

The legally binding text is the original French version

## TRANSPARENCY COMMITTEE

### Opinion

### 9 January 2013

#### INLYTA 1 mg, film-coated tablet

B/28 (CIP code: 34009 266 479 6 4)

B/56 (CIP code: 34009 266 480 4 6)

#### INLYTA 5 mg, film-coated tablet

B/28 (CIP code: 34009 266 481 0 7)

B/56 (CIP code: 34009 266 482 7 5)

Applicant: PFIZER

INN	Axitinib
ATC Code (2012):	L01XE10 (protein kinase inhibitors)
Reason for the request	<b>Inclusion</b>
Lists concerned	<b>National Health Insurance</b> (French Social Security Code L.162-17) <b>Inclusion for hospital use</b> (French Public Health Code L.5123-2)
Indication concerned	<b>“Treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine.”</b>

<b>Actual Benefit</b>	The actual benefit of INLYTA in the treatment of renal cell carcinoma after failure of prior treatment with sunitinib or a cytokine is substantial.
<b>Improvement in Actual Benefit</b>	The Committee assigns INLYTA a minor improvement in actual benefit (IAB level IV) in terms of efficacy by comparison with NEXAVAR (sorafenib) in the second-line treatment of advanced renal cell carcinoma.
<b>Therapeutic use</b>	Axitinib (INLYTA) is a second-line option for the treatment of advanced renal cell carcinoma after failure of prior treatment with a cytokine and mainly after failure of sunitinib. However, the therapeutic use of axitinib by comparison with everolimus (AFINITOR) has still to be determined.

## 01 ADMINISTRATIVE AND REGULATORY INFORMATION

---

Marketing Authorisation (centralised procedure)	3 September 2012
Prescribing and dispensing conditions/special status	List I Medicine for hospital prescription only. Prescription restricted to oncologists or doctors with cancer training. Medicine requiring special monitoring during treatment.  Temporary usage authorisation (TUA) since April 2011: 8 patients included on 24.10.2012

ATC Classification	2012 L Antineoplastic and immunomodulating agents L01 Antineoplastic agents L01X Other antineoplastic agents L01XE Protein kinase inhibitors L01XE17 axitinib
--------------------	--

## 02 BACKGROUND

---

Axitinib (INLYTA) is a selective tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2 and VEGFR-3) which are implicated in pathological angiogenesis, tumour growth and metastatic progression of cancer.

## 03 THERAPEUTIC INDICATION

---

“Treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine.”

## 04 DOSAGE

---

“Treatment with INLYTA should be initiated by a physician experienced in the use of anticancer therapies.

### *Posology*

The recommended starting dose of axitinib is 5 mg twice daily.

Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs that cannot be managed by symptomatic treatments or dose adjustments.”

### *“Dose adjustments*

Dose increase or reduction is recommended based on individual safety and tolerability.

Patients who tolerate the axitinib starting dose of 5 mg twice daily with no adverse reactions > Grade 2 (i.e. without severe adverse reactions according to the Common Terminology Criteria for Adverse Events [CTCAE] version 3.0) for two consecutive weeks may have their dose increased to 7 mg twice daily unless the patient’s blood pressure is > 150/90 mmHg or the patient is receiving antihypertensive treatment. Subsequently, using the same criteria, patients who tolerate an axitinib dose of 7 mg twice daily may have their dose increased to a maximum of 10 mg twice daily.

Management of some adverse reactions may require temporary or permanent discontinuation and/or dose reduction of axitinib therapy (see section 4.4). When dose reduction is necessary, the axitinib dose may be reduced to 3 mg twice daily and further to 2 mg twice daily.

Dose adjustment is not required on the basis of patient age, race, gender, or body weight.”

*Concomitant strong CYP3A4/5 inhibitors or strong CYP3A4/5 inducers: See SPC*

*Special populations: See SPC*

### *“Method of administration*

Axitinib should be taken orally twice daily approximately 12 hours apart with or without food (see section 5.2). Axitinib tablets should be swallowed whole with a glass of water.”

## 05 THERAPEUTIC NEED

---

Renal cell carcinomas account for 2 to 3% of cancers in adults.<sup>1</sup> Histologically, 70 to 75% of these are clear cell tumours. Since the advent of targeted therapies, the median survival time for metastatic renal cell cancer is estimated to be 40 months.<sup>2</sup>

The aim when treating advanced renal cell carcinoma is to improve overall survival and quality of life.

The treatment of advanced renal cell carcinoma is a function of the prognostic criteria defined by the classification of the Memorial Sloan Kettering Cancer Center (MSKCC)<sup>3</sup> which takes into account general condition (Karnofsky index), the time between the initial diagnosis and first-line treatment, the LDH and haemoglobin levels and the corrected serum calcium level.

Until 2006, the treatment options essentially consisted of immunotherapy (interleukin-2 and interferon-alpha).

### ► First-line treatments

In patients with a good or intermediate prognosis, the first-line treatments are: sunitinib (SUTENT) used in about 2/3 of patients or the combination bevacizumab (AVASTIN)/interferon-alpha (ROFERON-A).

In patients with a good prognosis such as patients with one metastatic site and a Karnofsky index of > 80%, the alternatives are cytokines [aldesleukin (PROLEUKIN) or interferon-alpha (ROFERON-A)].<sup>4,5</sup>

In patients with a poor prognosis, the recommended treatment is temsirolimus (TORISEL), an mTOR inhibitor.

### ► Second-line treatments

If cytokines fail [aldesleukin (PROLEUKIN) or interferon-alpha (ROFERON-A)], tyrosine kinase inhibitors can be offered: sorafenib (NEXAVAR) or sunitinib (SUTENT).

If TKI-VEGFRs fail (sunitinib, sorafenib and bevacizumab), everolimus (AFINITOR), a selective mTOR inhibitor, is available as second- or third-line treatment.

Note: pazopanib (VOTRIENT) which has Marketing Authorisation (June 2010) in the first-line treatment of advanced renal cell carcinoma or in patients who have received prior treatment with cytokines is not reimbursed at present<sup>6</sup>, since the Transparency Committee believed (February 2011) that the actual benefit provided was insufficient to justify reimbursement by National Health Insurance.

---

<sup>1</sup> Rini B, Campbell S, Escudier B. Renal cell carcinoma. *Lancet* 2009; 373 (9669): 1119–1132

<sup>2</sup> Thuret R et al. Treatment of metastatic renal cell carcinoma. *Progrès en Urologie*. 2011; 21: 233–244.

<sup>3</sup> Motzer R.J., Bacik J., Murphy B.A., Russo P., Mazumdar M. Interferon alpha as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. *J Clin Oncol* 2002; 20: 289-296.

<sup>4</sup> Méjean A et al. Renal cell carcinomas. *Progrès en urologie* 2004; 14: 997-1035.

<sup>5</sup> Pouessel D, Culine S. Targeted therapies in metastatic renal cell carcinoma: the light at the end of the tunnel. *Exp Rev Anticancer Ther* 2006; 6: 1761-7

<sup>6</sup> Transparency Committee opinion of 02.02.11 on VOTRIENT

## 06 CLINICALLY RELEVANT COMPARATORS

### 06.1 Medicinal products

In the second-line treatment of advanced renal cell carcinoma:

Name (INN) Company	<b>AFINITOR</b> (everolimus) <i>Novartis</i>	<b>NEXAVAR</b> (sorafenib) <i>Bayer</i>	<b>SUTENT</b> (sunitinib) <i>Pfizer</i>
TC* identical yes/no	No	Yes	Yes
Indication	Advanced renal cell carcinoma in patients with disease progression on or after targeted anti-VEGF therapy	Advanced renal cell carcinoma after failure of treatment based on interferon-alpha or interleukin-2 or in patients for whom these treatments are inappropriate	Advanced and/or metastatic renal cell carcinomas (1st and 2nd line)
Date of opinion	13/01/10	06/09/06	20/09/06 (2nd line)
Actual Benefit	Substantial	Substantial	Substantial
Improvement in Actual Benefit (wording)	IV in therapeutic use (2nd or 3rd line)	II in the management of renal cell carcinoma	III in disease management (2nd line)
Main results of pivotal studies (from TC opinions)	Double-blind, randomised placebo-controlled study Interim analysis: PFS (primary endpoint): 4.9 months versus 1.9 months ( $p < 0.001$ )  Marketing Authorisation: 03/08/2009	Double-blind, randomised placebo-controlled study Interim analysis: PFS (primary endpoint): 5.6 months versus 2.8 months ( $p < 10^{-6}$ ) OS (primary endpoint): not achieved vs 14.7 months  Marketing Authorisation: 19/07/2006	Noncomparative phase II studies after failure of a cytokine Objective response rate (primary endpoint): 34-36.5%  Conditional Marketing Authorisation: 19/07/2006

\*therapeutic category

#### Conclusion

The clinically relevant comparators are:

- NEXAVAR (sorafenib) in patients with failure of treatment based on interferon-alpha or interleukin-2,
- AFINITOR (everolimus) in patients with disease progression on or after targeted anti-VEGF therapy.

It should be noted that AFINITOR has had Marketing Authorisation since 03.08.2009, i.e. not long after first inclusion in the phase III study evaluating INLYTA which was carried out on 15.09.2008 and that SUTENT also has Marketing Authorisation in second line treatment but that its role has been assessed only after failure of a cytokine in noncomparative phase II studies in this indication.

## 07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	REIMBURSED	
	YES/NO If not, why not	Population(s) That of the Marketing Authorisation or restricted
AUSTRIA	YES	Population of the Marketing Authorisation
GERMANY	YES	Population of the Marketing Authorisation
NETHERLANDS	YES	Population of the Marketing Authorisation
SWITZERLAND	YES	Population of the Marketing Authorisation
DENMARK	YES	Population of the Marketing Authorisation
UK	NO, since NEXAVAR is not recommended in second-line treatment.	
UNITED STATES	YES	Patients with advanced renal cell carcinoma after failure of a first therapy

## 08 ANALYSIS OF AVAILABLE DATA

In support of its application for inclusion, the company supplied a clinical dossier comprising four studies:

- three dose-finding noncomparative, phase II studies (A4061012a, 14061035c and A4061023b); they will therefore not be used for the analysis of the therapeutic benefit of INLYTA because of their objective.
- a randomised, open phase III study (A4061032 or AXIS) versus sorafenib.

Indirect comparisons made by the company were also supplied.

### 08.1 Efficacy

#### 8.1.1 AXIS study (A4061032): inclusion from 15.09.2008 to 23.07.2010

Randomised, open phase III study with the aim of evaluating the efficacy and safety of axitinib (INLYTA) in the dosage 5 mg orally twice daily versus sorafenib (NEXAVAR) in the dosage 400 mg orally twice daily in patients with metastatic renal cell carcinoma after failure of systemic first-line treatment with sunitinib, bevacizumab+IFN $\alpha$ , temsirolimus or cytokine.

##### Inclusion criteria:

- patients over 18 years of age with histologically or cytologically confirmed clear-cell renal cell carcinoma, with metastases
- with failure of first-line treatment with sunitinib, bevacizumab+IFN $\alpha$ , temsirolimus or cytokine
- progression of disease on treatment with sunitinib, bevacizumab + IFN $\alpha$ , temsirolimus or cytokine
- ECOG score of 0 or 1
- life expectancy equal to or greater than 12 months.

##### Among the noninclusion criteria:

- patients who have received several prior treatments, an adjuvant or neoadjuvant treatment
- uncontrolled, pre-existing hypertension.

##### Treatments:

Patients were openly randomised (1:1) to one of the following two groups:

- axitinib group (n=361): 5 mg orally twice daily.

The dosage could be increased to 7 mg and up to 10 mg twice daily if there was no adverse event with a grade of more than 2 with the initial dose for two consecutive weeks, except in hypertensive patients or those treated with antihypertensives.

- sorafenib group (n=362): 400 mg orally twice daily.

Note: in this study, a particular inclusion criterion of which was the failure of first-line treatment with sunitinib, bevacizumab+IFN $\alpha$ , temsirolimus or cytokine, sorafenib was used in an indication broader than the one validated by its Marketing Authorisation which is limited to the treatment of advanced renal cell carcinoma after the failure of treatment based on interferon-alpha or interleukin-2 or in patients for whom these treatments are inappropriate.

Randomisation was stratified according to the ECOG score (0 versus 1) and the prior first-line treatment received (sunitinib versus bevacizumab versus temsirolimus versus cytokine).

Primary efficacy endpoint: progression-free survival, defined as the time between randomisation and the date on which objective tumour progression occurred, in accordance with the RECIST criteria, or death from any cause (evaluated by an independent committee).

The principal analysis was scheduled after the occurrence of 409 events on progression-free survival (31 August 2010).

The initial study protocol made provision for the inclusion of 540 patients. Because the number of drop-outs from the study was underestimated, the protocol was amended on 16 November 2009 to increase the number of subjects to be included from 540 to 650.

Another analysis was made with additional follow-up of about 9 months (cut-off on 3 June 2011).

#### Among the secondary endpoints:

- overall survival, defined as the time from randomisation to death from any cause;
- percentage objective response rate (complete or partial, confirmed according to the RECIST criteria);<sup>7</sup>
- duration of response defined as the time between the date of the objective response and the date of a progression occurring in accordance with the RECIST criteria or of death from any cause;
- quality of life measured using the EQ-5D and FKSII questionnaires (FACT-Kidney Symptom Index).

#### Results:

A total of 723 patients with advanced renal cell carcinoma were randomised: 361 patients to the axitinib group and 362 to the sorafenib group.

The median age of the patients was 61 years. More than half the patients in each group were in good general condition (ECOG 0): 54% in the axitinib group and 55% for sorafenib.

In 42% of cases, patients had a favourable prognosis and in 57% of cases an intermediate prognosis according to the MSKCC classification.<sup>8</sup>

More than 90% of patients had undergone nephrectomy and almost 20% had previously been treated with radiotherapy.

The first-line drug treatments contained sunitinib (54%), a cytokine (35%), bevacizumab (8%) or temsirolimus (3%).

Note: The current first-line treatment strategy for metastatic renal cell carcinoma is based mainly on sunitinib (about 2/3 of patients).

## ► Results for the primary endpoint

### Results for the overall population

In the main analysis, median progression-free survival (primary endpoint) was 6.7 months in the axitinib group and 4.7 months in the sorafenib group, a gain in absolute terms of 2 months in

<sup>7</sup> Complete response: disappearance of all tumoral lesions

Partial response: reduction of 30% in the largest lesion diameter

Disease progression: increase of 20% in the largest lesion diameter

Stable disease: changes in tumour size not meeting the conditions previously described

<sup>8</sup> The MSKCC score was calculated from the LDH level (>1.5 x the upper limit), the haemoglobin level (below the lower limit), the corrected serum calcium level (>10 mg/dl) and the absence of prior nephrectomy

favour of axitinib (HR = 0.67; 95% CI [0.54-0.81];  $p < 0.0001$ ) according to the evaluation of the independent review committee.

With an additional 9 months' follow-up, the results for median progression-free survival were similar: 6.8 months in the axitinib group and 4.7 months in the sorafenib group (HR = 0.67; 95% CI [0.56-0.81];  $p < 0.0001$ ).

#### Results in the subgroups as a function of the prior treatment:

- In the subgroup of patients treated with first-line sunitinib  
Median progression-free survival was 4.8 months in the axitinib group and 3.4 months in the sorafenib group, a gain in absolute terms of 1.4 months in favour of axitinib (HR = 0.74; 95% CI [0.57-0.96];  $p < 0.01$ ) according to the evaluation of the independent review committee.  
Note: The MA for sorafenib is validated only after failure of treatment based on interferon-alpha or interleukin-2 or in patients for whom these treatments are inappropriate.
- In the subgroup of patients treated with first-line cytokine  
Median progression-free survival was 12.1 months in the axitinib group and 6.5 months in the sorafenib group, a gain in absolute terms of 5.6 months in favour of axitinib (HR = 0.46; 95% CI [0.32-0.68];  $p < 0.0001$ ) according to the evaluation of the independent review committee.
- In the subgroup of patients treated with temsirolimus or bevacizumab-IFN $\alpha$   
In the subgroups of patients who previously received first-line treatment with temsirolimus (n=25) or bevacizumab-IFN $\alpha$  (n=59), no conclusion can be drawn. Consequently, the Marketing Authorisation indication for axitinib was limited to patients previously treated with sunitinib or cytokine.

#### **► Results for the main secondary endpoints (determination by the independent committee)**

##### Results for the overall population

- In the main analysis of progression-free survival (primary endpoint), median overall survival was not achieved (223 of the 723 patients included had died). Survival at 12 months was estimated at 66% in the axitinib group and 67.8% in the sorafenib group (HR = 1.01; 95% CI [0.77-1.31]; NS). In the updated analysis of overall survival (on 1 November 2011), the medians for overall survival did not differ: 20.1 months in the axitinib group versus 19.2 months in the sorafenib group (HR = 0.97; [0.80-1.17]; NS).
- The percentage objective response was 19.4% in the axitinib group and 9.4% in the sorafenib group (HR = 2.056 95% CI [1.41-3.00];  $p < 0.0001$ ) with no complete response.
- The mean duration of response was 11 months in the axitinib group and 10.6 months in the sorafenib group.
- The data suggest that there is no difference between the axitinib and sorafenib groups in quality of life according to the questionnaires EQ-5D and FKSI (FACT-Kidney Symptom Index). Since this was an open study, no reliable conclusion can be drawn from the results of this analysis.

##### Results in the main subgroups as a function of the prior treatment

- In the subgroup of patients treated with first-line sunitinib
  - Since median overall survival was not achieved in the main analysis, median overall survival was estimated as 15.2 months in the axitinib group and 18 months in the sorafenib group (HR = 1.07; 95% CI [0.77-1.49]; NS).  
The updated analysis of overall survival (on 1 November 2011) showed that median overall survival was 15.2 months in the axitinib group and 16.5 months in the sorafenib group (HR = 0.99; [0.78-1.27]; NS).
  - The percentage objective response was 11.3% in the axitinib group and 7.7% in the sorafenib group (HR = 1.48 95% CI [0.79-2.75]; NS) with no complete response.
  - The mean duration of response was 11 months in the axitinib group and 11.1 months in the sorafenib group.

- In the subgroup of patients treated with first-line cytokine
  - It was not possible to estimate median overall survival in the main analysis (HR = 0.74; 95% CI [0.42-1.31]; NS).  
The updated analysis of overall survival (on 1 November 2011) showed that median overall survival was 29.4 months in the axitinib group and 27.8 months in the sorafenib group (HR = 0.81; [0.56-1.19]; NS).
  - The percentage objective response was 32.5% in the axitinib group and 13.6% in the sorafenib group (HR = 2.39 95% CI [1.43-3.99]; p = 0.0002) with no complete response.
  - The mean duration of response was 11 months in the axitinib group and 10.6 months in the sorafenib group.

Table 1: Main efficacy results of the AXIS study in the overall population and in the main subgroups (corresponding to the population of the Marketing Authorisation) (ITT)

<b>Total study population</b>		
	<b>Axitinib (n = 361)</b>	<b>Sorafenib (n = 362)</b>
<b>Progression-free survival (primary endpoint)*</b>		
Median (months)	6.7	4.7
Difference in medians (months)	2	
Relative risk [95% CI]; p	0.67 [0.54; 0.81]; p<0.0001	
<b>Overall survival**</b>		
Median (months)	20.1	19.2
Difference in medians (months)	0.9	
Relative risk [95% CI]; p	0.97 [0.80; 1.17]; NS	
<b>Subgroup of patients previously treated with sunitinib</b>		
	<b>Axitinib (n = 194)</b>	<b>Sorafenib (n = 195)</b>
<b>Progression-free survival*</b>		
Median (months)	4.8	3.4
Difference in medians (months)	1.4	
Relative risk [95% CI]; p	0.74 [0.57; 0.96]; p<0.01	
<b>Overall survival**</b>		
Median (months)	15.2	16.5
Difference in medians (months)	-1.3	
Relative risk [95% CI]; p	0.99 [0.78; 1.27]; NS	
<b>Subgroup of patients previously treated with cytokine</b>		
	<b>Axitinib (n = 126)</b>	<b>Sorafenib (n = 125)</b>
<b>Progression-free survival*</b>		
Median (months)	12.1	6.5
Difference in medians (months)	5.6	
Relative risk [95% CI]; p	0.46 [0.32 - 0.68]; p<0.0001	
<b>Overall survival**</b>		
Median (months)	29.4	27.8
Difference in medians (months)	1.6	
Relative risk [95% CI]; p	0.81 [0.56; 1.19]; NS	

\* main analysis (cut-off on 31.08.2010)

\*\* updated analysis (cut-off on 1 November 2011)

## 8.1.2 Indirect comparisons

There is no comparative study versus AFINITOR (everolimus) because of their concomitant development.

Indirect comparisons<sup>9</sup> in terms of efficacy versus sorafenib, everolimus and pazopanib<sup>10</sup> in second-line treatment have been made by the company using:

- the AXIS study (axitinib versus sorafenib)
- the TARGET study (sorafenib versus placebo)
- the RECORD-1 study (everolimus versus placebo)

These indirect comparisons are however of limited interest, since:

- the network corresponding to these indirect comparisons is very small, and the indirect comparison of axitinib versus sorafenib merely confirms the results of the pivotal study comparing axitinib with sorafenib which is analysed by the Transparency Committee in this Opinion;
- the characteristics of the patients included in these studies differ between the studies;
- the number of lines and the type of prior treatments differ (AXIS study: a single line of prior treatment with cytokine, sunitinib bevacizumab or everolimus; TARGET study: a single line of prior treatment with cytokine; RECORD-1: at least one line of prior treatment with cytokine or tyrosine kinase inhibitors);
- certain levels of effect are derived from the results of interim analyses (RECORD-1 study), and are therefore potentially biased (possible overestimation of the effect of treatment).

Overall, the results are not very informative and are instead exploratory in nature, and do not allow any conclusions to be drawn with a high level of evidence as regards the benefit of axitinib as compared with everolimus (AFINITOR).

Finally, no comparison with the adverse effects observed for the above treatments was supplied (a dedicated, specific meta-analysis would have been required).

## 08.2 Safety/Adverse effects

The safety data are based on the AXIS study and cover the overall study population; the data for the main subgroups as a function of prior treatment (in particular with failure of sunitinib or a cytokine corresponding to the populations validated by the Marketing Authorisation) are not available in the study report.

Treatment discontinuations due to adverse events affected 9% (33/359) of the patients in the axitinib group and 13% (46/355) of the patients in the sorafenib group.

The percentage of patients who had serious adverse events was 30% (108/359) in the axitinib group and 31% (110/355) in the sorafenib group.

Events of grades 3 or 4 affected 64% of the patients in the axitinib group (228/359) and 67% of the patients (237/355) in the sorafenib group.

The commonest events in the axitinib group (n=359) were, by comparison with sorafenib (n=355): diarrhoea (55% of which 11% of grades  $\geq 3$  vs 53% of which 7% with grades  $\geq 3$ ), hypertension (40% of which 16% with grades  $\geq 3$  vs 29% of which 11% with grades  $\geq 3$ ), fatigue (39% of which 11% with grades  $\geq 3$  vs 32% of which 5% with grades  $\geq 3$ ).

The commonest events in the sorafenib group (n=355) were, by comparison with axitinib (n=359): palmar-plantar erythrodysesthesia (51% of which 16% with grades  $\geq 3$  vs 27% of which 5% with grades  $\geq 3$ ), alopecia (32% vs 4%, with no events of grades  $\geq 3$ ) and rash (32% of which 4% with grades  $\geq 3$  vs 13% of which 0.3% with grades  $\geq 3$ ).

---

<sup>9</sup> Statistical analysis of second line treatment of advanced/metastatic renal cell carcinoma (RCC): Efficacy Final Report, Dr Sarah Collins  
<sup>10</sup> The results for pazopanib (VOTRIENT) were not presented by the company in its dossier because this medicinal product is not reimbursed.

### Among the particular adverse events

#### Hypertension

Hypertension was reported in 40% (of which 16% of grades  $\geq 3$ ) of patients in the axitinib group and in 29% (of which 11% of grades  $\geq 3$ ) in the sorafenib group.

#### Thyroid dysfunction

Hypothyroidism was reported in 19% of patients in the axitinib group and in 8% of the sorafenib group. Hyperthyroidism was reported with comparable frequency in the two groups (1%).

#### Venous embolic and thrombotic events

Venous thromboembolic events were reported in 3.1% of patients in the axitinib group (of which 2.5% of grades 3-4) and in 0.6% (grades 3-4) in the sorafenib group. The commonest venous thromboembolic event was pulmonary embolism of grades 3-4, one of them fatal in the axitinib group (1.7% versus 0.6%).

#### Arterial embolic and thrombotic events

Arterial thromboembolic events were reported in 1.1% of patients in the axitinib group (grades 3-4) and in 0.8% (of which 0.6% of grades 3-4) in the sorafenib group. The commonest arterial thromboembolic event in the axitinib group was transient ischaemia (0.8%).

#### Haemorrhage

Haemorrhage events were reported in 16.2% (of which 1.4% of grades 3-4) of patients in the axitinib group and in 18% (of which 3.1% of grades 3-4) in the sorafenib group. The most frequently reported haemorrhagic events were: epistaxis (6.1 versus 4.2%), haemoptysis (2.2% versus 3.9%), haematuria (3.3% versus 2%), rectal bleeding (2.2% versus 3.9%) and gum bleeding (1.1% versus 2.3%).

## **08.3 Summary & discussion**

Oral axitinib (5 mg twice a day) was compared with oral sorafenib (400 mg twice a day) in an open-label study in 723 patients with metastatic, clear-cell renal cell carcinoma in whom first-line treatment with sunitinib, bevacizumab+IFN $\alpha$ , temsirolimus or cytokine had failed.

The patients' median age was 61 years and more than half were in good general condition (ECOG 0): 54% in the axitinib group and 55% for sorafenib. The patients had a favourable or intermediate prognosis according to the MSKCC classification. The first-line treatments were sunitinib (54%), a cytokine (35%), bevacizumab (8%) or temsirolimus (3%). Data are therefore very limited for patients who received first-line treatment with bevacizumab or temsirolimus (83/723 patients).

Median progression-free survival (primary endpoint)

- in the overall study population, it was longer in the axitinib group than in the sorafenib group (6.7 versus 4.7 months;  $p < 0.0001$ ), a gain in absolute terms of 2 months (HR = 0.67; 95% CI [0.54-0.81]);
- in the subgroup of patients who received first-line treatment with sunitinib or cytokine, corresponding to the population covered by the Marketing Authorisation, the gain was less in patients previously treated with sunitinib (4.8 months versus 3.4 months, a gain of 1.4 months) than in those previously treated with cytokine (12.1 months versus 6.5 months, a gain of 5.6 months).

There was no difference in overall survival between axitinib and sorafenib in the overall population or in the subgroups as a function of prior treatment in the main, updated analysis.

The percentage objective response was higher with axitinib than with sorafenib in the overall population (19.4% versus 9.4%,  $p < 0.0001$ ) and in patients previously treated with cytokine (32.5% versus 13.6%,  $p = 0.0002$ ) but no different in patients previously treated with sunitinib.

There was no difference in quality of life between axitinib and sorafenib, but since this was an open study, no reliable conclusion can be drawn from these results.

The frequency of serious adverse events (30%) was of the same order between axitinib and sorafenib. Treatment discontinuations due to adverse events affected 9% (33/359) of the patients in the axitinib group and 13% (46/355) of those in the sorafenib group.

The safety profile differed between these two tyrosine kinase inhibitors; the commonest events were:

- in the axitinib group: hypertension (40% vs 29%) and fatigue (39% vs 32%);
- in the sorafenib group: palmar-plantar erythrodysesthesia (51% vs 27%) and alopecia (32% vs 4%).

The Committee emphasises the following points about this study:

- the open design of this study despite the same route of administration of the medicinal products evaluated; the risk of bias reduces the robustness of its results;
- axitinib was compared with an active treatment, sorafenib (NEXAVAR), including in patients in whom sunitinib had failed. However, sorafenib has Marketing Authorisation only in patients previously treated with cytokine (interferon or interleukin);
- in patients previously treated with sunitinib, a tyrosine kinase inhibitor (about half the patients included) which is the current therapeutic use, the therapeutic benefit of a second tyrosine kinase inhibitor, axitinib, in second-line treatment, is not quantifiable versus everolimus (AFINITOR), a selective mTOR inhibitor, in the absence of a comparative study. The results of indirect comparisons carried out by the company, in particular versus everolimus, are exploratory in nature from no conclusions can be drawn with a sufficient level of evidence, particularly as regards the benefit of axitinib by comparison with everolimus (see section 7.1.2 Indirect comparisons).

## 08.4 Programme of studies

The company is planning to market dosages of 3 and 7 mg.

Studies are in progress in the first-line treatment of advanced and/or metastatic renal cell carcinoma.

## 09 THERAPEUTIC USE

---

In the second-line treatment of advanced renal cell carcinoma:

► **In patients with failure of prior treatment with sunitinib** (tyrosine kinase inhibitor):

If TKI-VEGFRs such as sunitinib fail, everolimus (AFINITOR), a selective mTOR inhibitor, is available as second- or third-line treatment.

In the absence of any comparative study versus everolimus (AFINITOR), the place of a second tyrosine kinase inhibitor, axitinib, has still to be determined.

► **In patients with failure of a prior treatment with cytokine:**

Patients receiving first-line treatment with cytokine [aldesleukin (PROLEUKIN) or interferon-alpha (ROFERON-A)] have, since the advent of first-line tyrosine kinase inhibitors, been a very limited subgroup of patients with a good prognosis. Axitinib would be an alternative to the other tyrosine kinase inhibitors, sorafenib (NEXAVAR) and sunitinib (SUTENT).

Overall, axitinib (INLYTA) is an option for the second-line treatment of advanced renal cell carcinoma after failure of prior treatment with a cytokine and mainly after failure of sunitinib. However, the place in therapeutic use of axitinib by comparison with everolimus (AFINITOR) has still to be determined.

**In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:**

### 010.1 Actual benefit

- ▶ Advanced renal cell carcinoma is a serious and life-threatening disease.
- ▶ These proprietary medicinal products are intended as specific curative cancer therapy.
- ▶ The efficacy/adverse effects ratio is high.

#### ▶ Public health benefit:

In France, the public health burden of renal cell carcinoma can be regarded as moderate (approximately 11,000 new cases in 2011). In terms of mortality, it accounts for about 2.5% of all deaths from cancer. That concerning the subpopulation of patients with advanced renal cell carcinoma who are likely to benefit from second-line treatment with INLYTA can only be small.

Improving the management of cancer patients and their quality of life is a public health need which is an established priority (French Public Health Law of 2004, the Cancer Plan and the Plan for improving the quality of life of patients with chronic diseases).

In view of the clinical study results available [in particular a phase III study, in second-line treatment versus NEXAVAR, showing a gain in progression-free survival of 2 months (but less (1.4 months) in patients previously treated with SUTENT) with no gain in terms of overall survival or quality of life], the expected impact of INLYTA in terms of morbidity, mortality and quality of life, can only be small.

The transferability of these results to clinical practice is not assured, given the change in therapeutic use leading to the treatment of mainly patients previously treated with SUTENT, a profile for which the gain in progression-free survival on INLYTA is smaller.

No impact on the organisation of healthcare is expected.

The medicinal product INLYTA is therefore unlikely to meet any identified public health need.

Consequently, it is not expected that the medicinal product INLYTA will benefit public health in this indication.

- ▶ Alternative medicinal products exist.
- ▶ This is a second-line treatment used after the failure of sunitinib or a cytokine.

**Taking account of these points, the Committee considers that the actual benefit of INLYTA is substantial in the Marketing Authorisation indication.**

**The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indication and at the dosage in the Marketing Authorisation.**

- ▶ **Proposed reimbursement rate: 100%**

## 010.2 Improvement in actual benefit (IAB)

In metastatic renal cell carcinoma, INLYTA (axitinib) was compared with an active medicinal product (sorafenib, NEXAVAR) and showed an increase only in progression-free survival of 2 months in absolute terms (clinically relevant but modest) by comparison with NEXAVAR (sorafenib): 6.7 months in the axitinib group versus 4.7 months for sorafenib in the overall study population. This study showed no impact on overall survival and has methodological weaknesses (open study whereas a double-blind design was possible in view of the same oral route of administration for the two medicines compared and recalculation of the number of subjects needed during the study).

Taking account of these points, the Committee attributes to INLYTA (axitinib) a minor improvement in actual benefit (IAB level IV) in terms of efficacy by comparison with NEXAVAR (sorafenib) in the second-line treatment of advanced renal cell carcinoma.

Since NEXAVAR (sorafenib) has Marketing Authorisation only for use after the failure of cytokines, the Transparency Committee stresses the absence of comparative data versus the second-line alternatives available which have Marketing Authorisation in patients with failure of prior treatment with sunitinib, particularly AFINITOR (everolimus). Consequently, the Committee cannot quantify the therapeutic benefit of INLYTA in current therapeutic use, i.e. as second-line treatment after the failure of sunitinib.

## 010.3 Target population

The target population for INLYTA (axitinib) consists of patients with advanced (locally advanced and/or metastatic) renal cell carcinoma after failure of prior first-line treatment with sunitinib or cytokine.

This population can be estimated from the following data:

- for 2011, a projection by the InVS [French National Health Monitoring Institute]<sup>11</sup> estimates that in France there were 11,092 new cases of renal cell carcinoma.
- clear-cell renal cell carcinoma accounts for 70 to 85% of renal cancers,<sup>12</sup> i.e. between 7764 and 9428 patients.
- depending on the publication, the frequency of patients newly diagnosed with locally advanced and/or metastatic renal cell carcinoma varies between 15% and 50%.<sup>13,14,15</sup> The mean value of 30% quoted in the EPAR for INLYTA will be used for the calculation (i.e. between 2329 and 2828 patients). Between 30%<sup>14</sup> and 40%<sup>16</sup> of localized stages will progress to an advanced or metastatic stage (i.e. between 1630 and 2640 patients). Thus the number of patients in the advanced stage is between 3960 and 5468 patients per year in first-line treatment.

We do not have any exact data on the proportion of patients who received first-line treatment with sunitinib or cytokine. Nevertheless, some proportions can be calculated approximately from the results of a market study carried out by PFIZER (see description in annex).

- In second-line treatment after failure of sunitinib: 71% of first-line patients were treated with sunitinib<sup>17</sup> (i.e. between 2812 and 3882 patients) and 51% of first-line patients will received 2nd line treatment:<sup>15</sup> between 1434 and 1979 patients a year are eligible for second-line treatment after the failure of sunitinib.

<sup>11</sup><http://www.invs.sante.fr/Publications-et-outils/Rapports-et-syntheses/Maladies-chroniques-et-traumatismes/2011/Projection-de-l-incidence-et-de-la-mortalite-par-cancer-en-France-en-2011>

<sup>12</sup> Escudier, T. Eisen, C. Porta J. J. Patard, Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 23 (Supplement 7): 65–71, 2012.

<sup>13</sup> Zini L, Capitanio U, Perrotte P, et al. Population-based assessment of survival after cytoreductive nephrectomy versus no surgery in patients with metastatic renal cell carcinoma. *Urology* 2009; 73 (2): 342-6.

<sup>14</sup> M. Gross-Goupil, B. Escudier Thérapies ciblées: traitements séquentiels et combinés. *Bull Cancer* vol. 97, supplement 2, April 2010.

<sup>15</sup> Transparency Committee opinion of 13.01.10 on AFINITOR.

<sup>16</sup> Thuret R et al. Traitement du carcinome rénal métastatique. *Progrès en Urologie*. Volume 21, Issue 4, April 2011, Pages 233–244.

<sup>17</sup> Market survey carried out by PFIZER, see description in annex.

- In second-line treatment after failure of a cytokine: since the first-line use of cytokines has become a rarity, the population of patients with failure of this line who would be eligible for treatment with INLYTA cannot be quantified.

**Overall, the target population for INLYTA is estimated to be between 1430 and 1980 patients a year.**

## **011**      **TRANSPARENCY COMMITTEE RECOMMENDATIONS**

---

### **► Packaging**

It is not appropriate for the prescription conditions.

The Committee point out that, in accordance with its deliberations of 20 July 2005, it recommends the harmonisation of packaging sizes for treatments lasting one month on 30 days' treatment and consequently of those for treatments lasting three months on 90 days' treatment.

## ANNEX

Survey carried out between 5 January 2012 and 30 March 2012 in five countries (Germany, UK, France, Spain and Italy) among 589 doctors, including 116 French doctors (87% oncologists and 13% urologists). These practitioners worked at a university hospital (31%), a university/general hospital (31%), a private institution (19%) or a cancer centre (18%).

Each practitioner had to supply the data for the last three patients treated with chemotherapy or targeted therapy (whatever the line of treatment) and the data for two patients who received second- or third-line treatment.

Overall, the results of this survey are taken from the retrospective analysis of the data for 2397 patients (468 of them in France) with metastatic renal cell carcinoma who were undergoing treatment (irrespective of the line) and for 1096 patients (214 of them in France) receiving second-line treatment during the survey.

The patients' mean age was 63.7 years (64.1 years in France). Patients were in good general condition (ECOG 0) in 32% of cases (24% in France) and had an ECOG 1 in 53% of cases (57% in France). Patients had a favourable prognosis in 34% of cases and an intermediate prognosis in 44% of cases (33% and 41% in France). The proportion of patients who had undergone nephrectomy is not available.

Of the 2397 patients included retrospectively, 1807 were on first-line treatment (352 of them in France) and 69% were being treated with sunitinib (71% in France).