NOVARTIS

AFINITOR® (everolimus)

Tablets: 2.5 mg, 5 mg and 10 mg
Dispersible tablets: 2 mg, 3 mg and 5 mg

Malaysia Basic Succinct Statement
Version 3.1

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This material is only meant for Healthcare Professionals

AFINITOR®

Important note: Before prescribing, consult the full prescribing information.

Presentation: ♦Tablets containing 2.5 mg, 5 mg or 10 mg of everolimus. ♦Dispersible Tablets containing 2 mg, 3 mg or 5 mg of everolimus.

Indications: ♦**Tablets**: Treatment of postmenopausal women with advanced hormone receptor-positive HER2-negative breast cancer (advanced HR+BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole; Treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.; Treatment of progressive neuroendocrine tumors of pancreatic origin (PNET) in patients with unresectable, locally advanced or metastatic disease. AFINITOR is not indicated for the treatment of patients with functional carcinoid tumours; Treatment of adult patients with progressive, well-differentiated (Grade 1 or Grade 2), non-functional neuroendocrine tumours (NET) of gastrointestinal (GI) or lung origin with unresectable, locally advanced or metastatic disease. AFINITOR is not indicated for the treatment of patients with functional carcinoid tumours; Treatment of adult and paediatric patients, 1 years of age and older, with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not candidates for curative surgical resection. The effectiveness of AFINITOR is based on an analysis of change in SEGA volume (see section CLINICAL STUDIES). Clinical benefit such as improvement in disease-related symptoms or increase in overall survival has not been demonstrated; Treatment of adult patients with renal angiomyolipoma (AML) and tuberous sclerosis complex (TSC), not requiring immediate surgery. The effectiveness of AFINITOR in the treatment of renal angiomyolipoma is based on an analysis of durable objective responses in patients treated for a median of 8.3 months. Further follow-up of patients is required to determine long-tern outcomes. ♦**Dispersible Tablets**: Treatment of adult and paediatric patients, 1 years of age and older, with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not candidates for curative surgical resection. The effectiveness of AFINITOR is based on an analysis of change in SEGA volume (see section CLINICAL STUDIES). Clinical benefit such as improvement in disease-related symptoms or increase in overall survival has not been demonstrated.

Dosage and administration: ♦**BC, NET, RCC, TSC with renal angiomyolipoma**: 10 mg once daily. ♦**TSC with SEGA:** starting daily dose is 4.5 mg/m^2 according to body surface area (BSA) rounded to the nearest milligram strength of AFINITOR Tablets or AFINITOR Dispersible Tablets. Everolimus whole blood trough concentrations should be assessed approximately 1 to 2 weeks after the initial dose, after any change in dosage, after the switch between AFINITOR and AFINITOR Dispersible Tablets. Everolimus whole blood trough concentrations should be assessed approximately 2 weeks after initiation of or discontinuation of co-administration of CYP3A4/PgP inducers and/or inhibitors, change in hepatic (Child-Pugh) status. Therapeutic drug monitoring is required and dosing should be titrated to attain everolimus trough concentrations of 5 to 15 ng/mL. ♦The daily dose should be taken orally at the same time every day, either consistently with or consistently without food. ♦Dispersible

Tablets are to be taken as a suspension only and should not be swallowed whole, chewed, or crushed.

♦**Dose modification:** Dose interruption (with or without dose reduction) or discontinuation may be required to manage adverse drug reactions (ADRs). Dose modification may be required with concomitant use of moderate CYP3A4/PgP inhibitors or strong CYP3A4 inducers, hepatic impairment, or change in dosage form in patients being treated for TSC with SEGA. ♦**Pediatric patients: BC, NET, RCC, TSC with renal angiomyolipoma**: safety and effectiveness in pediatric patients have not been established. **TSC with SEGA:** can be used in children and adolescents with normal hepatic function; has not been studied in patients <1 year of age ♦**Patients with hepatic impairment: BC, NET, RCC, TSC with renal angiomyolipoma:** recommended dose is 7.5 mg once daily in patients with mild hepatic impairment (Child-Pugh A) and the dose may be decreased to 5mg once daily if not well tolerated; 5 mg once daily in patients with moderate hepatic impairment (Child-Pugh B) and the dose may be decreased to 2.5 mg once daily if not well tolerated; 2.5mg once daily in patients with severe hepatic impairment (Child-Pugh C) if the desired benefit outweighs the risk, do not exceed a dose of 2.5 mg once daily. **TSC with SEGA:** 2.5 mg/m^2 once daily in patients with severe hepatic impairment (Child-Pugh C).

♦**Missed Dose:** AFINITOR can still be taken up to 6 hours after the time it is normally taken. After more than 6 hours, the dose should be skipped for that day. The next day, AFINITOR should be taken at its usual time. Double doses should not be taken to make up for the one that was missed.

Contraindications: Hypersensitivity to the active substance, to other rapamycin derivatives or to any of the excipients.

Warnings and precautions: ♦**Non-infectious pneumonitis:** Cases have been described in patients taking AFINITOR, some of these have been severe and on rare occasions, a fatal outcome was observed. A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms. Opportunistic infections such as pneumocystis jirovecii pneumonia (PJP) should be considered in the differential diagnosis of non-infectious pneumonitis. In some cases, management of pneumonitis may require interruption or discontinuation of treatment. The use of corticosteroids may be indicated. Administer prophylaxis for PJP when concomitant use of corticosteroids or other immunosuppressive agents are required. The development of pneumonitis has been reported even at a reduced dose.♦**Infections:** AFINITOR has immunosuppressive properties. Localized and systemic bacterial, fungal, viral, or protozoal infections (e.g. pneumonia, aspergillosis, candidiasis, or PJP and hepatitis B reactivation) have been described in patients taking AFINITOR; some of these have been severe or fatal. Treatment of pre-existing invasive fungal infections should be completed prior to starting treatment. Monitor for signs and symptoms of infection. Withhold or permanently discontinue AFINITOR/AFINITOR DISPERSIBLE based on severity of infection. Administer prophylaxis for PJP when concomitant use of corticosteroids or other immunosuppressive agents are required. ♦**Hypersensitivity reactions** have been observed and include anaphylaxis, dyspnea, flushing, chest pain, and angioedema (e.g., swelling of the airways or tongue, with or without respiratory impairment). ♦**Angioedema:** Patients taking concomitant ACE inhibitor with AFINITOR may be at increased risk for angioedema (e.g. swelling of the

airways or tongue, with or without respiratory impairment). Permanently discontinue AFINITOR/AFINITOR DISPERSIBLE for angioedema. ♦**Stomatitis**: Stomatitis is the most commonly reported ADR in patients treated with AFINITOR and mostly occurs within the first 8 weeks of treatment. Topical treatments are recommended, but alcohol-, hydrogen peroxide, iodine-, or thyme containing mouthwashes should be avoided. Do note administer antifungal agents unless fungal infection has been diagnosed. ♦**Renal failure events:** Cases of renal failure (including acute renal failure), some fatal, have occured in patients taking AFINITOR. Monitor renal function prior to starting AFINITOR and annually thereafter. Monitor renal function at least every 6 months in patients who have additional risk factors for renal failure.♦**Impaired wound healing:** AFINITOR delays wound healing and increases occurrence of wound-related complications like wound dehiscence, wound infection, incisional hernia, lymphocele, and seroma. Exercise caution with the use of AFINITOR in the peri-surgical period. ♦**Geriatric patients:** Careful monitoring and appropriate dose adjustments for adverse reactions are recommended. ♦**Metabolic disorders**: Hyperglycemia, hypercholesterolemia, and hypertriglyceridemia have been reported in patients taking AFINITOR. In non-diabetic patients, monitor fasting serum glucose prior to starting AFINITOR and annually thereafter. In diabetic patients, monitor fasting serum glucose more frequently as clinically indicated. Monitor lipid profile prior to starting AFINITOR and annually thereafter. When possible, achieve optimal glucose and lipid control prior to starting AFINITOR.♦**Myelosuppression:** Anemia, lymphopenia, neutropenia, and thrombocytopenia have been reported in patients taking AFINITOR. Monitor complete blood count prior to starting AFINITOR every 6 months for the first year of treatment and annually thereafter. Withhold or permanently discontinue AFINITOR/AFINITOR DISPERSIBLE based on severity. ♦**Vaccination:** Due to the potential increased risk of infection, avoid use of live vaccines and close contact with people who have received live vaccines during treatment with AFINITOR. Due to the potential increased risk of infection or reduced immune response with vaccination, complete the recommended childhood series of vaccination prior to the start of the AFINITOR therapy, according to ACIP guidelines. ♦**Embryo-Fetal toxicity:** Advise pregnant women of the potential risk to a fetus. Advise female patients of reproductive potential to avoid becoming pregnant and to use effective contraception during treatment with AFINITOR and for 8 weeks after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with AFINITOR and for 4 weeks after the last dose.

Adverse drug reactions: **BC: ♦Very common (≥10%):** stomatitis, diarrhea, nausea, vomiting, constipation, dry mouth, fatigue, edema peripheral, pyrexia, asthenia, infection, weight decreased, decreased appetite, hyperglycemia, arthralgia, back pain, pain in extremity, dysgeusia, headache, insomnia, cough, dyspnea, epistaxis, pneumonitis, rash, pruritis, alopecia, hot flush, decreased hemoglobin, white blood cell, platelets, lymphocytes and neutrophils, increased glucose, cholesterol, aspartate transaminase (AST), alanine transaminase (ALT) and triglycerides, decreased albumin, potassium and increased creatinine. **PNET: ♦Very common (≥10%):** stomatitis, diarrhea, abdominal pain, nausea, vomiting, constipation, dry mouth, fatigue/malaise, oedema (general and peripheral), fever, asthenia, nasopharyngitis/rhinitis/upper respiratory tract infection, urinary tract infection, weight decreased, decreased appetite, diabetes mellitus, arthralgia, back pain, pain in

extremity, muscle spasms, headache/migraine, dysgeusia, dizziness, insomnia, cough/productive cough, epistaxis, dyspnea/dyspnea excertional, pneumonitis, oropharyngeal pain, rash, nail disorders, pruritus/pruritus generalised, dry skin/xeroderma, hypertension, decreased haemoglobin, lymphocytes, platelets, white blood cells and neutrophils, increased alanine phosphate, fasting glucose and cholesterol, decreased bicarbonate, increased aspartare transaminase (AST) and alanine transaminase (ALT), decreased phosphate, increased triglycerides, decreased calcium and potassium, increased creatinine, decreased sodium and albumin and increased bilirubin and potassium. **Non-Functional NET of Gastrointestinal or Lung Origin: ♦Very common (≥10%):** Stomatitis, diarrhea, nausea, vomiting, peripheral edema, fatigue, asthenia, pyrexia, infections, decreased weight, decreased appetite, dysgeusia, cough, dyspnea, pneumonitis, epistaxis, rash, pruritus, anemia, lymphopenia, leukopenia, thrombocytopenia, neutropenia, hypercholesterolemia, elevated AST, hyperglycemia (fasting), elevated ALT, hypophosphatemia, hypertriglyceridemia, hypokalemia and hypoalbuminemia. **RCC**: **♦Very common (≥10%):** stomatitis, diarrhea, nausea, vomiting, asthenia, fatigue, oedema peripheral, pyrexia, mucosal inflammation, cough, dyspnea, epistaxis, pneumonitis, rash, pruritis, dry skin, anorexia, headache, dysgeusia, pain in extremity. **TSC with renal angiomyolipoma: ♦Very common (≥10%):** stomatitis, vomiting, diarrhea, peripheral edema, upper respiratory tract infection, arthralgia, cough, acne. **TSC with SEGA: ♦Very common (≥10%):** stomatitis, vomiting, diarrhea, constipation, respiratory tract infection, gastroenteritis, pharyngitis streptococcal, pyrexia, fatigue, anxiety, aggression or other behavioral disturbance, rash, acne.