SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ADCO EVEROLIMUS 2,5 mg tablets

ADCO EVEROLIMUS 5 mg tablets

ADCO EVEROLIMUS 10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ADCO EVEROLIMUS 2,5 mg tablet: Each tablet contains 2,5 mg everolimus

ADCO EVEROLIMUS 5 mg tablet: Each tablet contains 5 mg everolimus

ADCO EVEROLIMUS 10 mg tablet: Each tablet contains 10 mg everolimus

Excipients with known effects

Contains sugar:

ADCO EVEROLIMUS 2,5 mg tablet: (74,3 mg lactose per tablet).

ADCO EVEROLIMUS 5 mg tablet: (148,5 mg lactose per tablet).

ADCO EVEROLIMUS 10 mg tablet: (297,0 mg lactose per tablet).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

ADCO EVEROLIMUS 2,5 mg: White to off-white, oval, biconvex tablets, debossed with E9VS on one side and 2,5 on the other side.

ADCO EVEROLIMUS 5 mg: White to off-white, oval, biconvex tablets, debossed with E9VS 5 on one side.

ADCO EVEROLIMUS 10 mg: White to off-white, oval, biconvex tablets, debossed with E9VS 10 on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ADCO EVEROLIMUS is indicated for:

- The palliative treatment of patients with advanced renal cell carcinoma, who failed prior treatment with vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFTR-TKI) therapy.
- The treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS).
- In combination with exemestane for palliative treatment of postmenopausal women with oestrogen receptor-positive, HER2/neu negative advanced breast cancer with recurrence or progression after prior treatment with a non-steroidal aromatase inhibitor.
- Treatment of patients with tuberous sclerosis complex (TSC) who have renal angiomyolipoma not requiring immediate surgery.

4.2 Posology and method of administration

Treatment with ADCO EVEROLIMUS should be initiated by a healthcare practitioner experienced in the use of anticancer therapies.

Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

Posology

General target population:

Adults

- Dosing in advanced renal cell carcinoma, advanced breast cancer and tuberous sclerosis complex (TSC) with renal angiomyolipoma.

The recommended dose of ADCO EVEROLIMUS is 10 mg, orally to be taken once daily.

Management of severe and/or intolerable suspected adverse reactions may require temporary dose reduction and/or interruption of ADCO EVEROLIMUS therapy. If dose reduction is required, the suggested dose is 5 mg orally to be taken once daily.

Moderate CYP3A4 or PgP inhibitors: Use caution when administered in combination with moderate CYP3A4 or PgP inhibitors. If patients require co-administration of a moderate CYP3A4 or PgP inhibitor, the dose should be reduced to 5 mg daily. Further dose reduction to 5 mg every other day or 2,5 mg daily may be required to manage adverse reactions (see **sections 4.4 and 4.5**).

If the moderate inhibitor is discontinued, a washout period of at least 2 to 3 days (average for most commonly used moderate inhibitors) should be allowed before the ADCO EVEROLIMUS dose increase. The ADCO EVEROLIMUS dose should be returned to the dose used prior to initiation of the moderate CYP3A4/PgP inhibitor (see **sections 4.4 and 4.5**).

Strong CYP3A4 inducers: Avoid the use of concomitant strong CYP3A4 inducers. If patients require co-administration of a strong CYP3A4 inducer, consider doubling the daily dose of ADCO EVEROLIMUS based on pharmacokinetic data, using 5 mg increments or less. This dose of ADCO EVEROLIMUS is predicted to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued, consider a washout period of at least 3 to 5 days (reasonable time for significant enzyme de-induction), before ADCO EVEROLIMUS dose is resumed to the dose used prior to initiation of the strong CYP3A4 inducer (see **sections 4.4 and 4.5**).

- Dosing in subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS):

Treatment with ADCO EVEROLIMUS should be initiated by a healthcare practitioner experienced in the treatment of patients with TS and with access to ADCO EVEROLIMUS therapeutic drug monitoring services. Therapeutic drug monitoring of ADCO EVEROLIMUS blood concentrations is required for patients treated for SEGA (see “Therapeutic Drug Monitoring” in the text below).

Titration may be required to obtain the optimal therapeutic effect. Doses that are tolerated and effective vary between patients. Concomitant antiepileptic therapy may affect the metabolism of everolimus, as in ADCO EVEROLIMUS, and may contribute to this variance (see **section 4.5**).

Table 1: Recommended starting dose of ADCO EVEROLIMUS for treatment of patients with SEGA:

Body surface area (BSA)	**Starting daily dose**
≤ 1,2 m^2	2,5 mg
1,3 – 2,1 m^2	5 mg
≥ 2,2 m^2	7,5 mg

Everolimus whole blood trough concentrations should be assessed approximately 2 weeks after commencing treatment. Dosing should be titrated to attain trough concentrations of 5 – 15 ng/mL. If concentrations are below 5 ng/mL, the daily dose may be increased by 2,5 mg every 2 weeks, subject to tolerability (see **section 5**).

SEGA volume should be evaluated approximately 3 months after commencing ADCO EVEROLIMUS therapy, with subsequent dose adjustments taking into consideration changes in SEGA volume, corresponding trough concentration, and tolerability (see **section 5**). Responses have been observed at trough concentrations as low as 2 ng/mL, as such, once acceptable efficacy has been achieved, additional dose increase may not be necessary.

Management of severe or intolerable adverse reactions may require temporary dose reduction and/or interruption of therapy (see **section 4.4**). If dose reduction is required for patients receiving 2,5 mg daily, alternate day dosing should be considered.

Moderate CYP3A4 or PgP inhibitors: Use caution when administered in combination with moderate CYP3A4 inhibitors or PgP inhibitors. If patients require co-administration of a moderate CYP3A4 or PgP inhibitor, reduce the daily dose by approximately 50 %. Further dose reduction may be required to manage adverse reaction (see **sections 4.4 and 4.5**). Everolimus trough concentrations should be assessed approximately 2 weeks after the addition of a moderate CYP3A4 or PgP inhibitor. If the moderate inhibitor is discontinued, the ADCO EVEROLIMUS dose should be returned to the dose used prior to initiation of the moderate CYP3A4 or PgP inhibitor and the everolimus trough concentration should be re-assessed approximately 2 weeks later (see **sections 4.4 and 4.5**).

Strong CYP3A4 inducers: Avoid the use of concomitant strong CYP3A4 inducers. Patients receiving concomitant strong CYP3A4 inducers (e.g. enzyme-inducing antiepileptic medicine) may require an increased ADCO EVEROLIMUS dose to attain trough concentrations of 5 ng/mL to 15 ng/mL.

If concentrations are below 5 ng/mL, the daily dose may be increased by 2,5 mg every 2 weeks, checking the trough level and assessing tolerability before increasing the dose. If the strong inducer is discontinued, the ADCO EVEROLIMUS dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer and the everolimus trough concentrations should be assessed approximately 2 weeks later (see **sections 4.4 and 4.5**).

Therapeutic drug monitoring for patients treated for SEGA

Therapeutic drug monitoring of everolimus blood concentrations is required for patients treated for SEGA using a validated bioanalytical LC/MS method. Trough concentrations should be assessed approximately 2 weeks after the initial dose, after any change in dose, or after an initiation or change in co-administration of CYP3A4 inducers or inhibitors (see **sections 4.4 and 4.5**). Dosing should be titrated with the objective of attaining everolimus trough concentrations of 5 to 15 ng/mL, subject to tolerability (see **section 5**).

Adverse drug reactions (ADRs)

Table 2 summarises recommendations for dose reduction, interruption or discontinuation of ADCO EVEROLIMUS in the management of ADRs. General management recommendations are also provided as applicable. Clinical judgement of the treating healthcare practitioner should guide the management plan of each patient based on individual benefit/risk assessment.

Table 2: ADCO EVEROLIMUS dose adjustment and management recommendations for ADRs

Adverse drug reaction	**Severity[1]**	**ADCO EVEROLIMUS dose adjustment[2] and management recommendations**
Non-infectious interstitial pneumonitis	Grade 1 Asymptomatic, radiographic findings only	No dose adjustment required. Initiate appropriate monitoring.
	Grade 2	Consider interruption of therapy, rule out infection and consider treatment

	Symptomatic, not interfering with ADL[3]	with corticosteroids until symptoms improve to Grade ≤ 1. Re-initiate ADCO EVEROLIMUS at a lower dose. Discontinue treatment if failure to recover within 4 weeks.
	Grade 3 Symptomatic interfering with ADL[3] O_2 indicated	Interrupt ADCO EVEROLIMUS until symptoms resolve to Grade ≤ 1. Rule out infection and consider treatment with corticosteroids. Consider re-initiating ADCO EVEROLIMUS at a lower dose. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4 Life-threatening, ventilatory support indicated	Discontinue ADCO EVEROLIMUS, rule out infection and consider treatment with corticosteroids.
Stomatitis	Grade 1 Minimal symptoms, normal diet	No dose adjustment required. Manage with non-alcoholic or salt water (0,9 %) mouth wash several times a day.
	Grade 2 Symptomatic but can eat and swallow modified diet	Temporary dose interruption until recovery to Grade ≤ 1. Re-initiate ADCO EVEROLIMUS at the same dose. If stomatitis recur at Grade 2, interrupt dose until recovery to Grade ≤ 1. Re-initiate ADCO EVEROLIMUS at a lower dose. Manage with topical analgesic mouth treatments (e.g. benzocaine, butyl amino benzoate, tetracaine hydrochloride, menthol or

		phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[4]
	Grade 3 Symptomatic and unable to adequately eat or hydrate orally	Temporary dose interruption until recovery to Grade ≤ 1. Re-initiate ADCO EVEROLIMUS at a lower dose. Manage with topical analgesic mouth treatments (e.g. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[4]
	Grade 4 Symptoms associated with life-threatening	Discontinue ADCO EVEROLIMUS and treat with appropriate medical therapy.
Severity grade description: 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms; 4 = life-threatening symptoms. If dose reduction is required, the suggested dose is approximately 50 % lower than the dose previously administered. Activities of daily living (ADL). Avoid using medicines containing alcohol, hydrogen peroxide, iodine and thyme derivatives in management of stomatitis as they may worsen mouth ulcers.		

Special populations

Elderly patients (≥ 65 years): No dose adjustment is required (see **section 5.2**).

Renal impairment: No dose adjustment is required (see **section 5.2**).

Hepatic impairment: *Hormone receptor-positive advanced breast cancer, advanced renal cell carcinoma and TSC with renal angiomyolipoma*

- Mild hepatic impairment (Child-Pugh A): the recommended dose is 7,5 mg daily.
- Moderate hepatic impairment (Child-Pugh B): the recommended dose is 5 mg daily; the dose may be decreased to 2,5 mg if not well tolerated.
- Severe hepatic impairment (Child-Pugh C): not recommended.
- Dose adjustments should be made if a patient's hepatic status (Child-Pugh) changes during treatment.
- Advanced renal cell carcinoma: the dose should be reduced to 5 mg daily.

SEGA: Moderate hepatic impairment (Child-Pugh B):

The dose should be reduced by approximately 50 % and titrate to trough concentrations of 5 to 15 ng/ml for patients with severe hepatic impairment (Child-Pugh class C): not recommended.

Paediatric population: The safety and efficacy of ADCO EVEROLIMUS in children aged 0 to 18 years have not been established. No data are available.

Method of administration

ADCO EVEROLIMUS should be administered orally once daily at the same time every day, either consistently with or consistently without food (see **section 5**).

ADCO EVEROLIMUS tablets should be swallowed whole with a glass of water. The tablets should not be chewed or crushed. For patients unable to swallow tablets, ADCO EVEROLIMUS tablet(s) should be dispersed completely in a glass of water (containing approximately 30 mL) by gently stirring, immediately prior to drinking. The glass should be rinsed with the same volume of water and the rinse completely swallowed to ensure the entire dose is administered.

4.3 Contraindications

- Hypersensitivity to everolimus, other rapamycin derivatives, or any of the other ingredients of ADCO EVEROLIMUS (see **section 6.1**).
- Concomitant use of live vaccines (see **section 4.5**).
- Pregnancy and lactation (see **section 4.6**).

4.4 Special warnings and precautions for use

Non-infectious pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives, including everolimus. Non-infectious pneumonitis (including interstitial lung disease) has been frequently reported in patients taking ADCO EVEROLIMUS (see **section 4.8**). Some cases were severe and a fatal outcome was observed. A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnoea, and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations. Opportunistic infections such as *Pneumocystis jirovecii (carinii)* pneumonia (PJP, PCP) should be ruled out in the differential diagnosis of non-infectious pneumonitis (see INFECTIONS). Patients should be advised to report promptly any new or worsening respiratory symptoms.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue ADCO EVEROLIMUS therapy without dose adjustments. If symptoms are moderate (Grade 2) or severe (Grade 3) the use of corticosteroids may be indicated until clinical symptoms resolve.

For patients who require use of corticosteroids for treatment of non-infectious pneumonitis, prophylaxis for *Pneumocystis jirovecii (carinii)* pneumonia (PJP, PCP) may be considered.

For cases of Grade 4 non-infectious interstitial pneumonitis, ADCO EVEROLIMUS should be discontinued.

Infections

Everolimus, as in ADCO EVEROLIMUS, has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoan infections, including infections with opportunistic pathogens (see **section 4.8**). Localised and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections such as aspergillosis, candidiasis or *Pneumocystis jirovecii (carinii)* pneumonia (PJP/PCP) and viral infections including reactivation of hepatitis B virus, have been described in patients taking ADCO EVEROLIMUS. Some of these infections have been severe (e.g. leading to sepsis, respiratory or hepatic failure) and occasionally fatal.

Healthcare providers and patients should be aware of the increased risk of infection with ADCO EVEROLIMUS. Pre-existing infections should be treated appropriately and should have resolved fully before starting treatment with ADCO EVEROLIMUS. While taking ADCO EVEROLIMUS, be vigilant for symptoms and signs of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of ADCO EVEROLIMUS.

If a diagnosis of invasive systemic fungal infection is made, the ADCO EVEROLIMUS treatment 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 medicines. Prophylaxis for PJP/PCP should be considered when concomitant use of corticosteroids or other immunosuppressive medicines are required.

Hypersensitivity reactions

Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnoea, flushing, chest pain or angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus (see **section 4.3**).

Concomitant use of angiotensin-converting enzyme (ACE) inhibitors

Patients taking concomitant ACE inhibitor (e.g. ramipril) therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see **section 4.5**).

Stomatitis

Stomatitis, including mouth ulcerations and oral mucositis, is the most commonly reported adverse reaction in patients treated with ADCO EVEROLIMUS (see **section 4.8**). Stomatitis mostly occurs within the first 8 weeks of treatment. A single-arm study in postmenopausal breast cancer patients treated with ADCO EVEROLIMUS plus exemestane suggested that an alcohol-free corticosteroid oral solution, administered as a mouthwash during the initial 8 weeks of treatment, may decrease the incidence and

severity of stomatitis (see **section 5.1**). 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. However, products containing alcohol, hydrogen peroxide, iodine and thyme derivatives should be avoided as they may exacerbate the condition. Monitoring for and treatment of fungal infection is recommended, especially in patients being treated with steroid-based medications. Antifungal medicines should not be used unless fungal infection has been diagnosed (see **section 4.5**).

Renal failure events

Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with ADCO EVEROLIMUS (see **section 4.8**). Renal function should be monitored particularly where patients have additional risk factors that may further impair renal function.

Laboratory tests and monitoring

Renal function

Elevations of serum creatinine, usually mild, and proteinuria have been reported (see **section 4.8**). Monitoring of renal function, including measurement of blood urea, urinary protein or serum creatinine, is recommended prior to the start of ADCO EVEROLIMUS therapy and periodically thereafter.

Blood glucose

Hyperglycaemia has been reported (see **section 4.8**). Monitoring of fasting serum glucose is recommended prior to the start of ADCO EVEROLIMUS therapy and periodically thereafter. More frequent monitoring is recommended when ADCO EVEROLIMUS is co-administered with other medicines that may induce hyperglycaemia. Optimal glycaemic control should be achieved before starting a patient on ADCO EVEROLIMUS.

Blood lipids

Dyslipidaemia (including hypercholesterolaemia and hypertriglyceridaemia) has been reported. Monitoring of blood cholesterol and triglycerides prior to the start of ADCO EVEROLIMUS therapy and periodically thereafter, as well as management with appropriate medical therapy, is recommended.

Haematological parameters

Decreased haemoglobin, lymphocytes, neutrophils and platelets have been reported (see **section 4.8**). Monitoring of complete blood count is recommended prior to the start of ADCO EVEROLIMUS therapy and periodically thereafter.

Functional carcinoid tumours

The safety and efficacy of ADCO EVEROLIMUS in patients with functional carcinoid tumours have not been established.

Interactions

Co-administration with inhibitors and inducers of CYP3A4 and/or the multidrug efflux pump PgP should be avoided. If co-administration of a moderate CYP3A4 and/or PgP inhibitor or inducer cannot be avoided, dose adjustments of ADCO EVEROLIMUS can be taken into consideration based on predicted AUC (see **section 4.5**).

Concomitant treatment with potent CYP3A4 inhibitors results in dramatically increased plasma concentrations of everolimus, as in ADCO EVEROLIMUS (see **section 4.5**). There are currently not sufficient data to allow dosing recommendations in this situation. Hence, concomitant treatment of ADCO EVEROLIMUS and potent inhibitors is not recommended.

Caution should be exercised when ADCO EVEROLIMUS is taken in combination with orally administered CYP3A4 substrates with a narrow therapeutic index due to the potential for interactions. If ADCO EVEROLIMUS is taken with orally administered CYP3A4 substrates with a narrow therapeutic index (e.g. pimozide, terfenadine, quinidine or ergot alkaloid derivatives), the patient should be monitored for undesirable effects described in the professional information of the orally administered CYP3A4 substrate (see **section 4.5**).

Hepatic impairment

Exposure to ADCO EVEROLIMUS was increased in patients with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment (see **section 5.2**).

ADCO EVEROLIMUS is not recommended for use in patients with severe hepatic impairment (Child-Pugh C) if the potential benefit outweighs the risk (see **section 4.2**).

No clinical safety or efficacy data are currently available to support dose adjustment recommendations for the management of adverse reactions in patients with hepatic impairment.

Vaccinations

The use of live vaccines is contraindicated during treatment with ADCO EVEROLIMUS and close contact with those who have received the live vaccinations should be avoided during treatment with ADCO EVEROLIMUS (see **section 4.5**).

Wound healing complications

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

Lactose warning

ADCO EVEROLIMUS contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary conditions of galactose intolerance, e.g. galactosaemia, total lactase deficiency or glucose-galactose malabsorption should not take ADCO EVEROLIMUS.

4.5 Interaction with other medicines and other forms of interaction

Everolimus, as in ADCO EVEROLIMUS, is a substrate of CYP3A4, and also a substrate and moderate inhibitor of PgP. Therefore, absorption and subsequent elimination of everolimus may be influenced by medicines that affect CYP3A4 and/or PgP. *In vitro*, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.

Known and theoretical interactions with selected inhibitors and inducers of CYP3A4 and PgP are listed in Table 3 below.

CYP3A4 and PgP inhibitors increasing ADCO EVEROLIMUS concentrations

Substances that are inhibitors of CYP3A4 or PgP may increase the blood concentrations of everolimus, as in ADCO EVEROLIMUS, by decreasing metabolism or the efflux of everolimus from intestinal cells.

CYP3A4 and PgP inducers decreasing ADCO EVEROLIMUS concentrations

Substances that are inducers of CYP3A4 or PgP may decrease the blood concentrations of everolimus, as in ADCO EVEROLIMUS, by increasing metabolism or the efflux of everolimus from intestinal cells.

Table 3: Effects of other active substances on ADCO EVEROLIMUS

Active substance by interaction	**Interaction – Change in ADCO EVEROLIMUS AUC/C_{max} Geometric mean ratio (observed range)**	**Recommendations concerning co-administration**
***Potent* CYP3A4/PgP inhibitors**		
Ketoconazole	AUC ↑ 15,3-fold (range 11,2 – 22,5) C_{max} ↑ 4,1-fold (range 2,6 – 7,0)	Concomitant treatment of ADCO EVEROLIMUS and potent inhibitors is not recommended.
Itraconazole, posaconazole, voriconazole	Not studied. Large increase in everolimus concentration is expected.	
Telithromycin, clarithromycin		
Nefazodone		
Ritonavir, atazanavir, saquinavir,		

darunavir, indinavir, nelfinavir		
Moderate CYP3A4/PgP inhibitors		
Erythromycin	AUC ↑ 4,4-fold (range 2,0 – 12,6) C_{max} ↑ 2,0-fold (range 0,9 – 3,5)	Use caution when co-administration of moderate CYP3A4 inhibitors or PgP inhibitors cannot be avoided. If patients require co-administration of a moderate CYP3A4 or PgP inhibitor, dose reduction to 5 mg daily or 2,5 mg daily may be considered. However, there are no clinical data with this dose adjustment. Due to between subject variability the recommended dose adjustments may not be optimal in all individuals, therefore close monitoring of side effects is recommended. If the moderate inhibitor is discontinued, consider a washout period of at least 2 to 3 days (average elimination time for most commonly used moderate inhibitors) before the ADCO EVEROLIMUS dose is returned to the dose used prior to initiation of the co-administration.
Imatinib	AUC ↑ 3,7-fold C_{max} ↑ 2,2-fold	
Verapamil	AUC ↑ 3,5-fold (range 2,2 – 6,3) C_{max} ↑ 2,3-fold (range 1,3 – 3,8)	
Ciclosporin oral	AUC ↑ 2,7-fold (range 1,5 – 4,7) C_{max} ↑ 1,8-fold (range 1,3 – 2,6)	
Fluconazole	Not studied. Increased exposure expected.	
Diltiazem		
Dronedarone	Not studied. Increased exposure expected.	
Amprenavir, fosamprenavir	Not studied. Increased exposure expected.	
Grapefruit juice or other food affecting CYP3A4/PgP	Not studied. Increased exposure expected (the effect varies widely).	Combination should be avoided.

***Potent and moderate* CYP3A4 inducers**		
Rifampicin	AUC ↓ 63 % (range 0 – 80 %) C_{max} ↓ 58 % (range 10 – 70 %)	Avoid the use of concomitant potent CYP3A4 inducers. If patients require co-administration of a potent CYP3A4 inducer, an ADCO EVEROLIMUS dose increase from 10 mg daily up to 20 mg daily should be considered using 5 mg increments or less applied on Day 4 and 8 following start of the inducer. This dose of ADCO EVEROLIMUS is predicted to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment. If treatment with the inducer is discontinued, consider a washout period of at least 3 to 5 days (reasonable time for significant enzyme de-induction), before the ADCO EVEROLIMUS dose is returned to the dose used prior to initiation of the co-administration.
Dexamethasone	Not studied. Decreased exposure expected.	
Carbamazepine, phenobarbital, phenytoin	Not studied. Decreased exposure expected.	
Efavirenz, nevirapine	Not studied. Decreased exposure expected.	
St John's wort (*Hypericum perforatum*)	Not studied. Large decrease in exposure expected.	Preparations containing St John's wort should not be used during treatment with ADCO EVEROLIMUS.

Medicine whose plasma concentration may be altered by ADCO EVEROLIMUS

Based on *in vitro* results, the systemic concentrations obtained after oral daily doses of 10 mg make inhibition of PgP, CYP3A4 and CYP2D6 unlikely. However, inhibition of CYP3A4 and PgP in the gut cannot be excluded. Co-administration of an oral dose of midazolam, a sensitive CYP3A substrate probe,

with ADCO EVEROLIMUS resulted in a 25 % increase in midazolam C_{max} and a 30 % increase in midazolam $AUC_{(0-\infty)}$. The effect is likely to be due to inhibition of intestinal CYP3A4 by ADCO EVEROLIMUS. Hence ADCO EVEROLIMUS may affect the bioavailability of orally co-administered CYP3A4 substrates. However, a clinically relevant effect on the exposure of systemically administered CYP3A4 substrates is not expected (**see section 4.4**).

Co-administration of ADCO EVEROLIMUS and depot octreotide increased octreotide C_{min} with a geometric mean ratio (everolimus/placebo) of 1,47.

Co-administration of ADCO EVEROLIMUS and exemestane increased exemestane C_{min} and C_{2h} by 45 % and 64 %, respectively. However, the corresponding estradiol levels at steady state (4 weeks) were not different between the two treatment arms. No increase in adverse events related to exemestane was observed in patients with hormone receptor-positive advanced breast cancer receiving the combination. The increase in exemestane levels is unlikely to have an impact on efficacy or safety.

Concomitant use of angiotensin-converting enzyme (ACE) inhibitors

Patients taking concomitant ACE inhibitor (e.g. ramipril) therapy may be at increased risk for angioedema (**see section 4.4**).

Vaccinations

The immune response to vaccination may be affected and, therefore, vaccination may be less effective during treatment with ADCO EVEROLIMUS. The use of live vaccines is contraindicated during treatment with ADCO EVEROLIMUS (**see section 4.4**). Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG (Bacillus Calmette-Guérin), yellow fever, varicella, and TY21a typhoid vaccines.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential must use a highly effective method of contraception (e.g. oral, injected, or implanted non-estrogen-containing hormonal method of birth control, progesterone-based

contraceptives, hysterectomy, tubal ligation, complete abstinence, barrier methods, intrauterine device [IUD], and/or female/male sterilisation) while receiving ADCO EVEROLIMUS, and for up to 8 weeks after ending treatment. Male patients should not be prohibited from attempting to father children.

Pregnancy

ADCO EVEROLIMUS should not be given to pregnant women (see **section 4.3**). Studies in animals have shown reproductive toxicity effects including embryotoxicity and fetotoxicity. The potential risk for humans is unknown.

ADCO EVEROLIMUS is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breastfeeding

It is not known whether ADCO EVEROLIMUS is excreted in human breast milk. Animal studies indicated that everolimus, as in ADCO EVEROLIMUS, and/or its metabolites readily pass into the milk. Therefore, women taking ADCO EVEROLIMUS should not breastfeed during treatment and for 2 weeks after the last dose.

Fertility

Based on non-clinical findings, male and female fertility may be compromised by treatment with ADCO EVEROLIMUS.

4.7 Effects on ability to drive and use machines

ADCO EVEROLIMUS may have a minor or moderate influence on the ability to drive a vehicle and use machines. Patients should be advised to be cautious when performing tasks that require their attention, until they know how they will react to ADCO EVEROLIMUS.

4.8 Undesirable effects

Infections and infestations*

Frequent: Pneumonia, urinary tract infection

Less frequent: Bronchitis, herpes zoster, sepsis, abscess, opportunistic infections [e.g. aspergillosis, candidiasis, *Pneumocystis jirovecii (carinii)* pneumonia (PJP, PCP), hepatitis B (**see section 4.4**)], viral myocarditis

Blood and lymphatic system disorders

Frequent: Anaemia, thrombocytopenia, neutropenia, leukopenia, lymphopenia

Less frequent: Pancytopenia, pure red cell aplasia

Immune system disorders

Less frequent: Hypersensitivity, angioedema

Metabolism and nutrition disorders

Frequent: Decreased appetite, hyperglycaemia, hypercholesterolaemia, hypertriglyceridaemia, hypophosphataemia, diabetes mellitus, hyperlipidaemia, hypokalaemia, dehydration, hypocalcaemia

Psychiatric disorders

Frequent: Insomnia

Nervous system disorders

Frequent: Dysgeusia, headache

Less frequent: Ageusia

Eye disorders

Frequent: Eyelid oedema

Less frequent: Conjunctivitis

Cardiac disorders

Less frequent: Congestive cardiac failure

Vascular disorders

Frequent: Haemorrhage[a], hypertension

Less frequent: Flushing, deep vein thrombosis

Respiratory, thoracic and mediastinal disorders

Frequent: Pneumonitis, interstitial lung disease, lung infiltration epistaxis, cough, dyspnoea

Less frequent: Haemoptysis, pulmonary embolism, acute respiratory distress syndrome, pulmonary alveolar haemorrhage, pulmonary toxicity, alveolitis

Gastrointestinal disorders

Frequent: Stomatitis, aphthous stomatitis, mouth, tongue ulceration, diarrhoea, nausea, vomiting, dry mouth, abdominal pain, mucosal inflammation, oral pain, dyspepsia, dysphagia

Less frequent: Glossodynia, glossitis

Hepato-biliary disorders

Frequent: Increased aspartate aminotransferase, increased alanine aminotransferase

Skin and subcutaneous tissue disorders

Frequent: Rash, pruritus, dry skin, nail disorders, mild alopecia, acne, erythema, onchoclasis, palmar-plantar erythrodysaesthesia syndrome, skin exfoliation, skin lesion

Musculoskeletal, connective tissue and bone disorders

Frequent: Arthralgia

Renal and urinary disorders

Frequent: Proteinuria*, increased blood creatinine, renal failure*

Less frequent: Increased daytime urination, acute renal failure*

Reproductive system and breast disorders

Frequent: Irregular menstruation[b]

Less frequent: Amenorrhoea[b]

General disorders and administration site conditions

Frequent: Fatigue, asthenia, peripheral oedema

Less frequent: Pyrexia, non-cardiac chest pain, impaired wound healing

Investigations

Frequent: Decreased body mass

* See also subsection "Description of selected side effects" below.

[a] Includes different bleeding events from different sites not listed individually.

[b] Frequency based upon number of women from 10 to 55 years of age in the pooled data.

Description of selected side effects

ADCO EVEROLIMUS may be associated with serious cases of hepatitis B reactivation, including fatal outcome. Reactivation of infection is an expected event during periods of immunosuppression.

ADCO EVEROLIMUS may be associated with renal failure events (including fatal outcome) and proteinuria. Monitoring of renal function is recommended (**see section 4.4**).

ADCO EVEROLIMUS may be associated with cases of amenorrhoea (secondary amenorrhoea and other menstrual irregularities).

ADCO EVEROLIMUS may be associated with cases of *Pneumocystis jirovecii (carinii)* pneumonia (PJP, PCP), some with fatal outcome (**see section 4.4**).

Angioedema has been reported with and without concomitant use of ADCO EVEROLIMUS in combination with ACE inhibitors (**see section 4.4**).

Discontinuation of ADCO EVEROLIMUS:

Elderly patients (≥ 65 years of age) had more adverse reactions, leading to discontinuation of ADCO EVEROLIMUS. The most frequently occurring side effects, leading to discontinuation of ADCO EVEROLIMUS were pneumonitis (including interstitial lung disease), stomatitis, fatigue and dyspnoea.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

Adverse reactions can also be reported to the Adcock Ingram Pharmacovigilance department by e-mail to Adcock.Aereports@adcock.com, fax to +27 86 553 0128 or call 011 635 0134.

4.9 Overdose

General asymptomatic and supportive measures should be initiated in all cases of overdose.

In overdose, side effects can be precipitated and/or be of increased severity (**see section 4.8**).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 26 Cytostatic medicines

Mechanism of action

Everolimus is a selective mTOR (mammalian target of rapamycin) inhibitor. mTOR is a key serine-threonine kinase, the activity of which is known to be upregulated in a number of human cancers.

Everolimus binds to the intracellular protein FKBP-12, forming a complex that inhibits mTOR complex-1 (mTORC1) activity. Inhibition of the mTORC1 signalling pathway interferes with the translation and synthesis of proteins by reducing the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4EBP-1) that regulate proteins involved in the cell cycle,

angiogenesis and glycolysis. S6K1 is thought to phosphorylate the activation function domain 1 of the oestrogen receptor, which is responsible for ligand-independent receptor activation. Everolimus reduces levels of vascular endothelial growth factor (VEGF), which potentiates tumour angiogenic processes. Everolimus is a potent inhibitor of the growth and proliferation of tumour cells, endothelial cells, fibroblasts and blood vessel-associated smooth muscle cells and has been shown to reduce glycolysis in solid tumours *in vitro* and *in vivo*.

5.2 Pharmacokinetic properties

Absorption

In patients with advanced solid tumours, peak everolimus concentrations are reached 1 to 2 hours after administration of an oral dose of 5 to 70 mg everolimus under fasting conditions or with a light fat-free snack. C_{max} is dose-proportional between 5 and 10 mg in the daily and weekly regimens. At doses of 20 mg/week and higher, the increase in C_{max} is less than dose-proportional, however AUC shows dose-proportionality over the 5 to 70 mg dose range.

Food effect

In healthy subjects, high fat meals reduced systemic exposure to everolimus 10 mg (as measured by AUC) by 22 % and the peak plasma concentration C_{max} by 54 %. Light fat meals reduced AUC by 32 % and C_{max} by 42 %. Food, however, had no apparent effect on the post absorption phase concentration time profile.

Distribution

The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 ng/mL to 5 000 ng/mL, is 17 % to 73 %. The amount of everolimus confined to the plasma is approximately 20 % at blood concentrations observed in cancer patients given everolimus 10 mg/day. Plasma protein binding is approximately 74 % both in healthy subjects and in patients with moderate hepatic impairment.

Following intravenous administration in a rat model, everolimus was shown to cross the blood-brain barrier in a non-linear dose-dependent manner, suggesting saturation of an efflux pump at the blood-brain barrier. Brain penetration of everolimus has also been demonstrated in rats receiving oral doses of everolimus.

Metabolism

Everolimus is a substrate of CYP3A4 and PgP. Following oral administration, everolimus is the main circulating component in human blood. Six main metabolites of everolimus have been detected in human blood, including three monohydroxylated metabolites, two hydrolytic ring-opened products, and a phosphatidylcholine conjugate of everolimus. These metabolites were also identified in animal species used in toxicity studies and showed approximately 100 times less activity than everolimus itself. Hence, everolimus is considered to contribute the majority of the overall pharmacological activity.

Elimination

No specific excretion studies have been undertaken in cancer patients, however, data are available from the transplantation setting. Following the administration of a single dose of radio labelled everolimus in conjunction with cyclosporine, 80 % of the radioactivity was recovered from the faeces, while 5 % was extracted in the urine. The parent substance was not detected in urine or faeces.

Steady-state pharmacokinetics

After daily or weekly administration of everolimus in patients with advanced solid tumours, steady-state $AUC_{0-\tau}$ was dose-proportional over the range of 5 mg to 10 mg in the daily dosing regimen and 5 mg to 70 mg on the weekly regimen. Steady-state was achieved within two weeks with the daily dosing regimen. C_{max} is dose-proportional between 5 mg and 10 mg on the daily and weekly regimens. At doses of 20 mg/week and higher, the increase in C_{max} is less than dose-proportional. T_{max} occurs at 1 to 2 hours post-dose. There was a significant correlation between $AUC_{0-\tau}$ and pre-dose trough concentration at steady-state on the daily regimen. The mean elimination half-life of everolimus is approximately 30 hours.

Special populations

Patients with hepatic impairment

The safety, tolerability and pharmacokinetics were evaluated in a single oral dose study of everolimus in 34 subjects with impaired hepatic function relative to subjects with normal hepatic function. Compared to normal subjects, there was a 1,6 fold, 3,3 fold and 3,6 fold increase in exposure (i.e. $AUC_{(0-inf)}$ for subjects with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment, respectively. Simulations of multiple dose pharmacokinetics supports the dosing recommendations in hepatic impaired patients based on their Child-Pugh status.

Dose adjustment is recommended for patients with hepatic impairment (**see sections 4.2** and **4.4**).

Patients with renal impairment

In a population pharmacokinetic analysis of 170 patients with advanced cancer, no significant influence of creatinine clearance (25 mL/min – 178 mL/min) was detected on CL/F of everolimus. Post-transplant renal impairment (creatinine clearance range 11 mL/min – 107 mL/min) did not affect the pharmacokinetics of everolimus in transplant patients.

Paediatric patients

Everolimus has not been studied in children with renal carcinoma.

- There is no indication for use of everolimus in the paediatric cancer population or in paediatric patients with tuberous sclerosis complex (TSC) who have renal angiomyolipoma in the absence of subependymal giant cell astrocytoma (SEGA) (**see section 4.2**).
- In patients with subependymal giant cell astrocytoma (SEGA), intra-patient steady-state trough concentration were dose-proportional at daily doses of 1,5 g to 14,6 mg/m^2 (**see section 4.2**).

Elderly patients

In a population pharmacokinetic evaluation in cancer patients, no significant influence of age (27 – 85 years) on oral clearance (CL/F: range 4,8 to 54,5 litres/hour) of everolimus was detected.

Ethnicity

Oral clearance (CL/F) is similar in Japanese and Caucasian cancer patients with similar liver functions. Based on analysis of population pharmacokinetics, oral clearance (CL/F) is on average 20 % higher in black transplant patients.

Exposure-response relationships

There was a moderate correlation between the decrease in the phosphorylation of 4E-BP1 (P4E-BP1) in tumour tissue and the average everolimus C_{min} at steady state in blood after daily administration of 5 mg or 10 mg everolimus.

Further data suggest that the inhibition of phosphorylation of the S6 kinase is very sensitive to the mTOR inhibition by everolimus. Inhibition of phosphorylation of eLF-4G was complete at all C_{min} values after the 10 mg daily dose.

In patients with SEGA, higher everolimus trough concentrations appear to be associated with larger reductions in SEGA volume. However, as responses have been observed at trough concentrations as low

as 2 ng/mL, once acceptable efficacy has been achieved, additional dose increase may not be necessary (see **section 4.2**).

A non-significant trend suggestive of longer progression-free survival with higher time-normalised exposure everolimus C_{min} was observed in patients with advanced carcinoid tumour (risk ratio 0,66; 95 % CI: 0,40 to 1058). Everolimus C_{min} impacted the possibility of tumour size reduction ($p < 0,001$) with the odds ratio of 1,62 and 1,46, respectively, for a change in exposure from 5 ng/mL to 10 ng/mL in patients with advanced carcinoid tumour.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Butylhydroxytoluene

Crospovidone

Hypromellose

Lactose

Lactose monohydrate

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf life: 24 months

The expiry date can be found on the blister strips and outer carton.

Store at or below 25 °C.

6.4 Special precautions for storage

Keep blister strips in outer carton until required for use in order to protect from light

6.5 Nature and contents of container

oPA/Al/PVC/Al blister strips packed into an outer carton.

Pack size: 30 tablets.

6.6 Special precautions for disposal and other handling

Any unused (including expired) product or waste material should be disposed of in accordance with local requirements.'

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road,

Erand Gardens,

Midrand 1685

Private Bag X69

Bryanston 2021

Telephone number

0860 ADCOCK (232625)

E-mail

info@adcock.com

Medical information e-mail

helpdesk.medinfo@adcock.com

8. REGISTRATION NUMBERS

EVERZOR 2,5 mg: 53/34/0489

EVERZOR 5 mg: 53/34/0490

EVERZOR 10 mg: 53/34/0491

ADCO EVEROLIMUS 2,5 mg: 53/34/0492.489

ADCO EVEROLIMUS 5 mg: 53/34/0493.490

ADCO EVEROLIMUS 10 mg: 53/34/0494.491

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 February 2021

10. DATE OF REVISION OF THE TEXT

29 April 2022