Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

pazopanib 200mg, 400mg film-coated tablets (Votrient®) SMC No. (820/12)

GlaxoSmithKline UK

09 November 2012

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 Scotland. The advice is summarised as follows:

ADVICE: following a full submission

pazopanib (Votrient®) is not recommended for use within NHS Scotland.

Indication under review: 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.

In a pivotal study, pazopanib significantly improved progression-free survival compared with placebo in adult patients with selective subtypes of advanced STS. However there was no significant improvement in overall survival.

The submitting company'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 submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

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.

Dosing Information

800mg orally once daily. Pazopanib should be taken without food, at least one hour before or two hours after a meal. The film-coated tablets should be taken whole with water and not broken or crushed.

Pazopanib treatment should only be initiated by a physician experienced in the administration of anti-cancer agents.

Product availability date

August 2012

Summary of evidence on comparative efficacy

Soft tissue sarcomas (STS) are a rare form of connective tissue cancers originating from the mesenchymal cells and their precursors. There are approximately 50 different histological types of STS and the annual incidence is approximately five cases per 100,000 population in Europe. In patients with metastatic STS, the prognosis is poor with a median overall survival of about 12 months.

Pazopanib is an oral, selective tyrosine kinase inhibitor (TKI) that targets vascular endothelial growth factor receptor, platelet-derived growth factor receptor and c-Kit. It has a marketing authorisation for second-line use in selective subtypes of STS who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo) adjuvant therapy. The submitting company has requested that SMC considers the use of pazopanib when positioned for use in the treatment of adult patients with selective subtypes of advanced STS who have received prior anthracycline-based chemotherapy for advanced/metastatic disease.

The evidence to support the use of pazopanib in STS comes from the results of one pivotal, randomised, double-blind, phase III study (PALETTE).[1,2] Eligible patients were aged ≥18 years and had advanced, metastatic STS (excluding the following subtypes: adipocytic sarcoma, embryonal rhabdomyosarcoma, chondrosarcoma, osteosarcoma, Ewing tumours, primitive neuroectodermal tumour, gastrointestinal stromal tumour, dermatofibrosarcoma protuberans, inflammatory myofibroblastic sarcoma, malignant mesothelioma and mixed mesodermal tumours of the uterus). They had disease progression as defined by Response Evaluation Criteria In Solid Tumours (RECIST) in the 6 months before receiving study drug (or 12 months for previous adjuvant treatment). They had received at least one prior anthracycline-containing regimen and up to four prior lines of systemic therapy for metastatic disease (or two lines of combination therapy) and had WHO performance status 0 or 1.

Eligible patients were randomised to receive pazopanib (800mg daily, n=246) or placebo (n=123) until disease progression, death, unacceptable toxicity or withdrawal of consent. Randomisation was stratified by the number of previous lines of systemic therapy for advanced disease (0 or 1 versus ≥2) and WHO performance status (0 versus 1). Crossover was not permitted at disease progression but post-protocol treatments were given at the discretion of the patients and physicians.

There were two separate analyses of the data: one for regulatory purposes[2] and the other for academic purposes conducted by the EORTC and published.[1] The results from these analyses differ slightly and the efficacy results presented below are from the academic analysis.

The primary outcome was progression-free survival (PFS) (defined as the time from randomisation until disease progression [according to RECIST criteria by masked independent radiology review] or death from any cause). The primary analysis of PFS was performed at cut-off date 22 November 2010 after 274 events. The median duration of treatment in the pazopanib and placebo groups was 16.4 weeks and 8.1 weeks, respectively. The median duration of follow-up was 14.9 months and 14.6 months respectively. Disease progression or death had been reported in 68% (168/246) of pazopanib and 86% (106/123) of placebo patients. Median PFS was 4.6 months versus 1.6 months respectively corresponding to a hazard ratio (HR) of 0.31 (95% confidence interval [CI]: 0.24 to 0.40), $p<0.0001$.[1] Pazopanib was consistently significantly more effective than placebo in a number of sensitivity and subgroup analyses of PFS.

The key secondary endpoint was overall survival (OS, defined as the time from randomisation until death from any cause). At the time of the primary PFS analysis (cut-off date 22 November 2010) median OS was 11.9 months in the pazopanib group and 10.4 months in the placebo group (HR: 0.83 [95% CI: 0.62 to 1.09], p=0.18). At the final analysis of OS (cut-off date 24 October 2011), the difference was also not significant (12.5 months versus 10.7 months respectively: HR: 0.86 [95% CI: 0.67 to 1.11], p=0.251).[1]

Response rate (defined as the percentage of patients who achieved either confirmed complete response or partial response) was assessed by external review and was achieved by 5.7% (14/246) of pazopanib patients and no placebo patients. All responses were partial. Stable disease was reported in 67% (164/246) pazopanib and 38% (47/123) placebo patients.[1]

Quality of life was assessed as an exploratory endpoint using the Quality of Life Questionnaire (QLQ)-C30 and EQ-5D with assessments made to 12 weeks. Results found no significant difference between pazopanib and placebo in terms of QLQ-C30 global health status/QOL summary score and EQ-5D visual analogue scale. Individual component scales on diarrhoea, loss of appetite, nausea and vomiting and fatigue were significantly worse on pazopanib.[1,2]

Summary of evidence on comparative safety

Safety data are reported from both the academic and regulatory analyses as indicated depending on available published data.

In the safety population (regulatory analysis) (pazopanib: n=240 and placebo: n=123) of the pivotal study, adverse events were reported by 99% pazopanib and 89% placebo patients. Serious adverse events were reported in 41% and 24% of patients respectively and these were considered related to study treatment in 24% and 4.9% of patients respectively. Discontinuation due to adverse events occurred in 20% pazopanib and 4.9% placebo patients.[2]

The most frequently reported adverse events (related and unrelated) (academic analysis) in the pazopanib and placebo groups respectively were: fatigue, 65% versus 49%; diarrhoea, 58% versus 16%; nausea, 54% versus 28%: weight loss, 48% versus 20%; hypertension, 41% versus 6.5%; anorexia, 40% versus 20%; hair hypopigmentation, 38% versus 2.4%; vomiting, 33% versus 11%; dysgeusia, 27% versus 4.1%; rash or desquamation, 18% versus 11% and mucositis, 12% versus 3.3%.[1]

The most frequently reported serious adverse events (regulatory analysis) in the pazopanib and placebo groups respectively were: dyspnoea, 4.2% versus 2.4%; increased alanine aminotransferase, 3.8% versus 0.8%; decreased haemoglobin, 3.3% versus 1.6%: increased aspartate aminotransferase, 2.5% versus 0; increased gamma glutamyltransferase, 2.5% versus 0; pneumothorax, 2.5% versus 0; embolism, 2.5% versus 1.6%; fatigue, 2.1% versus 0.8% and left ventricular dysfunction, 2.1% versus 0.[2]

There was one death due to multi-organ failure in a pazopanib-treated patient which may have been related to study drug or antibiotics.[1]

Summary of clinical effectiveness issues

Pazopanib is the first oral targeted treatment for advanced soft tissue sarcoma. The submitting company has requested that SMC considers the use of pazopanib when positioned for use in adult patients with selective subtypes of advanced STS who have received prior anthracycline-based chemotherapy for advanced/metastatic disease. This is slightly narrower than the licensed indication by specifying the type of prior chemotherapy. In practice, since doxorubicin is the standard first-line treatment recommended by clinical guidelines, this positions pazopanib for second- or subsequent-line treatment. Evidence from the pivotal study supports this positioning in that study patients had received at least one prior anthracycline-containing regimen. However, the study patients had been heavily pre-treated with 54% of pazopanib patients having received prior second-line therapy, 21% prior third-line therapy and 6.5% prior fourth-line therapy. In terms of prior therapy these patients had received, 98% of the pazopanib-treated patients had received doxorubicin, 67% ifosfamide, 35% gemcitabine, 28% docetaxel and 15% trabectedin.[2]

Since the study excluded patients with certain STS histological subtypes, the summary of product characteristics notes that efficacy and safety has only been established in certain STS histological tumour subtypes. Results demonstrated a statistically significant improvement in

the primary outcome measure, PFS, with pazopanib compared with placebo and the PFS benefit was considered clinically relevant. Results for the key secondary endpoint, overall survival, failed to reach a significant difference but the results may have been confounded by post-protocol treatment including post-protocol chemotherapy, received by 45% (103/228) pazopanib and 62% (75/122) placebo patients.

Study patients had performance status of 0 or 1 so the efficacy and tolerability of pazopanib in patients with poorer performance status is unclear. Given that pazopanib has the advantage of being orally administered, it may be a suitable option for patients who are not considered eligible for current second- or subsequent lines of therapy in clinical practice.

The tolerability profile of pazopanib differs from other chemotherapy and is not associated with haematological toxicity. However, other serious adverse events reported with pazopanib include increased liver transaminases, pneumothorax, embolism, fatigue and cardiac dysfunction.[2]

There are no comparative data with other therapies used for the treatment of STS. The submitting company presented a naïve, unadjusted indirect comparison of pazopanib with ifosfamide, which is one potential second-line treatment option. Ifosfamide is, however, associated with relatively poor tolerability. Data from the pazopanib arm (n=246) of the pivotal study, described above,[1,2] were compared with data from the ifosfamide arm (3g/m^2 as a 4 hour infusion on days 1, 2 and 3, n=40) of a study comparing two doses of ifosfamide for soft tissue sarcoma (STS).[3] This ifosfamide dose appears to be in-line with the 9 to 10g/m^2 dose recommended in British sarcoma guidelines.[5] Results for PFS for pazopanib and time to progression (TTP) for ifosfamide were compared and suggested a numerical but not significant difference in favour of pazopanib. The submitting company also noted that pazopanib appears to have a favourable toxicity profile relative to ifosfamide, particularly in relation to haematological adverse events. Due to the differences between the studies, their populations and endpoints, as well as the naïve unadjusted methodology used, it is difficult to reach any firm conclusion. However, there is no evidence of a difference in efficacy between the two treatments.

SMC clinical experts have advised that effective treatment options for sarcoma other than first-line doxorubicin are limited. Existing treatment options are given by injection. As an oral therapy pazopanib would be expected to have important patient and service benefits.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing pazopanib-plus-best-supportive care (BSC) to (i) BSC alone and (ii) ifosfamide-plus-BSC, where the patient had already received an anthracycline. BSC was based on the main clinical study and included the transfusion of blood and blood products, treatment with antibiotics, anti-emetics, anti-diarrhoeal agents, analgesics, antihypertensives, erythropoietin, or bisphosphonates, etc when appropriate. This was assumed to represent routine care of STS in Scotland.

The comparison with BSC alone was based on the main clinical study and extrapolated PFS and OS data to make an estimate of costs and quality adjusted life years (QALYs) over a 10-year time horizon which covered the life expectancy of the vast majority of patients.

Utility data were taken from the main clinical study for pre- and post-progression states but the post-progression utility was then modelled to decline linearly over time from its value immediately after progression to a value obtained for the final month of life (from a survey of UK members of the public).

Costs included medicines, dispensing, managing adverse events and subsequent lines of treatment. Data on subsequent lines of treatment were taken from the main clinical study and costed on the basis of the most frequently used regimes. Other monthly costs of STS were based on a survey of English treatment centres.

The cost per QALY versus BSC alone was £74,807 based on an incremental cost of £9,598 and a QALY gain of 0.13. A patient access scheme was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. The PAS offered a simple 12.5% discount on the list price of pazopanib. With the PAS, the submitting company estimated that pazopanib would increase costs by £8,065 and QALYs by 0.13, to give a net cost per QALY gained of £62,856.

In a probabilistic sensitivity analysis, the chance the cost per QALY was below £30,000 was 2%. Sensitivity analyses of various patient subgroups indicated a wide range of cost effectiveness ratios which may be partly due to small patient numbers but illustrates some volatility and uncertainty in the data.

The comparison with ifosfamide was based on an indirect comparison, as described in the Clinical Effectiveness Section. Because of issues with the data the company made the simplifying assumption that there was no difference in post-progression survival so the analysis hinged on the difference in PFS, adverse events (costs and utilities) and costs (medicines and pre-progression routine care of STS). PFS estimates were taken from the indirect comparison and adverse event rates were taken from a comparison of the ifosfamide arm of a published paper and the pazopanib arm of the main clinical study. Disutilities were assigned to adverse events using a number of assumptions and drawing on previously published work.

An important source of cost saving for pazopanib was the reduced need for intravenous (iv) infusions and the insertion of a central venous access device. All the other inputs to the model such as costs of routine care were the same as for the comparison with BSC.

With the PAS, compared to ifosfamide, the submission predicted a reduction in overall costs of £3,873 and a gain in QALYs of 0.033. The company concluded that pazopanib dominated ifosfamide (cheaper, more effective). Without the PAS, the results also showed pazopanib to be the dominant treatment.

In a series of sensitivity analyses the only scenario where this conclusion was reversed was when ifosfamide had the most favourable PFS assumption that was still within the 95% confidence interval around the central estimate.

There were a number of weaknesses with the analysis. In the comparison with BSC alone:

- The cost per QALY submitted by the company was high, even with the proposed PAS.
- The economic model that extrapolated the main clinical study results over the lifetime of the patient made clear that the impact on overall survival of adding pazopanib to BSC was very limited and the main health benefit was switching remaining survival time from post-progression to pre-progression.

- The estimate of the utility gain from maintaining a patient in a progression-free state was based in part on the modelling of post-progression utility. The attempt to move away from the simplistic assumption of one utility pre-progression and another post-progression with no decline over time is welcome, but the company made the strong assumption that utility declines in a linear way between progression and death and used this to estimate an average post-progression utility. There was no evidence base for this assumption.
- The company noted the high rates of post-study anti-cancer treatment (PSACT) in its correspondence with SMC as a confounding factor in demonstrating clinical effectiveness. At least in a sensitivity analysis more could have been done to control for this factor using statistical methods.
- PSACT also entered into the costing of the economics model but it was noted that the company had used rates at the end of the follow-up of the main study without extrapolating the Kaplan-Meier plots as would be the case with PFS. This may reduce the savings from pazopanib on this heading as PSACT could be postponed rather than avoided.

In the comparison with ifosfamide:

- SMC were informed by clinicians that a variety of treatments were used in STS. The company selected ifosfamide as the only comparator in the economic model apart from BSC alone but this was questioned since it is one of the most expensive (taking account of iv administration) and associated with side-effects. The submission did not clearly demonstrate which patients currently receive ifosfamide and why, or model the costs and benefits for patients who would currently be ifosfamide candidates alone.
- The indirect comparison was seen to be seriously flawed, as noted elsewhere in this document. There was concern the problems of comparability across trials was such that few conclusions could be drawn from the evidence presented.
- The analysis presented by the company assumed no difference in post-progression survival (PPS) with pazopanib, which was in contrast to the assumption made in the comparison with BSC alone. With an assumed difference in PFS and the same PPS this meant there was a difference in OS. This was felt to go beyond anything the clinical evidence could support.
- A PFS advantage was claimed for pazopanib compared to ifosfamide but the 95% confidence interval around the HR for PFS from the indirect comparison included 1.0 and hence it is not statistically significant. The SMC's normal practice is not to consider such differences and this accounted for the majority of the estimated QALY gain for pazopanib.

SMC considered the likely range of cost-effectiveness ratios for pazopanib with the application of the PAS and the remaining uncertainties in the economic case. The committee considered the benefits of pazopanib in the context of the SMC decision modifiers for the comparison against BSC. However, modifiers only apply when the Committee is satisfied that the clinical and economic case for the medicine is robust and this was not demonstrated with pazopanib.

The Committee therefore considered that due to the weaknesses and uncertainties in the economic case and the relatively high ICER the cost-effectiveness for pazopanib in this indication has not been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was received from Sarcoma UK.

Additional information: guidelines and protocols

The European Society for Medical Oncology (ESMO) and European Sarcoma Network Working Group produced updated clinical practice guidelines "Soft tissue and visceral sarcomas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up" in 2012 via a consensus process.[4] These guidelines state that standard chemotherapy is based on anthracyclines as first line treatment for advanced disease. Although multi-agent chemotherapy is not superior to single-agent doxorubicin in terms of overall survival, it may be in terms of response rate. When anthracycline-based chemotherapy has failed or cannot be used, high-level evidence is lacking but the following may apply:

- Ifosfamide if it has not been used previously or high dose ifosfamide in patients who have already received the drug.
- Trabectedin, which has been shown to be effective in leiomyosarcoma and liposarcoma, is recommended as an alternative second line option. Responses to trabectedin have also been seen in synovial sarcoma and in myxoid liposarcoma, although a peculiar pattern of tumour response was noted in myxoid liposarcoma.
- Pazopanib as an option in non-adipogenic soft tissue sarcoma. Its clinical efficacy in selected subgroups is still to be determined through further studies, to optimise the clinical use.
- Additional second line options are given (gemcitabine +/- docetaxel, dacarbazine +/- gemcitabine) but the guidelines advise that, in general, advanced pretreated patients are candidates for clinical studies and also give best supportive care as an option for advanced patients especially if they have failed on further line therapies.

British guidelines, which represent a consensus view of UK sarcoma specialists following a meeting convened by the British Sarcoma Group, were also published in 2010 and were supported by an educational grant from PharmaMar.[5] They make similar recommendations as the ESMO guidelines for first line treatment and note that ifosfamide is standard second-line treatment but advise that there is no standard for second line therapy for patients who fail on doxorubicin and ifosfamide. They note that other agents (dacarbazine, gemcitabine, taxanes and trabectedin) have activity in STS.

Additional information: comparators

Second and subsequent lines of treatment for advanced STS depend on the subtype of the disease, prior treatment and patient characteristics but include ifosfamide BSC, trabectedin (not recommended for use by SMC) and clinical trial treatment.

Cost of relevant comparators

Drug	Dose Regimen	Cost per 21 day cycle (£)	Cost per course (£)
pazopanib	800mg orally once daily continuously	1,569	8,594* for 115 days
trabectedin**	1.5mg/m^2 as a 24 hour intravenous infusion every 3 weeks	3,821	19,105 for 105 days (5 cycles) or 22,926 for 126 days (6 cycles)
ifosfamide***	3g/m^2 daily by intravenous infusion on days 1 to 3	798	3,192 (4 cycles)

Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF March 2012.

* pazopanib is given daily continuously. The cost per course is based on 16.4 weeks (115 days) of treatment which was the median duration in the pivotal study.

**trabectedin was not recommended for use by the SMC for STS; cost based on a body surface area of 1.8m^2.

*** ifosfamide dose of 3g/m^2 daily on days 1 to 3 is based on study used in indirect comparison.

Additional information: budget impact

Without PAS:

The submitting company estimated the population eligible for treatment to be 13 in all five years with an estimated uptake rate of 20% in year 1 and 50% in year 5. The gross impact on the medicines budget was estimated to be £31k in year 1 and £77k in year 5. As other drugs were assumed to be displaced the net medicines budget impact is expected to be £25k in year 1 and £63k in year 5.

With PAS:

The submitting company estimated the population eligible for treatment to be 13 in all five years with an estimated uptake rate of 20% in year 1 and 50% in year 5. The gross impact on the medicines budget was estimated to be £27k in year 1 and £68k in year 5. As other drugs were assumed to be displaced the net medicines budget impact is expected to be £21k in year 1 and £53k in year 5.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. 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.

2. European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) Type II Variation Assessment Report for Votrient® EMEA/H/C/001141/II/0007 www.ema.europa.eu [accessed 20 August 2012]

3. 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.

4. The ESMO / European Sarcoma Network Working Group. Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2012 Oct 1;23(suppl 7):vii92-vii99.

5. Grimer R, Judson I, Peake D, Seddon B. Guidelines for the management of soft tissue sarcomas. Sarcoma 2010;2010:506182.

This assessment is based on data submitted by the applicant company up to and including 12 October 2012.

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.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

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.