Caprelsa® Practical Guide

Caprelsa™
vandetanib

is a tyrosine kinase inhibitor[1]

Caprelsa® has both direct and indirect antitumour activity, by selectively inhibiting VEGFR, EGFR and RET signalling (observed in *vitro* and in *vivo*). The precise mechanism of action of vandetanib in locally advanced or metastatic MTC is unknown. [1]

1. Caprelsa® Summary of Product Characteristics (SmPC November 2022).

version 1.0 dated July-2025

For who[1]?

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

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

Use of Caprelsa® is contraindicated in cases of:

- **Hypersensitivity** to the active substance or to any of the excipients listed listed in section 6.1 of the Summary of Product cteristics.
- Congenital **long QTc** syndrome.
- Patients with a **QTc interval >480 msec.**
- Concomitant use with the following drugs : Arsenic, cisapride, erythromycin intravenous (IV), toremifene, mizolastine, moxifl oxacin, Class IA and III antiarrhythmics.
- **Breast-feedina.**

Use of Caprelsa® in special patient populations

	YES	NO	Comment
Elderly	✓		No adjustment in starting dose is required. There is limited clinical data with Caprelsa® in patients with MTC aged over 75 years
Paediatric population		✓	Not indicated. The safety and efficacy of Caprelsa® in children have not been established
No RET mutation identified		✓	Limited data available. The activity of Caprelsa is considered insufficient in patients with no RET mutation identified.
Mild renal impairment	✓		No change in the starting dose is required
Moderate renal impairment	✓		The starting dose could be reduced to 2 tablets of 100 mg (safety and efficacy have however not been established with 2X100 mg*
Severe renal impairment		✓	Limited data available and safety and efficacy have not been established.
Hepatic impairment		✓	Limited data available and safety and efficacy have not been established.
Patients with congenital long QTc syndrome or with a QTc interval >480 msec		✓	Contraindicated

*There are limited data with 300 mg in patients with moderate renal impairment: in a pharmacokinetic study, the dose needed to be lowered to 200 mg in 5 out of 6 patients.

1. Caprelsa® Summary of Product Characteristics (SmPC November 2022)

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Daily[1]

Posology and dose adjustment in adults

Starting dose	Frequency	Duration
300 mg 	1 x day	Until the patient no longer benefits from treatment or a grade 3 or higher toxicity (CTCAE* scale), or prolongation of the ECG QTc interval, Caprelsa® should be temporarily stopped and resumed at a reduced dose when toxicity has resolved or improved to CTCAE grade 1.
Dose reduction	**Frequency**	**Duration**
2X 100 mg  (2 tablets of 100 mg)	1 x day	In the event of a grade 3 or higher toxicity (CTCAE* scale), or prolongation of the ECG QTc interval, Caprelsa® should be temporarily stopped and resumed at a reduced dose when toxicity has resolved or improved to CTCAE grade 1.
Dose reduction	**Frequency**	**Duration**
100 mg 	1 x day	In the event of a grade 3 or higher toxicity (CTCAE* scale), or prolongation of the ECG QTc interval, Caprelsa® should be temporarily stopped and resumed at a reduced dose when toxicity has resolved or improved to CTCAE grade 1.

Tablets not to scale. *CTCAE: Common Terminology Criteria for Adverse Events.

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Recommendation for taking Caprelsa®

- Taken once a day, at approximately the same time each day, with or without food.
- For patients who have difficulty swallowing, Caprelsa® 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 and the resultant dispersion swallowed immediately. Any residues in the glass are to be mixed with half a glass of water and swallowed.

If a dose is missed[1]:

- If the time before taking the next dose is **greater than 12 hours**, the missed dose must be taken as soon as the patient remembers,
- If the time before taking the next dose is **less than 12 hours**, the patient should not take the missed dose.

In all cases, patients **should not take a double dose** (two doses at the same time) to make up for a forgotten dose.

Caprelsa® vandetanib

Patient monitoring[1]

	Before treatment	1 week	3 weeks	6 weeks	12 weeks	6 months	9 months	12 months
ECG	✓	✓	✓	✓	✓	✓	✓	✓
Serum potassium	✓	✓	✓	✓	✓	✓	✓	✓
Serum calcium	✓	✓	✓	✓	✓	✓	✓	✓
Serum magnesium	✓	✓	✓	✓	✓	✓	✓	✓
TSH level	✓	✓	✓	✓	✓	✓	✓	✓

TSH: Thyroid stimulating hormone.

If clinically indicated during this period and afterwards, ECG and blood tests should also be obtained. Frequent ECG monitoring of the QTc interval should be continued. Due to the **19-day** half-life of Caprelsa®, adverse reactions including a prolonged QTc interval, may not resolve quickly.

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

Serum potassium, magnesium and calcium should be kept within normal range to reduce the risk of ECG QTc prolongation.

If the **QTc increases markedly but stays below 500 msec**, cardiologist advice should be sought.

1. Caprelsa® Summary of Product Characteristics (SmPC November 2022)

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

Patients who develop a single value of a QTc interval ≥500 msec should stop taking Caprelsa®. Dosing can be resumed at a reduced dose after return of the QTc interval to pretreatment status has been confirmed and correction of a possible electrolyte imbalance has been made.

1. Caprelsa® Summary of Product Characteristics (SmPC November 2022)

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Safety profile[1]

What to do if any of the following occur

Posterior reversible encephalopathy syndrome (PRES; also known as reversible posterior leukoencephalopathy syndrome, RPLS)

Suggestive signs:

- Seizures
- Headache
- Visual disturbances
- Confusion
- Altered mental function

What to do?

A brain MRI should be performed in any patient presenting with such signs.

Skin reactions

- Rash
- Other skin reactions, including photosensitivity reactions and palmar-plantar erythrodysaesthesia syndrome

What to do?

- Mild to moderate skin reactions can be managed by symptomatic treatment, or by dose reduction or interruption.
- For 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 applying sunscreen, due to the potential risk of phototoxicity reactions associated with Caprelsa® treatment,and may require systemic glucocorticosteroids and permanent discontinuation of vandetanib.

Diarrhoea

Diarrhoea is a disease-related symptom as well as a known undesirable effect of Caprelsa®.

What to do?

- Administration of routine anti-diarrhoeal agents is recommended.
- If severe diarrhoea (CTCAE grade 3–4) develops, Caprelsa® should be stopped until the diarrhoea improves. Treatment should then be resumed at a reduced dose.
- QTc and serum electrolytes should be monitored more frequently.
- Additional **warnings and precautions for use** are listed on section 4.4 of the SmPC; such as haemorrhage, heart failure, hypertension, patients with renal impairment, patients with hepatic impairment, alanine aminotransferase elevations, interstitial lung disease, CYP3A4 inducers, calcitonin less than 500 pg/ml. Please refer to it for further information.

Overdose

In the event of an overdose, further doses must be interrupted and appropriate measures taken to assure that an adverse event has not occurred, i.e., ECG within 24 hours to determine QTc prolongation.
Adverse reactions associated with an overdose may be prolonged due to the long half-life of Caprelsa® (19 days).
Adverse reactions should be treated symptomatically, in particular severe diarrhoea.

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This document is approved by The Executive Directorate of Pharmacovigilance, at SFDA.

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Safety profile of Caprelsa®[1]

The most commonly reported adverse drug reactions have been **diarrhoea, rash, nausea, hypertension and headache.**

Events such as Torsades de pointes, Stevens-Johnson syndrome, erythema multiforme, interstitial lung disease (sometimes fatal) **and PRES** (RPLS) have occurred in patients treated with Caprelsa® monotherapy. It is expected that these would be uncommon adverse reactions in patients receiving Caprelsa® for MTC.

Ocular events such as blurred vision are common in patients who received Caprelsa® for MTC. Scheduled slit lamp examinations have revealed corneal opacities (vortex keratopathies) in treated patients. However, routine slit lamp examinations are not required for patients receiving Caprelsa®.

At various exposure durations, median **haemoglobin levels** in patients treated with Caprelsa® were increased by 0.5–1.5 g/dl compared to baseline. The following adverse reactions have been identified in clinical studies in patients receiving Caprelsa® as treatment for MTC.

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Caprelsa® vandetanib | Safety profile[1]

Caprelsa® adverse events by system organ class and frequency

System organ class	Very common
Infection and infestation disorders	Nasopharyngitis bronchitis, upper respiratory tract infections, urinary tract infections
Endocrine disorders	
Metabolism and nutritional disorders	Appetite decreased, Hypocalcaemia
Psychiatric disorders	Insomnia, Depression
Nervous system disorders	Headache, paraesthesia, dysaesthesia, dizziness
Eye disorders	Vision blurred, corneal structural change (including corneal deposits and corneal opacity)
Cardiac disorders	Prolongation of ECG QTc interval(*) (**)
Vascular disorders	Hypertension
Respiratory, thoracic and mediastinal disorders	
Gastrointestinal disorders	Abdominal pain, diarrhoea, nausea, vomiting, dyspepsia
Hepatobiliary disorders	
Skin and subcutaneous tissue disorders	Photosensitivity reaction, rash and other skin reactions (including acne, dry skin, dermatitis, pruritis), nail disorders
Renal and urinary tract disorders	Proteinuria, nephrolithiasis
General disorders and administration site conditions	Asthenia, fatigue, pain, oedema
Investigations	ECG QTc interval prolonged

The frequency of occurrence of adverse events is defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1 /10,000) and not known (cannot be estimated from the available data). This section presents only data from completed studies in which patient exposure is known.

Common	Uncommon	Unknown
Pneumonia, sepsis, influenza, cystitis, sinusitis, laryngitis, folliculitis, furuncle, fungal infection, pyelonephritis	Appendicitis, staphylococcal infection, diverticulitis, cellulitis, abdominal wall abscess	
Hypothyroidism		
Hypokalaemia, hypercalcaemia, hyperglycemia, dehydration, hyponatremia	Malnutrition	
Anxiety		
Tremor, lethargy, loss of consciousness, balance disorders, dysgeusia	Convulsion, clonus, brain oedema	
Visual impairment, halo vision, photopsia, glaucoma, conjunctivitis, dry eye, keratopathy	Cataract, accommodation disorders	
	Heart failure, acute heart failure, rate and rhythm disorders, cardiac conduction disorders, ventricular arrhythmia and cardiac arrest	
Hypertensive crisis, ischaemic cerebrovascular conditions		Aneurysms and artery dissections
Epistaxis, haemoptysis, pneumonitis	Respiratory failure, pneumonia aspiration	
Colitis, dry mouth, stomatitis, dysphagia, constipation, gastritis, gastrointestinal haemorrhage	Pancreatitis, peritonitis, ileus, intestinal perforation, faecal incontinence	
Cholelithiasis		
Palmar-plantar erythrodysaesthiesia syndrome, alopecia	Bullous dermatitis	
Dysuria, hematuria, renal failure, pollakiuria, micturition urgency	Chromaturia, anuria	
Pyrexia	Impaired healing	
Increase of serum ALT and AST, weight decreased, blood creatinine increased	Increased haemoglobin, serum amylase increased	

*13.4% of patients on Caprelsa® had QTc (Bazett's) ≥500 ms compared with 1.0% of placebo patients. QTcF prolongation was >20 ms in over 91% of patients, >60 ms in 35%, >100 msec in 1.7%. Eight percent of patients had a dose reduction due to QTc prolongation.
**Including two deaths in patients with QTc >550 ms (one due to sepsis and one due to heart failure).

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Caprelsa® vandetanib | And other drugs[1]

Caprelsa® has been shown to prolong the ECG QTc interval; Torsades de pointes has been uncommonly reported.

Therefore, the concomitant use of Caprelsa® 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.

Use of Caprelsa® is **contraindicated** with concomitant administration of:

Cisapride, erythromycine intravenous (IV), toremifene, mizolastine, moxifloxacin, arsenic, Class IA and III antiarrhythmics.

Use of Caprelsa® is **not recommended** when administered concomitantly with:

Methadone, haloperidol, amisulpride, chlorpromazine, sulpiride, zuclopenthixol, halofantrine, pentamidine, ondansetron and lumefantrine.

Vitamin K antagonists:

Due to the increased thrombotic risk in patients with cancer, the use of anticoagula-tion is frequent. In consideration of the high intra-individual variability of the response to anticoagulation, and the possibility of interaction between vitamin K antagonists and chemotherapy, an increased frequency of the International Normalised Ratio monitoring is recommended, if it is decided to treat the patient with vitamin K antagonists.

If there is no appropriate alternative therapy, non-recommended combinations with Caprelsa® may be made with:

- additional ECG monitoring of the QTc interval

-evaluation of electrolytes

- further control at onset or worsening of diarrhoea.

Results of a pharmacodynamic and pharmacokinetic interaction study indicated that co-administration with ondansetron in healthy patients appeared to have little effect on the pharmacokinetics of vandetanib, but had a small additive effect on the prolongation of the QTc interval of approximately 10 ms. Therefore, the concomitant use of ondansetron with vandetanib is not recommended. If ondansetron is administered with vandetanib, closer monitoring of serum electrolytes and ECGs and aggressive management of any abnormalities is required.

For complete information on the pharmacokinetic interactions, refer to the Caprelsa® SmPC.

Caprelsa® vandetanib | Risk management plan[1]

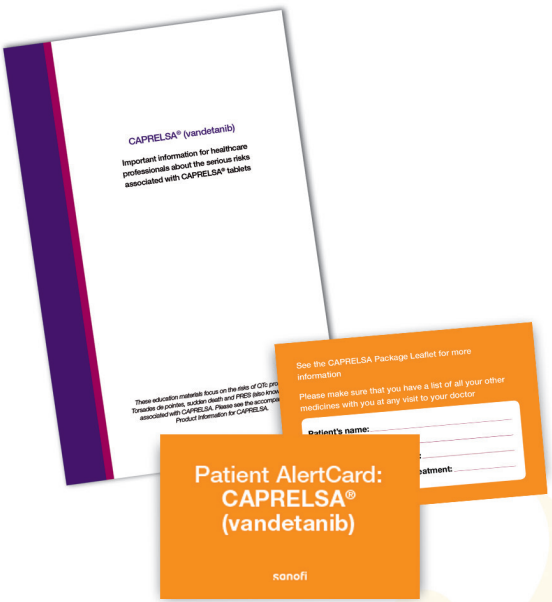
Before prescribing Caprelsa®, you must be familiar with the Physician Information and Management Guidelines.

This information includes:

- **A handbook for healthcare professionals** discussing the serious risks, especially QTc interval prolongation and PRES (RPLS), as well as ways to mitigate them.
- **Patient Alert Cards,** drawing the attention of patients to the adverse reactions. Your patients will receive this Alert Card with each prescription.

You should discuss the risks of Caprelsa® treatment with your patients.

Additional information is available in the document for healthcare professionals developed within the framework of the Caprelsa® risk management plan.



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In case of any drug related adverse events, please contact:

The National Pharmacovigilance Centre (NPC- Saudi Food and Drug Authority (SFDA))
Call Center: 19999
E-mail: npc.drug@sfda.gov.sa
https://ade.sfda.gov.sa

For SANOFI Pharmacovigilance center, please contact:+966-544-284-797
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