CAPRELSA
(Vandetanib)

IMPORTANT RISK MINIMISATION INFORMATION FOR HEALTHCARE PROFESSIONALS

The educational material for healthcare professionals contains the following elements:

Part 1

Important information for healthcare professionals about the serious risks associated with Vandetanib

- Serious risks for both paediatric and adult population
- Risks applicable only for the paediatric population: Risk of teeth and bone abnormalities and risk of medications errors

Part 2

Vandetanib physicians' dosing and monitoring guide for paediatric patients

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PART 1

IMPORTANT INFORMATION FOR HEALTHCARE PROFESSIONALS ABOUT THE SERIOUS RISKS ASSOCIATED WITH VANDETANIB

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions by contacting HPRA Pharmacovigilance, website: **www.hpra.ie**.

Adverse reactions should also be reported to Sanofi: Tel: **01 403 5600**, e-mail: **IEPharmacovigilance@sanofi.com**

Serious risks for both paediatric and adult population

QTc PROLONGATION, TORSADES DE POINTES, SUDDEN DEATH AND POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME (PRES; ALSO KNOWN AS REVERSIBLE POSTERIOR LEUKOENCEPHALOPATHY SYNDROME [RPLS]) are important safety concerns with vandetanib.

Physicians prescribing vandetanib should:

- Review the HCP education materials and the full Product Information for Vandetanib, including:

  - Risk information including QTc prolongation, Torsades de pointes, sudden death and PRES (also known as RPLS) with Vandetanib
  - Considerations for patient selection
  - ECG and electrolyte monitoring requirements
  - Drug interaction information

- Review the Patient Alert Card and explain its role and use to patients who will receive Vandetanib. The patient should be provided with the Patient Alert Card with each prescription.

  - It is important to counsel patients/caregivers about the risk of prolonged QTc and PRES and inform them of what symptoms and signs to be aware of and actions to take.

These education materials focus on the risks of QTc prolongation, Torsades de pointes, sudden death and PRES associated with Vandetanib. These are not the only risks associated with Vandetanib. Please see the accompanying full Product Information for Vandetanib.

All suspected adverse reactions should be reported to Sanofi and/or your local regulatory body.

QT prolongation, Torsades de pointes and sudden death

- Torsades de pointes, ventricular tachycardia and sudden deaths have been reported in patients administered Vandetanib
- Vandetanib can prolong the QTc interval in a concentration-dependent manner
- Diarrhoea can cause electrolyte imbalances, which can increase the risk of prolongation of the electrocardiogram (ECG) QTc interval
- Diarrhoea can lead to dehydration and worsening renal function
- Please see the accompanying full Product Information for Vandetanib for more information

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 and Class IA and III antiarrhythmics

  – Combinations not recommended: methadone, amisulpride, chlorpromazine, haloperidol, sulpiride, zuclopenthixol, halofantrine, pentamidine, lumefantrine and ondansetron

- If there is no appropriate alternative therapy, not recommended combinations with Vandetanib may be made with additional ECG monitoring of the QTc interval, evaluation of electrolytes and further control at onset or worsening of diarrhoea

Posterior reversible encephalopathy syndrome (reversible posterior leukoencephalopathy syndrome)

- Posterior reversible encephalopathy syndrome (PRES; also known as reversible posterior leukoencephalopathy syndrome [RPLS]) is a syndrome of subcortical vasogenic oedema diagnosed by an MRI of the brain

- PRES has been reported infrequently in patients administered Vandetanib. There have been no confirmed cases of PRES in patients with medullary thyroid cancer receiving Vandetanib; however, cases of PRES have occurred in the Vandetanib clinical programme

- This syndrome should be considered in any patient presenting with seizures, headaches, visual disturbances, confusion or altered mental function

- Patients should be informed of the symptoms of PRES and should be instructed to contact a physician immediately if they experience any of the symptoms

- If a patient presents with symptoms suggestive of PRES, it is recommended that physicians immediately perform an MRI of the brain

Patient selection

When thinking about the risks of QTc prolongation, Torsades de pointes, sudden death and PRES (also known as RPLS) associated with Vandetanib, consider the following when deciding whether a patient is appropriate for Vandetanib treatment.

Considerations for patient selection

- Vandetanib should not be administered to patients in whom rearranged during transfection (RET) mutation status is not known or is negative.

- Prior to initiation of treatment with Vandetanib, the presence of a RET mutation should be determined by a validated test.

- Do not use Vandetanib in patients with congenital long QTc syndrome

- Vandetanib treatment must not be started in patients whose QTc interval is >480 msec

- Vandetanib should not be given to patients who have a history of:
  - Torsades de pointes
  - Bradyarrhythmias
  - Uncompensated heart failure

- Vandetanib has not been studied in patients with ventricular arrhythmias or recent myocardial infarction

ECG monitoring
Recommendations for ECG monitoring

- ECGs should be obtained:
  - At baseline
  - 1, 3, 6 and 12 weeks after starting treatment with Vandetanib and every 3 months for at least a year thereafter – ECGs and blood tests should also be obtained as clinically indicated during this period and afterwards
  - Following any dose reduction for QTc prolongation or any dose interruptions >2 weeks (monitor as described above)

- Patients who develop a single value of QTc interval ≥ 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

- If QTc increases markedly but stays below 500 msec, cardiologist advice should be sought

- ECGs may require more frequent monitoring in cases of diarrhoea/ dehydration, electrolyte imbalance and/or impaired renal function

Electrolyte monitoring
Recommendations for electrolyte monitoring

- Vandetanib should not be used in patients with hypocalcaemia, hypokalaemia or hypomagnesaemia. These must be corrected prior to Vandetanib administration and should be periodically monitored

- To help reduce the risk of QTc prolongation:
  - Serum potassium, magnesium and calcium levels should be kept within normal range

- Levels of serum potassium, calcium, magnesium and thyroid-stimulating hormone (TSH) should be obtained:
  - At baseline
  - 1, 3, 6 and 12 weeks after starting treatment with Vandetanib and every 3 months for at least a year thereafter – ECGs and blood tests should also be obtained as clinically indicated during this period and afterwards
  - Following any dose reduction for QTc prolongation or any dose interruptions >2 weeks (monitor as described above)

- Electrolytes may require more frequent monitoring in cases of diarrhoea/ dehydration, electrolyte imbalance and/or impaired renal function

Risks applicable for the paediatric population

Potential risk of teeth and bone abnormalities

In preclinical studies conducted in young dogs and rats receiving vandetanib, cases of physical dysplasia, with evidence of open growth plates and effects on teeth, were observed. Those effects were attributable to inhibition of vascular endothelial growth factor receptor (VEGFR) or epidermal growth factor receptor (EGFR) by vandetanib. Moreover, in preclinical studies carried out with other anti-angiogenic agents targeted to VEGF, a suppression of trabecular bone growth formation in the epiphyseal growth plate was identified.

In phase I/II trials of vandetanib at the National Institute of Health (NIH), conducted in children and adolescents (ages 5-17) with medullary thyroid cancer, serial MRIs of the knee (13 patients) to quantify growth plate volume as a monitor for potential bone toxicity were obtained and linear growth was monitored at each patient visit. As a result, it was found that vandetanib did not impair linear growth.

However, because of the results from the non-clinical studies, teeth and bone abnormalities in the paediatric population is considered an important potential risk and as such, should be closely monitored.

Potential risk of medications errors

To avoid the potential risk of medication errors induced by the different dose regimens, physicians are advised to:

- read the physician's dosing guide for paediatric patients
- complete the patient dosing and monitoring guide (daily tracker table) at first prescription and for each dose adjustment.

Notes

PART 2

VANDETANIB PHYSICIANS' DOSING AND MONITORING GUIDE FOR PAEDIATRIC PATIENTS

This Dosing and Monitoring guide for Vandetanib is made to help you to find the right dose and dose adjustments according to the Body Surface Area (BSA) of paediatric patients.

To avoid the risk of medication errors induced by the different dose regimens, you will also have to complete the patient dosing and monitoring guide (daily tracker table) at first prescription and for each dose adjustment.

What is vandetanib and what does it treat?

Vandetanib is an orally administered Tyrosine Kinase Inhibitor (TKI) with activity against the Rearranged during Transfection (RET) proto-oncogene, the Vascular Endothelial Growth Factor receptor (VEGFR) and Epidermal Growth Factor Receptor (EGFR).
The precise mechanism of action of vandetanib in locally advanced or metastatic medullary thyroid cancer (MTC) is unknown.

Vandetanib is indicated for the treatment of aggressive and symptomatic RET mutant medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease.

Vandetanib is indicated in adults, children and adolescents aged 5 years and older and a body surface area (BSA) of ≥ 0.7 m2.

Prior to initiation of treatment with Vandetanib, the presence of a RET mutation should be determined by a validated test. The activity of Vandetanib, based on available data, is considered insufficient in patients with no identified RET mutation.

The product is formulated as immediate release tablets of two strengths.

100 mg  (Tablet not actual size)	300 mg  (Tablet not actual size)
The 100 mg strength is presented as a round, biconvex, white, film-coated tablet with ‘Z100’ impressed on one side; the other side is plain.	The 300 mg strength is presented as an oval-shaped, biconvex, white, film-coated tablet with ‘Z300’ impressed on one side; the other side is plain.

How is the dose of Vandetanib calculated for infants and children?

Calculation of the body surface area

Dosing for paediatric patients should be on the basis of BSA in mg/m^2 calculated according to the formula below (or other formula adapted for paediatric patients):

$$\sqrt{\text{Height (cm) x Weight (kg)} \div 3600} = \text{BSA (m}^2\text{)}$$

Example of dose calculation

If a patient's height = 125 cm and weight = 35 kg

$$\sqrt{125 \text{ x } 35 \div 3600} = 1.10 \text{ m}^2$$

BSA should be measured to the nearest 2 decimal places.

Vandetanib posology regimens according to the patient's BSA

There are 4 main posology regimens, depending on the BSA (see overview in table 1).
Each regimen includes a starting dose, which can be changed for:

- an increased dose, when vandetanib is well tolerated after 8 weeks at the starting dose
- a reduced dose, in case of undesirable side effects

Depending on cases, the dosage schedule corresponds to one of the 3 following schemes:

- “daily” schedule (same dose every day: D1=D2=D3 etc)
- “every other day” schedule (same dose every other day D1=D3=D5 etc)
- “7 day” schedule (two doses alternately, be aware that D1 = D8)

Patients aged 5-18 years should be dosed according to the nomogram in Table 1.

Table 1: Dosing nomogram for Paediatric Patients with MTC

BSA (m^2)	Start dose* (mg)	Dose increase (mg) when tolerated well after 8 weeks at starting dose	Dose reduction (mg)
0.7 - <0.9	100 every other day	100 daily	-
0.9 - <1.2	100 daily	7 day schedule: 100-200-100-200-100-200-100	100 every other day
1.2 - <1.6	7 day schedule: 100-200-100-200-100-200-100	200 daily	100 daily
≥ 1.6	200 daily	300 daily	7 day schedule: 100-200-100-200-100-200-100

* The starting dose is the dose at which treatment should be initiated.
Vandetanib doses higher than 150 mg/m^2 have not been used in clinical studies in paediatric patients.

The total daily dose in children must not exceed 300 mg.

For children with **moderate renal impairment, the reduced dose** as specified in Table 1 could be used. Individual patient management will be required by the physician, especially in paediatric patients with low BSA.

Vandetanib is not recommended in paediatric patients with severe renal impairment.

Vandetanib is not recommended for children with hepatic impairment.

Patients with an adverse reaction requiring a dose reduction should stop taking vandetanib for at least a week. Dosing can be resumed at a reduced dose thereafter when fully recovered from adverse reactions.

In the event of CTCAE grade 3 or higher toxicity or prolongation of the ECG QTc interval, dosing with vandetanib should be at least temporarily stopped and resumed at a reduced dose when toxicity has resolved or improved to CTCAE grade 1:

- Patients who are on the starting dose, should be recommenced at the reduced dose.
- Patients who are on the increased dose, should be recommenced at the starting dose.

If another event of common terminology criteria for adverse events (CTCAE) grade 3 or higher toxicity or prolongation of the ECG QTc interval occurs, dosing with vandetanib should be at least temporarily stopped and resumed at a reduced dose when toxicity has resolved or improved to CTCAE grade 1.

If a further event of CTCAE grade 3 or higher toxicity or prolongation of the ECG QTc interval occurs, dosing with vandetanib should be permanently stopped.

The patient must be monitored appropriately (see last part of guide and section 4.4 of SmPC). Due to the 19 day half-life, adverse reactions including a prolonged QTc interval may not resolve quickly.

Detailed recommendations by BSA ranges for a 14 day schedule (Tables 2 to 5)

DOSES AVAILABLE (tablets not actual size)	
100 mg	
200 mg (2 x 100mg)	
300 mg	

Be aware that the “7 day” schedule includes 2 consecutive days with the same dose.

*Table 2: Vandetanib posology regimen for children with BSA 0.7 m^2 to <0.9 m^2**

Dose	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Starting dose[a]	-	100 mg	-	100 mg	-	100 mg	-	100 mg	-	100 mg	-	100 mg	-	100 mg
Increased dose[b]	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg

* A reduced dose is not applicable: in case of side effects, treatment has to be suspended as described above.

[a] The starting dose is the dose at which treatment should be initiated.
[b] Higher vandetanib doses than 150 mg/m^2 have not been used in clinical studies in paediatric patients.

Table 3: Vandetanib posology regimen for children with BSA 0.9 m^2 to <1.2 m^2

Dose	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Starting dose[a]	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg
Increased dose[b]	100 mg	200 mg	100 mg	200 mg	100 mg	200 mg	100 mg	100 mg	200 mg	100 mg	200 mg	100 mg	200 mg	100 mg
Reduced dose[c]	-	100 mg	-	100 mg	-	100 mg	-	100 mg	-	100 mg	-	100 mg	-	100 mg

[a] The starting dose is the dose at which treatment should be initiated.
[b] Higher vandetanib doses than 150 mg/m^2 have not been used in clinical studies in paediatric patients.
[c] Patients with an adverse reaction requiring a dose reduction should stop taking vandetanib for at least a week. Dosing can be resumed at a reduced dose thereafter when fully recovered from adverse reactions.

Table 4: Vandetanib posology regimen for children with BSA 1.2m^2 to <1.6 m^2

Dose	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Starting dose[a]	100 mg	200 mg	100 mg	200 mg	100 mg	200 mg	100 mg	100 mg	200 mg	100 mg	200 mg	100 mg	200 mg	100 mg
Increased dose[b]	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg
Reduced dose[c]	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg

[a] The starting dose is the dose at which treatment should be initiated.
[b] Higher vandetanib doses than 150 mg/m^2 have not been used in clinical studies in paediatric patients.
[c] Patients with an adverse reaction requiring a dose reduction should stop taking vandetanib for at least a week. Dosing can be resumed at a reduced dose thereafter when fully recovered from adverse reactions.

Table 5: Vandetanib posology regimen for children with BSA ≥ 1.6 m^2

Dose	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Starting dose[a]	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg
Increased dose[b]	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg
Reduced dose[c]	100 mg	200 mg	100 mg	200 mg	100 mg	200 mg	100 mg	100 mg	200 mg	100 mg	200 mg	100 mg	200 mg	100 mg

[a] The starting dose is the dose at which treatment should be initiated.
[b] Higher vandetanib doses than 150 mg/m^2 have not been used in clinical studies in paediatric patients.
[c] Patients with an adverse reaction requiring a dose reduction should stop taking vandetanib for at least a week. Dosing can be resumed at a reduced dose thereafter when fully recovered from adverse reactions.

How is Vandetanib used?

The calculated dose should be taken with or without food at about the same time of the day.

For patients who have trouble swallowing the tablet, it can be mixed with water as follows:

- Take half a glass of still (non-carbonated) water. Only use water, do not use any other liquids.
- Put tablet in the water.
- Stir the tablet until it has dispersed into the water. This may take about 10 mins.
- Then ensure the patient drinks the solution straight away.
- To make sure there is no medicine left, half fill the glass with water again and ensure that the patient drinks all of it.

For paediatric patients following QD posology regimens, if a dose is missed, it should be taken as soon as the patient or caregiver 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.

Dosing and monitoring guide for paediatric patients and caregivers of patients treated with vandetanib

Patients and/or caregivers of patients treated with vandetanib must be given the dosing guide and the patient alert card which are available in order:

- to inform patients or patient's caregivers and any healthcare professional about the risks associated with vandetanib treatment and the posology regimens
- to promote compliance and monitoring to reduce the risk of side effects and medication errors

The physician has to complete the "prescriber part" with the BSA of the patient and the recommended posology regimen. The patient has to complete the tracker daily and has the possibility to make comments.

At the time of initial prescription and at each subsequent dose adjustment (increase, decrease or by change in the BSA range), a new sheet of the daily tracker must be used and provided to the patient or patient's caregiver.

Summary of Product Characteristics can be found at **www.medicines.ie**

SANOFI GENZYME

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