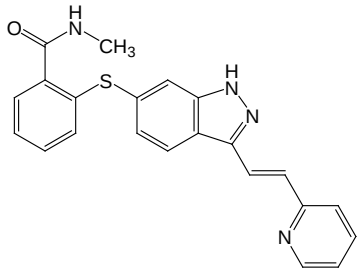
PRODUCT INFORMATION

INLYTA (axitinib)

NAME OF THE MEDICINE

Axitinib has the chemical name *N*-methyl-2-[3-((*E*)-2-pyridin-2-yl-vinyl)-1*H*-indazol-6-ylsulfanyl]-benzamide. The molecular formula is $C_{22}H_{18}N_4OS$ and the molecular weight is 386.47 Daltons. The CAS Registry Number is 319460-85-0. The chemical structure is:



DESCRIPTION

Axitinib is a white to light-yellow powder with a pKa of 4.8. The solubility of axitinib in aqueous media over the range pH 1.1 to pH 7.8 is in excess of 0.2 μg/mL. The partition coefficient (n-octanol/water) is 3.5.

INLYTA is supplied as red film-coated tablets containing either 1 mg or 5 mg of axitinib together with cellulose - microcrystalline, lactose, croscarmellose sodium, magnesium stearate, and Opadry II red 32K15441 as inactive ingredients. The Opadry II red 32K15441 film coating contains lactose, HPMC 2910/Hypromellose 15cP, titanium dioxide, glycerol triacetate, and iron oxide red.

PHARMACOLOGY

Mechanism of Action

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

Pharmacodynamics

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

Pharmacokinetics

Absorption and Distribution

After oral administration of INLYTA tablets, the mean absolute bioavailability is 58% compared to intravenous administration. The plasma half life of INLYTA ranges from 2.5 to 6.1 hours. Dosing of INLYTA at 5 mg twice daily resulted in <2-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.

Peak axitinib concentrations in plasma are generally reached within 4 hours following oral administration of INLYTA with the median T_{max} ranging from 2.5 to 4.1 hours. Administration of INLYTA 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. INLYTA may be administered with or without food (See Dosage and Administration).

The average C_{max} and area under the curve (AUC) increased proportionally over an INLYTA 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.

Metabolism and Elimination

Axitinib is metabolized 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

Gender, Ethnicity, Elderly (>65 years) patients

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.

Children and Adolescents

INLYTA has not been studied in patients <18 years of age.

Renal Impairment

Unchanged axitinib is not detected in the urine. INLYTA has not been studied in subjects with renal impairment. In clinical studies with INLYTA for the treatment of patients with RCC, patients with serum creatinine >1.5 times the upper limit of normal (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 INLYTA is recommended.

Hepatic Impairment

In vitro and *in vivo* data indicate that axitinib is primarily metabolized by the liver. Compared to subjects with normal hepatic function, systemic exposure following a single dose of INLYTA was similar to subjects with mild hepatic impairment (Child-Pugh class A) and higher (approximately 2-fold) in subjects with moderate hepatic impairment (Child-Pugh class B). INLYTA has not been studied in subjects with severe hepatic impairment (Child-Pugh class C) (See Precautions; Dosage and Administration).

CLINICAL TRIALS

The safety and efficacy of INLYTA were evaluated in a randomized, open-label, multicenter Phase 3 study. Patients (N=723) with advanced renal cell carcinoma (RCC) whose disease had progressed on or after treatment with one prior systemic therapy, including sunitinib-, bevacizumab-, temsirolimus-, or cytokine-containing regimens were randomized (1:1) to receive INLYTA (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 INLYTA and sorafenib groups with regard to age, gender, race, Eastern Cooperative Oncology Group (ECOG) performance status, geographic region, and prior treatment.

There was a statistically significant advantage for INLYTA over sorafenib for the primary endpoint of PFS (see Table 1 and Figure 1). There was no statistically significant difference between the arms in OS.

Table 1: Efficacy Results by Independent Assessment

Endpoint / Study Population	INLYTA	Sorafenib	HR (95% CI)	P-value
PFS [a,b]				
Overall ITT Median, months (95% CI)	N = 361 6.7 (6.3, 8.6)	N = 362 4.7 (4.6, 5.6)	0.67 (0.54, 0.81)	<0.0001[c]
Sunitinib-refractory subgroup Median, months (95% CI)	N = 194 4.8 (4.5, 6.4)	N = 195 3.4 (2.8, 4.7)	0.74 (0.57, 0.96)	0.0107[d]
Cytokine-refractory subgroup Median, months (95% CI)	N = 126 12.1 (10.1, 13.9)	N = 125 6.5 (6.3, 8.3)	0.46 (0.32, 0.68)	<0.0001[d]
OS				
Median, months (95% CI)	20.1 (16.7, 23.4)	19.2 (17.5, 22.3)	0.97 (0.80, 1.17)	0.374[e]
ORR				
% (95% CI)	N = 361 19.4 (15.4, 23.9)	N = 362 9.4 (6.6, 12.9)	2.06[f] (1.41, 3.00)	0.0001[g]

CI: Confidence interval; HR: Hazard ratio (INLYTA/sorafenib); ITT: Intent to treat; ORR: Objective response rate; PFS: Progression-free survival

[a] Time from randomization to progression or death due to any cause, whichever occurs first.

[b] Assessed by independent radiology review according to RECIST.

[c] One-sided p-value from a log-rank test of treatment stratified by ECOG performance status and prior therapy (comparison is considered statistically significant if the one-sided p-value is <0.023).

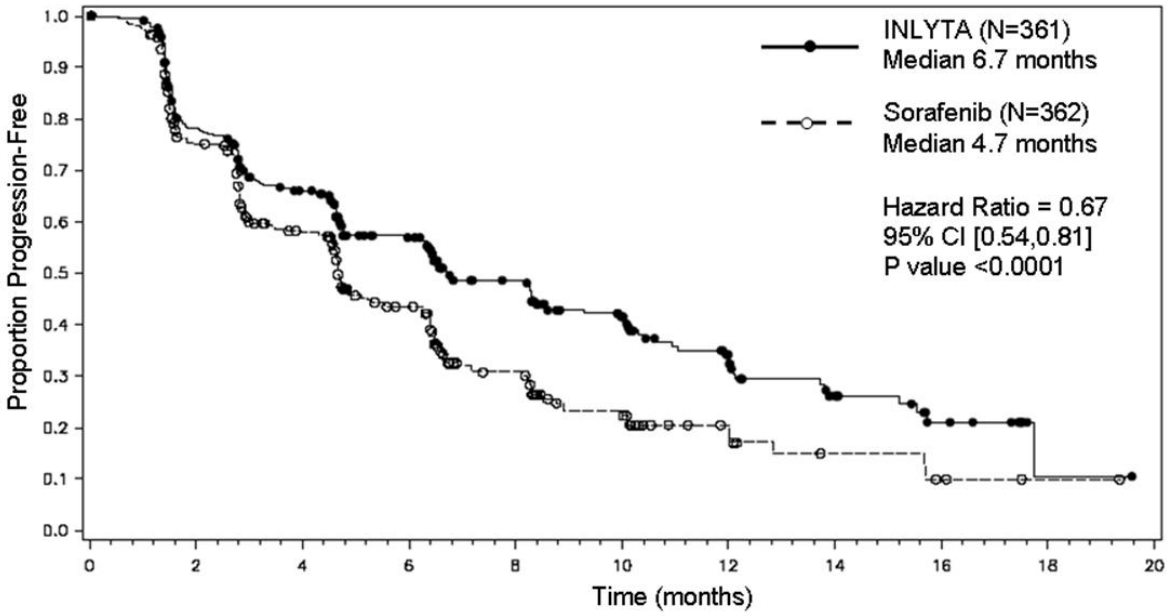
[d] One-sided p-value from a log-rank test of treatment stratified by ECOG performance status.

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

[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.

Figure 1: Kaplan-Meier Curve for Progression-Free Survival by Independent Assessment for the Overall Population



INDICATIONS

INLYTA is indicated for the treatment of patients with advanced renal cell carcinoma after failure of one prior systemic therapy.

CONTRAINDICATIONS

Hypersensitivity to axitinib or to any of the excipients.

PRECAUTIONS

Hypertension

In a controlled clinical study with INLYTA for the treatment of patients with RCC, hypertension was reported in 40.4% of patients receiving INLYTA (N=359) and 29.0% receiving sorafenib (N=355) (see Adverse Effects). Grade 3 hypertension was observed in 15.3% of patients receiving INLYTA and 10.7% of patients receiving sorafenib and Grade 4 hypertension was observed in 0.3% of patients receiving INLYTA and 0.3% of patients receiving sorafenib. Hypertensive crisis was reported in 0.6% of patients receiving INLYTA and in none of the patients receiving sorafenib. 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 INLYTA or sorafenib treatment and blood pressure increases have been observed as early as 4 days after starting INLYTA. Hypertension was managed with standard antihypertensive therapy. Discontinuation of INLYTA treatment due to hypertension occurred in 0.3% of patients receiving INLYTA and in none of the patients receiving sorafenib (see Adverse Effects).

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

Thyroid Dysfunction

In a controlled clinical study with INLYTA for the treatment of patients with RCC, hypothyroidism was reported in 19.2% of patients receiving INLYTA (N=359) and 8.2% of patients receiving sorafenib (N=355) (see Adverse Effects). Hyperthyroidism was reported in 1.1% of patients receiving INLYTA and 1.1% of patients receiving sorafenib. In patients who had thyroid stimulating hormone (TSH) <5 μU/mL before treatment, elevations of TSH to ≥10 μU/mL occurred in 32.2% of patients receiving INLYTA and 10.8% of patients receiving sorafenib (see Adverse Effects).

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

Arterial Thromboembolic Events

In a controlled clinical study with INLYTA for the treatment of patients with RCC, Grade 3/4 arterial thromboembolic events were reported in 1.1% of patients receiving INLYTA (N=359) and 1.1% of patients receiving sorafenib (N=355). The most frequent arterial thromboembolic event was transient ischemic attack (1.0%) (see Adverse Effects). Fatal cerebrovascular accident was reported in 0.3% of patients receiving INLYTA and none of the patients receiving sorafenib.

In monotherapy studies with INLYTA (N=699), arterial thromboembolic events (including transient ischemic attack, cerebrovascular accident, myocardial infarction, and retinal artery occlusion) were reported in 2.3% of patients receiving INLYTA.

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

Venous Thromboembolic Events

In a controlled clinical study with INLYTA for the treatment of patients with RCC, venous thromboembolic events were reported in 3.1% of patients receiving INLYTA (N=359) and 0.6% of patients receiving sorafenib (N=355). Grade 3/4 venous thromboembolic events were reported in 2.5% of patients receiving INLYTA (including pulmonary embolism, deep vein thrombosis, and retinal vein occlusion/thrombosis) and 0.6% of patients receiving sorafenib (see Adverse Effects). Fatal pulmonary embolism was reported in one patient (0.3%) receiving INLYTA and in none of the patients receiving sorafenib.

INLYTA should be used with caution in patients who are at risk for, or who have a history of, these events. INLYTA has not been studied in patients who had a venous thromboembolic 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 INLYTA. An increase in red blood cell mass may increase the risk of thromboembolic events.

Elevated haemoglobin above the ULN was observed in 9.7% of patients receiving INLYTA (N=320) and 0.9% of patients receiving sorafenib (N=316).

Monitor haemoglobin or haematocrit before initiation of, and periodically throughout, treatment with INLYTA. 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 a controlled clinical study with INLYTA for the treatment of patients with RCC, in which patients with untreated brain metastasis were excluded, haemorrhagic events were reported in 16.2% of patients receiving INLYTA (N=359) and 18.0% of patients receiving sorafenib (N=355). The most common haemorrhagic events in patients treated with INLYTA were epistaxis (6.1%), haematuria (3.3%), haemoptysis (2.2%), and rectal haemorrhage (2.2%) (see Adverse Effects). Grade 3/4 haemorrhagic events were reported in 1.4% of patients

receiving INLYTA (including cerebral haemorrhage, haematuria, haemoptysis, lower gastrointestinal haemorrhage, and melaena) and 3.1% of patients receiving sorafenib. Fatal haemorrhage was reported in one patient (0.3%) receiving INLYTA (gastric haemorrhage) and three patients (0.8%) receiving sorafenib.

INLYTA 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 INLYTA dose.

Gastrointestinal Perforation and Fistula Formation

In a controlled clinical study with INLYTA for the treatment of patients with RCC, gastrointestinal perforation was reported 0.3% of patients receiving INLYTA (N=359) and in none of the patients receiving sorafenib (N=355). In addition to cases of gastrointestinal perforation, fistulas were reported in 0.6% of patients receiving INLYTA and 0.3% of patients receiving sorafenib. In monotherapy studies with INLYTA (N=699), fatal gastrointestinal perforation was reported in one patient (0.1%).

Monitor for symptoms of gastrointestinal perforation periodically throughout treatment with INLYTA.

Wound Healing Complications

No formal studies of the effect of INLYTA on wound healing have been conducted. Treatment with INLYTA should be stopped at least 24 hours prior to scheduled surgery. The decision to resume INLYTA therapy after surgery should be based on clinical judgment of adequate wound healing.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

In a controlled clinical study with INLYTA for the treatment of patients with RCC, reversible posterior leukoencephalopathy syndrome (RPLS) was reported in one patient (0.3%) receiving INLYTA (N=359) and in none of the patients receiving sorafenib (N=355) (see Adverse Effects).

RPLS 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 RPLS. In patients with signs/symptoms of RPLS, temporarily interrupt or permanently discontinue INLYTA. The safety of reinitiating INLYTA therapy in patients previously experiencing RPLS is not known.

Proteinuria

In a controlled clinical study with INLYTA for the treatment of patients with RCC, proteinuria was reported in 10.9% of patients receiving INLYTA (N=359) and 7.3% of patients receiving sorafenib (N=355) (see Adverse Effects). Grade 3 proteinuria was reported in 3.1% of patients receiving INLYTA and 1.7% of patients receiving sorafenib.

Monitoring for proteinuria before initiation of, and periodically throughout, treatment with INLYTA. For patients who develop moderate to severe proteinuria, reduce the dose or temporarily interrupt INLYTA treatment (See Dosage and Administration).

Elevation of Liver Enzymes

In a clinical dose-finding study, concurrent elevations of alanine aminotransferase (ALT) (12 times the upper limit of normal [ULN]) and bilirubin (2.3 times the ULN), considered to be drug-related hepatotoxicity, were observed in 1 patient who received INLYTA at a starting dose of 20 mg twice daily (4 times the recommended starting dose). In a controlled clinical study with INLYTA for the treatment of patients with RCC, no concurrent elevations of ALT (>3 times the ULN) and bilirubin (>2 times the ULN) were observed for INLYTA (N=359) or sorafenib (N=355).

Monitor liver function tests before initiation of, and periodically throughout, treatment with INLYTA.

Use in Hepatic Impairment

In clinical studies with INLYTA, the systemic exposure to INLYTA was approximately 2-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 INLYTA to patients with moderate hepatic impairment (Child-Pugh class B) (see Pharmacokinetics).

INLYTA has not been studied in patients with severe hepatic impairment (Child-Pugh class C).

Use in Renal Impairment

A dedicated renal impairment trial for axitinib has not been conducted. Based on the population pharmacokinetic analyses, no significant difference in axitinib clearance was observed in patients with mild to severe renal impairment (creatinine clearance [CrCL] from 15 to 89 mL/min). No dose adjustment is needed for patients with mild to severe renal impairment. Caution should be used in patients with end-stage renal disease (CrCL <15 mL/min).

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.

Effects on Fertility

INLYTA has the potential to impair reproductive function and fertility in humans. Findings in the male reproductive tract were observed in the testes/epididymis (decreased organ weight, atrophy or degeneration, decreased numbers of germinal cells, hypospermia or abnormal sperm forms) in mice and dogs. Axitinib did not affect mating or fertility in male mice at any dose tested up to 100 mg/kg/day. However, reduced testicular weights, sperm density and/or count were noted at ≥ 10 mg/kg/day (approximately 4 times the AUC at the recommended starting dose in humans) following at least 70 days of treatment with axitinib. Male reproductive toxicity was evident in the dog at ≥ 3 mg/kg/day, 0.2 times the AUC at the recommended starting dose in humans.

Findings in the female reproductive tract in mice and dogs included signs of delayed sexual maturity, reduced or absent corpora lutea, decreased uterine weights and uterine atrophy. In

female mice, reduced fertility and embryonic viability were observed at all doses tested (≥ 30 mg/kg/day) following at least 15 days of treatment with axitinib (approximately 11 times the AUC at the recommended starting dose in humans). Female reproductive toxicity in the dog was observed at ≥ 10 mg/kg/day.

Use in Pregnancy Category D

There are no studies in pregnant women using INLYTA. As angiogenesis is a critical component of embryonic and fetal development, INLYTA may cause fetal harm if administered to a pregnant woman. Axitinib has been shown to be embryotoxic and teratogenic when administered to mice and rabbits at exposures similar to or below clinical exposure.

An increase in post-implantation loss and reduced embryonic survival was observed in female mice exposed to axitinib (30 mg/kg/day, or 11 times the AUC at the recommended starting dose in humans) prior to mating and through the first week of pregnancy. Pregnant mice exposed to axitinib showed an increased occurrence of cleft palate at an oral dose level of 3 mg/kg/day (approximately half the AUC at the recommended starting dose in humans) and common variations in skeletal ossification at ≥1 mg/kg/day (approximately 0.15 times the AUC at the recommended starting dose in humans). Limited investigations in rabbits showed high embryo and fetal loss at exposures considerably lower than the recommended clinical dose.

INLYTA should not be used during pregnancy. Women of childbearing potential must be advised to avoid becoming pregnant while receiving treatment with INLYTA. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Adequate contraception should be used during therapy and for at least 4 weeks after completion of therapy.

Use in Lactation

No studies have been conducted in humans to assess the effect of axitinib on milk production, its presence in breast milk, or its effects of the breast-fed child. It is unknown whether axitinib is excreted in human milk. Since many drugs are commonly excreted in human milk, and because of the potential for serious adverse reactions in nursing infants due to exposure to axitinib, women should discontinue breastfeeding during treatment with axitinib.

Paediatric Use

The safety and efficacy of INLYTA in children and adolescents (<18 years) have not been studied. Physeal dysplasia was observed in immature mice and dogs given axitinib at doses ≥30 mg/kg/day for at least 1 month (approximately 6 times the AUC at the recommended starting dose in humans); the incidence and severity was dose-related and the effects were reversible when treatment stopped. Dental caries were observed in mice treated for more than 1 month at axitinib doses ≥10 mg/kg/day (approximately 2 times the AUC at the recommended starting dose in humans); residual findings, indicative of partial reversibility, were observed when treatment stopped. For physeal dysplasia, no effect levels of 10 mg/kg/day in mouse (approximately 1.4 times the AUC at the recommended starting dose in humans) and 10 mg/kg/day in dogs were determined in animals given axitinib for 1 month. A no effect level was not defined for caries of the incisors in mice. Other toxicities of potential concern to paediatric patients have not been evaluated in juvenile animals.

Use in the Elderly

In a controlled clinical study with INLYTA for the treatment of patients with RCC, 34.3% of patients treated with INLYTA were ≥65 years of age. Although greater sensitivity in some older individuals cannot be ruled out, no overall differences were observed in the safety and effectiveness of INLYTA between patients who were ≥65 years of age and younger.

No dosage adjustment is required in elderly patients (see Pharmacokinetics).

Genotoxicity

Axitinib was tested using a series of genetic toxicology assays consisting of *in vitro* bacterial reverse mutation (Ames), human lymphocyte chromosome aberration, and *in vivo* mouse bone marrow micronucleus assays. Axitinib was not mutagenic in these assays, but induced polyplody in human lymphocytes *in vitro*, and was aneugenic in the micronucleus assay at exposure levels approximately 154 times the recommended starting dose in humans.

Carcinogenicity

Carcinogenicity studies have not been performed with axitinib.

INTERACTIONS WITH OTHER MEDICINES

In vitro data indicate that axitinib is metabolized 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 AUC 2-fold and C_{max} 1.5-fold of a single 5-mg oral dose of INLYTA in healthy volunteers.

Co-administration of INLYTA with strong CYP3A4/5 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin) may increase axitinib plasma concentrations. Grapefruit may also increase axitinib plasma concentrations.

Selection of concomitant medication with no or minimal CYP3A4/5 inhibition potential is recommended. If a strong CYP3A4/5 inhibitor must be co-administered, a dose adjustment of INLYTA is recommended (See Dosage and Administration).

CYP3A4/5 Inducers

Rifampin, 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 INLYTA in healthy volunteers.

Co-administration of INLYTA with strong CYP3A4/5 inducers (e.g., rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentin, phenobarbital, and *Hypericum perforatum* [also known as St. John's wort]) may decrease axitinib plasma concentrations.

Selection of concomitant medication with no or minimal CYP3A4/5 induction potential is recommended. If a strong CYP3A4/5 inducer must be co-administered, a dose adjustment of INLYTA is recommended (See Dosage and Administration).

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 INLYTA 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 INLYTA 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 INLYTA 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 INLYTA is not expected to increase the plasma concentration of digoxin, or other P-glycoprotein substrates, *in vivo*.

Effects on Ability to Drive and Use of Machines

No studies on the effect of INLYTA on the ability to drive and use machines have been performed. Patients should be advised that they may experience events such as dizziness and/or fatigue during treatment with INLYTA.

ADVERSE EFFECTS

The safety of INLYTA has been evaluated in 699 patients in monotherapy studies, which included 537 patients with advanced RCC. The data described reflect exposure to INLYTA in 359 patients with advanced RCC who participated in a randomized clinical study versus sorafenib (see Clinical Trials).

The median duration of treatment was 6.4 months (range 0.03 to 22.0) for patients who received INLYTA and 5.0 months (range 0.03 to 20.1) for patients who received sorafenib. Dose modifications or temporary delay of treatment due to an adverse event occurred in 55.4% of patients receiving INLYTA and 61.9% of patients receiving sorafenib. Permanent discontinuation due to an adverse event occurred in 9.2% of patients receiving INLYTA and 13.0% of patients receiving sorafenib.

The most common (≥20%) adverse reactions observed following treatment with INLYTA were diarrhoea, hypertension, fatigue, decreased appetite, nausea, dysphonia, palmar-plantar

erythrodysaesthsia (hand-foot) syndrome, weight decreased, vomiting, asthenia, and constipation.

The following risks, including appropriate action to be taken, are discussed in greater detail under Precautions: hypertension, thyroid dysfunction, arterial thromboembolic events, venous thromboembolic events, elevation of haemoglobin or haematocrit, haemorrhage, gastrointestinal perforation and fistula formation, wound healing complications, reversible posterior leukoencephalophathy syndrome, proteinuria, and elevation of liver enzymes.

Table 2 presents adverse reactions reported in patients who received INLYTA or sorafenib. 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), not known (cannot be estimated from the available data).

Table 2: Adverse Reactions Reported in the RCC Study in Patients who Received INLYTA or Sorafenib

System Organ Class	Frequency Category	Preferred Term	INLYTA (N= 359)		Sorafenib (N=355)	
			All Grades[a]	Grade ≥3	All Grades[a]	Grade ≥3
			%	%	%	%
Blood and lymphatic system disorders	Common	Anaemia	3.6	0.6	11.5	3.9
	Uncommon	Polycythaemia	0.8	0.3	0	0
Endocrine disorders	Very Common	Hypothyroidism	19.2	0.3	8.2	0
Metabolism and nutrition disorders	Very Common	Decreased appetite	34.0	5.0	28.5	3.7
	Common	Dehydration	6.4	3.6	2.5	1.1
		Hyperkalaemia	3.1	1.4	2.3	0.8
		Hypercalcaemia	5.7	0	1.5	0
Nervous system disorders	Very Common	Headache	13.6	0.6	11.3	0
		Dysgeusia	10.6	0	8.2	0
	Common	Dizziness	9.2	0.6	4.2	0
	Uncommon	Transient ischaemic attack	0.8	0.8	0	0
		Cerebrovascular accident	0.3	0.3	0.3	0.3
		Reversible Posterior Leukoencephalopathy Syndrome	0.3	0.3	0	0
Eye disorders	Uncommon	Retinal vein occlusion / thrombosis	0.6	0.6	0	0
Ear and labyrinth disorders	Common	Tinnitus	3.1	0	0.8	0
Vascular disorders	Very Common	Hypertension	40.4	15.6	29.0	11.0
	Uncommon	Deep vein thrombosis	0.6	0.6	0	0
Respiratory, thoracic and	Very Common	Dyspnoea	14.8	2.5	12.1	2.8
		Cough	15.3	0.8	16.6	0.6

System Organ Class	Frequency Category	Preferred Term	INLYTA (N= 359)		Sorafenib (N=355)	
			All Grades[a]	Grade ≥3	All Grades[a]	Grade ≥3
			%	%	%	%
mediastinal disorders		Dysphonia	30.9	0	13.5	0
	Common	Pulmonary embolism	1.9	1.9	0.6	0.6
		Haemoptysis	2.2	0.3	3.9	0.6
		Epistaxis	6.1	0	4.2	0
Gastrointestinal disorders	Very Common	Diarrhoea	54.9	10.6	53.2	7.3
		Vomiting	23.7	3.3	17.2	0.8
		Nausea	32.3	2.5	21.7	1.1
		Abdominal pain	14.2	2.2	10.7	0.8
		Stomatitis	15.0	1.4	12.4	0.3
		Constipation	20.3	1.1	20.3	0.8
		Upper abdominal pain	8.1	0.8	3.9	0.3
		Dyspepsia	10.0	0	2.3	0
	Common	Haemorrhoids	4.2	0	1.4	0.3
		Rectal haemorrhage	2.2	0	1.4	0
		Gastrointestinal perforation and fistula[b]	1.0	0	0.3	0
Hepatobiliary disorders	Uncommon	Hyperbilirubinaemia	0.8	0.3	0.8	0.6
Skin and subcutaneous tissue disorders	Very Common	Palmar-plantar erythrodysaesthesia (hand-foot syndrome)	27.3	5.0	51.0	16.1
		Rash	12.5	0.3	31.5	3.9
		Dry skin	10.0	0	10.7	0
	Common	Erythema	2.2	0	10.1	0.3
		Pruritis	6.7	0	12.4	0
		Alopecia	3.9	0	32.4	0
Musculoskeletal and connective tissue disorders	Very Common	Arthralgia	15.0	1.9	11.0	1.4
		Pain in extremity	12.5	0.6	13.5	0.6
	Common	Myalgia	7.0	0.8	2.8	0
Renal and urinary disorders	Very Common	Proteinuria	10.9	3.1	7.3	1.7
	Common	Haematuria	3.3	0.3	2.0	0
General disorders and administration site conditions	Very Common	Fatigue	39.0	11.4	31.5	5.1
		Asthaenia	20.6	5.3	14.1	2.5
		Mucosal inflammation	15.3	1.4	12.4	0.6
Investigations	Very Common	Weight decreased	24.8	2.2	20.8	1.4
	Common	Lipase increased	2.5	0.6	5.4	3.4
		Creatinine increased	2.8	0.3	0.8	0
		Alanine aminotranferase increased	2.2	0.3	3.7	1.7
		Alkaline phosphatase increased	1.9	0.3	2.0	0

System Organ Class	Frequency Category	Preferred Term	INLYTA (N= 359)		Sorafenib (N=355)	
			All Grades[a]	Grade ≥3	All Grades[a]	Grade ≥3
			%	%	%	%
		Aspartate aminotransferase increased	1.1	0.3	3.7	1.1
		Amylase increase	1.7	0	3.9	0.3

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0
[b] Including fistula, anal fistula, and gastrointestinal perforation

DOSAGE AND ADMINISTRATION

Recommended Dose

The recommended starting oral dose of INLYTA is 5 mg twice daily. INLYTA may be taken with or without food.

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 Adjustment

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

Patients who tolerate the INLYTA starting dose of 5 mg twice daily with no adverse reactions >Grade 2 (according to the Common Toxicity Criteria for Adverse Events [CTCAE]) for two consecutive weeks, are normotensive, and are not receiving anti-hypertension medication, may have their dose increased to 7 mg twice daily. Subsequently, using the same criteria, patients who tolerate the INLYTA dose of 7 mg twice daily, may have their dose increased to a maximum of 10 mg twice daily.

Management of some adverse drug reactions may require temporary or permanent discontinuation and/or dose reduction of INLYTA therapy (see Precautions). When dose reduction is necessary, the INLYTA 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 INLYTA with strong CYP3A4/5 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin) may increase axitinib plasma concentrations. Grapefruit may also increase axitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal CYP3A4/5 inhibition potential is recommended.

Although INLYTA 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 INLYTA to approximately half the dose (e.g., from a starting dose of 5 mg twice daily to a reduced dose of 2 mg twice daily) is recommended. If co-administration of the

strong inhibitor is discontinued, a return to the INLYTA dose used prior to initiation of the strong CYP3A4/5 inhibitor should be considered.

Concomitant Strong CYP3A4/5 Inducers

Co-administration of INLYTA with strong CYP3A4/5 inducers (e.g., rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentin, phenobarbital, and *Hypericum perforatum* [also known as St. John's wort]) may decrease axitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal CYP3A4/5 induction potential is recommended.

Although INLYTA 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 INLYTA is recommended. If the dose of INLYTA is increased, the patient should be monitored carefully for toxicity. If co-administration of the strong inducer is discontinued, the INLYTA dose should be immediately returned to the dose used prior to initiation of the strong CYP3A4/5 inducer.

Use in Hepatic Impairment

No dose adjustment is required when administering INLYTA to patients with mild hepatic impairment (Child-Pugh class A). A dose decrease is recommended when administering INLYTA 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]. INLYTA has not been studied in patients with severe hepatic impairment (Child-Pugh class C).

Use in Renal Impairment

No dose adjustment is required (see Pharmacokinetics).

Use in Children

The safety and efficacy of INLYTA in children and adolescents (<18 years) have not been established.

Use in the Elderly

No dose adjustment is required (see Pharmacokinetics).

OVERDOSAGE

There is no specific treatment for INLYTA overdose. For information on the management of overdose, contact the Poison Information Centre on 131126.

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

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

PRESENTATION AND STORAGE CONDITIONS

Store below 30°C.

INLYTA 1 mg film-coated tablets

Red, film-coated, oval tablets, debossed with "Pfizer" on one side and "1 XNB" on the other.

Packs containing 28 (14 tablets/blister x 2 blisters) or 56* (14 tablets/blister x 4 blisters) tablets.

High-density polyethylene (HDPE) bottle with desiccant and a child-resistant closure containing 180 tablets.*

INLYTA 5 mg film-coated tablets

Red, film-coated, triangular tablets, debossed with "Pfizer" on one side and "5 XNB" on the other.

Packs containing 28 (14 tablets/blister x 2 blisters) or 56* (14 tablets/blister x 4 blisters) tablets.

High-density polyethylene (HDPE) bottle with desiccant and a child-resistant closure containing 60 tablets.*

*Not marketed.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
A.B.N. 5000 8422 348
38-42 Wharf Road
WEST RYDE NSW 2114

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Medicine)

DATE OF FIRST INCLUSION IN THE ARTG

26 July 2012