**PRIOR AUTHORIZATION POLICY**

**POLICY:**
Oncology – Afinitor® (everolimus tablets – Novartis)
Afinitor Disperz® (everolimus tablets for oral suspension – Novartis)

**TAC APPROVAL DATE:**
04/11/2018

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**OVERVIEW**
Afinitor, a kinase inhibitor, is indicated for the following conditions:¹

1) treatment of postmenopausal women with advanced hormone receptor-positive (HR+), human epidermal growth factor receptor 2 (HER2)-negative breast cancer (advanced HR+ breast cancer) in combination with exemestane, after failure of treatment with letrozole or anastrozole;

2) treatment of adult patients with progressive neuroendocrine tumors (NETs) of pancreatic origin (PNET) and adults with progressive, well-differentiated, non-functional NETs of gastrointestinal (GI) or lung origin that are unresectable, locally advanced or metastatic. **Limitation of Use:** Afinitor is not indicated for the treatment of patients with functional carcinoid tumors;

3) treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of treatment with Sutent® (sunitinib capsules) or Nexavar® (sorafenib tablets);

4) treatment of adult patients with renal angiomyolipoma and tuberous sclerosis complex (TSC) not requiring immediate surgery; and

5) treatment of adult patients with TSC who have subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected.¹

Afinitor Disperz is indicated for the treatment of adult and pediatric patients aged ≥ 1 years with TSC who have SEGA that requires therapeutic intervention but cannot be curatively resected.¹ Afinitor Disperz is also indicated for the adjunctive treatment of adult and pediatric patients aged ≥ 2 years with TSC-associated partial-onset seizures.

Afinitor inhibits mammalian target of rapamycin (mTOR), a serine-threonine kinase. The mTOR pathway is dysregulated in several human cancers. **Of note,** Zortress®, (everolimus tablets) is indicated in combination with other drugs for prophylaxis of organ rejection in adult patients undergoing kidney or liver transplant.² The tablet strengths and dosing is different for Zortress than with Afinitor.

**Guidelines**
Afinitor features prominently in the National Comprehensive Cancer Network (NCCN) guidelines for breast cancer, neuroendocrine tumors, kidney cancer, and many other uses.

**POLICY STATEMENT**
Prior authorization is recommended for prescription benefit coverage of Afinitor and Afinitor Disperz. All approvals are provided for 3 years in duration.

**Automation:** None.

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04/11/2018
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RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Afinitor or Afinitor Disperz is recommended in those who meet the following criteria:

FDA-Approved Indications

1. Breast Cancer. Approve for 3 years if the patient meets the following criteria (A, B, C, D, E, and F):
   A) The patient has recurrent, Stage IV, or metastatic breast cancer; AND
   B) The patient has tried anastrozole, letrozole, or tamoxifen; AND
   C) The patient meets ONE of the following conditions (i or ii):
      i. The patient is postmenopausal; OR
      ii. The patient is premenopausal or perimenopausal AND is receiving ovarian suppression/ablation with a gonadotropin-releasing hormone (GnRH) agonist (e.g., Lupron® [leuprolide], Trelstar® [triptorelin], Zoladex® [goserelin]), or has had surgical bilateral oophorectomy or ovarian irradiation;
   AND
   D) The patient meets ONE of the following conditions (i or ii):
      i. Patient has hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}] disease; OR
      ii. Patient has hormone receptor (HR)-negative disease with clinical characteristics predicting a HR+ tumor (e.g., long disease-free interval, limited sites of recurrence, indolent disease, older age), according to the prescribing physician;
   AND
   E) The patient meets ONE of the following conditions (i or ii):
      i. Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer AND Afinitor will be used in combination with exemestane; OR
      ii. Afinitor will be used in combination with Faslodex® (fulvestrant intramuscular) or tamoxifen;
   AND
   F) The patient has not had disease progression while on Afinitor.

The NCCN breast cancer guidelines (version 1.2018) recommend Afinitor be considered as endocrine therapy for the following uses:

1) In combination with exemestane for HR+, HER2-negative recurrent or Stage IV disease that has progressed while on or within 12 months of nonsteroidal aromatase inhibitor therapy (i.e., anastrozole, letrozole), or if the patient was treated with tamoxifen at any time in postmenopausal women who have had prior endocrine therapy within 1 year or in premenopausal women who have had prior endocrine therapy within 1 year and were treated with ovarian ablation/suppression (category 2A recommendation);

2) In combination with Faslodex or tamoxifen for postmenopausal women or for premenopausal women treated with ovarian ablation/suppression and who have had prior endocrine therapy within 1 year and who have recurrent or Stage IV disease with asymptomatic visceral disease characterized as HR+ or HR-negative with clinical characteristics predicting a HR+ tumor (category 2A). Examples of clinical characteristics that predict a HR+ tumor include long disease-free interval, limited sites of recurrence, indolent disease, older age. False-negative ER and/or PR determinations occur and there may be discordance between ER and/or PR determination between the primary and metastatic tumor(s). Premenopausal and postmenopausal women with HR+, HER2-positive tumors may receive the regimens listed in the guidelines for patients with HR+ and HER2-negative disease; and
3) In combination with Faslodex or tamoxifen for recurrent or Stage IV, HR+, HER2-negative disease in postmenopausal women who have been treated with prior endocrine therapy within 1 year or premenopausal women treated with ovarian ablation/suppression who have had prior endocrine therapy within 1 year.

Notes: If there is disease progression while on an Afinitor-containing regimen, there are no data to support another Afinitor regimen. Men with breast cancer should be treated similarly to postmenopausal women, except that use of an aromatase inhibitor is ineffective without concomitant suppression of testicular steroidogenesis.

In one Phase III trial (BOLERO-2 [Breast Cancer Trials of Oral Everolimus-2]), postmenopausal women with ER+, HER2-negative advanced breast cancer who had recurrence or progression during therapy with a nonsteroidal aromatase inhibitor (letrozole or anastrozole) in the adjuvant setting or to treat advanced disease (or both) were randomized to exemestane with or without Afinitor. Median progression-free survival (PFS), according to independent central radiological assessment, was 11.0 months with Afinitor plus exemestane vs. 4.1 months with placebo plus exemestane (hazard ratio [HR] 0.38; 95% confidence interval [CI]: 0.3, 0.5; P < 0.0001). Median overall survival (OS) was not statistically significantly improved with adding Afinitor to exemestane. Median OS in patients taking Afinitor plus exemestane was 31.0 months vs. 26.6 months with placebo plus exemestane (HR 0.89; 95% CI: 0.73, 1.10; P = 0.14). Based on the BOLERO-2 trial results of improved PFS, the NCCN panel recommends considering adding Afinitor to exemestane in women who fulfill the entry criteria for this trial (i.e., progressed within 12 months or progressed on nonsteroidal aromatase inhibitor).

In a recent open-label, single-arm, Phase II trial (BOLERO-4), postmenopausal women (n = 202) with HR+, HER2-negative, metastatic or locally advanced breast cancer received Afinitor plus letrozole as first-line endocrine therapy. Second-line therapy with Afinitor plus exemestane was offered at the investigator’s discretion in patients who progressed on the first-line regimen. The median follow-up was 29.5 months. Median investigator-assessed PFS was 22.0 months (95% CI: 18.1, 25.1) with Afinitor plus letrozole. Median OS was not reached. Fifty patients started second-line therapy and median PFS was 3.7 months. First-line endocrine therapy with Afinitor is not included in the NCCN guidelines, and further data are required from randomized trials that compare Afinitor plus letrozole with other first-line endocrine therapies.

2. Neuroendocrine Tumors (NETS), Advanced, Unresectable, or Metastatic. Approve for 3 years.

The NCCN neuroendocrine and adrenal tumors guideline (version 1.2018) recommendations for Afinitor in NETS of the GI tract, lung and thymus (these are carcinoid tumors) are as follows:

1) Consider for the management of locoregional (Stage IIIA/B) thymic disease with radiation after incomplete resection and/or positive margins or with or without radiation for locally unresectable disease (category 2A);

2) Consider for the management of locoregional bronchopulmonary disease as adjuvant therapy with or without radiation following resection of Stage IIIA intermediate grade (atypical) histology or with or without radiation for unresectable Stage IIIA or IIIB disease (use following resection is a category 2B recommendation, and use with radiation for unresectable low grade [typical] histology is a category 3 recommendation);

3) For the management of locoregional advanced bronchopulmonary/thymic disease and/or distant metastases, consider use in the following: patients with clinically significant tumor burden and low grade (typical) histology or evidence of progression, in patients with intermediate grade (atypical) histology;

4) If there is progression on first-line therapy (category 2A recommendations); and
5) As a single agent, for the management of progressive locoregional advanced disease of the GI tract and/or distant metastases. Regarding PNETs, the guidelines recommend Afinitor as a single agent for the management of progressive locoregional advanced disease and/or distant metastatic disease.

In one Phase III, double-blind, multicenter trial (RADIANT-4), adults with advanced, progressive well-differentiated, non-functional NETS of lung or GI origin were randomized to receive Afinitor (n = 205) or placebo (n = 97). Median PFS assessed by central radiological review, the primary endpoint, was 11.0 months (95% CI: 9.2, 13.3) in patients on Afinitor and 3.9 months (95% CI: 3.6, 7.4) in patients on placebo (HR for disease progression or death 0.48; 95% CI: 0.35, 0.67; P < 0.00001). The first pre-planned interim OS analysis results indicated there was not a statistically significant difference between Afinitor and placebo. Final OS results are pending.

3. Renal Cell Carcinoma (RCC), Advanced. Approve for 3 years if the patient meets ONE of the following criteria (A or B):
   A) Patient meets the following criteria (i and ii):
      i. Patient has RCC with predominant clear cell histology; AND
      ii. Patient has tried Inlyta (axitinib tablets), Votrient (pazopanib tablets), Sutent (sunitinib capsules), Cabometyx (cabozantinib tablets) or Nexavar (sorafenib tablets); OR
   B) Patient has RCC with non-clear cell histology.

The NCCN kidney cancer guidelines (version 3.2018) recommend Afinitor as a single agent (category 2A) or in combination with Lenvima® (lenvatinib tablets) [category 1] for patients with relapsed or Stage IV RCC as subsequent therapy for predominant clear cell histology. For non-clear cell histology, Afinitor as a single agent or in combination with Lenvima or Avastin® (bevacizumab intravenous) [in selected patients with advanced papillary RCC including hereditary leiomyomatosis and renal cell cancer{HLRCC}], are the systemic therapy options for relapse or Stage IV disease (category 2A). There are limited efficacy data with Afinitor in patients with RCC of non-clear cell histology.

4. Renal Angiomyolipoma and Tuberous Sclerosis Complex (TSC). Approve for 3 years.

5. Tuberous Sclerosis Complex (TSC) for the Treatment of Subependymal Giant Cell Astrocytoma (SEGA). Approve for 3 years if therapeutic intervention is required but SEGA cannot be curatively resected.


Other Uses with Supportive Evidence

7. Differentiated (i.e., papillary, follicular, and Hürthle cell) Thyroid Carcinoma. Approve for 3 years if refractory to radioactive iodine therapy.

The NCCN thyroid carcinoma guidelines (version 2.2017) state that Afinitor can be considered if clinical trials or other systemic therapies are not available or appropriate for treatment of progressive and/or symptomatic iodine-refractory unresectable recurrent or persistent locoregional disease or distant metastatic disease (category 2A). In one Phase II trial, patients with progressive metastatic or locally advanced radioactive iodine therapy refractory differentiated thyroid cancer (n = 28) received Afinitor. Median duration of follow-up was 38 months. In all, 61% of patients (n = 17/28) had stable...
disease as the best response. There were no complete responses (CRs) or partial responses (PRs). Estimated median PFS was 9 months (95% CI: 4, 14), and median OS was 18 months (95% CI: 7, 29). In one Phase II trial conducted in Korea, patients with thyroid cancer of any histology that was resistant to or not appropriate for radioactive iodine therapy received Afinitor. Sixteen patients had papillary histology, 8 patients had follicular histology, 9 patients had medullary histology, 6 patients had anaplastic histology, and 1 patient had poorly differentiated histology. The disease control rate (PR plus stable disease ≥ 12 weeks) was 81% (n = 31/38). Stable disease was reported in 76% of patients (n = 29/38). Median PFS was 47 weeks (95% CI: 14.9, 78.5).

8. **Endometrial Carcinoma.** Approve for 3 years if the patient meets the following criteria (A and B):
   A) Afinitor will be used in combination with letrozole; AND
   B) Patient has recurrent, metastatic, or high-risk disease.


   In one Phase II trial, Afinitor plus letrozole was given to women with recurrent endometrial cancer (n = 35) until progression, toxicity, or CR. These patients had been treated with up to two prior cytotoxic regimens. The primary end point was the clinical benefit rate (CBR), which was defined as CR, PR, or stable disease (≥ 16 weeks) by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.0 criteria. In all, 35 patients were evaluable for response. The CBR rate was 40% (n = 14/35). The objective response rate (ORR) was 32% of patients (n = 11/35) with nine CRs and two PRs. In one Phase II study, Afinitor demonstrated some single-agent activity in pretreated patients with recurrent endometrial carcinoma (n = 35). Of the 28 evaluable patients, 12 patients (43%) had not demonstrated disease progression at 8 weeks. There were no CRs or PRs noted. The confirmed CBR rate was 21% at 20 weeks of treatment. In another open-label Phase II study in patients with advanced or metastatic endometrial cancer refractory to one or two previous chemotherapies, Afinitor demonstrated some efficacy. Of the 44 patients, a total of four patients had PRs by 6 months. The median PFS and OS were 2.8 months and 8.1 months, respectively.

9. **Gastrointestinal Stromal Tumors (GIST).** Approve for 3 years if the patient meets the following criteria (A, B, C, and D):
   A) The patient has tried imatinib (Gleevec® tablets, generics); AND
   B) The patient has tried Sutent (sunitinib capsules); AND
   C) The patient has tried Stivarga® (regorafenib tablets); AND
   D) Afinitor will be used in combination with imatinib (Gleevec tablets, generics), Sutent, or Stivarga.

   The NCCN soft tissue sarcoma guidelines (version 2.2018) recommend Afinitor in combination with imatinib (Gleevec, generics), Sutent, or Stivarga for the treatment of GIST for disease progression after single-agent therapy with imatinib, Sutent, and Stivarga (category 2A). In one Phase I/II study, Afinitor in combination with imatinib was studied in patients with advanced GIST and progression on imatinib (n = 23) or progression on imatinib and Sutent or another tyrosine kinase inhibitor (n = 35). In patients with progression after imatinib only, median PFS was 1.9 months and median OS was 14.9 months.
10. **Hodgkin Lymphoma, Classical (nodular sclerosis, mixed cellularity, lymphocyte depleted, and lymphocyte-rich subtypes of Hodgkin lymphoma).** Approve for 3 years in adults ≥ 18 years of age with relapsed or refractory classical Hodgkin lymphoma.

The NCCN Hodgkin Lymphoma clinical practice guidelines (version 1.2018) recommend Afinitor as a subsequent systemic therapy option for treatment of classical Hodgkin lymphoma as a single agent for relapsed or refractory disease in patients aged ≥ 18 years (category 2A). Afinitor is also recommended in older adults (aged > 60 years) with classical Hodgkin lymphoma for palliative therapy as a single agent for relapsed or refractory disease (category 2A).

One Phase II study evaluated single-agent Afinitor in patients (n = 19) with heavily pretreated classical Hodgkin lymphoma. Patients had failed or were ineligible for stem cell transplant, and had failed a median of six previous therapies. The ORR was 47% (95% CI: 24%, 71%); eight patients achieved a PR and one patient achieved a CR. Median time to progression was 7.2 months, and four of the responders remained progression free at 12 months.

11. **Meningioma.** Approve for 3 years if the patient has recurrent or progressive disease.

The NCCN central nervous system cancers guidelines (version 1.2018) recommend Afinitor therapy as treatment for surgically inaccessible recurrent or progressive meningiomas when radiation is not possible (category 2B). In one Phase II trial patients (n = 17) with recurrent, progressive meningioma after treatment with surgical resection and local radiotherapy when appropriate, received Avastin (bevacizumab intravenous) and Afinitor. The best response was stable disease in 88% of patients (n = 15/17) with 6 patients having stable disease for >12 months. Overall median PFS was 22 months (95% CI: 4.5, 26.8).

12. **Osteosarcoma.** Approve for 3 years if the patient meets the following criteria (A and B):

A) Patient has tried chemotherapy for osteosarcoma; AND

B) Patient has relapsed/refractory or metastatic disease.

The NCCN bone cancer guidelines (version 2.2018) recommend Afinitor in combination with Nexavar as second-line therapy for relapsed/refractory or metastatic osteosarcoma (category 2A) and for dedifferentiated chondrosarcoma or high-grade undifferentiated pleomorphic sarcoma (category 2B). In one Phase II trial, patients with unresectable or relapsed high grade osteosarcoma (n = 38) who had progressed after standard treatment (i.e., methotrexate, cisplatin, and doxorubicin ± ifosfamide) received Nexavar plus Afinitor until disease progression or unacceptable toxicity. At 6 months, 45% of patients (n = 17/38; 95% CI: 28, 61) were progression free. Toxic effects led to dose reductions, or short interruptions, or both in 66% of patients (n = 25/38) and permanent discontinuation in two patients (5%).

13. **Perivascular Epitheloid Cell Tumors (PEComa), Recurrent Angiomyolipoma, Lymphangioleiomyomatosis.** Approve for 3 years.


14. **Thymomas and Thymic Carcinomas.** Approve for 3 years if the patient has tried chemotherapy (e.g., cisplatin plus doxorubicin, cisplatin plus etoposide, carboplatin plus paclitaxel).
The NCCN thymomas and thymic carcinomas guidelines (version 2.2018) recommend second-line single-agent therapy with Afinitor (category 2A). In one multicenter, open-label, Phase II trial, patients with advanced or recurrent thymomas and thymic carcinomas previously-treated with cisplatin-based chemotherapy received Afinitor until disease progression, unacceptable toxicity, or patient refusal. In the 50 patients enrolled, one patient had complete remission, five patients had a partial remission, and 21 patients had stable disease with a disease control rate of 88% (n = 22/50). With a median follow-up of 25.7 months, median PFS was 10.1 months and median OS was 25.7 months. This trial is ongoing.

15. Waldenström’s Macroglobulinemia/Lymphoplasmacytic Lymphoma (WM/LPL). Approve for 3 years in patients who meet the following criteria (A or B):

A) The patient has not responded to primary therapy (e.g., Velcade® [bortezomib intravenous or subcutaneous injection] with dexamethasone with or without Rituxan® [rituximab intravenous injection]; Treanda® [bendamustine intravenous] with Rituxan; Rituxan with cyclophosphamide and dexamethasone; Treanda; Velcade with or without Rituxan; Velcade with dexamethasone; Kyprolis® [carfilzomib intravenous injection] with Rituxan and dexamethasone; cyclophosphamide/ doxorubicin/vincristine/prednisone/Rituxan; Imbruvica® [ibrutinib capsules]; Rituxan; OR

B) The patient has progressive or relapsed disease.

The NCCN WM/LPL guidelines (version 1.2018) recommend use of single-agent Afinitor as one of the many non-stem cell toxic options for patients with previously-treated WM/LPL that does not respond to primary therapy or for progressive or relapsed disease (category 2A). In one Phase II study, patients (n = 60) with WM who had previously received therapy and had experienced relapse or were refractory to their last treatment received Afinitor. A total of 97% of patients had received prior Rituxan-based therapy, and 60% of patients had received alkylator-based therapy. In all 50% of patients (n = 30/60; 95% CI: 37%, 63%) achieved a partial remission; there were no complete remissions. An additional 23% of patients (n = 14/60) achieved a minimal response (MR) for an overall CBR of 73% (95% CI: 60%, 84%). The median time to response in patients who achieved partial remission was 2 months (range, 1 to 26 months); the median duration of response has not been reached in these patients. Median time to progression, PFS, and OS were 25 months (95% CI: 13, not reached [NR]), 21 months (95% CI: 12, 41), and median NR (95% CI: 46, NR), respectively. Grade 3 or higher toxicities were reported in 67% of patients. In one Phase II trial patients (n = 46) with relapsed or refractory WM received six cycles of the combination of Afinitor plus Rituxan or Afinitor with Velcade and Rituxan. Maintenance therapy with Afinitor continued until progression. In all, 78% of patients (n = 36/46) received full dose therapy with the three drugs. Of these 36, two patients had complete remission, and 89% of patients (n = 32/36) experienced at least a MR. In the 36 patients receiving full dose therapy, median PFS was 21 months (95% CI: 21, not estimable)

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Afinitor has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. Autosomal Dominant Polycystic Kidney Disease (ADPKD). In one 2-year Phase III study in patients (n = 433) with ADPKD, total kidney volume increased between baseline and 2 years by 230 mL and 301 mL in the Afinitor and placebo groups, respectively (P = 0.06). The mean decrement in the
estimated glomerular filtration rate after 24 months was 8.9 mL/min/1.73 m² of body surface area (BSA) vs. 7.7 mL/min/1.73 m² of BSA in the Afinitor and placebo groups, respectively (P = 0.015). Therefore, no significant benefit with Afinitor was observed. In another study, Afinitor 2.5 mg daily was added to octreotide 40 mg intramuscularly every 4 weeks and this was compared with octreotide monotherapy.31 Among the 44 patients, 29 patients had autosomal dominant polycystic liver disease (PCLD) and 15 patients had ADPKD. After 48 weeks of treatment, liver volume decreased by 3.5% in the monotherapy group, compared with 3.8% in the combination therapy group. Overall, the addition of Afinitor to octreotide does not increase liver volume and may reduce the effect of octreotide.

2. **Colorectal Cancer.** In one Phase II study in patients (n = 50) with refractory metastatic colorectal cancer, Afinitor plus Avastin had modest activity.32 In another Phase II study in patients refractory to other regimens, Afinitor did not confer meaningful efficacy using either weekly or daily dosing schedules.33 Additional studies are needed.

3. **Gastric Cancer.** In one Phase II study in patients (n = 54) with advanced gastric cancer who failed both fluoropyrimidine and platinum therapy, Afinitor demonstrated minimal clinical benefit with two patients achieving a PR.34 At a median follow-up of 8.7 months, the 4-month PFS was 18.4%, not fulfilling the primary hypothesis. In another Phase II study in patients (n = 53) with previously-treated metastatic gastric cancer, no CRs or PRs were obtained after treatment with Afinitor.35 Afinitor use in one Phase III study in patients (n = 656) with advanced gastric cancer that progressed after one or two regimens of systemic chemotherapy also did not significantly improve OS.36 The median OS was 5.4 months with Afinitor compared with 4.3 months on placebo. Median PFS was 1.7 months and 1.4 months for Afinitor and placebo, respectively. In one Phase II multicenter trial conducted in the US, patients with refractory metastatic gastric and esophagus adenocarcinomas received Afinitor.39 In all, 45 patients were evaluable (n = 21 gastric cancer, n = 11 esophageal cancer, and n = 13 gastroesophageal junction cancer). One patient had a PR and 39% of evaluable patients had stable disease for a disease control rate of 40%. Median OS was 3.4 months (95% CI: 2.7, 5.6) and PFS was 1.8 months (95% CI: 1.7, 2.2). The biomarker, pS6 in tumor samples was strongly correlated with better PFS and disease control rate.

4. **Glioblastoma.** In one Phase II study, the efficacy of Avastin plus Afinitor added to standard radiation therapy plus temozolomide in the first-line treatment of patients with glioblastoma was evaluated.41 The standard treatment approach includes surgical resection, concurrent radiation therapy and temozolomide, plus temozolomide maintenance that provide a median survival of 14.6 months and a 2-year survival of 26.5%. In this study, Avastin was initiated concurrently with standard radiation therapy plus temozolomide. Afinitor was begun after radiation therapy was complete and was administered in combination with Avastin until tumor progression occurred. Therefore, maintenance treatment with temozolomide, which has been part of the standard treatment regimen, was not used. The use of Avastin and Afinitor provided a PFS of 11.3 months (95% CI: 9.3, 13.1). The substitution of Afinitor for temozolomide in the maintenance phase of treatment was feasible and well-tolerated, but the role of Afinitor in treatment of glioblastoma remains unclear. Combining Avastin with temozolomide may have resulted in a more active regimen. In another Phase II study, Afinitor in combination with Iressa® (gefitinib tablets) failed to demonstrate a clinical benefit in patients with recurrent glioblastoma.42 In one Phase II trial, the combination of Afinitor with conventional temozolomide-based chemoradiotherapy was evaluated in newly diagnosed patients with glioblastoma multiforme.43 Afinitor was started 1 week before radiation and temozolomide, followed by adjuvant temozolomide, and continued until disease progression. In all, 100 patients were evaluable. At 12 months, OS was 64% and median time to progression was 6.4 months. Fourteen percent of patients
had grade 4 hematologic toxicities, and 12% of patients had at least one Grade 4 non-hematologic toxicity. There was one treatment-related death.

5. Hepatocellular Carcinoma (HCC). In one Phase I/II study in patients with advanced HCC (n = 28), Afinitor as a single agent was well-tolerated; however, the study did not meet the predefined criteria to proceed to the second stage of Phase II.44 Median PFS was 3.8 months. In another Phase III trial, Afinitor was compared with placebo in patients with advanced HCC (n = 546) who had discontinued Nexavar due to disease progression or drug intolerance.45 There was no significant difference in OS between the two treatments with deaths in 83.7% of patients (n = 303/362) in the Afinitor group and 82.1% of patients (151/184) in the placebo group (HR 1.05; 95% CI: 0.86, 1.27; P = 0.68). Median OS was 7.6 months with Afinitor and 7.3 months with placebo.

6. Metastatic Melanoma. In one Phase II study in patients with metastatic melanoma (n = 57), Afinitor (administered in combination with Avastin) demonstrated modest clinical benefit.46 Two other Phase II studies with Afinitor failed to show significantly improved efficacy when compared with other established therapies in patients with advanced or metastatic melanoma.47-48 One study was in the first-line setting with Afinitor, paclitaxel, and carboplatin; the other study used Afinitor in combination with temozolomide.

7. Non-Small Cell Lung Cancer (NSCLC). In one Phase II study (n = 62), the PR rate observed did not meet the prespecified response threshold to pursue further study of the combination of Iressa and Afinitor in patients with either treatment-naïve or previously-treated NSCLC.34 In another Phase II study (n = 28), docetaxel in combination with Afinitor as salvage therapy for advanced NSCLC only showed modest efficacy.35 The 6-month PFS was 5% and the median OS was 9.6 months. In another open-label Phase II study (n = 133), patients with advanced NSCLC that progressed after one or two previous chemotherapy regimens were randomized to receive Tarceva with or without Afinitor.40 The disease control rate at 3 months was 39.4% compared with 28.4% for combination therapy and Tarceva monotherapy, respectively. Median PFS was 2.9 months and 2 months, respectively (HR 0.769; 95% CI: 0.506, 1.167; P = 0.228). The combination therapy was not considered sufficiently efficacious per the predefined study criteria. Afinitor is recommended for patients with NETS of the lung, see Neuroendocrine Tumors, Advanced, Unresectable.

8. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES
1. Afinitor® tablets, Afinitor Disperz® tablets for oral suspension [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; April 2018.

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**Other References Utilized**


### HISTORY

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| Annual revision  | • Breast Cancer: Criteria were revised to add tamoxifen to drugs that have been tried.  
• Renal Cell Carcinoma: Advanced was added to the condition.  
• Osteosarcoma: New indication added.  
• Thymomas and Thymic Carcinomas: New indication added.  
• Conditions Not Recommended for Approval: Myelofibrosis, Primary or Postpolycythemia Vera/Postessential Thrombocythemia and Systemic Mastocytosis were removed. In this section, “adenocarcinoma” was added to the condition of Pancreatic Cancer. | 02/10/2016 |
| DEU revision     | New FDA-approved indication in adults with progressive, well-differentiated, non-functional neuroendocrine tumors of gastrointestinal or lung origin was added. Afinitor Disperz indication added; not a new indication. | 03/09/2016 |
| Selected revision| • Breast Cancer: Criteria were revised to delete the word “woman” since gender does not need to be specified. Now the criteria states “Patient is postmenopausal.” | 08/10/2016 |
| Annual revision  | • Neuroendocrine Tumors, Advanced, Unresectable: Metastatic was added to the condition.  
• Differentiated (i.e. papillary, follicular, and Hürthle cell) Thyroid Carcinoma: Added this condition.  
• Hodgkin Lymphoma, Classical: Added that the patients are ≥ 18 years of age.  
• Conditions Not Recommended for Approval: Non-Hodgkin Lymphoma was removed. | 03/08/2017 |
| Annual revision  | • Breast Cancer: Criteria were revised to add premenopausal or perimenopausal patients who are receiving ovarian suppression or ablation. Advanced disease was revised to say recurrent, Stage IV, or metastatic disease. Patients with HR-receptor-negative disease with clinical characteristics predicting a HR+ tumor was added as an option. Afinitor use in combination with Faslodex or tamoxifen was added. Afinitor in combination with exemestane continues to be an option in patient with HR+ and HER2-negative breast cancer. The patient has not had disease progression while on Afinitor was added to criteria.  
• Renal Cell Carcinoma, Advanced: Cabometyx was added to the list of agents tried before receiving Afinitor.  
• Tuberculous Sclerosis Complex (TSC) Associated Partial Onset Seizures: Added new FDA approved use.  
• Advanced Breast Cancer in Patients with HER2-negative Disease Already Started on Afinitor Therapy. This use was removed.  
• Endometrial Carcinoma: This condition was added.  
• Gastrointestinal Stromal Tumors: This condition was added.  
• Meningioma: This condition was added.  
• Conditions Not Recommended for Approval: Endometrial Carcinoma and Gastrointestinal Stromal Tumors were removed and added to Other Uses with Supportive Evidence. Chronic Lymphocytic Leukemia, Pancreatic Adenocarcinoma, and Small Cell Lung Cancer were removed. | 04/11/2018 |

TAC – Therapeutic Assessment Committee; DEU – Drug Evaluation Unit; HR+ – Hormone receptor positive; HR-negative – Hormone receptor negative; HER2 – Human epidermal growth factor 2; * For a further summary of criteria changes, refer to respective TAC minutes available at: [http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx](http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx).