**Vandetanib Therapy**

**INDICATIONS FOR USE:**

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICD10</th>
<th>Regimen Code</th>
<th>*Reimbursement Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease.</td>
<td>C73</td>
<td>00242a</td>
<td>CDS</td>
</tr>
</tbody>
</table>

*If the reimbursement status is not defined*, the indication has yet to be assessed through the formal HSE reimbursement process.

**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 patient's individual clinical circumstances.

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vandetanib</td>
<td>300 mg daily</td>
<td>PO Take with or without food</td>
<td>Continuous</td>
</tr>
</tbody>
</table>

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.
- 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

**EXCLUSIONS:**
- Hypersensitivity to vandetanib or any of the excipients

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.
NCCP Chemotherapy Regimen

- Significant cardiac, hematopoietic, 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>
<thead>
<tr>
<th>Renal Impairment</th>
<th>Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical data suggest that no change in starting dose is required in patients with mild renal impairment.</td>
<td>Vandetanib is not recommended for use in patients with hepatic impairment (serum bilirubin &gt; 1.5 times ULN), since there is limited data in patients with hepatic impairment, and safety and efficacy have not been established.</td>
</tr>
<tr>
<td>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.</td>
<td>Pharmacokinetic data from volunteers, suggests that no change in starting dose is required in patients with mild, moderate or severe hepatic impairment</td>
</tr>
</tbody>
</table>

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### Management of adverse events:

#### Table 2: Dose Modification of Vandetanib for Adverse Events

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Recommended dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥3 reaction or Prolongation of the ECG QTc interval</td>
<td>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 200 mg (two 100 mg tablets).</td>
</tr>
<tr>
<td>• First Occurrence</td>
<td>Dosing should be at least temporarily stopped and resumed at a reduced dose of 100 mg 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.</td>
</tr>
<tr>
<td>• Second Occurrence</td>
<td>Stevens-Johnson syndrome: Permanently discontinue treatment</td>
</tr>
<tr>
<td></td>
<td>Interstitial lung disease: Permanently discontinue treatment</td>
</tr>
</tbody>
</table>

### SUPPORTIVE CARE:

#### EMETOGENIC POTENTIAL: Low (Refer to local policy).

#### PREMEDICATIONS: Not usually required

#### OTHER SUPPORTIVE CARE:
- Medication may be required for management of diarrhoea, e.g. loperamide (4 mg at first onset followed by 2 mg 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.

- **Diarrhoea:** This is a disease related symptom as well as a known undesirable effect of vandetanib. Routine anti-diarrheal 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 1).

- **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 I A 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 not-recommended
- Current drug interaction databases should be consulted for more information.
ATC CODE:
Vandetanib L01XE12

COMPANY SUPPORT RESOURCES/Useful Links:
Please note that this is for information only and does not constitute endorsement by the NCCP


REFERENCES:

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Approved By</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10/01/2015</td>
<td></td>
<td>Dr Liam Grogan</td>
</tr>
<tr>
<td>2</td>
<td>11/01/2017</td>
<td>Review: Clarified, information relating to severe skin reaction and provided link to Company HCP Guide</td>
<td>Prof Maccon Keane</td>
</tr>
<tr>
<td>3</td>
<td>16/01/2019</td>
<td>Updated to new NCCP template Updated dosing in renal impairment as per SmPC</td>
<td>Prof Maccon Keane</td>
</tr>
</tbody>
</table>

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

1 ODMS – Oncology Drug Management System

NCCP Regimen: Vandetanib Monotherapy
Published: 10/01/2015
Review: 21/01/2021
Version number: 3

Tumour Group: Head and Neck
NCCP Regimen Code: 00242
ISMO Contributor: Dr Liam Grogan, Prof Maccon Keane

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<tr>
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<th>Published: 10/01/2015</th>
<th>Version number: 3</th>
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<td></td>
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<tr>
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</table>

CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes

Further details on the Cancer Drug Management Programme is available at; http://www.hse.ie/eng/services/list/5/cancer/proffinfo/medonc/cdmp/