Vandetanib Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease.	C73	00242a	CDS

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.

Vandetanib is administered once daily until disease progression or unacceptable toxicity develops.

Drug	Dose	Route	Cycle
Vandetanib	300 mg once daily	PO Take with or without food, at the same time each day	Continuous
If a dose is missed, it should be taken as soon as the patient remembers. If it is less than 12 hours to the next dose, the patient should not take the missed dose. Patients should not take a double dose (two doses at the same time) to make up for a forgotten dose.			
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 (approx 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.			
The prescriber must discuss the risks of vandetanib with the patient. Patients treated with vandetanib must be given the **patient alert card with each prescription**.			

ELIGIBILITY:

- Indications as above
- Use of vandetanib in patients with indolent, asymptomatic or slowly progressing disease should be carefully considered because of the treatment related risks of vandetanib[1].
- For patients in whom Rearranged during Transfection (RET) mutation is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision.
- Serum calcitonin level ≥ 500 pg/mL
- ECOG status 0-2

[1] In view of the associated risks, it is important to limit treatment with vandetanib to patients who are in real need for treatment, i.e. with a symptomatic-aggressive course of the disease. Either symptomatic disease or progressive disease alone is not enough to prompt the need of treatment with vandetanib. Rate of change in biomarker levels such as of calcitonin (CTN) and/or carcinoembryonic antigen (CEA) as well as the rate of change of tumor volume during watchful waiting might help to identify not only patients in need for treatment but also the optimal moment to commence treatment with vandetanib.

EXCLUSIONS:

- Hypersensitivity to vandetanib or any of the excipients
- Significant cardiac, haematopoietic, hepatic, or renal dysfunction.
- Congenital long QTc syndrome or patients with a QTc interval over 480 msec.
- Breast-feeding.

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profiles
- ECG, serum potassium, calcium and magnesium and thyroid stimulating hormone (TSH)
- Rearranged during Transfection (RET) mutation status* if available.
  * See under Adverse Effects and Regimen Specific Complications.

Regular tests:

- FBC, renal and liver profiles week 1, 3, 6 and 12 weeks after starting treatment.
- Calcitonin weekly
- ECG, serum potassium, calcium and magnesium and TSH:1, 3, 6 and 12 weeks after starting treatment and every 3 months for at least a year thereafter. This schedule should apply to the period after dose reduction due to QTc prolongation and after dose interruption for more than two weeks.
- Frequent ECG monitoring of the QTc interval and blood tests should be continued after completion of treatment as clinically indicated.

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.

Renal and Hepatic Impairment:

Table 1: Dose modification of vandetanib in renal and hepatic impairment

Renal Impairment	Hepatic Impairment
• Clinical data suggest that no change in starting dose is required in patients with mild renal impairment. • Vandetanib is not recommended for use in patients with moderate or severe renal impairment since there is limited data and safety and efficacy have not been established.	• Vandetanib is not recommended for use in patients with hepatic impairment (serum bilirubin > 1.5 times ULN), since there is limited data in patients with hepatic impairment, and safety and efficacy have not been established. • Pharmacokinetic data from volunteers, suggests that no change in starting dose is required in patients with mild, moderate or severe hepatic impairment

Management of adverse events:

Table 2: Dose Modification of vandetinib for Adverse Events

Adverse reactions	Recommended dose modification
Grade ≥3 reaction or Prolongation of the ECG QTc interval	
• First Occurrence	Dosing should be at least temporarily stopped and resumed at a reduced dose when toxicity has resolved or improved to grade 1. The 300 mg daily dose can be reduced to 200mg (two 100 mg tablets).
• Second Occurrence	Dosing should be at least temporarily stopped and resumed at a reduced dose of 100mg when toxicity has resolved or improved to grade 1. The patient must be monitored appropriately. Due to the 19-day half-life, adverse reactions including a prolonged QTc interval may not resolve quickly.
Stevens-Johnson syndrome	Permanently discontinue treatment
Interstitial lung disease	Permanently discontinue treatment

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal to Low (**Refer to local policy).**

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE:

Medication may be required for management of diarrhoea, e.g. loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day) or see local policy.

See local skin care policy for the prevention and treatment of EGFR-inhibitor adverse skin reactions.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

- **QTc prolongation and Torsades de Pointes:**
  - Vandetanib at a dose of 300 mg is associated with a substantial and concentration dependent prolongation in QTc (mean 28 msec, median 35 msec).
  - First QT prolongations occurred most often in the first 3 months of treatment, but continued to first occur after this time.
  - The half-life of vandetanib (19 days) renders this prolongation in QTc interval particularly problematic.
  - Vandetanib treatment must not be started in patients whose ECG QTc interval is greater than 480 msec.
  - Vandetanib should not be given to patients who have a history of Torsades de pointes unless all risk factors that contributed to Torsades have been corrected.

  - Vandetanib has not been studied in patients with ventricular arrhythmias or recent myocardial infarction.
  - Patients who develop a single value of a QTc interval of ≥500 msec should stop taking vandetanib. Dosing can be resumed at a reduced dose after return of the QTc interval to pretreatment status has been confirmed and correction of possible electrolyte imbalance has been made.
- **Posterior reversible encephalopathy syndrome (PRES):** This syndrome has been observed infrequently with vandetanib treatment. Brain MRI should be performed in any patient presenting with seizures, confusion or altered mental status.
- **Rearranged during Transfection (RET) status:** Patients without RET mutation may have a decreased benefit from vandetanib treatment and the benefit/risk balance for this group of patients may therefore differ from that of the group with RET mutations. For patients whose RET mutation status could be negative, a possible lower benefit should be taken into account before individual treatment decisions and the use of vandetanib should be carefully considered because of the treatment related risks. Therefore, RET mutation testing is recommended. When establishing RET mutation status, tissue samples should be obtained if possible at the time of initiation of treatment rather than at the time of diagnosis.
- **Skin reactions:** Rash and other skin reactions (including photosensitivity reactions and palmar-plantar erythrodysaesthesia syndrome) have been observed in patients who have received vandetanib. Mild to moderate skin reactions can be managed by symptomatic treatment, or by dose reduction or interruption. More severe skin reactions (such as Stevens-Johnson syndrome) referral of the patient to seek urgent medical advice is recommended.
  Care should be taken with sun exposure by wearing protective clothing and /or sunscreen due to the potential risk of phototoxicity reactions associated with vandetanib treatment.
- **Diarrhoea:** This is a disease related symptom as well as a known undesirable effect of vandetanib. Routine anti-diarrhoeal agents are recommended for the treatment of diarrhoea. QTc and serum electrolytes should be monitored more frequently. If severe diarrhoea (CTCAE grade 3-4) develops, vandetanib should be stopped until diarrhoea improves. Upon improvement, treatment should be resumed at a reduced dose (see Table 2).
- **Haemorrhage:** Caution should be used when administering vandetanib to patients with brain metastases, as intracranial haemorrhage has been reported.
- **Interstitial Lung Disease (ILD):** This has been reported in patients treated with EGFR inhibitors. In patients who develop acute onset of new and/or progressive unexplained pulmonary symptoms such as dyspnoea, cough and fever, vandetanib therapy should be interrupted pending diagnostic evaluation.

DRUG INTERACTIONS:

- Concomitant use of vandetanib with medicinal products known to also prolong the QTc interval and/or induce Torsades de pointes is either contraindicated or not recommended depending on existing alternative therapies.
  - Combinations contraindicated: cisapride, erythromycin intravenous (IV), toremifene , mizolastine, moxifloxacin, arsenic, Class IA and III antiarrhythmics
  - Combinations not recommended: Methadone, haloperidol, amisulpride, chlorpromazine, sulpiride, zuclopenthixol, halofantrine, pentamidine and lumefantrine.
- Administration of vandetanib with potent CYP3A4 inducers should be avoided.
- Concomitant use of ondansetron with vandetanib is notrecommended.

- Current drug interaction databases should be consulted for more information.

COMPANY SUPPORT RESOURCES/Useful Links:

Please note that this is for information only and does not constitute endorsement by the NCCP

CAPRELSA HCP Guide: IMPORTANT RISK MINIMISATION INFORMATION FOR HEALTHCARE PROFESSIONALS.
Available at:
https://www.hpra.ie/img/uploaded/swedocuments/RMP%20CAPRELSA%20HCP%20GUIDE%20ELECTRONIC%20CERTIFIED%2029.11.17-2197992-08052018130552-636613815575156250.pdf

Patient Alert Card: CAPRELSA (vandetinib).
Available at:
https://www.hpra.ie/img/uploaded/swedocuments/PATIENT%20ALERT%20CARD%20ELECTRONIC%20CERTIFIED%2029.11.2017-2197992-08052018130400-636613814597343750.pdf

Dosing and Monitoring Guide for Patients: CAPRELSA (vandetinib).
Available at:
https://www.hpra.ie/img/uploaded/swedocuments/RMP%20CAPRELSA%20PATIENT%20GUIDE%20ELECTRONIC%20CERTIFIED%2029.11.17-2197992-08052018130503-636613815080781250.pdf

REFERENCES:

1. Wells SA Jr, Robinson BG et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial.J Clin Oncol. 2012; 30(2):134-41
2. Wells SA Jr, Gosnell JE et al. Vandetanib for the treatment of patients with locally advanced or metastatic hereditary medullary thyroid cancer.J Clin Oncol. 2010;28(5):767-72.
3. Caprelsa ®Summary of Product Characteristics Accessed Nov 2018 Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002315/WC500123555.pdf
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V2 2019. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf

Version	Date	Amendment	Approved By
1	10/01/2015		Dr Liam Grogan
2	11/01/2017	Review: Clarified, information relating to severe skin reaction and provided link to Company HCP Guide	Prof Maccon Keanee
3	16/01/2019	Updated to new NCCP template Updated dosing in renal impairment as per SmpC	Prof Maccon Keane
4	22/01/2021	Amended emetogenic potential	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.