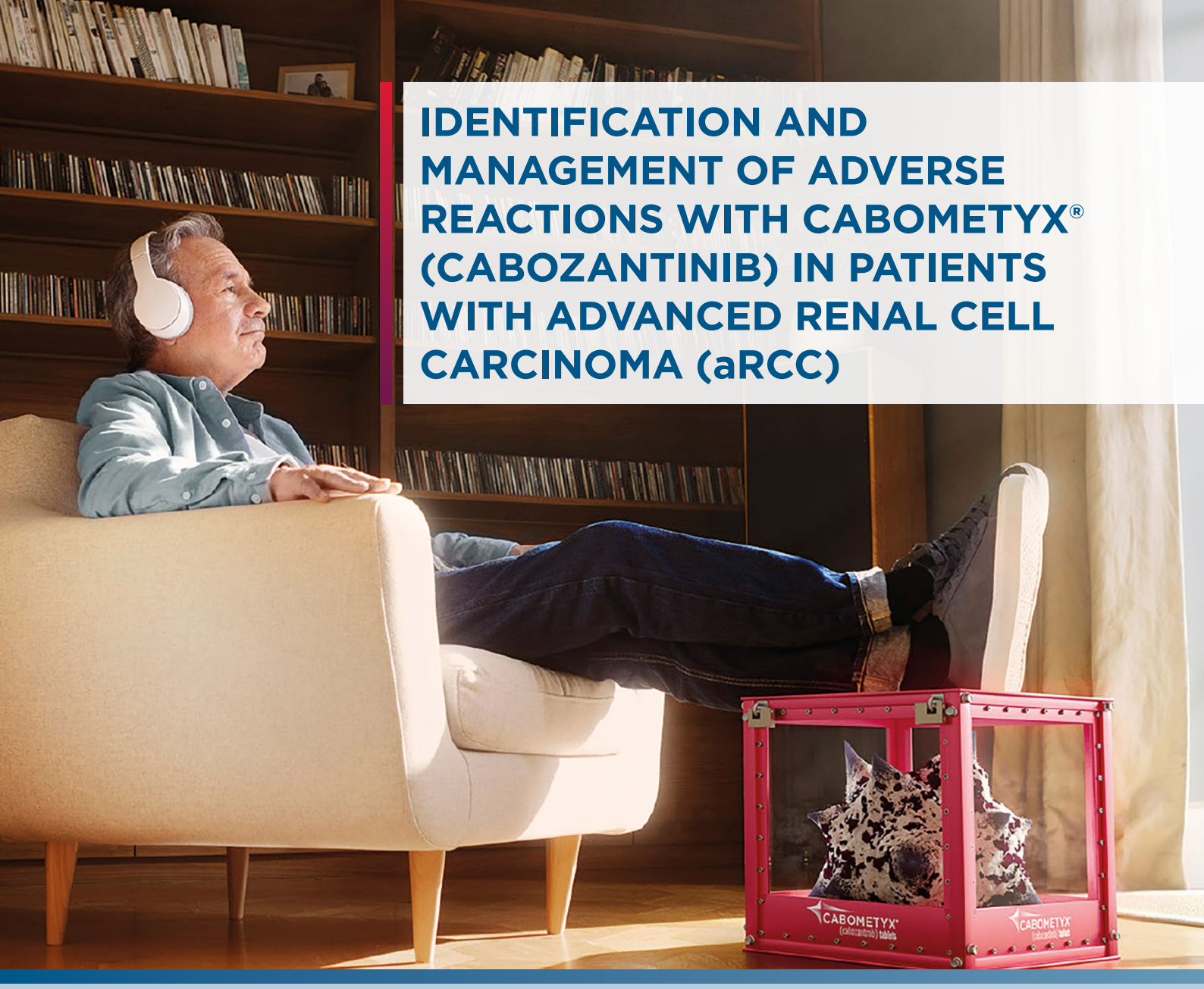


IDENTIFICATION AND MANAGEMENT OF ADVERSE REACTIONS WITH CABOMETYX® (CABOZANTINIB) IN PATIENTS WITH ADVANCED RENAL CELL CARCINOMA (aRCC)

A GUIDE FOR HEALTHCARE PROFESSIONALS

Cabometyx® (cabozantinib) is indicated as a monotherapy for aRCC[1]

- as first-line treatment of adult patients with intermediate or poor risk
- in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy

Cabometyx®, in combination with nivolumab, is indicated for the first-line treatment of advanced renal cell carcinoma in adults.[1]

Please refer to the Summary of Product Characteristics (SmPC) for further information.[1]
Prescribing Information can be found here.

Reporting adverse events:
Adverse events should be reported. Reporting form and information can be found at: www.hpra.ie.
Adverse events should also be reported to the Ipsen Medical Information Department on: +353 18098256 or pharmacovigilance.uk-ie@ipsen.com

This material is intended for Irish healthcare professionals only

CABOMETYX® (cabozantinib) tablets

IPSEN

CMX-IE-000556
February 2025

CONTENTS

ABOUT THIS GUIDE

Most adverse reactions (ARs) with Cabometyx® in patients with aRCC occur early during treatment; therefore, it is important to monitor patients closely during the first 8 weeks of treatment to determine if dose modifications are warranted.[1]

This guide has been produced to help healthcare professionals identify and manage some very common (≥1/10) ARs observed in patients, focusing on palmar-plantar erythrodysaesthesia syndrome (PPES), gastrointestinal ARs, hypertension, and laboratory abnormalities.

Each section describes the different grades for the AR and outlines strategies to pre-empt its occurrence. It also discusses how to manage and keep the grade of the reaction as low as possible should the AR occur.

Please refer to section 4.8 of the SmPC for the full list of ARs and to your local guidelines for additional information on each AR.[1]

OVERVIEW OF THE MANAGEMENT OF ADVERSE REACTIONS WITH CABOMETYX®

This document focuses on the management of ARs of any grade reported in patients with renal cell carcinoma (RCC) receiving Cabometyx®[1]

With Cabometyx® as a monotherapy:

- Very common ARs of any grade (experienced by at least 25% of patients) in the RCC population included diarrhoea, fatigue, nausea, decreased appetite, PPES, hypertension, weight decrease, vomiting, dysgeusia, constipation and aspartate aminotransferase (AST) increase[1]
- Hypertension was observed more frequently in the treatment-naïve RCC population (67%) compared with those who had received prior VEGF-targeted therapy (37%)[1]

With Cabometyx® in combination with nivolumab:

- The most frequent adverse reactions (experienced by at least 25% of patients) were diarrhoea, fatigue, PPES, stomatitis, musculoskeletal pain, hypertension, rash, hypothyroidism, decrease appetite, nausea, abdominal pain[1]

Please refer to the SmPC for a full list of other and serious ARs.[1] When managing ARs, the reference point must always be the guidance in the Cabometyx® SmPC.[1]

DOSE MODIFICATIONS

Recommended dose modifications of Cabometyx® for ARs*[1,2]

	GRADE 1	GRADE 2	GRADE 3 (EXCEPT CLINICALLY NON-RELEVANT LABORATORY ABNORMALITIES)	GRADE 4 (EXCEPT CLINICALLY NON-RELEVANT LABORATORY ABNORMALITIES)
SYMPTOMS	**Mild:** • Asymptomatic or mild symptoms • Cinical or diagnostic observations only • Intervention not indicated	**Moderate:** • Minimal, local or non-invasive intervention indicated • Limiting age-appropriate instrumental activities of daily living (ADL)†	**Severe or medically significant but not immediately life-threatening:** • Hospitalisation or prolongation of hospitalisation indicated • Disabling • Limiting self-care ADL‡	**Life-threatening consequences:** Urgent intervention indicated
RECOMMENDED DOSE MODIFICATIONS	Dose adjustment is usually not required	For **tolerable** ARs, dose adjustment is usually not required For **intolerable** ARs that cannot be managed with a dose reduction or supportive care, interrupt treatment until the AR resolves to Grade ≤1	Interrupt treatment until the AR resolves to Grade ≤1	Interrupt treatment Institute appropriate medical care
ADDITIONAL CARE AND TREATMENT RE-INITIATION	Add supportive care as indicated	Add supportive care as indicated Consider re-initiating at a reduced dose	Add supportive care as indicated Re-initiate at a reduced dose	If AR resolved to Grade ≤1, re-initiate at a reduced dose If AR does not resolve, permanently discontinue

*Grading of ARs according to Common Terminology Criteria for Adverse Events (CTCAE V5.0).[2]
†For example, preparing meals, shopping, using the telephone, managing money.[2] ‡For example, bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.[2]

DOSE INTERRUPTIONS AND REDUCTIONS

Dose interruptions are recommended for the management of CTCAE V.5.0 Grade 3 or greater toxicities or intolerable Grade 2 toxicities.[1]

Dose reductions are recommended for events that, if persistent, could become serious or intolerable.[1]

Cabometyx® monotherapy:[1]

Optimised starting dose

60 mg
Once daily

First reduction*

40 mg
Once daily

Second reduction*

20 mg
Once daily

Cabometyx® in combination with nivolumab:[1]

Optimised starting dose

40 mg
Once daily

First reduction*

20 mg
Once daily

Second reduction*

20 mg
Every other day

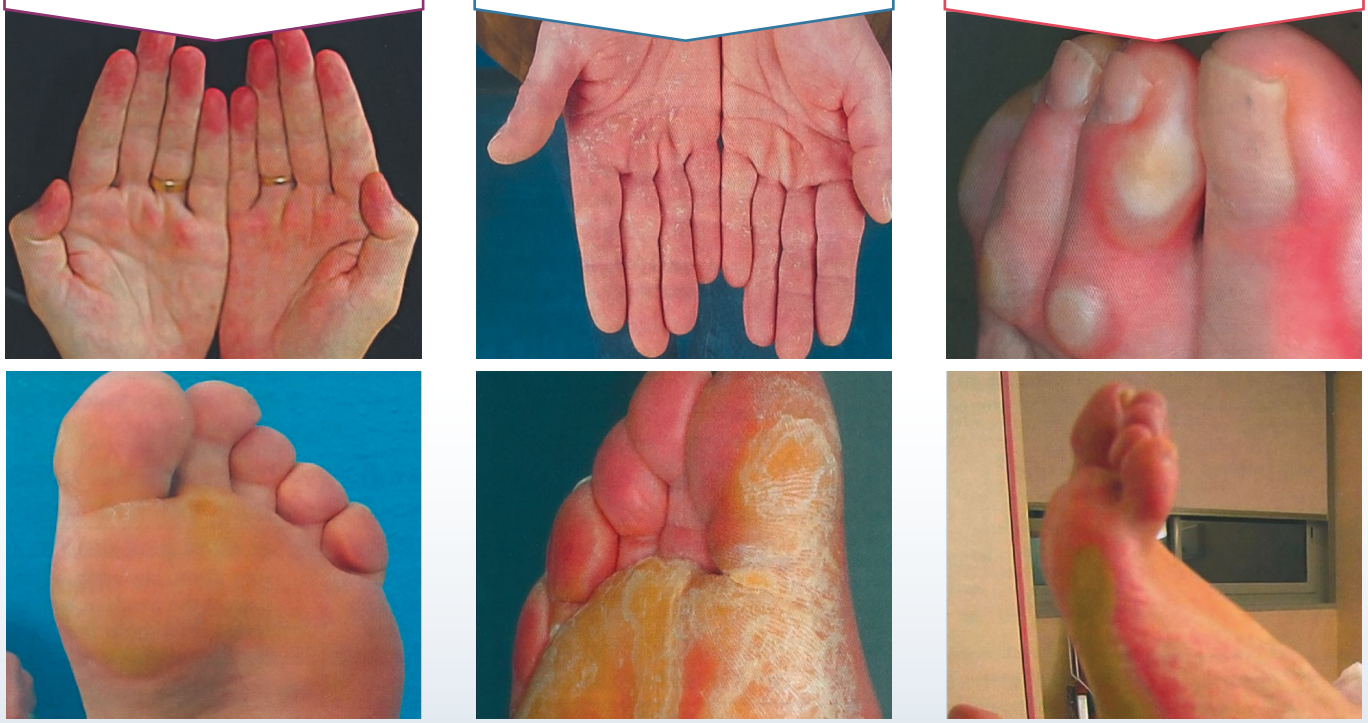
*If required.

PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME

PPES is a skin toxicity induced by certain chemotherapy drugs and is also known as hand-foot syndrome.[2,3] It is characterised by redness, marked discomfort, swelling and tingling in the palms of the hands or the soles of the feet.[2] The affected areas may become dry and peel.[2] The severity of the clinical presentation of PPES appears to be correlated with drug exposure.[3]

There are three grades of PPES:[2]

GRADE 1	GRADE 2	GRADE 3
Minimal skin changes or dermatitis (e.g. erythema, oedema or hyperkeratosis) with no pain	Skin changes (e.g. peeling, blisters, bleeding, fissures, oedema or hyperkeratosis) with pain; instrumental ADL are limited	Severe skin changes (e.g. peeling, blisters, bleeding, fissures, oedema or hyperkeratosis) with pain, limiting self-care ADL



Images from Lipworth AD, *et al*. 2009.[4]

Ways of preventing PPES[5,6]

Preventive measures are aimed at reducing friction and heat exposure:

- Advise patients on ways to protect their hands and feet from hot water, pressure and friction (e.g. avoid tight-fitting shoes)
- Emollients and moisturising creams can be used from the beginning of treatment. Recommend the use of hypoallergenic skin moisturisers containing colloidal oatmeal
- Advise patients to use a sunscreen with a high skin protection factor (SPF ≥30)
- Suggest the wearing of thick cotton gloves/socks at night and the use of gel shoe inserts
- Remove hyperkeratotic areas (e.g. calluses)

Management of patients who develop PPES[3,5,6]

- Advise patients to get pedicures and/or manicures to remove hyperkeratosis
- Recommend exfoliating products (urea- and salicylic acid-based)
- Suggest patients wear cotton gloves and socks at night to protect their hands and feet
- Suggest patients wear shoes with soft insoles and keep their palms and soles dry to protect pressure-sensitive areas
- Advise patients to avoid contact with hot water and trauma/friction/excessive pressure
- Recommend patients use medical-grade skin adhesives to encourage healing of cracked and painful regions
- Provide patients with topical or oral analgesics to relieve pain
- Please note that pyridoxine (vitamin B6) is not recommended

GASTROINTESTINAL ADVERSE REACTIONS

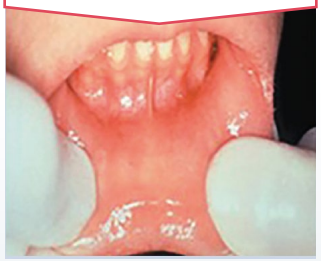
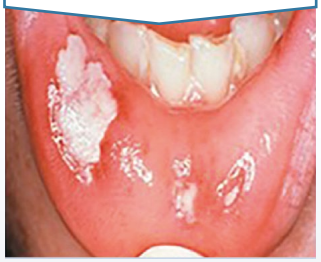
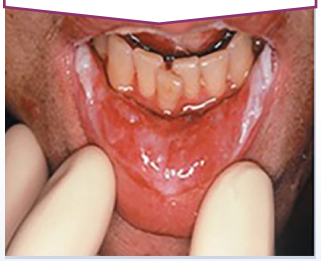
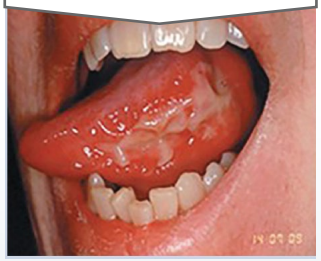
Stomatitis

Also known as oral mucositis, stomatitis manifests as ulceration or inflammation of the mucous membrane of the mouth, including the lips, cheeks, gums, tongue and throat.[2,6]

Patients may not have any visible signs of inflammation and their mouth and tongue may look completely normal, but they may complain of sensitivity or a burning sensation in their mouth.[3]

Stomatitis often reduces the patient's quality of life, and permanent stomatitis may cause the patient to stop eating, resulting in malnutrition, fatigue and anorexia.[3] Stomatitis generally resolves rapidly once the drug is withdrawn or the dose is reduced.[3]

There are four grades of stomatitis:[2]

GRADE 1	GRADE 2	GRADE 3	GRADE 4
Asymptomatic or mild symptoms; intervention not indicated	Moderate pain or ulceration that does not interfere with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated
			

Ways of preventing stomatitis[5,6]

- Suggest patients receive a comprehensive dental examination and treatment, including replacement or removal of ill-fitting dentures
- Advise patients to protect their oral cavity by avoiding foods that may irritate, such as hot, salty, spicy and acidic foods (e.g. crackers, pickles, citrus fruits and raw vegetables). They should be encouraged to consume soft foods cut into small pieces, to use straws for drinking and to avoid the use of tobacco and alcohol
- Encourage all patients, including those with dentures, to carry out regular, gentle oral hygiene (e.g. use a paediatric toothpaste, a soft toothbrush, flossing, oral rinses)
- Advise patients to avoid oral rinses containing alcohol because they can make a dry mouth worse

Management of patients who develop stomatitis[5,6]

- Advise patients to avoid spicy, sticky food and other foods that could cause irritation
- Suggest patients use appropriate mouthwash or oral rinses
- Advise patients to avoid oral rinses with alcohol

Diarrhoea

Diarrhoea is characterised by an increase in frequency and/or loose or watery bowel movements.[2]

There are four grades of diarrhoea:[2]

GRADE 1	GRADE 2	GRADE 3	GRADE 4
Increase of less than four stools per day over baseline; mild increase in ostomy output compared with baseline	Increase of four to six stools per day over baseline; moderate increase in ostomy output compared with baseline; limiting instrumental ADL	Increase of seven or more stools per day over baseline; hospitalisation indicated; severe increase in ostomy output compared with baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated

Prevention and management of diarrhoea[3,5–8]

- If a patient notices that their bowel function is worse, advise them to keep a note of what they had eaten and drunk beforehand to determine what has made their bowel function worse
  - An assessment of baseline bowel movements may be made through the number of bowel movements, stool characteristics and any co-existing symptoms and how long they last; it is also important to know whether there are any potential secondary causes, such as pancreatic insufficiency, bile acid malabsorption or small intestinal bacterial overgrowth, all of which are treatable
- Regularly discuss the patient's food and water intake with them
- Suggest patients take oral hydration and anti-diarrhoeal medications, such as loperamide, to manage diarrhoea where appropriate
- Advise patients to continue to limit/avoid foods that could cause gastrointestinal events and inform them of other dietary strategies (e.g. eating frequent and small meals)
- Instruct patients to drink plenty of water to maintain hydration levels and avoid alcohol
- Advise patients to clean and dry their rectal area with mild soap and water and use disposable wipes and a moisture-barrier ointment

Nausea and vomiting

Nausea is characterised as a queasy sensation, which may or may not be accompanied by an urge to vomit.[2]

Vomiting is characterised by the reflexive act of ejecting the contents of the stomach through the mouth.[2]

There are three grades of nausea:[2]

GRADE 1	GRADE 2	GRADE 3
Loss of appetite without alteration in eating habits	Decreased oral intake without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, total parenteral nutrition or hospitalisation indicated

There are four grades of vomiting:[2]

GRADE 1	GRADE 2	GRADE 3	GRADE 4
Intervention not indicated	Outpatient intravenous hydration; medical intervention indicated	Tube feeding, total parenteral nutrition solutions or hospitalisation indicated	Life-threatening consequences

Prevention and management of nausea and vomiting[5–7]

- Provide patients with antiemetics for prophylactic use
- Suggest that patients eat small meals and eat more frequently each day
- Advise patients to drink plenty of water and other fluids
- In severe cases, consider guidelines for gastro-oesophageal reflux disease, including lifestyle and dietary modifications and the use of proton-pump inhibitors

HYPERTENSION

Hypertension is defined as a pathological increase in blood pressure (BP), with a persistent elevation above 140/90 mmHg.[9]

There are four grades of hypertension:[2]

GRADE 1

Systolic BP 120–139 mmHg or diastolic BP 80–89 mmHg

GRADE 2

Systolic BP 140–159 mmHg or diastolic BP 90–99 mmHg if previously within normal limits; change in baseline medical intervention indicated; recurrent or persistent (≥24 hours); symptomatic increase by >20 mmHg (diastolic) or to >140/90mmHg; indicated monotherapy initiated

GRADE 3

Systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated

GRADE 4

Life-threatening consequences (e.g. malignant hypertension, transient or permanent neurological deficit, hypertensive crisis); urgent intervention indicated

Ways of monitoring hypertension[1,5,6]

- Check the patient's baseline BP and make sure they understand the importance of monitoring and treating hypertension
- Assess the patient's risk before treatment with Cabometyx® through more than two measurements of BP; BP should be controlled before treatment is started
- Carry out a thorough patient history, physical examination and laboratory evaluation and monitor the patient's BP routinely
- Plan for BP monitoring at home

Management of patients who develop hypertension[6,9]

- Advise patients to stop smoking and reduce excessive caffeine consumption
- Ensure their diet is low in salt
- Encourage patients to take regular exercise
- Regularly monitor blood pressure throughout treatment and follow local guidelines for antihypertensive treatment and hypertensive management
- Treat patients as needed with standard therapy calcium channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors, angiotensin-2 receptor blockers (ARBs), beta blockers or thiazide diuretics
    - ACE inhibitors, ARBs or CCBs may be preferred over thiazide diuretics to reduce electrolyte loss and risks of QT interval prolongation
    - Provide up to three standard antihypertensive agents, but do not combine ACE inhibitors and ARBs
    - Avoid cytochrome P450 3A4 (CYP3A4) inhibitors/inducers (e.g. verapamil, diltiazem)
- If hypertension cannot be managed using the approaches outlined above, patients may need onward referral

GENERAL DISORDERS AND INVESTIGATIONS

Weight loss

Weight loss is very common and may have several causes, including treatment-related nausea.[2,7]

There are three grades of weight loss:[2]

GRADE 1	GRADE 2	GRADE 3
5 to <10% from baseline; intervention not indicated	10 to <20% from baseline; nutritional support indicated	≥20% from baseline; tube feeding or total parenteral nutrition indicated

Prevention and management of weight loss[6]

- Talk to patients and their caregivers regularly about the patient's diet and their appetite
- Encourage patients to eat nutritious foods high in calories and proteins and to snack throughout the day on foods such as eggs, poultry, fish, cheese or honey
- Advise patients to limit and/or avoid foods that could cause gastrointestinal problems

Fatigue

Fatigue is characterised by overall weakness and a pronounced inability to summon sufficient energy to carry out daily activities.[2] Multiple factors, including the side-effects of Cabometyx® (e.g. anaemia and dehydration because of diarrhoea), may contribute to fatigue.[3] Fatigue is also associated with other underlying factors, such as depression.[3]

There are three grades of fatigue:[2]

GRADE 1	GRADE 2	GRADE 3
Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest; limiting self-care ADL

Prevention and management of fatigue[5–7,10]

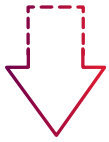
- Educate patients on ways to monitor fatigue, conserve energy and use distraction techniques to take their minds away from their fatigue; light exercise for 20–30 minutes per day may be beneficial, particularly if it is carried out at a time when the patient has good energy levels
- Encourage patients to carry out relaxing activities and rest often; some patients may be able to take part in aerobic activity or resistance training
- Advise patients to eat regular small meals and drink plenty of fluids to prevent dehydration
- Discuss and address any issues of depression, anxiety, mood disturbance or insomnia; psychostimulants may be beneficial in certain patients
- Suggest non-pharmacological strategies to help manage fatigue (e.g. acupressure and breathing exercises)

LABORATORY ABNORMALITIES

Patients may also experience a range of abnormalities in lab results, including:[1]

- Increase in alanine aminotransferase (ALT)
- Increase in AST
- Increase in bilirubin
- Increase in creatinine
- Increase in triglycerides
- Increase in cholesterol

- Increase/decrease in potassium
- Increase/decrease in calcium
- Increase/decrease in magnesium
- Increase/decrease in sodium



- Decrease in red blood cells, white blood cells and/or platelets
- Decrease in phosphate

- High blood sugar
- Low blood sugar

Liver enzymes elevations for RCC patients treated with Cabometyx® in combination with nivolumab:[1]

ALT or AST >3 times the upper limit of normal (ULN) but ≤10 times ULN without concurrent total bilirubin ≥2 times ULN

- Interrupt Cabometyx® with nivolumab until these adverse reactions resolves to Grade ≤1
- Corticosteroid therapy may be considered if immune-mediated reaction is suspected (refer to nivolumab SmPC)
- Re-initiate with a single medicine or sequential re-initiating with both medicines after recovery may be considered. If re-initiating with nivolumab, refer to nivolumab SmPC

ALT or AST >10 times ULN or >3 times ULN with concurrent total bilirubin ≥2 times ULN

- Permanently discontinue Cabometyx® and nivolumab
- Corticosteroid therapy may be considered if immune-mediated reaction is suspected (refer to nivolumab SmPC)

FURTHER SUPPORT

Please refer to the Cabometyx® SmPC for a full list of ARs and more information on managing ARs.[1] Consult your local guidelines for additional information on each AR.

References

1. CABOMETYX® (cabozantinib) Summary of Product Characteristics. Ipsen Ltd. 2023. Available at: https://www.medicines.ie/medicines/cabometyx-tablets-31523/spc (Accessed February 2025).
2. National Cancer Institute. Common Terminology Criteria for Adverse Events v5.0. NCI, NIH, DHHS. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf (Accessed: February 2025).
3. Schmidinger M. *EJC Suppl.* 2013;11(2):172–191.
4. Lipworth AD, *et al. Oncology.* 2009;77:257–271.
5. Schmidinger M and Danesi R. *Oncologist.* 2018;23(3):306–315.
6. Gerendash BS and Creel P. *Onco Targets Ther.* 2017;10:5053–5064.
7. Cohen RB and Oudard S. *Invest New Drugs.* 2012;30(5):2066–2079.
8. Lightowlers SV, *et al. Ann Oncol.* 2019;30(1):150–151.
9. NHS. High blood pressure. Available at: https://www.nhs.uk/conditions/high-blood-pressure (Accessed: February 2025).
10. NHS Inform. Cancer-related fatigue. Available at: https://www.nhsinform.scot/illnesses-and-conditions/cancer/side-effects/cancer-related-fatigue (Accessed: February 2025).

CABOMETYX® (cabozantinib) tablets

IPSEN

CMX-IE-000556
February 2025