SMC Scottish Medicines Consortium
Advising on new medicines for Scotland
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NHS SCOTLAND
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tivozanib 890 micrograms and 1,340 micrograms hard capsules, (Fotivda®)

SMC No 1335/18

Eusa Pharma Limited

8 June 2018

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

ADVICE: following a full submission assessed under the end of life process

tivozanib (Fotivda®) is accepted for restricted use within NHSScotland.

Indication under review: the first-line treatment of adult patients with advanced renal cell carcinoma and for adult patients who are vascular endothelial growth factor receptor and mammalian target of rapamycin pathway inhibitor-naïve following disease progression after one prior treatment with cytokine therapy for advanced renal cell carcinoma (RCC).

SMC restriction: to first-line treatment of advanced RCC.

In a phase III, open-label, randomised, controlled study tivozanib increased progression free survival when compared with a multi-kinase inhibitor in patients with advanced RCC.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of tivozanib. This advice is contingent upon the continuing availability of the PAS in NHSScotland or a list price that is equivalent or lower.

This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting.

Vice Chairman
Scottish Medicines Consortium

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Indication

Tivozanib is indicated for the first line treatment of adult patients with advanced renal cell carcinoma (RCC) and for adult patients who are vascular endothelial growth factor receptor (VEGFR) and mammalian target of rapamycin (mTOR) pathway inhibitor-naïve following disease progression after one prior treatment with cytokine therapy for advanced RCC.[1]

Dosing Information

The recommended dose of tivozanib is 1,340 micrograms once daily for 21 days, followed by a 7-day rest period to comprise one complete treatment cycle of 4 weeks. This treatment schedule should be continued until disease progression or unacceptable toxicity.

The occurrence of undesirable effects may require temporary interruption and/or dose reduction of tivozanib therapy. When dose reduction is necessary, the tivozanib dose can be reduced to 890 microgram once daily with the normal treatment schedule of 21 days of dosing, followed by a 7-day rest period.

Tivozanib should be supervised by a physician experienced in the use of anticancer therapies.[1]

Product availability date

February 2018

Tivozanib meets SMC end of life criteria.

Summary of evidence on comparative efficacy

Tivozanib is a potent and selective inhibitor of VEGF receptors 1, 2 and 3 associated kinase signalling following binding of the VEGF ligand. By inhibiting the signalling through VEGF receptors tivozanib blocks angiogenesis and vascular permeability in tumour tissues.[1]

The submitting company has requested that SMC considers tivozanib when positioned for use as a first line treatment of adult patients with advanced RCC.

The pivotal study, TIVO-1, was an open-label, multicentre, randomised, active controlled, phase III study that included patients aged 18 years or older with prior partial or complete nephrectomy, histologically confirmed RCC with a clear cell component and recurrence or metastases of RCC. Patients had measurable disease per Response Evaluation Criteria in Solid Tumours criteria, Eastern Cooperative Oncology Group performance status (ECOG PS) 0 to 1, life expectancy of at least three months and were treatment-naive or treatment experienced with one or fewer prior systemic treatments (immunotherapy, chemotherapy, or hormonal therapy) for metastatic RCC. Prior systemic therapy given as an adjuvant following nephrectomy was counted as a prior therapy if recurrence was detected within six months of completing treatment. Patients were randomised equally to receive either oral tivozanib 1,340 micrograms once daily for three weeks followed by one week off treatment (four week cycle; treatment cycles were continuous) (n=260); or oral sorafenib 400mg (taken as two 200mg tablets) twice daily continuously for four week cycles (n=257). Study treatment was continued until disease progression, unacceptable toxicity, discontinuation for any other reason or death. Patients were stratified by number of prior treatments for metastatic disease, number of metastatic sites/organs involved and geographic region.[1 2 3] Dose adjustments were specified for treatment related adverse events (AEs) of

grades 3 and 4. Patients in the sorafenib group who experienced progressive disease (PD) were given the option to switch to tivozanib in the extension protocol and patients randomised to tivozanib were discontinued from the study once progression was confirmed and continued treatment with standard of care as per local availability of therapy.[3]

The primary outcome was progression free survival (PFS) assessed by blinded independent radiological review (IRR), in the intention-to-treat population. The overall estimated median PFS at the primary analysis after 310 PFS events was 11.9 months in the tivozanib group and 9.1 months in the sorafenib group, hazard ratio (HR) 0.80 (95% confidence interval (CI):0.64 to 0.99, p=0.04).[2] [3] Important secondary analyses are reported in table 1.

Table 1. Important pre-specified subgroup analyses of the TIVO-1 study.[2, 3]

	Tivozanib (PFS, months)	**Sorafenib (PFS, months)**	**Hazard ratio**	**p-value**
No prior treatment (n=181 in each treatment group)	12.7	9.1	HR = 0.76 95% CI 0.58 to 0.98	0.04
ECOG PS 0 (n=116 tivozanib; n=139 sorafenib)	14.8	9.1	HR = 0.62 95% CI 0.44 to 0.86	0.004
ECOG PS 1 (n=144 tivozanib; n=118 sorafenib	9.1	9.0	HR = 0.92 95% CI 0.68 to 1.24	0.59

PFS = progression free survival, HR = hazards ratio, ECOG PS = Eastern Co-operative group performance status, CI = confidence interval, n = number of patients

The objective response rates, based on blinded IRR were as follows for the tivozanib and sorafenib groups respectively: overall response 33% (n=86/260) versus 23% (n=60/257); complete response 1.2% (n=3/260) versus 0.8% (n=2/257), and partial response 32% (n=83/260) versus 23% (n=58/257). The odds ratio for overall response was 1.62 (95% CI:1.10 to 2.39, p=0.013).[3]

The final protocol-specified median overall survival (OS) (24 months after final patient enrolled) for tivozanib and sorafenib was 28.8 months and 29.3 months respectively, HR 1.24 (95% CI: 0.95 to 1.62).[4] An updated OS analysis (at study end) reported 28.2 months for tivozanib and 30.8 months for sorafenib, HR 1.15 (95% CI: 0.90 to 1.47).[5]

Post-hoc analyses of OS in treatment naïve patients and a Cox regression analysis adjusting for imbalances in baseline characteristics and access to next-line of treatment were in line with the updated OS analysis, suggesting no statistically significant difference between the treatments.[3] [4] Analyses of OS, adjusted for cross-over using the inverse probability of censoring (IPCW) and rank preserving structural failure time (RPSFT) methods gave OS results similar to the primary analysis.

Patient reported Quality of life (QoL) outcomes were measured using multiple questionnaires: EuroQol-5D, Functional Assessment of Cancer Therapy-General (FACT-G), and FACT Kidney Symptom Index–Disease-Related Symptoms. Small reductions in QoL scales, indicating a worsening of QoL, were reported for each tool used but scores were comparable between both treatment arms and there was no statistically significant difference between them.[2, 3] The TIVO-1 extension study reported similar findings for PFS to the TIVO-1 study.[3]

Summary of evidence on comparative safety

In the TIVO-1 study, the median duration of treatment in the tivozanib group was 12 months and in the sorafenib group was 9.5 months.[2] Any treatment-related adverse event (AE) was reported by 78% of patients in the tivozanib group (n=259) and 90% in the sorafenib group (n=257).[3] In the tivozanib and sorafenib groups respectively, patients reporting a grade 3 or higher AE were 61% versus 70%, patients with a dose reduction due to treatment emergent AEs were 14% versus 43%, the proportion of AEs that led to dose interruptions were 19% versus 36%, and patients discontinuing therapy due to an AE was 4% versus 5%.[2]

The most common AEs occurring in the tivozanib and sorafenib groups of the TIVO-1 study respectively were; hypertension (45% versus 35%), diarrhoea (24% versus 33%), dysphonia (21% versus 5%), fatigue (21% versus 16%), asthenia (17% versus 17%) back pain (15% versus 8%), hand-foot syndrome (14% versus 54%), nausea (13% versus 7%), headache (9% versus 4%) and alopecia (2% versus 21%). Hypertension and dysphonia are considered to be on-target AEs of tivozanib. There were 13 deaths occurring in patients treated with tivozanib not considered to be a result of disease progression, it is unclear if these deaths were treatment related.[2, 3]

Posterior reversible encephalopathy syndrome (PRES) was reported in one patient following treatment with tivozanib; it is a neurological disorder which can cause headache, seizures, blindness and other neurological disturbances. Tivozanib must be discontinued if PRES develops.[1]

Summary of clinical effectiveness issues

RCC is the most common type of kidney cancer accounting for 90 to 95% of kidney neoplasms and it most commonly occurs between the ages of 60 and 70 years. At the time of diagnosis approximately 25 to 30% of patients have metastatic disease with a 10% chance of 5 year survival.[3] Surgical resection is most commonly used in localised disease and targeted therapies are most commonly recommended in metastatic disease.[3] SMC clinical experts advise the tyrosine kinase inhibitors, pazopanib and sunitinib, are currently the first line systemic treatment option for patients with advanced or metastatic RCC in Scotland. Tivozanib meets SMC end of life criteria.

The submitting company has requested that SMC considers tivozanib when positioned for use as a first line treatment of adult patients with advanced RCC. This subgroup accounted for 70% (362/517) of patients in the TIVO-1 study.

In the TIVO-1 study, tivozanib was associated with a statistically significant increase in median PFS by 2.8 months over sorafenib, and patients in both groups had similar median OS.[1,3,4] Similar results were reported in the subgroup of patients with no prior treatment.[4,5]

The TIVO-1 study had a one-way treatment switching design, which allowed patients on sorafenib to switch to tivozanib following progression, but patients on tivozanib received local physician's choice, potentially confounding the OS result. The proportions of patients who received treatment with a next line therapy were 38% (81/211) in the tivozanib group and 76% (174/230) in the sorafenib group. Access to next line of treatment was varied by geographical region; in particular, access to second line targeted therapies was lower in centres in Russia and Ukraine, which combined to account for 56% of the patients in the TIVO-1 study.[3]

The study comparator, sorafenib, is not commonly used in Scotland for the treatment of advanced RCC. Other limitations of the study include the open-label design and an imbalance in baseline characteristics

indicating that patients in the sorafenib group may have had less severe disease. The TIVO-1 study enrolled only 40 patients from North America and Western Europe. Cross-over of the Kaplan-Maier survival curves for PFS and OS suggest that the proportional hazards assumption may not be valid. The TIVO-1 study only included patients with clear cell or with a clear cell component of RCC, however this accounts for between 75 to 90% of RCC.[3] In the subgroup of patients with ECOG PS 1 at baseline, there was no PFS advantage for tivozanib over sorafenib.[4]

There are no direct comparative data for tivozanib versus pazopanib or sunitinib, the most relevant comparators for use in Scotland. The submitting company presented four matching adjusted indirect comparisons (MAICs) of PFS and OS in treatment naïve patients, using patient level data from the tivozanib arm of the TIVO-1 study and the published information on pazopanib and sunitinib from the COMPARZ study.[7] A conventional mixed treatment comparison (MTC) was not performed due to non-proportional hazards. Matching was conducted based on age, gender, number of metastatic sites, Memorial Sloan-Kettering Cancer Centre (MSKCC) score, (which is used to predict survival in RCC), and switching to a next-line of therapy. The results indicated there was no statistically significant difference between tivozanib and pazopanib or sunitinib for PFS or OS. Limitations of this analysis included; possible confounding differences in baseline characteristics which were unaccounted for during the matching process and difference in length of follow up. The company also provided Bayesian MTCs of five AEs of interest (diarrhoea, hand-foot syndrome, anaemia, asthenia/fatigue and hypertension) for tivozanib, pazopanib and sunitinib. The only comparison that produced an odds ratio with credible intervals that did not include one was the comparison of tivozanib with sunitinib in hand foot syndrome, which favoured tivozanib. For all other comparisons the credible intervals were wide, making it difficult to assess the true value of these comparisons.

There is no restriction on co-administration with potent CYP3A4 inhibitors for tivozanib, this is in contrast to pazopanib and sunitinib, which include warnings about interactions in their respective Summaries of Product Characteristics.[1, 5 6]

Clinical experts consulted by SMC considered that the place in therapy of tivozanib may be as an alternative treatment option to pazopanib and sunitinib.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of tivozanib, as an end of life medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- RCC affects patients from a wide age range and is often only detected when it has reached the later stages of disease. Life expectancy of advanced RCC is poor with a median survival of 2 to 3 years. Symptoms of progressive disease such as fatigue, fever and night sweats, have considerable impact on patient quality of life.
- In addition, adverse effects (AEs) associated with the use of existing first-line tyrosine kinase inhibitor (TKI) therapy also impact on daily life. Such AEs include hand and foot syndrome, diarrhoea and fatigue. The patient group described how fear of disease progression in the context of limited treatment options for advanced RCC may result in some patients choosing to persist with treatment despite the heavy AE burden.
- According to the 2016 Kidney Cancer UK annual survey, approximately a third of patients on first-line TKIs consider side-effects of treatment to be unmanageable. Additional evidence

suggests that around one quarter of patients discontinue existing TKIs because of unpleasant AEs.[7, 8]

- PACE clinicians suggested that tivozanib was likely to have similar benefits to existing first-line TKIs in terms of the ability to delay disease progression, however they noted that a different and potentially more favourable AE profile may allow patients to maintain a better quality of life and continue to live a more normal life for longer.
- PACE participants were of the view that tivozanib offered a valuable additional first-line oral treatment option which may be particularly relevant for patients unable to tolerate existing first-line TKIs.

Additional Patient and Carer Involvement

We received a patient group submission from Kidney Cancer Scotland. Kidney Cancer Scotland is a registered charity. Kidney Cancer Scotland has received 9% pharmaceutical company funding in the past two years, including from the submitting company. A representative from Kidney Cancer Scotland participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing tivozanib to sunitinib and pazopanib for the treatment of adult patients with advanced renal cell carcinoma. The company has positioned tivozanib for use in patients who are treatment naïve. Based on SMC expert responses sunitinib and pazopanib are the comparators most likely to be displaced in Scotland.

A three state partitioned survival model was presented which included the health states alive pre-progression, alive post-progression and death. The time horizon for the analysis was 10 years. In the economic analysis, the company adjusted the patient characteristics from the TIVO-1 study to match those in the sunitinib and pazopanib arms of the COMPARZ study.[4 7] For tivozanib PFS and OS were estimated by fitting the adjusted Kaplan Meier data to independent parametric curves. For the comparator arms, Kaplan Meier data were extracted from the COMPARZ study. The company used the Weibull function to extrapolate long term outcomes for all treatments. It is worth noting that the company also conducted a MAIC as described above. Hazard ratios for both PFS and OS were estimated and were non-significant, however these were not used in the economic analysis. Based on the MAIC, PFS and OS curves for tivozanib versus sunitinib and tivozanib versus pazopanib crossed suggesting that the assumption of proportional hazards did not hold.

Utilities for the pre-progression and post-progression health states were estimated to be 0.73 and 0.65 respectively. The company derived these values directly from the TIVO-1 study.[4] Patients completed the EQ-5D-5L questionnaire on the first day of each treatment cycle (for as long as the patient remained in the study).

Medicine acquisition costs for all treatments were included in the analysis. Health state costs included monitoring costs associated with being in the pre-progression and post-progression health states, which consisted of a monthly consultant led oncology outpatient visit, CT scan (3 monthly), blood tests, full blood count, liver function tests (3 monthly) and thyroid function tests (3 monthly). Adverse event costs associated with grade 3 or more events were included.

A Patient Access Scheme (PAS) was proposed by the submitting company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS a simple discount is offered on the price of the medicine. PASs are in place for sunitinib and

pazopanib and these were included in the analysis by using an estimate of the PAS prices of sunitinib and pazopanib based on information that is in the public domain.

Table 2: Base case results (List price for all medicines)

Tivozanib vs sunitinib	Costs	QALYs	ICER
Tivozanib	£54,603	1.89	
Sunitinib	£52,265	1.98	
Incremental	£2,338	-0.08	dominated
Tivozanib vs pazopanib			
Tivozanib	£53,826	1.89	
Pazopanib	£50,318	2.04	
Incremental	£3,508	-0.15	dominated

Table 3: Scenario analysis (Cost-minimisation analysis)

Base case	**Incremental costs/savings**
Versus sunitinib	-£998
Versus pazopanib	-£469
Sensitivity analysis using relative dosing intensities (Tivozanib 94%, pazopanib and sunitinib 86%)	
Versus sunitinib	£2,063
Versus pazopanib	£2,518

SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented. When the PAS for tivozanib was included in the results, tivozanib became a cost-effective treatment option.

There were some limitations with the analysis which include the following;

- There are no directly comparative PFS and OS data versus sunitinib and pazopanib. As such there is some uncertainty surrounding the long term comparative effectiveness of tivozanib versus sunitinib and pazopanib.
- Based on the results of the MAIC, tivozanib resulted in a non-significant difference for PFS and OS versus both sunitinib and pazopanib. Given that no significant differences between treatments were demonstrated for these outcomes, the results of the cost minimisation analysis (table 3), which removed all non-significant differences between the treatments, were considered to be the most relevant results for decision making.

After considering all the available evidence and the output from the PACE process, the Committee accepted tivozanib for restricted use in NHS Scotland.

Additional information: guidelines and protocols

The European Society of Medical Oncology (ESMO) produced a clinical practice guideline in 2016 titled ‘Renal cell carcinoma: ESMO Clinical practice guidelines for diagnosis, treatment and follow-up’. The guideline advises partial or radical nephrectomy for patients with local or locoregional RCC. Radiofrequency ablation, cryoablation and active surveillance are alternative options for some patient groups. Radical nephrectomy is suggested for patients with locally advanced disease. For the management of patients with metastatic disease the guideline notes that the recommendations primarily

relate to patients with clear cell histology, as most studies were conducted in this group of patients. For patients with metastatic disease and good or intermediate prognosis; sunitinib or pazopanib monotherapy (most commonly used), or bevacizumab with interferon are recommended first line treatments. High dose interleukin-2, sorafenib and low dose interferon with bevacizumab are listed as alternative first line treatment options. For patients with a poor prognosis temsirolimus is the preferred option with sunitinib, pazopanib and sorafenib as alternative options. Best supportive care is also a management option in patients with poor prognosis.[9]

The European Association of Urology (EAU) guidelines on renal cell carcinoma were most recently updated in 2017. The recommendations in this guideline for the first line treatment of metastatic clear cell RCC are in line with the ESMO recommendations above. This guideline additionally recommends sunitinib in patients requiring treatment for non-clear cell RCC.[10]

Additional information: comparators

Pazopanib and sunitinib are the relevant comparators which are used as first line treatment for patients with advanced RCC in NHS Scotland.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
Tivozanib	**1340 microgram orally daily for three weeks followed by a one-week treatment free period to complete a four week cycle**	**26,676**
Pazopanib	800mg orally daily	27,203
Sunitinib	50mg orally daily for four weeks followed by a 2-week treatment free period to complete a six week cycle	27,202

Doses are for general comparison and do not imply therapeutic equivalence. Costs from dm+d and BNF online on 21 February 2018. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 755 patients eligible for treatment with tivozanib in year 1 rising to 833 patients in year 5. The estimated uptake rate was 10% in year 1 (76 patients) and 30% in year 5 (250 patients). A discontinuation rate of 11.5% was applied to each year.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

References

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This assessment is based on data submitted by the applicant company up to and including **13 April 2018.**

Medicine prices are those available at the time the papers were issued to SMC for consideration. 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.