VANDETANIB

Vandetanib is a VEGFR-2, EGFR and RET tyrosine kinase inhibitor, licensed for patients with symptomatic-aggressive locally advanced unresectable, or metastatic, medullary thyroid cancer
Individual funding must be obtained before treatment may start

N.B. This drug is contra-indicated in patients with a baseline QTc > 480 msec

Drug/Dosage:	**Vandetanib**	300 mg po once daily continuous therapy

Administration: Available as 300mg and 100mg tablets, which should be swallowed whole and may be taken either with or without food. If a dose is missed, it may be taken up to 12 hours before the next dose is due. Otherwise, the dose should be omitted.

For patients who have difficulty swallowing, vandetanib tablets may be dispersed in half a glass of non-carbonated drinking water. No other liquids should be used. The tablet is to be dropped in water, without crushing, stirred until dispersed (approximately 10 minutes) and the resultant dispersion swallowed immediately. Any residues in the glass are to be mixed with half a glass of water and swallowed. The liquid can also be administered through nasogastric or gastrostomy tubes.

Frequency: continue for as long as there is clinical benefit, or unacceptable toxicity.

Main Toxicities: diarrhoea; rash, including PPE and photosensitivity reactions; hypertension; QTc prolongation; ALT elevations (usually resolve without stopping treatment); posterior reversible encephalopathy syndrome;

Anti- emetics: mildly emetogenic – domperidone or ondansetron are not recommended

Regular:	FBC	whenever bloods are done
Investigations:	U&Es *	baseline, at 1, 3, 6 and 12 weeks after starting treatment, then every 3 months for at least a year thereafter, then as indicated
	Ca^{2+} & Mg^{2+} *	baseline, at 1, 3, 6 and 12 weeks after starting treatment, then every 3 months for at least a year thereafter, then as indicated
	LFTs	whenever bloods are done
	TSH	baseline, at 1, 3, 6 and 12 weeks after starting treatment, then every 3 months for at least a year thereafter, then as indicated
	ECG / QT interval	performed by cardiology – pre-treatment, at 1, 3, 6 and 12 weeks after starting treatment, then every 3 months for at least a year thereafter, plus as indicated
	Blood pressure	weekly for the first 4 weeks, then as indicated

*Potassium, magnesium and calcium should be kept within normal range to reduce the risk of QTc prolongation. Additional monitoring of QTc, electrolytes and renal function are required in cases of diarrhoea, dehydration, electrolyte imbalance or impaired renal function.

Comments: Patients must be given the Patient Alert card with each prescription, and warned of the risks of vandetanib.

Vandetanib is associated with a substantial and concentration dependent prolongation in QTc (mean 28 msec, median 35 msec). First QT prolongations occur most often in the first 3 months of treatment, but continue to first occur after this time.

Reason for Update: CDF drug	Approved by Consultant: Dr S Whitaker
Version: 1	Approved by Lead Chemotherapy Nurse: V Mumford
Supersedes: None	Date: 1.4.14
Prepared by: S Taylor	Checked by: C Tucker

Torsades de pointes and ventricular tachycardia have been uncommonly reported in patients on vandetanib. The risk of torsades may be increased in patients with electrolyte imbalance. Vandetanib must not be started in patients whose ECG QTc interval is > 480 msec, or who have a history of Torsades de pointes unless all risk factors that contributed to Torsades have been corrected**.**
The administration of vandetanib with substances known to prolong the ECG QTc interval is contraindicated (erythromycin IV, toremifene, mizolastine, moxifloxacin, Class IA and III antiarrhythmics) or not recommended (e.g. ondansetron, domperidone, haloperidol)

Elimination of vandetabib is mainly through hepatic metabolism. Concomitant use of enzyme inducers (e.g. rifampicin, phenytoin, carbamazepine, St Johns wort) with vandetanib should be avoided, as this may increase the risk of therapeutic failure.

If the patient is taking warfarin, monitor the INR closely when initiating vandetanib.

Dose Modifications **Patients who develop a single recording of a QTc ≥ 500 msec should stop vandetanib.**
N.B. The long half-life of vandetanib (19 days) makes any prolongation in QTc interval particularly problematic, and any adverse reactions may not resolve quickly.

Prolonged QT interval:

QTc value	Recommended Management
QTc > 480ms at baseline	Vandetanib is contra-indicated
QTc increases markedly but remains < 500ms	Seek cardiologist advice*
1st occurrence of QTc ≥ 500ms	Stop treatment* until QTc decreases to pre-treatment levels. If vandetanib is re-started, then resume treatment at 200mg od. ECG and electrolyte monitoring should be carried out at a minimum of 1, 3, 6 and 12 weeks after re-starting.
2nd occurrence of QTc ≥ 500ms	Stop treatment* until QTc decreases to pre-treatment levels. If vandetanib is re-started, then resume treatment at 100mg od. ECG and electrolyte monitoring should be carried out at a minimum of 1, 3, 6 and 12 weeks after re-starting.

*Also ensure that any electrolyte abnormalities (including Mg^{2+}) are corrected, and any cardiac risk factors for QT prolongation are controlled.

Any other ADR: For any other Grade 3-4 adverse reaction, vandetanib should be stopped until the toxicity has resolved to Grade 1. If vandetanib is re-started, it should be resumed at the reduced daily dose of 200mg, and then down to 100mg od if necessary.

Mild to moderate skin reactions can be managed symptomatically, or by dose reduction or interruption.
Avoid sun exposure while on vandetanib, due to the risk of photosensitivity reactions. Patients should wear protective clothing in sunny weather and apply sunscreen.

Hepatic Impairment: If bilirubin > 1.5 x ULN, vandetanib is not recommended.
(however, pharmacokinetic data from volunteers suggests that no change in starting dose is required in patients with mild, moderate or severe hepatic impairment)

Renal Impairment: No change in starting dose is required if CrCl ≥ 50ml/min.
There is limited data for patients with CrCl 30 – 49ml/min: the dose needed to be lowered to 200 mg in 5 out of 6 patients. The starting dose could be reduced to 200 mg in patients with moderate renal impairment; however safety and efficacy have not been established at 200mg daily.
Vandetanib is not recommended in patients with CrCl < 30ml/min.