erdafitinib film-coated tablets (Balversa®)

Janssen-Cilag Ltd

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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 NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the end of life and orphan equivalent medicine process

erdafitinib (Balversa®) is accepted for use within NHSScotland.

Indication under review: as monotherapy for the treatment of adult patients with unresectable or metastatic urothelial carcinoma (UC), harbouring susceptible FGFR3 genetic alterations who have previously received at least one line of therapy containing a PD-1 or PD-L1 inhibitor in the unresectable or metastatic treatment setting.

In a phase III study of patients with metastatic UC and fibroblast growth factor receptor (FGFR) alterations who had progression after one or two previous treatments that included a programmed cell death protein 1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor, erdafitinib significantly improved overall survival compared with investigators choice of single agent chemotherapy.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

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

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Erdafitinib is a pan-fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor that blocks the activity of abnormal FGFR on the surface of cancer cells. Mutations and translocations in FGFR genes have been associated with neoplastic progression and tumour vascularisation in urothelial cancer. Inhibition of FGFRs stops the protein from functioning and thereby slows the growth and spread of cancer.[1, 2]

A susceptible FGFR3 gene alteration must be confirmed as determined by a validated test method before taking erdafitinib. The recommended starting dose is 8 mg orally once daily, taken with or without food. Serum phosphate level should be assessed prior to the first dose and between 14 and 21 days after initiating treatment and the dose up-titrated to 9 mg once daily if the serum phosphate level is <2.91 mmol/L, and there is no drug-related toxicity. If the phosphate level is >2.91 mmol/L then relevant dose modifications should be made as outlined in the Summary of Product Characteristics (SPC). After day 21 the serum phosphate level should not be used to guide up-titration decisions but should be monitored monthly. Treatment should continue until disease progression or unacceptable toxicity occurs. See the summary of product characteristics (SPC) for further information including recommended monitoring, dose modifications and management of adverse reactions. [3]

1.2. Disease background

Most cases of bladder cancer (90%) are classified as urothelial carcinomas where the cancer develops in the transitional (urothelial) cells that line the upper and lower urothelial tract. Approximately 15% to 20% of patients with metastatic or advanced urothelial carcinoma harbour FGFR gene mutations or translocations. The most significant risk factor for bladder cancer is smoking, which is associated with around 50% of diagnoses; other risk factors include previous occupational exposure to aromatic amines or polycyclic aromatic hydrocarbons, and ionising radiation. Bladder cancer is more prevalent in men and in older people.[2, 4, 5]

1.3. Treatment pathway and relevant comparators

Unresectable and metastatic urothelial carcinoma is an incurable disease with a poor prognosis. Progression or recurrence after first line treatment is common and median overall survival (OS) after first line platinum-based chemotherapy is 12 to 14 months. The recommended first line treatment for fit patients is cisplatin-based chemotherapy, most commonly with gemcitabine. Carboplatin may be used as an alternative in patients unsuitable for cisplatin. Patients who are progression-free after completing platinum-based chemotherapy receive maintenance treatment with avelumab until disease progression or unacceptable toxicity (SMC2359). If patients experience a relapse following platinum chemotherapy, pembrolizumab monotherapy may be used second line (SMC1291/18). Subsequent treatment options following avelumab or pembrolizumab are limited. Clinical experts consulted by SMC indicated that taxane monotherapy may be considered however benefit is limited. Experts also noted that retreatment with platinum-based chemotherapy may be an option for patients who had a durable initial response. Enfortumab vedotin and vinflunine are recommended as potential treatments in guidelines but

are not recommended for use by SMC (SMC2505 and SMC686/11). Other options include best supportive care or enrolment in a clinical trial.[2, 6, 7] The submitting company considered that paclitaxel monotherapy was the only relevant comparator for this submission.

1.4. Category for decision-making process

Erdafitinib meets SMC end of life and orphan equivalent criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of erdafitinib for this indication is from cohort 1 of the THOR study. Details are presented in Table 2.1.[2, 8]

Table 2.1. Overview of relevant studies

Criteria	THOR cohort 1[8]
Study design	Multicentre, randomised, open-label, phase III study
Eligible patients	• Adults ≥ 18 years with histologically confirmed transitional cell carcinoma of the urothelium (minor components [<50% overall] of variant histology such as glandular or squamous differentiation, or evolution to more aggressive phenotypes such as sarcomatoid or micropapillary change were acceptable). • Metastatic or unresectable disease, with disease progression requiring a change in treatment prior to randomisation. • Up to two prior treatment lines with one to include an anti–programmed cell death protein 1 (PD-1) or anti-programmed death-ligand 1 (PD-L1) agent as monotherapy or as combination therapy. • Tumours must have at least one of the following fusions: FGFR2-BICC1, FGFR2-CASP7, FGFR3-TACC3, FGFR3-BAIAP2L1; or one of the following FGFR3 mutations: R248C, S249C, G370C, Y373C as determined by central laboratory screening or by local historical test results (from tissue or blood). • Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2 and adequate organ function.
Treatments	Oral erdafitinib 8 mg daily in a 21-day cycle (with a dose increase to 9 mg on day 14 if serum phosphate level was <9.0 mg/dL (<2.91 mmol/L) and there was no drug-related toxicity), or Investigators choice of chemotherapy: vinflunine 320 mg/m^2 body surface area (BSA) or docetaxel 75 mg/m^2 BSA, both administered once every 3 weeks via intravenous infusion. Treatment was to continue until disease progression or unacceptable toxic effects.
Randomisation	Patients were randomised equally to erdafitinib (n=136) or chemotherapy (n=130). Randomisation was stratified according to region (North America versus Europe versus rest of world), ECOG PS (0 or 1 versus 2) and disease distribution (presence versus absence of visceral metastases: lung, liver or bone).
Primary outcome	The primary outcome was overall survival (OS) and was defined as the time between date of randomisation and death due to any cause.
Secondary outcomes	• Progression free survival (PFS), defined as the duration in days between date of randomisation to the date of disease progression or death due to any cause, whichever occurred first, assessed by the investigator per RECIST v1.1 criteria.

	• Objective response rate (ORR), defined as the proportion of patients that achieved a complete response (CR) or partial response (PR) assessed by the investigator per RECIST v1.1. • Time until Urinary bladder cancer Symptom Deterioration (TUSD)-3 is based on a urinary bladder cancer symptom score from three items from the Functional Assessment of Cancer Therapy–Bladder Cancer (FACT-Bl) (BL1: urinary incontinence, BL2: urinary frequency and BL3: urinary pain) and is defined as the first time to increase in urinary symptoms score from the day of randomisation beyond a meaningful change threshold compared to baseline.
Statistical analysis	A hierarchical statistical testing strategy was applied in the study with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Therefore, the results reported for these outcomes are descriptive only and not inferential (no p-values reported). The following secondary outcomes were tested sequentially: PFS, ORR and TUSD-3.

At the interim analysis (data cut-off 15 January 2023), conducted after a median survival follow-up of 15.9 months, erdafitinib demonstrated superiority to investigators choice of chemotherapy (docetaxel or vinflunine). This was considered the final analysis and study data was unblinded, patients in the chemotherapy group were permitted to cross-over to receive erdafitinib.[2, 8]

Table 2.2: Primary and selected secondary outcome results from the THOR cohort 1 at the interim (final) analysis in the ITT population[2, 8]

	Erdafitinib n=136	**Chemotherapy[A] n=130**
Median follow-up (months)	18.0	14.9
Primary outcome: overall survival		
Deaths, n	77	78
Median OS, months	12.1	7.8
HR, 95% CI	0.64 (0.47 to 0.88), p=0.005	
KM estimated OS at 12 months	51%	38%
Secondary outcome: investigator assessed progression free survival per RECIST v1.1		
PFS events, n	101	90
Median PFS, months	5.6	2.7
HR, 95% CI	0.58 (0.44 to 0.78), p<0.001	
KM estimated PFS at 12 months	17%	8%
Secondary outcome: investigator assessed objective response rate per RECIST v1.1		
ORR, % (n)	46% (62)	12% (15)
Relative risk (95% CI)	3.94 (2.37 to 6.57), p<0.001	
CR	6.6%	0.8%
PR	39%	11%

CI= confidence interval, CR=complete response, HR= hazard ratio, ITT=intention-to-treat, KM= Kaplan Meier, ORR= objective response rate, OS=overall survival, PFS= progression free survival, PR=partial response, RECIST v1.1= Response Evaluation Criteria In Solid Tumours version 1.1. [A] Investigators choice of docetaxel (n=82) or vinflunine (n=48).

2.2. Health-related quality of life outcomes

Health-Related Quality of Life (HRQoL) was assessed using patient reported questionnaires: Functional Assessment of Cancer Therapy-Bladder Cancer (FACT-Bl), Time until Urinary bladder

cancer Symptom Deterioration (TUSD-3) and EQ-5 D-5 L. FACT-BI and EQ-5 D-5 L utility index and visual analogue scores were similar between groups and were maintained between groups up to cycle 11. TUSD-3 (a subset of FACT-BI items) was the third secondary outcome included in the hierarchical testing procedure, results indicated no statistically significant difference between groups for the time to first clinically meaningful urinary symptom deterioration. [2, 9]

*Other data were also assessed but remain confidential.**

2.3. Supportive studies

Study BLC2001 was an uncontrolled, open-label, phase II study in patients with locally advanced, metastatic or surgically unresectable urothelial carcinoma who had FGFR alterations (similar to THOR cohort 1) and received at least one previous chemotherapy, or were treatment naïve but ineligible for the standard chemotherapy regimen. In a subgroup of 99 patients that received oral erdafitinib 8 mg daily (with individualised up-titration to 9 mg daily), the confirmed investigator assessed ORR was 40%, investigator assessed median progression free survival (PFS) was 5.5 months and median OS was 13.8 months.[2, 10]

2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing erdafitinib with paclitaxel, the submitting company conducted indirect treatment comparisons. The economic base case includes OS data from the UK real world (RW) metastatic urothelial carcinoma (mUC) registry comparison and PFS data from the PLUTO comparison. Further details have been provided in Table 2.3.

Table 2.3: Summary of indirect treatment comparisons

Criteria	Overview	
Design	Unanchored, population-adjusted ITC	Unanchored MAIC
Population	• Adult patients with unresectable or metastatic urothelial carcinoma • Had received no more than two lines of treatment that included a PD-1 or PD-L1 inhibitor (THOR cohort 1) • Had received at least one line of treatment that included a PD-1 or PD-L1 inhibitor (UK RW mUC) • FGFR3/2 genetic alterations (reported for erdafitinib only)	• Adult patients with locally advanced or metastatic transitional cell carcinoma • Progressive disease during or after one prior platinum-containing regimen (PLUTO) • Progressive disease after at least one prior chemotherapy (BLC2001) • Had received no more than two lines of treatment that included a PD-1 or PD-L1 inhibitor (THOR cohort 1) • FGFR3/2 genetic alterations (reported for erdafitinib only)
Comparators	Erdafitinib versus paclitaxel	Erdafitinib versus paclitaxel
Studies included	THOR cohort 1[8] (erdafitinib), n=126 [A] UK RW mUC cohort study (paclitaxel), n=54	THOR cohort 1[8] (erdafitinib), n=136 BLC2001[10] (erdafitinib), n=99 PLUTO[11] (paclitaxel), n=65
Outcomes	OS and TTNT	OS, PFS and ORR
Results	ATC adjusted results[B] OS HR: 0.38 (95% CI: 0.25 to 0.59) TTNT HR: 0.59 (95% CI: 0.39 to 0.87)	OS HR: 0.59 (95% CI: 0.42 to 0.85) PFS HR: 0.81 (95% CI: 0.59 to 1.11) ORR OR: 4.40 (95% CI: 1.95 to 9.94)

ATC: average treatment effect for the control; CI: confidence interval; FGFR: fibroblast growth factor receptor; HR: hazard ratio; IPD: individual patient data; ITC: indirect treatment comparison; ITT: intention-to-treat; MAIC: match-adjusted indirect comparison; mUC: metastatic urothelial carcinoma; ORR: objective response rate; OS: overall survival; PFS: progression free survival; PD-1: programmed death receptor-1; PD-(L)1; programmed death-ligand 1; OR: Odds Ratio; RW: real world; TTNT: time to next treatment

[A] Nine patients with cancer stage 0 and one patient who had received 3 prior lines of treatment from the THOR ITT population were excluded. [B]THOR trial data was reweighted to mimic the patient characteristics of the UK RW mUC cohort study.

3. Summary of Safety Evidence

Overall, the regulator stated that the safety profile of erdafitinib was consistent with non-clinical studies and known class effects of FGFR inhibitors. It noted that risks associated with erdafitinib toxicities are clinically relevant but manageable with treatment interruption and dose modification.[2]

In THOR cohort 1, at the January 2023 data cut-off the median duration of treatment in the erdafitinib group was 4.8 months and in the chemotherapy group was 1.4 months. Any treatment-related adverse event (TRAE) was reported by 97% (131/135) of patients in the erdafitinib group and 87% (97/112) in the chemotherapy group and these events were classified as grade 3 or 4 in 46% of both treatment groups. In the erdafitinib and chemotherapy group respectively, patients with a reported serious TRAE were 13% versus 24%, dose reductions due to TRAEs were required in 66% versus 21%, the proportion of TRAEs that led to dose interruptions were 66% versus 20% and patients discontinuing therapy due to a TRAE was 8.1% versus 13%.[8]

The most frequently reported TRAEs of grade 3 or higher in the erdafitinib group were: palmar–plantar erythrodysesthesia syndrome (9.6% versus 0), stomatitis (8.1% versus 1.8%), onycholysis, (5.9% versus 0), and hyperphosphatemia (5.2% versus 0). In the chemotherapy group these were: neutropenia (0 versus 13%) and anaemia (3.0% versus 6.3%).[8]

Hyperphosphataemia is an expected transient pharmacodynamic class effect of FGFR inhibitors. In a pooled analysis including THOR cohorts 1 and 2 (n=308), the median time to hyperphosphataemia onset was 15.5 days, 8.1% of patients required a dose reduction or interruption and the incidence of prolonged cases was low. Other clinically important AEs associated with erdafitinib (and the incidence of grade 3 or 4 events in THOR cohort 1) include skin disorders (12%), nail disorders (11%), central serous retinopathy (2.2%) and other eye disorders (2.2%). See the SPC for further information including advice on monitoring, dose modifications and treatment interruption and withdrawal.[2, 3, 8]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In THOR cohort 1, at the January 2023 data cut-off with a median survival follow-up of 15.9 months, compared with investigators choice of chemotherapy, erdafitinib was associated with a statistically significant improvement in overall survival and was considered clinically relevant by the regulator. Significant improvements were also observed in hierarchically tested secondary outcomes including PFS and objective response rate (ORR) for erdafitinib compared with chemotherapy. Subgroup analyses were generally supportive.[2, 8]

4.2. Key uncertainties

- There is no standard treatment for unresectable or metastatic urothelial carcinoma following platinum-based chemotherapy and PD-L1 therapy in Scottish clinical practice.

Options include taxane monotherapy (most SMC experts indicated with paclitaxel) which is considered on an individual basis, retreatment with platinum-based chemotherapy depending on previous response, enrolment in a clinical trial or best supportive care. There is no direct evidence comparing erdafitinib with these treatments.

- In the absence of direct evidence, the submitting company conducted indirect comparisons with erdafitinib and paclitaxel which were associated with a number of limitations.
    - For the comparison between erdafitinib (THOR cohort 1) and paclitaxel from the UK RW mUC, there were differences in the patient populations based on FGFR alteration status and there was a large quantity of missing data which included ECOG status and tumour stage diagnosis that required imputation. There was methodological heterogeneity in study design and size, and known limitations associated with the use of registry data that may have introduced bias. For the comparison between erdafitinib (THOR cohort 1 and BLC2001) and paclitaxel (PLUTO) there were significant differences in the patient populations including FGFR alteration status, number of prior treatments and prior PD-L1 treatment which limits generalisability to the target population. Due to the limitations described, the results of both indirect comparisons are highly uncertain.
    - SMC clinical experts considered that paclitaxel may have broadly similar efficacy to the chemotherapy group (docetaxel [63%] and vinflunine [37%]) and therefore direct data from the THOR study may also be relevant for decision-making.
- Subsequent anticancer therapy was received by 32% of patients in the erdafitinib group and 37% in the chemotherapy group, this included treatment with antibody drug conjugates (such as enfortumab vedotin) and retreatment with FGFR or PD-L1 inhibitors which are not reflective of the treatment pathway in Scotland. This may confound overall survival and increase uncertainty regarding the magnitude of benefit that may be observed in Scottish practice.[8]
- Compared with the chemotherapy group, there was a higher proportion of patients aged <65 years in the erdafitinib group (43% versus 35%) and more patients had received only one line of prior treatment (33% versus 25%), this could potentially bias the results in favour of erdafitinib if the population in this group is younger and has required only one prior line of therapy. [8]

4.3. Clinical expert input

Clinical experts consulted by SMC considered that erdafitinib fills an unmet need as there are limited effective treatment options in this setting, they indicated that it is a therapeutic advance because of the improvement in survival outcomes compared with docetaxel or vinflunine observed in THOR cohort 1. It is likely to be used as per the licence in eligible patients whose disease has progressed following treatment with immunotherapy.

4.4. Service implications

Additional clinical service capacity may be required to dispense, prescribe, monitor and treat toxicities. Erdafitinib may be advantageous for patients as it is an oral formulation that can be

taken at home compared to some alternative treatments that may require inpatient administration.

Diagnostic test required to identify patients eligible for treatment: contact local laboratory for information.

5. 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 erdafitinib, as an orphan-equivalent and end of life medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Advanced or metastatic urothelial carcinoma is a severe condition associated with significant morbidity and a poor prognosis. There is a high symptom burden at this stage of disease and significant toxicities associated with current treatment options can leave patients feeling physically and emotionally exhausted. A high level of care is needed during the metastatic course of disease which requires significant support from family and carers.
- There is a high unmet need in this patient population because of the poor prognosis and lack of effective treatments available. Some patients may be eligible for taxane-based chemotherapy which has poor response rates, no meaningful survival benefit and is associated with significant toxicity. Most patients are not suitable or choose to decline further chemotherapy and will receive best supportive care.
- Erdafitinib is a targeted treatment for patients with susceptible FGFR3 alterations that may improve survival outcomes and delay disease progression. Well-managed side effects and a reduction in symptom burden mean that quality of life could also be maintained for longer. These potential benefits could improve physical and mental well-being, allow patients to continue normal daily activities and spend quality time with loved ones. PACE participants described how patients would welcome the availability of this novel precision medicine and hope that it will drive further innovation and therapeutic advances in the treatment of bladder cancer.
- Erdafitinib is an oral medication which is advantageous for patients as it can be self-administered at home with fewer and less burdensome hospital visits required compared with chemotherapy.
- Genetic testing for FGFR3 mutations or translocations is required to select eligible patients. This is not routinely carried out in NHSScotland and will therefore have implications for laboratory services but would bring bladder cancer into step with other malignancies. Patients would need to attend regular appointments to monitor efficacy and side effects. Hyperphosphataemia is a common side effect that needs to be actively managed.
- The place in treatment for erdafitinib would be on disease progression for patients who have previously received at least one line of therapy containing a PD-1 or PD-L1 inhibitor in the

unresectable or metastatic treatment setting as per the UK marketing authorisation.

Additional Patient and Carer Involvement

We received patient group submissions from Action Bladder Cancer and Fight Bladder Cancer. Action Bladder Cancer is a registered charity and Fight Bladder cancer is a Scottish charitable incorporated organisation. Action Bladder Cancer has received 7.6% pharmaceutical company funding in the past two years, including from the submitting company. Fight Bladder Cancer has received 28% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from both patient groups participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

A summary of the economic analysis provided by the submitting company is outlined in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	40-year time horizon. A shorter time horizon of 20 years was used in sensitivity analysis.
Population	Adult patients with unresectable or metastatic urothelial carcinoma, harbouring susceptible FGFR3 genetic alterations who have previously received at least one line of therapy containing a PD-1 or PD-L1 inhibitor in the unresectable or metastatic treatment setting.
Comparators	Paclitaxel monotherapy
Model description	A partitioned survival model was used with three mutually exclusive health states: PFS, progressed disease and death. Time to discontinuation (TTD) data were used to estimate when patients were on and off treatment in the progression-free and progressed disease health states. Following progression, around 30% of patients received subsequent treatment based on the THOR study, with the distribution of treatments estimate from the UK RW mUC study.
Clinical data	The key clinical data source for the erdafitinib arm was the THOR study, with patient characteristics adjusted to reflect the UK RW mUC study. For paclitaxel, the data from the UK RW mUC study informed OS and time to next treatment (TTNT) with the PLUTO study used for PFS and adverse event rates. A scenario analysis using the TTNT data as a proxy for PFS was also explored.
Extrapolation	The THOR OS data for erdafitinib were extrapolated beyond the follow up period (median 15.9 months) with curve selection based on a combination of goodness-of-fit statistics, visual inspection and plausibility of the survival estimates. The submitting company's clinical experts estimated 3-year survival of 15% (range 5%-25%), 5-year survival of 5% (1%-10%) and 10-year survival of 1% (0%-10%). On this basis the log-logistic was selected as it had a better statistical fit than the log-normal, a similar hazard function to the observed hazard and provided slightly more conservative estimates. The log-logistic was also selected for PFS and TTNT. For the paclitaxel arm, OS was informed by survival models fitted to the UK RW mUC cohort data. As all models had a similar fit, clinical plausibility was used to select the most appropriate curve for the base case analysis. On this basis the log-logistic curve was selected as it has a hazard function similar to the observed hazard. In the absence of PFS data from the UK RW mUC study, a MAIC analysis comparing erdafitinib with paclitaxel using the PLUTO study estimated a hazard ratio of 0.81 (95% CI: 0.59, 1.11). As the PFS curves for erdafitinib in

	the base case (ATC-adjusted analysis) and the MAIC were similar, the company concluded it would be reasonable to apply this MAIC-derived HR to estimate PFS in the paclitaxel arm.
Quality of life	EQ-5D data were collected in THOR study at baseline, day 14 of cycle 1 (when serum phosphate levels are measured), and day 1 of every subsequent cycle. In the base case analysis, utility value estimates for the PF and progressed disease health states were estimated using pooled data from both treatment arms.
Costs and resource use	Medicine acquisition, administration, adverse event and subsequent treatment costs were included. Other costs included in the model were health state resource use/disease management costs (included ongoing monitoring and follow-up), adverse event costs, costs of FGFR testing and ophthalmology assessments, subsequent treatment costs and end-of-life care costs.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS a discount was offered on the list price.

6.2. Results

A summary of the base case results with the PAS is provided in Table 6.2. The key driver of the incremental cost for erdafitinib was the medicine acquisition cost with most of the quality-adjusted life-year (QALY) gains occurring in the progressed disease health state.

Table 6.2 Base Case Results (PAS price)

	Incr. LYG	ICER (£/QALY)
erdafitinib	0.91	21,770
paclitaxel	-	-

Abbreviations: Incr. = incremental; ICER = incremental cost-effectiveness ratio; LYG= life years gained; PAS = patient access scheme; QALYs =quality-adjusted life years

6.3. Sensitivity analyses

The company provided deterministic, probabilistic and scenario analyses to test the key uncertainties in the model. Selected sensitivity analyses are provided in Table 6.3 below. The results were particularly sensitive to the OS estimates and comparative data source.

Table 6.3 Sensitivity and Scenario Analysis Results (PAS price)

	Parameter	Base case	Scenario	ICER (£/QALY)
	Base case			21,770
1	Erdafitinib overall survival	Log-logistic	Lower bound of log-logistic scale parameter	26,806
2		Log-logistic	Upper bound of log-logistic shape parameter	25,536
3		Log-logistic	Gamma	23,388
4	Comparative data source	ITC using THOR and UK mUC study	Direct data from THOR study comparing erdafitinib versus chemotherapy	50,918
5	Paclitaxel arm data source	UK mUC study	PLUTO study	26,178

6	Alternative utility values	Progression-based	Time to death	18,396
7		Progression-based	Progression-based from multivariate regression model	23,489
8	Time horizon	Lifetime (40 years)	20 years	21,803
9	Subsequent treatments	8.82% receive pembrolizumab after paclitaxel	4.16%	26,153
10		8.49% receive pembrolizumab after erdafitinib	14.46%	27,356
11	Comparative data source	ITC using THOR and UK mUC study	HRs for PFS and OS for erdafitinib vs chemo from THOR study applied to modelled UK RW mUC curves	26,409
Additional sensitivity analysis results using THOR data directly				
	Base case (THOR study)			50,918
12	Erdafitinib overall survival	Log-logistic	Gamma	69,309
13		Log-logistic	lognormal	49,258
14	Chemotherapy overall survival	Exponential	Gamma	50,831
15			Weibull	51,340
16	Time horizon	40 years	20 years	51,280
17			10 years	53,525

Abbreviations: Incr. = Incremental; ICER =incremental cost-effectiveness ratio; ITC = indirect treatment comparison; PFS = progression free survival; QALY = quality-adjusted life year

6.4. Key strengths

- The model structure was appropriate and the approach used was clearly described. Scenario analyses provided were helpful to explore the key uncertainties in the model.
- Utility values used in the model were based on EQ-5D data collected in the THOR study providing a robust data source for quality of life estimates used in the model.

6.5. Key uncertainties

- Direct study data are available from the THOR study comparing erdafitinib with chemotherapy, which included docetaxel (63%) vinflunine (37%). These data were not used in the model base case as paclitaxel monotherapy was not a comparator in this study and therefore the company considered it was more appropriate to use the indirect treatment comparison to estimate the comparative efficacy of erdafitinib versus paclitaxel monotherapy. However, clinical experts consulted by SMC indicated it would be reasonable to use the THOR data directly in the model on the basis that docetaxel and

paclitaxel have comparable efficacy and that the chemotherapy arm of THOR was a reasonable proxy for the efficacy of current treatment. When the THOR study data were used directly in the model the incremental cost-effectiveness ratio (ICER) increased significantly (scenario 4). SMC considered this to be a more appropriate base case analysis and noted the uncertainty around this figure in scenarios 12-17.

- Efficacy data used in the economic analysis were taken from an ITC which combined the clinical study data from the erdafitinib arm of the THOR study with real world data from the RW mUK study. This indirect comparison was associated with several limitations meaning the economic results based on this are highly uncertain and may be biased in favour of erdafitinib. Using more conservative estimates of overall survival increased the ICER (scenarios 1-3). There is some uncertainty regarding the comparator used in the model as other treatments are used in practice, in addition to paclitaxel monotherapy. SMC clinical experts indicated best supportive care, docetaxel and vinflunine were alternative treatments in this patient group. This further strengthens the case for using the THOR data directly in the model.
- There is some uncertainty regarding the proportions receiving subsequent treatment and the mix of treatments given in practice. However, sensitivity analysis was provided showing this is not a key driver of the model.

7. Conclusion

The Committee considered the benefits of erdafitinib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for a substantial improvement in life expectancy was satisfied. In addition, as erdafitinib is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted erdafitinib for use in NHSScotland.

8. Guidelines and Protocols

The European Society for Medical Oncology (ESMO) published Bladder cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up in 2021.[7]

National Institute for Health and Care Excellence (NICE) published Bladder cancer: diagnosis and management. NICE guideline [NG2] in February 2015.[12]

9. Additional Information

9.1. Product availability date

21 January 2024

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per 28 days (£)
Erdafitinib	**8 mg orally once daily**	**12,750**

Costs from Dictionary of Medicines and Devices Browser on 10/12/24. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 10 patients eligible for treatment with erdafitinib in year 1 and 9 patients in year 5. The estimated uptake rate was 80% in year 1 and 95% in year 5 with a discontinuation rate of 0% applied each year. This resulted in 8 patients estimated to receive treatment in year 1 rising to 9 patients in year 5.

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.

*Other data were also assessed but remain confidential.**

References

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This assessment is based on data submitted by the applicant company up to and including 14 February 2025.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

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 medicine 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 NHSScotland 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 NHSScotland 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.