



AFINITOR (everolimus)

A PRACTICAL GUIDE TO PATIENT MANAGEMENT

Prescribing information can be found on page 42.
This guide has been produced and funded by Novartis.



ABOUT THIS GUIDE

The guide has been written to provide practical information and advice on using AFINITOR (everolimus) and managing any associated adverse events. This is guidance only; the advice and recommendations contained within this guide should not supersede your own medical judgement or experience with a patient.

In the first section, the indication, dosage, adverse events, dose adjustments, and contraindications are described. This is followed by more in-depth information describing each adverse event and suggested management approaches.

An appendix containing a list of detailed drug interactions is also provided.



ABOUT AFINITOR

Indication

AFINITOR is indicated for the treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor.

AFINITOR is also indicated for the treatment of patients with:

- Advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.¹
- Unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease.¹
- Unresectable or metastatic, well-differentiated (Grade 1 or 2) non-functional neuroendocrine tumours of gastrointestinal or lung origin in adults with progressive disease.¹

AFINITOR is a therapy that has been demonstrated to significantly increase progression-free survival in breast cancer patients who have received first-line hormone therapy with a non-steroidal aromatase inhibitor.² It can delay reductions in the quality of life for cancer patients and increase progression-free survival.^{3,4}

As a means of selecting patients for AFINITOR therapy, it is suggested that the selection criteria used in the phase III BOLERO-2 trial are used:²

- Post-menopausal, ER +ve, HER2 –ve metastatic breast cancer

- Previous treatment with a non-steroidal aromatase inhibitor
- No symptomatic visceral disease
- No more than one line of chemotherapy for the treatment of advanced breast cancer
- Not end stage patients

Dosage

The recommended dose of AFINITOR is 10 mg once daily (taken as a single oval tablet). It should be administered orally at the same time every day, either with or without food (avoid grapefruit and grapefruit juice).

If a dose is missed, the patient should not take an additional dose, but take the usual prescribed next dose.

Tablets should be swallowed whole with a glass of water and should not be chewed or crushed.

No dose adjustment is required for elderly patients or patients with renal impairment at drug initiation. Dose reduction is required if renal impairment develops whilst on AFINITOR.

AFINITOR is also available in 5 mg and 2.5 mg tablets for dose modification in response to tolerability issues. If dose reduction is required, the recommended dose is 5 mg daily and must not be lower than 5 mg daily.¹



Adverse Events

The majority of adverse events (AEs) associated with AFINITOR treatment can be successfully managed.⁵ The most common adverse events are:⁶⁻⁸

- Stomatitis
- Skin Rash
- Fatigue
- Diarrhoea

Affect 1 in 3 patients

- Haematological Abnormalities
- Lipid Abnormalities
- Glycaemic Abnormalities
- Infections
- Non-infectious Pneumonitis
- Non-haematological Abnormalities

Generally, most grade 1 or 2 AEs occur soon after treatment initiation, and are manageable with treatment and/or dose changes.^{1,5} By contrast, grade 3 or 4 AEs have a relatively slow rate of onset, but resolve rapidly upon dose suspension.⁵

The most common grade 3 or 4 AEs seen are stomatitis, anaemia, and hyperglycaemia.⁵

Dose adjustments

Although many low grade AEs associated with AFINITOR can be treated, patients can also benefit from dose interruptions and reductions.⁵ Clinicians should be prepared to interrupt dosing for a short period of time in order to successfully manage an AE.

Further analysis of the phase III BOLERO 2 trial reported that 62% of patients treated with AFINITOR had dose interruptions/reductions, as opposed to 12% of patients receiving placebo.⁵ Following interruption, approximately half of the patients resumed treatment at the full dose, and 76% of these patients experienced resolution of the adverse event within 2 weeks.⁵

34% of patients receiving AFINITOR required a dosage reduction.⁵ If dose reduction is required, the recommended dose is 5 mg daily.¹

The most common AEs leading to dose interruption, reduction, or suspension are: stomatitis, non-infectious pneumonitis, dyspnoea, and fatigue.⁵ Generally speaking, dose adjustment is not usually required if the AE is grade 1, but please refer to the guidance within the specific sections for further information.^{1,5,9}



CONTRAINDICATIONS AND PRECAUTIONS FOR USE

Hepatic impairment

Hepatic impairment increases patient exposure to AFINITOR.¹ Patients with hepatic impairment should be carefully assessed prior to commencing AFINITOR therapy. The initial dose of AFINITOR should be adjusted as follows:^{1,10}

- Mild hepatic impairment (Child-Pugh A) – recommended dose is 7.5 mg daily. If not tolerated, reduce down to 5 mg daily
- Moderate hepatic impairment (Child-Pugh B) – recommended dose is 5 mg daily. If not tolerated, reduce down to 2.5 mg daily
- Severe hepatic impairment (Child-Pugh C) – ONLY recommended if the desired benefit outweighs the risk. In this case, a dose of 2.5 mg **must not** be exceeded

Dose adjustments should be made if a patient's hepatic (Child-Pugh) status changes during treatment.

ACE inhibitors

Patients taking concomitant ACE inhibitor (e.g. ramipril) therapy may be at increased risk for angioedema.¹

Lactose intolerance

Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.¹

Diabetes

Increases in serum glucose are common during AFINITOR treatment, and this may alter insulin and/or hypoglycemic therapy requirements in patients with diabetes. Patients with diabetes are not contraindicated from taking AFINITOR, but it is suggested that optimal glycaemic control is achieved before starting the drug.¹⁰

The risk for new-onset diabetes is increased with AFINITOR use, therefore at-risk patients should achieve optimal glucose levels prior to treatment.¹⁰

Hyperlipidemia

Use AFINITOR with caution in patients with hyperlipidemia, as this may increase serum lipids (cholesterol and triglycerides).¹⁰



Sensitivity to rapamycin derivatives

AFINITOR is contraindicated by hypersensitivity to the active substance or any excipients, or to other rapamycin derivatives such as sirolimus.¹⁰

Wound healing and surgery

Impaired wound healing is a class effect of rapamycin derivatives, including everolimus. Caution should therefore be exercised with the use of Afinitor in the peri-surgical period.¹

Pregnancy and breast feeding

AFINITOR is not licensed for use during pregnancy. Suspend treatment immediately if a patient becomes pregnant.¹ AFINITOR may also be excreted in breast milk, therefore women taking the product should be advised not to breast feed during treatment and for 2 weeks after the last dose.¹

Medical

Certain treatments, notably CYP3A4/PgP inhibitors, should not be combined with AFINITOR. Patients receiving the following treatments are therefore contraindicated.^{1,10}

Treatment	Reason for Contraindication ¹⁰
BCG	Immunosuppression of patient
CYP3A4 Inducers (Strong)	May decrease serum concentration of AFINITOR
CYP3A4 Inhibitors (Strong)	May increase serum concentration of AFINITOR
Grapefruit Juice	May increase serum concentration of AFINITOR
Natalizumab	May increase risk of concurrent infection
Pimecrolimus	Immunosuppression of patient
St. John's Wort	May decrease serum concentration of AFINITOR
Tacrolimus (Topical)	May modulate immunosuppression
Vaccines (Live)	Immunosuppression of patient

Please note that this is not an exhaustive list and that the AFINITOR SPC¹ should be consulted if there are any concerns or doubts about the suitability of co-treatment and other contraindications.

A more detailed list of drug interactions is provided in the appendix.

MONITORING

Monitoring is a key component of AFINITOR therapy. Early recognition of signs and symptoms aids the management of AEs, as well as patient adherence to therapy. There are a number of haematological and metabolic abnormalities that may occur with the use of AFINITOR, and patients should have a comprehensive baseline assessment, as well as regular routine check-ups scheduled throughout treatment.

For detailed guidance on dose modification for non-haematological effects, please refer to the Summary of Product Characteristics.¹

Recommendations for haematological and metabolic monitoring are summarised in the following table.

Please note that the following recommendations are ideal in theory. In practice, it may not be possible to deliver the full range of testing within the recommended time frames. In these instances, thorough testing before treatment is recommended as a priority, as this will help with the management and continuation of therapy. However, monitoring during treatment can be conducted at the discretion of the healthcare professional(s) involved.

Recommended Monitoring Tests and Frequencies^{1,10}

Investigation	Baseline
Full Blood Count (FBC)	✓
Fasting Blood Glucose	✓
Lipid Profile (Blood cholesterol and triglycerides)	✓
Urea and Electrolytes (U&Es)	✓
Liver Function Tests (LFTs)	✓
Hepatitis B Screen	✓
Infections (Particularly fungal)	✓
Oral assessment for infection or gum disease	✓
CT Scan, chest X-ray, and lung function tests	✓
Monitoring of renal function including blood urea nitrogen, urinary protein / serum creatinine levels	✓
Question patients about the appearance of skin rash	✓

Thorough baseline testing is recommended, as this can identify patients that are at risk for particular adverse events (e.g. hyperglycaemia).

Although regular monitoring is a key component of adverse event management, please refer to your local guidelines for specific advice on the frequency of subsequent testing.

STOMATITIS

Stomatitis (including mouth and tongue ulcers and oral mucositis) is inflammation of the mucous membranes in the oral cavity or tongue and is associated with redness, swelling, burning sensation, dysphagia and occasionally bleeding.¹¹ Aphthous-like ulcers are characterised by discrete, ovoid, superficial well-demarcated ulcerations with a greyish-white pseudomembrane. Although the aetiology of AFINITOR-associated stomatitis is not clearly understood, it is thought to be a T cell-mediated inflammatory condition.¹²

Stomatitis is very common in patients treated with AFINITOR: Approximately 2/3 patients will develop this AE.¹³ Stomatitis is usually seen within the first 8

weeks of treatment and fortnightly monitoring of patients during the first four weeks is highly recommended.^{1,5,13,14}

Most episodes of stomatitis can be successfully managed with palliative interventions and temporary dose modifications. In BOLERO-2, only 3% of patients receiving AFINITOR discontinued treatment due to stomatitis.¹⁵

Proactive management of stomatitis is key, as the associated pain and infection may limit oral intake and affect quality of life, reducing patient adherence to AFINITOR.¹⁴

TIME COURSE



Data from clinical trials suggest that approximately one-third of all stomatitis grade ≥ 2 events occur within the first two weeks of treatment, and the incidence of new events plateaus by week 6.⁵

Grade 1 and 2 stomatitis usually resolve within 72 hours of suspending AFINITOR treatment, whereas the majority of Grade 3 and 4 events require 3.1 weeks on average to resolve to grade ≤ 1 and 7.4 weeks to resolve completely.⁵

This illustrates the importance of early intervention. Although the incidence of new events is significantly reduced by week 6, healthcare professionals should be aware of the chance of recurrence of this AE and continue to monitor patients. The average

time to recurrence for each grade of stomatitis is:¹⁵

- Grade 1: 54 days
- Grade 2: 31 days
- Grade 3: 20 days

The time course of stomatitis management is summarised below.

1. BEFORE COMMENCING TREATMENT

Full oral assessment for infection or gum disease (see “Monitoring”). Delay treatment until infection or disease resolves

3. AT THE END OF WEEK 2

Given the high incidence of stomatitis during the first two weeks of treatment, it is highly recommended that the first follow up occurs near this time.

WEEK 1

WEEK 2

WEEK 7

2. WEEKS ONE TO SIX

The majority of incidents will occur during this time. Consider a higher frequency of monitoring and educate patients about signs and symptoms

4. WEEK SEVEN ONWARDS

Continue regular monitoring for signs of recurrence and encourage patient reporting of any signs and symptoms

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(everolimus) Tablets

GRADING

In addition to maintaining regular monitoring, you should ensure that the diagnosis of any incident is as accurate as possible, so that the correct treatment plan is implemented. Below are guideline images to assist with diagnosis:

Grade 1: Erythema of the mucosa with minimal symptoms



Grade 2: Patchy ulcerations or pseudomembranes with difficulties eating and swallowing



Grades 3 and 4: Confluent ulcerations or pseudomembranes and minor bleeding (grade 3), progressing to tissue necrosis and significant spontaneous bleeding (grade 4).



Photographs reproduced with permission.

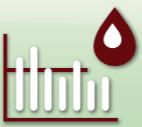
Stomatitis grades 1, 3, 4 reprinted from de Oliveira M *et al.*, *Oral Oncol* 2011;47(10):998–1003

Grade 2 reprinted from Ferte C *et al.*, *Eur J Cancer* 2011;47(15):2249–2255

MANAGEMENT

Prior to commencing AFINITOR therapy, perform a baseline oral assessment to ensure that no gum irritation or mouth sores are present. Inform patients of the possibility of experiencing stomatitis and educate them about good oral hygiene and other precautionary measures to take, including the need for regular dental examinations.

During treatment, early diagnosis and preventative measures are key to management. It is especially important for physicians and patients to recognise the signs and symptoms and intervene early, and patients should be routinely educated on these throughout treatment.



Beyond patient communication and regular check-ups, a proactive mouthcare regime should be introduced to prevent the development of stomatitis, particularly within the first 6–8 weeks of treatment when the patient is at the highest risk.^{1,5}

Two regimens that have been successfully employed are as follows:

- Raspberry mucilage with dispersible aspirin as a mouth wash; sucralfate suspension to rinse and swallow; oral Gelclair for symptomatic ulcers (Royal Marsden)¹⁶
- Alcohol-free corticosteroid oral solution (dexamethasone 0.5 mg/5 ml alcohol-free oral solution), administered as a mouthwash¹

PRACTICAL ADVICE^{1,2,9,11,17}



- Avoid mouthwashes containing alcohol, hydrogen peroxide, iodine and thyme derivatives¹
- Consider evaluation for herpes virus or fungal infections – initiate antiviral agent or antifungal agent only if infection diagnosed. Note that, due to potential interactions between systemic imidazole antifungal agents and AFINITOR, mouthwashes and a topical antifungal agent are preferred²
- Selected topical treatments, such as dexamethasone are recommended to ease discomfort and pain

ADVICE TO PATIENTS^{9,11,14,18}

Stomatitis has a direct and significant impact on patient health and lifestyle. Patients should be sufficiently educated to recognise and report signs and symptoms, and be prepared to make adjustments to their normal routines. In general, you should:

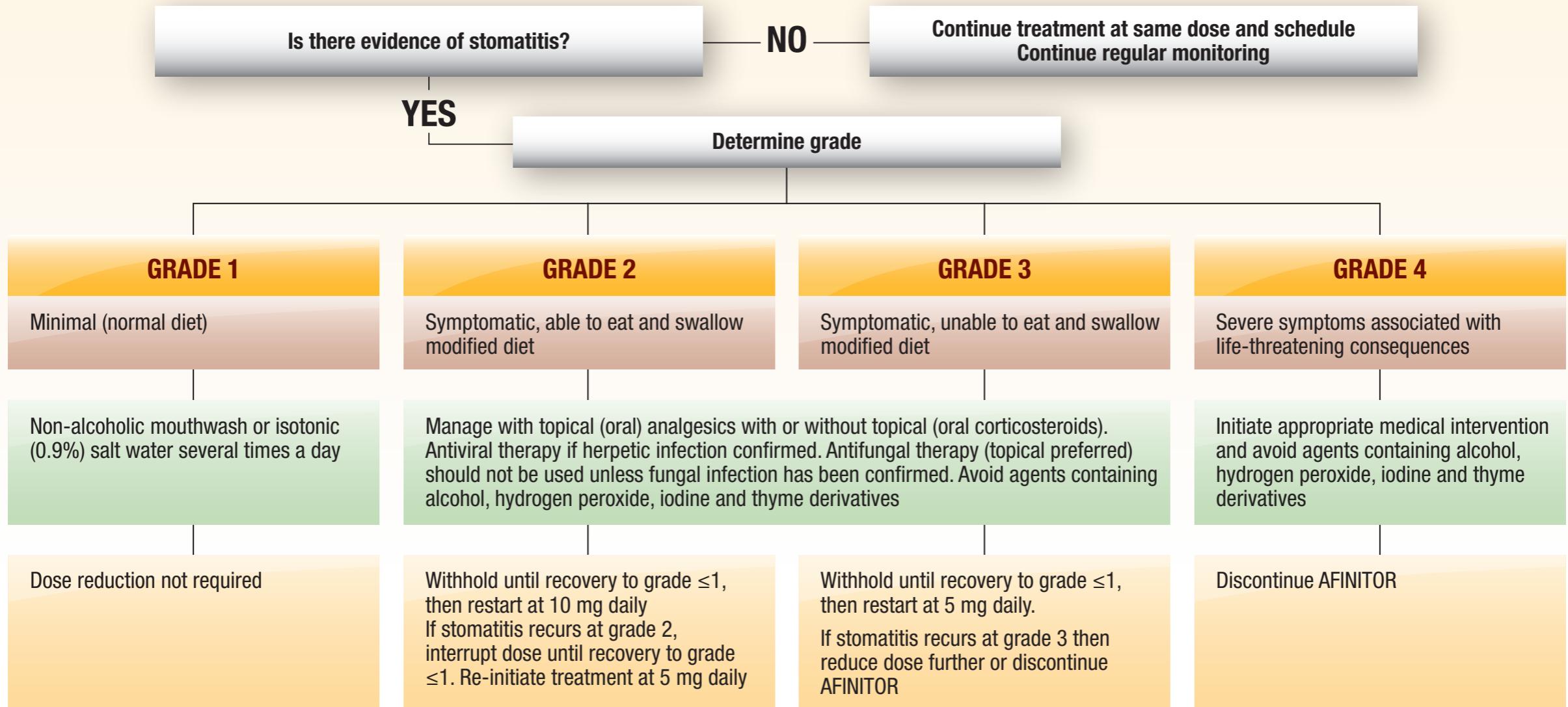
- Advise patients about the early incidence of stomatitis, and the likelihood that it may recur during treatment
- Stress the importance of early recognition and management
- Encourage good oral hygiene and the immediate reporting of signs and symptoms.

In addition, encourage patients to do the following:

Things to do	Things to avoid
Brush consistently, regularly, and thoroughly with a soft toothbrush that is changed on a regular basis	Avoid strong flavoured toothpastes
Rinse frequently with bland rinses such as sterile water, normal saline, or sodium bicarbonate, and use prophylactic and/or topical treatments as mouthwash, such as an alcohol-free corticosteroid oral solution	Avoid mouthwashes containing alcohol, hydrogen peroxide, iodine and thyme derivatives
Keep the mouth and lips moist	Avoid drying of the lips
Use milder, sodium lauryl sulfate-free toothpaste (e.g. children's toothpaste)	Avoid toothpastes containing sodium lauryl sulfate
Eat and drink carefully. Eat 5-6 smaller meals a day and use straws to keep liquid away from sore areas	Avoid acidic, sour, salty, spicy, hard or crunchy foods
Consume foods that are tepid rather than hot in temperature	Avoid foods that are either hot or cold in temperature



MANAGING STOMATITIS^{1,8-11}



SKIN RASH

Skin rash adverse events typically occur as maculopapular or papulopustular lesions, often with pruritus, erythematous papules or pustules. Patients may also experience dry skin, contact dermatitis, cellulitis, acne and eczema.¹

Rash primarily occurs on the trunk, scalp, face and neck, but extremities are also commonly involved. This adverse event usually develops during the first cycle of treatment, but can appear at any time.

MANAGEMENT

Typically, patients experience symptoms no greater than grade 1 or 2. However, the appearance of rash, as well as the pain and discomfort it causes, can significantly disrupt a patient's quality of life and reduce adherence to AFINITOR. Skin rash can also develop if left unchecked, so patients should be educated about this AE prior to commencing therapy.



Consider consultation with a dermatologist for the treatment of patients. Topical corticosteroids, such as alclometasone or mometasone, are recommended at grade 1, whereas oral antibiotics and corticosteroids, such as dexamethasone and prednisone can be recommended at higher grades.¹⁸

PRACTICAL CONSIDERATIONS¹

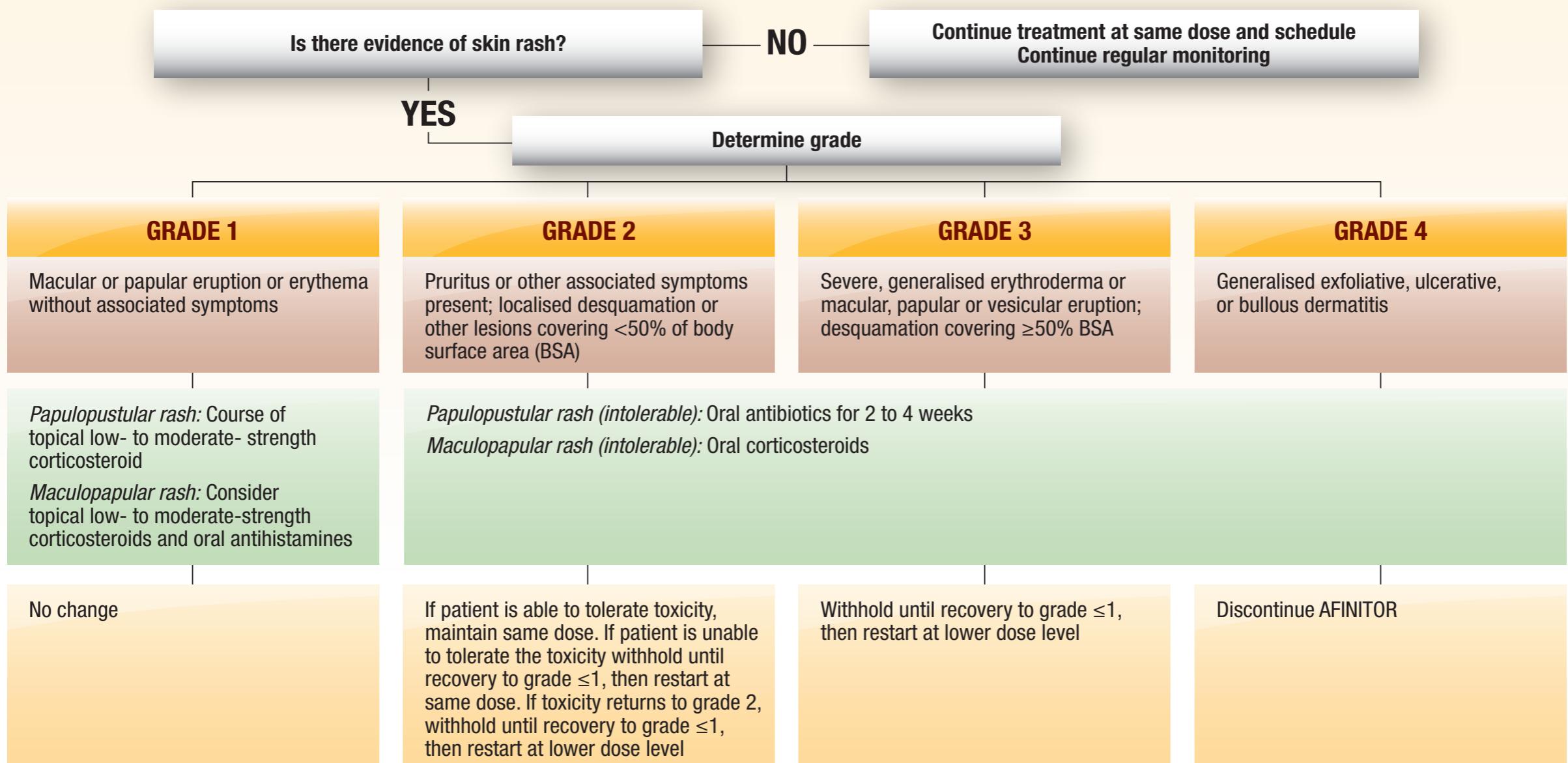


- Some patients with acne may benefit from topical, as well as oral antibiotic therapy before starting AFINITOR
- Avoid retinoids as they may disrupt skin integrity and introduce risk of infection
- Question patients about skin rash at every check-up

ADVICE TO PATIENTS

- Avoid products containing alcohol, benzoyl peroxide or retinoids
- Moisturise frequently using a thick, hypoallergenic, alcohol-free emollient cream
- Take short, lukewarm showers using mild moisturising fragrance-free soap
- Use a sunscreen with a SPF of at least 15, preferably one containing zinc oxide or titanium oxide, and reapply every 2 hours

MANAGING SKIN RASH^{1,8,19}



FATIGUE

Fatigue is a common adverse event, and can severely impact the lives of patients.^{5,16} Patients suffering from fatigue may exhibit other symptoms including insomnia, anorexia and depression.²⁰

MANAGEMENT



It is important that fatigue is identified and managed appropriately. Importantly, fatigue may be a symptom of another adverse event, such as anaemia or infection, and these possibilities should be investigated first.²⁰

If other causes can be ruled out, take steps to educate the patient on how best to manage fatigue. If fatigue persists or worsens, consider dose reduction of AFINITOR.

Patients should also be advised to be cautious when driving or using machines if they experience fatigue during treatment with AFINITOR.¹

TIME COURSE



Approximately half of fatigue events (grade ≥ 2) reported in patients receiving AFINITOR occur within the first four weeks of therapy.⁵

Among patients with grade 3 or 4 fatigue, 72% of patients receiving AFINITOR experience resolution (usually following dose interruption / reduction) to grade ≤ 1 after a median of 8.0 weeks.

Complete resolution is reported in 56% of AFINITOR patients after a median of 18.7 weeks.⁵

PRACTICAL CONSIDERATIONS

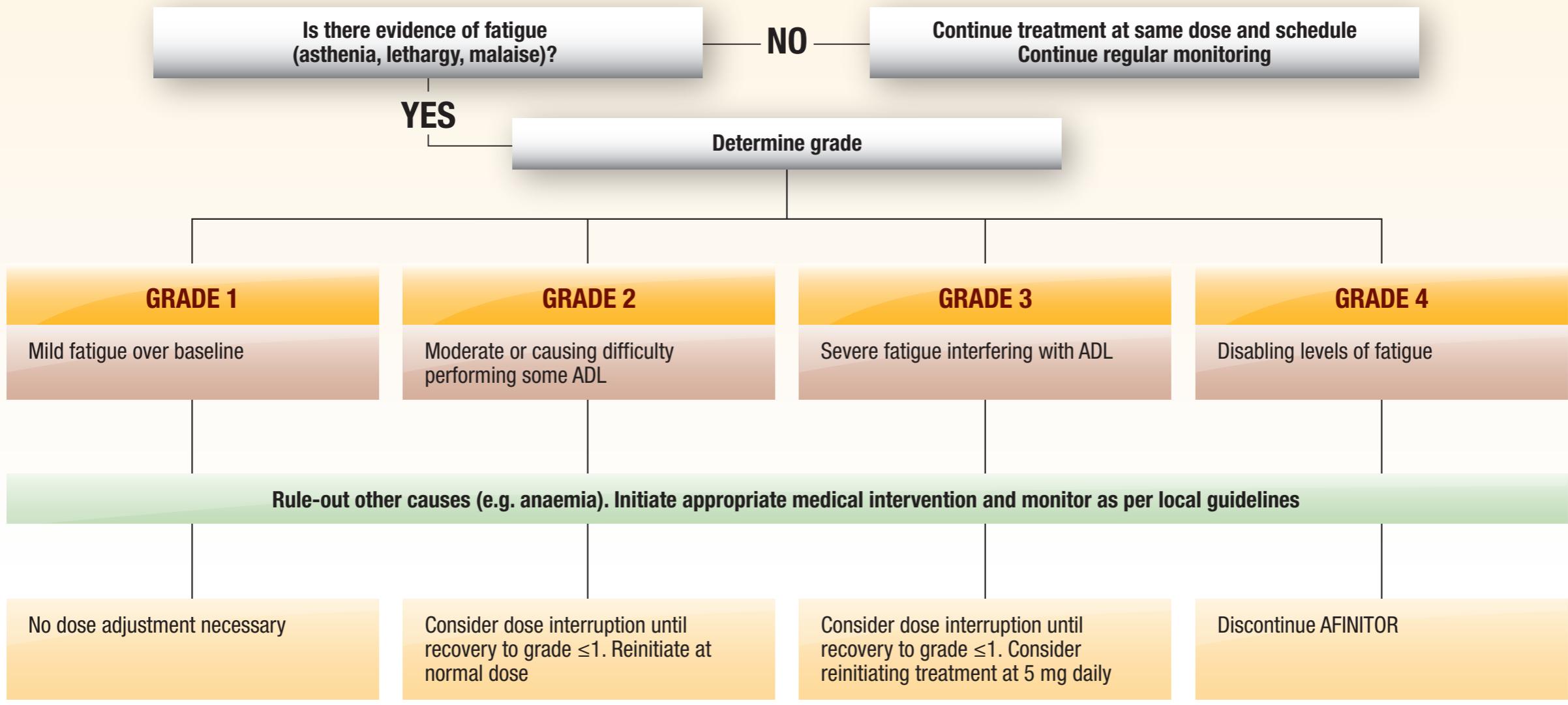


- Due to its early onset, patients should be made aware of the possibility of fatigue prior to commencing AFINITOR therapy
- Fatigue can be managed through appropriate strategies, and patients should be made aware of this
- Consider the possibility of other causes of fatigue and, where appropriate, treat these first

ADVICE TO PATIENTS

- Take rests between activities
- Use energy saving tools where possible
- Prioritise activities and create reasonable schedules for each day
- Get plenty of sleep
- Encourage exercise

MANAGING FATIGUE⁸



ADL = activities of daily living

HAEMATOLOGICAL ABNORMALITIES

AFINITOR can exert a bone marrow suppressive effect and can decrease the effectiveness of the patient's immune response.¹⁰ Decreased haemoglobin level, and lymphocyte, neutrophil and platelet counts are commonly associated with AFINITOR treatment, and patients should be monitored for these changes.¹

The problems that are associated with these changes are twofold: they may lead to specific adverse events, such as anaemia, or may cause complications

including infections. In particular, patients with decreased neutrophil counts may develop febrile neutropenia and bacteraemia, and low haemoglobin levels can contribute to fatigue. Guidance on the two most common haematological abnormalities, thrombocytopenia and neutropenia, is provided.

In all cases, routine monitoring and the identification of at-risk patients can facilitate detection and treatment. Be prepared to educate patients on possible symptoms to watch for.

MANAGEMENT

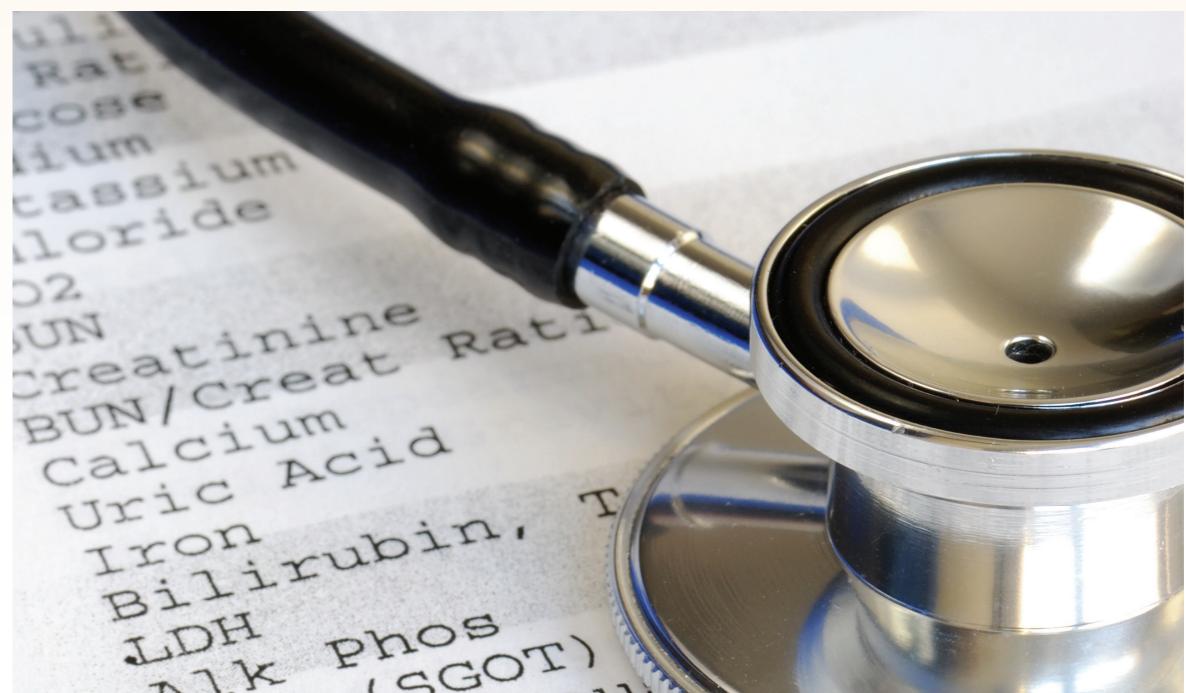


Monitor haematological parameters prior to commencing treatment and periodically thereafter as per local guidelines.

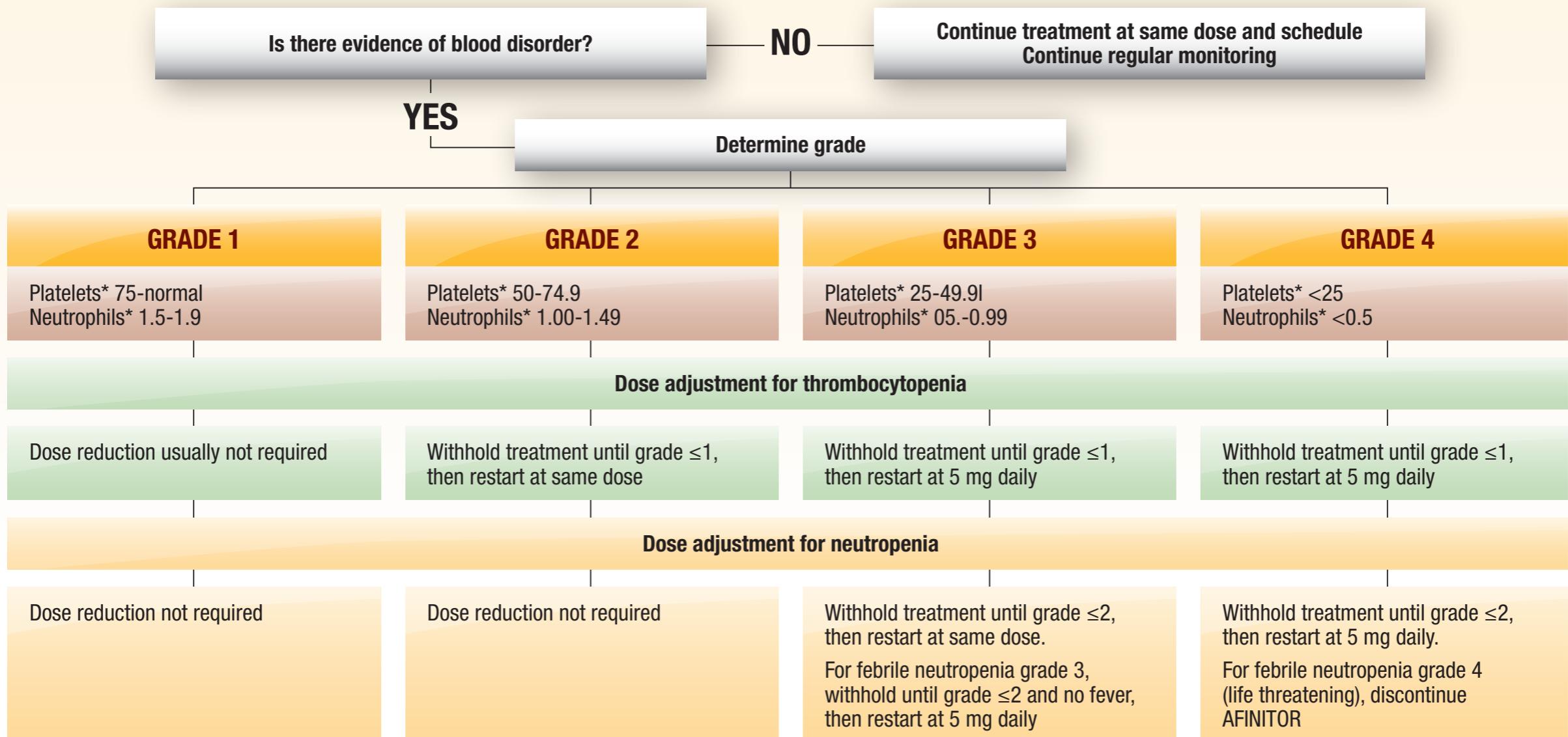
For events of neutropenia, interrupt dosing at grade 3; for thrombocytopenia, interrupt dosing at grade 2.

ADVICE TO PATIENTS

- Understand the importance of good hygiene and diet
- Be aware of signs of infection (e.g. monitor temperature if feeling unwell)
- Look out for signs of bruising or bleeding (e.g. epistaxis)
- Be aware of fatigue, shortness of breath and pale skin (e.g. anaemia)



MANAGING HAEMATOLOGICAL ABNORMALITIES^{1,8}



*x10⁹/L

LIPID ABNORMALITIES

Dyslipidaemia (including hypercholesterolaemia and hypertriglyceridaemia) are common side effects associated with AFINITOR.¹ Use AFINITOR with caution in patients with hyperlipidemia, as treatment may increase serum lipids (cholesterol and triglycerides).¹⁰

MANAGEMENT



Monitoring of blood cholesterol and triglycerides prior to the start of AFINITOR therapy and periodically thereafter, as well as management with appropriate medical therapy is recommended.¹

If lipid levels remain elevated and the AE continues to grade 3, suspend AFINITOR therapy until optimal lipid control is achieved. Following establishment of lipid control, resume therapy at a reduced dose.

PRACTICAL CONSIDERATIONS⁹

- Optimal lipid control should be achieved prior to starting therapy
- Consider other possible causes of hyperlipidaemia (e.g. hypothyroidism, thiazide diuretics)
- The use of statins does not affect the clearance of AFINITOR
- Omega fatty acids and niacin may be used as supplements to lower triglycerides
- Patients with very high triglycerides (>5.6 mmol/L) are at risk of pancreatitis and should be treated with fibrates

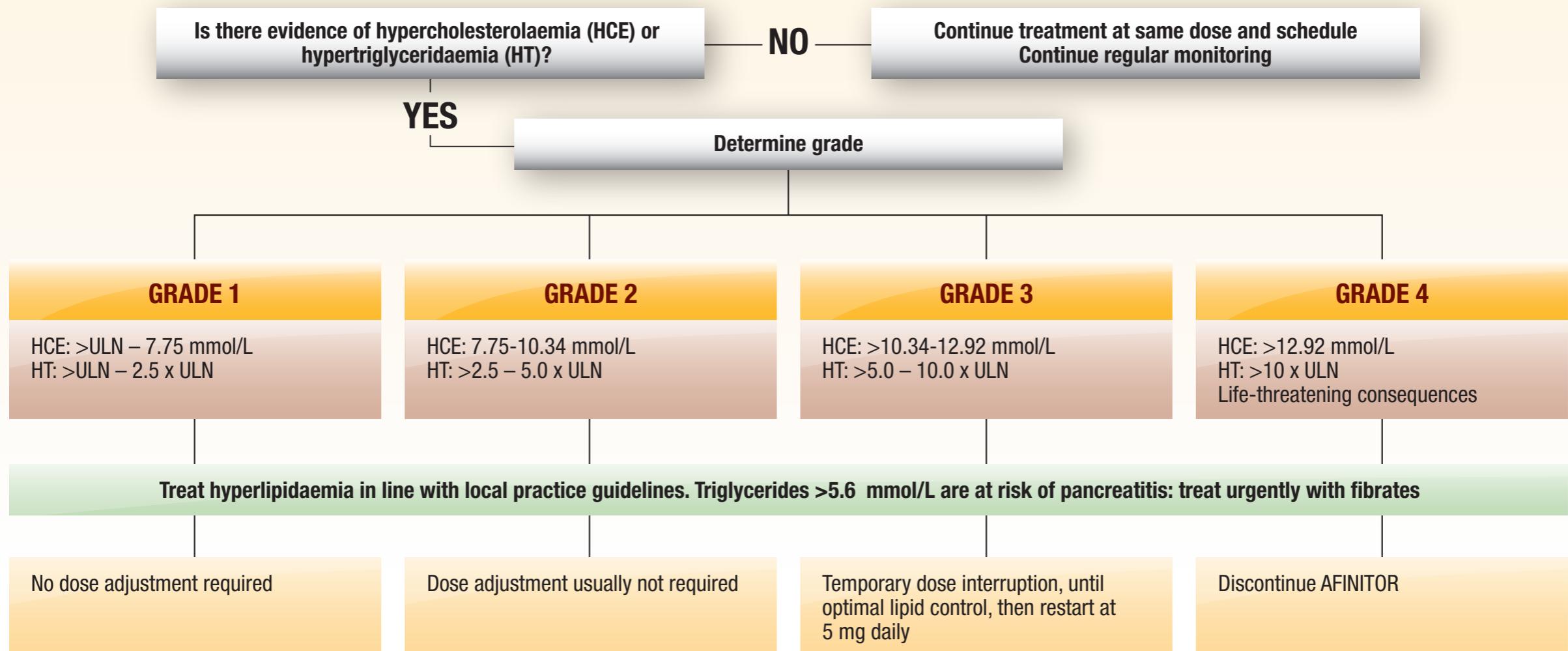


ADVICE TO PATIENTS

Where appropriate, encourage patients to undertake:

- Dietary modifications
- Weight loss
- Increased physical activity

MANAGING LIPID ABNORMALITIES^{1,8,9}



ULN = upper limit of normal

GLYCAEMIC ABNORMALITIES

Hyperglycaemia is a very common side effect associated with AFINITOR.¹ Symptoms include frequent urination, increased thirst, fatigue, blurred vision, weight loss, headaches and difficulty concentrating. Hyperglycaemia is generally well tolerated, with a low incidence of discontinuation, but a proactive approach is key to managing this AE.

MANAGEMENT



Monitoring of fasting serum glucose is recommended prior to the start of therapy and periodically thereafter. More frequent monitoring is recommended when AFINITOR is co-administered with other medicinal products that may induce hyperglycaemia.¹

Patients with diabetes are at particular risk, as treatment may alter insulin and/or hypoglycemic therapy requirements. It is important that diabetic patients achieve optimal glucose levels prior to starting treatment, and are regularly monitored throughout.¹⁰

TIME COURSE



Approximately half of all hyperglycaemia / new-onset diabetes mellitus grade ≥ 2 events occur within the first 6 weeks of treatment.⁵ Consider monitoring patients at risk on a weekly basis during this period.

A recent study reported that 46% of patients with grade 3 or 4 hyperglycaemic events experienced resolution to grade ≤ 1 after a median of 29.1 weeks.⁵

PRACTICAL CONSIDERATIONS⁹

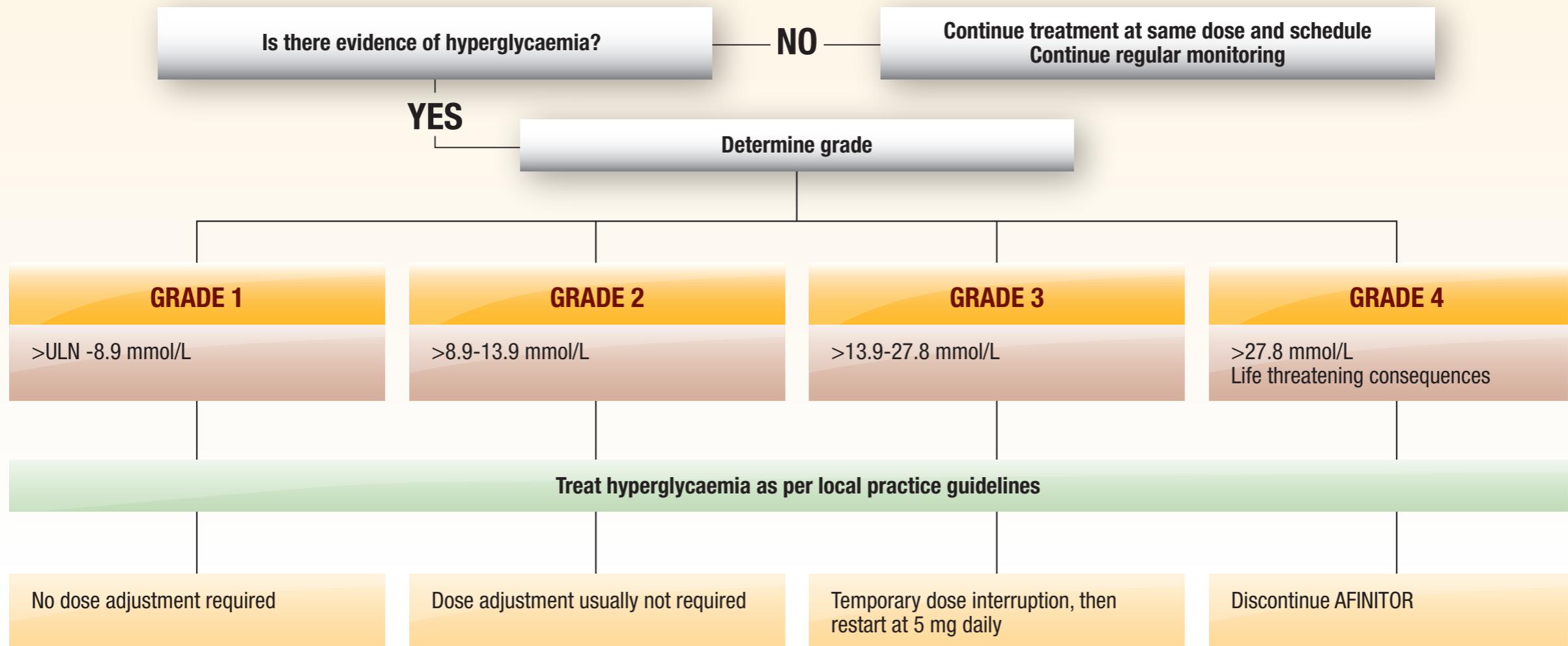


- Hyperglycaemia occurs primarily in those patients with abnormal pre-treatment fasting glucose
- When possible, optimal glycaemic control should be achieved before starting a patient on AFINITOR¹
- Monitor blood glucose periodically or as per local guidelines
- Take extra care with diabetic patients

ADVICE TO PATIENTS

- Outline signs and symptoms of raised glucose levels:
 - increased thirst
 - frequency of urination
 - headaches
 - tiredness
 - blurred vision
- Encourage early reporting
- Recommend healthy lifestyle changes:
 - drink plenty of water
 - exercise regularly
 - reduce dietary amounts of carbohydrate and sugar

MANAGING GLYCAEMIC ABNORMALITIES^{1,8-10}



ULN = upper limit of normal

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INFECTIONS

AFINITOR has immunosuppressant properties and may predispose patients to infections, including opportunistic pathogens.¹⁰ The mechanism behind this is thought to be related to the drug's ability to inhibit T- and B-cell proliferation by blocking G1 and S phase transition in the cell cycle, as well as inhibiting antibody production.^{21,22}

Infections are very common in patients taking AFINITOR, and these may include pneumonia, other bacterial infections, invasive fungal infections such as aspergillosis or candidiasis, and viral infections including reactivation of hepatitis

B virus.¹ As discussed previously, the bone marrow suppressive effects of AFINITOR treatment can lead to haematological abnormalities that impact on immune function. Healthcare professionals should monitor for blood lymphocyte and neutrophil counts and take appropriate caution when these are reduced.

In addition, impaired wound healing is a class effect of rapamycin derivatives, and AFINITOR may delay wound healing and increase the occurrence of wound-related complications (e.g. wound dehiscence, infection, incisional hernia, lymphocele, seroma).¹⁰

MANAGEMENT: PREPARATION



Physicians should take a full medical history of prior infection and undertake relevant laboratory tests before AFINITOR initiation to identify at-risk patients. Patients with low neutrophil or lymphocyte counts, as detected by haematological monitoring, may also be at an increased risk of developing infections.

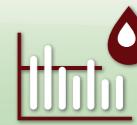
MANAGEMENT: GENERAL



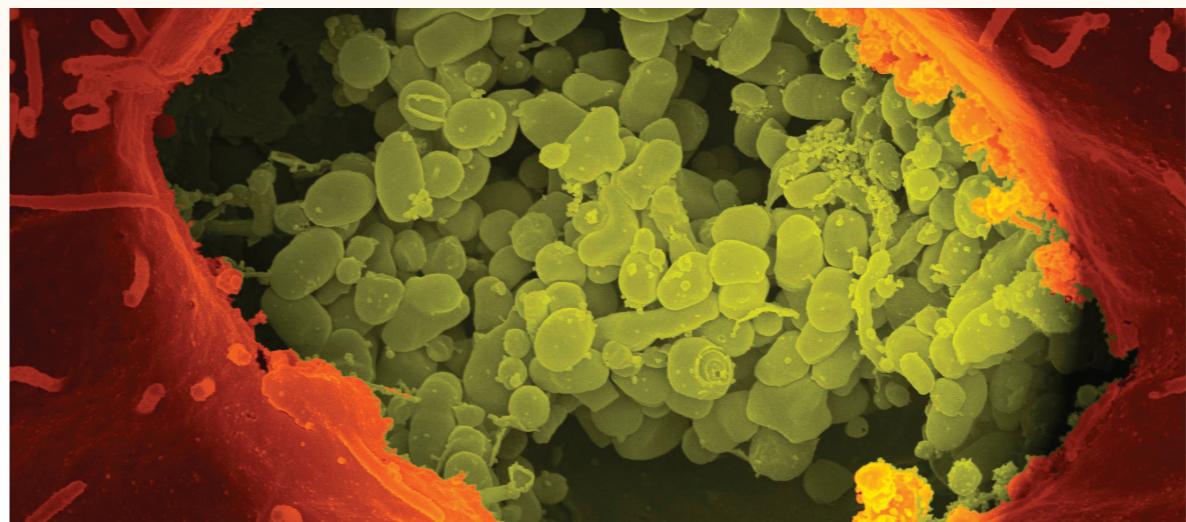
Exercise caution with other treatments that have an immunosuppressive effect, such as clozapine, leflunomide, and denosumab, as this may enhance the chance of infection.¹⁰

The use of AFINITOR is not recommended in the peri-surgical period.¹

MANAGEMENT: VACCINES



The immune response to vaccination may be affected and therefore, vaccination may be less effective during treatment with AFINITOR. The use of live vaccines (e.g. intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines) should be avoided.^{1,10}



"Coxiella burnetii, the Bacteria That Cause Q Fever" by NIAID is licensed under CC BY 2.0

PRACTICAL CONSIDERATIONS⁹

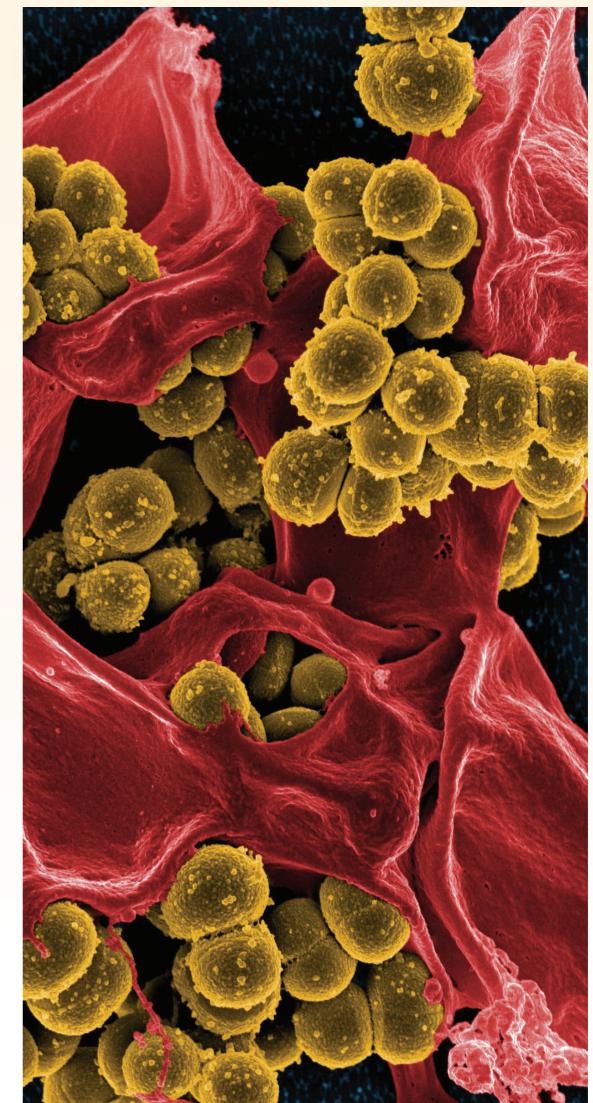
- Take a full medical history of prior infection and laboratory tests before AFINITOR initiation to identify at-risk patients
- Use with caution in patients with a history of prior infections (hepatitis, fungal, other opportunistic infections), or those identified at increased risk of developing infections
- Pre-existing infections should be treated and fully resolved prior to starting AFINITOR¹
- If a diagnosis of invasive systemic fungal infection is made during treatment,



- AFINITOR should be discontinued promptly and permanently and the infection treated with appropriate antifungal therapy¹
- Patients with hepatitis B infection should be monitored for hepatitis B virus (HBV) DNA. Consider preventive therapy for hepatitis B infection to avoid reactivation
 - Question patients about signs of infection at every routine follow up

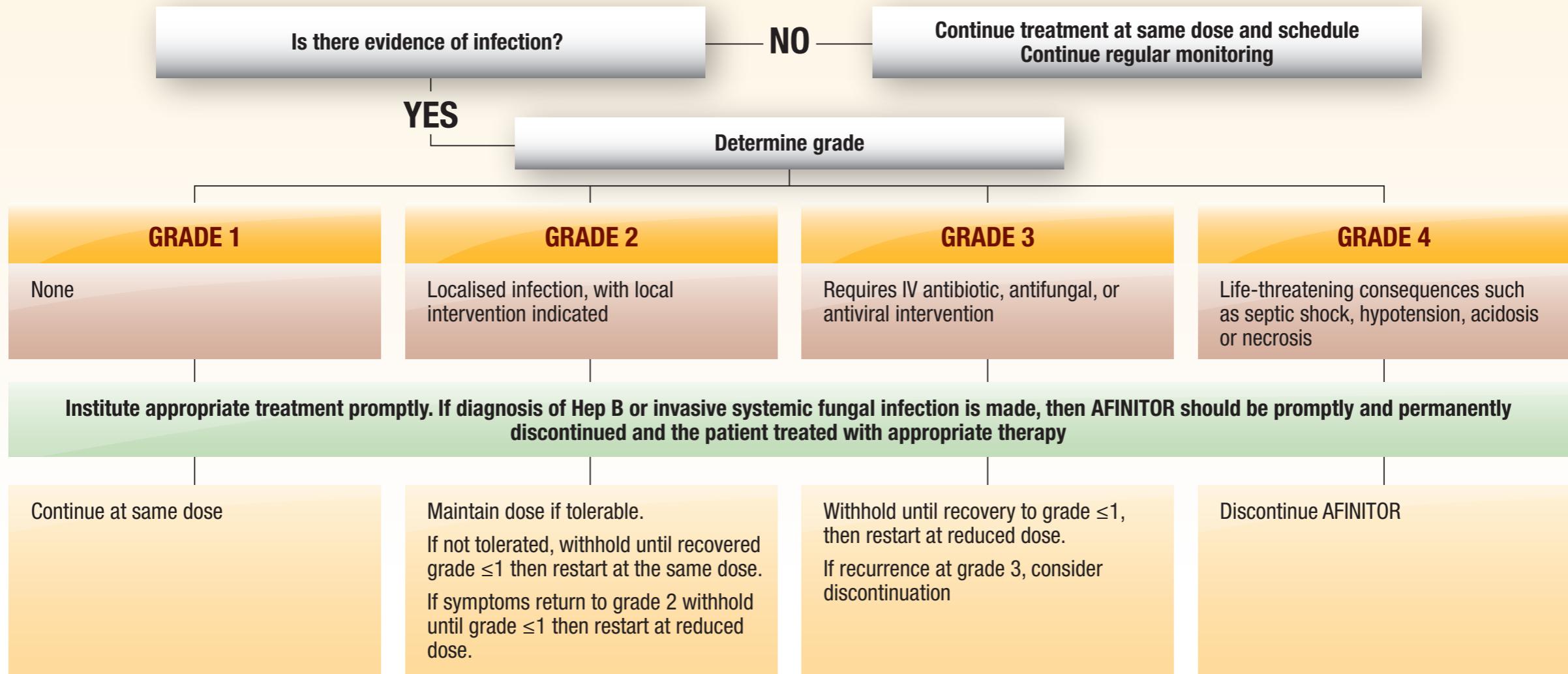
ADVICE TO PATIENTS

- Patients need to be aware that they may be at increased risk of contracting infections and should let their doctor / nurse know immediately if they are feeling unwell (e.g. fever or cold)
- Patients should also be advised to:
 - practice good hygiene with minor cuts
 - utilise thorough and frequent handwashing
 - follow good food hygiene and avoid the consumption of raw foods such as sushi
 - avoid cleaning up after pets or changing cat litter
 - avoid visits to developing countries



"Micrograph of Methicillin-Resistant Staphylococcus aureus (MRSA)" by NIAID is licensed under CC BY 2.0

MANAGING INFECTIONS^{8,9}



NON-INFECTIOUS PNEUMONITIS (NIP)

Non-infectious pneumonitis is a non-malignant infiltration of the lungs and is a class effect of rapamycin analogues, such as AFINITOR, which modulate immunity.²³ Most cases usually occur within the first six months of therapy, are of mild to moderate severity, and are reversible.⁵

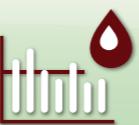
Common radiographic changes include ground-glass opacities and focal consolidation, predominantly in the lower lobes.^{9,24} Perform baseline CT scan and lung function tests in patients with respiratory symptoms or multiple lung metastases; delay AFINITOR until tests have normalised.

Consider a diagnosis of non-infectious pneumonitis in patients presenting with new or worsening signs of non-specific respiratory symptoms, such as:^{9,24}

- Cough and/or dyspnoea
- Hypoxia
- Pleural effusion

However, infectious, neoplastic and other non-medicinal causes should be excluded by means of appropriate investigations prior to diagnosis of NIP.¹ Consider diagnostic investigations to exclude infectious causes of lung pathology, e.g. bronchoalveolar lavage.⁹

MANAGEMENT



Treatment interruption, dose reductions and treatment with corticosteroids and antibiotics are the most frequently cited management strategies for NIP.^{1,24,25} Importantly, the use of corticosteroids is only possible if an infectious aetiology is ruled out.

Early proactive management is a must, and dose reduction should be considered as early as grade 1, with suspension of treatment at grade 2.²⁵ Progression to a grade 3 event should be avoided, as prompt diagnosis and management can result in full resolution or downgrading to grade 1.¹⁶ Patients should be instructed to report any signs of cough or breathlessness as soon as they occur.

Some patients may remain asymptomatic (especially grade 1 and 2), and diagnosis should depend on clinical and radiological criteria.¹⁶ Clinicians should take a proactive approach, and question patients about signs of non-infectious pneumonitis at every 2-week follow up and consider CT scan, chest X-ray and lung function tests.

Patients that develop radiological changes suggestive of NIP and have few or no symptoms may continue AFINITOR therapy without dose adjustments.¹ Patients should report any signs of breathlessness or cough **as soon as they occur.**¹

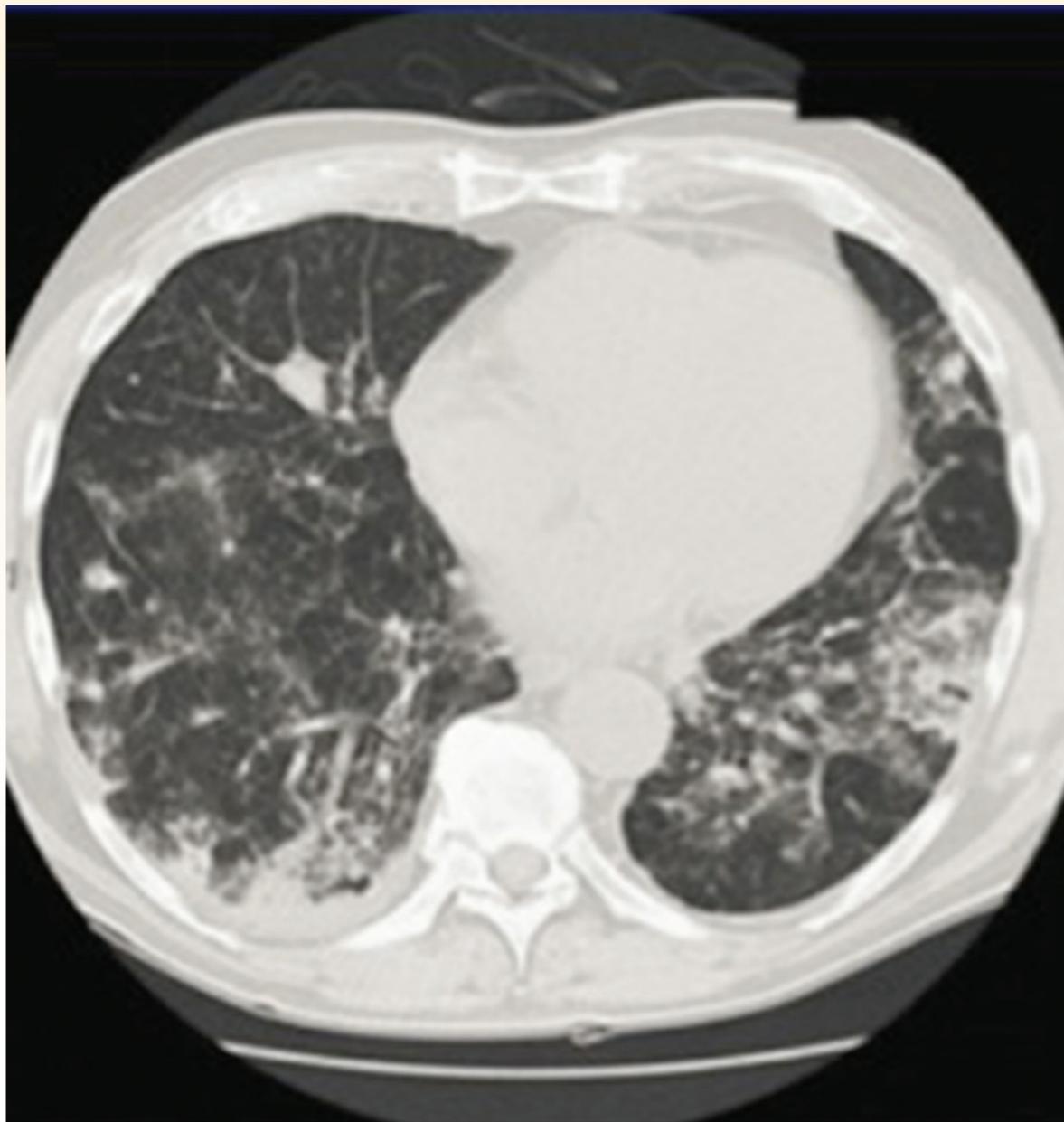


Image courtesy of Memorial Sloan-Kettering Cancer Centre, New York, NY.



TIME COURSE



NIP differs from other AEs as there are few early events, and no appreciable plateau. In a recent trial, 80% of grade 3 events resolved to grade ≤ 1 after a median of 3.8 weeks. Complete resolution of grade ≥ 3 events was reported in 75% patients after a median of 5.4 weeks.⁵

As there is no definite time of onset and early symptoms can be hard to identify, patients must be regularly monitored. Where possible, intervene at grade 2 to minimise disruption to AFINITOR treatment.¹⁰

PRACTICAL ADVICE



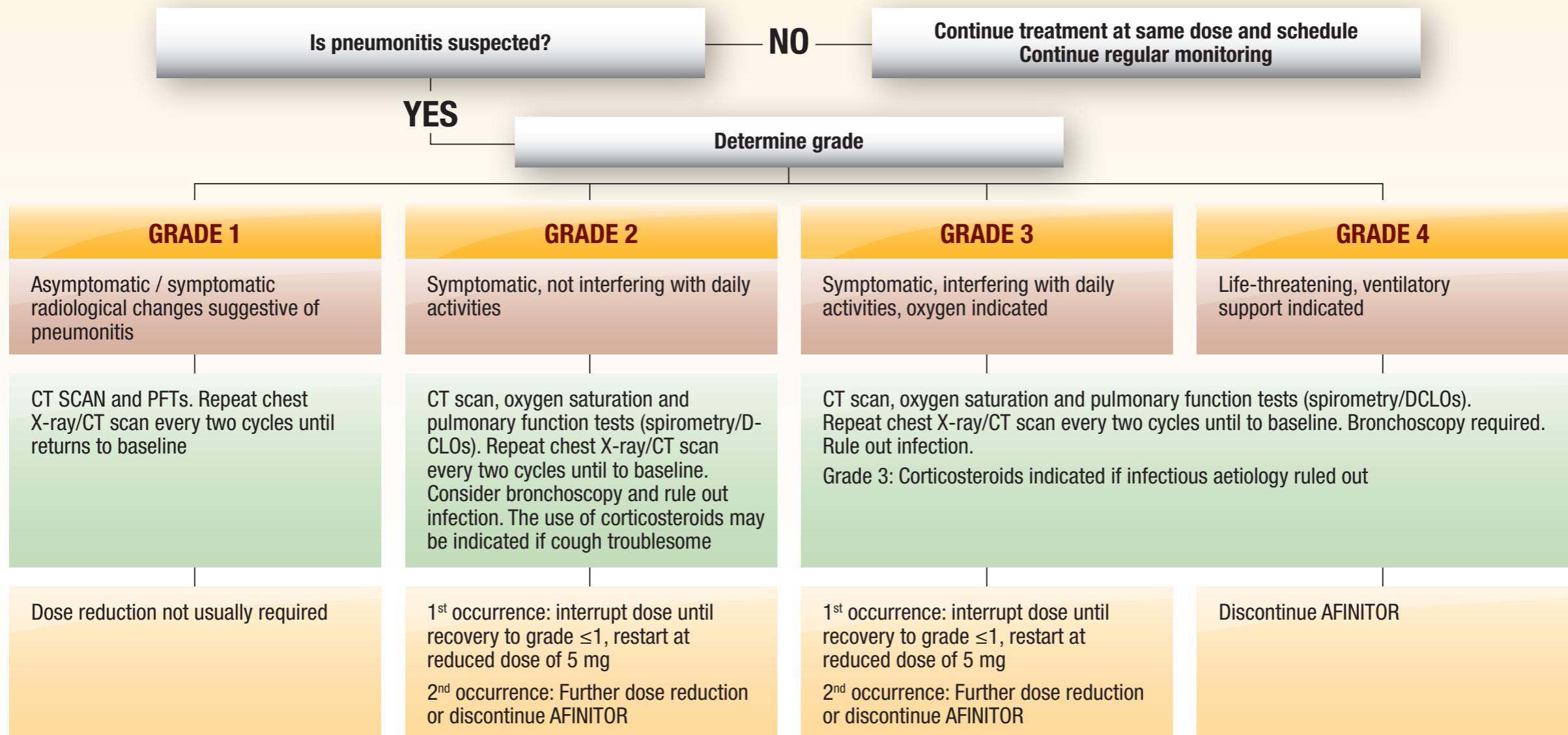
- Scan patients before initiating treatment
- Patients with respiratory abnormalities should be normalised prior to commencing AFINITOR
- If a patient develops symptoms of NIP, scan immediately
- If grade 2 or higher NIP is diagnosed then strongly consider treatment suspension. Restart at a reduced dose

ADVICE TO PATIENTS^{9,18,26}

- Seek medical advice if short of breath, or have difficulty breathing, with or without a cough
- Avoid allergens such as smoke and pollen if pneumonitis is present
- Drink plenty of fluid and take light exercise
- Report signs and symptoms as early as possible

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MANAGING NON-INFECTIOUS PNEUMONITIS^{1,8,27}



NON-HAEMATOLOGICAL ABNORMALITIES (EXCLUDING METABOLIC EVENTS)

This section covers a large number of possible adverse events. During AFINITOR therapy, common non-haematological, non-metabolic adverse events include: gastro-intestinal disorders, haemorrhage, hypertension and proteinuria.¹

MANAGEMENT



Monitoring of renal function, including measurement of blood urea nitrogen (BUN), urinary protein or serum creatinine, is recommended prior to the start of AFINITOR therapy and periodically thereafter.¹

Avoid using AFINITOR in patients at risk of renal failure, or with comorbidities that can be exacerbated by the drug.¹

PRACTICAL CONSIDERATIONS¹

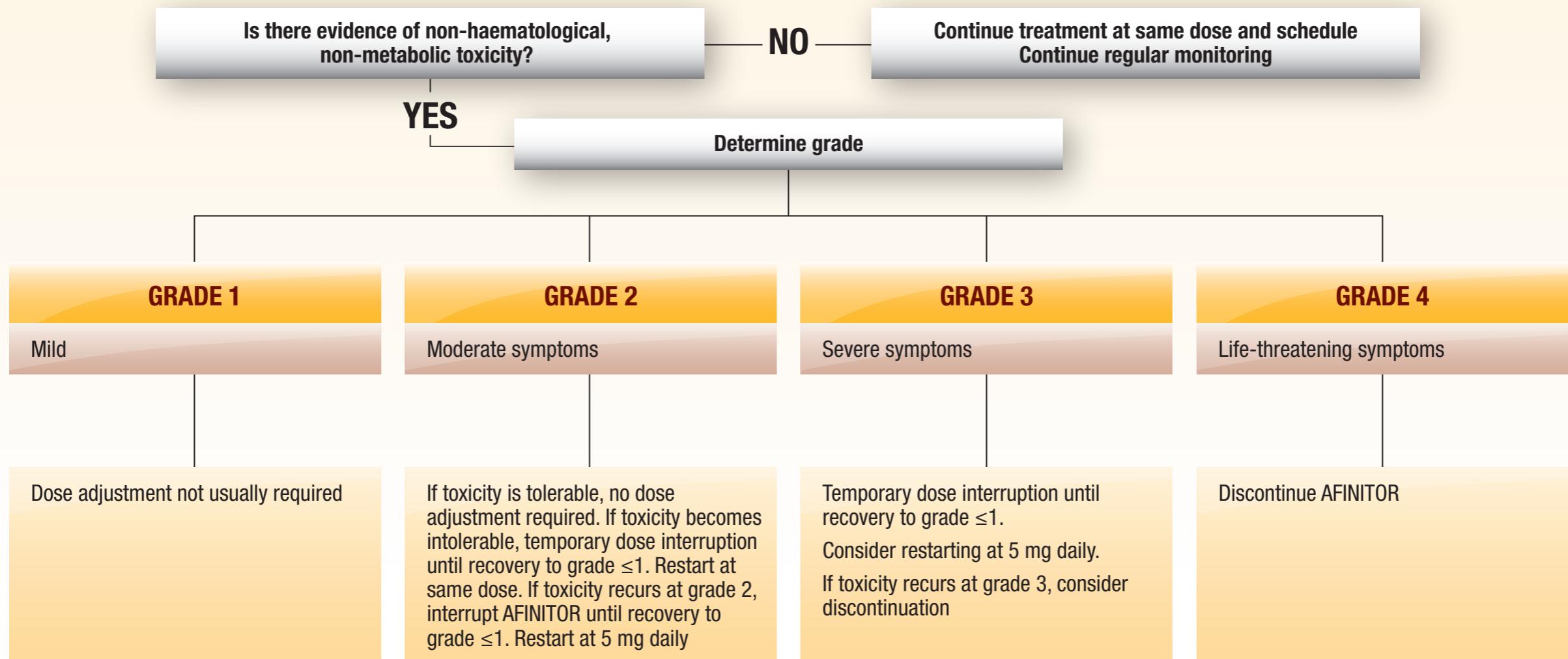


- Whilst changes to serum creatinine or proteinuria are often mild in severity, consider dose reduction or temporary suspension
- Renal function should be monitored periodically (or as per local guidelines), particularly where patients have additional risk factors that may further impair renal function
- Measurements should include blood urea nitrogen, urinary protein or serum creatinine

ADVICE TO PATIENTS

- Emphasise the importance of prompt reporting of signs and symptoms
- Reassure patients that most adverse events are mild-to-moderate in severity and can be managed by dose reductions or interruption

MANAGING NON-HAEMATOLOGICAL, NON-METABOLIC EVENTS (GENERAL)¹

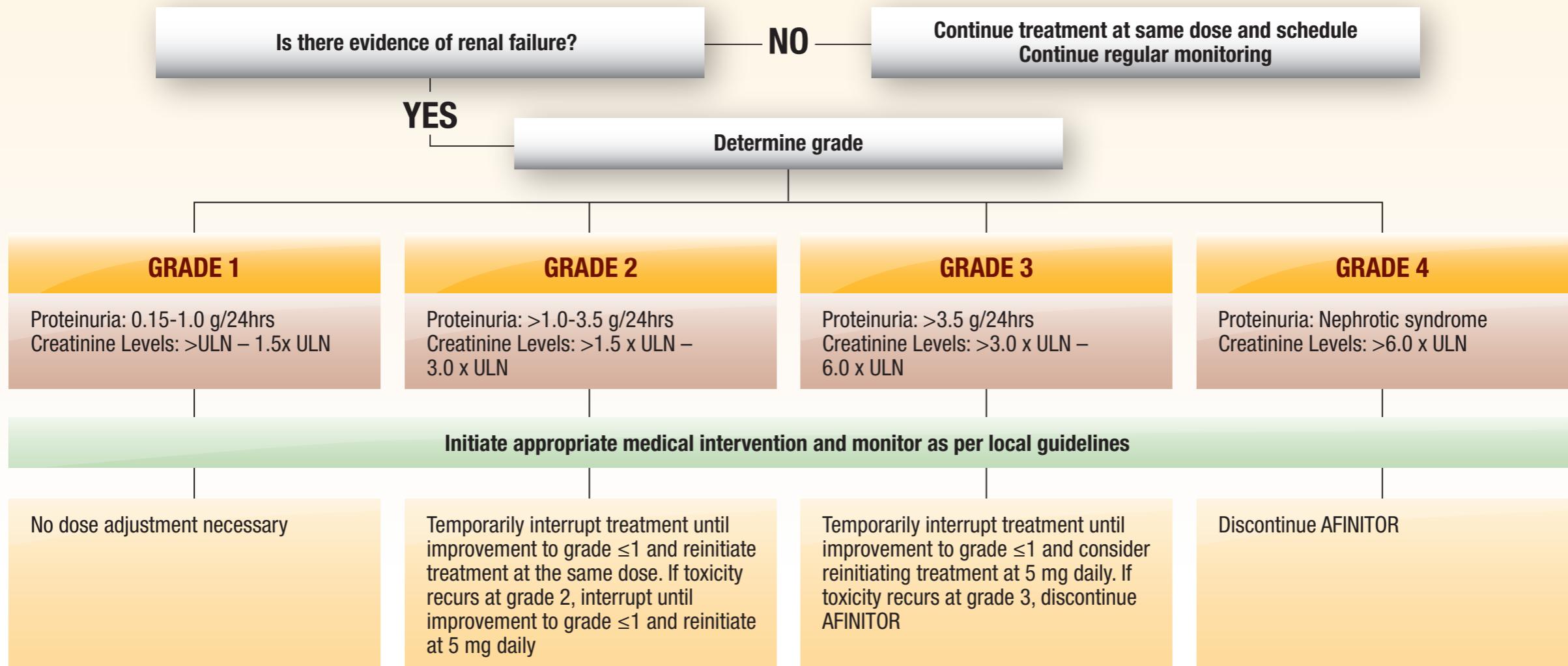


Special: Renal Failure

In clinical studies and post-marketing surveillance, AFINITOR has been associated with renal failure events.¹ Creatinine changes, proteinuria, and renal failure may be associated with AFINITOR and should be monitored from the start of treatment.¹

The risk of nephrotoxicity may be increased when AFINITOR is co-administered with calcineurin inhibitors (e.g. cyclosporine, tacrolimus). Dosage reduction of calcineurin inhibitors is necessary when co-administered with AFINITOR.¹⁰

MANAGING RENAL FAILURE^{1,8}



APPENDIX: DRUG INTERACTIONS^{1,10}

Actions

If avoiding co-administration is not an option, drug combinations have three recommended actions:

- 1. Monitor therapy.** Start this drug as normal, but closely monitor the patient for the signs and symptoms of AEs associated with the drug or AFINITOR. If AEs develop, suspend or reduce dose as required.
- 2. Consider therapy modification.** Either reduce the dose of AFINITOR prior to commencing co-administration, or reduce the initial dose of the co-administered drug. Closely monitor the patient for the signs and symptoms of AEs associated with the drug or AFINITOR. If AEs develop, suspend or reduce the dose further as required.
- 3. Avoid combination.** Do not co-administer this drug with AFINITOR. Suspend AFINITOR treatment prior to commencing therapy and do not resume AFINITOR dosing until course is complete and a suitable washout period has elapsed.

Highlight: CYP3A4/PgP inhibitors and inducers

AFINITOR is a substrate of CYP3A4, and also a substrate and moderate inhibitor of PgP. Therefore, absorption and subsequent elimination of AFINITOR may be influenced by products that affect CYP3A4 and/or PgP.¹ Furthermore, co-administration may lead to toxic accumulation of CYP3A4 and PgP modulators in the gut.¹

Caution should be exercised when AFINITOR is taken in combination with orally administered CYP3A4 substrates with a narrow therapeutic index due to the potential for drug interactions.¹ If taken with such substances, the patient should be monitored for undesirable effects and AEs.¹

Highlight: Immunosuppressants and drugs with Immunosuppressant toxicity

AFINITOR has immunosuppressant properties and may predispose patients to infections, due to an ability to inhibit B- and T-cell proliferation.^{10,21} Caution should be exercised when co-administering drugs that have immunosuppressant effects or toxicities.



Table of Drug Interactions^{1,10}

Please note that this is not an exhaustive list. Consult the AFINITOR SPC¹ if there are any concerns or doubts about the suitability of co-treatment

Drug name / type	Reason	Action
ACE Inhibitors	Increased risk of angioedema	Monitor AFINITOR therapy
Amprenavir	CYP3A4 inhibition may increase serum concentration of AFINITOR	Use caution and see 2 below
Atazanavir	Potent Inhibition of CYP3A4/PgP	Avoid combination and see 3 below
Barbiturates	CYP3A4/PgP induction may decrease serum concentration of AFINITOR	Consider therapy modification and see 1 below
BCG	Immunosuppression due to AFINITOR	Avoid combination
Carbamazepine	CYP3A4/PgP induction may decrease serum concentration of AFINITOR	Consider therapy modification and see 1 below
Clarithromycin	Potent inhibition of CYP3A4/PgP	Avoid combination and see 3 below
Coccidioidin Skin Test	Immunosuppression of patient	Monitor AFINITOR therapy
Ciclosporin	May increase serum concentration of AFINITOR and increased immunosuppression	Use caution. See 2
Darunavir	Potent Inhibition of CYP3A4/PgP	Avoid combination and see 3 below
Dasatanib	May increase serum concentration of CYP3A4 substrates	Monitor AFINITOR therapy
Deferasirox	May decrease serum concentration of CYP3A4 substrates	Monitor AFINITOR therapy
Denosumab	May increase immunosuppression leading to infection	Monitor therapy
Dexamethasone	Induction of CYP3A4/PgP may decrease serum concentration of AFINITOR	Consider therapy modification and see 1 below
Diltiazem	Inhibition of CYP3A4/PgP may increase serum concentration of AFINITOR	Use caution and see 2 below
Dronedarone	Inhibition of CYP3A4/PgP may increase serum concentration of AFINITOR	Use caution and see 2 below
Echinacea	May diminish therapeutic effect of immunosuppressants	Consider therapy modification
Efavirenz	Induction of CYP3A4/PgP may decrease serum concentration of AFINITOR	Consider therapy modification and see 1 below
Erythromycin	Inhibition of CYP3A4/PgP may increase serum concentration of AFINITOR	Use caution and see 2 below
Fluconazole	Inhibition of CYP3A4/PgP may increase serum concentration of AFINITOR	Use caution and see 2 below
Fosamprenavir	Inhibition of CYP3A4/PgP may increase serum concentration of AFINITOR	Use caution and see 2 below

Drug name / type	Reason	Action
Grapefruit Juice or other food affecting CYP3A4/PgP	Inhibition of CYP3A4/PgP may increase serum concentration of AFINITOR	Avoid combination and see 2 below
Imatinib	Inhibition of CYP3A4/PgP may increase serum concentration of AFINITOR	Use caution and see 2 below
Indinavir	Potent inhibition of CYP3A4/PgP	Avoid combination and see 3 below
Itraconazole	Potent Inhibition of CYP3A4/PgP	Avoid combination and see 3 below
Ketoconazole	Potent Inhibition of CYP3A4/PgP	Avoid combination and see 3 below
Leflunomide	AFINITOR may increase risk of haematologic toxicity: pancytopenia, agranulocytosis, and/or thrombocytopenia	Consider AFINITOR dose reduction and/or reduce loading dose of leflunomide
Natalizumab	Immunosuppression may lead to infection	Avoid combination
Nefazadone	Potent Inhibition of CYP3A4/PgP	Avoid combination and see 3 below
Nelfinavir	Potent Inhibition of CYP3A4/PgP	Avoid combination and see 3 below
Nevirapine	Induction of CYP3A4/PgP may decrease serum concentration of AFINITOR	Consider therapy modification and see 1 below
P-glycoprotein/ABCB1 Inducers	May decrease serum concentration of P-glycoprotein/ABCB1 substrates	Monitor therapy
P-glycoprotein/ABCB1 Inhibitors	May increase serum concentration of P-glycoprotein/ABCB1 substrates	Consider therapy modification
Phenytoin	Induction of CYP3A4/PgP may decrease serum concentration of AFINITOR	Consider therapy modification and see 1 below
Pimecrolimus	Immunosuppression of patient	Avoid combination
Posaconazole	Potent inhibition of CYP3A4/PgP	Avoid combination and see 3 below
Rifampicin	Induction of CYP3A4/PgP may decrease serum concentration of AFINITOR	Consider therapy modification and see 1 below
Ritonavir	Potent inhibition of CYP3A4/PgP	Avoid combination and see 3 below
Roflumilast	May increase immunosuppression, leading to infection	Consider therapy modification
Saquinavir	Potent inhibition of CYP3A4/PgP	Avoid combination and see 3 below

Drug name / type	Reason	Action
Sipuleucel-T	Immunosuppression of patient	Monitor therapy
St. John's Wort	Induction of CYP3A4/PgP may decrease serum concentration of AFINITOR	Consider therapy modification and see 1 below
Tacrolimus (Topical)	May modulate immunosuppression	Avoid combination
Telithromycin	Potent inhibition of CYP3A4/PgP	Avoid combination and see 3 below
Tocilizumab	May decrease serum concentration of CYP3A4 substrates	Monitor therapy
Trastuzumab	May modulate immunosuppression	Monitor therapy
Vaccines (Inactivated)	Immunosuppression of patient	Monitor therapy
Vaccines (Live)	Immunosuppression of patient	Avoid combination
Verapamil	Inhibition of CYP3A4/PgP may increase serum concentration of AFINITOR	Use caution and see 2 below
Voriconazole	Potent Inhibition of CYP3A4/PgP	Avoid combination and see 3 below

Notes

1. Potent CYP3A4 / PgP Inducer: Can decrease AFINITOR blood concentrations and co-administration should be avoided.

If patients require co-administration, consider adjusting AFINITOR dose from 10 mg to 20 mg daily, using 5 mg increments on days 4 and 8 following start of inducer. Consider a washout period of 3-5 days following discontinuation of inducer, prior to reducing AFINITOR dose back to 10 mg daily.^{1,10}

2. Moderate CYP3A4 / PgP Inhibitor: Can increase AFINITOR blood concentrations and co-administration should be avoided unless no alternative treatment is available.

If patient requires co-administration, consider AFINITOR dose reduction to 5 mg or 2.5 mg daily. If the inhibitor is discontinued, a washout period of at least 2 to 3 days before the AFINITOR dose is increased should be considered.¹

3. Potent CYP3A4 / PgP Inhibitor: Concomitant treatment of AFINITOR and potent inhibitors is not recommended.

Suspend AFINITOR prior to inhibitor treatment and restart following inhibitor discontinuation and 3-5 day washout period.^{1,10}

AFINITOR® (EVEROLIMUS) PRESCRIBING INFORMATION

AFINITOR® (everolimus) Prescribing Information

Before prescribing Afinitor please refer to the Summary of Product Characteristics (SPC). **Presentation:** Available as 10mg, 5mg and 2.5mg tablets: **Indication:** Hormone receptor-positive advanced breast cancer; Afinitor is indicated for the treatment of hormone receptor positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor. **Neuroendocrine tumours of pancreatic origin:** Afinitor is indicated for the treatment of unresectable or metastatic, well or moderately differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease. **Neuroendocrine tumours of gastrointestinal or lung origin:** Afinitor is indicated for the treatment of unresectable or metastatic, well-differentiated (Grade 1 or Grade 2) non-functional neuroendocrine tumours of gastrointestinal or lung origin in adults with progressive disease. **Renal cell carcinoma:** Afinitor is indicated for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy. **Dosage:** The recommended dose of Afinitor is 10mg everolimus once daily. For oral use. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs. Management of severe and/or intolerable suspected adverse reactions may require dose reduction and/or and/or temporary interruption. Prescribers should consult the SPC for detailed information and guidance on dose adjustment due to adverse events and in patients with hepatic impairment. No dose adjustment is required for elderly patients and patients with renal impairment. No data are available for paediatric population. **Contraindications:** Hypersensitivity to the active substance, to other rapamycin derivatives or to any of the excipients. **Special Warnings and Precautions:** **Non-infectious pneumonitis:** Non-infectious pneumonitis is a class effect of rapamycin derivatives, including Afinitor, and has been frequently reported. Some cases were severe and on rare occasions, fatal. Patients should be advised to report promptly any new or worsening respiratory symptoms. **Infections:** Afinitor has immunosuppressive properties and may predispose patients to or exacerbate pre-existing localised and systemic infections. Severe (e.g. leading to sepsis, respiratory or hepatic failure) and occasionally fatal cases have been reported. Pre-existing infections should be treated and resolved fully before starting Afinitor. If infection is diagnosed, consider interruption or discontinuation of Afinitor. If a diagnosis of invasive systemic fungal infection is made, treatment with Afinitor should be promptly and permanently discontinued and the patient treated with appropriate antifungal therapy. Cases of pneumocystis jirovecii (carinii) pneumonia (PJP, PCP), some with fatal outcome, have been reported in patients who received everolimus. PJP/PCP may be associated with concomitant use of corticosteroids or other immunosuppressive agents. Prophylaxis for PJP/PCP should be considered when concomitant use of corticosteroids or other immunosuppressive agents are required. **Hypersensitivity:**

Hypersensitivity reactions including but not limited to anaphylaxis, dyspnoea, flushing, chest pain or angioedema have been observed. **ACE inhibitors:** Patients taking concomitant ACE inhibitor therapy may be at increased risk of angioedema. **Stomatitis:** Stomatitis, including mouth ulcerations and oral mucositis is the most commonly reported adverse reaction in patients treated with Afinitor and mostly occurs within the first 8 weeks of treatment. Management of stomatitis may therefore include prophylactic and/or therapeutic use of topical treatments, such as an alcohol-free corticosteroid oral solution as a mouthwash. Monitoring for and treatment of fungal infection is recommended, especially in patients being treated with steroid-based medications. **Renal failure:** Cases of renal failure, some with fatal outcome have been observed. **Laboratory tests and monitoring:** Monitoring of renal function, including measurement of blood urea nitrogen (BUN), urinary protein or serum creatinine is recommended prior to the start of therapy and periodically thereafter. Monitoring of complete blood count, fasting serum glucose, and blood cholesterol and triglycerides is recommended prior to the start of therapy and periodically thereafter. **Functional carcinoid tumours:** The safety and efficacy of Afinitor in patients with functional carcinoid tumours has not been established. **Prognostic factors in neuroendocrine tumours of gastrointestinal or lung origin:** In patients with non-functional gastrointestinal or lung neuroendocrine tumours and good prognostic baseline factors, an individual benefit-risk assessment should be performed prior to start of therapy. A limited evidence of PFS benefit was reported in the subgroup of patients with ileum as primary tumour origin. **Interactions:** Co-administration with inhibitors and inducers of CYP3A4 and/or the multidrug efflux pump P-glycoprotein (PgP) should be avoided. If co-administration of a moderate CYP3A4 and/or PgP inhibitor or inducer cannot be avoided, dose adjustments may be required based on predicted AUC. Concomitant treatment with potent CYP3A4 inhibitors result in dramatically increased plasma concentrations of Afinitor hence is not recommended. Caution should be exercised when Afinitor is taken in combination with orally administered CYP3A4 substrates with a narrow therapeutic index. For more details on dosing recommendations, please refer to the full SPC. **Hepatic impairment:** Exposure to everolimus was increased in patients with (hepatic impairment (Child Pugh A, B and C). Afinitor is only recommended for use in patients with severe hepatic impairment (Child Pugh C) if the potential benefit outweighs the risk. **Vaccinations:** The use of live vaccines should be avoided during treatment with Afinitor. **Lactose:** Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take Afinitor. **Wound healing complications:** Wound healing is a class effect of rapamycin derivatives. Caution should be exercised with the use of Afinitor in the peri-surgical period. **Other important info:** Women of childbearing potential must use a highly effective method of contraception while receiving everolimus, and for up to 8 weeks after ending treatment. Male patients should not be prohibited from attempting to father children. Afinitor is not

recommended during pregnancy and in women of childbearing potential not using contraception. Women taking Afinitor should not breast-feed during treatment and for 2 weeks after the last dose. Based on non-clinical findings, male and female fertility may be compromised by treatment with Afinitor. Afinitor may have a minor or moderate influence on the ability to drive and use machines. Reported experience with overdose in humans is very limited. **Adverse Reactions:** **Very common ($\geq 1/10$):** Infections, anaemia, decreased appetite, hyperglycaemia, hypercholesterolaemia, dysgeusia, headache, pneumonitis, epistaxis, cough, stomatitis, diarrhoea, nausea, rash, pruritus, fatigue, asthenia, oedema peripheral, and weight decreased. **Common ($\geq 1/100$ to $<1/10$):** Thrombocytopenia, neutropenia, leukopenia, lymphopenia, hypertriglyceridaemia, hypophosphataemia, diabetes mellitus, hyperlipidaemia, hypokalaemia, dehydration, hypocalcaemia, insomnia, eyelid oedema, haemorrhage, hypertension, dyspnoea, vomiting, dry mouth, abdominal pain, mucosal inflammation, oral pain, dyspepsia, dysphagia, aspartate aminotransferase increased, alanine aminotransferase increased, dry skin, nail disorders, mild alopecia, acne, erythema, onychoclasia, palmar-plantar erythrodysesthesia syndrome, skin exfoliation, skin lesion, arthralgia, proteinuria, blood creatinine increased, renal failure, menstruation irregular, and pyrexia. **Uncommon ($\geq 1/1,000$ to $<1/100$):** Pancytopenia, hypersensitivity, ageusia, conjunctivitis, congestive cardiac failure, flushing, deep vein thrombosis, haemoptysis, pulmonary embolism, increased daytime urination, acute renal failure, amenorrhoea, non cardiac chest pain, and impaired wound healing. **Rare ($\geq 1/10,000$ to $<1/1,000$):** Pure red cell aplasia, acute respiratory distress syndrome, and angioedema. For more details in regards with selected adverse events and elderly patients, please refer to full SPC. Legal Category: P.O.M. Marketing authorisation holder: Novartis Europharm Limited, Frimley Business Park, Camberley, GU16 7SR, UK. Packs and Marketing authorisation numbers: AFINITOR 10mg tablets, 3x10 tablets pack- MA Number EU/1/09/538/004. Basic NHS price £2,673.00 AFINITOR 5mg tablets, 3x10 tablets pack - MA Number EU/1/09/538/001. Basic NHS price £2,250.00 AFINITOR 2.5mg tablets, 3x10 tablets pack- MA Number EU/1/09/538/009. Basic NHS price £1,200.00. AFINITOR® is a registered Trade Mark. Before prescribing please refer to the SPC. Full prescribing information is available from Novartis Pharmaceuticals UK Ltd, Frimley Business Park, Frimley, Camberley, Surrey, GU16 7SR, UK. Telephone Medical Information on 01276 698370, email medinfo.uk@novartis.com.

V_2.1 Date of Preparation: August 2017 AF15-C001(4)

Adverse events should be reported. Reporting forms and information can be found at <https://yellowcard.mhra.gov.uk/>.
Adverse events can also be reported to Novartis via 01276 698370 or online through the patient safety information tool at <https://psi.novartis.com>.



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