REGIMEN TITLE: Vandetanib in Thyroid carcinoma

Indication: Medullary thyroid carcinoma
NHS England CDF criteria to be met (CDF funding approval required):
- Locally advanced and unresectable or metastatic medullary thyroid cancer
- Symptomatic disease
- No previous biological therapy

Patient able to tolerate and comply with oral dosage forms

Notes: Electrolyte imbalances (Ca, K, Mg) should be corrected before starting the treatment.

Vandetanib has not been studied in patients with ventricular arrhythmias or recent myocardial infarction. Caution should be used when administering vandetanib to patients with brain metastases, as intracranial haemorrhage has been reported.

ECG QTc interval should not be greater than 480 msec.
Serum calcitonin level should be ≥ 500 pg/ml.
Patient should have no history of Torsades de pointes, unless all risk factors that contributed to Torsades have been corrected.

Vandetanib is contra-indicated with the following medicinal products known to prolong the QTc interval and/or induce Torsades de pointes: Arsenic, cisapride, erythromycin intravenous (IV), toremifene, mizolastine, moxifloxacin, Class IA and III antiarrhythmics.

Contra-indicated in congenital long QTc syndrome.

Existing hypertension should be well controlled before starting treatment.

Regimen details: Vandetanib 300mg PO Once daily
Continuous therapy.

Administration: Available as 100mg and 300mg film-coated tablets (30 tablet packs)
Take tablets with or without food, at the same time each day.
Swallow whole with a glass of water.

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: Prescribed in 4 week cycles - continued until disease progression or unacceptable toxicity
Anti-emetics: Mildly emetogenic

Reason for Update: Updated CDF guidance
Approved by Consultant: Mary Lei
Version: 1
Date: 18/06/2013
Supersedes: None
Checked by (Principal Pharmacist): J. Turner
Prepared by: S.Eestilä Feb-April 2013
Date: 20/06/2013
Supportive medication: Diarrhoea can be managed with loperamide – 2mg PRN (max. 16mg/day). Mouthwashes according to local mouth care guidance if needed.

Regular investigations:

<table>
<thead>
<tr>
<th>Test</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>LFTs</td>
<td>Prior each cycle</td>
</tr>
<tr>
<td>FBC</td>
<td>Prior each cycle</td>
</tr>
<tr>
<td>CrCl (C&amp;G or EDTA)</td>
<td>Prior each cycle</td>
</tr>
<tr>
<td>U&amp;Es (K)</td>
<td>*Baseline, weeks 2, 4, 8 and 12 after starting, then every 3 months</td>
</tr>
<tr>
<td>Ca, Mg</td>
<td>*Baseline, weeks 2, 4, 8 and 12 after starting, then every 3 months</td>
</tr>
<tr>
<td>ECG (QTc)</td>
<td>*Baseline, weeks 2, 4, 8 and 12 after starting, then every 3 months</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Prior each cycle</td>
</tr>
<tr>
<td>Thyroid function</td>
<td>*Baseline, weeks 1, 2, 4 and 12 after starting, then every 3 months</td>
</tr>
<tr>
<td>Urinalysis (proteinuria)</td>
<td>Periodically when required</td>
</tr>
<tr>
<td>RET mutation status</td>
<td>Baseline (see comments below)</td>
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</tbody>
</table>

*This schedule should also apply to the period after dose reduction due to QTc prolongation and after dose interruption for more than two weeks.

Additional monitoring of QTc, electrolytes and renal function are required especially in case of diarrhoea, dehydration, electrolyte imbalance and/or impaired renal function.

Comments: To be supplied to the patient for oral self-administration. Ensure that the patient has an information pack and the treatment plan.

Adequate contraception methods to be applied during and for at least 4 months after the therapy.

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.

Toxicities: QTc interval prolongation and other cardiac effects (Torsades de pointes, ventricular tachycardia, heart failure), posterior reversible encephalopathy syndrome (PRES), haemorrhage, skin reactions (acne, dry skin, dermatitis, pruritis, Stevens-Johnson), photosensitivity, PPE, diarrhoea, hypertension, ALT elevations, interstitial lung disease,
nausea, headache, UTI, hypothyroidism, decreased appetite, insomnia, depression, eye disorders, GI symptoms, proteinuria, fatigue

Precautions and Dose Modifications

Haematological toxicity

Baseline levels
- Neutrophils $\geq 1.5 \times 10^9/L$
- Platelets $\geq 100 \times 10^9/L$

100% dose

Discuss lower than normal haematological findings and treatment doses with consultant.

Non-Haematological Toxicity

When dose reduction of vandetanib is necessary due to any toxicity, the vandetanib dose may be reduced to 200 mg daily and further to 100mg daily.

Generally dose should be withheld in any grade 3 or higher toxicity, and resumed with reduced dosing level after toxicity has improved to grade 1.

QT interval changes

Vandetanib at a dose of 300mg daily is associated with a substantial and concentration dependent prolongation in QTc (mean 28 ms, median 35 ms). First QT prolongations occurred most often in the first 3 months of treatment, but continued to first occur after this time.

The patient must be monitored carefully when changes in QT interval are detected. Due to the 19-day half-life, adverse reactions including a prolonged QTc interval may not resolve quickly.

If QTc increases markedly but stays below 500 ms, cardiologist advice should be sought.

Dose modifications based on prolongation of the QT interval

<table>
<thead>
<tr>
<th>QTc Value</th>
<th>Vandetanib Dose Modification Algorithms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline QTc $&gt; 480$ ms</td>
<td>Do not start treatment, until QTc $&lt; 480$ ms</td>
</tr>
<tr>
<td>QTc $&gt; 500$ms</td>
<td>Step 1. Interrupt treatment until QTc reduced to pre-treatment status. Correct any electrolyte imbalances. Step 2. Reduce dose one dosing level</td>
</tr>
<tr>
<td>QTc increase meets values of both $&gt; 500$ ms and $&gt; 60$ ms change from pre-treatment baseline values</td>
<td>Discontinue treatment</td>
</tr>
</tbody>
</table>
Posterior reversible encephalopathy syndrome, PRES (Reversible posterior leukoencephalopathy syndrome- RPLS)

PRES is a syndrome of subcortical vasogenic oedema diagnosed by a MRI of the brain. PRES has been observed in patients receiving vandetanib. This syndrome should be considered in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Brain MRI should be performed in any patient presenting with seizures, confusion or altered mental status.

Diarrhoea

Stop treatment in Grade 3 diarrhoea. Re-start with a reduced dose once diarrhoea has subsided.

Hypertension

Blood pressure should be well controlled prior to initiating vandetanib.

Patients should be monitored for hypertension and treated as needed with standard antihypertensive therapy. In the case of persistent hypertension, despite use of antihypertensive medicinal products, consider vandetanib dose reduction. For patients who develop severe hypertension, temporarily interrupt vandetanib and restart at a lower dose once the patient is normotensive. If vandetanib is interrupted, patients receiving antihypertensive medicinal products should be monitored for hypotension.

In case of severe or persistent arterial hypertension and symptoms suggestive of posterior reversible encephalopathy syndrome (headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances), a diagnostic brain magnetic resonance image (MRI) should be considered. Temporarily interrupt or permanently withdraw treatment.

Interstitial lung disease

Interstitial Lung Disease (ILD) has been observed in patients receiving vandetanib and some cases have been fatal. If a patient presents with respiratory symptoms such as dyspnoea, cough and fever, vandetanib treatment should be interrupted and prompt investigation initiated. If ILD is confirmed, vandetanib should be permanently discontinued and the patient treated appropriately.

Hand-feet symptoms

Encourage regular use of moisturizers to hand and feet regularly. Advise minimizing activities that put pressure on feet or hands, as usually the pressure point areas are affected. Keeping skin cool is beneficial, avoiding extreme heat (such as strong sunlight or hot baths). Support use of non-deodorant, non-fragrance products. Consider products with anti-itch additions in pruritus, and exfoliating urea containing products in hyperkeratosis. Anti-dandruff shampoo may help in management of itchy scalp. Non-steroidal anti-
inflammatory creams and analgesia may help but a 1-2 week dose interruption may be necessary for painful symptoms.

**Renal Impairment**

<table>
<thead>
<tr>
<th>CrCl</th>
<th>Dose</th>
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</thead>
<tbody>
<tr>
<td>&gt;50ml/min</td>
<td>100%</td>
</tr>
<tr>
<td>30-49ml/min</td>
<td>Reduce dose from 300mg to 200mg, monitor</td>
</tr>
<tr>
<td>&lt;30ml/min</td>
<td>Not recommended</td>
</tr>
<tr>
<td></td>
<td>Discuss treatment of such patients with the consultant.</td>
</tr>
</tbody>
</table>

**Hepatic Impairment**

Vandetanib is not recommended in hepatic impairment.

<table>
<thead>
<tr>
<th>Bilirubin</th>
<th>Dose</th>
</tr>
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<tbody>
<tr>
<td>≤1.5 x ULN</td>
<td>Give 100%</td>
</tr>
<tr>
<td>&gt;1.5 x ULN</td>
<td>Not recommended. Discuss with the consultant.</td>
</tr>
</tbody>
</table>

Alanine aminotransferase elevations occur commonly in patients treated with vandetanib. The majority of elevations resolve while continuing treatment, others usually resolve after a 1-2 week interruption in therapy. Periodic monitoring of alanine aminotransferase is recommended.

**Drug interactions:**

Caution with a history of QT interval prolongation or relevant pre-existing cardiac disease, and concurrent antiarrhythmics or other medicines that may prolong the QT interval and/or induce Torsades de pointes :

- 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.

The concomitant use of vandetanib with ondansetron is not recommended.

Concurrent use of P-gp or CYP3A4 inducers (e.g. phenytoin, carbamazepine, rifampicin, barbiturates, dexamethasone, St John’s Wort) can decrease vandetanib plasma concentration and reduce efficacy.

Concurrent use of P-gp or CYP3A4 inhibitors (e.g. amiodarone, cyclosporine, ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, verapamil, quinidine, grape fruit juice) can increase vandetanib plasma concentration and increase toxicity.

Vandetanib is an inhibitor of the organic cation transporter 2 (OCT2). Therefore vandetanib may have the potential to decrease the elimination of medicinal products known to be excreted by OCT2 and increase a patient’s exposure to these medicinal products. Metformin is a substrate of OCT2 and patients who are receiving vandetanib and metformin (or other substrate of OCT2) may require more careful monitoring, and possible dose adjustment of metformin.
The effect of proton pump inhibitors on the gastrointestinal absorption of vandetanib has not been determined. Vandetanib demonstrates pH dependent solubility; therefore the co-administration of vandetanib with proton pump inhibitors may reduce a patient's exposure to vandetanib. The concomitant use with these therapeutic classes is therefore not recommended.

References:  
www.medicines.org.uk  
www.micromedex.com  
Wells S.A. et al. (2012); JCO 30(2):134-141