ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Inlyta 1 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 1 mg of axitinib.

Excipients with known effect:
Each film-coated tablet contains 33.6 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Red oval film-coated tablet debossed with “Pfizer” on one side and “1 XNB” on the other

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Inlyta is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine.

4.2 Posology and method of administration

Treatment with Inlyta should be conducted by a physician experienced in the use of anticancer therapies.

Posology

The recommended 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 concomitant medicinal products or dose adjustments.

If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time.

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
Co-administration of axitinib with strong CYP3A4/5 inhibitors may increase axitinib plasma concentrations (see section 4.5). Selection of an alternate concomitant medicinal product with no or minimal CYP3A4/5 inhibition potential is recommended.

Although axitinib dose adjustment has not been studied in patients receiving strong CYP3A4/5 inhibitors, if a strong CYP3A4/5 inhibitor must be co-administered, a dose decrease of axitinib to approximately half the dose (e.g. the starting dose should be reduced from 5 mg twice daily to 2 mg twice daily) is recommended. Management of some adverse reactions may require temporary or permanent discontinuation of axitinib therapy (see section 4.4). If co-administration of the strong inhibitor is discontinued, a return to the axitinib dose used prior to initiation of the strong CYP3A4/5 inhibitor should be considered (see section 4.5).

Concomitant strong CYP3A4/5 inducers
Co-administration of axitinib with strong CYP3A4/5 inducers may decrease axitinib plasma concentrations (see section 4.5). Selection of an alternate concomitant medicinal product with no or minimal CYP3A4/5 induction potential is recommended.

Although axitinib dose adjustment has not been studied in patients receiving strong CYP3A4/5 inducers, if a strong CYP3A4/5 inducer must be co-administered, a gradual dose increase of axitinib is recommended. Maximal induction with high-dose strong CYP3A4/5 inducers has been reported to occur within one week of treatment with the inducer. If the dose of axitinib is increased, the patient should be monitored carefully for toxicity. Management of some adverse reactions may require temporary or permanent discontinuation and/or dose reduction of axitinib therapy (see section 4.4). If co-administration of the strong inducer is discontinued, the axitinib dose should be immediately returned to the dose used prior to initiation of the strong CYP3A4/5 inducer (see section 4.5).

<u>Special populations</u>

Older people (≥ 65 years): No dose adjustment is required (see sections 4.4 and 5.2).

Renal impairment: No dose adjustment is required (see section 5.2). Virtually no data are available regarding axitinib treatment in patients with a creatinine clearance of < 15 mL/min.

Hepatic impairment: No dose adjustment is required when administering axitinib to patients with mild hepatic impairment (Child-Pugh class A). A dose decrease is recommended when administering axitinib to patients with moderate hepatic impairment (Child-Pugh class B) (e.g. the starting dose should be reduced from 5 mg twice daily to 2 mg twice daily). Axitinib has not been studied in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this population (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of axitinib in children and adolescents < 18 years have not been established. No data are available.

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.

4.3 Contraindications

Hypersensitivity to axitinib or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Specific safety events should be monitored before initiation of, and periodically throughout, treatment with axitinib as described below.

Cardiac failure events
In clinical studies with axitinib for the treatment of patients with RCC, cardiac failure events (including cardiac failure, cardiac failure congestive, cardiopulmonary failure, left ventricular dysfunction, ejection fraction decreased, and right ventricular failure) were reported (see section 4.8).

Signs or symptoms of cardiac failure should periodically be monitored throughout treatment with axitinib. Management of cardiac failure events may require temporary interruption or permanent discontinuation and/or dose reduction of axitinib therapy.

Hypertension
In clinical studies with axitinib for the treatment of patients with RCC, hypertension was very commonly reported (see section 4.8).

In a controlled clinical study, the median onset time for hypertension (systolic blood pressure > 150 mmHg or diastolic blood pressure > 100 mmHg) was within the first month of the start of axitinib treatment and blood pressure increases have been observed as early as 4 days after starting axitinib.

Blood pressure should be well-controlled prior to initiating axitinib. Patients should be monitored for hypertension and treated as needed with standard antihypertensive therapy. In the case of persistent hypertension, despite use of antihypertensive medicinal products, the axitinib dose should be reduced. For patients who develop severe hypertension, temporarily interrupt axitinib and restart at a lower dose once the patient is normotensive. If axitinib is interrupted, patients receiving antihypertensive medicinal products should be monitored for hypotension (see section 4.2).

In case of severe or persistent arterial hypertension and symptoms suggestive of posterior reversible encephalopathy syndrome (PRES) (see below), a diagnostic brain magnetic resonance image (MRI) should be considered.

Thyroid dysfunction
In clinical studies with axitinib for the treatment of patients with RCC, events of hypothyroidism and, to a lesser extent, hyperthyroidism, were reported (see section 4.8).

Thyroid function should be monitored before initiation of, and periodically throughout, treatment with axitinib. Hypothyroidism or hyperthyroidism should be treated according to standard medical practice to maintain euthyroid state.

Arterial embolic and thrombotic events
In clinical studies with axitinib, arterial embolic and thrombotic events (including transient ischemic attack, myocardial infarction, cerebrovascular accident and retinal artery occlusion) were reported (see section 4.8).

Axitinib should be used with caution in patients who are at risk for, or who have a history of, these events. Axitinib has not been studied in patients who had an arterial embolic or thrombotic event within the previous 12 months.

Venous embolic and thrombotic events
In clinical studies with axitinib, venous embolic and thrombotic events (including pulmonary embolism, deep vein thrombosis, and retinal vein occlusion/thrombosis) were reported (see section 4.8).

Axitinib should be used with caution in patients who are at risk for, or who have a history of, these events. Axitinib has not been studied in patients who had a venous embolic or thrombotic event within the previous 6 months.

Elevation of haemoglobin or haematocrit
Increases in haemoglobin or haematocrit, reflective of increases in red blood cell mass, may occur during treatment with axitinib (see section 4.8, polycythaemia). An increase in red blood cell mass may increase the risk of embolic and thrombotic events.

Haemoglobin or haematocrit should be monitored before initiation of, and periodically throughout, treatment with axitinib. If haemoglobin or haematocrit becomes elevated above the normal level, patients should be treated according to standard medical practice to decrease haemoglobin or haematocrit to an acceptable level.

Haemorrhage
In clinical studies with axitinib, haemorrhagic events were reported (see section 4.8).

Axitinib has not been studied in patients who have evidence of untreated brain metastasis or recent active gastrointestinal bleeding, and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the axitinib dose.

Gastrointestinal perforation and fistula formation
In clinical studies with axitinib, events of gastrointestinal perforation and fistulas were reported (see section 4.8).

Symptoms of gastrointestinal perforation or fistula should be periodically monitored for throughout treatment with axitinib.

Wound healing complications
No formal studies of the effect of axitinib on wound healing have been conducted.

Treatment with axitinib should be stopped at least 24 hours prior to scheduled surgery. The decision to resume axitinib therapy after surgery should be based on clinical judgment of adequate wound healing.

Posterior reversible encephalopathy syndrome (PRES)
In clinical studies with axitinib, events of PRES were reported (see section 4.8).

PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES. In patients with signs or

symptoms of PRES, temporarily interrupt or permanently discontinue axitinib treatment. The safety of reinitiating axitinib therapy in patients previously experiencing PRES is not known.

Proteinuria
In clinical studies with axitinib, proteinuria, including that of Grade 3 and 4 severity, was reported (see section 4.8).

Monitoring for proteinuria before initiation of, and periodically throughout, treatment with axitinib is recommended. For patients who develop moderate to severe proteinuria, reduce the dose or temporarily interrupt axitinib treatment (see section 4.2).

Liver-related adverse reactions
In a controlled clinical study with axitinib for the treatment of patients with RCC, liver-related adverse reactions were reported. The most commonly reported liver-related adverse reactions included increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and blood bilirubin (see section 4.8). No concurrent elevations of ALT (> 3 times the upper limit of normal [ULN]) and bilirubin (> 2 times the ULN) were observed.

In a clinical dose-finding study, concurrent elevations of ALT (12 times the ULN) and bilirubin (2.3 times the ULN), considered to be drug-related hepatotoxicity, were observed in 1 patient who received axitinib at a starting dose of 20 mg twice daily (4 times the recommended starting dose).

Liver function tests should be monitored before initiation of, and periodically throughout, treatment with axitinib.

Hepatic impairment
In clinical studies with axitinib, the systemic exposure to axitinib was approximately two-fold higher in subjects with moderate hepatic impairment (Child-Pugh class B) compared to subjects with normal hepatic function. A dose decrease is recommended when administering axitinib to patients with moderate hepatic impairment (Child-Pugh class B) (see section 4.2).

Axitinib has not been studied in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this population.

Older people (≥ 65 years) and race
In a controlled clinical study with axitinib for the treatment of patients with RCC, 34% of patients treated with axitinib were ≥ 65 years of age. The majority of patients were White (77%) or Asian (21%). Although greater sensitivity to develop adverse reactions in some older patients and Asian patients cannot be ruled out, overall, no major differences were observed in the safety and effectiveness of axitinib between patients who were ≥ 65 years of age and non-elderly, and between White patients and patients of other races.

No dosage adjustment is required on the basis of patient age or race (see sections 4.2 and 5.2).

Lactose
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro data indicate that axitinib is metabolised primarily by CYP3A4/5 and, to a lesser extent, CYP1A2, CYP2C19, and uridine diphosphate-glucuronosyltransferase (UGT) 1A1.

CYP3A4/5 inhibitors
Ketoconazole, a strong inhibitor of CYP3A4/5, administered at a dose of 400 mg once daily for 7 days, increased the mean area under the curve (AUC) 2-fold and C_{max} 1.5-fold of a single 5-mg oral dose of axitinib in healthy volunteers. Co-administration of axitinib with strong CYP3A4/5 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, erythromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin) may increase axitinib plasma concentrations. Grapefruit may also increase axitinib plasma concentrations. Selection of concomitant medicinal products with no or minimal CYP3A4/5 inhibition potential is recommended. If a strong CYP3A4/5 inhibitor must be co-administered, a dose adjustment of axitinib is recommended (see section 4.2).

CYP1A2 and CYP2C19 inhibitors
CYP1A2 and CYP2C19 constitute minor (< 10%) pathways in axitinib metabolism. The effect of strong inhibitors of these isozymes on axitinib pharmacokinetics has not been studied. Caution should be exercised due to the risk of increased axitinib plasma concentrations in patients taking strong inhibitors of these isozymes.

CYP3A4/5 inducers
Rifampicin, a strong inducer of CYP3A4/5, administered at a dose of 600 mg once daily for 9 days, reduced the mean AUC by 79% and C_{max} by 71% of a single 5 mg dose of axitinib in healthy volunteers.

Co-administration of axitinib with strong CYP3A4/5 inducers (e.g. rifampicin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentin, phenobarbital, and *Hypericum perforatum* [St. John's wort]) may decrease axitinib plasma concentrations. Selection of concomitant medicinal products with no or minimal CYP3A4/5 induction potential is recommended. If a strong CYP3A4/5 inducer must be co-administered, a dose adjustment of axitinib is recommended (see section 4.2).

In vitro studies of CYP and UGT inhibition and induction
In vitro studies indicated that axitinib does not inhibit CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, or UGT1A1 at therapeutic plasma concentrations.

In vitro studies indicated that axitinib has a potential to inhibit CYP1A2. Therefore, co-administration of axitinib with CYP1A2 substrates may result in increased plasma concentrations of CYP1A2 substrates (e.g. theophylline).

In vitro studies also indicated that axitinib has the potential to inhibit CYP2C8. However, co-administration of axitinib with paclitaxel, a known CYP2C8 substrate, did not result in increased plasma concentrations of paclitaxel in patients with advanced cancer, indicating lack of clinical CYP2C8 inhibition.

In vitro studies in human hepatocytes also indicated that axitinib does not induce CYP1A1, CYP1A2, or CYP3A4/5. Therefore co-administration of axitinib is not expected to reduce the plasma concentration of co-administered CYP1A1, CYP1A2, or CYP3A4/5 substrates *in vivo*.

In vitro studies with P-glycoprotein
In vitro studies indicated that axitinib inhibits P-glycoprotein. However, axitinib is not expected to inhibit P-glycoprotein at therapeutic plasma concentrations. Therefore, co-administration of axitinib is not expected to increase the plasma concentration of digoxin, or other P-glycoprotein substrates, *in vivo*.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data regarding the use of axitinib in pregnant women. Based on the pharmacological properties of axitinib, it may cause foetal harm when administered to a pregnant woman. Studies in animals have shown reproductive toxicity including malformations (see section 5.3). Axitinib should not be used during pregnancy unless the clinical condition of the woman requires treatment with this medicinal product.

Women of childbearing potential must use effective contraception during and up to 1 week after treatment.

Breast-feeding
It is unknown whether axitinib is excreted in human milk. A risk to the suckling child cannot be excluded. Axitinib should not be used during breast-feeding.

Fertility
Based on non-clinical findings, axitinib has the potential to impair reproductive function and fertility in humans (see section 5.3).

4.7 Effects on ability to drive and use machines

Axitinib has a minor influence on the ability to drive and use machines. Patients should be advised that they may experience events such as dizziness and/or fatigue during treatment with axitinib.

4.8 Undesirable effects

Summary of the safety profile
The following risks, including appropriate action to be taken, are discussed in greater detail in *Section 4.4:* cardiac failure events, hypertension, thyroid dysfunction, arterial thromboembolic events, venous thromboembolic events, elevation of haemoglobin or haematocrit, haemorrhage, gastrointestinal perforation and fistula formation, wound healing complications, PRES, proteinuria, and elevation of liver enzymes.

The most common (≥ 20%) adverse reactions observed following treatment with axitinib were diarrhoea, hypertension, fatigue, decreased appetite, nausea, weight decreased, dysphonia, palmar-plantar erythrodysaesthesia (hand-foot) syndrome, haemorrhage, hypothyroidism, vomiting, proteinuria, cough, and constipation.

Tabulated list of adverse reactions
Table 1 presents adverse reactions reported in a pooled dataset of 672 patients who received axitinib in clinical studies for the treatment of patients with RCC (see section 5.1).

The adverse reactions are listed by system organ class, frequency category and grade of severity. Frequency categories are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), and not known (cannot be estimated from the available data). The current safety database for axitinib is too small to detect rare and very rare adverse reactions.

Categories have been assigned based on absolute frequencies in the pooled clinical studies data. Within each system organ class, adverse reactions with the same frequency are presented in order of decreasing seriousness.

Table 1. Adverse reactions reported in RCC studies in patients who received axitinib (N = 672)

System Organ Class	Frequency Category	Adverse Reactions[a]	All Grades[b] %	Grade 3[b] %	Grade 4[b] %
Blood and lymphatic system disorders	Common	Anaemia	6.3	1.2	0.4
		Thrombocytopenia	1.6	0.1	0
		Polycythaemia[c]	1.5	0.1	0
	Uncommon	Neutropaenia	0.3	0.1	0
		Leukopaenia	0.4	0	0
Endocrine disorders	Very Common	Hypothyroidism[c]	24.6	0.3	0
	Common	Hyperthyroidism[c]	1.6	0.1	0.1
Metabolism and nutrition disorders	Very Common	Decreased appetite	39.0	3.6	0.3
	Common	Dehydration	6.7	3.1	0.3
		Hyperkalaemia	2.7	1.2	0.1
		Hypercalcaemia	2.2	0.1	0.3
Nervous system disorders	Very Common	Headache	16.2	0.7	0
		Dysgeusia	11.5	0	0
	Common	Dizziness	9.1	0.6	0
	Uncommon	Posterior reversible encephalopathy syndrome[e]	0.3	0.1	0
Ear and labyrinth disorders	Common	Tinnitus	3.1	0	0
Cardiac disorders	Common	Cardiac failure events[c,d,f]	1.8	0.3	0.7
Vascular disorders	Very Common	Hypertension[g]	51.2	22.0	1.0
		Haemorrhage[c,d,h]	25.7	3.0	1.0
	Common	Venous embolic and thrombotic events[c,d,i]	2.8	0.9	1.2
		Arterial embolic and thrombotic events[c,d,j]	2.8	1.2	1.3
Respiratory, thoracic and mediastinal disorders	Very Common	Dyspnoea[d]	17.1	3.6	0.6
		Cough	20.4	0.6	0
		Dysphonia	32.7	0	0.1
	Common	Oropharyngeal pain	7.4	0	0
Gastrointestinal disorders	Very Common	Diarrhoea	55.4	10.1	0.1
		Vomiting	23.7	2.7	0.1
		Nausea	33.0	2.2	0.1
		Abdominal pain	14.7	2.5	0.3
		Constipation	20.2	1.0	0
		Stomatitis	15.5	1.8	0
		Dyspepsia	11.2	0.1	0
	Common	Upper abdominal pain	9.4	0.9	0
		Flatulence	4.5	0	0
		Haemorrhoids	3.3	0	0
		Glossodynia	2.8	0	0
		Gastrointestinal perforation and fistula[c,k]	1.9	0.9	0.3
Hepatobiliary disorders	Common	Hyperbilirubinaemia	1.3	0.1	0.1

System Organ Class	Frequency Category	Adverse Reactions[a]	All Grades[b] %	Grade 3[b] %	Grade 4[b] %
Skin and subcutaneous tissue disorders	Very Common	Palmar-plantar erythrodysaesthesia (hand-foot syndrome)	32.1	7.6	0
		Rash	14.3	0.1	0
		Dry skin	10.1	0.1	0
	Common	Pruritus	6.0	0	0
		Erythema	3.7	0	0
		Alopecia	5.7	0	0
Musculoskeletal and connective tissue disorders	Very Common	Arthralgia	17.7	1.9	0.3
		Pain in extremity	14.1	1.0	0.3
	Common	Myalgia	8.2	0.6	0.1
Renal and urinary disorders	Very Common	Proteinuria[l]	21.1	4.8	0.1
	Common	Renal failure[m]	1.6	0.9	0.1
General disorders and administration site conditions	Very Common	Fatigue	45.1	10.6	0.3
		Asthaenia[d]	13.8	2.8	0.3
		Mucosal inflammation	13.7	1.0	0
Investigations	Very Common	Weight decreased	32.7	4.9	0
	Common	Lipase increased	3.7	0.7	0.7
		Alanine aminotransferase increased	6.5	1.2	0
		Amylase increased	3.4	0.6	0.4
		Aspartate aminotransferase increased	6.1	1.0	0
		Alkaline phosphatase increased	4.8	0.3	0
		Creatinine increased	5.7	0.4	0
		Thyroid stimulating hormone increased	7.9	0	0

[a] Adverse reactions are according to treatment-emergent, all causality frequency.
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0
[c] See Description of selected adverse reactions section.
[d] Fatal (Grade 5) cases were reported.
[e] Including Leukoencephalopathy.
[f] Including cardiac failure, cardiac failure congestive, cardiopulmonary failure, ejection fraction decreased, left ventricular dysfunction and right ventricular failure.
[g] Including accelerated hypertension, blood pressure increased, hypertension and hypertensive crisis.
[h] Including activated partial thromboplastin time prolonged, anal haemorrhage, arterial haemorrhage, blood urine present, central nervous system haemorrhage, cerebral haemorrhage, coagulation time prolonged, conjunctival haemorrhage, contusion, diarrhea haemorrhagic, dysfunctional uterine bleeding, epistaxis, gastric haemorrhage, gastrointestinal haemorrhage, gingival bleeding, haematemesis, haematochezia, haematocrit decreased, haematoma, haematuria, haemoglobin decreased, haemoptysis, haemorrhage, haemorrhage coronary artery, haemorrhage urinary tract, haemorrhoidal haemorrhage, haemostasis, increased tendency to bruise, international normalized ratio increased, lower gastrointestinal haemorrhage, melaena, petechiae, pharyngeal haemorrhage, prothrombin time prolonged, pulmonary haemorrhage, purpura, rectal haemorrhage, red blood cell count decreased, renal haemorrhage, scleral haemorrhage, scrotal haematocoele, splenic haemotoma, splinter haemorrhage, subarachnoid haemorrhage, tongue haemorrhage, upper gastrointestinal haemorrhage and vaginal haemorrhage.
[i] Including Budd-Chiari syndrome, deep vein thrombosis, jugular vein thrombosis, pelvic venous thrombosis, pulmonary embolism, retinal vein occlusion, retinal vein thrombosis, subclavian vein thrombosis, venous thrombosis, and venous thrombosis limb.

[j] Including acute myocardial infarction, embolism, myocardial infarction, retinal artery occlusion and transient ischaemic attack.
[k] Gastrointestinal perforation and fistula includes the following preferred terms: abdominal abscess, anal abscess, anal fistula, fistula, gastrointestinal anastomotic leak, gastrointestinal perforation, large intestine perforation, oesophagobronchial fistula and peritonitis.
[l] Proteinuria includes the following preferred terms: protein urine, protein urine present and proteinuria.
[m] Including acute renal failure

Description of selected adverse reactions

Cardiac failure events (see section 4.4)
In a controlled clinical study with axitinib (N = 359) for the treatment of patients with RCC, cardiac failure events were reported in 1.7 % patients receiving axitinib, including cardiac failure (0.6%), cardiopulmonary failure (0.6%), left ventricular dysfunction (0.3%), and right ventricular failure (0.3%). Grade 4 cardiac failure adverse reactions were reported in 0.6 % of patients receiving axitinib. Fatal cardiac failure was reported in 0.6 % of patients receiving axitinib.

In monotherapy studies with axitinib (N = 672) for the treatment of patients with RCC, cardiac failure events (including cardiac failure, cardiac failure congestive, cardiopulmonary failure, left ventricular dysfunction, ejection fraction decreased, and right ventricular failure) were reported in 1.8% patients receiving axitinib. Grade 3/4 cardiac failure events were reported in 1.0% patients and fatal cardiac failure events were reported in 0.3% patients receiving axitinib.

Thyroid dysfunction (see section 4.4)
In a controlled clinical study with axitinib for the treatment of patients with RCC, hypothyroidism was reported in 20.9% of patients and hyperthyroidism was reported in 1.1% of patients. Thyroid stimulating hormone (TSH) increased was reported as an adverse reaction in 5.3% of patients receiving axitinib. During routine laboratory assessments, in patients who had TSH < 5 μU/mL before treatment, elevations of TSH to ≥ 10 μU/mL occurred in 32.2% of patients receiving axitinib.

In pooled clinical studies with axitinib (N = 672) for the treatment of patients with RCC, hypothyroidism was reported in 24.6% of patients receiving axitinib. Hyperthyroidism was reported in 1.6% of patients receiving axitinib.

Venous embolic and thrombotic events (see section 4.4)
In a controlled clinical study with axitinib for the treatment of patients with RCC, venous embolic and thrombotic adverse reactions were reported in 3.9% of patients receiving axitinib, including pulmonary embolism (2.2%), retinal vein occlusion/thrombosis (0.6%) and deep vein thrombosis (0.6%). Grade 3/4 venous embolic and thrombotic adverse reactions were reported in 3.1% of patients receiving axitinib. Fatal pulmonary embolism was reported in one patient (0.3%) receiving axitinib.

In pooled clinical studies with axitinib (N = 672) for the treatment of patients with RCC, venous embolic and thrombotic events were reported in 2.8% of patients receiving axitinib. Grade 3 venous embolic and thrombotic events were reported in 0.9% of patients. Grade 4 venous embolic and thrombotic events were reported in 1.2% of patients. Fatal venous embolic and thrombotic events were reported 0.1% patients receiving axitinib.

Arterial embolic and thrombotic events (see section 4.4)
In a controlled clinical study with axitinib for the treatment of patients with RCC, arterial embolic and thrombotic adverse reactions were reported in 4.7% of patients receiving axitinib, including myocardial infarction (1.4%), transient ischemic attack (0.8%) and cerebrovascular accident (0.6%). Grade 3/4 arterial embolic and thrombotic adverse reactions were reported in 3.3% of patients receiving axitinib. A fatal acute myocardial infarction and cerebrovascular accident was reported in one patient each (0.3%). In monotherapy studies with axitinib (N = 850), arterial embolic and

thrombotic adverse reactions (including transient ischemic attack, myocardial infarction, and cerebrovascular accident) were reported in 5.3% of patients receiving axitinib.

In pooled clinical studies with axitinib (N = 672) for the treatment of patients with RCC, arterial embolic and thrombotic events were reported in 2.8% of patients receiving axitinib. Grade 3 arterial embolic and thrombotic events were reported in 1.2% of patients. Grade 4 arterial embolic and thrombotic events were reported in 1.3% of patients. Fatal arterial embolic and thrombotic events were reported in 0.3% patients receiving axitinib.

*Polycythaemia (*see *Elevation of haemoglobin or haematocrit* in section 4.4)
In a controlled clinical study with axitinib for the treatment of patients with RCC, polycythaemia was reported in 1.4% of patients receiving axitinib. Routine laboratory assessments detected elevated haemoglobin above ULN in 9.7% of patients receiving axitinib. In four clinical studies with axitinib for the treatment of patients with RCC (N = 537), elevated haemoglobin above ULN was observed in 13.6% receiving axitinib.

In pooled clinical studies with axitinib (N = 672) for the treatment of patients with RCC, polycythaemia was reported in 1.5% of patients receiving axitinib.

Haemorrhage (see section 4.4)
In a controlled clinical study with axitinib for the treatment of patients with RCC that excluded patients with untreated brain metastasis, haemorrhagic adverse reactions were reported in 21.4% of patients receiving axitinib. The haemorrhagic adverse reactions in patients treated with axitinib included epistaxis (7.8%), haematuria (3.6%), haemoptysis (2.5%), rectal haemorrhage (2.2%), gingival bleeding (1.1%), gastric haemorrhage (0.6%), cerebral haemorrhage (0.3%) and lower gastrointestinal haemorrhage (0.3%). Grade $\geq$ 3 haemorrhagic adverse reactions were reported in 3.1% of patients receiving axitinib (including cerebral haemorrhage, gastric haemorrhage, lower gastrointestinal haemorrhage and haemoptysis). Fatal haemorrhage was reported in one patient (0.3%) receiving axitinib (gastric haemorrhage). In monotherapy studies with axitinib (N = 850), haemoptysis was reported in 3.9% of patients; Grade $\geq$ 3 haemoptysis was reported in 0.5% of patients.

In pooled clinical studies with axitinib (N = 672) for the treatment of patients with RCC, haemorrhagic events were reported in 25.7% of patients receiving axitinib. Grade 3 haemorrhagic adverse reactions were reported in 3% of patients. Grade 4 haemorrhagic adverse reactions were reported in 1% of patients and fatal haemorrhage were reported in 0.4% of patients receiving axitinib.

Gastrointestinal perforation and fistula formation (see section 4.4)
In a controlled clinical study with axitinib for the treatment of patients with RCC, gastrointestinal perforation-type events were reported in 1.7% of patients receiving axitinib, including anal fistula (0.6%), fistula (0.3%) and gastrointestinal perforation (0.3%).In monotherapy studies with axitinib (N = 850), gastrointestinal perforation-type events were reported in 1.9% of patients and fatal gastrointestinal perforation was reported in one patient (0.1%).

In pooled clinical studies with axitinib (N = 672) for the treatment of patients with RCC, gastrointestinal perforation and fistula were reported in 1.9% of patients receiving axitinib.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no specific treatment for axitinib overdose.

In a controlled clinical study with axitinib for the treatment of patients with RCC, one patient inadvertently received a dose of 20 mg twice daily for 4 days and experienced dizziness (Grade 1).

In a clinical dose finding study with axitinib, subjects who received starting doses of 10 mg twice daily or 20 mg twice daily experienced adverse reactions which included hypertension, seizures associated with hypertension, and fatal haemoptysis.

In cases of suspected overdose, axitinib should be withheld and supportive care instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE17

Mechanism of action
Axitinib is a potent and selective tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, VEGFR-2 and VEGFR-3. These receptors are implicated in pathologic angiogenesis, tumour growth, and metastatic progression of cancer. Axitinib has been shown to potently inhibit VEGF-mediated endothelial cell proliferation and survival. Axitinib inhibited the phosphorylation of VEGFR-2 in xenograft tumour vasculature that expressed the target *in vivo* and produced tumour growth delay, regression, and inhibition of metastases in many experimental models of cancer.

Effect on QTc interval
In a randomised, 2-way crossover study, 35 healthy subjects were administered a single oral dose of axitinib (5 mg) in the absence and presence of 400 mg ketoconazole for 7 days. Results of this study indicated that axitinib plasma exposures up to two-fold greater than therapeutic levels expected following a 5 mg dose, did not produce clinically-significant QT interval prolongation.

Clinical efficacy
The safety and efficacy of axitinib were evaluated in a randomised, open-label, multicenter Phase 3 study. Patients (N = 723) with advanced RCC whose disease had progressed on or after treatment with one prior systemic therapy, including sunitinib-, bevacizumab-, temsirolimus-, or cytokine-containing regimens were randomised (1:1) to receive axitinib (N = 361) or sorafenib (N = 362). The primary endpoint, progression-free survival (PFS), was assessed using a blinded independent central review. Secondary endpoints included objective response rate (ORR) and overall survival (OS).

Of the patients enrolled in this study, 389 patients (53.8%) had received one prior sunitinib-based therapy, 251 patients (34.7%) had received one prior cytokine-based therapy (interleukin-2 or interferon-alpha), 59 patients (8.2%) had received one prior bevacizumab-based therapy, and 24 patients (3.3%) had received one prior temsirolimus-based therapy. The baseline demographic and disease characteristics were similar between the axitinib and sorafenib groups with regard to age, gender, race, Eastern Cooperative Oncology Group (ECOG) performance status, geographic region, and prior treatment.

In the overall patient population and the two main subgroups (prior sunitinib treatment and prior cytokine treatment), there was a statistically significant advantage for axitinib over sorafenib for the primary endpoint of PFS (see Table 2 and Figures 1, 2 and 3). The magnitude of median PFS effect was different in the subgroups by prior therapy. Two of the subgroups were too small to give reliable results (prior temsirolimus treatment or prior bevacizumab treatment). There were no statistically significant differences between the arms in OS in the overall population or in the subgroups by prior therapy.

Table 2. Efficacy results

Endpoint / Study Population	Axitinib	Sorafenib	HR (95% CI)	p-value
Overall ITT	**N = 361**	**N = 362**		
Median PFS [a,b] in months (95% CI)	6.8 (6.4, 8.3)	4.7 (4.6, 6.3)	0.67 (0.56, 0.81)	< 0.0001[c]
Median OS [d] in months (95% CI)	20.1 (16.7, 23.4)	19.2 (17.5, 22.3)	0.97 (0.80, 1.17)	NS
ORR [b,e] % (95% CI)	19.4 (15.4, 23.9)	9.4 (6.6, 12.9)	2.06[f] (1.41, 3.00)	0.0001[g]
Prior sunitinib treatment	**N = 194**	**N = 195**		
Median PFS [a,b] in months (95% CI)	4.8 (4.5, 6.5)	3.4 (2.8, 4.7)	0.74 (0.58, 0.94)	0.0063[h]
Median OS [d] in months (95% CI)	15.2 (12.8, 18.3)	16.5 (13.7, 19.2)	1.00 (0.78, 1.27)	NS
ORR [b,e] % (95% CI)	11.3 (7.2, 16.7)	7.7 (4.4, 12.4)	1.48[f] (0.79, 2.75)	NS
Prior cytokine treatment	**N = 126**	**N = 125**		
Median PFS [a,b] in months (95% CI)	12.0 (10.1, 13.9)	6.6 (6.4, 8.3)	0.52 (0.38, 0.72)	< 0.0001[h]
Median OS [d] in months (95% CI)	29.4 (24.5, NE)	27.8 (23.1, 34.5)	0.81 (0.56, 1.19)	NS
ORR [b,e] % (95% CI)	32.5 (24.5, 41.5)	13.6 (8.1, 20.9)	2.39[f] (1.43-3.99)	0.0002[i]

CI = Confidence interval, HR = Hazard ratio (axitinib/sorafenib); ITT: Intent-to-treat; NE: not estimable; NS: not statistically significant; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival.

[a] Time from randomisation to progression or death due to any cause, whichever occurs first. Cutoff date: 03 June 2011.

[b] Assessed by independent radiology review according to Response Evaluation Criteria in Solid Tumours (RECIST).

[c] One-sided p-value from a log-rank test of treatment stratified by ECOG performance status and prior therapy.

[d] Cutoff date: 01 November 2011.

[e] Cutoff date: 31 August 2010.

[f] Risk ratio is used for ORR. A risk ratio > 1 indicated a higher likelihood of responding in the axitinib arm; a risk ratio < 1 indicated a higher likelihood of responding in the sorafenib arm.

[g] One-sided p-value from Cochran-Mantel-Haenszel test of treatment stratified by ECOG performance status and prior therapy.

[h] One-sided p-value from a log-rank test of treatment stratified by ECOG performance status.

[i] One-sided p-value from Cochran-Mantel-Haenszel test of treatment stratified by ECOG performance status.

Figure 1. Kaplan-Meier curve of progression-free survival by independent assessment for the overall population

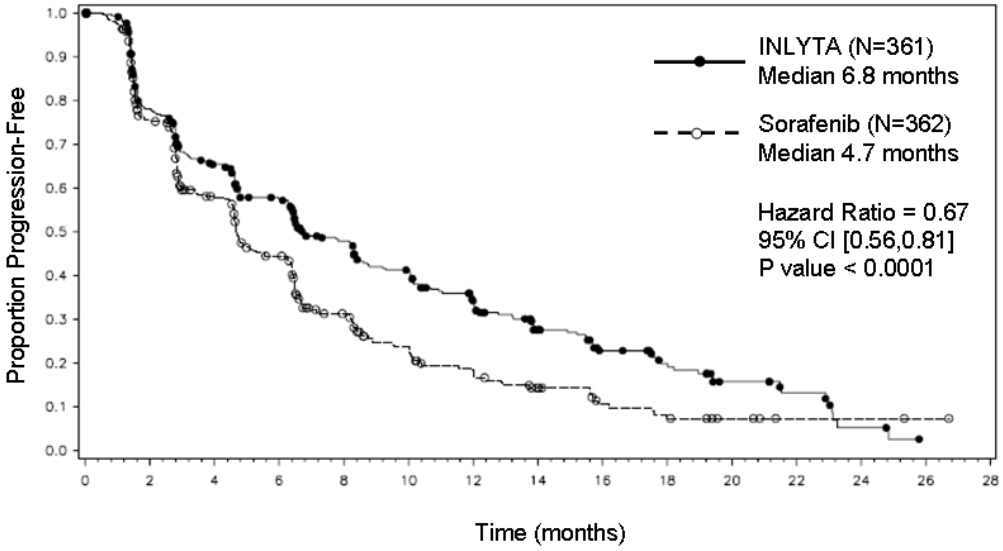


Figure 2. Kaplan-Meier curve of progression-free survival by independent assessment for the prior sunitinib subgroup

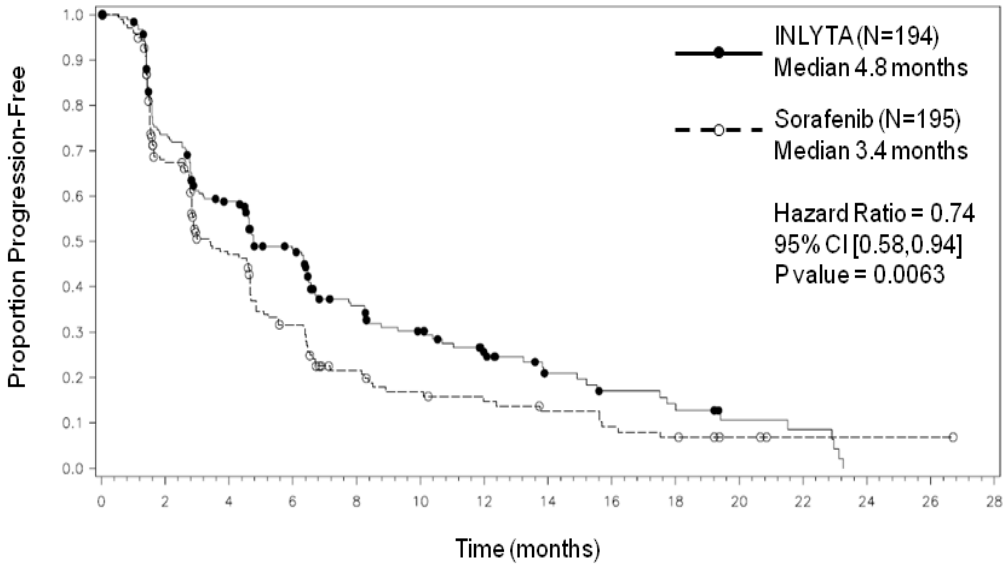
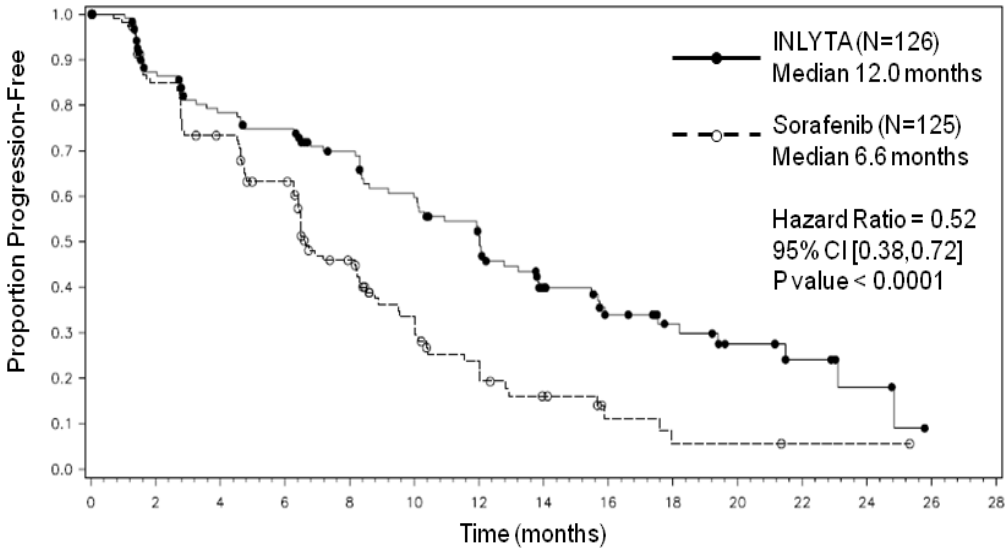


Figure 3. Kaplan-Meier curve of progression-free survival by independent assessment for the prior cytokine subgroup



Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with axitinib in all subsets of the paediatric population for treatment of kidney and renal pelvis carcinoma (excluding nephroblastoma, nephroblastomatosis, clear cell sarcoma, mesoblastic nephroma, renal medullary carcinoma and rhabdoid tumour of the kidney) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

After oral administration of axitinib tablets, the mean absolute bioavailability is 58% compared to intravenous administration. The plasma half life of axitinib ranges from 2.5 to 6.1 hours. Dosing of axitinib at 5 mg twice daily resulted in less than two-fold accumulation compared to administration of

a single dose. Based on the short half-life of axitinib, steady state is expected within 2 to 3 days of the initial dose.

Absorption and distribution
Peak axitinib concentrations in plasma are generally reached within 4 hours following oral administration of axitinib with median T_{max} ranging from 2.5 to 4.1 hours. Administration of axitinib with a moderate fat meal resulted in 10% lower exposure compared to overnight fasting. A high fat, high-calorie meal resulted in 19% higher exposure compared to overnight fasting. Axitinib may be administered with or without food (see section 4.2).

The average C_{max} and AUC increased proportionally over an axitinib dosing range of 5 to 10 mg. *In vitro* binding of axitinib to human plasma proteins is > 99% with preferential binding to albumin and moderate binding to α_1-acid glycoprotein. At the 5 mg twice daily dose in the fed state, the geometric mean peak plasma concentration and 24-hour AUC were 27.8 ng/mL and 265 ng.h/mL, respectively, in patients with advanced RCC. The geometric mean oral clearance and apparent volume of distribution were 38 L/h and 160 L, respectively.

Biotransformation and elimination
Axitinib is metabolised primarily in the liver by CYP3A4/5 and to a lesser extent by CYP1A2, CYP2C19, and UGT1A1.

Following oral administration of a 5 mg radioactive dose of axitinib, 30-60% of the radioactivity was recovered in faeces and 23% of the radioactivity was recovered in urine. Unchanged axitinib, accounting for 12% of the dose, was the major component identified in faeces. Unchanged axitinib was not detected in urine; the carboxylic acid and sulfoxide metabolites accounted for the majority of radioactivity in urine. In plasma, the N-glucuronide metabolite represented the predominant radioactive component (50% of circulating radioactivity) and unchanged axitinib and the sulfoxide metabolite each accounted for approximately 20% of the circulating radioactivity.

The sulfoxide and N-glucuronide metabolites show approximately 400-fold and 8000-fold less *in vitro* potency, respectively, against VEGFR-2 compared to axitinib.

Special populations

Older people, gender, and race
Population pharmacokinetic analyses in patients with advanced cancer (including advanced RCC) and healthy volunteers indicate that there are no clinically relevant effects of age, gender, body weight, race, renal function, UGT1A1 genotype, or CYP2C19 genotype.

Paediatric population
Axitinib has not been studied in patients < 18 years of age.

Hepatic impairment
In vitro and *in vivo* data indicate that axitinib is primarily metabolised by the liver.

Compared to subjects with normal hepatic function, systemic exposure following a single dose of axitinib was similar in subjects with mild hepatic impairment (Child-Pugh class A) and higher (approximately two-fold) in subjects with moderate hepatic impairment (Child-Pugh class B). Axitinib has not been studied in subjects with severe hepatic impairment (Child-Pugh class C) and should not be used in this population (see section 4.2 for dose adjustment recommendations).

Renal impairment
Unchanged axitinib is not detected in the urine.

Axitinib has not been studied in subjects with renal impairment. In clinical studies with axitinib for the treatment of patients with RCC, patients with serum creatinine > 1.5 times the ULN or calculated

creatinine clearance < 60 mL/min were excluded. Population pharmacokinetic analyses have shown that axitinib clearance was not altered in subjects with renal impairment and no dose adjustment of axitinib is required.

5.3 Preclinical safety data

Repeat dose toxicity
Major toxicity findings in mice and dogs following repeated dosing for up to 9 months were the gastrointestinal, haematopoietic, reproductive, skeletal and dental systems, with No Observed Adverse Effect Levels (NOAEL) approximately equivalent to or below expected human exposure at the recommended clinical starting dose (based on AUC levels).

Carcinogenicity
Carcinogenicity studies have not been performed with axitinib.

Genotoxicity
Axitinib was not mutagenic or clastogenic in conventional genotoxicity assays *in vitro*. A significant increase in polyploidy was observed *in vitro* at concentrations > 0.22 µg/mL, and an elevation in micronucleated polychromatic erythrocytes was observed *in vivo* with No Observed Effect Level (NOEL) 69-fold the expected human exposure. Genotoxicity findings are not considered clinically relevant at exposure levels observed in humans.

Reproduction toxicity
Axitinib-related findings in the testes and epididymis included decreased organ weight, atrophy or degeneration, decreased numbers of germinal cells, hypospermia or abnormal sperm forms, and reduced sperm density and count. These findings were observed in mice at exposure levels approximately 12-fold the expected human exposure, and in dogs at exposure levels below the expected human exposure. There was no effect on mating or fertility in male mice at exposure levels approximately 57-fold the expected human exposure. Findings in females included signs of delayed sexual maturity, reduced or absent corpora lutea, decreased uterine weights and uterine atrophy at exposures approximately equivalent to the expected human exposure. Reduced fertility and embryonic viability were observed in female mice at all doses tested, with exposure levels at the lowest dose approximately 10-fold the expected human exposure.

Pregnant mice exposed to axitinib showed an increased occurrence of cleft palate malformations and skeletal variations, including delayed ossification, at exposure levels below the expected human exposure. Perinatal and postnatal developmental toxicity studies have not been conducted.

Toxicity findings in immature animals
Reversible physeal dysplasia was observed in mice and dogs given axitinib for at least 1 month at exposure levels approximately six-fold higher than the expected human exposure. Partially reversible dental caries were observed in mice treated for more than 1 month at exposure levels similar to the expected human exposure. Other toxicities of potential concern to paediatric patients have not been evaluated in juvenile animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Magnesium stearate

Tablet film-coating:
Hypromellose
Titanium dioxide (E171)
Lactose monohydrate
Triacetin (E1518)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/aluminium blister containing 14 film-coated tablets. Each pack contains 28 or 56 film-coated tablets.

HDPE bottle with a silica gel desiccant and a polypropylene closure containing 180 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich, Kent CT13 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/777/001
EU/1/12/777/002
EU/1/12/777/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3 September 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Inlyta 3 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 3 mg of axitinib.

Excipients with known effect:
Each film-coated tablet contains 35.3 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Red round film-coated tablet debossed with “Pfizer” on one side and “3 XNB” on the other

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Inlyta is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine.

4.2 Posology and method of administration

Treatment with Inlyta should be conducted by a physician experienced in the use of anticancer therapies.

Posology

The recommended 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 concomitant medicinal products or dose adjustments.

If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time.

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
Co-administration of axitinib with strong CYP3A4/5 inhibitors may increase axitinib plasma concentrations (see section 4.5). Selection of an alternate concomitant medicinal product with no or minimal CYP3A4/5 inhibition potential is recommended.

Although axitinib dose adjustment has not been studied in patients receiving strong CYP3A4/5 inhibitors, if a strong CYP3A4/5 inhibitor must be co-administered, a dose decrease of axitinib to approximately half the dose (e.g. the starting dose should be reduced from 5 mg twice daily to 2 mg twice daily) is recommended. Management of some adverse reactions may require temporary or permanent discontinuation of axitinib therapy (see section 4.4). If co-administration of the strong inhibitor is discontinued, a return to the axitinib dose used prior to initiation of the strong CYP3A4/5 inhibitor should be considered (see section 4.5).

Concomitant strong CYP3A4/5 inducers
Co-administration of axitinib with strong CYP3A4/5 inducers may decrease axitinib plasma concentrations (see section 4.5). Selection of an alternate concomitant medicinal product with no or minimal CYP3A4/5 induction potential is recommended.

Although axitinib dose adjustment has not been studied in patients receiving strong CYP3A4/5 inducers, if a strong CYP3A4/5 inducer must be co-administered, a gradual dose increase of axitinib is recommended. Maximal induction with high-dose strong CYP3A4/5 inducers has been reported to occur within one week of treatment with the inducer. If the dose of axitinib is increased, the patient should be monitored carefully for toxicity. Management of some adverse reactions may require temporary or permanent discontinuation and/or dose reduction of axitinib therapy (see section 4.4). If co-administration of the strong inducer is discontinued, the axitinib dose should be immediately returned to the dose used prior to initiation of the strong CYP3A4/5 inducer (see section 4.5).

<u>Special populations</u>

Older people (≥ 65 years): No dose adjustment is required (see sections 4.4 and 5.2).

Renal impairment: No dose adjustment is required (see section 5.2). Virtually no data are available regarding axitinib treatment in patients with a creatinine clearance of < 15 mL/min.

Hepatic impairment: No dose adjustment is required when administering axitinib to patients with mild hepatic impairment (Child-Pugh class A). A dose decrease is recommended when administering axitinib to patients with moderate hepatic impairment (Child-Pugh class B) (e.g. the starting dose should be reduced from 5 mg twice daily to 2 mg twice daily). Axitinib has not been studied in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this population (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of axitinib in children and adolescents < 18 years have not been established. No data are available.

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.

4.3 Contraindications

Hypersensitivity to axitinib or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Specific safety events should be monitored before initiation of, and periodically throughout, treatment with axitinib as described below.

Cardiac failure events
In clinical studies with axitinib for the treatment of patients with RCC, cardiac failure events (including cardiac failure, cardiac failure congestive, cardiopulmonary failure, left ventricular dysfunction, ejection fraction decreased, and right ventricular failure) were reported (see section 4.8).

Signs or symptoms of cardiac failure should periodically be monitored throughout treatment with axitinib. Management of cardiac failure events may require temporary interruption or permanent discontinuation and/or dose reduction of axitinib therapy.

Hypertension
In clinical studies with axitinib for the treatment of patients with RCC, hypertension was very commonly reported (see section 4.8).

In a controlled clinical study, the median onset time for hypertension (systolic blood pressure > 150 mmHg or diastolic blood pressure > 100 mmHg) was within the first month of the start of axitinib treatment and blood pressure increases have been observed as early as 4 days after starting axitinib.

Blood pressure should be well-controlled prior to initiating axitinib. Patients should be monitored for hypertension and treated as needed with standard antihypertensive therapy. In the case of persistent hypertension, despite use of antihypertensive medicinal products, the axitinib dose should be reduced. For patients who develop severe hypertension, temporarily interrupt axitinib and restart at a lower dose once the patient is normotensive. If axitinib is interrupted, patients receiving antihypertensive medicinal products should be monitored for hypotension (see section 4.2).

In case of severe or persistent arterial hypertension and symptoms suggestive of posterior reversible encephalopathy syndrome (PRES) (see below), a diagnostic brain magnetic resonance image (MRI) should be considered.

Thyroid dysfunction
In clinical studies with axitinib for the treatment of patients with RCC, events of hypothyroidism and, to a lesser extent, hyperthyroidism, were reported (see section 4.8).

Thyroid function should be monitored before initiation of, and periodically throughout, treatment with axitinib. Hypothyroidism or hyperthyroidism should be treated according to standard medical practice to maintain euthyroid state.

Arterial embolic and thrombotic events
In clinical studies with axitinib, arterial embolic and thrombotic events (including transient ischemic attack, myocardial infarction, cerebrovascular accident and retinal artery occlusion) were reported (see section 4.8).

Axitinib should be used with caution in patients who are at risk for, or who have a history of, these events. Axitinib has not been studied in patients who had an arterial embolic or thrombotic event within the previous 12 months.

Venous embolic and thrombotic events
In clinical studies with axitinib, venous embolic and thrombotic events (including pulmonary embolism, deep vein thrombosis, and retinal vein occlusion/thrombosis) were reported (see section 4.8).

Axitinib should be used with caution in patients who are at risk for, or who have a history of, these events. Axitinib has not been studied in patients who had a venous embolic or thrombotic event within the previous 6 months.

Elevation of haemoglobin or haematocrit
Increases in haemoglobin or haematocrit, reflective of increases in red blood cell mass, may occur during treatment with axitinib (see section 4.8, polycythaemia). An increase in red blood cell mass may increase the risk of embolic and thrombotic events.

Haemoglobin or haematocrit should be monitored before initiation of, and periodically throughout, treatment with axitinib. If haemoglobin or haematocrit becomes elevated above the normal level, patients should be treated according to standard medical practice to decrease haemoglobin or haematocrit to an acceptable level.

Haemorrhage
In clinical studies with axitinib, haemorrhagic events were reported (see section 4.8).

Axitinib has not been studied in patients who have evidence of untreated brain metastasis or recent active gastrointestinal bleeding, and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the axitinib dose.

Gastrointestinal perforation and fistula formation
In clinical studies with axitinib, events of gastrointestinal perforation and fistulas were reported (see section 4.8).

Symptoms of gastrointestinal perforation or fistula should be periodically monitored for throughout treatment with axitinib.

Wound healing complications
No formal studies of the effect of axitinib on wound healing have been conducted.

Treatment with axitinib should be stopped at least 24 hours prior to scheduled surgery. The decision to resume axitinib therapy after surgery should be based on clinical judgment of adequate wound healing.

Posterior reversible encephalopathy syndrome (PRES)
In clinical studies with axitinib, events of PRES were reported (see section 4.8).

PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES. In patients with signs or

symptoms of PRES, temporarily interrupt or permanently discontinue axitinib treatment. The safety of reinitiating axitinib therapy in patients previously experiencing PRES is not known.

Proteinuria
In clinical studies with axitinib, proteinuria, including that of Grade 3 and 4 severity, was reported (see section 4.8).

Monitoring for proteinuria before initiation of, and periodically throughout, treatment with axitinib is recommended. For patients who develop moderate to severe proteinuria, reduce the dose or temporarily interrupt axitinib treatment (see section 4.2).

Liver-related adverse reactions
In a controlled clinical study with axitinib for the treatment of patients with RCC, liver-related adverse reactions were reported. The most commonly reported liver-related adverse reactions included increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and blood bilirubin (see section 4.8). No concurrent elevations of ALT (> 3 times the upper limit of normal [ULN]) and bilirubin (> 2 times the ULN) were observed.

In a clinical dose-finding study, concurrent elevations of ALT (12 times the ULN) and bilirubin (2.3 times the ULN), considered to be drug-related hepatotoxicity, were observed in 1 patient who received axitinib at a starting dose of 20 mg twice daily (4 times the recommended starting dose).

Liver function tests should be monitored before initiation of, and periodically throughout, treatment with axitinib.

Hepatic impairment
In clinical studies with axitinib, the systemic exposure to axitinib was approximately two-fold higher in subjects with moderate hepatic impairment (Child-Pugh class B) compared to subjects with normal hepatic function. A dose decrease is recommended when administering axitinib to patients with moderate hepatic impairment (Child-Pugh class B) (see section 4.2).

Axitinib has not been studied in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this population.

Older people (≥ 65 years) and race
In a controlled clinical study with axitinib for the treatment of patients with RCC, 34% of patients treated with axitinib were ≥ 65 years of age. The majority of patients were White (77%) or Asian (21%). Although greater sensitivity to develop adverse reactions in some older patients and Asian patients cannot be ruled out, overall, no major differences were observed in the safety and effectiveness of axitinib between patients who were ≥ 65 years of age and non-elderly, and between White patients and patients of other races.

No dosage adjustment is required on the basis of patient age or race (see sections 4.2 and 5.2).

Lactose
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro data indicate that axitinib is metabolised primarily by CYP3A4/5 and, to a lesser extent, CYP1A2, CYP2C19, and uridine diphosphate-glucuronosyltransferase (UGT) 1A1.

CYP3A4/5 inhibitors
Ketoconazole, a strong inhibitor of CYP3A4/5, administered at a dose of 400 mg once daily for 7 days, increased the mean area under the curve (AUC) 2-fold and C_{max} 1.5-fold of a single 5-mg oral dose of axitinib in healthy volunteers. Co-administration of axitinib with strong CYP3A4/5 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, erythromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin) may increase axitinib plasma concentrations. Grapefruit may also increase axitinib plasma concentrations. Selection of concomitant medicinal products with no or minimal CYP3A4/5 inhibition potential is recommended. If a strong CYP3A4/5 inhibitor must be co-administered, a dose adjustment of axitinib is recommended (see section 4.2).

CYP1A2 and CYP2C19 inhibitors
CYP1A2 and CYP2C19 constitute minor (< 10%) pathways in axitinib metabolism. The effect of strong inhibitors of these isozymes on axitinib pharmacokinetics has not been studied. Caution should be exercised due to the risk of increased axitinib plasma concentrations in patients taking strong inhibitors of these isozymes.

CYP3A4/5 inducers
Rifampicin, a strong inducer of CYP3A4/5, administered at a dose of 600 mg once daily for 9 days, reduced the mean AUC by 79% and C_{max} by 71% of a single 5 mg dose of axitinib in healthy volunteers.

Co-administration of axitinib with strong CYP3A4/5 inducers (e.g. rifampicin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentin, phenobarbital, and *Hypericum perforatum* [St. John's wort]) may decrease axitinib plasma concentrations. Selection of concomitant medicinal products with no or minimal CYP3A4/5 induction potential is recommended. If a strong CYP3A4/5 inducer must be co-administered, a dose adjustment of axitinib is recommended (see section 4.2).

In vitro studies of CYP and UGT inhibition and induction
In vitro studies indicated that axitinib does not inhibit CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, or UGT1A1 at therapeutic plasma concentrations.

In vitro studies indicated that axitinib has a potential to inhibit CYP1A2. Therefore, co-administration of axitinib with CYP1A2 substrates may result in increased plasma concentrations of CYP1A2 substrates (e.g. theophylline).

In vitro studies also indicated that axitinib has the potential to inhibit CYP2C8. However, co-administration of axitinib with paclitaxel, a known CYP2C8 substrate, did not result in increased plasma concentrations of paclitaxel in patients with advanced cancer, indicating lack of clinical CYP2C8 inhibition.

In vitro studies in human hepatocytes also indicated that axitinib does not induce CYP1A1, CYP1A2, or CYP3A4/5. Therefore co-administration of axitinib is not expected to reduce the plasma concentration of co-administered CYP1A1, CYP1A2, or CYP3A4/5 substrates *in vivo*.

In vitro studies with P-glycoprotein
In vitro studies indicated that axitinib inhibits P-glycoprotein. However, axitinib is not expected to inhibit P-glycoprotein at therapeutic plasma concentrations. Therefore, co-administration of axitinib is not expected to increase the plasma concentration of digoxin, or other P-glycoprotein substrates, *in vivo*.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data regarding the use of axitinib in pregnant women. Based on the pharmacological properties of axitinib, it may cause foetal harm when administered to a pregnant woman. Studies in animals have shown reproductive toxicity including malformations (see section 5.3). Axitinib should not be used during pregnancy unless the clinical condition of the woman requires treatment with this medicinal product.

Women of childbearing potential must use effective contraception during and up to 1 week after treatment.

Breast-feeding
It is unknown whether axitinib is excreted in human milk. A risk to the suckling child cannot be excluded. Axitinib should not be used during breast-feeding.

Fertility
Based on non-clinical findings, axitinib has the potential to impair reproductive function and fertility in humans (see section 5.3).

4.7 Effects on ability to drive and use machines

Axitinib has a minor influence on the ability to drive and use machines. Patients should be advised that they may experience events such as dizziness and/or fatigue during treatment with axitinib.

4.8 Undesirable effects

Summary of the safety profile
The following risks, including appropriate action to be taken, are discussed in greater detail in *Section 4.4:* cardiac failure events, hypertension, thyroid dysfunction, arterial thromboembolic events, venous thromboembolic events, elevation of haemoglobin or haematocrit, haemorrhage, gastrointestinal perforation and fistula formation, wound healing complications, PRES, proteinuria, and elevation of liver enzymes.

The most common (≥ 20%) adverse reactions observed following treatment with axitinib were diarrhoea, hypertension, fatigue, decreased appetite, nausea, weight decreased, dysphonia, palmar-plantar erythrodysaesthesia (hand-foot) syndrome, haemorrhage, hypothyroidism, vomiting, proteinuria, cough, and constipation.

Tabulated list of adverse reactions
Table 1 presents adverse reactions reported in a pooled dataset of 672 patients who received axitinib in clinical studies for the treatment of patients with RCC (see section 5.1).

The adverse reactions are listed by system organ class, frequency category and grade of severity. Frequency categories are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), and not known (cannot be estimated from the available data). The current safety database for axitinib is too small to detect rare and very rare adverse reactions.

Categories have been assigned based on absolute frequencies in the pooled clinical studies data. Within each system organ class, adverse reactions with the same frequency are presented in order of decreasing seriousness.

Table 1. Adverse reactions reported in RCC studies in patients who received axitinib (N = 672)

System Organ Class	Frequency Category	Adverse Reactions[a]	All Grades[b] %	Grade 3[b] %	Grade 4[b] %
Blood and lymphatic system disorders	Common	Anaemia	6.3	1.2	0.4
		Thrombocytopenia	1.6	0.1	0
		Polycythaemia[c]	1.5	0.1	0
	Uncommon	Neutropaenia	0.3	0.1	0
		Leukopaenia	0.4	0	0
Endocrine disorders	Very Common	Hypothyroidism[c]	24.6	0.3	0
	Common	Hyperthyroidism[c]	1.6	0.1	0.1
Metabolism and nutrition disorders	Very Common	Decreased appetite	39.0	3.6	0.3
	Common	Dehydration	6.7	3.1	0.3
		Hyperkalaemia	2.7	1.2	0.1
		Hypercalcaemia	2.2	0.1	0.3
Nervous system disorders	Very Common	Headache	16.2	0.7	0
		Dysgeusia	11.5	0	0
	Common	Dizziness	9.1	0.6	0
	Uncommon	Posterior reversible encephalopathy syndrome[e]	0.3	0.1	0
Ear and labyrinth disorders	Common	Tinnitus	3.1	0	0
Cardiac disorders	Common	Cardiac failure events[c,d,f]	1.8	0.3	0.7
Vascular disorders	Very Common	Hypertension[g]	51.2	22.0	1.0
		Haemorrhage[c,d,h]	25.7	3.0	1.0
	Common	Venous embolic and thrombotic events[c,d,i]	2.8	0.9	1.2
		Arterial embolic and thrombotic events[c,d,j]	2.8	1.2	1.3
Respiratory, thoracic and mediastinal disorders	Very Common	Dyspnoea[d]	17.1	3.6	0.6
		Cough	20.4	0.6	0
		Dysphonia	32.7	0	0.1
	Common	Oropharyngeal pain	7.4	0	0
Gastrointestinal disorders	Very Common	Diarrhoea	55.4	10.1	0.1
		Vomiting	23.7	2.7	0.1
		Nausea	33.0	2.2	0.1
		Abdominal pain	14.7	2.5	0.3
		Constipation	20.2	1.0	0
		Stomatitis	15.5	1.8	0
		Dyspepsia	11.2	0.1	0
	Common	Upper abdominal pain	9.4	0.9	0
		Flatulence	4.5	0	0
		Haemorrhoids	3.3	0	0
		Glossodynia	2.8	0	0
		Gastrointestinal perforation and fistula[c,k]	1.9	0.9	0.3
Hepatobiliary disorders	Common	Hyperbilirubinaemia	1.3	0.1	0.1

System Organ Class	Frequency Category	Adverse Reactions[a]	All Grades[b] %	Grade 3[b] %	Grade 4[b] %
Skin and subcutaneous tissue disorders	Very Common	Palmar-plantar erythrodysaesthesia (hand-foot syndrome)	32.1	7.6	0
		Rash	14.3	0.1	0
		Dry skin	10.1	0.1	0
	Common	Pruritus	6.0	0	0
		Erythema	3.7	0	0
		Alopecia	5.7	0	0
Musculoskeletal and connective tissue disorders	Very Common	Arthralgia	17.7	1.9	0.3
		Pain in extremity	14.1	1.0	0.3
	Common	Myalgia	8.2	0.6	0.1
Renal and urinary disorders	Very Common	Proteinuria[l]	21.1	4.8	0.1
	Common	Renal failure[m]	1.6	0.9	0.1
General disorders and administration site conditions	Very Common	Fatigue	45.1	10.6	0.3
		Asthaenia[d]	13.8	2.8	0.3
		Mucosal inflammation	13.7	1.0	0
Investigations	Very Common	Weight decreased	32.7	4.9	0
	Common	Lipase increased	3.7	0.7	0.7
		Alanine aminotransferase increased	6.5	1.2	0
		Amylase increased	3.4	0.6	0.4
		Aspartate aminotransferase increased	6.1	1.0	0
		Alkaline phosphatase increased	4.8	0.3	0
		Creatinine increased	5.7	0.4	0
		Thyroid stimulating hormone increased	7.9	0	0

[a] Adverse reactions are according to treatment-emergent, all causality frequency.
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0
[c] See Description of selected adverse reactions section.
[d] Fatal (Grade 5) cases were reported.
[e] Including Leukoencephalopathy.
[f] Including cardiac failure, cardiac failure congestive, cardiopulmonary failure, ejection fraction decreased, left ventricular dysfunction and right ventricular failure.
[g] Including accelerated hypertension, blood pressure increased, hypertension and hypertensive crisis.
[h] Including activated partial thromboplastin time prolonged, anal haemorrhage, arterial haemorrhage, blood urine present, central nervous system haemorrhage, cerebral haemorrhage, coagulation time prolonged, conjunctival haemorrhage, contusion, diarrhea haemorrhagic, dysfunctional uterine bleeding, epistaxis, gastric haemorrhage, gastrointestinal haemorrhage, gingival bleeding, haematemesis, haematochezia, haematocrit decreased, haematoma, haematuria, haemoglobin decreased, haemoptysis, haemorrhage, haemorrhage coronary artery, haemorrhage urinary tract, haemorrhoidal haemorrhage, haemostasis, increased tendency to bruise, international normalized ratio increased, lower gastrointestinal haemorrhage, melaena, petechiae, pharyngeal haemorrhage, prothrombin time prolonged, pulmonary haemorrhage, purpura, rectal haemorrhage, red blood cell count decreased, renal haemorrhage, scleral haemorrhage, scrotal haematocoele, splenic haemotoma, splinter haemorrhage, subarachnoid haemorrhage, tongue haemorrhage, upper gastrointestinal haemorrhage and vaginal haemorrhage.
[i] Including Budd-Chiari syndrome, deep vein thrombosis, jugular vein thrombosis, pelvic venous thrombosis, pulmonary embolism, retinal vein occlusion, retinal vein thrombosis, subclavian vein thrombosis, venous thrombosis, and venous thrombosis limb.

[j] Including acute myocardial infarction, embolism, myocardial infarction, retinal artery occlusion and transient ischaemic attack.
[k] Gastrointestinal perforation and fistula includes the following preferred terms: abdominal abscess, anal abscess, anal fistula, fistula, gastrointestinal anastomotic leak, gastrointestinal perforation, large intestine perforation, oesophagobronchial fistula and peritonitis.
[l] Proteinuria includes the following preferred terms: protein urine, protein urine present and proteinuria.
[m] Including acute renal failure

Description of selected adverse reactions

Cardiac failure events (see section 4.4)
In a controlled clinical study with axitinib (N = 359) for the treatment of patients with RCC, cardiac failure events were reported in 1.7 % patients receiving axitinib, including cardiac failure (0.6%), cardiopulmonary failure (0.6%), left ventricular dysfunction (0.3%), and right ventricular failure (0.3%). Grade 4 cardiac failure adverse reactions were reported in 0.6 % of patients receiving axitinib. Fatal cardiac failure was reported in 0.6 % of patients receiving axitinib.

In monotherapy studies with axitinib (N = 672) for the treatment of patients with RCC, cardiac failure events (including cardiac failure, cardiac failure congestive, cardiopulmonary failure, left ventricular dysfunction, ejection fraction decreased, and right ventricular failure) were reported in 1.8% patients receiving axitinib. Grade 3/4 cardiac failure events were reported in 1.0% patients and fatal cardiac failure events were reported in 0.3% patients receiving axitinib.

Thyroid dysfunction (see section 4.4)
In a controlled clinical study with axitinib for the treatment of patients with RCC, hypothyroidism was reported in 20.9% of patients and hyperthyroidism was reported in 1.1% of patients. Thyroid stimulating hormone (TSH) increased was reported as an adverse reaction in 5.3% of patients receiving axitinib. During routine laboratory assessments, in patients who had TSH < 5 μU/mL before treatment, elevations of TSH to ≥ 10 μU/mL occurred in 32.2% of patients receiving axitinib.

In pooled clinical studies with axitinib (N = 672) for the treatment of patients with RCC, hypothyroidism was reported in 24.6% of patients receiving axitinib. Hyperthyroidism was reported in 1.6% of patients receiving axitinib.

Venous embolic and thrombotic events (see section 4.4)
In a controlled clinical study with axitinib for the treatment of patients with RCC, venous embolic and thrombotic adverse reactions were reported in 3.9% of patients receiving axitinib, including pulmonary embolism (2.2%), retinal vein occlusion/thrombosis (0.6%) and deep vein thrombosis (0.6%). Grade 3/4 venous embolic and thrombotic adverse reactions were reported in 3.1% of patients receiving axitinib. Fatal pulmonary embolism was reported in one patient (0.3%) receiving axitinib.

In pooled clinical studies with axitinib (N = 672) for the treatment of patients with RCC, venous embolic and thrombotic events were reported in 2.8% of patients receiving axitinib. Grade 3 venous embolic and thrombotic events were reported in 0.9% of patients. Grade 4 venous embolic and thrombotic events were reported in 1.2% of patients. Fatal venous embolic and thrombotic events were reported 0.1% patients receiving axitinib.

Arterial embolic and thrombotic events (see section 4.4)
In a controlled clinical study with axitinib for the treatment of patients with RCC, arterial embolic and thrombotic adverse reactions were reported in 4.7% of patients receiving axitinib, including myocardial infarction (1.4%), transient ischemic attack (0.8%) and cerebrovascular accident (0.6%). Grade 3/4 arterial embolic and thrombotic adverse reactions were reported in 3.3% of patients receiving axitinib. A fatal acute myocardial infarction and cerebrovascular accident was reported in one patient each (0.3%). In monotherapy studies with axitinib (N = 850), arterial embolic and

thrombotic adverse reactions (including transient ischemic attack, myocardial infarction, and cerebrovascular accident) were reported in 5.3% of patients receiving axitinib.

In pooled clinical studies with axitinib (N = 672) for the treatment of patients with RCC, arterial embolic and thrombotic events were reported in 2.8% of patients receiving axitinib. Grade 3 arterial embolic and thrombotic events were reported in 1.2% of patients. Grade 4 arterial embolic and thrombotic events were reported in 1.3% of patients. Fatal arterial embolic and thrombotic events were reported in 0.3% patients receiving axitinib.

*Polycythaemia (*see *Elevation of haemoglobin or haematocrit* in section 4.4)
In a controlled clinical study with axitinib for the treatment of patients with RCC, polycythaemia was reported in 1.4% of patients receiving axitinib. Routine laboratory assessments detected elevated haemoglobin above ULN in 9.7% of patients receiving axitinib. In four clinical studies with axitinib for the treatment of patients with RCC (N = 537), elevated haemoglobin above ULN was observed in 13.6% receiving axitinib.

In pooled clinical studies with axitinib (N = 672) for the treatment of patients with RCC, polycythaemia was reported in 1.5% of patients receiving axitinib.

Haemorrhage (see section 4.4)
In a controlled clinical study with axitinib for the treatment of patients with RCC that excluded patients with untreated brain metastasis, haemorrhagic adverse reactions were reported in 21.4% of patients receiving axitinib. The haemorrhagic adverse reactions in patients treated with axitinib included epistaxis (7.8%), haematuria (3.6%), haemoptysis (2.5%), rectal haemorrhage (2.2%), gingival bleeding (1.1%), gastric haemorrhage (0.6%), cerebral haemorrhage (0.3%) and lower gastrointestinal haemorrhage (0.3%). Grade $\geq$ 3 haemorrhagic adverse reactions were reported in 3.1% of patients receiving axitinib (including cerebral haemorrhage, gastric haemorrhage, lower gastrointestinal haemorrhage and haemoptysis). Fatal haemorrhage was reported in one patient (0.3%) receiving axitinib (gastric haemorrhage). In monotherapy studies with axitinib (N = 850), haemoptysis was reported in 3.9% of patients; Grade $\geq$ 3 haemoptysis was reported in 0.5% of patients.

In pooled clinical studies with axitinib (N = 672) for the treatment of patients with RCC, haemorrhagic events were reported in 25.7% of patients receiving axitinib. Grade 3 haemorrhagic adverse reactions were reported in 3% of patients. Grade 4 haemorrhagic adverse reactions were reported in 1% of patients and fatal haemorrhage were reported in 0.4% of patients receiving axitinib.

Gastrointestinal perforation and fistula formation (see section 4.4)
In a controlled clinical study with axitinib for the treatment of patients with RCC, gastrointestinal perforation-type events were reported in 1.7% of patients receiving axitinib, including anal fistula (0.6%), fistula (0.3%) and gastrointestinal perforation (0.3%).In monotherapy studies with axitinib (N = 850), gastrointestinal perforation-type events were reported in 1.9% of patients and fatal gastrointestinal perforation was reported in one patient (0.1%).

In pooled clinical studies with axitinib (N = 672) for the treatment of patients with RCC, gastrointestinal perforation and fistula were reported in 1.9% of patients receiving axitinib.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no specific treatment for axitinib overdose.

In a controlled clinical study with axitinib for the treatment of patients with RCC, one patient inadvertently received a dose of 20 mg twice daily for 4 days and experienced dizziness (Grade 1).

In a clinical dose finding study with axitinib, subjects who received starting doses of 10 mg twice daily or 20 mg twice daily experienced adverse reactions which included hypertension, seizures associated with hypertension, and fatal haemoptysis.

In cases of suspected overdose, axitinib should be withheld and supportive care instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE17

Mechanism of action
Axitinib is a potent and selective tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, VEGFR-2 and VEGFR-3. These receptors are implicated in pathologic angiogenesis, tumour growth, and metastatic progression of cancer. Axitinib has been shown to potently inhibit VEGF-mediated endothelial cell proliferation and survival. Axitinib inhibited the phosphorylation of VEGFR-2 in xenograft tumour vasculature that expressed the target *in vivo* and produced tumour growth delay, regression, and inhibition of metastases in many experimental models of cancer.

Effect on QTc interval
In a randomised, 2-way crossover study, 35 healthy subjects were administered a single oral dose of axitinib (5 mg) in the absence and presence of 400 mg ketoconazole for 7 days. Results of this study indicated that axitinib plasma exposures up to two-fold greater than therapeutic levels expected following a 5 mg dose, did not produce clinically-significant QT interval prolongation.

Clinical efficacy
The safety and efficacy of axitinib were evaluated in a randomised, open-label, multicenter Phase 3 study. Patients (N = 723) with advanced RCC whose disease had progressed on or after treatment with one prior systemic therapy, including sunitinib-, bevacizumab-, temsirolimus-, or cytokine-containing regimens were randomised (1:1) to receive axitinib (N = 361) or sorafenib (N = 362). The primary endpoint, progression-free survival (PFS), was assessed using a blinded independent central review. Secondary endpoints included objective response rate (ORR) and overall survival (OS).

Of the patients enrolled in this study, 389 patients (53.8%) had received one prior sunitinib-based therapy, 251 patients (34.7%) had received one prior cytokine-based therapy (interleukin-2 or interferon-alpha), 59 patients (8.2%) had received one prior bevacizumab-based therapy, and 24 patients (3.3%) had received one prior temsirolimus-based therapy. The baseline demographic and disease characteristics were similar between the axitinib and sorafenib groups with regard to age, gender, race, Eastern Cooperative Oncology Group (ECOG) performance status, geographic region, and prior treatment.

In the overall patient population and the two main subgroups (prior sunitinib treatment and prior cytokine treatment), there was a statistically significant advantage for axitinib over sorafenib for the primary endpoint of PFS (see Table 2 and Figures 1, 2 and 3). The magnitude of median PFS effect was different in the subgroups by prior therapy. Two of the subgroups were too small to give reliable results (prior temsirolimus treatment or prior bevacizumab treatment). There were no statistically significant differences between the arms in OS in the overall population or in the subgroups by prior therapy.

Table 2. Efficacy results

Endpoint / Study Population	Axitinib	Sorafenib	HR (95% CI)	p-value
Overall ITT	**N = 361**	**N = 362**		
Median PFS [a,b] in months (95% CI)	6.8 (6.4, 8.3)	4.7 (4.6, 6.3)	0.67 (0.56, 0.81)	< 0.0001[c]
Median OS [d] in months (95% CI)	20.1 (16.7, 23.4)	19.2 (17.5, 22.3)	0.97 (0.80, 1.17)	NS
ORR [b,e] % (95% CI)	19.4 (15.4, 23.9)	9.4 (6.6, 12.9)	2.06[f] (1.41, 3.00)	0.0001[g]
Prior sunitinib treatment	**N = 194**	**N = 195**		
Median PFS [a,b] in months (95% CI)	4.8 (4.5, 6.5)	3.4 (2.8, 4.7)	0.74 (0.58, 0.94)	0.0063[h]
Median OS [d] in months (95% CI)	15.2 (12.8, 18.3)	16.5 (13.7, 19.2)	1.00 (0.78, 1.27)	NS
ORR [b,e] % (95% CI)	11.3 (7.2, 16.7)	7.7 (4.4, 12.4)	1.48[f] (0.79, 2.75)	NS
Prior cytokine treatment	**N = 126**	**N = 125**		
Median PFS [a,b] in months (95% CI)	12.0 (10.1, 13.9)	6.6 (6.4, 8.3)	0.52 (0.38, 0.72)	< 0.0001[h]
Median OS [d] in months (95% CI)	29.4 (24.5, NE)	27.8 (23.1, 34.5)	0.81 (0.56, 1.19)	NS
ORR [b,e] % (95% CI)	32.5 (24.5, 41.5)	13.6 (8.1, 20.9)	2.39[f] (1.43-3.99)	0.0002[i]

CI = Confidence interval, HR = Hazard ratio (axitinib/sorafenib); ITT: Intent-to-treat; NE: not estimable; NS: not statistically significant; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival.

[a] Time from randomisation to progression or death due to any cause, whichever occurs first. Cutoff date: 03 June 2011.

[b] Assessed by independent radiology review according to Response Evaluation Criteria in Solid Tumours (RECIST).

[c] One-sided p-value from a log-rank test of treatment stratified by ECOG performance status and prior therapy.

[d] Cutoff date: 01 November 2011.

[e] Cutoff date: 31 August 2010.

[f] Risk ratio is used for ORR. A risk ratio > 1 indicated a higher likelihood of responding in the axitinib arm; a risk ratio < 1 indicated a higher likelihood of responding in the sorafenib arm.

[g] One-sided p-value from Cochran-Mantel-Haenszel test of treatment stratified by ECOG performance status and prior therapy.

[h] One-sided p-value from a log-rank test of treatment stratified by ECOG performance status.

[i] One-sided p-value from Cochran-Mantel-Haenszel test of treatment stratified by ECOG performance status.

Figure 1. Kaplan-Meier curve of progression-free survival by independent assessment for the overall population

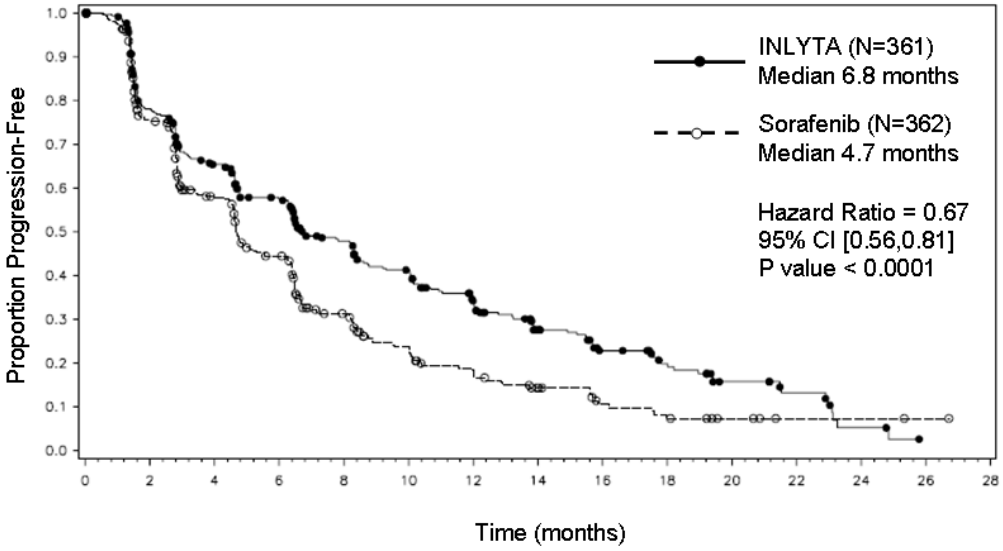


Figure 2. Kaplan-Meier curve of progression-free survival by independent assessment for the prior sunitinib subgroup

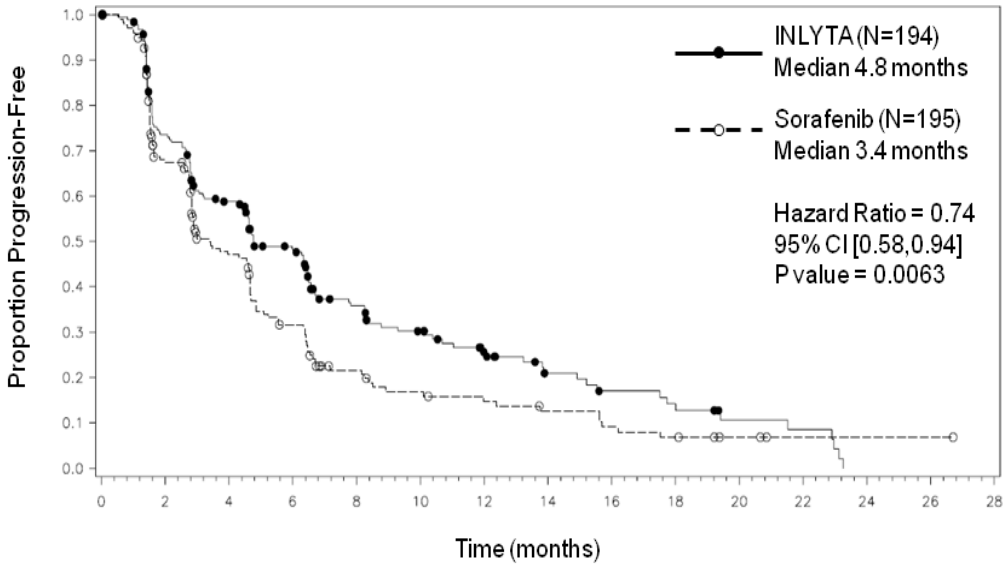
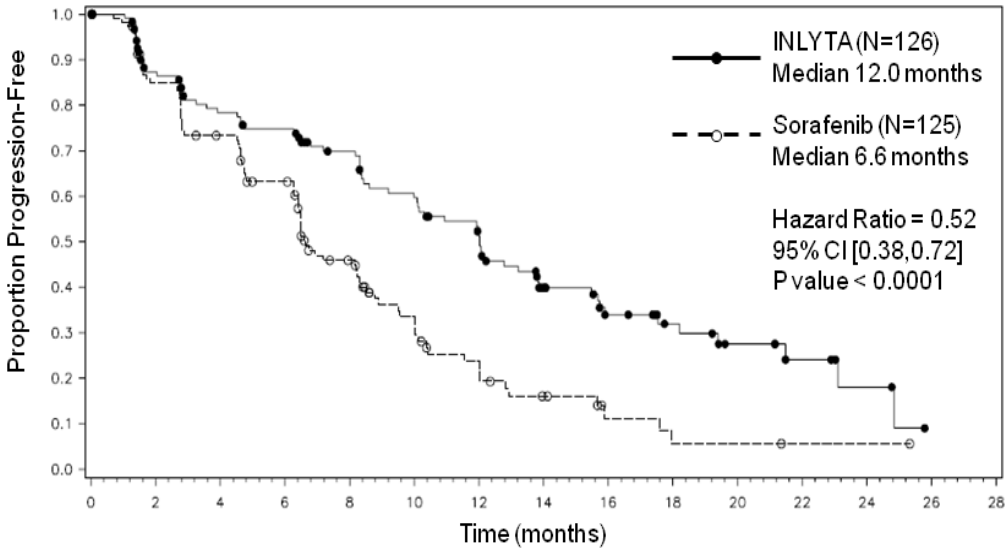


Figure 3. Kaplan-Meier curve of progression-free survival by independent assessment for the prior cytokine subgroup



Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with axitinib in all subsets of the paediatric population for treatment of kidney and renal pelvis carcinoma (excluding nephroblastoma, nephroblastomatosis, clear cell sarcoma, mesoblastic nephroma, renal medullary carcinoma and rhabdoid tumour of the kidney) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

After oral administration of axitinib tablets, the mean absolute bioavailability is 58% compared to intravenous administration. The plasma half life of axitinib ranges from 2.5 to 6.1 hours. Dosing of axitinib at 5 mg twice daily resulted in less than two-fold accumulation compared to administration of

a single dose. Based on the short half-life of axitinib, steady state is expected within 2 to 3 days of the initial dose.

Absorption and distribution
Peak axitinib concentrations in plasma are generally reached within 4 hours following oral administration of axitinib with median T_{max} ranging from 2.5 to 4.1 hours. Administration of axitinib with a moderate fat meal resulted in 10% lower exposure compared to overnight fasting. A high fat, high-calorie meal resulted in 19% higher exposure compared to overnight fasting. Axitinib may be administered with or without food (see section 4.2).

The average C_{max} and AUC increased proportionally over an axitinib dosing range of 5 to 10 mg. *In vitro* binding of axitinib to human plasma proteins is > 99% with preferential binding to albumin and moderate binding to α_1-acid glycoprotein. At the 5 mg twice daily dose in the fed state, the geometric mean peak plasma concentration and 24-hour AUC were 27.8 ng/mL and 265 ng.h/mL, respectively, in patients with advanced RCC. The geometric mean oral clearance and apparent volume of distribution were 38 L/h and 160 L, respectively.

Biotransformation and elimination
Axitinib is metabolised primarily in the liver by CYP3A4/5 and to a lesser extent by CYP1A2, CYP2C19, and UGT1A1.

Following oral administration of a 5 mg radioactive dose of axitinib, 30-60% of the radioactivity was recovered in faeces and 23% of the radioactivity was recovered in urine. Unchanged axitinib, accounting for 12% of the dose, was the major component identified in faeces. Unchanged axitinib was not detected in urine; the carboxylic acid and sulfoxide metabolites accounted for the majority of radioactivity in urine. In plasma, the N-glucuronide metabolite represented the predominant radioactive component (50% of circulating radioactivity) and unchanged axitinib and the sulfoxide metabolite each accounted for approximately 20% of the circulating radioactivity.

The sulfoxide and N-glucuronide metabolites show approximately 400-fold and 8000-fold less *in vitro* potency, respectively, against VEGFR-2 compared to axitinib.

Special populations

Older people, gender, and race
Population pharmacokinetic analyses in patients with advanced cancer (including advanced RCC) and healthy volunteers indicate that there are no clinically relevant effects of age, gender, body weight, race, renal function, UGT1A1 genotype, or CYP2C19 genotype.

Paediatric population
Axitinib has not been studied in patients < 18 years of age.

Hepatic impairment
In vitro and *in vivo* data indicate that axitinib is primarily metabolised by the liver.

Compared to subjects with normal hepatic function, systemic exposure following a single dose of axitinib was similar in subjects with mild hepatic impairment (Child-Pugh class A) and higher (approximately two-fold) in subjects with moderate hepatic impairment (Child-Pugh class B). Axitinib has not been studied in subjects with severe hepatic impairment (Child-Pugh class C) and should not be used in this population (see section 4.2 for dose adjustment recommendations).

Renal impairment
Unchanged axitinib is not detected in the urine.

Axitinib has not been studied in subjects with renal impairment. In clinical studies with axitinib for the treatment of patients with RCC, patients with serum creatinine > 1.5 times the ULN or calculated

creatinine clearance < 60 mL/min were excluded. Population pharmacokinetic analyses have shown that axitinib clearance was not altered in subjects with renal impairment and no dose adjustment of axitinib is required.

5.3 Preclinical safety data

Repeat dose toxicity
Major toxicity findings in mice and dogs following repeated dosing for up to 9 months were the gastrointestinal, haematopoietic, reproductive, skeletal and dental systems, with No Observed Adverse Effect Levels (NOAEL) approximately equivalent to or below expected human exposure at the recommended clinical starting dose (based on AUC levels).

Carcinogenicity
Carcinogenicity studies have not been performed with axitinib.

Genotoxicity
Axitinib was not mutagenic or clastogenic in conventional genotoxicity assays *in vitro*. A significant increase in polyploidy was observed *in vitro* at concentrations > 0.22 µg/mL, and an elevation in micronucleated polychromatic erythrocytes was observed *in vivo* with No Observed Effect Level (NOEL) 69-fold the expected human exposure. Genotoxicity findings are not considered clinically relevant at exposure levels observed in humans.

Reproduction toxicity
Axitinib-related findings in the testes and epididymis included decreased organ weight, atrophy or degeneration, decreased numbers of germinal cells, hypospermia or abnormal sperm forms, and reduced sperm density and count. These findings were observed in mice at exposure levels approximately 12-fold the expected human exposure, and in dogs at exposure levels below the expected human exposure. There was no effect on mating or fertility in male mice at exposure levels approximately 57-fold the expected human exposure. Findings in females included signs of delayed sexual maturity, reduced or absent corpora lutea, decreased uterine weights and uterine atrophy at exposures approximately equivalent to the expected human exposure. Reduced fertility and embryonic viability were observed in female mice at all doses tested, with exposure levels at the lowest dose approximately 10-fold the expected human exposure.

Pregnant mice exposed to axitinib showed an increased occurrence of cleft palate malformations and skeletal variations, including delayed ossification, at exposure levels below the expected human exposure. Perinatal and postnatal developmental toxicity studies have not been conducted.

Toxicity findings in immature animals
Reversible physeal dysplasia was observed in mice and dogs given axitinib for at least 1 month at exposure levels approximately six-fold higher than the expected human exposure. Partially reversible dental caries were observed in mice treated for more than 1 month at exposure levels similar to the expected human exposure. Other toxicities of potential concern to paediatric patients have not been evaluated in juvenile animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Magnesium stearate

Tablet film-coating:
Hypromellose
Titanium dioxide (E171)
Lactose monohydrate
Triacetin (E1518)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/aluminium blister containing 14 film-coated tablets. Each pack contains 28 or 56 film-coated tablets.

HDPE bottle with a silica gel desiccant and a polypropylene closure containing 60 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich, Kent CT13 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/777/007
EU/1/12/777/008
EU/1/12/777/009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3 September 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Inlyta 5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5 mg of axitinib.

Excipients with known effect:
Each film-coated tablet contains 58.8 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Red triangular film-coated tablet debossed with “Pfizer” on one side and “5 XNB” on the other

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Inlyta is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine.

4.2 Posology and method of administration

Treatment with Inlyta should be conducted by a physician experienced in the use of anticancer therapies.

Posology

The recommended 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 concomitant medicinal products or dose adjustments.

If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time.

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
Co-administration of axitinib with strong CYP3A4/5 inhibitors may increase axitinib plasma concentrations (see section 4.5). Selection of an alternate concomitant medicinal product with no or minimal CYP3A4/5 inhibition potential is recommended.

Although axitinib dose adjustment has not been studied in patients receiving strong CYP3A4/5 inhibitors, if a strong CYP3A4/5 inhibitor must be co-administered, a dose decrease of axitinib to approximately half the dose (e.g. the starting dose should be reduced from 5 mg twice daily to 2 mg twice daily) is recommended. Management of some adverse reactions may require temporary or permanent discontinuation of axitinib therapy (see section 4.4). If co-administration of the strong inhibitor is discontinued, a return to the axitinib dose used prior to initiation of the strong CYP3A4/5 inhibitor should be considered (see section 4.5).

Concomitant strong CYP3A4/5 inducers
Co-administration of axitinib with strong CYP3A4/5 inducers may decrease axitinib plasma concentrations (see section 4.5). Selection of an alternate concomitant medicinal product with no or minimal CYP3A4/5 induction potential is recommended.

Although axitinib dose adjustment has not been studied in patients receiving strong CYP3A4/5 inducers, if a strong CYP3A4/5 inducer must be co-administered, a gradual dose increase of axitinib is recommended. Maximal induction with high-dose strong CYP3A4/5 inducers has been reported to occur within one week of treatment with the inducer. If the dose of axitinib is increased, the patient should be monitored carefully for toxicity. Management of some adverse reactions may require temporary or permanent discontinuation and/or dose reduction of axitinib therapy (see section 4.4). If co-administration of the strong inducer is discontinued, the axitinib dose should be immediately returned to the dose used prior to initiation of the strong CYP3A4/5 inducer (see section 4.5).

<u>Special populations</u>

Older people (≥ 65 years): No dose adjustment is required (see sections 4.4 and 5.2).

Renal impairment: No dose adjustment is required (see section 5.2). Virtually no data are available regarding axitinib treatment in patients with a creatinine clearance of < 15 mL/min.

Hepatic impairment: No dose adjustment is required when administering axitinib to patients with mild hepatic impairment (Child-Pugh class A). A dose decrease is recommended when administering axitinib to patients with moderate hepatic impairment (Child-Pugh class B) (e.g. the starting dose should be reduced from 5 mg twice daily to 2 mg twice daily). Axitinib has not been studied in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this population (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of axitinib in children and adolescents < 18 years have not been established. No data are available.

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.

4.3 Contraindications

Hypersensitivity to axitinib or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Specific safety events should be monitored before initiation of, and periodically throughout, treatment with axitinib as described below.

Cardiac failure events
In clinical studies with axitinib for the treatment of patients with RCC, cardiac failure events (including cardiac failure, cardiac failure congestive, cardiopulmonary failure, left ventricular dysfunction, ejection fraction decreased, and right ventricular failure) were reported (see section 4.8).

Signs or symptoms of cardiac failure should periodically be monitored throughout treatment with axitinib. Management of cardiac failure events may require temporary interruption or permanent discontinuation and/or dose reduction of axitinib therapy.

Hypertension
In clinical studies with axitinib for the treatment of patients with RCC, hypertension was very commonly reported (see section 4.8).

In a controlled clinical study, the median onset time for hypertension (systolic blood pressure > 150 mmHg or diastolic blood pressure > 100 mmHg) was within the first month of the start of axitinib treatment and blood pressure increases have been observed as early as 4 days after starting axitinib.

Blood pressure should be well-controlled prior to initiating axitinib. Patients should be monitored for hypertension and treated as needed with standard antihypertensive therapy. In the case of persistent hypertension, despite use of antihypertensive medicinal products, the axitinib dose should be reduced. For patients who develop severe hypertension, temporarily interrupt axitinib and restart at a lower dose once the patient is normotensive. If axitinib is interrupted, patients receiving antihypertensive medicinal products should be monitored for hypotension (see section 4.2).

In case of severe or persistent arterial hypertension and symptoms suggestive of posterior reversible encephalopathy syndrome (PRES) (see below), a diagnostic brain magnetic resonance image (MRI) should be considered.

Thyroid dysfunction
In clinical studies with axitinib for the treatment of patients with RCC, events of hypothyroidism and, to a lesser extent, hyperthyroidism, were reported (see section 4.8).

Thyroid function should be monitored before initiation of, and periodically throughout, treatment with axitinib. Hypothyroidism or hyperthyroidism should be treated according to standard medical practice to maintain euthyroid state.

Arterial embolic and thrombotic events
In clinical studies with axitinib, arterial embolic and thrombotic events (including transient ischemic attack, myocardial infarction, cerebrovascular accident and retinal artery occlusion) were reported (see section 4.8).

Axitinib should be used with caution in patients who are at risk for, or who have a history of, these events. Axitinib has not been studied in patients who had an arterial embolic or thrombotic event within the previous 12 months.

Venous embolic and thrombotic events
In clinical studies with axitinib, venous embolic and thrombotic events (including pulmonary embolism, deep vein thrombosis, and retinal vein occlusion/thrombosis) were reported (see section 4.8).

Axitinib should be used with caution in patients who are at risk for, or who have a history of, these events. Axitinib has not been studied in patients who had a venous embolic or thrombotic event within the previous 6 months.

Elevation of haemoglobin or haematocrit
Increases in haemoglobin or haematocrit, reflective of increases in red blood cell mass, may occur during treatment with axitinib (see section 4.8, polycythaemia). An increase in red blood cell mass may increase the risk of embolic and thrombotic events.

Haemoglobin or haematocrit should be monitored before initiation of, and periodically throughout, treatment with axitinib. If haemoglobin or haematocrit becomes elevated above the normal level, patients should be treated according to standard medical practice to decrease haemoglobin or haematocrit to an acceptable level.

Haemorrhage
In clinical studies with axitinib, haemorrhagic events were reported (see section 4.8).

Axitinib has not been studied in patients who have evidence of untreated brain metastasis or recent active gastrointestinal bleeding, and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the axitinib dose.

Gastrointestinal perforation and fistula formation
In clinical studies with axitinib, events of gastrointestinal perforation and fistulas were reported (see section 4.8).

Symptoms of gastrointestinal perforation or fistula should be periodically monitored for throughout treatment with axitinib.

Wound healing complications
No formal studies of the effect of axitinib on wound healing have been conducted.

Treatment with axitinib should be stopped at least 24 hours prior to scheduled surgery. The decision to resume axitinib therapy after surgery should be based on clinical judgment of adequate wound healing.

Posterior reversible encephalopathy syndrome (PRES)
In clinical studies with axitinib, events of PRES were reported (see section 4.8).

PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES. In patients with signs or

symptoms of PRES, temporarily interrupt or permanently discontinue axitinib treatment. The safety of reinitiating axitinib therapy in patients previously experiencing PRES is not known.

Proteinuria
In clinical studies with axitinib, proteinuria, including that of Grade 3 and 4 severity, was reported (see section 4.8).

Monitoring for proteinuria before initiation of, and periodically throughout, treatment with axitinib is recommended. For patients who develop moderate to severe proteinuria, reduce the dose or temporarily interrupt axitinib treatment (see section 4.2).

Liver-related adverse reactions
In a controlled clinical study with axitinib for the treatment of patients with RCC, liver-related adverse reactions were reported. The most commonly reported liver-related adverse reactions included increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and blood bilirubin (see section 4.8). No concurrent elevations of ALT (> 3 times the upper limit of normal [ULN]) and bilirubin (> 2 times the ULN) were observed.

In a clinical dose-finding study, concurrent elevations of ALT (12 times the ULN) and bilirubin (2.3 times the ULN), considered to be drug-related hepatotoxicity, were observed in 1 patient who received axitinib at a starting dose of 20 mg twice daily (4 times the recommended starting dose).

Liver function tests should be monitored before initiation of, and periodically throughout, treatment with axitinib.

Hepatic impairment
In clinical studies with axitinib, the systemic exposure to axitinib was approximately two-fold higher in subjects with moderate hepatic impairment (Child-Pugh class B) compared to subjects with normal hepatic function. A dose decrease is recommended when administering axitinib to patients with moderate hepatic impairment (Child-Pugh class B) (see section 4.2).

Axitinib has not been studied in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this population.

Older people (≥ 65 years) and race
In a controlled clinical study with axitinib for the treatment of patients with RCC, 34% of patients treated with axitinib were ≥ 65 years of age. The majority of patients were White (77%) or Asian (21%). Although greater sensitivity to develop adverse reactions in some older patients and Asian patients cannot be ruled out, overall, no major differences were observed in the safety and effectiveness of axitinib between patients who were ≥ 65 years of age and non-elderly, and between White patients and patients of other races.

No dosage adjustment is required on the basis of patient age or race (see sections 4.2 and 5.2).

Lactose
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro data indicate that axitinib is metabolised primarily by CYP3A4/5 and, to a lesser extent, CYP1A2, CYP2C19, and uridine diphosphate-glucuronosyltransferase (UGT) 1A1.

CYP3A4/5 inhibitors
Ketoconazole, a strong inhibitor of CYP3A4/5, administered at a dose of 400 mg once daily for 7 days, increased the mean area under the curve (AUC) 2-fold and C_{max} 1.5-fold of a single 5-mg oral dose of axitinib in healthy volunteers. Co-administration of axitinib with strong CYP3A4/5 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, erythromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin) may increase axitinib plasma concentrations. Grapefruit may also increase axitinib plasma concentrations. Selection of concomitant medicinal products with no or minimal CYP3A4/5 inhibition potential is recommended. If a strong CYP3A4/5 inhibitor must be co-administered, a dose adjustment of axitinib is recommended (see section 4.2).

CYP1A2 and CYP2C19 inhibitors
CYP1A2 and CYP2C19 constitute minor (< 10%) pathways in axitinib metabolism. The effect of strong inhibitors of these isozymes on axitinib pharmacokinetics has not been studied. Caution should be exercised due to the risk of increased axitinib plasma concentrations in patients taking strong inhibitors of these isozymes.

CYP3A4/5 inducers
Rifampicin, a strong inducer of CYP3A4/5, administered at a dose of 600 mg once daily for 9 days, reduced the mean AUC by 79% and C_{max} by 71% of a single 5 mg dose of axitinib in healthy volunteers.

Co-administration of axitinib with strong CYP3A4/5 inducers (e.g. rifampicin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentin, phenobarbital, and *Hypericum perforatum* [St. John's wort]) may decrease axitinib plasma concentrations. Selection of concomitant medicinal products with no or minimal CYP3A4/5 induction potential is recommended. If a strong CYP3A4/5 inducer must be co-administered, a dose adjustment of axitinib is recommended (see section 4.2).

In vitro studies of CYP and UGT inhibition and induction
In vitro studies indicated that axitinib does not inhibit CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, or UGT1A1 at therapeutic plasma concentrations.

In vitro studies indicated that axitinib has a potential to inhibit CYP1A2. Therefore, co-administration of axitinib with CYP1A2 substrates may result in increased plasma concentrations of CYP1A2 substrates (e.g. theophylline).

In vitro studies also indicated that axitinib has the potential to inhibit CYP2C8. However, co-administration of axitinib with paclitaxel, a known CYP2C8 substrate, did not result in increased plasma concentrations of paclitaxel in patients with advanced cancer, indicating lack of clinical CYP2C8 inhibition.

In vitro studies in human hepatocytes also indicated that axitinib does not induce CYP1A1, CYP1A2, or CYP3A4/5. Therefore co-administration of axitinib is not expected to reduce the plasma concentration of co-administered CYP1A1, CYP1A2, or CYP3A4/5 substrates *in vivo*.

In vitro studies with P-glycoprotein
In vitro studies indicated that axitinib inhibits P-glycoprotein. However, axitinib is not expected to inhibit P-glycoprotein at therapeutic plasma concentrations. Therefore, co-administration of axitinib is not expected to increase the plasma concentration of digoxin, or other P-glycoprotein substrates, *in vivo*.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data regarding the use of axitinib in pregnant women. Based on the pharmacological properties of axitinib, it may cause foetal harm when administered to a pregnant woman. Studies in animals have shown reproductive toxicity including malformations (see section 5.3). Axitinib should not be used during pregnancy unless the clinical condition of the woman requires treatment with this medicinal product.

Women of childbearing potential must use effective contraception during and up to 1 week after treatment.

Breast-feeding
It is unknown whether axitinib is excreted in human milk. A risk to the suckling child cannot be excluded. Axitinib should not be used during breast-feeding.

Fertility
Based on non-clinical findings, axitinib has the potential to impair reproductive function and fertility in humans (see section 5.3).

4.7 Effects on ability to drive and use machines

Axitinib has a minor influence on the ability to drive and use machines. Patients should be advised that they may experience events such as dizziness and/or fatigue during treatment with axitinib.

4.8 Undesirable effects

Summary of the safety profile
The following risks, including appropriate action to be taken, are discussed in greater detail in *Section 4.4:* cardiac failure events, hypertension, thyroid dysfunction, arterial thromboembolic events, venous thromboembolic events, elevation of haemoglobin or haematocrit, haemorrhage, gastrointestinal perforation and fistula formation, wound healing complications, PRES, proteinuria, and elevation of liver enzymes.

The most common (≥ 20%) adverse reactions observed following treatment with axitinib were diarrhoea, hypertension, fatigue, decreased appetite, nausea, weight decreased, dysphonia, palmar-plantar erythrodysaesthesia (hand-foot) syndrome, haemorrhage, hypothyroidism, vomiting, proteinuria, cough, and constipation.

Tabulated list of adverse reactions
Table 1 presents adverse reactions reported in a pooled dataset of 672 patients who received axitinib in clinical studies for the treatment of patients with RCC (see section 5.1).

The adverse reactions are listed by system organ class, frequency category and grade of severity. Frequency categories are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), and not known (cannot be estimated from the available data). The current safety database for axitinib is too small to detect rare and very rare adverse reactions.

Categories have been assigned based on absolute frequencies in the pooled clinical studies data. Within each system organ class, adverse reactions with the same frequency are presented in order of decreasing seriousness.

Table 1. Adverse reactions reported in RCC studies in patients who received axitinib (N = 672)

System Organ Class	Frequency Category	Adverse Reactions[a]	All Grades[b] %	Grade 3[b] %	Grade 4[b] %
Blood and lymphatic system disorders	Common	Anaemia	6.3	1.2	0.4
		Thrombocytopenia	1.6	0.1	0
		Polycythaemia[c]	1.5	0.1	0
	Uncommon	Neutropaenia	0.3	0.1	0
		Leukopaenia	0.4	0	0
Endocrine disorders	Very Common	Hypothyroidism[c]	24.6	0.3	0
	Common	Hyperthyroidism[c]	1.6	0.1	0.1
Metabolism and nutrition disorders	Very Common	Decreased appetite	39.0	3.6	0.3
	Common	Dehydration	6.7	3.1	0.3
		Hyperkalaemia	2.7	1.2	0.1
		Hypercalcaemia	2.2	0.1	0.3
Nervous system disorders	Very Common	Headache	16.2	0.7	0
		Dysgeusia	11.5	0	0
	Common	Dizziness	9.1	0.6	0
	Uncommon	Posterior reversible encephalopathy syndrome[e]	0.3	0.1	0
Ear and labyrinth disorders	Common	Tinnitus	3.1	0	0
Cardiac disorders	Common	Cardiac failure events[c,d,f]	1.8	0.3	0.7
Vascular disorders	Very Common	Hypertension[g]	51.2	22.0	1.0
		Haemorrhage[c,d,h]	25.7	3.0	1.0
	Common	Venous embolic and thrombotic events[c,d,i]	2.8	0.9	1.2
		Arterial embolic and thrombotic events[c,d,j]	2.8	1.2	1.3
Respiratory, thoracic and mediastinal disorders	Very Common	Dyspnoea[d]	17.1	3.6	0.6
		Cough	20.4	0.6	0
		Dysphonia	32.7	0	0.1
	Common	Oropharyngeal pain	7.4	0	0
Gastrointestinal disorders	Very Common	Diarrhoea	55.4	10.1	0.1
		Vomiting	23.7	2.7	0.1
		Nausea	33.0	2.2	0.1
		Abdominal pain	14.7	2.5	0.3
		Constipation	20.2	1.0	0
		Stomatitis	15.5	1.8	0
		Dyspepsia	11.2	0.1	0
	Common	Upper abdominal pain	9.4	0.9	0
		Flatulence	4.5	0	0
		Haemorrhoids	3.3	0	0
		Glossodynia	2.8	0	0
		Gastrointestinal perforation and fistula[c,k]	1.9	0.9	0.3
Hepatobiliary disorders	Common	Hyperbilirubinaemia	1.3	0.1	0.1

System Organ Class	Frequency Category	Adverse Reactions[a]	All Grades[b] %	Grade 3[b] %	Grade 4[b] %
Skin and subcutaneous tissue disorders	Very Common	Palmar-plantar erythrodysaesthesia (hand-foot syndrome)	32.1	7.6	0
		Rash	14.3	0.1	0
		Dry skin	10.1	0.1	0
	Common	Pruritus	6.0	0	0
		Erythema	3.7	0	0
		Alopecia	5.7	0	0
Musculoskeletal and connective tissue disorders	Very Common	Arthralgia	17.7	1.9	0.3
		Pain in extremity	14.1	1.0	0.3
	Common	Myalgia	8.2	0.6	0.1
Renal and urinary disorders	Very Common	Proteinuria[l]	21.1	4.8	0.1
	Common	Renal failure[m]	1.6	0.9	0.1
General disorders and administration site conditions	Very Common	Fatigue	45.1	10.6	0.3
		Asthaenia[d]	13.8	2.8	0.3
		Mucosal inflammation	13.7	1.0	0
Investigations	Very Common	Weight decreased	32.7	4.9	0
	Common	Lipase increased	3.7	0.7	0.7
		Alanine aminotransferase increased	6.5	1.2	0
		Amylase increased	3.4	0.6	0.4
		Aspartate aminotransferase increased	6.1	1.0	0
		Alkaline phosphatase increased	4.8	0.3	0
		Creatinine increased	5.7	0.4	0
		Thyroid stimulating hormone increased	7.9	0	0

[a] Adverse reactions are according to treatment-emergent, all causality frequency.
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0
[c] See Description of selected adverse reactions section.
[d] Fatal (Grade 5) cases were reported.
[e] Including Leukoencephalopathy.
[f] Including cardiac failure, cardiac failure congestive, cardiopulmonary failure, ejection fraction decreased, left ventricular dysfunction and right ventricular failure.
[g] Including accelerated hypertension, blood pressure increased, hypertension and hypertensive crisis.
[h] Including activated partial thromboplastin time prolonged, anal haemorrhage, arterial haemorrhage, blood urine present, central nervous system haemorrhage, cerebral haemorrhage, coagulation time prolonged, conjunctival haemorrhage, contusion, diarrhea haemorrhagic, dysfunctional uterine bleeding, epistaxis, gastric haemorrhage, gastrointestinal haemorrhage, gingival bleeding, haematemesis, haematochezia, haematocrit decreased, haematoma, haematuria, haemoglobin decreased, haemoptysis, haemorrhage, haemorrhage coronary artery, haemorrhage urinary tract, haemorrhoidal haemorrhage, haemostasis, increased tendency to bruise, international normalized ratio increased, lower gastrointestinal haemorrhage, melaena, petechiae, pharyngeal haemorrhage, prothrombin time prolonged, pulmonary haemorrhage, purpura, rectal haemorrhage, red blood cell count decreased, renal haemorrhage, scleral haemorrhage, scrotal haematocoele, splenic haemotoma, splinter haemorrhage, subarachnoid haemorrhage, tongue haemorrhage, upper gastrointestinal haemorrhage and vaginal haemorrhage.
[i] Including Budd-Chiari syndrome, deep vein thrombosis, jugular vein thrombosis, pelvic venous thrombosis, pulmonary embolism, retinal vein occlusion, retinal vein thrombosis, subclavian vein thrombosis, venous thrombosis, and venous thrombosis limb.

[j] Including acute myocardial infarction, embolism, myocardial infarction, retinal artery occlusion and transient ischaemic attack.
[k] Gastrointestinal perforation and fistula includes the following preferred terms: abdominal abscess, anal abscess, anal fistula, fistula, gastrointestinal anastomotic leak, gastrointestinal perforation, large intestine perforation, oesophagobronchial fistula and peritonitis.
[l] Proteinuria includes the following preferred terms: protein urine, protein urine present and proteinuria.
[m] Including acute renal failure

Description of selected adverse reactions

Cardiac failure events (see section 4.4)
In a controlled clinical study with axitinib (N = 359) for the treatment of patients with RCC, cardiac failure events were reported in 1.7 % patients receiving axitinib, including cardiac failure (0.6%), cardiopulmonary failure (0.6%), left ventricular dysfunction (0.3%), and right ventricular failure (0.3%). Grade 4 cardiac failure adverse reactions were reported in 0.6 % of patients receiving axitinib. Fatal cardiac failure was reported in 0.6 % of patients receiving axitinib.

In monotherapy studies with axitinib (N = 672) for the treatment of patients with RCC, cardiac failure events (including cardiac failure, cardiac failure congestive, cardiopulmonary failure, left ventricular dysfunction, ejection fraction decreased, and right ventricular failure) were reported in 1.8% patients receiving axitinib. Grade 3/4 cardiac failure events were reported in 1.0% patients and fatal cardiac failure events were reported in 0.3% patients receiving axitinib.

Thyroid dysfunction (see section 4.4)
In a controlled clinical study with axitinib for the treatment of patients with RCC, hypothyroidism was reported in 20.9% of patients and hyperthyroidism was reported in 1.1% of patients. Thyroid stimulating hormone (TSH) increased was reported as an adverse reaction in 5.3% of patients receiving axitinib. During routine laboratory assessments, in patients who had TSH < 5 μU/mL before treatment, elevations of TSH to ≥ 10 μU/mL occurred in 32.2% of patients receiving axitinib.

In pooled clinical studies with axitinib (N = 672) for the treatment of patients with RCC, hypothyroidism was reported in 24.6% of patients receiving axitinib. Hyperthyroidism was reported in 1.6% of patients receiving axitinib.

Venous embolic and thrombotic events (see section 4.4)
In a controlled clinical study with axitinib for the treatment of patients with RCC, venous embolic and thrombotic adverse reactions were reported in 3.9% of patients receiving axitinib, including pulmonary embolism (2.2%), retinal vein occlusion/thrombosis (0.6%) and deep vein thrombosis (0.6%). Grade 3/4 venous embolic and thrombotic adverse reactions were reported in 3.1% of patients receiving axitinib. Fatal pulmonary embolism was reported in one patient (0.3%) receiving axitinib.

In pooled clinical studies with axitinib (N = 672) for the treatment of patients with RCC, venous embolic and thrombotic events were reported in 2.8% of patients receiving axitinib. Grade 3 venous embolic and thrombotic events were reported in 0.9% of patients. Grade 4 venous embolic and thrombotic events were reported in 1.2% of patients. Fatal venous embolic and thrombotic events were reported 0.1% patients receiving axitinib.

Arterial embolic and thrombotic events (see section 4.4)
In a controlled clinical study with axitinib for the treatment of patients with RCC, arterial embolic and thrombotic adverse reactions were reported in 4.7% of patients receiving axitinib, including myocardial infarction (1.4%), transient ischemic attack (0.8%) and cerebrovascular accident (0.6%). Grade 3/4 arterial embolic and thrombotic adverse reactions were reported in 3.3% of patients receiving axitinib. A fatal acute myocardial infarction and cerebrovascular accident was reported in one patient each (0.3%). In monotherapy studies with axitinib (N = 850), arterial embolic and

thrombotic adverse reactions (including transient ischemic attack, myocardial infarction, and cerebrovascular accident) were reported in 5.3% of patients receiving axitinib.

In pooled clinical studies with axitinib (N = 672) for the treatment of patients with RCC, arterial embolic and thrombotic events were reported in 2.8% of patients receiving axitinib. Grade 3 arterial embolic and thrombotic events were reported in 1.2% of patients. Grade 4 arterial embolic and thrombotic events were reported in 1.3% of patients. Fatal arterial embolic and thrombotic events were reported in 0.3% patients receiving axitinib.

*Polycythaemia (*see *Elevation of haemoglobin or haematocrit* in section 4.4)
In a controlled clinical study with axitinib for the treatment of patients with RCC, polycythaemia was reported in 1.4% of patients receiving axitinib. Routine laboratory assessments detected elevated haemoglobin above ULN in 9.7% of patients receiving axitinib. In four clinical studies with axitinib for the treatment of patients with RCC (N = 537), elevated haemoglobin above ULN was observed in 13.6% receiving axitinib.

In pooled clinical studies with axitinib (N = 672) for the treatment of patients with RCC, polycythaemia was reported in 1.5% of patients receiving axitinib.

Haemorrhage (see section 4.4)
In a controlled clinical study with axitinib for the treatment of patients with RCC that excluded patients with untreated brain metastasis, haemorrhagic adverse reactions were reported in 21.4% of patients receiving axitinib. The haemorrhagic adverse reactions in patients treated with axitinib included epistaxis (7.8%), haematuria (3.6%), haemoptysis (2.5%), rectal haemorrhage (2.2%), gingival bleeding (1.1%), gastric haemorrhage (0.6%), cerebral haemorrhage (0.3%) and lower gastrointestinal haemorrhage (0.3%). Grade $\geq$ 3 haemorrhagic adverse reactions were reported in 3.1% of patients receiving axitinib (including cerebral haemorrhage, gastric haemorrhage, lower gastrointestinal haemorrhage and haemoptysis). Fatal haemorrhage was reported in one patient (0.3%) receiving axitinib (gastric haemorrhage). In monotherapy studies with axitinib (N = 850), haemoptysis was reported in 3.9% of patients; Grade $\geq$ 3 haemoptysis was reported in 0.5% of patients.

In pooled clinical studies with axitinib (N = 672) for the treatment of patients with RCC, haemorrhagic events were reported in 25.7% of patients receiving axitinib. Grade 3 haemorrhagic adverse reactions were reported in 3% of patients. Grade 4 haemorrhagic adverse reactions were reported in 1% of patients and fatal haemorrhage were reported in 0.4% of patients receiving axitinib.

Gastrointestinal perforation and fistula formation (see section 4.4)
In a controlled clinical study with axitinib for the treatment of patients with RCC, gastrointestinal perforation-type events were reported in 1.7% of patients receiving axitinib, including anal fistula (0.6%), fistula (0.3%) and gastrointestinal perforation (0.3%).In monotherapy studies with axitinib (N = 850), gastrointestinal perforation-type events were reported in 1.9% of patients and fatal gastrointestinal perforation was reported in one patient (0.1%).

In pooled clinical studies with axitinib (N = 672) for the treatment of patients with RCC, gastrointestinal perforation and fistula were reported in 1.9% of patients receiving axitinib.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no specific treatment for axitinib overdose.

In a controlled clinical study with axitinib for the treatment of patients with RCC, one patient inadvertently received a dose of 20 mg twice daily for 4 days and experienced dizziness (Grade 1).

In a clinical dose finding study with axitinib, subjects who received starting doses of 10 mg twice daily or 20 mg twice daily experienced adverse reactions which included hypertension, seizures associated with hypertension, and fatal haemoptysis.

In cases of suspected overdose, axitinib should be withheld and supportive care instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE17

Mechanism of action
Axitinib is a potent and selective tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, VEGFR-2 and VEGFR-3. These receptors are implicated in pathologic angiogenesis, tumour growth, and metastatic progression of cancer. Axitinib has been shown to potently inhibit VEGF-mediated endothelial cell proliferation and survival. Axitinib inhibited the phosphorylation of VEGFR-2 in xenograft tumour vasculature that expressed the target *in vivo* and produced tumour growth delay, regression, and inhibition of metastases in many experimental models of cancer.

Effect on QTc interval
In a randomised, 2-way crossover study, 35 healthy subjects were administered a single oral dose of axitinib (5 mg) in the absence and presence of 400 mg ketoconazole for 7 days. Results of this study indicated that axitinib plasma exposures up to two-fold greater than therapeutic levels expected following a 5 mg dose, did not produce clinically-significant QT interval prolongation.

Clinical efficacy
The safety and efficacy of axitinib were evaluated in a randomised, open-label, multicenter Phase 3 study. Patients (N = 723) with advanced RCC whose disease had progressed on or after treatment with one prior systemic therapy, including sunitinib-, bevacizumab-, temsirolimus-, or cytokine-containing regimens were randomised (1:1) to receive axitinib (N = 361) or sorafenib (N = 362). The primary endpoint, progression-free survival (PFS), was assessed using a blinded independent central review. Secondary endpoints included objective response rate (ORR) and overall survival (OS).

Of the patients enrolled in this study, 389 patients (53.8%) had received one prior sunitinib-based therapy, 251 patients (34.7%) had received one prior cytokine-based therapy (interleukin-2 or interferon-alpha), 59 patients (8.2%) had received one prior bevacizumab-based therapy, and 24 patients (3.3%) had received one prior temsirolimus-based therapy. The baseline demographic and disease characteristics were similar between the axitinib and sorafenib groups with regard to age, gender, race, Eastern Cooperative Oncology Group (ECOG) performance status, geographic region, and prior treatment.

In the overall patient population and the two main subgroups (prior sunitinib treatment and prior cytokine treatment), there was a statistically significant advantage for axitinib over sorafenib for the primary endpoint of PFS (see Table 2 and Figures 1, 2 and 3). The magnitude of median PFS effect was different in the subgroups by prior therapy. Two of the subgroups were too small to give reliable results (prior temsirolimus treatment or prior bevacizumab treatment). There were no statistically significant differences between the arms in OS in the overall population or in the subgroups by prior therapy.

Table 2. Efficacy results

Endpoint / Study Population	Axitinib	Sorafenib	HR (95% CI)	p-value
Overall ITT	**N = 361**	**N = 362**		
Median PFS [a,b] in months (95% CI)	6.8 (6.4, 8.3)	4.7 (4.6, 6.3)	0.67 (0.56, 0.81)	< 0.0001[c]
Median OS [d] in months (95% CI)	20.1 (16.7, 23.4)	19.2 (17.5, 22.3)	0.97 (0.80, 1.17)	NS
ORR [b,e] % (95% CI)	19.4 (15.4, 23.9)	9.4 (6.6, 12.9)	2.06[f] (1.41, 3.00)	0.0001[g]
Prior sunitinib treatment	**N = 194**	**N = 195**		
Median PFS [a,b] in months (95% CI)	4.8 (4.5, 6.5)	3.4 (2.8, 4.7)	0.74 (0.58, 0.94)	0.0063[h]
Median OS [d] in months (95% CI)	15.2 (12.8, 18.3)	16.5 (13.7, 19.2)	1.00 (0.78, 1.27)	NS
ORR [b,e] % (95% CI)	11.3 (7.2, 16.7)	7.7 (4.4, 12.4)	1.48[f] (0.79, 2.75)	NS
Prior cytokine treatment	**N = 126**	**N = 125**		
Median PFS [a,b] in months (95% CI)	12.0 (10.1, 13.9)	6.6 (6.4, 8.3)	0.52 (0.38, 0.72)	< 0.0001[h]
Median OS [d] in months (95% CI)	29.4 (24.5, NE)	27.8 (23.1, 34.5)	0.81 (0.56, 1.19)	NS
ORR [b,e] % (95% CI)	32.5 (24.5, 41.5)	13.6 (8.1, 20.9)	2.39[f] (1.43-3.99)	0.0002[i]

CI = Confidence interval, HR = Hazard ratio (axitinib/sorafenib); ITT: Intent-to-treat; NE: not estimable; NS: not statistically significant; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival.

[a] Time from randomisation to progression or death due to any cause, whichever occurs first. Cutoff date: 03 June 2011.

[b] Assessed by independent radiology review according to Response Evaluation Criteria in Solid Tumours (RECIST).

[c] One-sided p-value from a log-rank test of treatment stratified by ECOG performance status and prior therapy.

[d] Cutoff date: 01 November 2011.

[e] Cutoff date: 31 August 2010.

[f] Risk ratio is used for ORR. A risk ratio > 1 indicated a higher likelihood of responding in the axitinib arm; a risk ratio < 1 indicated a higher likelihood of responding in the sorafenib arm.

[g] One-sided p-value from Cochran-Mantel-Haenszel test of treatment stratified by ECOG performance status and prior therapy.

[h] One-sided p-value from a log-rank test of treatment stratified by ECOG performance status.

[i] One-sided p-value from Cochran-Mantel-Haenszel test of treatment stratified by ECOG performance status.

Figure 1. Kaplan-Meier curve of progression-free survival by independent assessment for the overall population

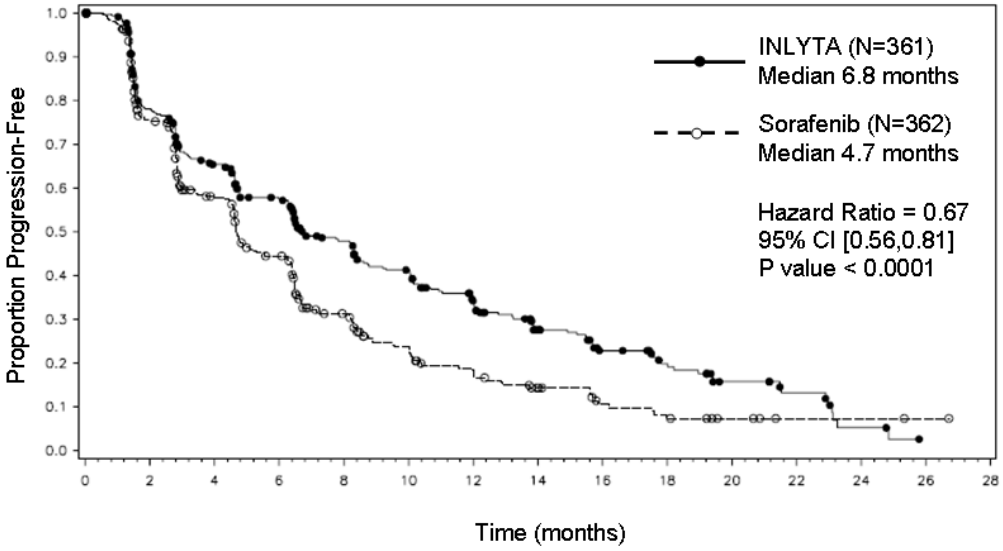


Figure 2. Kaplan-Meier curve of progression-free survival by independent assessment for the prior sunitinib subgroup

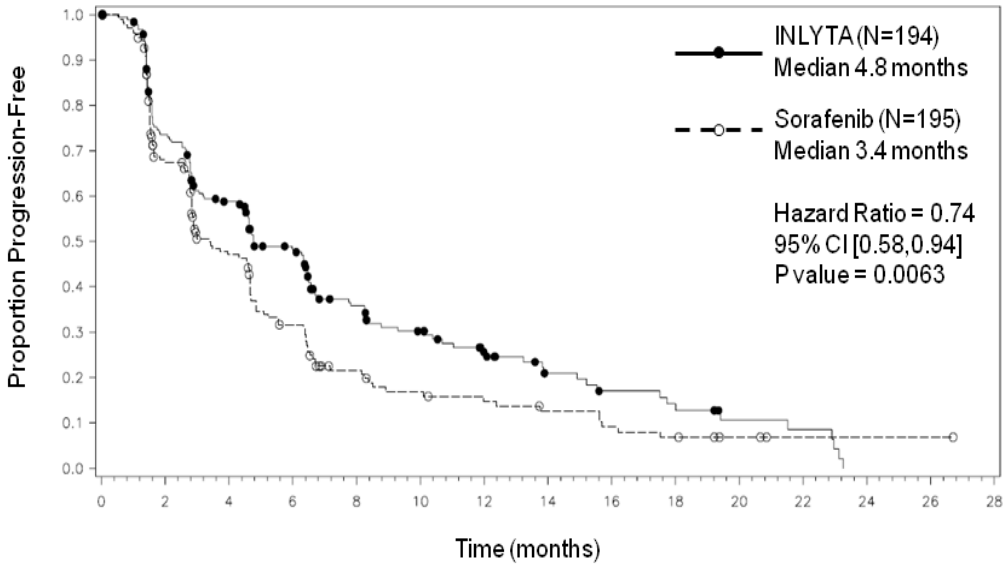
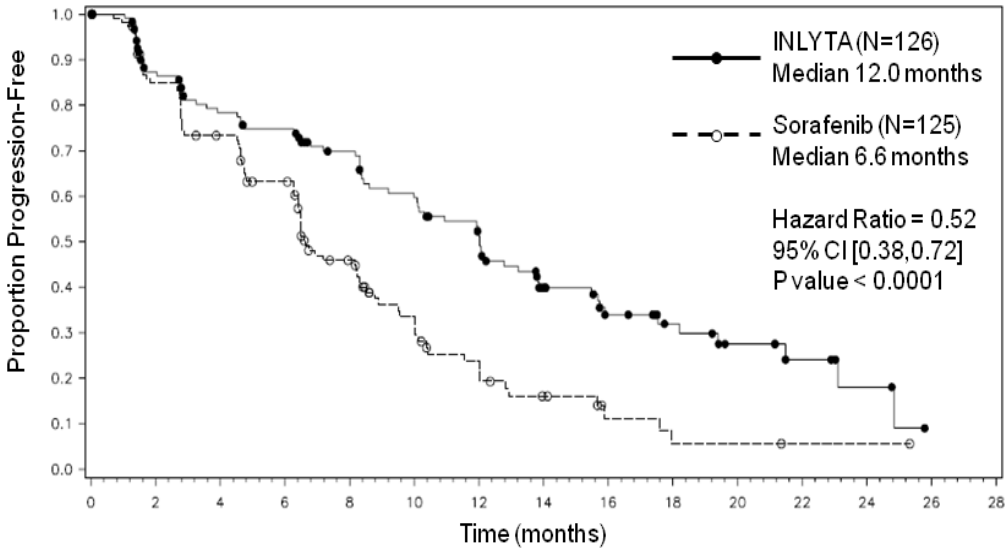


Figure 3. Kaplan-Meier curve of progression-free survival by independent assessment for the prior cytokine subgroup



Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with axitinib in all subsets of the paediatric population for treatment of kidney and renal pelvis carcinoma (excluding nephroblastoma, nephroblastomatosis, clear cell sarcoma, mesoblastic nephroma, renal medullary carcinoma and rhabdoid tumour of the kidney) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

After oral administration of axitinib tablets, the mean absolute bioavailability is 58% compared to intravenous administration. The plasma half life of axitinib ranges from 2.5 to 6.1 hours. Dosing of axitinib at 5 mg twice daily resulted in less than two-fold accumulation compared to administration of

a single dose. Based on the short half-life of axitinib, steady state is expected within 2 to 3 days of the initial dose.

Absorption and distribution
Peak axitinib concentrations in plasma are generally reached within 4 hours following oral administration of axitinib with median T_{max} ranging from 2.5 to 4.1 hours. Administration of axitinib with a moderate fat meal resulted in 10% lower exposure compared to overnight fasting. A high fat, high-calorie meal resulted in 19% higher exposure compared to overnight fasting. Axitinib may be administered with or without food (see section 4.2).

The average C_{max} and AUC increased proportionally over an axitinib dosing range of 5 to 10 mg. *In vitro* binding of axitinib to human plasma proteins is > 99% with preferential binding to albumin and moderate binding to α_1-acid glycoprotein. At the 5 mg twice daily dose in the fed state, the geometric mean peak plasma concentration and 24-hour AUC were 27.8 ng/mL and 265 ng.h/mL, respectively, in patients with advanced RCC. The geometric mean oral clearance and apparent volume of distribution were 38 L/h and 160 L, respectively.

Biotransformation and elimination
Axitinib is metabolised primarily in the liver by CYP3A4/5 and to a lesser extent by CYP1A2, CYP2C19, and UGT1A1.

Following oral administration of a 5 mg radioactive dose of axitinib, 30-60% of the radioactivity was recovered in faeces and 23% of the radioactivity was recovered in urine. Unchanged axitinib, accounting for 12% of the dose, was the major component identified in faeces. Unchanged axitinib was not detected in urine; the carboxylic acid and sulfoxide metabolites accounted for the majority of radioactivity in urine. In plasma, the N-glucuronide metabolite represented the predominant radioactive component (50% of circulating radioactivity) and unchanged axitinib and the sulfoxide metabolite each accounted for approximately 20% of the circulating radioactivity.

The sulfoxide and N-glucuronide metabolites show approximately 400-fold and 8000-fold less *in vitro* potency, respectively, against VEGFR-2 compared to axitinib.

Special populations

Older people, gender, and race
Population pharmacokinetic analyses in patients with advanced cancer (including advanced RCC) and healthy volunteers indicate that there are no clinically relevant effects of age, gender, body weight, race, renal function, UGT1A1 genotype, or CYP2C19 genotype.

Paediatric population
Axitinib has not been studied in patients < 18 years of age.

Hepatic impairment
In vitro and *in vivo* data indicate that axitinib is primarily metabolised by the liver.

Compared to subjects with normal hepatic function, systemic exposure following a single dose of axitinib was similar in subjects with mild hepatic impairment (Child-Pugh class A) and higher (approximately two-fold) in subjects with moderate hepatic impairment (Child-Pugh class B). Axitinib has not been studied in subjects with severe hepatic impairment (Child-Pugh class C) and should not be used in this population (see section 4.2 for dose adjustment recommendations).

Renal impairment
Unchanged axitinib is not detected in the urine.

Axitinib has not been studied in subjects with renal impairment. In clinical studies with axitinib for the treatment of patients with RCC, patients with serum creatinine > 1.5 times the ULN or calculated

creatinine clearance < 60 mL/min were excluded. Population pharmacokinetic analyses have shown that axitinib clearance was not altered in subjects with renal impairment and no dose adjustment of axitinib is required.

5.3 Preclinical safety data

Repeat dose toxicity
Major toxicity findings in mice and dogs following repeated dosing for up to 9 months were the gastrointestinal, haematopoietic, reproductive, skeletal and dental systems, with No Observed Adverse Effect Levels (NOAEL) approximately equivalent to or below expected human exposure at the recommended clinical starting dose (based on AUC levels).

Carcinogenicity
Carcinogenicity studies have not been performed with axitinib.

Genotoxicity
Axitinib was not mutagenic or clastogenic in conventional genotoxicity assays *in vitro*. A significant increase in polyploidy was observed *in vitro* at concentrations > 0.22 µg/mL, and an elevation in micronucleated polychromatic erythrocytes was observed *in vivo* with No Observed Effect Level (NOEL) 69-fold the expected human exposure. Genotoxicity findings are not considered clinically relevant at exposure levels observed in humans.

Reproduction toxicity
Axitinib-related findings in the testes and epididymis included decreased organ weight, atrophy or degeneration, decreased numbers of germinal cells, hypospermia or abnormal sperm forms, and reduced sperm density and count. These findings were observed in mice at exposure levels approximately 12-fold the expected human exposure, and in dogs at exposure levels below the expected human exposure. There was no effect on mating or fertility in male mice at exposure levels approximately 57-fold the expected human exposure. Findings in females included signs of delayed sexual maturity, reduced or absent corpora lutea, decreased uterine weights and uterine atrophy at exposures approximately equivalent to the expected human exposure. Reduced fertility and embryonic viability were observed in female mice at all doses tested, with exposure levels at the lowest dose approximately 10-fold the expected human exposure.

Pregnant mice exposed to axitinib showed an increased occurrence of cleft palate malformations and skeletal variations, including delayed ossification, at exposure levels below the expected human exposure. Perinatal and postnatal developmental toxicity studies have not been conducted.

Toxicity findings in immature animals
Reversible physeal dysplasia was observed in mice and dogs given axitinib for at least 1 month at exposure levels approximately six-fold higher than the expected human exposure. Partially reversible dental caries were observed in mice treated for more than 1 month at exposure levels similar to the expected human exposure. Other toxicities of potential concern to paediatric patients have not been evaluated in juvenile animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Magnesium stearate

Tablet film-coating:
Hypromellose
Titanium dioxide (E171)
Lactose monohydrate
Triacetin (E1518)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/aluminium blister containing 14 film-coated tablets. Each pack contains 28 or 56 film-coated tablets.

HDPE bottle with a silica gel desiccant and a polypropylene closure containing 60 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich, Kent CT13 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/777/004
EU/1/12/777/005
EU/1/12/777/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3 September 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Inlyta 7 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 7 mg of axitinib.

Excipients with known effect:
Each film-coated tablet contains 82.3 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Red diamond shaped film-coated tablet debossed with “Pfizer” on one side and “7 XNB” on the other

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Inlyta is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine.

4.2 Posology and method of administration

Treatment with Inlyta should be conducted by a physician experienced in the use of anticancer therapies.

Posology

The recommended 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 concomitant medicinal products or dose adjustments.

If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time.

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
Co-administration of axitinib with strong CYP3A4/5 inhibitors may increase axitinib plasma concentrations (see section 4.5). Selection of an alternate concomitant medicinal product with no or minimal CYP3A4/5 inhibition potential is recommended.

Although axitinib dose adjustment has not been studied in patients receiving strong CYP3A4/5 inhibitors, if a strong CYP3A4/5 inhibitor must be co-administered, a dose decrease of axitinib to approximately half the dose (e.g. the starting dose should be reduced from 5 mg twice daily to 2 mg twice daily) is recommended. Management of some adverse reactions may require temporary or permanent discontinuation of axitinib therapy (see section 4.4). If co-administration of the strong inhibitor is discontinued, a return to the axitinib dose used prior to initiation of the strong CYP3A4/5 inhibitor should be considered (see section 4.5).

Concomitant strong CYP3A4/5 inducers
Co-administration of axitinib with strong CYP3A4/5 inducers may decrease axitinib plasma concentrations (see section 4.5). Selection of an alternate concomitant medicinal product with no or minimal CYP3A4/5 induction potential is recommended.

Although axitinib dose adjustment has not been studied in patients receiving strong CYP3A4/5 inducers, if a strong CYP3A4/5 inducer must be co-administered, a gradual dose increase of axitinib is recommended. Maximal induction with high-dose strong CYP3A4/5 inducers has been reported to occur within one week of treatment with the inducer. If the dose of axitinib is increased, the patient should be monitored carefully for toxicity. Management of some adverse reactions may require temporary or permanent discontinuation and/or dose reduction of axitinib therapy (see section 4.4). If co-administration of the strong inducer is discontinued, the axitinib dose should be immediately returned to the dose used prior to initiation of the strong CYP3A4/5 inducer (see section 4.5).

<u>Special populations</u>

Older people (≥ 65 years): No dose adjustment is required (see sections 4.4 and 5.2).

Renal impairment: No dose adjustment is required (see section 5.2). Virtually no data are available regarding axitinib treatment in patients with a creatinine clearance of < 15 mL/min.

Hepatic impairment: No dose adjustment is required when administering axitinib to patients with mild hepatic impairment (Child-Pugh class A). A dose decrease is recommended when administering axitinib to patients with moderate hepatic impairment (Child-Pugh class B) (e.g. the starting dose should be reduced from 5 mg twice daily to 2 mg twice daily). Axitinib has not been studied in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this population (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of axitinib in children and adolescents < 18 years have not been established. No data are available.

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.

4.3 Contraindications

Hypersensitivity to axitinib or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Specific safety events should be monitored before initiation of, and periodically throughout, treatment with axitinib as described below.

Cardiac failure events
In clinical studies with axitinib for the treatment of patients with RCC, cardiac failure events (including cardiac failure, cardiac failure congestive, cardiopulmonary failure, left ventricular dysfunction, ejection fraction decreased, and right ventricular failure) were reported (see section 4.8).

Signs or symptoms of cardiac failure should periodically be monitored throughout treatment with axitinib. Management of cardiac failure events may require temporary interruption or permanent discontinuation and/or dose reduction of axitinib therapy.

Hypertension
In clinical studies with axitinib for the treatment of patients with RCC, hypertension was very commonly reported (see section 4.8).

In a controlled clinical study, the median onset time for hypertension (systolic blood pressure > 150 mmHg or diastolic blood pressure > 100 mmHg) was within the first month of the start of axitinib treatment and blood pressure increases have been observed as early as 4 days after starting axitinib.

Blood pressure should be well-controlled prior to initiating axitinib. Patients should be monitored for hypertension and treated as needed with standard antihypertensive therapy. In the case of persistent hypertension, despite use of antihypertensive medicinal products, the axitinib dose should be reduced. For patients who develop severe hypertension, temporarily interrupt axitinib and restart at a lower dose once the patient is normotensive. If axitinib is interrupted, patients receiving antihypertensive medicinal products should be monitored for hypotension (see section 4.2).

In case of severe or persistent arterial hypertension and symptoms suggestive of posterior reversible encephalopathy syndrome (PRES) (see below), a diagnostic brain magnetic resonance image (MRI) should be considered.

Thyroid dysfunction
In clinical studies with axitinib for the treatment of patients with RCC, events of hypothyroidism and, to a lesser extent, hyperthyroidism, were reported (see section 4.8).

Thyroid function should be monitored before initiation of, and periodically throughout, treatment with axitinib. Hypothyroidism or hyperthyroidism should be treated according to standard medical practice to maintain euthyroid state.

Arterial embolic and thrombotic events
In clinical studies with axitinib, arterial embolic and thrombotic events (including transient ischemic attack, myocardial infarction, cerebrovascular accident and retinal artery occlusion) were reported (see section 4.8).

Axitinib should be used with caution in patients who are at risk for, or who have a history of, these events. Axitinib has not been studied in patients who had an arterial embolic or thrombotic event within the previous 12 months.

Venous embolic and thrombotic events
In clinical studies with axitinib, venous embolic and thrombotic events (including pulmonary embolism, deep vein thrombosis, and retinal vein occlusion/thrombosis) were reported (see section 4.8).

Axitinib should be used with caution in patients who are at risk for, or who have a history of, these events. Axitinib has not been studied in patients who had a venous embolic or thrombotic event within the previous 6 months.

Elevation of haemoglobin or haematocrit
Increases in haemoglobin or haematocrit, reflective of increases in red blood cell mass, may occur during treatment with axitinib (see section 4.8, polycythaemia). An increase in red blood cell mass may increase the risk of embolic and thrombotic events.

Haemoglobin or haematocrit should be monitored before initiation of, and periodically throughout, treatment with axitinib. If haemoglobin or haematocrit becomes elevated above the normal level, patients should be treated according to standard medical practice to decrease haemoglobin or haematocrit to an acceptable level.

Haemorrhage
In clinical studies with axitinib, haemorrhagic events were reported (see section 4.8).

Axitinib has not been studied in patients who have evidence of untreated brain metastasis or recent active gastrointestinal bleeding, and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the axitinib dose.

Gastrointestinal perforation and fistula formation
In clinical studies with axitinib, events of gastrointestinal perforation and fistulas were reported (see section 4.8).

Symptoms of gastrointestinal perforation or fistula should be periodically monitored for throughout treatment with axitinib.

Wound healing complications
No formal studies of the effect of axitinib on wound healing have been conducted.

Treatment with axitinib should be stopped at least 24 hours prior to scheduled surgery. The decision to resume axitinib therapy after surgery should be based on clinical judgment of adequate wound healing.

Posterior reversible encephalopathy syndrome (PRES)
In clinical studies with axitinib, events of PRES were reported (see section 4.8).

PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES. In patients with signs or

symptoms of PRES, temporarily interrupt or permanently discontinue axitinib treatment. The safety of reinitiating axitinib therapy in patients previously experiencing PRES is not known.

Proteinuria
In clinical studies with axitinib, proteinuria, including that of Grade 3 and 4 severity, was reported (see section 4.8).

Monitoring for proteinuria before initiation of, and periodically throughout, treatment with axitinib is recommended. For patients who develop moderate to severe proteinuria, reduce the dose or temporarily interrupt axitinib treatment (see section 4.2).

Liver-related adverse reactions
In a controlled clinical study with axitinib for the treatment of patients with RCC, liver-related adverse reactions were reported. The most commonly reported liver-related adverse reactions included increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and blood bilirubin (see section 4.8). No concurrent elevations of ALT (> 3 times the upper limit of normal [ULN]) and bilirubin (> 2 times the ULN) were observed.

In a clinical dose-finding study, concurrent elevations of ALT (12 times the ULN) and bilirubin (2.3 times the ULN), considered to be drug-related hepatotoxicity, were observed in 1 patient who received axitinib at a starting dose of 20 mg twice daily (4 times the recommended starting dose).

Liver function tests should be monitored before initiation of, and periodically throughout, treatment with axitinib.

Hepatic impairment
In clinical studies with axitinib, the systemic exposure to axitinib was approximately two-fold higher in subjects with moderate hepatic impairment (Child-Pugh class B) compared to subjects with normal hepatic function. A dose decrease is recommended when administering axitinib to patients with moderate hepatic impairment (Child-Pugh class B) (see section 4.2).

Axitinib has not been studied in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this population.

Older people (≥ 65 years) and race
In a controlled clinical study with axitinib for the treatment of patients with RCC, 34% of patients treated with axitinib were ≥ 65 years of age. The majority of patients were White (77%) or Asian (21%). Although greater sensitivity to develop adverse reactions in some older patients and Asian patients cannot be ruled out, overall, no major differences were observed in the safety and effectiveness of axitinib between patients who were ≥ 65 years of age and non-elderly, and between White patients and patients of other races.

No dosage adjustment is required on the basis of patient age or race (see sections 4.2 and 5.2).

Lactose
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro data indicate that axitinib is metabolised primarily by CYP3A4/5 and, to a lesser extent, CYP1A2, CYP2C19, and uridine diphosphate-glucuronosyltransferase (UGT) 1A1.

CYP3A4/5 inhibitors
Ketoconazole, a strong inhibitor of CYP3A4/5, administered at a dose of 400 mg once daily for 7 days, increased the mean area under the curve (AUC) 2-fold and C_{max} 1.5-fold of a single 5-mg oral dose of axitinib in healthy volunteers. Co-administration of axitinib with strong CYP3A4/5 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, erythromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin) may increase axitinib plasma concentrations. Grapefruit may also increase axitinib plasma concentrations. Selection of concomitant medicinal products with no or minimal CYP3A4/5 inhibition potential is recommended. If a strong CYP3A4/5 inhibitor must be co-administered, a dose adjustment of axitinib is recommended (see section 4.2).

CYP1A2 and CYP2C19 inhibitors
CYP1A2 and CYP2C19 constitute minor (< 10%) pathways in axitinib metabolism. The effect of strong inhibitors of these isozymes on axitinib pharmacokinetics has not been studied. Caution should be exercised due to the risk of increased axitinib plasma concentrations in patients taking strong inhibitors of these isozymes.

CYP3A4/5 inducers
Rifampicin, a strong inducer of CYP3A4/5, administered at a dose of 600 mg once daily for 9 days, reduced the mean AUC by 79% and C_{max} by 71% of a single 5 mg dose of axitinib in healthy volunteers.

Co-administration of axitinib with strong CYP3A4/5 inducers (e.g. rifampicin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentin, phenobarbital, and *Hypericum perforatum* [St. John's wort]) may decrease axitinib plasma concentrations. Selection of concomitant medicinal products with no or minimal CYP3A4/5 induction potential is recommended. If a strong CYP3A4/5 inducer must be co-administered, a dose adjustment of axitinib is recommended (see section 4.2).

In vitro studies of CYP and UGT inhibition and induction
In vitro studies indicated that axitinib does not inhibit CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, or UGT1A1 at therapeutic plasma concentrations.

In vitro studies indicated that axitinib has a potential to inhibit CYP1A2. Therefore, co-administration of axitinib with CYP1A2 substrates may result in increased plasma concentrations of CYP1A2 substrates (e.g. theophylline).

In vitro studies also indicated that axitinib has the potential to inhibit CYP2C8. However, co-administration of axitinib with paclitaxel, a known CYP2C8 substrate, did not result in increased plasma concentrations of paclitaxel in patients with advanced cancer, indicating lack of clinical CYP2C8 inhibition.

In vitro studies in human hepatocytes also indicated that axitinib does not induce CYP1A1, CYP1A2, or CYP3A4/5. Therefore co-administration of axitinib is not expected to reduce the plasma concentration of co-administered CYP1A1, CYP1A2, or CYP3A4/5 substrates *in vivo*.

In vitro studies with P-glycoprotein
In vitro studies indicated that axitinib inhibits P-glycoprotein. However, axitinib is not expected to inhibit P-glycoprotein at therapeutic plasma concentrations. Therefore, co-administration of axitinib is not expected to increase the plasma concentration of digoxin, or other P-glycoprotein substrates, *in vivo*.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data regarding the use of axitinib in pregnant women. Based on the pharmacological properties of axitinib, it may cause foetal harm when administered to a pregnant woman. Studies in animals have shown reproductive toxicity including malformations (see section 5.3). Axitinib should not be used during pregnancy unless the clinical condition of the woman requires treatment with this medicinal product.

Women of childbearing potential must use effective contraception during and up to 1 week after treatment.

Breast-feeding
It is unknown whether axitinib is excreted in human milk. A risk to the suckling child cannot be excluded. Axitinib should not be used during breast-feeding.

Fertility
Based on non-clinical findings, axitinib has the potential to impair reproductive function and fertility in humans (see section 5.3).

4.7 Effects on ability to drive and use machines

Axitinib has a minor influence on the ability to drive and use machines. Patients should be advised that they may experience events such as dizziness and/or fatigue during treatment with axitinib.

4.8 Undesirable effects

Summary of the safety profile
The following risks, including appropriate action to be taken, are discussed in greater detail in *Section 4.4:* cardiac failure events, hypertension, thyroid dysfunction, arterial thromboembolic events, venous thromboembolic events, elevation of haemoglobin or haematocrit, haemorrhage, gastrointestinal perforation and fistula formation, wound healing complications, PRES, proteinuria, and elevation of liver enzymes.

The most common (≥ 20%) adverse reactions observed following treatment with axitinib were diarrhoea, hypertension, fatigue, decreased appetite, nausea, weight decreased, dysphonia, palmar-plantar erythrodysaesthesia (hand-foot) syndrome, haemorrhage, hypothyroidism, vomiting, proteinuria, cough, and constipation.

Tabulated list of adverse reactions
Table 1 presents adverse reactions reported in a pooled dataset of 672 patients who received axitinib in clinical studies for the treatment of patients with RCC (see section 5.1).

The adverse reactions are listed by system organ class, frequency category and grade of severity. Frequency categories are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), and not known (cannot be estimated from the available data). The current safety database for axitinib is too small to detect rare and very rare adverse reactions.

Categories have been assigned based on absolute frequencies in the pooled clinical studies data. Within each system organ class, adverse reactions with the same frequency are presented in order of decreasing seriousness.

Table 1. Adverse reactions reported in RCC studies in patients who received axitinib (N = 672)

System Organ Class	Frequency Category	Adverse Reactions[a]	All Grades[b] %	Grade 3[b] %	Grade 4[b] %
Blood and lymphatic system disorders	Common	Anaemia	6.3	1.2	0.4
		Thrombocytopenia	1.6	0.1	0
		Polycythaemia[c]	1.5	0.1	0
	Uncommon	Neutropaenia	0.3	0.1	0
		Leukopaenia	0.4	0	0
Endocrine disorders	Very Common	Hypothyroidism[c]	24.6	0.3	0
	Common	Hyperthyroidism[c]	1.6	0.1	0.1
Metabolism and nutrition disorders	Very Common	Decreased appetite	39.0	3.6	0.3
	Common	Dehydration	6.7	3.1	0.3
		Hyperkalaemia	2.7	1.2	0.1
		Hypercalcaemia	2.2	0.1	0.3
Nervous system disorders	Very Common	Headache	16.2	0.7	0
		Dysgeusia	11.5	0	0
	Common	Dizziness	9.1	0.6	0
	Uncommon	Posterior reversible encephalopathy syndrome[e]	0.3	0.1	0
Ear and labyrinth disorders	Common	Tinnitus	3.1	0	0
Cardiac disorders	Common	Cardiac failure events[c,d,f]	1.8	0.3	0.7
Vascular disorders	Very Common	Hypertension[g]	51.2	22.0	1.0
		Haemorrhage[c,d,h]	25.7	3.0	1.0
	Common	Venous embolic and thrombotic events[c,d,i]	2.8	0.9	1.2
		Arterial embolic and thrombotic events[c,d,j]	2.8	1.2	1.3
Respiratory, thoracic and mediastinal disorders	Very Common	Dyspnoea[d]	17.1	3.6	0.6
		Cough	20.4	0.6	0
		Dysphonia	32.7	0	0.1
	Common	Oropharyngeal pain	7.4	0	0
Gastrointestinal disorders	Very Common	Diarrhoea	55.4	10.1	0.1
		Vomiting	23.7	2.7	0.1
		Nausea	33.0	2.2	0.1
		Abdominal pain	14.7	2.5	0.3
		Constipation	20.2	1.0	0
		Stomatitis	15.5	1.8	0
		Dyspepsia	11.2	0.1	0
	Common	Upper abdominal pain	9.4	0.9	0
		Flatulence	4.5	0	0
		Haemorrhoids	3.3	0	0
		Glossodynia	2.8	0	0
		Gastrointestinal perforation and fistula[c,k]	1.9	0.9	0.3
Hepatobiliary disorders	Common	Hyperbilirubinaemia	1.3	0.1	0.1

System Organ Class	Frequency Category	Adverse Reactions[a]	All Grades[b] %	Grade 3[b] %	Grade 4[b] %
Skin and subcutaneous tissue disorders	Very Common	Palmar-plantar erythrodysaesthesia (hand-foot syndrome)	32.1	7.6	0
		Rash	14.3	0.1	0
		Dry skin	10.1	0.1	0
	Common	Pruritus	6.0	0	0
		Erythema	3.7	0	0
		Alopecia	5.7	0	0
Musculoskeletal and connective tissue disorders	Very Common	Arthralgia	17.7	1.9	0.3
		Pain in extremity	14.1	1.0	0.3
	Common	Myalgia	8.2	0.6	0.1
Renal and urinary disorders	Very Common	Proteinuria[l]	21.1	4.8	0.1
	Common	Renal failure[m]	1.6	0.9	0.1
General disorders and administration site conditions	Very Common	Fatigue	45.1	10.6	0.3
		Asthaenia[d]	13.8	2.8	0.3
		Mucosal inflammation	13.7	1.0	0
Investigations	Very Common	Weight decreased	32.7	4.9	0
	Common	Lipase increased	3.7	0.7	0.7
		Alanine aminotransferase increased	6.5	1.2	0
		Amylase increased	3.4	0.6	0.4
		Aspartate aminotransferase increased	6.1	1.0	0
		Alkaline phosphatase increased	4.8	0.3	0
		Creatinine increased	5.7	0.4	0
		Thyroid stimulating hormone increased	7.9	0	0

[a] Adverse reactions are according to treatment-emergent, all causality frequency.
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0
[c] See Description of selected adverse reactions section.
[d] Fatal (Grade 5) cases were reported.
[e] Including Leukoencephalopathy.
[f] Including cardiac failure, cardiac failure congestive, cardiopulmonary failure, ejection fraction decreased, left ventricular dysfunction and right ventricular failure.
[g] Including accelerated hypertension, blood pressure increased, hypertension and hypertensive crisis.
[h] Including activated partial thromboplastin time prolonged, anal haemorrhage, arterial haemorrhage, blood urine present, central nervous system haemorrhage, cerebral haemorrhage, coagulation time prolonged, conjunctival haemorrhage, contusion, diarrhea haemorrhagic, dysfunctional uterine bleeding, epistaxis, gastric haemorrhage, gastrointestinal haemorrhage, gingival bleeding, haematemesis, haematochezia, haematocrit decreased, haematoma, haematuria, haemoglobin decreased, haemoptysis, haemorrhage, haemorrhage coronary artery, haemorrhage urinary tract, haemorrhoidal haemorrhage, haemostasis, increased tendency to bruise, international normalized ratio increased, lower gastrointestinal haemorrhage, melaena, petechiae, pharyngeal haemorrhage, prothrombin time prolonged, pulmonary haemorrhage, purpura, rectal haemorrhage, red blood cell count decreased, renal haemorrhage, scleral haemorrhage, scrotal haematocoele, splenic haemotoma, splinter haemorrhage, subarachnoid haemorrhage, tongue haemorrhage, upper gastrointestinal haemorrhage and vaginal haemorrhage.
[i] Including Budd-Chiari syndrome, deep vein thrombosis, jugular vein thrombosis, pelvic venous thrombosis, pulmonary embolism, retinal vein occlusion, retinal vein thrombosis, subclavian vein thrombosis, venous thrombosis, and venous thrombosis limb.

[j] Including acute myocardial infarction, embolism, myocardial infarction, retinal artery occlusion and transient ischaemic attack.
[k] Gastrointestinal perforation and fistula includes the following preferred terms: abdominal abscess, anal abscess, anal fistula, fistula, gastrointestinal anastomotic leak, gastrointestinal perforation, large intestine perforation, oesophagobronchial fistula and peritonitis.
[l] Proteinuria includes the following preferred terms: protein urine, protein urine present and proteinuria.
[m] Including acute renal failure

Description of selected adverse reactions

Cardiac failure events (see section 4.4)
In a controlled clinical study with axitinib (N = 359) for the treatment of patients with RCC, cardiac failure events were reported in 1.7 % patients receiving axitinib, including cardiac failure (0.6%), cardiopulmonary failure (0.6%), left ventricular dysfunction (0.3%), and right ventricular failure (0.3%). Grade 4 cardiac failure adverse reactions were reported in 0.6 % of patients receiving axitinib. Fatal cardiac failure was reported in 0.6 % of patients receiving axitinib.

In monotherapy studies with axitinib (N = 672) for the treatment of patients with RCC, cardiac failure events (including cardiac failure, cardiac failure congestive, cardiopulmonary failure, left ventricular dysfunction, ejection fraction decreased, and right ventricular failure) were reported in 1.8% patients receiving axitinib. Grade 3/4 cardiac failure events were reported in 1.0% patients and fatal cardiac failure events were reported in 0.3% patients receiving axitinib.

Thyroid dysfunction (see section 4.4)
In a controlled clinical study with axitinib for the treatment of patients with RCC, hypothyroidism was reported in 20.9% of patients and hyperthyroidism was reported in 1.1% of patients. Thyroid stimulating hormone (TSH) increased was reported as an adverse reaction in 5.3% of patients receiving axitinib. During routine laboratory assessments, in patients who had TSH < 5 μU/mL before treatment, elevations of TSH to ≥ 10 μU/mL occurred in 32.2% of patients receiving axitinib.

In pooled clinical studies with axitinib (N = 672) for the treatment of patients with RCC, hypothyroidism was reported in 24.6% of patients receiving axitinib. Hyperthyroidism was reported in 1.6% of patients receiving axitinib.

Venous embolic and thrombotic events (see section 4.4)
In a controlled clinical study with axitinib for the treatment of patients with RCC, venous embolic and thrombotic adverse reactions were reported in 3.9% of patients receiving axitinib, including pulmonary embolism (2.2%), retinal vein occlusion/thrombosis (0.6%) and deep vein thrombosis (0.6%). Grade 3/4 venous embolic and thrombotic adverse reactions were reported in 3.1% of patients receiving axitinib. Fatal pulmonary embolism was reported in one patient (0.3%) receiving axitinib.

In pooled clinical studies with axitinib (N = 672) for the treatment of patients with RCC, venous embolic and thrombotic events were reported in 2.8% of patients receiving axitinib. Grade 3 venous embolic and thrombotic events were reported in 0.9% of patients. Grade 4 venous embolic and thrombotic events were reported in 1.2% of patients. Fatal venous embolic and thrombotic events were reported 0.1% patients receiving axitinib.

Arterial embolic and thrombotic events (see section 4.4)
In a controlled clinical study with axitinib for the treatment of patients with RCC, arterial embolic and thrombotic adverse reactions were reported in 4.7% of patients receiving axitinib, including myocardial infarction (1.4%), transient ischemic attack (0.8%) and cerebrovascular accident (0.6%). Grade 3/4 arterial embolic and thrombotic adverse reactions were reported in 3.3% of patients receiving axitinib. A fatal acute myocardial infarction and cerebrovascular accident was reported in one patient each (0.3%). In monotherapy studies with axitinib (N = 850), arterial embolic and

thrombotic adverse reactions (including transient ischemic attack, myocardial infarction, and cerebrovascular accident) were reported in 5.3% of patients receiving axitinib.

In pooled clinical studies with axitinib (N = 672) for the treatment of patients with RCC, arterial embolic and thrombotic events were reported in 2.8% of patients receiving axitinib. Grade 3 arterial embolic and thrombotic events were reported in 1.2% of patients. Grade 4 arterial embolic and thrombotic events were reported in 1.3% of patients. Fatal arterial embolic and thrombotic events were reported in 0.3% patients receiving axitinib.

*Polycythaemia (*see *Elevation of haemoglobin or haematocrit* in section 4.4)
In a controlled clinical study with axitinib for the treatment of patients with RCC, polycythaemia was reported in 1.4% of patients receiving axitinib. Routine laboratory assessments detected elevated haemoglobin above ULN in 9.7% of patients receiving axitinib. In four clinical studies with axitinib for the treatment of patients with RCC (N = 537), elevated haemoglobin above ULN was observed in 13.6% receiving axitinib.

In pooled clinical studies with axitinib (N = 672) for the treatment of patients with RCC, polycythaemia was reported in 1.5% of patients receiving axitinib.

Haemorrhage (see section 4.4)
In a controlled clinical study with axitinib for the treatment of patients with RCC that excluded patients with untreated brain metastasis, haemorrhagic adverse reactions were reported in 21.4% of patients receiving axitinib. The haemorrhagic adverse reactions in patients treated with axitinib included epistaxis (7.8%), haematuria (3.6%), haemoptysis (2.5%), rectal haemorrhage (2.2%), gingival bleeding (1.1%), gastric haemorrhage (0.6%), cerebral haemorrhage (0.3%) and lower gastrointestinal haemorrhage (0.3%). Grade $\geq$ 3 haemorrhagic adverse reactions were reported in 3.1% of patients receiving axitinib (including cerebral haemorrhage, gastric haemorrhage, lower gastrointestinal haemorrhage and haemoptysis). Fatal haemorrhage was reported in one patient (0.3%) receiving axitinib (gastric haemorrhage). In monotherapy studies with axitinib (N = 850), haemoptysis was reported in 3.9% of patients; Grade $\geq$ 3 haemoptysis was reported in 0.5% of patients.

In pooled clinical studies with axitinib (N = 672) for the treatment of patients with RCC, haemorrhagic events were reported in 25.7% of patients receiving axitinib. Grade 3 haemorrhagic adverse reactions were reported in 3% of patients. Grade 4 haemorrhagic adverse reactions were reported in 1% of patients and fatal haemorrhage were reported in 0.4% of patients receiving axitinib.

Gastrointestinal perforation and fistula formation (see section 4.4)
In a controlled clinical study with axitinib for the treatment of patients with RCC, gastrointestinal perforation-type events were reported in 1.7% of patients receiving axitinib, including anal fistula (0.6%), fistula (0.3%) and gastrointestinal perforation (0.3%).In monotherapy studies with axitinib (N = 850), gastrointestinal perforation-type events were reported in 1.9% of patients and fatal gastrointestinal perforation was reported in one patient (0.1%).

In pooled clinical studies with axitinib (N = 672) for the treatment of patients with RCC, gastrointestinal perforation and fistula were reported in 1.9% of patients receiving axitinib.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no specific treatment for axitinib overdose.

In a controlled clinical study with axitinib for the treatment of patients with RCC, one patient inadvertently received a dose of 20 mg twice daily for 4 days and experienced dizziness (Grade 1).

In a clinical dose finding study with axitinib, subjects who received starting doses of 10 mg twice daily or 20 mg twice daily experienced adverse reactions which included hypertension, seizures associated with hypertension, and fatal haemoptysis.

In cases of suspected overdose, axitinib should be withheld and supportive care instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE17

Mechanism of action
Axitinib is a potent and selective tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, VEGFR-2 and VEGFR-3. These receptors are implicated in pathologic angiogenesis, tumour growth, and metastatic progression of cancer. Axitinib has been shown to potently inhibit VEGF-mediated endothelial cell proliferation and survival. Axitinib inhibited the phosphorylation of VEGFR-2 in xenograft tumour vasculature that expressed the target *in vivo* and produced tumour growth delay, regression, and inhibition of metastases in many experimental models of cancer.

Effect on QTc interval
In a randomised, 2-way crossover study, 35 healthy subjects were administered a single oral dose of axitinib (5 mg) in the absence and presence of 400 mg ketoconazole for 7 days. Results of this study indicated that axitinib plasma exposures up to two-fold greater than therapeutic levels expected following a 5 mg dose, did not produce clinically-significant QT interval prolongation.

Clinical efficacy
The safety and efficacy of axitinib were evaluated in a randomised, open-label, multicenter Phase 3 study. Patients (N = 723) with advanced RCC whose disease had progressed on or after treatment with one prior systemic therapy, including sunitinib-, bevacizumab-, temsirolimus-, or cytokine-containing regimens were randomised (1:1) to receive axitinib (N = 361) or sorafenib (N = 362). The primary endpoint, progression-free survival (PFS), was assessed using a blinded independent central review. Secondary endpoints included objective response rate (ORR) and overall survival (OS).

Of the patients enrolled in this study, 389 patients (53.8%) had received one prior sunitinib-based therapy, 251 patients (34.7%) had received one prior cytokine-based therapy (interleukin-2 or interferon-alpha), 59 patients (8.2%) had received one prior bevacizumab-based therapy, and 24 patients (3.3%) had received one prior temsirolimus-based therapy. The baseline demographic and disease characteristics were similar between the axitinib and sorafenib groups with regard to age, gender, race, Eastern Cooperative Oncology Group (ECOG) performance status, geographic region, and prior treatment.

In the overall patient population and the two main subgroups (prior sunitinib treatment and prior cytokine treatment), there was a statistically significant advantage for axitinib over sorafenib for the primary endpoint of PFS (see Table 2 and Figures 1, 2 and 3). The magnitude of median PFS effect was different in the subgroups by prior therapy. Two of the subgroups were too small to give reliable results (prior temsirolimus treatment or prior bevacizumab treatment). There were no statistically significant differences between the arms in OS in the overall population or in the subgroups by prior therapy.

Table 2. Efficacy results

Endpoint / Study Population	Axitinib	Sorafenib	HR (95% CI)	p-value
Overall ITT	**N = 361**	**N = 362**		
Median PFS [a,b] in months (95% CI)	6.8 (6.4, 8.3)	4.7 (4.6, 6.3)	0.67 (0.56, 0.81)	< 0.0001[c]
Median OS [d] in months (95% CI)	20.1 (16.7, 23.4)	19.2 (17.5, 22.3)	0.97 (0.80, 1.17)	NS
ORR [b,e] % (95% CI)	19.4 (15.4, 23.9)	9.4 (6.6, 12.9)	2.06[f] (1.41, 3.00)	0.0001[g]
Prior sunitinib treatment	**N = 194**	**N = 195**		
Median PFS [a,b] in months (95% CI)	4.8 (4.5, 6.5)	3.4 (2.8, 4.7)	0.74 (0.58, 0.94)	0.0063[h]
Median OS [d] in months (95% CI)	15.2 (12.8, 18.3)	16.5 (13.7, 19.2)	1.00 (0.78, 1.27)	NS
ORR [b,e] % (95% CI)	11.3 (7.2, 16.7)	7.7 (4.4, 12.4)	1.48[f] (0.79, 2.75)	NS
Prior cytokine treatment	**N = 126**	**N = 125**		
Median PFS [a,b] in months (95% CI)	12.0 (10.1, 13.9)	6.6 (6.4, 8.3)	0.52 (0.38, 0.72)	< 0.0001[h]
Median OS [d] in months (95% CI)	29.4 (24.5, NE)	27.8 (23.1, 34.5)	0.81 (0.56, 1.19)	NS
ORR [b,e] % (95% CI)	32.5 (24.5, 41.5)	13.6 (8.1, 20.9)	2.39[f] (1.43-3.99)	0.0002[i]

CI = Confidence interval, HR = Hazard ratio (axitinib/sorafenib); ITT: Intent-to-treat; NE: not estimable; NS: not statistically significant; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival.

[a] Time from randomisation to progression or death due to any cause, whichever occurs first. Cutoff date: 03 June 2011.

[b] Assessed by independent radiology review according to Response Evaluation Criteria in Solid Tumours (RECIST).

[c] One-sided p-value from a log-rank test of treatment stratified by ECOG performance status and prior therapy.

[d] Cutoff date: 01 November 2011.

[e] Cutoff date: 31 August 2010.

[f] Risk ratio is used for ORR. A risk ratio > 1 indicated a higher likelihood of responding in the axitinib arm; a risk ratio < 1 indicated a higher likelihood of responding in the sorafenib arm.

[g] One-sided p-value from Cochran-Mantel-Haenszel test of treatment stratified by ECOG performance status and prior therapy.

[h] One-sided p-value from a log-rank test of treatment stratified by ECOG performance status.

[i] One-sided p-value from Cochran-Mantel-Haenszel test of treatment stratified by ECOG performance status.

Figure 1. Kaplan-Meier curve of progression-free survival by independent assessment for the overall population

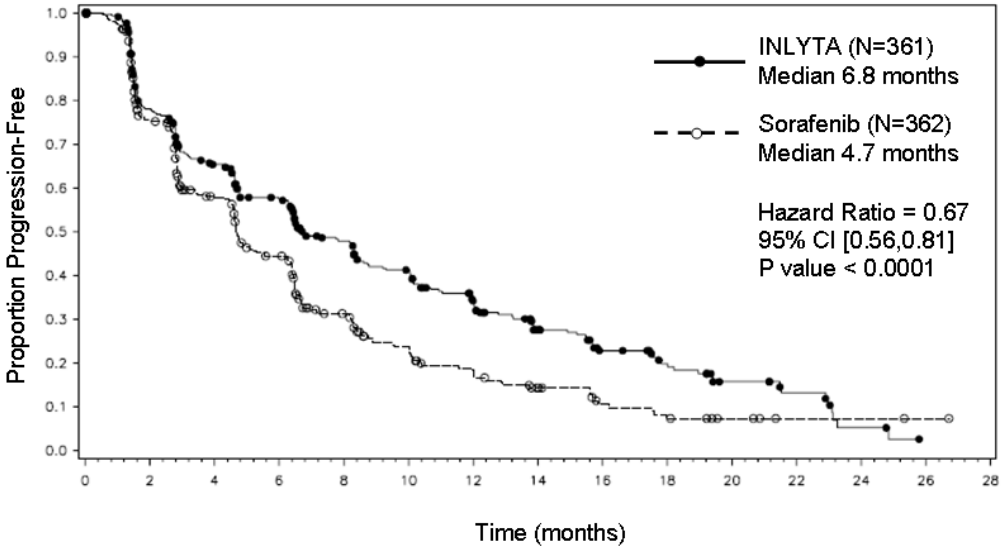


Figure 2. Kaplan-Meier curve of progression-free survival by independent assessment for the prior sunitinib subgroup

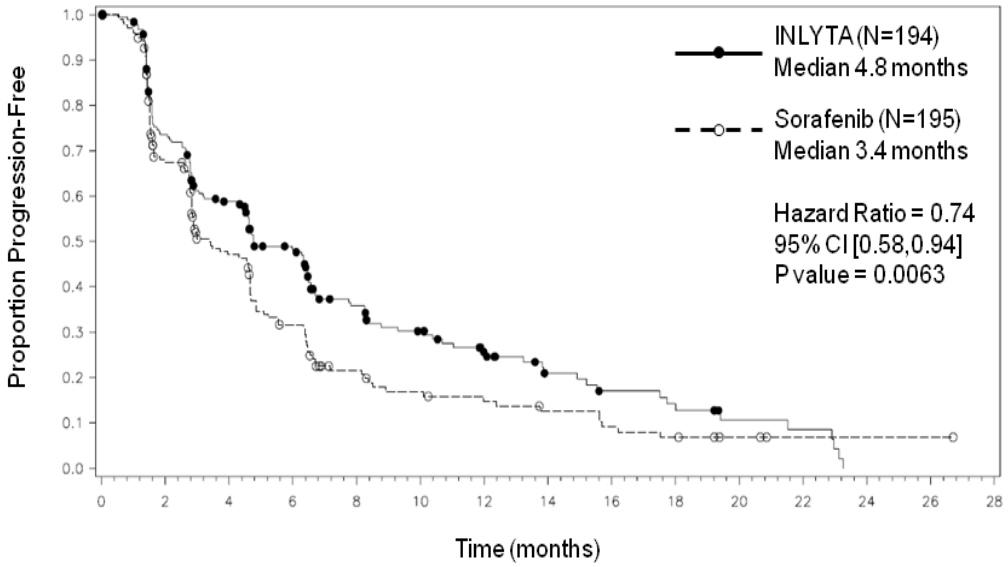
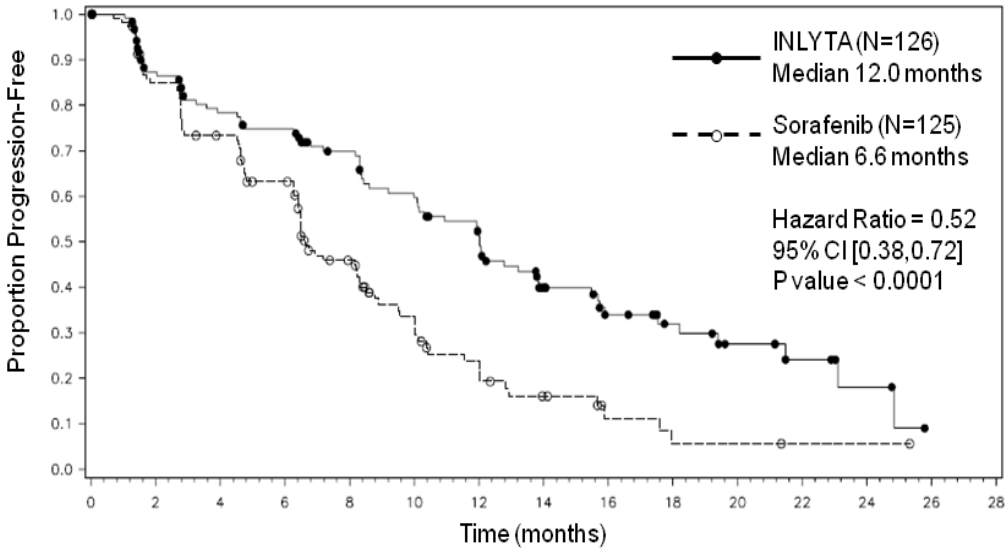


Figure 3. Kaplan-Meier curve of progression-free survival by independent assessment for the prior cytokine subgroup



Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with axitinib in all subsets of the paediatric population for treatment of kidney and renal pelvis carcinoma (excluding nephroblastoma, nephroblastomatosis, clear cell sarcoma, mesoblastic nephroma, renal medullary carcinoma and rhabdoid tumour of the kidney) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

After oral administration of axitinib tablets, the mean absolute bioavailability is 58% compared to intravenous administration. The plasma half life of axitinib ranges from 2.5 to 6.1 hours. Dosing of axitinib at 5 mg twice daily resulted in less than two-fold accumulation compared to administration of

a single dose. Based on the short half-life of axitinib, steady state is expected within 2 to 3 days of the initial dose.

Absorption and distribution
Peak axitinib concentrations in plasma are generally reached within 4 hours following oral administration of axitinib with median T_{max} ranging from 2.5 to 4.1 hours. Administration of axitinib with a moderate fat meal resulted in 10% lower exposure compared to overnight fasting. A high fat, high-calorie meal resulted in 19% higher exposure compared to overnight fasting. Axitinib may be administered with or without food (see section 4.2).

The average C_{max} and AUC increased proportionally over an axitinib dosing range of 5 to 10 mg. *In vitro* binding of axitinib to human plasma proteins is > 99% with preferential binding to albumin and moderate binding to α_1-acid glycoprotein. At the 5 mg twice daily dose in the fed state, the geometric mean peak plasma concentration and 24-hour AUC were 27.8 ng/mL and 265 ng.h/mL, respectively, in patients with advanced RCC. The geometric mean oral clearance and apparent volume of distribution were 38 L/h and 160 L, respectively.

Biotransformation and elimination
Axitinib is metabolised primarily in the liver by CYP3A4/5 and to a lesser extent by CYP1A2, CYP2C19, and UGT1A1.

Following oral administration of a 5 mg radioactive dose of axitinib, 30-60% of the radioactivity was recovered in faeces and 23% of the radioactivity was recovered in urine. Unchanged axitinib, accounting for 12% of the dose, was the major component identified in faeces. Unchanged axitinib was not detected in urine; the carboxylic acid and sulfoxide metabolites accounted for the majority of radioactivity in urine. In plasma, the N-glucuronide metabolite represented the predominant radioactive component (50% of circulating radioactivity) and unchanged axitinib and the sulfoxide metabolite each accounted for approximately 20% of the circulating radioactivity.

The sulfoxide and N-glucuronide metabolites show approximately 400-fold and 8000-fold less *in vitro* potency, respectively, against VEGFR-2 compared to axitinib.

Special populations

Older people, gender, and race
Population pharmacokinetic analyses in patients with advanced cancer (including advanced RCC) and healthy volunteers indicate that there are no clinically relevant effects of age, gender, body weight, race, renal function, UGT1A1 genotype, or CYP2C19 genotype.

Paediatric population
Axitinib has not been studied in patients < 18 years of age.

Hepatic impairment
In vitro and *in vivo* data indicate that axitinib is primarily metabolised by the liver.

Compared to subjects with normal hepatic function, systemic exposure following a single dose of axitinib was similar in subjects with mild hepatic impairment (Child-Pugh class A) and higher (approximately two-fold) in subjects with moderate hepatic impairment (Child-Pugh class B). Axitinib has not been studied in subjects with severe hepatic impairment (Child-Pugh class C) and should not be used in this population (see section 4.2 for dose adjustment recommendations).

Renal impairment
Unchanged axitinib is not detected in the urine.

Axitinib has not been studied in subjects with renal impairment. In clinical studies with axitinib for the treatment of patients with RCC, patients with serum creatinine > 1.5 times the ULN or calculated

creatinine clearance < 60 mL/min were excluded. Population pharmacokinetic analyses have shown that axitinib clearance was not altered in subjects with renal impairment and no dose adjustment of axitinib is required.

5.3 Preclinical safety data

Repeat dose toxicity
Major toxicity findings in mice and dogs following repeated dosing for up to 9 months were the gastrointestinal, haematopoietic, reproductive, skeletal and dental systems, with No Observed Adverse Effect Levels (NOAEL) approximately equivalent to or below expected human exposure at the recommended clinical starting dose (based on AUC levels).

Carcinogenicity
Carcinogenicity studies have not been performed with axitinib.

Genotoxicity
Axitinib was not mutagenic or clastogenic in conventional genotoxicity assays *in vitro*. A significant increase in polyploidy was observed *in vitro* at concentrations > 0.22 µg/mL, and an elevation in micronucleated polychromatic erythrocytes was observed *in vivo* with No Observed Effect Level (NOEL) 69-fold the expected human exposure. Genotoxicity findings are not considered clinically relevant at exposure levels observed in humans.

Reproduction toxicity
Axitinib-related findings in the testes and epididymis included decreased organ weight, atrophy or degeneration, decreased numbers of germinal cells, hypospermia or abnormal sperm forms, and reduced sperm density and count. These findings were observed in mice at exposure levels approximately 12-fold the expected human exposure, and in dogs at exposure levels below the expected human exposure. There was no effect on mating or fertility in male mice at exposure levels approximately 57-fold the expected human exposure. Findings in females included signs of delayed sexual maturity, reduced or absent corpora lutea, decreased uterine weights and uterine atrophy at exposures approximately equivalent to the expected human exposure. Reduced fertility and embryonic viability were observed in female mice at all doses tested, with exposure levels at the lowest dose approximately 10-fold the expected human exposure.

Pregnant mice exposed to axitinib showed an increased occurrence of cleft palate malformations and skeletal variations, including delayed ossification, at exposure levels below the expected human exposure. Perinatal and postnatal developmental toxicity studies have not been conducted.

Toxicity findings in immature animals
Reversible physeal dysplasia was observed in mice and dogs given axitinib for at least 1 month at exposure levels approximately six-fold higher than the expected human exposure. Partially reversible dental caries were observed in mice treated for more than 1 month at exposure levels similar to the expected human exposure. Other toxicities of potential concern to paediatric patients have not been evaluated in juvenile animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Magnesium stearate

Tablet film-coating:
Hypromellose
Titanium dioxide (E171)
Lactose monohydrate
Triacetin (E1518)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/aluminium blister containing 14 film-coated tablets. Each pack contains 28 or 56 film-coated tablets.

HDPE bottle with a silica gel desiccant and a polypropylene closure containing 60 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich, Kent CT13 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/777/010
EU/1/12/777/011
EU/1/12/777/012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3 September 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Pfizer Manufacturing Deutschland GmbH
Betriebsstätte Freiburg
Mooswaldallee 1
D-79090 Freiburg
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF 1 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Inlyta 1 mg film-coated tablets
axitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 1 mg axitinib.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 tablets
56 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich, Kent, CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/777/001	28 tablets
EU/1/12/777/002	56 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Inlyta 1 mg

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE OF 1 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Inlyta 1 mg film-coated tablets
axitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 1 mg axitinib.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

180 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich, Kent, CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/777/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Inlyta 1 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER OF 1 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Inlyta 1 mg film-coated tablets
axitinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF 3 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Inlyta 3 mg film-coated tablets
axitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 3 mg axitinib.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 tablets
56 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich, Kent, CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/777/007	28 tablets
EU/1/12/777/008	56 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Inlyta 3 mg

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE OF 3 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Inlyta 3 mg film-coated tablets
axitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 3 mg axitinib.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

60 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich, Kent, CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/777/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Inlyta 3 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER OF 3 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Inlyta 3 mg film-coated tablets
axitinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF 5 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Inlyta 5 mg film-coated tablets
axitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 5 mg axitinib.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 tablets
56 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich, Kent, CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/777/004	28 tablets
EU/1/12/777/005	56 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Inlyta 5 mg

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE OF 5 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Inlyta 5 mg film-coated tablets
axitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 5 mg axitinib.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

60 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich, Kent, CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/777/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Inlyta 5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER OF 5 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Inlyta 5 mg film-coated tablets
axitinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF 7 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Inlyta 7 mg film-coated tablets
axitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 7 mg axitinib.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 tablets
56 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich, Kent, CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/777/010	28 tablets
EU/1/12/777/011	56 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Inlyta 7 mg

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE OF 7 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Inlyta 7 mg film-coated tablets
axitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 7 mg axitinib.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

60 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich, Kent, CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/777/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Inlyta 7 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER OF 7 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Inlyta 7 mg film-coated tablets
axitinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Inlyta 1 mg film-coated tablets
Inlyta 3 mg film-coated tablets
Inlyta 5 mg film-coated tablets
Inlyta 7 mg film-coated tablets
axitinib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Inlyta is and what it is used for
2. What you need to know before you take Inlyta
3. How to take Inlyta
4. Possible side effects
5. How to store Inlyta
6. Contents of the pack and other information

1. What Inlyta is and what it is used for

Inlyta is a medicine containing the active substance axitinib. Axitinib reduces the blood supply to the tumour and slows down the growth of cancer.

Inlyta is indicated for the treatment of advanced kidney cancer (advanced renal cell carcinoma) in adults, when another medicine (called sunitinib or a cytokine) is no longer stopping disease from progressing.

If you have any questions about how this medicine works or why this medicine has been prescribed for you, ask your doctor.

2. What you need to know before you take Inlyta

Do not take Inlyta:
If you are allergic to axitinib or any of the other ingredients of this medicine (listed in section 6).
If you think you may be allergic, ask your doctor for advice.

Warnings and precautions

Talk to your doctor or nurse before taking Inlyta:

- **If you have high blood pressure.**
  Inlyta can raise your blood pressure. It is important to check your blood pressure before you take this medicine, and regularly while you are taking it. If you have high blood pressure (hypertension) you may be treated with medicines to reduce the blood pressure. Your doctor should make sure that your blood pressure is under control before starting Inlyta treatment, and while on treatment with this medicine.

- **If you have thyroid gland problems.**
  Inlyta can cause thyroid gland problems. Tell your doctor if you get tired more easily, generally feel colder than other people, or your voice deepens whilst taking this medicine. Your thyroid function should be checked before you take Inlyta and regularly while you are taking it. If your thyroid gland is not producing enough thyroid hormone before, or while on treatment with this medicine, you should be treated with thyroid hormone replacement.

- **If you have had a recent problem with blood clots in your veins and arteries (types of blood vessels), including stroke, heart attack, embolism, or thrombosis.**
  Get emergency help right away and call your doctor if you get symptoms such as chest pain or pressure; pain in your arms, back, neck or jaw; shortness of breath; numbness or weakness on one side of your body; trouble talking; headache; vision changes; or dizziness while on treatment with this medicine.

- **If you suffer from bleeding problems.**
  Inlyta may increase your chance of bleeding. Tell your doctor if you have any bleeding, coughing up of blood or bloody sputum while on treatment with this medicine.

- **If during treatment with this medicine you get severe stomach (abdominal) pain or stomach pain that does not go away.**
  Inlyta may increase the risk of developing a hole in the stomach or intestine or formation of fistula (abnormal tube-like passage from one normal body cavity to another body cavity or the skin).
  Tell your doctor if you have severe abdominal pain while on treatment with this medicine.

- **If you are going to have an operation or if you have an unhealed wound.**
  Your doctor should stop Inlyta at least 24 hours before your operation as it may affect wound healing. Your treatment with this medicine should be restarted when the wound has adequately healed.

- **If during treatment with this medicine, you get symptoms such as headache, confusion, seizures (fits), or changes in vision with or without high blood pressure.**
  Get emergency help right away and call your doctor. This could be a rare neurological side effect named posterior reversible encephalopathy syndrome.

- **If you have liver problems.**
  Your doctor should do blood tests to check your liver function before and during treatment with Inlyta.

- **If during treatment with this medicine, you get symptoms such as excessive tiredness, swelling of the abdomen, legs or ankles, shortness of breath, or protruding neck veins.**
  Inlyta may increase the risk of developing heart failure events. Your doctor should monitor for signs or symptoms of heart failure events periodically throughout treatment with axitinib.

Use in children and adolescents
Inlyta is not recommended for people aged under 18. This medicine has not been studied in children and adolescents.

Other medicines and Inlyta
Some medicines may affect Inlyta, or be affected by it. Please tell your doctor, pharmacist or nurse about all the medicines you have recently taken, are currently taking, or plan to take, including medicines obtained without a prescription, vitamins, and herbal medicines. The medicines listed in this leaflet may not be the only ones that could interact with Inlyta.

The following medicines may increase the risk of side effects with Inlyta:
- ketoconazole or itraconazole, used to treat fungal infections;
- clarithromycin, erythromycin or telithromycin, antibiotics used to treat bacterial infections;
- atazanavir, indinavir, nelfinavir, ritonavir or saquinavir, used to treat HIV infections/AIDS;
- nefazodone, used to treat depression.

The following medicines may reduce the effectiveness of Inlyta:
- rifampicin, rifabutin or rifapentin, used to treat tuberculosis (TB);
- dexamethasone, a steroid medicine prescribed for many different conditions, including serious illnesses;
- phenytoin, carbamazepine or phenobarbital, anti-epileptics used to stop seizures or fits;
- St. John's wort (*Hypericum perforatum*), a herbal product used to treat depression.

You **should not** take these medicines during your treatment with Inlyta. If you are taking any of them, tell your doctor, pharmacist or nurse. Your doctor may change the dose of these medicines, change the dose of Inlyta, or switch you to a different medicine.

Inlyta may increase side effects associated with theophylline, used to treat asthma or other lung diseases.

Inlyta with food and drink
You can take this medicine either with or without food.
Do not take this medicine with grapefruit or grapefruit juice, as it may increase the chance of side effects.

Pregnancy and breast-feeding
- Inlyta could harm an unborn baby or breast-fed baby.

- Do not take this medicine during pregnancy. Talk to your doctor before taking it if you are pregnant or might become pregnant.

- Use a reliable method of contraception while you are taking Inlyta and up to 1 week after the last dose of this medicine, to prevent pregnancy.

- Do not breast-feed during treatment with Inlyta. If you are breast-feeding, your doctor should discuss with you whether to discontinue breast-feeding or discontinue Inlyta treatment.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist or nurse for advice before taking this medicine.

Driving and using machines
If you experience dizziness and/or feel tired while on treatment with Inlyta, take special care when driving or using machines.

Inlyta contains lactose (milk sugar)
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Inlyta

Always take this medicine exactly as your doctor has told you. You should check with your doctor, pharmacist or nurse if you are not sure.

The recommended dose is 5 mg twice a day. Your doctor may subsequently increase or decrease your dose depending on how you tolerate treatment with Inlyta.

Swallow the tablets whole with water, with or without food. Take the Inlyta doses approximately 12 hours apart.

If you take more Inlyta than you should
If you accidentally take too many tablets or a higher dose than you need, contact a doctor for advice right away. If possible, show the doctor the pack, or this leaflet. You may require medical attention.

If you forget to take Inlyta
Take your next dose at your regular time. Do not take a double dose to make up for the forgotten tablets.

If you stop taking Inlyta
If you are not able to take this medicine as your doctor prescribed or you feel you do not need it anymore, contact your doctor right away.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects could be serious. You must immediately contact your doctor if you experience any of those following serious side effects (see also section 2 "What you need to know before you take Inlyta"):

- **Heart failure events.** Tell your doctor if you experience excessive tiredness, swelling of the abdomen, legs, or ankles, shortness of breath, or protruding neck veins.

- **Blood clots in your veins and arteries (types of blood vessels), including stroke, heart attack, embolism, or thrombosis.** Get emergency help right away and call your doctor if you get symptoms such as chest pain or pressure; pain in your arms, back, neck or jaw; shortness of breath; numbness or weakness on one side of your body; trouble talking; headache; vision changes: or dizziness.

- **Bleeding.** Tell your doctor right away if you have any of these symptoms or a serious bleeding problem during treatment with Inlyta: black tarry stools, coughing up of blood or bloody sputum, or change in your mental status.

- **Hole in the stomach or intestine or formation of fistula (abnormal tube-like passage from one normal body cavity to another body cavity or the skin).** Tell your doctor if you have severe abdominal pain.

- **Severe increase in blood pressure (hypertensive crisis).** Tell your doctor if you have a very high blood pressure, severe headache, or severe chest pain.

- **Reversible swelling of the brain (posterior reversible encephalopathy syndrome).** Get emergency help right away and call your doctor if you get symptoms such as headache, confusion, seizures (fits), or changes in vision with or without high blood pressure.

Other side effects with Inlyta may include:

Very common side effects (may affect more than 1 in 10 people):
- High blood pressure, or increases in blood pressure
- Diarrhoea, feeling or being sick (nausea or vomiting), stomach ache, indigestion, soreness of the mouth, tongue or throat, constipation
- Shortness of breath, cough, hoarseness
- Lack of energy, feeling weak or tired
- Under-active thyroid gland (may show in your blood tests)
- Redness and swelling of the palms of the hands or soles of the feet (hand-foot syndrome), skin rash, dryness of the skin
- Joint pain, pain in hands or feet
- Loss of appetite
- Protein in the urine (may show in your urine tests)
- Weight loss
- Headache, taste disturbance or loss of taste

Common side effects (may affect up to 1 in 10 people):
- Dehydration (loss of body fluids)
- Kidney failure
- Flatulence (wind), haemorrhoids, bleeding from gums, bleeding from the rectum, a burning or stinging sensation in the mouth
- Hyper-active thyroid gland (may show in your blood tests)
- Sore throat or nose and throat irritation
- Muscle pain
- Nose bleeding
- Skin itching, redness of the skin, hair loss
- Ringing/sound in the ears (tinnitus)
- Reduction in the number of red blood cells (may show in your blood tests)
- Reduction in the number of blood platelets (cells that help blood to clot) (may show in your blood tests)
- Presence of red blood cells in the urine (may show in your urine tests)
- Changes in the levels of different chemicals/enzymes in the blood (may show in your blood tests)
- Increase in the number of red blood cells (may show in your blood tests)
- Swelling of the abdomen, legs, or ankles, protruding neck veins, excessive tiredness, shortness of breath (signs of heart failure events)
- Fistula (abnormal tube like passage from one normal body cavity to another body cavity or the skin)
- Dizziness

Uncommon side effects (may affect up to 1 in 100 people):
- Reduction in the number of white blood cells (may show in your blood tests)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting

system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Inlyta

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the blister foil or bottle after "EXP". The expiry date refers to the last day of the month.

This medicine does not require any special storage conditions.

Do not use any pack that is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Inlyta contains

- The active substance is axitinib. Inlyta film-coated tablets come in different strengths.
  Inlyta 1 mg: each tablet contains 1 mg axitinib
  Inlyta 3 mg: each tablet contains 3 mg axitinib
  Inlyta 5 mg: each tablet contains 5 mg axitinib
  Inlyta 7 mg: each tablet contains 7 mg axitinib

- The other ingredients are microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide (E171), triacetin (E1518), iron oxide red (E172).

What Inlyta looks like and contents of the pack

Inlyta 1 mg film-coated tablets are red, oval and debossed with "Pfizer" on one side and "1 XNB" on the other. Inlyta 1 mg is available in bottles of 180 tablets and blister packs of 28 tablets and 56 tablets.

Inlyta 3 mg film-coated tablets are red, round and debossed with "Pfizer" on one side and "3 XNB" on the other. Inlyta 3 mg is available in bottles of 60 tablets and blister packs of 28 tablets and 56 tablets.

Inlyta 5 mg film-coated tablets are red, triangular and debossed with "Pfizer" on one side and "5 XNB" on the other. Inlyta 5 mg is available in bottles of 60 tablets and blister packs of 28 tablets and 56 tablets.

Inlyta 7 mg film-coated tablets are red, diamond shaped and debossed with "Pfizer" on one side and "7 XNB" on the other. Inlyta 7 mg is available in bottles of 60 tablets and blister packs of 28 tablets and 56 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Pfizer Limited
Ramsgate Road
Sandwich, Kent CT13 9NJ
United Kingdom

Manufacturer

Pfizer Manufacturing Deutschland GmbH
Betriebsstätte Freiburg
Mooswaldallee 1
79090 Freiburg
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

Belgique/ België /Belgien
Pfizer S.A. / N.V.
Tél/Tel: +32 (0)2 554 62 11

България
Пфайзер Люксембург САРЛ, Клон България
Тел.: +359 2 970 4333

Česká republika
Pfizer s.r.o.
Tel.: +420-283-004-111

Danmark
Pfizer ApS
Tlf: +45 44 20 11 00

Deutschland
Pfizer Pharma GmbH
Tel: +49 (0)30 550055 51000

Eesti
Pfizer Luxembourg SARL Eesti filiaal
Tel.: +372 666 7500

Ελλάδα
Pfizer Ελλάς A.E.
Τηλ: +30 210 6785 800

España
Pfizer S.L.
Tél: +34 91 490 99 00

Lietuva
Pfizer Luxembourg SARL filialas Lietuvoje
Tel. + 370 52 51 4000

Luxembourg/Luxemburg
Pfizer S.A.
Tél/Tel: +32 (0)2 554 62 11

Magyarország
Pfizer Kft.
Tel.: +36-1-488-37-00

Malta
V.J. Salomone Pharma Ltd.
Tel. +356 21220174

Nederland
Pfizer BV
Tel: +31 (0)10 406 43 01

Norge
Pfizer AS
Tlf: +47 67 52 61 00

Österreich
Pfizer Corporation Austria Ges.m.b.H.
Tel: +43 (0)1 521 15-0

Polska
Pfizer Polska Sp.z.o.o
Tel.:+48 22 335 61 00

France
Pfizer
Tél: +33 (0)1 58 07 34 40

Hrvatska
Pfizer Croatia d.o.o.
Tel: + 385 1 3908 777

Ireland
Pfizer Healthcare Ireland
Tel: 1800 633 363 (toll free)
+44 (0)1304 616161

Ísland
Icepharma hf.
Sími: +354 540 8000

Italia
Pfizer S.r.l.
Tel: +39 06 33 18 21

Κύπρος
Pfizer Ελλάς A.E. (Cyprus Branch)
Τηλ: +357 22 817690

Latvija
Pfizer Luxembourg SARL filiāle Latvijā
Tel.: + 371 670 35 775

Portugal
Pfizer Biofarmacêutica, Sociedade
Unipessoal Lda
Tel: +351 21 423 5500

România
Pfizer Romania S.R.L.
Tel: +40 (0) 21 207 28 00

Slovenija
Pfizer Luxembourg SARL
Pfizer, podružnica za svetovanje s področja
farmacevtske dejavnosti, Ljubljana
Tel.: + 386 (0)1 52 11 400

Slovenská republika
Pfizer Luxembourg SARL, organizačná zložka
Tel.: + 421 2 3355 5500

Suomi/Finland
Pfizer Oy
Puh./Tel: +358 (0)9 43 00 40

Sverige
Pfizer AB
Tel: +46 (0)8 550-52000

United Kingdom
Pfizer Limited
Tel: +44 (0) 1304 616161

This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.