OPTIMAL MANAGEMENT OF STOMATITIS IN AFINITOR-TREATED PATIENTS

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Not to be distributed to patients

Prescribing information can be found on the back page

NOVARTIS

AFINITOR®
(everolimus) tablets

RECOMMENDATIONS FOR MANAGING AFINITOR-RELATED STOMATITIS

STOMATITIS WAS THE MOST FREQUENT ADVERSE EVENT IN PHASE III AFINITOR CLINICAL TRIALS:[1-3]

- stomatitis includes mouth inflammation, ulceration and infection, as well as oral mucositis[4]
- in BOLERO-2, stomatitis occurred most frequently in the first 8 weeks of treatment[5]

STOMATITIS INCIDENCE IN THE BOLERO-2, BRAWO AND EVEREXES STUDIES[6-8]

STUDY	AFINITOR + EXEMESTANE All grade stomatitis incidence (Grade 3 incidence)
BOLERO-2	67% (8%)
BRAWO	45.8% (2.7%)
EVEREXES	66% (9%)

SWISH: A SINGLE-ARM, PHASE II POST-MARKETING TRIAL[9]

In this post-marketing study in postmenopausal women with advanced breast cancer (n=92), patients were treated with steroid-based alcohol-free mouthwash.

- The primary endpoint in the SWISH study: Grade 2 or worse stomatitis by 8 weeks, occurred in 2 out of 85 patients (2.4% [95% CI 0.29–8.24]) compared with 159 out of 482 patients (33.0% [95% CI 28.8–37.4]) for the duration of the historical control, BOLERO-2 study ($p<0.0001$)
- the incidence of Grade 1 stomatitis was 18.8%
- no Grade 3 or 4 cases were reported

Oral solution used in **SWISH:** dexamethasone 0.5 mg/5 ml alcohol-free oral solution.

PRACTICAL STEPS PATIENTS CAN TAKE BEFORE AFINITOR TREATMENT[5,8-13]

– have a dental check-up (and repeat regularly)

– clear any pre-existing conditions (e.g. fungal infection)

DURING AFINITOR TREATMENT

Prophylactic and/or therapeutic topical treatments can reduce the incidence of stomatitis.

– The SWISH trial used a regimen of an alcohol-free corticosteroid oral solution, administrated as a mouthwash for **2** minutes, **4** times a day for the initial **8** weeks of treatment.[5,9]

Use a steroid-based mouthwash (e.g. dexamethasone 0.5 mg/5 ml alcohol-free mouthwash) [5,9]

2 x minutes

4 x daily

8 x weeks of treatment

OTHER PRACTICAL STEPS TO MINIMISE STOMATITIS

Brush regularly and gently with a soft toothbrush

Use milder children's toothpaste, avoid strong flavours

Rinse frequently with bland mouthwashes such as water, normal saline or sodium bicarbonate

Floss daily

Have regular dental check-ups

Cool mouth by sucking on ice or frozen pineapple

Avoid hot food (in temperature and/or spiciness)

Eat smaller meals and use a straw to keep liquid away from sore areas

Products containing alcohol, hydrogen peroxide, iodine and thyme derivative should be avoided.[5]

EARLY RECOGNITION AND IMMEDIATE TREATMENT OF STOMATITIS IS ESSENTIAL TO REDUCE THE NUMBER AND SEVERITY OF ULCERS

SUGGESTED MANAGEMENT OF STOMATITIS BY GRADE OF SEVERITY[5]

GRADE 1

Erythema of the mucosa, minimal symptoms, normal diet[14]

ACTION

– No dose modification

PRACTICAL TIPS

1. Use an alcohol-free corticosteroid oral solution
2. Cool mouth by sucking ice
3. Take soluble aspirin or paracetamol

GRADE 2

Patchy ulcerations or pseudomembranes; symptomatic but can eat and swallow modified diet[14]

ACTION

– Temporary dose interruption until recovery to Grade ≤1, then restart at same dose

– Recurrence at Grade 2: as above, but restart at lower dose

PRACTICAL TIPS

1. Use an alcohol-free corticosteroid oral solution
2. Use a topical (oral) analgesic
3. Initiate antiviral therapy if herpetic infection confirmed
4. Avoid agents containing: alcohol, hydrogen peroxide, iodine and thyme derivatives
5. Avoid antifungal therapy unless fungal infection confirmed

GRADE 3

Confluent ulcerations or pseudomembranes; bleeding with minor trauma; symptomatic and unable to adequately eat or hydrate orally[15]

ACTION

– Temporary dose interruption until recovery to Grade ≤1, consider re-initiating at 5 mg daily[5]

PRACTICAL TIPS

1. Initiate appropriate medical intervention
2. Avoid agents containing: alcohol, hydrogen peroxide, iodine and thyme derivatives

GRADE 4

Tissue necrosis; significant spontaneous bleeding; symptoms associated with life-threatening consequences[15]

ACTION

– Discontinue AFINITOR and treat with appropriate medical therapy

PRACTICAL TIPS

1. Initiate appropriate medical intervention
2. Avoid agents containing: alcohol, hydrogen peroxide, iodine and thyme derivatives

AT-A-GLANCE TIMELINE FOR THE MANAGEMENT OF STOMATITIS

BEFORE INITIATION

REASON

Patients can reduce their risk or severity of stomatitis

ACTION

Regular dental check-ups

Maintain good oral care

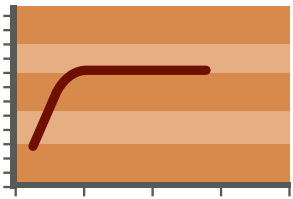
Clear pre-existing infections

Steroid-based mouthwash

WEEK 2 ONWARDS

REASON

Incidence of new events plateaus by week 6 but remain vigilant in case of recurrence[6,16]



ACTION

Continue monitoring and encouraging patient to report symptoms promptly

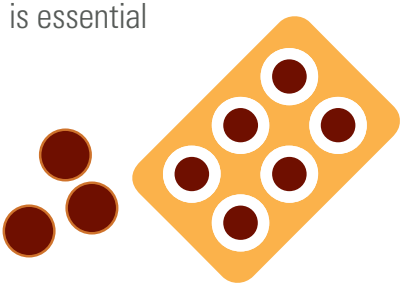
Average time to recurrence is:[16]

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

WEEK 2

REASON

Early monitoring and intervention is essential



ACTION

First telephone or clinic follow-up

If symptomatic:

- consider more frequent monitoring
- see prophylactic measures (overleaf)
- treat if Grade ≥2

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 (≥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 (≥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, onychoclasis, palmar-plantar erythrodysaesthesia syndrome, skin exfoliation, skin lesion, arthralgia, proteinuria, blood creatinine increased, renal failure, menstruation irregular, and pyrexia. Uncommon (≥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 (≥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.

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the patient safety information (PSI) tool at https://psi.novartis.com If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com

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