依维莫司片说明书

【药品名称】
通用名：依维莫司
商品名：Afinitor®
英文名：everolimus
依维莫司是一种口服的雷帕霉素(mTOR)抑制剂，是西罗莫司（sirolimus，又称雷帕霉素，即 rapamycin）的衍生物，故依维莫司又称 40-O-（2-羟乙基）-雷帕霉素，或 40-O-（2-羟乙基）-西罗莫司。

【开发与上市】
诺华公司(Novartis)开发，于 2009 年在美国首次上市。

【美 FDA 批准的适应症】

依维莫司是一种激酶抑制剂，适用于：

1） 舒尼替尼（sunitinib）或索拉非尼（sorafenib）治疗失败的晚期肾细胞癌。

2）需治疗但无法根治性手术切除的伴结节性硬化的室管膜下巨细胞星形细胞瘤(SEGA)。治疗 SEGA 的疗效是根据 SEGA 的体积改变来确定的。尚未证明本品可使 SEGA 患者临床获益（例如改善肿瘤相关症状、延长总生存时间）。

【用法用量】

1）晚期肾细胞癌：

每天一次，每次口服 10mg，与食物同服或不同服皆可。
中度肝功能损害患者，减量服用本品，每天一次，每次口服 5mg。
如需同时服用中度 CYP3A4 抑制剂或 P 糖蛋白抑制剂（如红霉素、氟康唑、维拉帕米），减量服用本品，每天一次，每次口服 2.5mg，如果患者能耐受，剂量可增至每次口服 5mg。
如需同时服用 CYP3A4 强诱导剂（如利福平、苯妥英），增量服用本品，每次增加 5mg，最大使用剂量可达每天一次，每次 20mg。

2）室管膜下巨细胞星形细胞瘤(SEGA)

初始剂量随着患者体表面积（BSA）的不同而不同（BSA 0.5 m2 ~1.2 m2，初始剂量 2.5 mg/天；BSA 1.3 m2 ~ 2.1 m2，5mg/天；BSA≥2.2 m2，7.5 mg/天），随后滴定剂量使血药谷浓度达到 5-10 ng/mL。

如需同时服用中度 CYP3A4 抑制剂或 P 糖蛋白抑制剂，大约减量 50%服用本

品。随后的剂量需根据血药浓度监测结果（TDM，therapeutic drug monitoring）来调整。

如需同时服用 CYP3A4 强诱导剂，加倍增量服用本品。随后的剂量需根据血药浓度监测结果（TDM）来调整。

处理药物不良反应时，可能需要减量服用本品，或中断本品治疗。

【性状】
本品为无划痕的 2.5 mg, 5 mg, 和 10 mg 的片剂。

【价格】 5mg, 30 片/盒，22000 元/盒；10mg, 30 片/盒，38000 元/盒；

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【禁忌症】
禁用于对本品、其它雷帕霉素衍生物或任何辅料过敏的患者。

【注意事项】

（1）非-感染性肺炎：监测临床症状或影象学改变; 曾发生致命性病例。减低本品剂量或停用本品直至症状缓解,可考虑使用皮质甾体激素。
（2）感染：本品可增加感染风险, 可能致命。监测体征和症状,及时治疗。
（3）口腔溃疡：口腔溃烂, 口内炎和口粘膜炎很常见。处理包括口腔冲洗(无酒精或过氧化物)和局部治疗。
（4）实验室检查的改变：可能发生血清肌酐，血糖，和血脂的升高。还可能发生血红蛋白，嗜中性粒细胞和血小板的减低。治疗前监测肾功能，血糖，血脂和血液学计数，并在治疗期间定期监测这些指标。
（5）免疫接种：避免接种活疫苗，避免密切接触曾接种活疫苗者。
（6）妊娠中使用：当给予妊娠妇女本品时可能危害胎儿。应告知妇女本品对胎儿的潜在危害。

【不良反应】

晚期肾细胞癌：最常见不良反应(发生率 ≥30%)是咽炎，感染，无力，疲乏，咳嗽和腹泻。

SEGA：最常见不良反应(发生率 ≥30%)是咽炎，上呼吸道感染，鼻窦炎、中耳炎和发热。

【药物相互作用】

依维莫司是 CYP3A4 的一种底物，而且也是多药流出泵 PgP 的一种底物和中度抑制剂。在体外，依维莫司是一种 CYP3A4 竞争性抑制剂和 CYP2D6 混合抑制剂。

7.1 可能增加本品血浓度的药物

CYP3A4 抑制剂和 PgP 抑制剂：在健康受试者中，当本品与以下药物同时给药时与单用本品治疗比较，本品浓度明显增加：
（1)酮康唑(一种强 CYP3A4 抑制剂和 PgP 抑制剂) - Cmax 和 AUC 分别增加 3.9-和 15.0-倍。
（2）红霉素(一种中度 CYP3A4 抑制剂和 PgP 抑制剂) - Cmax 和 AUC 分别增加 2.0-和 4.4-倍。
（3）维拉帕米(一种中度 CYP3A4 抑制剂和 PgP 抑制剂) - Cmax 和 AUC 分别增加 2.3-和 3.5-倍。

不应同时使用本品与 CYP3A4 强抑制剂[见警告和注意事项(5.5)]。

与中度 CYP3A4 或 PgP 抑制剂联用时慎用本品。如无替代治疗时，减低本品剂量[见剂量和给药方法(2.2)]。

7.2 可能减低本品血浓度的药物

CYP3A4 诱导剂：在健康受试者中，本品与利福平，一种 CYP3A4 强诱导剂，同时给药与单用本品比较分别减低本品的 AUC 和 Cmax 64%和 58%。当与 CYP3A4 或 PgP 强诱导剂同时给药时，如无替代治疗时，考虑增加本品剂量。St. John’s Wort 可能减低本品暴露，应避免使用[见剂量和给药方法(2.2)]。

7.3 可能改变本品的血浆浓度的药物

在健康受试者中研究表明，本品和 HMG-CoA 还原酶抑制剂阿伐他汀 [atorvastatin](一种 CYP3A4 底物)和普伐他丁 [pravastatin](一种非-CYP3A4 底物)间无临床上有意义的药代动力学相互作用，群体药代动力学分析也监测到辛伐他汀 [simvastatin](一种 CYP3A4 底物)对本品的清除率无影响。

FULL PRESCRIBING INFORMATION FROM FDA 2010：

1 INDICATIONS AND USAGE

1.1 Advanced Renal Cell Carcinoma (RCC)

AFINITOR® is indicated for the treatment of patients with advanced RCC after failure of treatment with sunitinib or sorafenib.

1.2 Subependymal Giant Cell Astrocytoma (SEGA)

AFINITOR® is indicated for the treatment of patients with SEGA associated with tuberous sclerosis (TS) 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 Clinical Studies (14.2)]. Clinical benefit such as improvement in disease-related symptoms or increase in overall survival has not been demonstrated.

2 DOSAGE AND ADMINISTRATION

Advanced RCC:
•10 mg once daily with or without food. (2.1)
•For patients with Child-Pugh class B hepatic impairment, reduce the AFINITOR dose to 5 mg once daily. (2.2)
•If moderate inhibitors of CYP3A4 and/or P-glycoprotein (PgP) are required, reduce the AFINITOR dose to 2.5 mg once daily; if tolerated, consider increasing to 5 mg once daily. (2.2)
•If strong inducers of CYP3A4 are required, increase AFINITOR dose in 5 mg increments to a maximum of 20 mg once daily. (2.2)

SEGA:
•Initial dose based on body surface area with subsequent titration to attain trough concentrations of 5-10 ng/mL. (2.3)
•If moderate inhibitors of CYP3A4 and/or PgP are required, reduce the AFINITOR dose by approximately 50%. Subsequent dosing should be based on therapeutic drug monitoring (TDM). (2.4)
•If strong inducers of CYP3A4 are required, double the AFINITOR dose. Subsequent dosing should be based on TDM. (2.4)

Dose reduction and/or treatment interruption may be needed to manage adverse drug reactions. (2.2, 2.4)

3 DOSAGE FORMS AND STRENGTHS
2.5 mg, 5 mg, and 10 mg tablets with no score.

4 CONTRAINDICATIONS
Hypersensitivity to everolimus, to other rapamycin derivatives, or to any of the excipients. (4)

5 WARNINGS AND PRECAUTIONS

•Non-infectious pneumonitis: Monitor for clinical symptoms or radiological changes; fatal cases have occurred. Manage by dose reduction or discontinuation until

symptoms resolve, and consider use of corticosteroids. (5.1)
•Infections: Increased risk of infections, some fatal. Monitor for signs and symptoms, and treat promptly. (5.2)
•Oral ulceration: Mouth ulcers, stomatitis, and oral mucositis are common. Management includes mouthwashes (without alcohol or peroxide) and topical treatments. (5.3)
•Laboratory test alterations: Elevations of serum creatinine, blood glucose, and lipids may occur. Decreases in hemoglobin, neutrophils, and platelets may also occur. Monitor renal function, blood glucose, lipids, and hematologic parameters prior to treatment and periodically thereafter. (5.4)
•Vaccinations: Avoid live vaccines and close contact with those who have received live vaccines. (5.7)
•Use in pregnancy: Fetal harm can occur when administered to a pregnant woman. Apprise women of potential harm to the fetus. (5.8, 8.1)

6 ADVERSE REACTIONS

Advanced RCC: Most common adverse reactions (incidence ≥30%) are stomatitis, infections, asthenia, fatigue, cough, and diarrhea. (6.1)
SEGA: Most common adverse reactions (incidence ≥30%) are stomatitis, upper respiratory tract infection, sinusitis, otitis media, and pyrexia. (6.2）

7 DRUG INTERACTIONS

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of the multidrug efflux pump PgP. In vitro, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.

7.1 Agents that may Increase Everolimus Blood Concentrations

CYP3A4 Inhibitors and PgP Inhibitors: In healthy subjects, compared to AFINITOR treatment alone there were significant increases in everolimus exposure when AFINITOR was coadministered with:
•ketoconazole (a strong CYP3A4 inhibitor and a PgP inhibitor) - Cmax and AUC increased by 3.9- and 15.0-fold, respectively.
•erythromycin (a moderate CYP3A4 inhibitor and a PgP inhibitor) - Cmax and AUC increased by 2.0- and 4.4-fold, respectively.
•verapamil (a moderate CYP3A4 inhibitor and a PgP inhibitor) - Cmax and AUC increased by 2.3- and 3.5-fold, respectively.

Concomitant strong inhibitors of CYP3A4 should not be used [see Dosage and Administration (2.2, 2.4) and Warnings and Precautions (5.5)].

Use caution when AFINITOR is used in combination with moderate CYP3A4 and/or PgP inhibitors. If alternative treatment cannot be administered reduce the AFINITOR dose [see Dosage and Administration (2.2, 2.4) and Warnings and Precautions (5.5)].

7.2 Agents that may Decrease Everolimus Blood Concentrations

CYP3A4 Inducers: In healthy subjects, co-administration of AFINITOR with rifampin, a strong inducer of CYP3A4, decreased everolimus AUC and Cmax by 63% and 58% respectively, compared to everolimus treatment alone. Consider a dose increase of AFINITOR when co-administered with strong CYP3A4 inducers if alternative treatment cannot be administered. St. John’s Wort may decrease everolimus exposure unpredictably and should be avoided [see Dosage and Administration (2.2, 2.4)].

7.3 Agents whose Plasma Concentrations may be Altered by Everolimus

Studies in healthy subjects indicate that there are no clinically significant pharmacokinetic interactions between AFINITOR and the HMG-CoA reductase inhibitors atorvastatin (a CYP3A4 substrate) and pravastatin (a non-CYP3A4 substrate) and population pharmacokinetic analyses also detected no influence of simvastatin (a CYP3A4 substrate) on the clearance of AFINITOR.