



Australian Government  
Department of Health  
Therapeutic Goods Administration

# Australian Public Assessment Report for Everolimus

Proprietary Product Name: Afinitor

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

**31 October 2017**

**TGA** Health Safety  
Regulation

## About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
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- To report a problem with a medicine or medical device, please see the information on the TGA website <<https://www.tga.gov.au>>.

## About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Abbreviation	Meaning
5-HIAA	5-hydroxyindole acetic acid
ACPM	Advisory Committee on Prescription Medicines
AE	Adverse event
AJCC	American Joint Committee on Cancer
ALT	Alanine transaminase
AML	Angiomyolipoma
ASA	Australian Specific Annex
AST	Aspartate transaminase
BSC	Best supportive care
CgA	Chromogranin A
CHMP	Committee on Medicinal Products for Human Use
CMI	Consumer Medicines Information
C <sub>min</sub>	Minimum plasma concentration
CT	Computerised tomography
DCR	Disease control rate
DLP	Data lock point
EMA	European Medicines Agency
ENETS	European Neuroendocrine Tumor Society
EU	European Union
FACT-G	Functional Assessment of Cancer Therapy (General)
FDA	Food and Drugs Administration
GCP	Good Clinical Practice
GEP	Gastro-entero-pancreatic
HPF	High power microscopic fields
HR	Hazard ratio
ICH	International Conference on Harmonisation

Abbreviation	Meaning
IRC	Independent radiology review committee
LLOQ	Lower limit of quantification
MEN1	Multiple endocrine neoplasia type 1
MEN2	Multiple endocrine neoplasia type 2
MRI	Magnetic resonance imaging
mTORC1	Mammalian 'target of rapamycin' complex 1
NANETS	North American Neuroendocrine Society
NCCN	National Comprehensive Cancer Network
NET	Neuroendocrine tumour
NSE	Neuron-specific enolase
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
PI	Product Information
PK	Pharmacokinetic(s)
PT	Preferred Term
QoL	Quality of Life
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RMP	Risk Management Plan
SEGA	Subependymal giant cell astrocytoma
SOC	System Organ Class
SSA	Somatostatin analogue
TNM	Tumour, nodes and metastasis cancer staging system
TSC	Tuberous sclerosis complex

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Abbreviation	Meaning
US	United States
VIPoma	Vasoactive intestinal peptide secreting tumour
WHO	World Health Organization
$\gamma$ -GT	Gamma-glutamyltransferase

## I. Introduction to product submission

### Submission details

<i>Type of submission:</i>	Extension of indications
<i>Decision:</i>	Approved
<i>Date of decision:</i>	13 January 2017
<i>Date of entry onto ARTG</i>	20 January 2017
<i>Active ingredient:</i>	Everolimus
<i>Product name:</i>	Afinitor
<i>Sponsor's name and address:</i>	Novartis Pharmaceuticals Australia Pty Ltd 54 Waterloo Road North Ryde NSW 2113
<i>Dose forms:</i>	Uncoated tablet, and dispersible tablet
<i>Strengths:</i>	Uncoated tablet: 2.5 mg, 5 mg, and 10 mg Dispersible tablet: 2 mg, 3 mg, and 5 mg
<i>Container(s):</i>	Blister pack
<i>Pack size(s):</i>	Uncoated tablet: Packs of 30, 50, 60, 100, and 120 tablets Dispersible tablet: Packs of 30, 50, 60, 100, and 120 tablets
<i>Approved therapeutic use:</i>	<i>Afinitor is indicated for the treatment of progressive, unresectable or metastatic, well-differentiated, non-functional neuroendocrine tumours (NET) of gastrointestinal or lung origin in adults.</i>
<i>Route(s) of administration:</i>	Oral
<i>Dosage:</i>	<i>The recommended dose of Afinitor is 10 mg to be taken once daily.</i> See the 'Dosage and Administration' in the Product Information (PI) available as Attachment 1, for further information.
<i>ARTG numbers:</i>	177648, 154661, 174663, 200203, 200204 and 200205

### Product background

This AusPAR describes the application by the sponsor to extend the indications for Afinitor (everolimus) in the dose forms and strengths listed above for the following indication:

*'Afinitor is indicated for the treatment of progressive, unresectable or metastatic, well-differentiated, non-functional neuroendocrine tumours (NET) of gastrointestinal or lung origin.'*

This AusPAR also briefly describes the sponsor's update to the Clinical Trials section of the Product Information (PI) following submission of updated long-term clinical trial data for some indications previously approved by the TGA. These indications are as follows:

*'Afinitor is indicated for the treatment of:*

*Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not candidates for curative surgical resection.*

*Patients with tuberous sclerosis complex (TSC) who have renal angiomyolipoma not requiring immediate surgery.'*

## **Neuroendocrine tumours (NETs)**

NETs are neoplasms derived from peptide producing and amine producing cells of the neuroendocrine system with histological markers such as chromogranin A (CgA). NETs can arise in most organs but overall are rare malignancies, with an estimated annual incidence of approximately 5 cases per 100,000 of population. NETs usually occur sporadically but may be a feature of various inherited genetic syndromes such as multiple endocrine neoplasia types 1 and 2 (MEN1 and MEN2), von Hippel-Lindau disease, tuberous sclerosis complex and neurofibromatosis.

NET classification is complex, including classification based on anatomical site of origin, 'carcinoid' or 'non-carcinoid/pancreatic', well or poorly differentiated and functionality. Features such as the proliferative rate of the tumour and extent of local spread are shared by most classification systems. More than 50% of gastrointestinal (GI) NETs and 90% of lung NETs are non-functional (that is, not producing hormones).

### ***Staging and natural history***

Extent of disease is usually described using a tumour, nodes and metastasis (TNM) staging system such as those produced by the American Joint Committee on Cancer (AJCC). Separate staging systems are used for the various anatomical sites of primary tumour. The most common sites for metastases are regional liver nodes, the liver and bone.<sup>1</sup>

Approximately 50% of subjects have metastatic disease at the time of initial diagnosis. NETs typically express receptors for somatostatin, an endogenous hormone with inhibitory effects on a number of cellular functions.

Surgery for cure is limited to early stage localised disease.

### ***Other therapies***

For patients with poorly differentiated unresectable or metastatic disease, cytotoxic chemotherapy is used (for example, use of platinum-based regimens).

For subjects with unresectable or metastatic well-differentiated disease, established treatments include: the somatostatin analogues (SSA) octreotide and lanreotide; sunitinib; and everolimus.

The approved indications for these products in Australia are summarised below in Table 1. The indications are limited to NETs arising in certain anatomical locations. Sunitinib and everolimus are currently restricted for use in subjects with pancreatic NETs.

Octreotide as Sandostatin LAR (long-acting repeatable octreotide also by Novartis Pharmaceuticals Australia) was approved in 2012 for the *'treatment of patients with*

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<sup>1</sup> National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Neuroendocrine Tumours. Version 1.2015 (2014).



*progression of well-differentiated, advanced neuroendocrine tumours of the midgut or suspected midgut origin'.*

The rationale for this submission was that there are limited treatment options available for subjects with advanced NETs arising from sites other than the pancreas.

### **Drug class and mechanism of action**

Everolimus (Afinitor) is a 'kinase inhibitor', a signal transduction inhibitor selectively inhibiting mTORC1 (mammalian 'target of rapamycin' complex 1). Everolimus interrupts the mTORC1 signalling cascade and thereby inhibits cell growth, proliferation and tumour angiogenesis.

**Table 1. Drugs registered in Australia for the treatment of NETs**

Generic	Tradename	Approved indication
Octreotide	Sandostatin	For the relief of symptoms associated with the following functional tumours of the gastro-entero-pancreatic endocrine system: <ul style="list-style-type: none"> <li>• Carcinoid tumours with features of the carcinoid syndrome;</li> <li>• Vasoactive intestinal peptide secreting tumours (VIPomas).</li> </ul> Sandostatin is not curative in these patients.
	Sandostatin LAR (long acting repeatable octeotride depot)	Treatment of patients with progression of well-differentiated, advanced neuroendocrine tumours of the midgut or suspected midgut origin. For the relief of symptoms associated with the following functional tumours of the gastro-entero-pancreatic endocrine system: <ul style="list-style-type: none"> <li>• Carcinoid tumours with features of the carcinoid syndrome;</li> <li>• Vasoactive intestinal peptide secreting tumours (VIPomas) in patients who are adequately controlled on subcutaneous treatment with Sandostatin.</li> </ul> Sandostatin LAR is not curative in these patients.
Lanreotide acetate	Somatuline Autogel	For the treatment of gastroenteropancreatic neuroendocrine tumours (GEP-NETs) in adult patients with unresectable locally advanced or metastatic disease. For the treatment of symptoms of carcinoid syndrome associated with carcinoid tumours.
Sunitinib malate	Sutent	For the treatment of unresectable, well-differentiated pancreatic neuroendocrine tumours (pancreatic NET).
Everolimus	Afinitor	Progressive, unresectable or metastatic, well or moderately differentiated neuroendocrine tumours (NETs) of pancreatic origin.

## Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 06 July 2009.

At the time of this evaluation, everolimus 'Afinitor' was approved by the TGA for oncology use, for the treatment of:

- advanced renal cell carcinoma (RCC) (29 July 2009)
- advanced pancreatic NET (10 July 2012)
- advanced hormone receptor-positive breast cancer (21 February 2013)
- subependymal giant-cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) (16 January 2012)
- renal angiomyolipoma (AML) associated with TSC (19 August 2013).

TGA approval for *the treatment of progressive, unresectable or metastatic, well or moderately differentiated, NETs of pancreatic origin* was based on the results of a Phase III randomised placebo controlled trial (Study CRAD001C2324, also referred to as the RADIANT-3 trial). In the same application the sponsor also sought approval for the indication of treatment of NETs of gastrointestinal or lung origin, based on the results of another Phase III randomised trial of Afinitor plus depot octreotide (Sandostatin LAR) versus placebo plus depot octreotide (Study CRAD001C2325, also referred to as the RADIANT-2 trial). Statistical significance was not achieved for the primary endpoint of progression-free survival (PFS) evaluated by RECIST as per independent radiological review.

The Advisory Committee on Prescription Medicines (ACPM) considered the submission outlined above at Meeting 284 in 2012. The Delegate's issues included: *'Study C2325 raises some doubts regarding the efficacy of everolimus in the treatment of NETs originating at anatomical sites other than the pancreas. Given the substantial toxicity produced by the product, a favourable benefit-risk balance for this patient group cannot be concluded.'*

At the time, the ACPM considered Afinitor products to have an overall positive benefit-risk profile for the indication: *'The treatment of progressive, unresectable or metastatic, well or moderately differentiated, neuroendocrine tumours (NETs) of pancreatic origin.'*

The ACPM specifically advised on the inclusion of 'a statement in the appropriate sections of the PI and Consumer Medicines Information (CMI) to accurately reflect the lack of efficacy in NETs with the exception of pancreatic origin' as reflected under 'Clinical Trials' in the PI.<sup>2</sup>

The current application seeks approval for use in advanced non-functional NETs of GI or lung origin, based on the new Phase III randomised placebo-controlled trial RADIANT-4.

## Regulatory status overseas

Similar applications were filed in the European Union (EU) on 3 August 2015, in the United States on 27 August 2015, in Switzerland on the 23 September 2015, and in Canada on 9 August 2015.

In the US, the Food and Drugs Administration (FDA) approved Afinitor for the following comparable indication in February 2016:

*'Advanced neuroendocrine tumors (NET)*

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<sup>2</sup> Australian PI for Afinitor Everolimus Novartis Pharmaceuticals Australia Pty Ltd (current at the time of submission).

*Afinitor is indicated for the treatment of adult patients with progressive neuroendocrine tumors of pancreatic origin (PNET) with unresectable, locally advanced or metastatic disease.*

*Afinitor is indicated for the treatment of adult patients with progressive, well-differentiated, non-functional neuroendocrine tumors (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 tumors (see Clinical Studies).<sup>3</sup>*

In the EU, the European Medicines Agency (EMA) Committee on Medicinal Products for Human Use (CHMP) provided a positive opinion 28 April 2016.

Therapeutic indications now include:

*'Neuroendocrine tumours of pancreatic origin*

*Afinitor is indicated for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease.*

*Neuroendocrine tumours of gastrointestinal or lung origin*

*Afinitor is indicated for the treatment of unresectable or metastatic, well-differentiated (Grade 1 or Grade 2) non-functional neuroendocrine tumours of gastrointestinal or lung origin in adults with progressive disease'.<sup>4</sup>*

Of note, both FDA and EMA indications specify use in adult patients.

## Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

## II. Quality findings

### Introduction

The submission included new quality data but this was only updated pharmaceutical development data. This was provided as the '2.5 mg, 5 mg and 10 mg Tablets Clinical trial formulae'. This data details the formulations used in all everolimus clinical trials.

The extension of indications relates to Study CRAD001T2302 (the RADIANT-4 trial) in 302 patients with advanced NET of GI or lung origin. Study CRAD001T2302 (RADIANT-4) used 5 mg tablets only.

### Quality summary and conclusions

Study CRAD001T2302 (RADIANT-4) used 5 mg tablets as currently registered or pharmaceutically equivalent. The results of the study relate directly to Australian Afinitor tablets.

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<sup>3</sup> FDA Label for Afinitor (2016)

<sup>4</sup> EMA SPC for Afinitor tablets (2015)

### III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

### IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

#### Introduction

##### Clinical rationale

A NET can be defined as a tumour that forms from cells that release hormones into the blood in response to a signal from the nervous system.<sup>5</sup> NETs are a diverse collection of tumours that demonstrate varied clinical behaviour.<sup>6</sup> They can arise in most organs of the body.<sup>7</sup> Common sites include the gastrointestinal tract, lungs, pancreas and thymus. Other less common sites include the parathyroid, thyroid, adrenal and pituitary glands.<sup>8</sup>

NETs are rare malignancies with an estimated annual incidence of approximately 5 cases per 100,000 of population.<sup>9</sup>

There are currently a number of systems used to classify grade and stage NETs. Relevant documents include guidelines produced by the World Health Organisation (WHO)<sup>10</sup>; the European Neuroendocrine Tumour Society (ENETS)<sup>11</sup>; the North American Neuroendocrine Tumor Society (NANETS)<sup>12</sup>; and guidelines produced by the National Comprehensive Cancer Network (NCCN) in the United States. Guidelines generally classify NETs as either well differentiated or poorly differentiated. They are also graded as low grade (Grade 1), intermediate grade (Grade 2) or high grade (Grade 3) tumours on the basis of the rate of proliferation of cells in the tumour. Rate of proliferation is determined using the number of mitoses per 10 high power microscopic fields (HPF) or the percentage of cells expressing Ki-67, a nuclear protein that is a general marker of tumour proliferation.

A proportion of NETs express excessive amounts of hormones, resulting in distinct clinical syndromes. Examples include Zollinger-Ellison syndrome associated with excess production of gastrin (gastrinoma) and hypoglycaemia with excess insulin (insulinoma). Tumours that secrete excess amounts of vasoactive peptides such as serotonin can be associated with a distinct clinical syndrome known as 'carcinoid syndrome' which is characterised by flushing, diarrhoea and abdominal pain. Tumours producing excessive amounts of hormones are referred to as 'functioning' NETs whereas those not producing

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<sup>5</sup> National Cancer Institute (NCI), NCI Dictionary of Cancer Terms

<sup>6</sup> Bergsland E. The evolving landscape of neuroendocrine tumors. *Semin Oncol.* 2013; 40 (1): 4-22.

<sup>7</sup> Klimstra D et al. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. *Pancreas.* 2010; 39 (6): 707-12.

<sup>8</sup> National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Neuroendocrine Tumours. Version 1.2015 (2014).

<sup>9</sup> Yao J et al. One hundred years after 'carcinoid': epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol.* 2008; 26:3063-72.

<sup>10</sup> Rindi G et al (2010) Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In: Bosman FT, Carneiro F, Hruban RH et al (eds.) WHO classification of Tumours of the Digestive System. 4th rev. ed; Lyon: IARC Press.

<sup>11</sup> European Neuroendocrine Tumour Society (ENETS). Current Guidelines. (2016).

<sup>12</sup> North American Neuroendocrine Tumor Society (NANETS). NANETS 2010 Guidelines (2010).

excessive hormones are referred to as 'non-functioning' NETs. Functioning NETs may produce more than one hormone.

CgA is a protein contained in the secretory granules of neuroendocrine cells. Serum CgA levels can be used to monitor disease burden for both functioning and non-functioning NETs.<sup>13</sup> Another biomarker often overexpressed by NETs is neuron-specific enolase (NSE), a glycolytic enzyme found in neuronal and neuroendocrine tissues.<sup>14</sup> Other biomarkers include 5-hydroxyindole acetic acid (5-HIAA), the urinary breakdown product of serotonin and specific hormones associated with functioning tumours (for example, gastrin and insulin).

Extent of disease is usually described using TNM staging systems such as those produced by the AJCC.<sup>15</sup> Separate staging systems are used for the various anatomical sites of primary tumour. The most common sites for metastases are regional liver nodes, the liver and bone. Approximately 50% of subjects have metastatic disease at the time of initial diagnosis.

NETs typically express receptors for somatostatin, an endogenous hormone that has inhibitory effects on a number of cellular functions. These receptors provide a target for imaging of the disease through the use of radiolabelled SSAs (use of Octreoscan, for example). SSAs are also used in the treatment of these tumours.

NETs usually occur sporadically but may be a feature of various inherited genetic syndromes such as MEN1 and MEN2, von Hippel-Lindau disease, tuberous sclerosis complex and neurofibromatosis.<sup>8</sup>

### **Treatment**

Surgery is the treatment of choice for patients with resectable disease. For patients with poorly differentiated unresectable or metastatic disease, cytotoxic chemotherapy is used (use of platinum-based regimens, for example).

For subjects with unresectable or metastatic well-differentiated disease, established treatments include the following:

- somatostatin analogues (SSAs): octreotide (Sandostatin) and lanreotide (Somatuline);
- sunitinib;
- everolimus.

The approved indications for these products in Australia have been summarised above in Table 1. The indications for the various products are limited to NETs arising in certain anatomical locations. In particular sunitinib and everolimus are currently restricted for use in subjects with pancreatic NETs. The rationale for this submission was that there are limited treatment options available for subjects with advanced NETs arising from sites other than the pancreas.

Other registered agents that are used for well-differentiated NETs but do not have regulatory approval in Australia include interferon alpha 2b and various cytotoxic agents (examples include temozolomide, 5-fluorouracil, capecitabine and dacarbazine). Radionuclide therapy with radiolabelled SSAs (LuTate for example) is an experimental therapy that has shown promising results in these patients.<sup>8</sup>

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<sup>13</sup> Oberg K. The Management of Neuroendocrine Tumours: Current and Future Medical Therapy Options. Clin Oncol. 2012; 24: 282-293.

<sup>14</sup> Oberg K et al. Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012;23 Suppl 7: vii 124-30.

<sup>15</sup> Edge S et al. AJCC Cancer Staging Handbook. 7<sup>th</sup> edition (2010). New York. Springer.

## Guidance

The following EU guidelines which have been adopted by the TGA are considered relevant to the current submission:

- Guideline on the evaluation of anticancer medicinal products;<sup>16</sup>
- Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man. (Methodological consideration for using progression-free survival or disease-free survival in confirmatory trials);<sup>17</sup>
- Points to consider on application with 1. Meta-analyses; 2. One pivotal study.<sup>18</sup>

## Contents of the clinical dossier

The submission contained the following clinical information relevant to the proposed new indication:

- A single pivotal efficacy/safety study (Study CRAD001T2302, otherwise referred to as the RADIANT-4 study).
- A Clinical Overview, Summary of Clinical Pharmacology, Summary of Clinical Efficacy, and a Summary of Clinical Safety.
- Literature references

In support of the updates to the PI concerning tuberous sclerosis complex (TSC) studies, the submission included final study reports for 3 trials: M2301, M2302, and C2485. The submission also included summaries of efficacy and safety for these studies.

## Paediatric data

The submission did not include paediatric data. The sponsor has obtained waivers for paediatric data from both the FDA in the USA and the EMA in Europe. In the US the waiver appears to have been based on the fact that the drug had received orphan designation. In Europe it appears that the waiver was granted on the grounds that GEP NETs do not normally occur in children.

## Good clinical practice

The submission included one new trial to support the proposed new indication. The study report included an assurance that the trial was conducted in accordance with the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP) and with the ethical principles laid down by the Declaration of Helsinki.

## Pharmacokinetics

The pivotal study in GIT/lung NETs collected a very limited amount of pharmacokinetic (PK) data. These data are summarised below in Table 2. No significant new information was generated regarding the PK of everolimus.

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<sup>16</sup> EMA/CHMP/205/95/Rev.4; (2012): Guideline on the evaluation of anticancer medicinal products in man; European Medicines Agency.

<sup>17</sup> EMA/CHMP/27994/2008/Rev.1; (2012): Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man. Methodological consideration for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials; European Medicines Agency.

<sup>18</sup> CPMP/EWP/2330/99 (2001): Points to consider on application with 1. Meta-analyses; 2. One pivotal study; European Medicines Agency.

**Table 2. Summary of the PK data from the RADIANT-4 study**

Summary of PK data																														
Objectives	This was the pivotal efficacy study supporting the proposed new indication. One of the secondary objectives of the study was to determine the exposure of everolimus at the steady state pre-dose minimum plasma concentration ( $C_{min}$ ) at Cycle 2 (Day 29). Two of the exploratory objectives were to explore the relationship between $C_{min}$ and progression-free survival (PFS), and to explore the relationship between $C_{min}$ and safety endpoints.																													
Methodology	<p><i>Design:</i> Details of the study design, treatments and so on are given in Section 7: Clinical Efficacy of Attachment 2.</p> <p><i>PK sampling and analysis:</i> A single blood sample for PK analysis was collected on pre-dose on day 29 of the study (that is, Day 1 of Cycle 2). Whole blood everolimus concentrations were determined by a liquid chromatography mass spectrometry method. The lower limit of quantification (LLOQ) was 0.3 ng/mL.</p>																													
Study participants	<p><i>Enrolled:</i> Full details of study participants are summarised under Section 7: Clinical efficacy of Attachment 2.</p> <p><i>Analysed:</i> Only 51 subjects in the everolimus arm provided suitable samples that were analysed. 48 subjects were receiving 10 mg per day and 3 subjects were receiving 5 mg/day.</p>																													
PK results	<table border="1"> <thead> <tr> <th rowspan="2">Dose variable</th> <th colspan="2">Everolimus + BSC N= 202</th> </tr> <tr> <th>10 mg/day</th> <th>5 mg/day</th> </tr> </thead> <tbody> <tr> <td>Pre-dose concentration (ng/mL)</td> <td></td> <td></td> </tr> <tr> <td>n</td> <td>48</td> <td>3</td> </tr> <tr> <td>Mean (SD)</td> <td>16.382 (13.2767)</td> <td>4.700 (3.8396)</td> </tr> <tr> <td>CV% mean</td> <td>81.05</td> <td>81.69</td> </tr> <tr> <td>Geometric mean</td> <td>12.805</td> <td>3.730</td> </tr> <tr> <td>CV% Geometric mean</td> <td>79.08</td> <td>100.73</td> </tr> <tr> <td>Median</td> <td>12.600</td> <td>3.360</td> </tr> <tr> <td>Min-Max</td> <td>2.40 - 72.30</td> <td>1.71 - 9.03</td> </tr> </tbody> </table> <p>- Only valid blood samples are included.  - Geometric mean = <math>\exp(\text{mean}(\log \text{ transformed data}))</math>.  - CV% Geometric mean = <math>\sqrt{\exp(\text{variance for log transformed data}) - 1} * 100</math>.</p> <p>According to the sponsor, these data were consistent with values observed in previous studies for the everolimus 5 mg and 10 mg daily doses.</p>	Dose variable	Everolimus + BSC N= 202		10 mg/day	5 mg/day	Pre-dose concentration (ng/mL)			n	48	3	Mean (SD)	16.382 (13.2767)	4.700 (3.8396)	CV% mean	81.05	81.69	Geometric mean	12.805	3.730	CV% Geometric mean	79.08	100.73	Median	12.600	3.360	Min-Max	2.40 - 72.30	1.71 - 9.03
Dose variable	Everolimus + BSC N= 202																													
	10 mg/day	5 mg/day																												
Pre-dose concentration (ng/mL)																														
n	48	3																												
Mean (SD)	16.382 (13.2767)	4.700 (3.8396)																												
CV% mean	81.05	81.69																												
Geometric mean	12.805	3.730																												
CV% Geometric mean	79.08	100.73																												
Median	12.600	3.360																												
Min-Max	2.40 - 72.30	1.71 - 9.03																												
PK efficacy analyses	The relationship between PFS and $C_{min}$ was analysed using a Cox regression analysis. For a two-fold increase in $C_{min}$ there was a non-significant trend towards improved PFS (hazard ratio (HR) = 0.898; 95%CI: 0.586, 1.374). Another analysis indicated that a two-fold increase in $C_{min}$ was associated with an increased probability of a reduction in tumour size (Odds ratio (OR) = 1.58; 95% CI: 1.23, 2.04). There was no relationship demonstrated between $C_{min}$ and the change from baseline in tumour biomarkers.																													
PK safety analyses	The relationship between $C_{min}$ and time to first onset of 3 adverse events (AE) (stomatitis, non-infectious pneumonitis and infections) were explored. No relationship was demonstrated.																													

Summary of PK data									
	<p align="center"><b>Cox regression analysis of the relationship between time-normalized everolimus C<sub>min</sub> and risk of clinical notable adverse events</b></p> <table border="1"> <thead> <tr> <th>Adverse event</th> <th>Hazard ratio (95% CI)</th> </tr> </thead> <tbody> <tr> <td>Stomatitis</td> <td>1.010 (95% CI: 0.740, 1.380)</td> </tr> <tr> <td>Non-infectious pneumonitis</td> <td>1.468 (95% CI: 0.741, 2.908)</td> </tr> <tr> <td>Infections</td> <td>1.096 (95% CI: 0.774, 1.550)</td> </tr> </tbody> </table>	Adverse event	Hazard ratio (95% CI)	Stomatitis	1.010 (95% CI: 0.740, 1.380)	Non-infectious pneumonitis	1.468 (95% CI: 0.741, 2.908)	Infections	1.096 (95% CI: 0.774, 1.550)
Adverse event	Hazard ratio (95% CI)								
Stomatitis	1.010 (95% CI: 0.740, 1.380)								
Non-infectious pneumonitis	1.468 (95% CI: 0.741, 2.908)								
Infections	1.096 (95% CI: 0.774, 1.550)								
Evaluator's comments	The study design, conduct and analysis were satisfactory.								

## Pharmacodynamics

There were no new pharmacodynamic data in the submission.

## Dosage selection for the pivotal studies

The dosage of everolimus used in the pivotal study was 10 mg once daily. This dose had been associated with evidence of efficacy in previous Phase II and Phase III studies conducted in patients with NETs (for example, in the RADIANT-2 AND RADIANT-3 studies).

## Efficacy

### Studies providing efficacy data

One pivotal efficacy study, Study CRAD001T2302 (RADIANT-4) was submitted.

### Evaluator's conclusions on efficacy

#### *Neuroendocrine tumours*

Study CRAD001T2302 (RADIANT-4) was well designed and executed. The design of the study complied with the recommendations of the relevant EMA guidelines adopted by the TGA for anticancer agents.<sup>16,17</sup> The study demonstrated that compared to placebo, everolimus was associated with a significant reduction in the risk of experiencing a PFS event. The magnitude of the reduction was clinically significant with a prolongation of median PFS of approximately 7 months and an increase in the proportion of subjects alive and progression-free at 12 months from 28.1% to 44.4%. The efficacy benefit was apparent across most patient subgroups. The magnitude of the clinical benefit also appeared comparable to that seen with other agents that have been granted TGA approval for NETs in recent years on the basis of PFS as the primary endpoint as shown below in Table 3.



**Table 3. Recent TGA drug approvals for NETs and pivotal Phase III studies using PFS as primary endpoint**

Trial	Indication	Drug	Comparator	HR (95% CI)	Median PFS (months)		p-value
					Drug	Comparator	
PROMID <sup>(a)</sup>	NET: GIT (midgut)	Octreotide LAR	Placebo	0.34 (0.20, 0.59)	14.3	6.0	= 0.000072
CLARINET <sup>(b)</sup>	NET: GIT or pancreas	Lanreotide	Placebo	0.47 (0.30, 0.73)	NR	18.0	< 0.001
NCT0042859 7 <sup>(c)</sup>	NET: Pancreas	Sunitinib	Placebo	0.42 (0.26, 0.66)	11.4	5.5	< 0.001
RADIANT- 3 <sup>(d)</sup>	NET: Pancreas	Everolimus	Placebo	0.35 (0.27, 0.45)	11.0	4.6	< 0.0001
Radiant-4	NET: GIT or lung	Everolimus	Placebo	0.48 (0.35, 0.67)	11.01	3.91	< 0.001

a) Rinke A et al. Placebo Controlled, Double Blind, Prospective, Randomised Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors: A Report From the PROMID Study Group. *J Clin Oncol.* 2009; 27 (28): 4656-4663.

b) Caplin M et al. Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors. *N Engl J Med* 2014; 371:224-33.

c) Raymond E et al. Sunitinib Malate for the Treatment of Pancreatic Neuroendocrine Tumors. *N Engl J Med* 2011; 364:501-13.

d) Yao J et al. Everolimus for Advanced Pancreatic Neuroendocrine Tumors. *N Engl J Med* 2011; 364:514-23.

Everolimus treatment was also associated with a non-significant trend towards improved overall survival. The sponsor should be asked to provide a summary of any further analyses of overall survival that have been conducted. The drug did not have any significant effects on quality of life compared to placebo.

The submission for the new indication is based on a single pivotal study and the TGA has adopted an EMA guideline that deals with this situation. This guideline sets out certain 'prerequisites' that must be met for approval of such a submission. In the opinion of the clinical evaluator, the design and results of the pivotal study allow the conclusion that these prerequisites have been met.

Overall the evidence submitted to support the efficacy of everolimus for the new indication is considered acceptable.

### ***Tuberous sclerosis***

Data from the three TSC studies demonstrate that efficacy of everolimus is maintained and even improved with long-term use.

## Safety

Safety issues previously identified with everolimus include the following:

- Non-infectious pneumonitis/interstitial lung disease;
- Immunosuppression resulting in infections;
- Impaired wound healing;
- Hypersensitivity reactions;
- Angioedema when used in common with ACE inhibitors;
- Stomatitis/oral mucositis;
- Renal impairment;
- Hyperglycaemia;
- Dyslipidaemia;
- Haematological cytopaenias.

### Studies providing safety data

Study CRAD001T2302 (RADIANT-4) was the only study submitted in support of the new indication.

### Patient exposure

The safety analysis set consisted of 300 subjects: 202 treated with everolimus and 98 subjects treated with placebo. Details of duration of exposure are summarised below in Table 4. Duration of exposure to study drug was longer in the everolimus arm than in the placebo arm (median duration: 40.43 versus 19.64 weeks; patient-years of exposure: 180.7 versus 65.8). In the everolimus arm 137 subjects were treated for at least 24 weeks and 86 were treated for at least 48 weeks. Mean dose intensity was 79.4% in the everolimus arm and 96.2% in the placebo arm.

**Table 4. Study CRAD001T2302 (RADIANT-4) Duration of exposure**

Exposure variable	Everolimus + BSC N=202	Placebo + BSC N=98
Exposure categories (weeks) – n (%)		
<4	13 (6.4)	0
4 to <8	8 (4.0)	6 (6.1)
8 to <12	11 (5.4)	18 (18.4)
12 to <24	33 (16.3)	29 (29.6)
24 to <36	24 (11.9)	15 (15.3)
36 to <48	27 (13.4)	4 (4.1)
48 to <60	13 (6.4)	4 (4.1)
60 to <72	9 (4.5)	2 (2.0)
72 to <84	32 (15.8)	8 (8.2)
≥ 84	32 (15.8)	12 (12.2)
Duration of exposure (weeks)		
n	202	98
Mean	46.68	35.02
SD	32.498	32.690
Median	40.43	19.64
Minimum	0.7	4.0
Maximum	120.4	130.3
Total patient-year exposure <sup>1</sup>	180.7	65.8

- A patient is counted in only one exposure category.

<sup>1</sup> Total patient-year exposure is the sum of each patient's exposure in days divided by 365.25.

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## **Safety issues with the potential for major regulatory impact**

### ***Liver toxicity***

#### *Neuroendocrine tumours*

Elevations in aspartate transaminase (AST), alanine transaminase (ALT), gamma glutamyltransferase ( $\gamma$ -GT) and alkaline phosphatase and decreases in serum albumin occurred more commonly in the everolimus arm in the pivotal study. However, elevations in bilirubin occurred more commonly in the placebo arm.

There were two cases of hepatic failure in the everolimus arm versus none in the placebo arm. Due to hepatic metastases in both cases it is difficult to attribute these events to everolimus.

#### *TSC studies*

There were no cases of serious hepatic toxicity in the three TSC studies.

### ***Haematological toxicity***

#### *Neuroendocrine tumours*

Everolimus is known to be associated with an increased incidence of haematological cytopaenias. This was confirmed in the pivotal study with increased incidence of anaemia (22.3% versus 9.2%), thrombocytopenia (3.5% versus 1.0%) and neutropenia (2.5% versus 1.0%) in the everolimus arm. There was one report of pancytopenia in the everolimus arm and none in the placebo arm.

#### *TSC studies*

Cytopaenias were also observed in the three TSC studies.

### ***Serious skin reactions***

#### *Neuroendocrine tumours*

Everolimus is known to be associated with dermatological toxicity. In the pivotal study skin disorders occurred in 67.8% of everolimus-treated subjects and 27.6% of placebo-treated subjects. The most common events were rash and pruritus. Serious skin disorders occurred in 2.0% of subjects with everolimus (n = 4) versus no subject with placebo. The specific serious events reported were angioedema, drug eruption, hyperhidrosis and toxic skin eruption (Grade 2).

#### *TSC studies*

No serious skin reactions were reported in the TSC studies.

### ***Cardiovascular safety***

#### *Neuroendocrine tumours*

There was an increase in the incidence of cardiac disorders with everolimus in the pivotal study. The most common event was cardiac failure. Table 5 (shown below) lists vascular AEs (irrespective of relationship to study treatment) observed in the study by System Organ Class (SOC) and Preferred Term (PT). AEs of hypertension and hypotension occurred more frequently with everolimus. The other vascular events occurred with comparable frequency in the two study arms.

**Table 5. Study CRAD001T2302 (RADIANT-4) Vascular AEs by SOC and PT**

Primary system organ class Preferred term	Everolimus + BSC N=202		Placebo + BSC N=98	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
-Total	46 (22.8)	13 (6.4)	16 (16.3)	3 (3.1)
Hypertension	24 (11.9)	8 (4.0)	8 (8.2)	3 (3.1)
Hypotension	6 (3.0)	3 (1.5)	0 (0.0)	0 (0.0)
Hot flush	4 (2.0)	0 (0.0)	2 (2.0)	0 (0.0)
Flushing	3 (1.5)	0 (0.0)	4 (4.1)	0 (0.0)
Deep vein thrombosis	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Peripheral coldness	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Phlebitis	2 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)
Thrombosis	2 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)
Intermittent claudication	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
Intra-abdominal haematoma	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphoedema	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Peripheral embolism	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
Peripheral venous disease	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Phlebitis superficial	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Thrombophlebitis	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Vena cava thrombosis	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Aortic stenosis	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)

*TSC studies*

Some serious cardiovascular AEs were reported in Study M2302. Hypertension (n = 2) was the only event reported in more than 1 subject.

***Unwanted immunological events****Neuroendocrine tumours*

Hypersensitivity events (for example, anaphylaxis and angioedema) are known to occur with everolimus. In the pivotal study, there were 2 cases of angioedema reported, both in the everolimus arm. There were no reports of anaphylaxis.

*TSC studies*

There were no reports of serious immunological reactions in the TSC studies.

**Post-marketing data**

No post-marketing data was submitted.

**Evaluator's conclusions on safety*****Neuroendocrine tumours (GIT/Lung)***

Data from the pivotal study indicate that everolimus is associated with significant toxicity in subjects with advanced neuroendocrine tumours. Compared to placebo, everolimus was associated with a notably increased incidence of Grade 3 or 4 AEs (69.3% versus 28.6%) and serious AEs (42.1% versus 19.4%). Approximately an extra 20% of subjects had to discontinue study treatment due to AEs (29.2% versus 7.1%). Some of the increased incidence in AEs may have been due to the longer duration of treatment with everolimus and therefore longer duration of follow-up for AEs. Table 6 (shown below) presents a cross-trial comparison of the incidence of AEs in Studies 2324 and CRAD001T2302 (RADIANT-4). Study 2324 (RADIANT-3) was the pivotal study that led to TGA approval of everolimus for pancreatic NETs. Although there were differences in the design of the 2 studies, a notable increase in the incidence of AEs compared to placebo was observed in both trials.

**Table 6. Comparison of AE incidence in pivotal NET studies**

	<b>Study 2324<sup>(a)</sup> (Pancreatic NETs) versus placebo</b>	<b>Study CRAD001T2302 (GIT/Lung NETs) versus placebo</b>
Grade 3 or 4 AEs	59.8% versus 38.9%	69.3% versus 28.6%
Serious AEs	40.2% versus 24.6%	42.1% versus 19.4%
Discontinuation due to AEs	19.1% versus 5.9%	29.2% versus 7.1%

a) Data available from the AusPAR for this TGA approved indication.<sup>19</sup>

There were two deaths on treatment that were plausibly related to everolimus. However, the drug was associated with a trend towards improved overall survival.

The pattern of AEs observed in the pivotal study was generally consistent with that previously observed with the drug. No new safety issues were identified.

### ***Tuberous sclerosis***

Long term follow-up of subjects in the three TSC studies did not identify any novel safety issues. The incidence of AEs generally decreased over time.

## **First Round Benefit-Risk Assessment**

### **First round assessment of benefits**

The benefits of everolimus in the proposed usage are:

- A significant reduction in the risk of experiencing a PFS event (disease progression or death), with prolongation of median PFS by approximately 7 months.

### **First round assessment of risks**

The risks of everolimus in the proposed usage are:

- A range of adverse events, consistent with those previously documented for the drug.
- Although the drug produces a notable increase in the risk of significant AEs (Grade 3 or 4 AEs, serious AEs and so on) compared to placebo, the increase is of a similar magnitude to that observed when everolimus is used for the treatment of pancreatic NETs.

### **First round assessment of benefit-risk balance**

#### ***Neuroendocrine tumours***

The benefit-risk balance of everolimus given the proposed usage is favourable.

#### ***Tuberous sclerosis***

The benefit-risk balance of everolimus in the treatment of TSC with SEGA or angiomyolipoma remains favourable.

<sup>19</sup> Therapeutic Goods Administration. Australian Public Assessment Report for Everolimus (Afinitor). February 2013

## **First Round Recommendation Regarding Authorisation**

### **Neuroendocrine tumours**

It is recommended that the proposed new indication (NETs of gastrointestinal or lung origin) be approved. The wording of the indication proposed by the sponsor is considered acceptable.

### **Tuberous sclerosis**

The updated data on TSC with SEGA or angiomyolipoma supports continued registration of these indications.

## **Clinical Questions**

The clinical evaluator had the following clinical questions for the sponsor:

1. Please provide an assurance that the formulation of everolimus tablets used in Study CRAD001T2302 (RADIANT-4) was identical to that currently registered in Australia.
2. Please provide a summary of the results of any further analyses of overall survival conducted for Study CRAD001T2302 (RADIANT-4).

## **Second Round Evaluation of clinical data submitted in response to questions**

For details of the sponsor's responses and the evaluation of these responses please see Attachment 2.

## **Second Round Benefit-Risk Assessment**

### **Second round assessment of benefits**

After consideration of the responses to clinical questions, the benefits of everolimus in the proposed usage are unchanged from those identified in the first round assessment of benefits.

### **Second round assessment of risks**

No new clinical information was submitted in response to questions. Accordingly, the risks of everolimus are unchanged from those identified in the first round assessment of risks.

### **Second round assessment of benefit-risk balance**

The benefit-risk balance of everolimus, given the proposed usage, is favourable.

## **Second round recommendation regarding authorisation**

It is recommended that the proposed new indication (NETs of gastrointestinal or lung origin) be approved.

## V. Pharmacovigilance findings

### Risk management plan

The sponsor submitted a Risk Management Plan (RMP): EU-RMP Version 12.1 (Afinitor)/Version 11 (Votubia) dated 25 April 2016, with a data lock point (DLP) of 31 March 2015 and an Australian Specific Annex (ASA) Version 7.0 (dated 11 July 2016) which was reviewed by the RMP evaluator.<sup>20</sup>

### Safety specification

The summary of the ongoing safety concerns as specified by the sponsor is shown below in Table 7.

**Table 7. Summary of safety concerns as specified by the sponsor**

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none"> <li>Non-infectious pneumonitis</li> <li>Severe infections</li> <li>Hypersensitivity (anaphylactic reactions)</li> <li>Stomatitis</li> <li>Wound healing complications</li> <li>Increased creatinine/proteinuria/renal failure</li> <li>Hyperglycaemia/new onset diabetes mellitus</li> <li>Dyslipidaemia</li> <li>Hypophosphatemia</li> <li>Cardiac failure</li> <li>Cytopaenia</li> <li>Haemorrhages</li> <li>Thrombotic and embolic events</li> <li>Female fertility (including secondary amenorrhoea)</li> <li>Pre-existing infection (reactivation, aggravation, or exacerbation)</li> <li>Safety in patients with hepatic impairment</li> </ul>
Important potential risks	<ul style="list-style-type: none"> <li>Postnatal developmental toxicity</li> <li>Pregnant or breast-feeding women</li> <li>Intestinal obstruction/ileus</li> <li>Male infertility</li> <li>Pancreatitis</li> </ul>

<sup>20</sup> Votubia is an alternative tradename for everolimus approved and marketed in the EU and other overseas regions.

Summary of safety concerns	
	<p>Cholelithiasis</p> <p>Muscle wasting/muscle loss</p>
Important identified interactions	<p>Strong CYP3A4 inhibitors and PgP inhibitors</p> <p>Moderate CYP3A4 inhibitors and PgP inhibitor</p> <p>Strong CYP3A4 inducers and PgP inducers</p> <p>CYP3A4 substrates and PgP substrates</p> <p>Increased risk for angioedema when combining mTOR inhibitors and ACE inhibitors</p>
Important potential interactions	<p>Everolimus with concomitant exemestane use (Oncology setting only)</p>
Missing information	<p>Off-label use in paediatric and adolescent patients</p> <p>Patients with renal impairment (Oncology setting only)</p> <p>Patients with CNS metastases (Oncology setting only)</p> <p>Patients with uncontrolled cardiac disease (Oncology setting only)</p> <p>Patients with impairment of GI function (Oncology setting only)</p> <p>Long term safety</p> <p>Onset of benign or malignant tumours</p> <p>Effects of everolimus on brain growth and development, particularly in patients under 3 years of age (TSC/SEGA setting only)</p> <p>Comparative safety of everolimus and exemestane therapy versus everolimus monotherapy (Oncology setting only)</p> <p>Safety in breast cancer patients pre-treated with cytotoxic therapies (Oncology setting only)</p>

### Pharmacovigilance plan

There are no new proposed additional pharmacovigilance activities; however ongoing additional pharmacovigilance activities are listed in Table 8 below. These include studies from which long term safety will be analysed and a patient registry (for TSC, not oncology patients).



**Table 8. Ongoing additional pharmacovigilance activities**

Study	Status	Inclusion of Australian patients	Protocol
<p>Disease registry/Study CRAD001MIC03</p> <p>An international disease registry collecting data on manifestations, interventions, and outcomes in patients with TSC (TOSCA).</p>	<p>CSR Disease registry: Q4 2017</p> <p>CSR Pass: Q4 2027</p>	Yes	Final
<p>Clinical Study CRAD001J2301</p> <p>A randomised, Phase III, double blind, placebo controlled multicentre trial of everolimus in combination with trastuzumab and paclitaxel as first line therapy in women with HER2 positive locally advanced or metastatic breast cancer.</p>	CSR: Q4 2016	Yes	Final
<p>Clinical Study CRAD001W2301</p> <p>A randomised, Phase III, double blind, placebo controlled multicentre trial of daily everolimus in combination with trastuzumab and vinorelbine, in pre-treated women with HER2/neu over-expressing locally advanced or metastatic breast cancer.</p>	CSR: Q4 2016	Yes	Final
<p>Clinical Study CRAD001Y2201</p> <p>A 3 arm randomised Phase II study investigating the combination of everolimus with exemestane versus everolimus alone versus capecitabine in patients with oestrogen receptor positive metastatic breast cancer after recurrence or progression on letrozole or anastrozole.</p>	CSR: Q3 2017	Yes	Final
<p>Statistical analysis/formal amenorrhoea analysis across the 3 TSC studies (Studies CRAD001C2485, CRAD001M2301, and CRAD001M2302) after study completion.</p>	Final Report: Q3 2015	Yes	Final

Study	Status	Inclusion of Australian patients	Protocol
Clinical Study CRAD001M2305 Long-term follow-up study to monitor for growth and development of paediatric patients previously treated with everolimus in Study CRAD001M2301.	Ongoing: Final CSR 2025	Yes	Final

### Risk minimisation activities

The sponsor states that no additional risk minimisation activities are planned.

### Reconciliation of issues outlined in the RMP report

Table 9 below summarises recommendations following the first round evaluation of the RMP, the sponsor's responses to issues raised and the RMP evaluation of the sponsor's responses.

**Table 9. Summary of the first round RMP recommendations with sponsor's responses and RMP evaluator's comments**

Summary of first round RMP recommendations with sponsor's responses and RMP evaluator's comments
<b>TGA recommendation 1:</b> Study CRAD001M2302 should be removed from the listed ongoing additional pharmacovigilance activities
<i>Sponsor's response:</i> The completed Study CRAD001M2302, has been removed from the list of ongoing pharmacovigilance activities in the most current EMA approved EU RMP version 12.1/11. The ASA version 7.0 has been updated to align with EU RMP version 12.1/11 and consequently, Study CRAD001M2302 has also been removed from the list of ongoing safety concerns in ASA version 7.0.
<b>RMP evaluator comment:</b> The ongoing pharmacovigilance activities have been updated in the RMP documents. The sponsor's response is acceptable.
<b>TGA recommendation 2:</b> The sponsor should append the targeted follow up questionnaires to the ASA.
<i>Sponsor's response:</i> The targeted follow-up questionnaires included in annex 7 of the EU RMP have also been attached to the ASA version 7.0. The reference to these questionnaires in the ASA version 7.0, has been updated to reference these questionnaires as an attachment to the ASA.
<b>RMP Evaluator comment:</b> The follow-up questionnaires are attached to the ASA. The sponsor's response is acceptable.
<b>TGA recommendation 3:</b> Product information document be revised to reflect the proposed indication for 'treatment of NET of GI and lung origin' in 'Dosage and

### Summary of first round RMP recommendations with sponsor's responses and RMP evaluator's comments

administration'.

*Sponsor's response:* No comment made.

**RMP Evaluator comment:** The PI has been updated appropriately in response to similar comments made by the clinical evaluator. The PI has been appended to the ASA document which is considered unnecessary by the evaluator. The sponsor is requested to remove this from subsequent revisions.

### Summary of recommendations

It is considered that the sponsor's response to TGA recommendations has adequately addressed all of the issues identified in the RMP evaluation report.

### Suggested wording for conditions of registration

The suggested wording is for the RMP/ASA is as follows:

- Implement European Union RMP Version 12.1 (Afinitor)/11 (Votubia) (dated 25 April 2016, DLP 31 March 2015) and Australian Specific Annex Version 7.0 (dated 11 July 2016) and any future updates as a condition of registration.

## VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

### Quality

Quality data provided with this submission detailed the tablet formulations for batches used in clinical studies.

The quality evaluator's recommendation was:

*'Study T2302 used 5 mg tablets as currently registered or pharmaceutically equivalent. The results of the Study relate directly to Australian Afinitor tablets.'*

### Recommended conditions of registration for quality issues

The quality evaluator did not raise any questions and no change was recommended.

### Nonclinical

No nonclinical data were included with this submission. There was no requirement for a nonclinical evaluation in a submission of this type.

### Clinical

There was a single pivotal study, Study CRAD001T2302 (RADIANT-4). The study overview is shown below in Table 10.

**Table 10. Study CRAD001T2302 (RADIANT-4) overview**

Study no.	Design	Population	Patients and treatments	Treatment duration	Endpoints
T2302 97 centers 25 countries	Multicenter, double-blind, randomized (2:1), parallel-group, Phase III Efficacy and safety	Patients with histologically-confirmed advanced (nonresectable or metastatic) low or intermediate grade non-functional NET of GI or lung origin (with measurable disease at baseline whose disease had progressed within the 6 months prior to randomization)	Total: 302 Everolimus 10 mg/day plus BSC (n=205) Placebo plus BSC (n=97)	Until disease progression, unacceptable toxicity or death, or withdrawal of consent	<i>Primary:</i> PFS <i>Key secondary:</i> OS <i>Other secondary:</i> safety and tolerability, ORR/DCR, QoL, biomarkers, WHO PS score

BSC Best supportive care; DCR Disease control rate; GI Gastrointestinal; NET Neuroendocrine tumor; ORR Objective response rate; OS Overall survival; PFS Progression-free survival; QoL Quality of life; WHO PS World Health Organization performance status

## Pharmacology

The pivotal study in GIT/lung NETs collected a very limited amount of PK data. See Attachment 2 for further details. No significant new information was generated regarding the PK of everolimus.

## Efficacy (neuroendocrine tumours)

Study T2302 was a randomised, double blind, placebo controlled Phase III study with 2 parallel groups (everolimus plus best supportive care (BSC), n = 205 versus placebo plus BSC, n = 97). The study schema is provided in Attachment 2. At the time of data cut-off the median duration of follow-up was 21.3 months. The evaluator considered that the study was well designed and executed.

## Inclusion and exclusion criteria

Subjects had pathologically confirmed, well differentiated advanced (unresectable or metastatic) NET of GI or lung origin, with no history or active symptoms of carcinoid syndrome, and good World Health Organization (WHO) performance status (0 or 1) and no more than one prior line of chemotherapy. In addition to treatment-naïve patients, patients previously treated with SSA, interferon, up to one prior line of chemotherapy, and/or peptide radionuclide receptor therapy, were allowed into the study. Pre-treated patients must have progressed on or after the last treatment. Patients had radiological documentation of disease progression within 6 months prior to randomisation and measurable disease according to RECIST version 1.0.<sup>21</sup>

The clinical evaluator noted that subjects with functioning tumours were excluded; treatment in this group would be with SSA.

## Randomisation and interventions

Subjects were randomised (2:1) to the everolimus 10 mg or placebo arm, stratified by prior SSA treatment (SSA continuously for  $\geq 12$  weeks any time prior to study), tumour origin and WHO performance status (0 versus 1).<sup>22</sup> Everolimus was supplied as 5 mg

<sup>21</sup> The Response Evaluation Criteria In Solid Tumors (RECIST) are a set of widely used published definitions to describe response of tumours in cancer patients.

<sup>22</sup> Tumour origin was specified as stratum A (better prognosis: appendix, caecum, jejunum, ileum, duodenum, carcinoma of unknown primary origin \*CUP)) versus stratum B (worse prognosis: lung, stomach, rectum, colon except caecum). CUP was defined as well differentiated (Grade 1 or Grade 2) NET where any other primary tumour origin than gastrointestinal or lung has been excluded by appropriate diagnostic procedures. NET lesions found solely in the liver were coded as CUP.

tablets. Treatment continued until disease progression, start of a new anticancer therapy, intolerable toxicity or withdrawal of consent. Study drug was taken continuously, in 'cycles' lasting 28 days. Patients in the placebo arm were not permitted to crossover to everolimus following disease progression.

BSC included all care deemed necessary by the treating physician, excluding anti-tumour therapies; palliative radiation, surgery and SSA therapy for patients whose tumours became functional were permitted. Dose delays and reductions to 5 mg daily, then 5 mg every other day were permitted in the event of toxicity prior to discontinuation.

### ***Demographic and baseline characteristics***

Median age was 63 years, 76% were Caucasian, approximately 70% had tumours arising in GI tissue, 30% in lung, and the majority (94.7%) had distant metastases. Overall the 2 treatment groups were reasonably well balanced with respect to baseline factors.

Over 50% had received prior SSAs, mostly octreotide LAR. Around 80% had received any prior antineoplastic therapy. Of note, in the placebo group a higher proportion of subjects was male (54.6% versus 43.4%) and also a greater proportion had prior surgery (72.2% versus 59.0%). The clinical evaluator commented that these differences would be unlikely to influence the results of the study.

### ***Efficacy assessment methodology***

Subjects had computerised tomography (CT) or magnetic resonance imaging (MRI) scans of the chest, abdomen and pelvis at screening. Subsequent imaging was every 8 weeks after randomisation for the first 12 months and every 12 weeks thereafter until disease progression was documented or the subject commenced new anticancer therapy. Imaging of the abdomen was always required and imaging of the chest and pelvis was required if involvement of these areas was documented at Baseline.

The FACT-G questionnaire was administered at randomisation and then every 8 weeks for the first 12 months and every 12 weeks thereafter.

The primary efficacy endpoint was PFS defined as the time from the date of randomisation to the date of first documented radiological progression or death due to any cause. Disease progression was defined according to a modified version of the RECIST version 1.0. Decision on progression was by a central independent review panel of diagnostic radiologists.

Overall survival (OS) was the key secondary endpoint. Other secondary endpoints included overall response rate (ORR), and disease control rate (DCR) and Quality of Life (QoL).

QoL was assessed by the Functional Assessment of Cancer Therapy: General (FACT-G) instrument. Details of FACT-G from the CSR for T2302 are as follows: it is comprised of 27 statements which patients need to endorse on a five-point scale (not at all, a little, somewhat, quite a bit, very much). The statements cover four subscales (Physical Well-being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being). For the Total Score of 27 FACT-G items, minimally important difference is established as 3 to 7 points which represents 3.7% to 6.5% of total score. For each of four subscales on Physical Well-being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being, minimally important difference is established as 2 or 3 points change. Higher scores indicate better quality of life. For this study, the specified endpoint of interest was time to definitive deterioration in FACT-G total score, where deterioration was defined as a decrease by at least 7 points compared to Baseline.

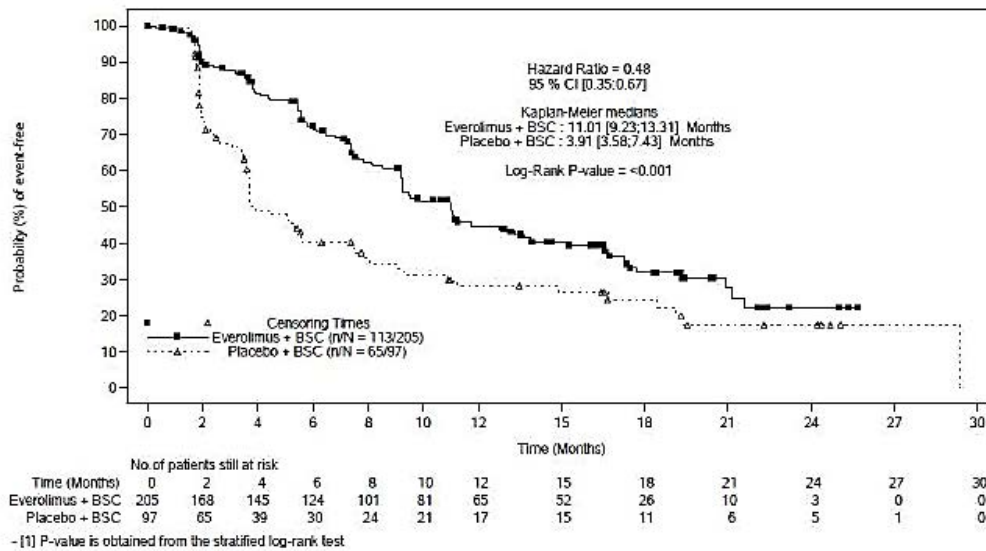
The evaluator considered the efficacy endpoints were standard for a Phase III oncology study and consistent with the relevant EMA guideline adopted by the TGA.

**Efficacy outcomes**

*Progression-free survival*

The analysis of PFS was conducted after a total of 178 PFS events had occurred.

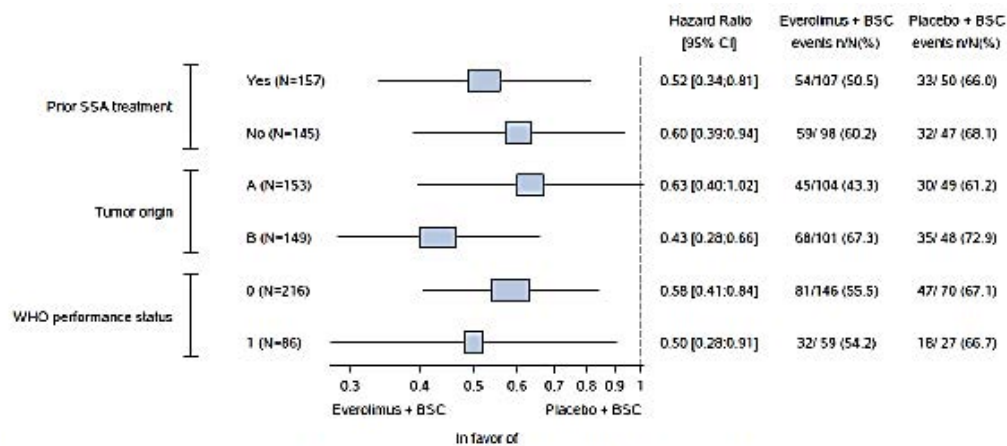
**Figure 1. Kaplan-Meier analysis of PFS**



Treatment with everolimus was associated with a significant reduction in the risk of a PFS event (HR = 0.48; 95% CI: 0.35 to 0.67; p < 0.001 as shown in Figure 1 above. Median PFS was increased by 7.1 months (11.01 versus 3.91 months).

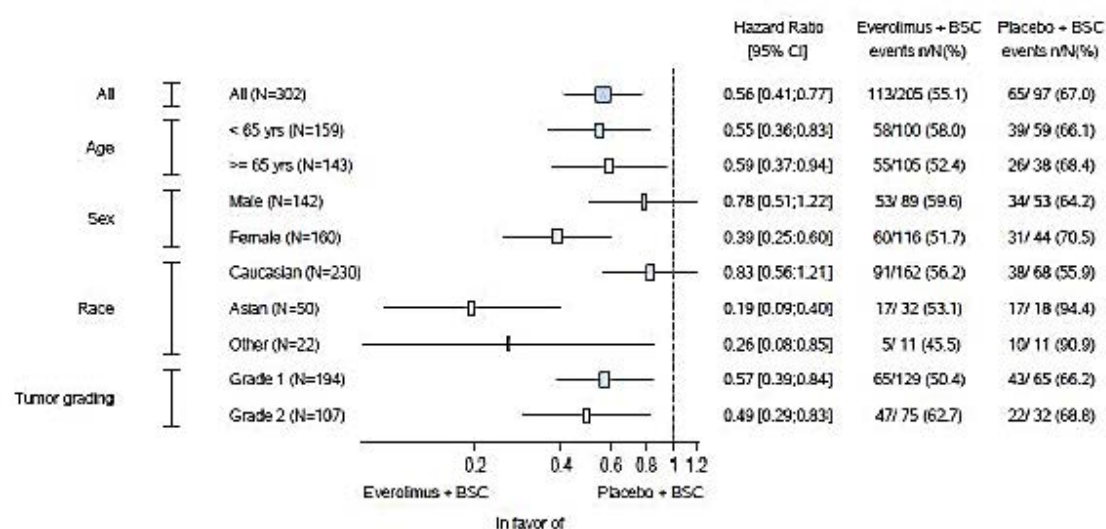
The results of PFS subgroup analyses are shown in Attachment 2. The effect of everolimus was consistent for PFS by stratification factor per central review, with hazard ratios all < 1.0 as shown below in Figure 2.

**Figure 2. PFS analysis (hazard ratios) of everolimus by central review stratification factors**

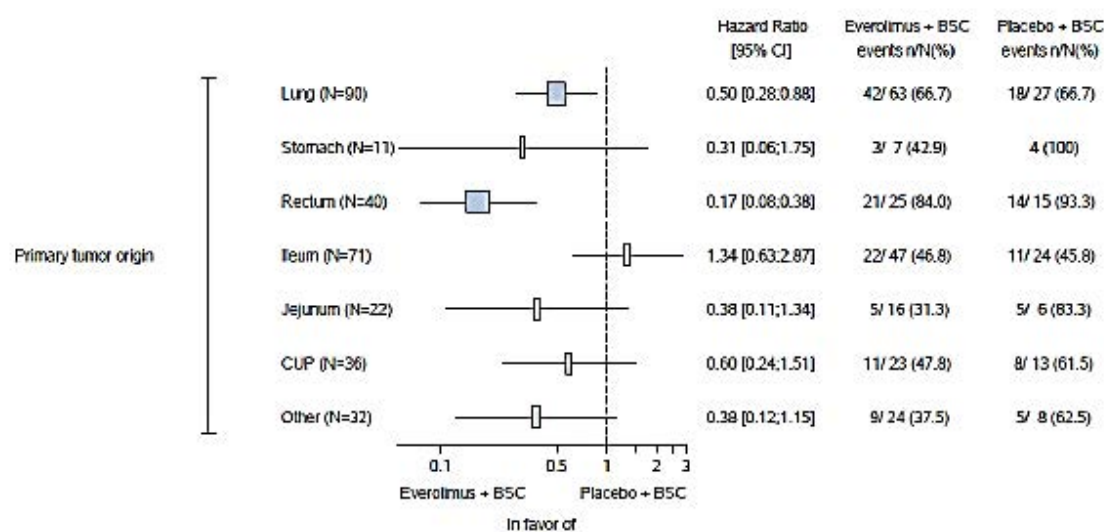


Tumor origin: stratum A - appendix, cecum, jejunum, ileum, duodenum, and carcinoma of unknown primary (CUP); stratum B - lung, stomach, rectum, and colon (with the exception of cecum)

In post-hoc subgroup analyses of PFS some differences in efficacy were suggested between gender and race, as shown below in Figure 3.

**Figure 3. Post-hoc subgroup PFS analyses (hazard ratios)**

There was a trend towards a harmful effect for everolimus in the group of subjects who had tumours arising in the ileum (HR = 1.34; 95% CI: 0.63 to 2.87), as shown in Figure 4 below.

**Figure 4. PFS analysis (hazard ratios) by site of primary tumour origin**

For the subgroup analyses hazard ratios were calculated using unstratified Cox analysis.

Further exploratory analyses using a stratified Cox analysis (using the three stratification factors at randomisation) and a stratified Cox analysis adjusted for baseline prognostic factors (such as tumour grade, prior chemotherapy, baseline biomarker levels, liver metastases and age) produced lower HRs for the ileum subgroup and reduced the variability between genders and races (see Table 11 below). The CSR for Study T2302 describes this as indicative of a confounding effect of other prognostic factors, including the known favourable prognosis for patients with small intestine (including jejunum and ileum) as the primary tumour origin.<sup>23,24</sup> It was proposed that the findings might be partly

<sup>23</sup> Yao J et al. One hundred years after 'carcinoid: epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. 2008; J Clin Oncol; 26: 3063-72.

<sup>24</sup> Rinke A et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: A report from the PROMID study group. 2009; J Clin Oncol; 27 (28):4656-63.

due to a random effect (smaller sample size and large number of subgroup analyses) and to the low number of events in the group with better prognosis.

**Table 11. Cox regression exploratory analyses of PFS (hazard ratio) by race, gender and primary site of tumour origin (ileum versus other site)**

	Stratified HR	Stratified and covariate-adjusted HR <sup>1</sup>
<b>Overall population</b>	<b>0.48 (0.35, 0.67)</b>	<b>0.42 (0.29, 0.60)</b>
<b>Race</b>		
Caucasian (n=230)	0.67 (0.45, 1.00)	0.56 (0.36, 0.87)
Asian (n=50)	0.12 (0.04, 0.32)	0.14 (0.04, 0.51)
Other (n=22)	0.19 (0.04, 0.91)	NE
<b>Gender</b>		
Male (n=142)	0.63 (0.39, 1.01)	0.52 (0.30, 0.90)
Female (n=160)	0.32 (0.20, 0.52)	0.25 (0.15, 0.43)
<b>Primary tumor origin</b>		
Ileum (n=71)	1.22 (0.56, 2.65)	1.01 (0.43, 2.37)
Other (n=231)	0.39 (0.27, 0.55)	0.35 (0.23, 0.52)

HR Hazard ratio; NE Not estimable

<sup>1</sup> Model fitted on the subset of 272 patients for whom all covariates were known

#### *Overall survival*

Interim analysis, with 70/302 patients having died, showed a trend towards improved survival with everolimus treatment (HR = 0.64; 95% CI: 0.40 to 1.05; p = 0.037).

At the second round, the sponsor provided a report on the results of the second interim analysis of overall survival from Study CRAD001T2302 (RADIANT-4); data cut-off date for inclusion in the report was 30 November 2015. The median duration of follow-up was 33.4 months (compared with a value of 21.3 months for the first interim analysis). A total of 101 deaths (33.4% of the population) had occurred (compared with 70 deaths for the first interim analysis).

Results of the analysis are summarised in Attachment 2. There was a trend towards improved survival with everolimus treatment (HR = 0.73; 95% CI: 0.48 to 1.11; p = 0.071) but the result was not statistically significant and is similar to the first analysis.

A greater proportion of subjects in the placebo arm had received further antineoplastic therapy after study discontinuation (62.9% versus 50.7%). However, only 4.1% of subjects randomised to placebo had received everolimus after study discontinuation. The sponsor estimates that the 191 deaths necessary for the final analysis will not occur until 2021/2022.

#### *Overall response rate*

There was no significant difference for overall response but the DCR was better for everolimus. See Attachment 2 for further details.

#### *Quality of life*

There was no significant difference between treatment arms for FACT-G questionnaire or WHO performance status; see Attachment 2 for further details.

#### *Biomarkers*

Increases over time were higher in placebo arm.

#### ***Tuberous sclerosis complex***

Final study reports were provided for three studies that were the basis for TGA approval of treatment for two manifestations of TSC, SEGA and renal angiomyolipoma, Studies C2485 and M2301 (SEGA), and Study M2302 (renal angiomyolipoma). See



Attachment 2 for further details. The evaluator considered that the data from the TSC studies demonstrated that efficacy of everolimus is maintained in these indications with long-term use.

### ***Efficacy conclusions***

The Delegate agrees with the clinical evaluator that Study T2302 complied with relevant guidelines and demonstrated prolongation of median PFS of approximately 7 months in the study population. This is comparable to that seen with other agents with approval for treatment for NETs with PFS.

### ***Issues***

Considering that in Australia octreotide has an indication for treatment of NETs of midgut origin, it might be considered that placebo treatment was not appropriate for the study patient group, but SSAs were not available as treatment for the complete study population. Overall 50% of the subjects had previously been exposed to octreotide, median duration 15 months.

In post-hoc analyses there was a trend towards a harmful effect for everolimus in the group of subjects who had tumours arising in the ileum (HR = 1.34; 95% CI: 0.63 to 2.87). This aspect is not included in the proposed PI.

### **Safety**

#### ***Exposure***

In Study T2302 the safety analysis set consisted of 300 subjects, everolimus n = 202 and placebo n = 98. Details of duration of exposure are summarised in Attachment 2.

Duration of exposure to study drug was longer for everolimus than placebo (median duration: 40.43 versus 19.64 weeks; patient-years of exposure: 180.7 versus 65.8). For everolimus 137 subjects were treated for at least 24 weeks and 86 for at least 48 weeks.

#### ***Adverse events***

Common AEs (those occurring in > 10% of subjects in either arm) are summarised in Attachment 2. Toxicities that occurred more frequently in the everolimus arm included GIT toxicity (stomatitis, diarrhoea, nausea, decreased appetite, dysgeusia); Skin toxicity (rash, pruritus); Respiratory toxicity (cough, dyspnoea, pneumonitis); Asthenia; Pyrexia; Peripheral oedema; Hyperglycaemia; Anaemia; Hypertension.

Common treatment related AEs (those occurring in > 10% of subjects in either arm) are detailed in Attachment 2. The most frequent Grade 3 or 4 reactions for everolimus versus placebo were stomatitis (7.4% versus 0), diarrhoea (7.4% versus 2%), anaemia (4% versus 1%), fatigue (3.5% versus 1%), hyperglycaemia (3.5% versus 0) peripheral oedema (2% versus 1%) and pyrexia (2% versus 0).

AEs lead to discontinuation more frequently across a range of SOCs in the everolimus arm and are detailed in Attachment 2.

Two deaths in the everolimus arm, due to interstitial pneumonitis and septic shock, were suspected and plausibly related to everolimus.

In two reported cases of hepatic failure in the everolimus arm, the patients had metastatic liver disease at baseline. Haematological cytopenias and skin disorders were observed with increased frequency for everolimus. Serious skin disorders reported for everolimus were angioedema, drug eruption, hyperhidrosis and toxic skin eruption (Grade 2) versus none for placebo.

In summary, there were significant toxicities reported for everolimus, although the pattern was consistent with that previously observed.

Clinically notable AEs occurring more frequently in the everolimus arm after adjustment for increased duration of treatment included stomatitis, infections, cytopaenias, pneumonitis, haemorrhage, and cardiac disorders (see Attachment 2 for further details).

- Haemorrhage (Grade 3 or 4 adjusted rate 2.2% versus 0%) is listed in the PI, and epistaxis and haemoptysis are specified in the PI. It is noted that Grade 3 or 4 cerebral haemorrhage and GI bleeds were reported in the pivotal trial.
- Cardiac disorders (Grade 3 or 4 adjusted rate 4.4% versus 0%) are represented in the PI by 'congestive cardiac failure' only.

### ***Tuberous sclerosis complex***

In long-term TSC studies, the incidence of AEs was consistent with the pattern previously established, and appeared to decrease with time.

### ***Safety conclusions***

The Delegate considers that there were no new safety concerns for everolimus raised by Study T2302 in progressive NETs of GI/Lung origin. Overall the AEs are adequately described in the PI.

### ***Issues***

While pattern of AEs observed in the pivotal study was consistent with that previously observed with the drug, everolimus is associated with significant toxicity in subjects with advanced NETs. Compared to placebo, everolimus was associated with a notably increased incidence of Grade 3 or 4 AEs (69.3% versus 28.6%) and serious AEs (42.1% versus 19.4%). An additional 20% of subjects had to discontinue study treatment due to AEs (29.2% everolimus versus 7.1% placebo).

AEs occurred with frequencies similar to those in Study 2324 'RADIANT-3' that supported approval of everolimus for pancreatic NETs but discontinuations due to AEs were higher (29.2% in Study T2302 for GIT/Lung NETs compared to 19.1% in pancreatic NETs from Study 2324).

This raises the possibility that for tumours of ileal origin, or with other good prognostic indicators, everolimus toxicities could negatively affect risk-benefit.

### **Clinical evaluator's recommendation**

The clinical evaluator recommended that the proposed new indication, for the treatment of progressive, unresectable or metastatic, well-differentiated, non-functional NETs of gastrointestinal or lung origin, be approved.

### **Risk management plan**

The proposed pharmacovigilance plan has not changed from that previously accepted and includes routine reporting and targeted follow-up questionnaires addressing the safety concerns. Additional pharmacovigilance studies and registries are also in place, and include Australian patients. No new additional pharmacovigilance activities are proposed.

The proposed additional pharmacovigilance activities do not include any specific study of the neuroendocrine tumour of GI or lung origin patient population and are limited to studies of patients receiving everolimus for other indications. The sponsor justified this with the following statement:

*'Based on the totality of the data, the safety profile of everolimus in the NET population is generally comparable to the safety profile of everolimus in the oncology setting. No new risks with NET were identified and the safety profile for NET is*

*provided on the basis of the current identified and potential risks of everolimus in this submission’.*

All identified issues were resolved, including dosage advice for the proposed indication, as also identified by the clinical evaluator. The evaluator recommended to the Delegate that the updated version of EU-RMP and the ASA is implemented.

### **Planned or ongoing studies**

There are currently no planned or on-going studies for this indication.

### **Recommended conditions of registration**

The suggested wording for conditions of registration is:

- Implement European Union RMP Version 12.1 (Afinitor)/11 (Votubia) (dated 25 April 2016, DLP 31 March 2015) and Australian Specific Annex Version 7.0 (dated 11 July 2016) and any future updates as a condition of registration.

### **Risk-benefit analysis**

Despite the marked difference in AE profile for everolimus compared to the placebo arm, there was no difference in outcomes in the reported QoL measurements. The study met criteria for efficacy for PFS. Overall risk-benefit assessment therefore appears positive for the indication sought:

*‘Afinitor is indicated for the treatment of progressive, unresectable or metastatic, well-differentiated, non-functional neuroendocrine tumours (NET) of gastrointestinal or lung origin.’*

The Delegate has reservations about the following aspects of the proposed PI:

- presentation of subgroup analyses in the Clinical Trials section
- complete omission of information about trial C2325 ‘Radiant-2’ from the PI.

### **Summary of issues**

Data from placebo controlled trial Study T2302 are considered to support the indication wording specifying the patient group:

- The Delegate is uncertain about the utility of the information from pre-specified subgroups and post-hoc subgroup analysis for sites of tumour origin as proposed for inclusion in the PI.

The proposed PI provided at the second round omits information about lack of efficacy in functional NETs of GI origin:

- The Delegate considers that complete omission of this information is not appropriate.

### **Proposed action**

The Delegate had no reason to say, at this time, that the application for extension of indications for everolimus (Afinitor) should not be approved for registration.

### **Request for ACPM advice**

The committee is requested to provide advice on the following specific issues:

1. Please comment on the adequacy of the data supporting the proposed extension of Indications in the population described.
2. Please provide advice regarding the adequacy of the proposed PI for presentation of clinically relevant information.

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

### **Response from sponsor**

The sponsor provided the following pre-ACPM responses to the issues raised for the Committees discussion.

#### ***Sponsor's response to issue 1***

*'Please comment on the adequacy of the data supporting the proposed extension of Indications in the population described'.*

Study T2302 enrolled patients with pathologically confirmed, well-differentiated (Grade 1 or Grade 2) advanced (unresectable or metastatic) NETs of GI or lung origin representative of the proposed indication. These patients had no history of, and no active symptoms related to, carcinoid syndrome. All patients had radiological documented disease progression within the 6 month period prior to randomisation and thus had progressive disease. Approximately 50% of the study population had progressed after SSA therapy. Furthermore, 90 patients (29.8%) in Study T2302 presented with lung as the primary site of tumour origin and represent a subgroup for which no treatment is current available.

In this trial, superiority was demonstrated relative to placebo for the primary endpoint of PFS per independent central radiology review committee (IRC). A 52% risk reduction was evident in favour of treatment with everolimus: this result was both clinically meaningful and statistically significant (HR 0.48; 95% CI: 0.35, 0.67;  $p < 0.001$ ). The 7.10 month prolongation in median PFS (from 3.91 months for placebo to 11.01 months for everolimus per IRC) represents an important clinical benefit. PFS analyses per local investigator assessment (HR 0.39; 95% CI: 0.28, 0.54) were consistent in the magnitude of the treatment effect and were supportive of the primary efficacy analysis. Multiple pre-planned sensitivity and subgroup analyses demonstrated that this observed benefit in PFS in favour of everolimus was robust and consistent, with a positive treatment effect evident irrespective of site of tumour origin, prior SSA exposure, and WHO performance status score, and across major demographic and prognostic subgroups. The only notable possible exception was the ileum as the site of primary tumour origin where a random effect due to the smaller sample size of this subgroup cannot be excluded. This exception is proposed to be addressed in the proposed PI (see response to issue 2 below). The OS results favoured the everolimus arm with an estimated 27% risk reduction relative to placebo although statistical significance was not achieved at the second interim OS analysis (HR 0.73; 95% CI: 0.48, 1.11;  $p = 0.071$  (when boundary for significance at this interim analysis was 0.001982)).

The safety and tolerability profile of everolimus was consistent with prior experience in the advanced NET and oncology settings and no new safety risk was identified in this study. The grading (severity) of most events was modest (typically Grade 1 or 2) and these events were generally manageable with existing AE management guidance (provided in the Dosage and Administration section of the PI). While many of the AEs reported may have a significant impact on QoL, it is important to note that QoL was not adversely impacted by AEs.

Overall, these results demonstrate a clinically meaningful and highly statistically significant improvement in PFS relative to placebo. Furthermore, preliminary OS results

also favoured treatment with everolimus. This is also the first study to have shown unequivocal treatment benefit for patients with NET of lung origin (HR 0.50; 95% CI: 0.28, 0.88). The proposed PI fully characterises both efficacy and safety to enable the appropriate use of Afinitor in patients with progressive non-functional NETs of GI or lung origin with unresectable or metastatic disease to maximise benefit while minimising risk to patients. The data provided in this application and the full characterisation of these data in the PI support the use of everolimus in the proposed indication.

### ***Sponsor's response to issue 2***

*'Please provide advice regarding the adequacy of the proposed PI for presentation of clinically relevant information'.*

This issue mainly concerns proposed changes to other sections of proposed PI. The Delegate has raised the following concerns:

- *Presentation of subgroup analyses in the clinical trials section*

The sponsor proposes to remove figures as recommended by the Delegate and replace with the pre-specified patient subgroup figure from the EU Summary of Product Characteristics (SmPC) with associated SmPC text for this figure.

- *Complete omission of information about trial C2325 'Radiant-2' from the PI*

The sponsor removed the information about trial C2325 on the recommendation of the clinical evaluator. The sponsor proposes to re-instate the complete details of this trial as previously approved by TGA. In line with the paragraph of the US PI quoted by the Delegate, and to avoid any confusion between the populations recruited in the C2325 and T2302 trials, the sponsor is proposing to clarify in the PI that the C2325 study was conducted in patients with functional carcinoid tumours.

Other PI concerns raised by the Delegate include:

- *The description of the patient group tumour characteristics should specify that the advanced non-functional NETs were 'well-differentiated'.*

The sponsor agrees to include 'well-differentiated' in the description of the patient group tumour characteristics.

- *With respect to baseline demographics please include that approximately 50% in both groups had a history of prior SSA use.*

The sponsor proposes to include this in baseline demographics text.

- *While the PFS efficacy variables shown in Table 3 and the primary efficacy variable K-M curve for PFS from independent radiological review shown in Figure 5 are acceptable, it is doubtful that there is additional benefit to the prescriber in showing the supportive analysis from local investigator assessment again at proposed Figure 6 and it is recommended that this figure is omitted.*

The sponsor proposes to remove Figure 6.

- *The 'waterfall' plot at Figure 9 appears unnecessary but it is noted that such detail is included for the TSC trials in the approved PI.*

Novartis proposes to keep Figure 9 as it visually supports the text on tumour shrinkage where the alternative to Afinitor is chemotherapy.

- *The Delegate considers that if C2325 is deleted from 'Clinical Trials', information should be added under 'Precautions' to explain that safety and efficacy of everolimus in patients with functional carcinoid tumours have not been established.*

The sponsor proposes to include the details of Study C2325 under the Clinical Trials section as previously approved by TGA.

- *The Delegate considers that additional information about outcomes of PFS in the subgroup with ileum as the primary tumour origin should be included under Precautions.*

The sponsor proposes to include additional information about outcomes of PFS in the subgroup of patients with ileum as the primary tumour origin in line with EU SmPC text quoted by the Delegate.

- *The number in the pooled oncology safety data base has increased from 1175 to 2672. As there were only 205 patients exposed to Afinitor in the T2302 trial, it is not obvious from the submission what other trials are contributing to these data. This number was not located by the Delegate in either the Summary of Clinical Safety or PSUR 10; please clarify.*

The current (N=1175) safety pool presented in the approved PI is based on the double blind periods of the 4 randomised double blind controlled Phase III studies supporting the registered indications as listed below (Table 12).

**Table 12. Oncology studies included in the current safety pool**

Studies	Combination partner	Number of patients receiving everolimus in double-blind period	Data Cut-off Date
<b>Renal Cell carcinoma indication</b>			
CRAD001C2240 (RECORD-1) A phase III study to compare the safety and efficacy of RAD001 plus Best Supportive Care (BSC) versus BSC plus Placebo in patients with metastatic RCC who have progressed on VEGF receptor TKIs	N/A	274	19-Mar-2012
<b>NET indication</b>			
CRAD001C2324 (RADIANT-3) A randomized double-blind phase III study of RAD001 10mg/d plus best supportive care versus placebo plus best supportive care in the treatment of patients with advanced pancreatic neuroendocrine tumor (NET)	N/A	204	23-Feb-2011
CRAD001C2325 (RADIANT-2) A randomized, double-blind, placebo-controlled, multicenter phase III study in patients with advanced carcinoid tumor receiving Sandostatin LAR <sup>®</sup> Depot and RAD001 10 mg/d or Sandostatin LAR <sup>®</sup> Depot and placebo	Octreotide	215	23-Apr-2012
<b>Breast cancer indication</b>			
CRAD001Y2301 (BOLERO-2) A randomized double-blind, placebo-controlled study of Everolimus in combination with Exemestane in the treatment of postmenopausal women with estrogen receptor positive locally advanced or metastatic breast cancer who are refractory to Letrozole or Anastrozole	Exemestane	482	16-Jul-2012
<b>Total number of patients</b>		<b>1175</b>	

The expanded safety pool (N = 2672) is based on the addition of the open label periods of the trials mentioned in Table 12 (above) as well as Phase I, II and Phase III trials which are related to the registered indications and were previously reported in the registration dossiers or Periodic Safety Update Reports (PSURs). This update is in line with the reference safety information, the Core Data Sheet, as shown in the Afinitor PSUR 10 (Oncology Setting) previously submitted to TGA. Detailed here, the updated safety pool includes:

1. The open label periods from the 4 randomised, double blind, controlled pivotal Phase III studies listed in Table 12.

2. The additional randomised double blind controlled Phase III study in advanced, progressive, non-functional neuroendocrine tumours of GI or lung origin (T2302 trial).
3. 3 additional open label Phase I and II studies (Studies L2201, L2202, and C2239). 2 of these open label studies are randomised studies with an active comparator arm (L2201 and L2202) and one (C2239) is a two stratum study (with and without octreotide).
4. Study C2222, a randomised, double blind, controlled Phase II study in patients with breast cancer.
5. Study L2101, an open label trial in patients with advanced RCC conducted in China.

Further details of the oncology studies in the updated safety pool are given in Table 13, below.

**Table 13. Oncology studies in the updated safety pool**

<b>Studies and study title</b>	<b>Combination partner</b>	<b>Numbers of patients receiving everolimus</b>	<b>Data cut-off date</b>
<b>Renal cell carcinoma indication</b>			
<b>CRAD001C2240 (RECORD-1)</b> A phase III study to compare the safety and efficacy of RAD001 plus Best Supportive Care (BSC) versus BSC plus Placebo in patients with metastatic RCC who have progressed on VEGF receptor TKIs	N/A	385	19-Mar-2012
<b>CRAD001L2101</b> Local Chinese phase I trial, single arm everolimus	N/A	64	31-Dec-2012
<b>CRAD001L2201</b> A randomized, open-label, multi-center phase II study to compare bevacizumab plus RAD001 versus interferon alfa-2a plus bevacizumab for the first-line treatment of patients with metastatic clear cell carcinoma of the kidney	Bevacizumab	180	26-Jun-2013
<b>CRAD001L2202</b> An open-label, multicenter phase II study to compare the efficacy and safety of RAD001 as first-line followed by second-line sunitinib versus sunitinib as first-line followed by second-line RAD001 in the treatment of patients with metastatic renal cell carcinoma	N/A	337	03-Sep-2012
<b>NET indications</b>			
<b>CRAD001C2324 (RADIANT-3)</b> A randomized double-blind phase III study of RAD001 10mg/d plus best supportive care versus placebo plus best supportive care in the treatment of patients with advanced pancreatic neuroendocrine tumor (NET)	N/A	376	05-Mar-2014
<b>CRAD001C2325 (RADIANT-2)</b> A randomized, double-blind, placebo-controlled, multicenter phase III study in patients with advanced carcinoid tumor receiving Sandostatin LAR <sup>®</sup> Depot and RAD001 10 mg/d or Sandostatin LAR <sup>®</sup> Depot and placebo	Octreotide	358	13-Jun-2013
<b>CRAD001C2239 (RADIANT-1)</b> An open label, stratified, single-arm phase II study of RAD001 in patients with advanced pancreatic neuroendocrine tumor (NET) after failure of cytotoxic chemotherapy	Stratum 1: NA Stratum 2: octreotide	Stratum 1: 115 Stratum 2: 45 Total: 160	23-Apr-2012
<b>CRAD001T2302 (RADIANT-4)</b> A randomized, double-blind, multicenter, Phase III study of everolimus (RAD001) plus best supportive care versus placebo plus best supportive care in the	N/A	202	28-Nov-2014



**Table 13 (continued). Oncology studies in the updated safety pool**

Studies and study title	Combination partner	Numbers of patients receiving everolimus	Data cut-off date
treatment of patients with advanced NET of GI or lung origin			
<b>Breast cancer indication</b>			
<b>CRAD001Y2301 (BOLERO-2)</b> A randomized double-blind, placebo-controlled study of Everolimus in combination with Exemestane in the treatment of postmenopausal women with estrogen receptor positive locally advanced or metastatic breast cancer who are refractory to Letrozole or Anastrozole	Exemestane	482	04-Dec-2014
<b>CRAD001C2222</b> A phase 2, double-blind, randomized, placebo-controlled, multi-center study assessing the value of adding RAD001 to letrozole (Femara <sup>®</sup> ) as preoperative therapy of primary breast cancer in postmenopausal women	Letrozole	128	02-May-2007
<b>Total numbers of patients</b>		<b>2672</b>	

### Advisory Committee considerations

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Afinitor tablet and dispersible tablet containing 2.5 mg, 5 mg, 10 mg (tablets), and 2 mg, 3 mg, 5 mg (dispersible tablets) of everolimus to have an overall positive benefit-risk profile for the modified indication:

*'Afinitor is indicated for the treatment of progressive, unresectable or metastatic, well-differentiated, non-functional neuroendocrine tumours (NET) of gastrointestinal or lung origin in adults'*

In making this recommendation the ACPM noted there were no data in paediatric populations and this is a very rare disease in those populations.

### Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration and advised on the inclusion of the following:

- Subject to satisfactory implementation of the Risk Management Plan most recently negotiated by the TGA.
- Negotiation of Product Information and Consumer Medicines Information to the satisfaction of the TGA.

### Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

- The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on amendments as detailed in Question 2 below.

### Specific advice

The ACPM advised the following in response to the delegate's specific questions on this submission:

1. *Please comment on the adequacy of the data supporting the proposed extension of Indications in the population described.*

The ACPM advised the Phase III study was a well performed randomised double blind trial in the target population that was adequately powered and demonstrated a statistically

significant and clinically meaningful difference in the primary endpoint of PFS. It must be noted that the trial is a significant undertaking in a small subgroup of a rare cancer. Another trial may not be realistic. The OS showed trends towards improved survival but the result was not statistically significant. Data are not mature to accurately assess OS; final analysis may not occur until 2021. Therefore OS is too early to assess. Although there were more toxicities with everolimus they were expected from previous studies and it is worth noting that no differences were found in quality of life between the everolimus and placebo group.

These results in this rare cancer subgroup provide adequate data to support the proposed extension of indications.

2. *Please provide advice regarding the adequacy of the proposed PI for presentation of clinically relevant information.*

On the issue of the removal of data about the pre-specified subgroups analysis and post-hoc analysis, this would remove data about the group with tumours arising from the ileum doing worse. These are referring to a subgroup of a subgroup and a result after multiple dips into the data that could have led to that result randomly. The ACPM advised that there is inadequate evidence to include these data at present in the PI and would favour removing the figures that illustrate these data as has been proposed. The ACPM agreed with the Delegate's suggestion of including the information about the possibility of patients with ileal tumours doing worse under the 'Precautions' section.

The ACPM also advised the RADIANT-2 study information about the safety and efficacy of everolimus not having been established in patients with functional carcinoid tumours can be removed from the 'Clinical Trials' section but should be reinforced in the 'Precautions' section. In addition, the proposed indication statement also makes it quite clear that functional carcinoid tumours are excluded.

For the issue of limiting the indication to adult patients; there are no data in children, the disease is very rare and everolimus is toxic so the ACPM strongly agreed with excluding children from this indication.

Changes such as including the term 'well differentiated' and the inclusion of the percentage of patients who had received SSAs are not controversial changes and should be added.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

## Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Afinitor tablets and dispersible tablets containing 2.5 mg, 5 mg, 10 mg (tablets), and 2 mg, 3 mg, 5 mg (dispersible tablets) of everolimus indicated for:

*'Afinitor is indicated for the treatment of progressive, unresectable or metastatic, well-differentiated, non-functional neuroendocrine tumours (NET) of gastrointestinal or lung origin in adults.'*

The full indications are now:

*'Afinitor is indicated for the treatment of:*

*Postmenopausal women with hormone receptor-positive, HER2 negative advanced breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole.*

*Progressive, unresectable or metastatic, well or moderately differentiated neuroendocrine tumours (NETs) of pancreatic origin.*

*Progressive, unresectable or metastatic, well-differentiated, non-functional neuroendocrine tumours (NET) of gastrointestinal or lung origin in adults.*

*Advanced renal cell carcinoma after failure of treatment with sorafenib or sunitinib.*

*Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not candidates for curative surgical resection.*

*Patients with tuberous sclerosis complex (TSC) who have renal angiomyolipoma not requiring immediate surgery.'*

### **Specific conditions of registration applying to these goods**

Implementation of The Afinitor EU Risk Management Plan (EU-RMP), Version 12.1 (Afinitor)/11 (Votubia) dated 25 April 2016, DLP 31 March 2015) and Australian Specific Annex Version 7.0 (dated 11 July 2016), and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

## **Attachment 1. Product Information**

The PI for Afinitor approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

## **Attachment 2. Extract from the Clinical Evaluation Report**

## **Therapeutic Goods Administration**

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