular endothelial growth factor receptors, platelet derived growth factor receptors and stem cell factor receptors[2]. The company estimate that based on Welsh Government statistics approximately 38 patients per year develop advanced STS and that 12 patients would be eligible for pazopanib treatment[1].

The company submission includes evidence for the use of pazopanib in adult patients with selective subtypes of advanced STS who have received prior anthracycline-based

chemotherapy for metastatic disease or who have progressed within 12 months after (neo) adjuvant therapy.

2.2 Comparators

The comparators requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) were trabectedin, ifosfamide, gemcitabine/docetaxel and best supportive care (BSC).

2.3 Guidance and related advice

- British Sarcoma Group (BSG). Grimer R, Judson I, Peake D and Seddon B. Guidelines for the Management of Soft Tissue Sarcomas. Sarcoma (2010)[4].
- National Institute for Health and Clinical Excellence (NICE). Technology appraisal 185. Trabectedin for the treatment of advanced soft tissue sarcoma (2010)[8].
- NICE. Guidance on Cancer Services: Improving Outcomes for People with Sarcoma – the Manual (2006)[9]

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission includes a phase III, randomised controlled trial (RCT) of pazopanib in patients with STS (PALETTE [VEG11027] study)[10] and an unadjusted indirect comparison of pazopanib and the requested comparators (see Section 2.2). The company referred to a supportive study of pazopanib in patients who had received prior chemotherapy for advanced STS (VEG20002), however this will not be discussed further as this was a smaller, uncontrolled phase II study[11].

It should be noted that two separate analyses of PALETTE study were undertaken; a regulatory analysis as reported by the Committee for Medicinal Products for Human Use (CHMP)[5] and an academic analysis conducted by the European Organisation for Research and Treatment of Cancer (EORTC)[10]. This report presents the data from the regulatory analysis as presented in the company submission.

3.1 PALETTE (VEG110727) study

The PALETTE study was a double-blind, randomised, multicentre, parallel group, phase III study designed to evaluate the efficacy and safety of pazopanib compared with placebo in patients with advanced STS. Patients (≥ 18 years) had metastatic STS (with or without locally advanced disease) and had all received prior chemotherapy. Patients (n=369) whose disease had progressed on or after, or been intolerant to an anthracycline-based regimen were randomised 2:1 to receive either pazopanib 800 mg once daily (n = 246) or placebo (n = 123). Randomisation was stratified by the number of previous lines of systemic therapy for advanced disease administered and by World Health Organisation (WHO) performance status[1,5].

The primary endpoint in the intention-to-treat (ITT) population was progression free survival (PFS). PFS was defined as the interval between the date of randomisation and the earliest date of radiologically documented disease progression (defined according to the Response Evaluation Criteria In Solid Tumours [RECIST] v1.0 guidelines) or death due to any cause. Secondary endpoints included overall survival (OS), defined as the time from randomisation until death from any cause, and health-related quality of life which was assessed using EuroQoL-5 dimensions (EQ-5D) questionnaire and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire version 3 (EORTC QLQ-C30), a cancer-specific (but not STS specific) questionnaire[1,5].

Treatment with pazopanib resulted in a statistically significant improvement in PFS compared to placebo. The median PFS was 4.6 months for pazopanib versus 1.6 months for placebo (hazard ratio (HR) = 0.35; 95% confidence interval [CI]: 0.26–

0.48; p < 0.001). Median OS was 12.6 months for pazopanib treated patients and 10.7 months for placebo treated patients (HR = 0.87; 95% CI: 0.67–1.12; p = 0.256)[1,5].

The EQ-5D scores showed a decline at week 4 from baseline in both the pazopanib and placebo arms but there were no statistically significant differences between treatment groups. EORTC QLQ-C30 questionnaire results showed no statistically significant differences between the pazopanib and placebo arms at weeks 4, 8 and 12[1].

3.2 Unadjusted indirect analysis

There are no head-to-head trials of pazopanib and the comparators requested by AWTTC (trabectedin, ifosfamide, gemcitabine/docetaxel). A systematic review by the company identified four RCTs[10,12–14] and four single arm non-RCTs[15–18] relevant to the licensed indication for pazopanib and the requested comparators[1]. No studies were identified which used a common comparator therefore an unadjusted indirect comparison was used to compare the relative efficacy of pazopanib, ifosfamide, trabectedin and gemcitabine/docetaxel. Studies identified by systematic review included patients (≥ 18 years of age) with locally advanced or metastatic STS who had received prior therapy with anthracyclines and/or ifosfamide for advanced disease (prior adjuvant treatment was not included). Efficacy and safety outcomes varied across the trials and those that reported PFS or time to progression (TTP) were included in the unadjusted indirect analysis (see Table 1)[1].

The results summarised in Table 1 show that pazopanib has similar efficacy to each of the comparators. The HR for PFS/TTP were 0.91 (95% CI: 0.73–1.14) versus ifosfamide; 0.90 (95% CI: 0.76–1.07) versus trabectedin and 0.99 (95% CI: 0.70–1.40) versus gemcitabine/docetaxel. Due to differences in the study protocols, patient populations and study endpoints it is difficult to draw any meaningful conclusions.

Table 1. Comparative clinical effectiveness.

Treatment (dose)	Trial type	N	Median PFS/TTP (months)	Hazard ratio (vs. pazopanib)	Median OS (months)
Pazopanib (800 mg/day)	Phase III RCT (placebo)[10]	246	4.6 (95% CI: 4.13-4.92)*	–	12.6 (95% CI: 10.9–14.9)
Ifosfamide (3 g/m^2/3 days every 3 weeks)	Phase II RCT (no placebo arm)[13]	40	3.2†	0.91 (95% CI: 0.73–1.14)	8.3
Trabectedin (1.5 mg/m^2 24-hour infusion every 3 weeks)	Phase II RCT (no placebo arm)[12]	136	3.7 (95% CI: 2.1–5.4)§	0.90 (95% CI: 0.76–1.07)	13.9 (95% CI: 12.5–18.6)
	Phase II single arm[15]	36	1.7 (95% CI: 1.3–4.4)¶		12.1 (95% CI: 8.1–26.5)
	Phase II single arm[16]	104	3.4 (95% CI: 2.5–4.1)**		9.1 (95% CI: 7.8–12.1)
	Phase II single arm[17]	54	1.9 (95% CI: 0.69–30.62) ††		12.8 (95% CI: 0.69–33.77)
Gemcitabine/ docetaxel* (Gemcitabine 900 mg/m^2 on day 1 and day 8 plus docetaxel 100 mg/m^2 on day 8, every 3 weeks)	Phase II RCT (no placebo arm)[14]	46	4.7 [Uterine LMS]§§ 3.4 [Non-uterine LMS]§§	0.99 (95% CI: 0.70–1.40)	23 [Uterine LMS] 13 [Non-uterine LMS]
	Phase II single arm[18]	48	6.7+ (95% CI: 0.7–27+)		14.7 (95% CI: 0.8–50.9+)

N: number of patients; PFS: progression free survival; TTP: time to progression; OS: overall survival; CI: confidence interval; LMS: leiomyosarcoma.
Definitions of PFS/TTP (terms used interchangeably in analysis)
*PFS: time from date of randomisation to date of documented progression or death.
†TTP: time from date of randomisation to date of first documented disease progression.
§TTP: time from random assignment to disease progression or death as a result of progressive disease.
¶TTP: time elapsed from date of registration to date of first documented evidence of progressive disease.
* *TTP: date of inclusion to date of documented progression.
††PFS: time from initiation of therapy to the first documentation of disease progression.
§§PFS: date of randomisation until date of first progression or death or last documented contact.
¶¶ PFS: definition not reported.

3.3 Comparative safety

Safety data from the PALETTE study showed that several common adverse events (AEs) such as fatigue, diarrhoea, nausea and hypertension were more frequently observed in pazopanib-treated patients than in placebo-treated patients. AEs directly relating to tumour symptoms such as tumour pain and musculoskeletal pain occurred with a similar frequency in both the pazopanib and control arms[5]. In the pazopanib-treated arm 49% of patients reported an AE of grade 3 severity and 10% an AE of grade 4 severity. In the placebo arm 19% of patients reported grade 3 events and 6% of patients reported grade 4 events[5].

Treatment-related serious adverse events (SAEs) were reported in 24% of pazopanib-treated patients compared to 5% of placebo-treated patients. The most common SAEs associated with pazopanib were increased liver transaminases, pneumothorax, embolism, fatigue and left ventricular systolic dysfunction. Twenty percent of pazopanib patients permanently discontinued the medication due to AEs compared to 5% of placebo patients. The most common AEs leading to pazopanib discontinuation were alanine transaminase (ALT) elevation, dyspnoea, left ventricular dysfunction, fatigue, hypertension and vomiting[5].

Indirect comparison of the safety data for pazopanib and the comparators using the studies referenced in Table 1 was difficult given the differences in design, methodology and patient characteristics. Pazopanib was associated with a lower level of haematological toxicity than the comparators however fatigue and hypertension were reported more frequently in pazopanib-treated patients[10,12,13,15–18].

3.4 AWTTC critique

- The company have requested that AWMSG consider the use of pazopanib in adult patients with selective subtypes of advanced STS who have received prior anthracycline-based chemotherapy for metastatic disease or who have progressed within 12 months after (neo) adjuvant therapy. In the PALETTE study 99% of patients had received prior anthracycline therapy. Furthermore, first line anthracycline-based chemotherapy is recommended by BSG 2010 guidelines and clinical experts consulted have confirmed this occurs in clinical practice.
- It should be noted that only 7% of patients in the PALETTE study were reported as having progressed on or following (neo) adjuvant treatment only.
- Results from the PALETTE trial demonstrated that PFS was greater for pazopanib versus placebo by three months ($p < 0.001$). CHMP noted that in all subgroup and sensitivity analysis, a very robust and consistent PFS benefit was found in favour of pazopanib[5]. The applicant company state that sarcoma experts consider this improvement in PFS to be clinically meaningful[1].
- Overall survival in the PALETTE trial failed to show a statistical difference between pazopanib and placebo arms, although numerically favoured pazopanib. It is noted that the trial was not adequately powered to detect differences in overall survival of less than four months[5]. In addition, more placebo patients received post study anti-cancer therapy than pazopanib (75% versus 61%, respectively).
- Quality of life measures (EQ-5D and EORTC QLQ-C30) showed no statistical differences between the pazopanib and placebo arms, although numerically favoured placebo. The company states that the higher withdrawal rate of patients from the placebo arm may have unfairly biased the quality of life measures against pazopanib since the remaining patients in the placebo group may have been in a better state of health.

- All patients in the PALETTE study had a WHO performance status of 0 or 1. No evidence is available for the efficacy and safety of pazopanib in patients with WHO performance status >1.
- No head-to-head comparisons of pazopanib against ifosfamide, trabectedin and gemcitabine/docetaxel for patients with metastatic STS, pre-treated with chemotherapy were available. In addition, no common interventions in any of the identified RCTs by which to link the studies were available; hence, an adjusted indirect comparison was not considered feasible. Unadjusted, indirect comparisons are subject to considerable uncertainty due to differences in study design, patient numbers and assessment methods; results should therefore be interpreted with caution.
- Pazopanib is an oral tablet therapy, which can be self-administered at home, whilst ifosfamide, trabectedin and gemcitabine/docetaxel, are intravenous treatments, requiring hospital administration.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company's submission[1] describes a cost-utility analysis of pazopanib plus BSC compared to: BSC alone; ifosfamide plus BSC; trabectedin plus BSC; and gemcitabine/docetaxel plus BSC, for the treatment of patients with selective subtypes of advanced STS. BSC alone was defined as treatment received by patients in the placebo arm of the PALETTE trial which included transfusion of blood and blood products, treatment with antibiotics, anti-emetics, anti-diarrhoeal agents, analgesics, anti-hypertensives, erythropoietin or bisphosphonates. Nearly all patients in the trial had received prior treatment with anthracycline based therapy. Therefore, although not a restriction of the licensed indication, the company has limited its submission to the use of pazopanib following anthracycline therapy.

The analysis of pazopanib versus BSC alone uses direct comparative data from the PALETTE trial. In contrast, the analyses comparing pazopanib with ifosfamide, trabectedin and gemcitabine/docetaxel use unadjusted indirect comparisons of PFS or TTP data from published studies and assumptions that post-progression survival (PPS) is equal for pazopanib and these comparators.

A partitioned survival analysis model has been developed, which considers three health states: 'alive, pre-progression', 'alive, post-progression' and 'dead'. Patients enter the model in the 'alive, pre-progression' health state which assumes that patients are progression-free for this line of treatment, although they have already experienced disease progression on prior therapies. The model assumes that patients will receive either pazopanib plus BSC, or ifosfamide plus BSC, or trabectedin plus BSC, or gemcitabine/docetaxel plus BSC, or BSC alone until they subsequently experience disease progression or death. The analyses assume a 12.5% patient access scheme (PAS) discount for pazopanib, in line with the NICE PAS for pazopanib in the treatment of renal cell carcinoma[19]. No acquisition costs are considered for trabectedin after five treatment cycles, in agreement with its NICE PAS[8].

It is assumed that subsequent-line chemotherapies following disease progression will not differ between treatment groups included in the model. However, the comparison of pazopanib plus BSC versus BSC alone incorporates costs associated with post-

study anti-cancer therapy (PSACT) derived from the PALETTE trial. Utility values for different health states and treatments are derived from mapping exercises using quality of life data collected in the PALETTE trial and a number of other sources. The model assumes a one week cycle and a ten-year (life-time) time horizon.

4.1.2 Results

Results of the base case analyses are summarised in Table 2. Pazopanib is estimated to be more effective and less costly compared to the ifosfamide, trabectedin, and gemcitabine/docetaxel treatment strategies. Pazopanib treatment was more effective and more costly compared to BSC alone, resulting in an incremental cost effectiveness ratio (ICER) of £62,162 per QALY gained.

Table 2. Company-reported results of the base case analyses.

Scenarios	Pazopanib	Comparator	ICER	Plausibility?
Base case: Pazopanib + BSC *vs.* BSC	£22,086 0.719 QALYs	£14,110 0.591 QALYs	£62,162 (3% probability <£30,000)	Direct trial data
Base case: Pazopanib + BSC vs. ifosfamide + BSC	£22,488 0.692 QALYs	£26,445 0.652 QALYs	Pazopanib Dominant* (100% probability <£30,000	Unadjusted indirect comparisons subject to considerable uncertainty. Pazopanib less costly and less effective in 31% of PSA simulations.
Base case: Pazopanib + BSC *vs*. trabectedin + BSC	£22,488 0.692 QALYs	£29,217 0.663 QALYs	Pazopanib Dominant* (100% probability <£30,000)	Unadjusted indirect comparisons subject to considerable uncertainty. Pazopanib less costly and less effective in 26% of PSA simulations.
Base case: Pazopanib + BSC *vs.* gemcitabine/ docetaxel + BSC	£22,488 0.692 QALYs	£25,175 0.690 QALYs	Pazopanib Dominant* (97% probability <£30,000)	Unadjusted indirect comparisons subject to considerable uncertainty. Pazopanib less costly and less effective in 51% of PSA simulations. Company considers there is minimal current use of gemcitabine/ docetaxel in practice (expert opinion).
*Pazopanib plus BSC as modelled is more effective and less costly than the comparator				
ICER: incremental cost effectiveness ratio; BSC: best supportive care; QALY: quality-adjusted life year gained; PSA: probabilistic sensitivity analysis				

Results for pazopanib versus BSC are driven mainly by acquisition costs and modelled longer PFS with pazopanib treatment. ICERs against the other comparators are driven by the modelled longer PFS with pazopanib and greater administration and adverse event costs associated with the comparators.

A wide range of one-way sensitivity and scenario analyses have been conducted by the company. The model is reported to be most sensitive to assumed mean OS for BSC, followed by mean OS for pazopanib, disutility for post-progression and PSACT costs. Table 3 lists some of the key analyses.

Table 3. Selected sensitivity and scenario analyses.

Scenarios	ICER (per QALY gained)	Plausibility?
Scenario: Pazopanib + BSC vs. BSC		
Range of 95% CI for mean OS for BSC Range of 95% CI for mean OS for pazopanib Disutility post- vs. pre-progression (+/-50%)	£37,958 to £508,342 £39,671 to £124,095 £50,748 to £80,201	Direct trial data but trial not sufficiently powered for OS, resulting in wide 95% CIs Confounding due to post progression treatments? Complex utility estimation
Scenario: Pazopanib + BSC *vs.* BSC		
WHO PS=0 WHO PS=1 Prior lines of therapy=1 Prior lines of therapy=2 Prior lines of therapy=3	£81,750 £45,579 £34,421 £75,047 £43,524	Direct trial data. Limitations as above
Scenario: Pazopanib + BSC *vs*. Ifosfamide + BSC		
Range of 95% CI for Ifosfamide PFS hazard ratio Ifosfamide PFS hazard ratio=1	£253,997 saved / QALY foregone to Dominant* Dominant*	Unadjusted indirect comparisons prone to bias Wide CI: ICER ranges from pazopanib being less costly and less effective than ifosfamide through to being less costly and more effective
Scenario: Pazopanib + BSC *vs*. Trabectedin + BSC		
Range of 95% CI for Trabectedin PFS hazard ratio Trabectedin PFS hazard ratio=1	£393,657 saved / QALY foregone to Dominant* Dominant*	Unadjusted indirect comparisons prone to bias Wide CI: ICER ranges from pazopanib being less costly and less effective than trabectedin through to being less costly and more effective
Base case: Pazopanib + BSC *vs.* gemcitabine / docetaxel + BSC		
Range of 95%CI for Gemcitabine/ docetaxel PFS hazard ratio Gemcitabine/ docetaxel PFS hazard ratio=1	£61,571 saved / QALY foregone to £6,016 / QALY gained >£5million/QALY gained	Unadjusted indirect comparisons prone to bias Wide CI: ICER ranges from pazopanib being less costly and less effective than gemcitabine / docetaxel through to being more costly and more effective. Small differences in QALY gains results in ICER being very sensitive to small changes
*Pazopanib plus BSC is more effective and less costly than the comparator		
ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year gained; BSC: best supportive care; CI: confidence interval; OS: overall survival; PSA: probabilistic sensitivity analysis ; WHO PS: World Health Organisation performance status		

4.1.3 AWTTC critique

The company has made considerable efforts to estimate the cost-effectiveness of pazopanib for the treatment of STS patients. The base case analysis of pazopanib versus BSC alone uses direct evidence from the PALETTE trial; however, there are limited data available to parameterise the economic model. Due to a lack of direct comparative studies for pazopanib versus ifosfamide, trabectedin and gemcitabine/docetaxel, these analyses were based on data derived from unadjusted, indirect comparisons of studies that varied widely with respect to baseline characteristics, tumour subtype, the number of prior lines of therapies, chemotherapy regimens, and outcome measures. Effectiveness estimates included in the model, and resultant model outputs are therefore subject to considerable uncertainty.

Strengths of the economic evidence include:

- In the absence of direct comparative data, the company has undertaken a systematic literature review to identify studies for inclusion in (unadjusted) indirect comparisons.
- A wide range of sensitivity and scenario analyses have been conducted to explore the impact of uncertainty associated with several key parameters.

Limitations of the economic evidence include:

- In the absence of direct comparative data, naive, unadjusted indirect comparisons of available trial data have been used. The included trials varied widely with respect to baseline characteristics, tumour subtype, the number of prior lines of therapies, and outcome measures. Unadjusted indirect comparisons are subject to considerable uncertainty and should be viewed with caution.
- Sensitivity analyses conducted by the company reveal significant uncertainty around ICER point estimates for the indirect comparisons against other treatments. The model was very sensitive to changes in hazard ratios for PFS derived from unadjusted indirect comparisons of other treatments, and also to changes in mean OS for the direct comparison against BSC. All analyses against these other treatments assume equal PPS, and no exploration of the use of available OS data for these other treatments has been attempted. Results of all base case analyses, therefore, should be interpreted with caution.
- In extrapolating the PALETTE trial data, the company has elected to use Weibull distributions for both PFS and OS as it is reported these fit the empirical data better. Log-logistic distributions may fit the data better in terms of the modelled difference in OS between pazopanib and BSC, and generate a marginally increased base case ICER of £62,788 per QALY gained for pazopanib versus BSC alone.
- A number of assumptions have been made to estimate utility values used in the model. The model was sensitive to disutilities associated with PFS and PPS, which contributes to uncertainty around estimated ICERs.
- The costs of STS management were taken from an unpublished 2006 study, updated to 2010/11 prices. It is unclear whether this study reflects current resource use for STS patients in Wales.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC identified a conference abstract of a cost utility analysis of pazopanib compared with placebo, ifosfamide and trabectedin, conducted from a UK NHS perspective[20]. Few details are provided in the abstract, but

it appears that this uses the same methods and data as the current submission, and the reported results of the base case analyses are the same.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Using the data on cancer incidence in Wales (2006–2010) published by the Welsh Cancer Intelligence and Surveillance Unit[21], the company estimated that there will be 138 patients diagnosed with STS each year in Wales. Based on the NICE costing report for use of trabectedin, 27.5% of these patients are expected to develop advanced disease, and 36% will receive second-line treatment. Approximately 11.5% of these patients will develop liposarcomas and will not be eligible for treatment with pazopanib. The estimated number of eligible patients, therefore, will be 12 per year. Assuming that pazopanib uptake rate will increase from 20% in year one to 50% in year five, the company estimates that that there will be two patients treated with pazopanib in year one increasing to six patients in year five.

5.1.2 Results of company's budget impact analysis

According to Welsh expert opinion[1], current treatment options for advanced STS patients in Wales include ifosfamide (approximately. 30-40%), trabectedin (approximately. 30-40%) and BSC alone (approximately. 30%). The company assumed that pazopanib will displace ifosfamide, trabectedin and all concomitant medication associated with these therapies in eligible patients. Gemcitabine/docetaxel was not considered in the budget impact analysis, since its use in the target population is considered to be minimal. The company estimated that treatment with pazopanib will cost £12,024 per patient per year compared to £15,979 for treatment with ifosfamide and £18,751 for treatment with trabectedin. A break-down of treatment costs for pazopanib, ifosfamide and trabectedin is summarised in Table 4.

Table 4. Company-reported costs associated with use of pazopanib, ifosfamide and trabectedin for the treatment of one STS patient per year.

	Pazopanib	Ifosfamide	Trabectedin
Expected length of treatment (months)	6.1	5.6	5.5
Medication (including concomitant medication)	£10,733	£5,675	£11,699
Administration & monitoring	£81	£6,516	£2,491
Primary Care	£0	£0	£0
Secondary & tertiary care (adverse events during PFS period)	£653	£2,706	£3,481
Secondary & tertiary care ('other costs' during PFS period)	£557	£1,082	£1,080
Total treatment costs	**£12,024**	**£15,979**	**£18,751**
STS: soft tissue sarcoma; PFS: progression free survival			

The estimated numbers of patients and the associated costs are summarised in Table 5. According to the company's estimations, displacement of ifosfamide and trabectedin (proportionally to their current use in Wales) with pazopanib will save £526 in year one rising to £1,306 in year five upon introduction.

Table 5. Company-reported costs associated with use of pazopanib (Votrient) for the treatment of patients with advanced STS.

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	12.1	12.1	12.1	12.1	12.1
Uptake	20%	35%	40%	50%	50%
Number of treated patients	2.4	4.2	4.8	6	6
Pazopanib + BSE treatment costs	£25,923	£45,365	£51,846	£64,808	£64,808
Overall net costs	**-£526**	**-£921**	**-£1,053**	**-£1,316**	**-£1,316**

The company conducted scenario analysis, which excludes costs of adverse events and other costs associated with PFS stage (cost of monitoring and follow-up). This scenario resulted in a total treatment cost of £3,818 in year one rising to £9,544 in year five.

5.1.3 AWTTC critique of the budget impact analysis

- Budget impact analysis presented by the company is based on the economic model; therefore, limitations of the model apply equally to the budget impact analysis. Moreover the net financial costs of introducing pazopanib in practice may not be equivalent to the opportunity costs calculated for the economic analysis.
- Due to a lack of epidemiological data for the STS population covered in this submission, a range of assumptions have been necessary to estimate the number of patients eligible for treatment with pazopanib.
- Predictions of uptake are based on the NICE costing template for the use of trabectedin, and so would seem a source of uncertainty.

5.2 Comparative unit costs

The estimation of comparative acquisition costs for chemotherapy regimens are complicated, as doses of individual components have to be calculated per body surface area (BSA) and individually adjusted according to toxicity (see relevant Summaries of Product Characteristics[22,23] for full dosing details). Examples of costs of chemotherapy regimens for patients with STS are shown in Table 6. The doses are calculated for an average BSA of 1.73m^2 and administered for the equivalent of six 21-day treatment cycles (126 days for pazopanib). Gemcitabine[24] and docetaxel[25] are not licensed for use in patients with STS and their use in Wales is believed to be minimal according to expert opinion[1].

Table 6. Example medication acquisition costs for the treatment of patients with advanced STS.

Regimens	Example doses	Cost per six cycles
Pazopanib (Votrient®▼) 200 mg and 400 mg tablets	800 mg once daily	£9,416 based on list price (£8,239 with 12.5% PAS discount)
Ifosfamide (non-proprietary) 1 g and 2 g powder for solution for injection/infusion	3 g/m^2/day for 3 days every 3 weeks†	£3,974*
Trabectedin (Yondelis®) 250 microgram and 1 mg powder for solution for infusion	1.5 mg/m^2 by iv infusion over 24 hours every 3 weeks	£20,748 (£17,290 with PAS)
See relevant Summaries of Product Characteristics for full dosing details[2,22,23]. †Based on dose used in economic model, as per van Oosterom 2002[13]. *Excludes cost of IV Mesna required for prevention of urothelial toxicity at approx cost £240 for 6 treatment cycles Costs are based on MIMS[26] or BNF[27] list prices as of 12/11/2012. This table does not imply therapeutic equivalence of treatments or the stated doses.		
STS: soft tissue sarcoma; PAS: patient access scheme;		

6.0 ADDITIONAL INFORMATION

6.1 Appropriate place for prescribing

AWTTC is of the opinion that, if recommended, pazopanib (Votrient®▼) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

6.4 Evidence search

Date of evidence search: 19 November 2012
Date range of evidence search: No date limits were applied to database searches.

6.5 Consideration of AWMSG policy on life-extending, end-of-life medicines

The criteria for appraising life-extending, end-of-life medicines apply when the most plausible ICER estimate exceeds £30,000 per QALY gained, and all the following conditions are satisfied:

- The medicine is indicated for patients with a short life expectancy, normally less than 24 months (e.g. estimated from the median survival of patients in the control group of the pivotal study).
- There is sufficient evidence to indicate that the medicine offers an extension to life, normally of at least an additional three months, compared to current NHS treatment. The estimates of the extension to life (e.g. based on the difference in median survival in the pivotal trial, or projected life-years gained) should be robust and shown (or reasonably inferred) from either progression free survival or overall survival.
- AWMSG/NMG will consider the cumulative population of each licensed indication of the medicine to be small[28].

The applicant company believe that the use of pazopanib for the treatment of adult patients with selective subtypes of advance STS meets the AWMSG end-of-life criteria:

- The ICER per QALY gained for pazopanib compared to BSC is £62,162.
- In the PALETTE trial patients with STS in the placebo arm had a median OS of 10.7 months.
- In the PALETTE trial PFS was greater for pazopanib versus placebo by three months ($p < 0.001$). The difference in OS between pazopanib-treated patients and placebo-treated patients was 1.9 months ($p = 0.256$).
- The modelled gain in (undiscounted) survival ranges from 1.1 day when compared to gemcitabine/docetaxel, to 1.38 months compared with BSC.
- The company estimate the cumulative population of each licensed indication is small.

6.6 Consideration of AWMSG policy relating to ultra-orphan medicines

The applicant company believe that the use of pazopanib in the given patient population may meet the AWMSG criteria for ultra-orphan status. Ultra-orphan medicines are orphan drugs that are licensed for the treatment of diseases with a prevalence of less than 1 in 50,000 persons in the European Union at the time of submission of the designation application to the European Medicines Agency (EMA). Pazopanib has not been granted orphan status by the EMA.

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REFERENCES

1 GlaxoSmithKline. Form B: Detailed appraisal submission. Pazopanib(Votrient®▼). Oct 2012.

2 GlaxoSmithKline. Votrient®▼ 200 mg and 400 mg film-coated tablets. Summary of Product Characteristics. Nov 2012. Available at: http://www.medicines.org.uk/EMC/medicine/23148/SPC/Votrient+200+mg+and+400+mg+film+coated+tablets/. Accessed Nov 2012.

3 European Medicines Agency. Votrient®. Procedural steps taken and scientific information after the authorisation. Nov 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/001141/WC500102180.pdf. Accessed Nov 2012.

4 Grimer R, Judson I, Peake D et al. Guidelines for the management of soft tissue sarcomas. *Sarcoma* 2010; 2010 (506182).

5 European Medicines Agency. Assessment Report for Votrient. Procedure No.: EMEA/H/C/001141/II/0007. May 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/001141/WC500131044.pdf. Accessed Nov 2012.

6 Italiano A Cesne AL, Mathoulin-Pelissier S, Terrier P et al. Trends in survival for patients with metastatic soft-tissue sarcoma. *Cancer* 2011; 117 (5): 1049-54.

7 Janssen-Cilag Ltd. Caelyx® 2 mg/ml concentrate for solution for infusion. Summary of Product Characteristics. Feb 2012. Available at: http://www.medicines.org.uk/EMC/medicine/7017/SPC/Caelyx+2mg+ml+concentrate+for+solution+for+infusion/. Accessed Dec 2012.

8 National Institute for Health and Clinical Excellence. Technology appraisal TA185. Trabectedin for the treatment of advanced soft tissue sarcoma. 2010. Available at: http://guidance.nice.org.uk/TA185/Guidance/pdf/English. Accessed Nov 2012.

9 National Institute for Health and Clinical Excellence. Improving Outcomes for People with Sarcoma - the Manual. Mar 2006. Available at: http://guidance.nice.org.uk/CSGSarcoma/Guidance/pdf/English. Accessed Dec 2012.

10 Van Der Graaf WT, Blay JY, Chawla SP et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2012; 379: 1879-86.

11 Sleijfer S, Ray-Coquard I, Papai Z et al. Pazaponib, a Multikinase Angiogenesis Inhibitor, in Patients With Relapsed or Refractory Advanced Soft Tissue Sarcoma: A Phase II Study From the European Organisation for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC Study 62043). *Am J Oncol* 2009; 27 (19): 3126-32.

12 Demetri GD, Chawla SP, von Mehren M et al. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: results of a randomized phase II study of two different schedules. *J Clin Oncol* 2009; 27 (25): 4188-96.

13 Van Oosterom AT, Mouridsen HT, Nielsen OS et al. Results of randomised studies of the EORTC Soft Tissue and Bone Sarcoma Group (STBSG) with two different ifosfamide regimens in first- and second-line chemotherapy in advanced soft tissue sarcoma patients. *Eur J Cancer* 2002; 38 (18): 2397-406.

14 Pautier P, Floquet A, Penel N et al. Randomized Multicenter and Stratified Phase II Study of Gemcitabine Alone Versus Gemcitabine and Docetaxel in Patients with Metastatic or Relapsed Leiomyosarcomas: A Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) French Sarcoma Group Study (TAXOGEM study). *The Oncologist* 2012; 17: 1213-20.
15 Garcia-Carbonero R, Supko JG, Manola J et al. Phase II and pharmacokinetic study of ecteinascidin 743 in patients with progressive sarcomas of soft tissues refractory to chemotherapy. *Journal of clinical oncology* 2004; 22 (8): 1480-90.
16 Le Cesne A, Blay JY, Judson I et al. Phase II study of ET-743 in advanced soft tissue sarcomas: a European Organisation for the Research and Treatment of Cancer (EORTC) soft tissue and bone sarcoma group trial. *Journal of clinical oncology* 2005; 23: 576-84.
17 Yovine A, Riofrio M, Blay JY et al. Phase II study of ecteinascidin-743 in advanced pretreated soft tissue sarcoma patients. *Journal of clinical oncology* 2004; 22: 890-9.
18 Hensley ML, Blessing JA, Degeest K et al. Fixed-dose rate gemcitabine plus docetaxel as second-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II study. *Gynecologic oncology* 2008; 109 (3): 323-8.
19 National Institute for Health and Clinical Excellence. Technology appraisal TA215. Renal cell carcinoma (First line metastatic) - pazopanib: guidance. Feb 2011. Available at: http://guidance.nice.org.uk/TA215/Guidance/pdf/English. Accessed Dec 2012.
20 Amdahl J, Manson S, Isbell R et al. Cost effectiveness of pazopanib in soft tissue sarcoma. *Value in Health ISPOR 15th Annual European Congress Berlin* 2012; 15 (7): A423-A424.
21 Welsh Cancer Incidence and Surveillance Unit. Cancer Incidence in Wales 2006-2010. Jan 2012. Available at: http://www.wales.nhs.uk/sites3/Documents/242/incpub2012.pdf. Accessed Nov 2012.
22 Medicines and Healthcare products Regulatory Agency. Ifosfamide 40 mg/ml solution for infusion. Summary of Product Characteristics. May 2006. Available at: http://www.mhra.gov.uk/home/groups/l-unit1/documents/websiteresources/con2032373.pdf. Accessed Dec 2012.
23 Pharma Mar SA. Yondelis®▼ 0.25 mg powder for concentrate for solution for infusion/ Yondelis 1 mg powder for concentrate for solution for infusion. Summary of Product Characteristics. Aug 2012. Available at: http://www.medicines.org.uk/EMC/medicine/20457/SPC/Yondelis+0.25+mg+powder+for+concentrate+for+solution+for+infusion+Yondelis+1+mg+powder+for+concentrate+for+solution+for+infusion/. Accessed Dec 2012.
24 Eli Lilly and Company Ltd. Gemzar 100 mg and 200 mg powder for solution for infusion. Summary of Product Characteristics. Aug 2011. Available at: http://www.medicines.org.uk/EMC/medicine/596/SPC/Gemzar+200mg+powder+for+solution+for+infusion%2c+Gemzar+1000mg+powder+for+solution+for+infusion/. Accessed Dec 2012.
25 Sanofi. Taxotere 160 mg/8 ml concentrate for solution for infusion. Summary of Product Characteristics. Sep 2012. Available at: http://www.medicines.org.uk/EMC/medicine/25464/SPC/Taxotere+160mg+8ml+concentrate+for+solution+for+infusion/. Accessed Dec 2012.
26 Haymarket Publications. Monthly Index of Medical Specialities (MIMS). Dec 2012. Available at: http://www.mims.co.uk/. Accessed Dec 2012.
27 British Medical Association, Royal Pharmaceutical Society of Great Britain. *British National Formulary. No. 64.* Oct 2012.

28 All Wales Medicines Strategy Group. AWMSG Policy on appraising life-extending, end-of-life medicines. Sep 2011. Available at: http://www.wales.nhs.uk/sites3/docmetadata.cfm?orgid=371&id=177718. Accessed Dec 2012.