Erdafitinib Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
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.	C67	00885a	N/A

* This applies to post 2012 indications

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Erdafitinib is administered orally and treatment should be continued until disease progression or unacceptable toxicity occurs.

Drug	Dose	Route	Cycle
Erdafitinib	8mg once daily[a,b,c,d]	PO	Continuous
[a]This dose should be maintained and serum phosphate level should be assessed between 14 and 21 days after initiating treatment. Up-titrate the dose to 9 mg once daily if the serum phosphate level is <9.0mg/dL (<2.91 mmol/L) and there is no drug-related toxicity. If the phosphate level is 9.0 mg/dL or higher follow the relevant dose modifications in Table 2. After day 21 the serum phosphate level should not be used to guide up-titration decision.			
[b]The tablets should be swallowed whole with or without food at about the same time each day. Grapefruit or Seville oranges should be avoided while taking erdafitinib due to strong CYP3A4 inhibition.			

[c]If a dose is missed, it can be taken as soon as possible. The regular daily dose schedule should be resumed the next day. Extra tablets should not be taken to make up for the missed dose. If vomiting occurs any time after taking erdafitinib, the next dose should be taken the next day.
[d]Erdafitinib is commonly available as 3mg, 4mg and 5mg tablets.

ELIGIBILITY:

- Indications as above
- ECOG 0-2
- Have at least 1 of the following *FGFR* fusions: *FGFR3-TACC3, FGFR3-BAIAP2L1;* or 1 of the following *FGFR3* gene mutations*: R248C, S249C, G370C, Y373C*
- Prior anti–PD-1 or anti–PD-L1 therapy in the unresectable or metastatic treatment setting
- Adequate haematological and organ function

CAUTIONS:

- Symptomatic CNS metastases
- Any active clinically significant infection requiring therapy
- History of uncontrolled cardiovascular disease

EXCLUSIONS:

- Hypersensitivity to erdafitinib or to any of the excipients
- Pregnancy
- Breastfeeding

PRESCRIPTIVE AUTHORITY:

- The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Serum phosphate
- Urea and electrolytes
- Baseline cardiac assessment including history and physical exam
- ECG
- *FGFR3* testing using a validated test method
- Ophthalmological assessment

Regular tests:

- FBC, renal and liver profile
- Serum phosphate 14-21 days after treatment initiation and then monthly thereafter
- Urea and electrolytes
- Cardiac assessment where clinically appropriate
- ECG
- Ophthalmological assessment monthly for first 4 months and every 3 months thereafter

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- Management of adverse reactions may require dose interruption and/or dose reduction as outlined in Tables 1-5

Table 1: Erdafitinib dose reduction schedule

Dose	1st dose reduction	2nd dose reduction	3rd dose reduction	4th dose reduction	5th dose reduction
9mg	8mg	6mg	5mg	4mg	Stop
8mg	6mg	5mg	4mg	Stop	

Table 2: Recommended dose modifications based on serum phosphate concentrations with the use of erdafitinib after up-titration

Serum phosphate concentration	Erdafitinib management
For phosphate concentrations >5.5 mg/dL, restrict phosphate intake to 600-800 mg/day.	
<6.99 mg/dL (<2.24 mmol/L)	Continue treatment at current dose.
7.00-8.99 mg/dL (2.25-2.90 mmol/L)	Continue treatment Start phosphate binder with food until phosphate level is <7.00 mg/dL. A dose reduction should be implemented for a sustained serum phosphate level of ≥7.00 mg/dL for a period of 2 months or in the presence of additional adverse events or additional electrolyte disturbances linked to prolonged hyperphosphataemia.
9.00-10.00 mg/dL (>2.91-3.20 mmol/L)	Withhold treatment until serum phosphate level returns to <7.00 mg/dL (weekly testing recommended). Start phosphate binder with food until serum phosphate level returns to <7.00 mg/dL.

	Re-start treatment at the same dose level (see Table 1). A dose reduction should be implemented for sustained serum phosphate level of ≥9.00 mg/dL for a period of 1 month or in the presence of additional adverse events or additional electrolyte disturbances linked to prolonged hyperphosphataemia.
>10.00 mg/dL (>3.20 mmol/L)	Withhold treatment until serum phosphate level returns to <7.00 mg/dL (weekly testing recommended). Re-start treatment at the first reduced dose level (see Table 1). If serum phosphate level of ≥10.00 mg/dL is sustained for >2 weeks, treatment should be discontinued permanently. Medical management of symptoms as clinically appropriate.
Significant alteration from baseline renal function or Grade 3 hypocalcaemia due to hyperphosphataemia.	Treatment should be discontinued permanently. Medical management as clinically appropriate.

Renal and Hepatic Impairment:

Table 3: Dose modification in renal and hepatic impairment

Renal Impairment		**Hepatic Impairment**	
CrCl (mL/min)	**Dose**	Child-Pugh A/B	No dose adjustment is needed
≥30	No dose adjustment is needed		
<30	No need for dose adjustment is expected		
Haemodialysis	80% of the original dose may be considered	Child-Pugh C	Not recommended
Source: Giraud et al 2023			

Management of adverse events:

Table 4: Guideline for management of eye disorders with use of erdafitinib

Severity Grading	Dose Management
Grade 1 Asymptomatic or mild symptoms; clinical or diagnostic observations only, or abnormal Amsler grid test.	Refer for an ophthalmologic examination (OE). If an OE cannot be performed within 7 days, withhold treatment until an OE can be performed. If no evidence of eye toxicity on OE, continue treatment at same dose level. If diagnosis from OE is keratitis or retinal abnormality (e.g., CSR[a]), withhold treatment until resolution. If reversible in 4 weeks on OE, resume at next lower dose. Upon restarting treatment, monitor for recurrence every 1-2 weeks for a month and as clinically appropriate thereafter. Consider dose re-escalation if no recurrence.
Grade 2 Moderate; limiting age appropriate instrumental activities of daily living (ADL).	Immediately withhold treatment and refer for an OE. If there is no evidence of eye toxicity, resume treatment at the next lower dose level upon resolution. If resolved (complete resolution or stabilisation and asymptomatic) within 4 weeks on OE, resume treatment at the next lower dose level. Upon restarting treatment, monitor for recurrence every 1 to 2 weeks for a month and as clinically appropriate thereafter.
Grade 3 Severe or medically significant but not immediate sight-threatening; limiting self-care ADL.	Immediately withhold treatment and refer for an OE. If resolved (complete resolution or stabilisation and asymptomatic) within 4 weeks, then treatment may be resumed at 2 dose levels lower. Upon restarting treatment, monitor for recurrence every 1 to 2 weeks for a month and as clinically appropriate thereafter. Consider permanent discontinuation of treatment for recurrence.
Grade 4 Sight-threatening consequences; blindness (20/200 or worse)	Permanently discontinue treatment. Monitor until complete resolution or stabilisation.

[a] CSR- Central serous retinopathy

Table 5: Recommended dose modifications for nail, skin and mucosal adverse reactions with use of erdafitinib

Severity of adverse reaction	Dose management
Nail disorder	
Grade 1	Continue treatment at current dose.
Grade 2	Withhold treatment with reassessment in 1-2 weeks. If first occurrence and it resolves to ≤Grade 1 or baseline within 2 weeks, restart at same dose. If recurrent event or takes >2 weeks to resolve to ≤Grade 1 or baseline, then restart at next lower dose.
Grade 3	Withhold treatment, with reassessment in 1-2 weeks. When resolves to ≤Grade 1 or baseline, restart at next lower dose.
Grade 4	Discontinue treatment.
Dry skin and skin toxicity	
Grade 1	Continue treatment at current dose.
Grade 2	Continue treatment at current dose.
Grade 3	Withhold treatment (for up to 28 days), with weekly reassessments of clinical condition. When resolves to ≤Grade 1 or baseline, restart at next lower dose.
Grade 4	Discontinue treatment
Oral Mucositis	
Grade 1	Continue treatment at current dose.
Grade 2	Withhold treatment if the subject has other concomitant erdafitinib related Grade 2 adverse reactions. Withhold treatment if the subject was already on symptom management for more than a week. If treatment is withheld, reassess in 1-2 weeks. If this is the first occurrence of toxicity and resolves to ≤Grade 1 or baseline within 2 weeks, restart at same dose. If recurrent event or takes >2 weeks to resolve to ≤Grade 1 or baseline, then restart at next lower dose.
Grade 3	Withhold treatment, with reassessments of clinical condition in 1-2 weeks. When resolves to ≤Grade 1 or baseline, restart at next lower dose.

Grade 4	Discontinue treatment.
Dry Mouth	
Grade 1	Continue treatment at current dose.
Grade 2	Continue treatment at current dose.
Grade 3	Withhold treatment (for up to 28 days), with weekly reassessments of clinical condition. When resolved to ≤Grade 1 or baseline, restart at next lower dose.

Table 6: Recommended dose modifications for other adverse reactions with use of erdafitinib

Other adverse reactions[a]	
Grade 3	Withhold treatment until toxicity resolves to Grade 1 or baseline, then may resume treatment at the next lower dose.
Grade 4	Permanently discontinue.

[a] CTCAE v5.0

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting -Available on the NCCP website

Erdafitinib: Minimal to low **(Refer to local policy).**

For information:

Within NCIS regimens, antiemetics have been standardised by the Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

PREMEDICATIONS:

- No specific recommendations

OTHER SUPPORTIVE CARE:

- Female patients of child-bearing potential should be advised to use highly effective contraception prior to and during treatment, and for 1 month after the last dose of erdafitinib. Male patients should be advised to use effective contraception (e.g., condom) and not donate or store semen during treatment with and for 1 month after the last dose of erdafitinib.

ADVERSE EFFECTS

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details
- This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information

REFERENCES:

1. Loriot Y et al. Erdafitinib or Chemotherapy in Advanced or Metastatic Urothelial Carcinoma. N Engl J Med 2023; 389:1961-1971. Available at: https://www.nejm.org/doi/full/10.1056/NEJMoa2308849?logout=true
2. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(23)00216-4/fulltext
3. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Antiemesis Version 2.2024 – September 27, 2024. Accessed June 2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf
4. Erdafitinib (Balversa®) Summary of Product Characteristics. Accessed September 2024.Available at: https://www.ema.europa.eu/en/documents/product-information/balversa-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	01/11/2024		Prof Maccon Keane

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