Axitinib (Inlyta) Tablets

**Manufacturer:** Pfizer Inc., New York, N.Y.

**Indication:** Axitinib is indicated for patients with advanced renal cell carcinoma (RCC) after the failure of one prior systemic therapy. RCC starts in the lining of small tubes in the kidney.

**Drug Class:** Axitinib is a tyrosine kinase receptor inhibitor. The drug’s chemical name is N-methyl-2-[[1(E)-2-pyridin-2-yl-vinyl)-1H-indazol-6-ylsulfanyl]-benzamide. The molecular formula is C_{22}H_{18}N_{4}O_{5}S, and the drug’s molecular weight is 386.47 daltons.

**Uniqueness of Drug:** Axitinib inhibits receptor tyrosine kinases, including vascular endothelial growth factor receptor 1 (VEGFR-1), VEGFR-2, and VEGFR-3 at therapeutic plasma levels. These receptors are implicated in pathological angiogenesis, tumor growth, and cancer progression. In mouse models, axitinib inhibited VEGF-mediated endothelial cell proliferation and survival in vitro. In tumor xenograft mouse models, axitinib inhibited tumor growth and phosphorylation of VEGFR-2.

**Warnings and Precautions:**

**Hypertension.** In a controlled clinical study of RCC, hypertension was reported in 145 of 359 patients (40%) receiving axitinib and in 103 of 355 patients (29%) receiving sorafenib. Grade 3 and 4 hypertension was observed in 56 patients (16%) who received axitinib and in 39 patients (11%) who received sorafenib. Hypertensive crisis was reported in two patients receiving axitinib but in none of the patients receiving sorafenib. The median onset of hypertension, with systolic blood pressure (BP) above 150 mm Hg or diastolic BP above 100 mm Hg, was within the first month of axitinib treatment, and elevated BP was noted as early as 4 days after the start of therapy. Hypertension was managed with standard antihypertensive agents. Axitinib was discontinued in one patient as a result of hypertension. Elevated BP did not develop in the sorafenib group.

BP should be well controlled before axitinib is initiated. Patients should be monitored for hypertension and treated with standard antihypertensive therapy as needed. If hypertension persists, the axitinib dose should be reduced.

If hypertension is severe and persists despite antihypertensive therapy and after the axitinib dose is reduced, axitinib therapy should be discontinued. If hypertensive crisis develops, discontinuation of axitinib therapy should be considered. If axitinib treatment is interrupted, patients receiving antihypertensive drugs should be monitored for hypotension.

**Arterial thromboembolic events.** In clinical trials, arterial thromboembolic events, including deaths, occurred. In a controlled clinical study of therapy for RCC, grade 3 and 4 arterial thromboembolic events were reported in 4 of 359 patients (1%) who received axitinib and in 4 of 355 patients (1%) who received sorafenib. A fatal cerebrovascular accident (CVA) was reported in one axitinib patient and in no sorafenib patients.

In clinical trials of axitinib, arterial thromboembolic events (including transient ischemic attacks, CVAs, myocardial infarction, and retinal artery occlusion) were reported in 17 of 715 patients (2%). Two deaths were secondary to a CVA.

Axitinib should be used with caution in patients who are at risk for, or who have a history of, these events.

**Venous thromboembolic events.** In clinical trials, venous thromboembolic events, including deaths, were reported. In a controlled clinical study of patients with RCC, venous thromboembolic events were reported in 11 of 359 patients (3%) receiving axitinib and in 2 of 355 patients (1%) receiving sorafenib. Grade 3 and 4 events (pulmonary embolism, deep vein thrombosis, retinal vein occlusion, and retinal vein thrombosis) were reported in 9 of 359 patients (3%) receiving axitinib and in two patients receiving sorafenib. A fatal pulmonary embolism was reported in one patient receiving axitinib and in none of those receiving sorafenib. In clinical trials, venous thromboembolic events were reported in 22 of 715 patients (3%) receiving axitinib. Two deaths were secondary to pulmonary embolism. Axitinib should be used with caution in patients at risk for, or with a history of, these events.

**Hemorrhage.** In a controlled clinical study of therapy for RCC, hemorrhagic events were reported in 58 of 359 patients (16%) receiving axitinib and in 64 of 355 patients (18%) receiving sorafenib. Grade 3 and 4 hemorrhagic events (cerebral hemorrhage, hematuria, hemoptysis, lower gastrointestinal [GI] hemorrhage, and melena) were reported in five axitinib patients and in 11 of 355 sorafenib patients (3%). Fatal (gastric) hemorrhage was reported in one patient receiving axitinib and in three patients receiving sorafenib.

Axitinib has not been studied in patients with evidence of untreated brain metastasis or recent active GI bleeding; therefore, it should not be used in these patients. If medical intervention is required because of bleeding, the axitinib dosage should be temporarily interrupted.

**GI perforation and fistula formation.** In a controlled clinical study of RCC, GI perforation was reported in 1 of 359 patients receiving axitinib and in no patients receiving sorafenib. In other clinical trials of axitinib, GI perforation was reported in 5 of 715 patients, including one death, and GI fistulas were reported in four of these patients. Patients should be monitored for symptoms of GI perforation or fistula periodically throughout treatment with axitinib.

**Thyroid dysfunction.** In a controlled clinical study of therapy for RCC, hypothyroidism was reported in 69 of 359 patients (19%) who received axitinib and in 29 of 359 patients (8%) who were given sorafenib. Hyperthyroidism was reported in four axitinib-treated patients and in four sorafenib-treated patients.

In patients with a thyroid-stimulating hormone (TSH) level below 5 U/mL before treatment, TSH levels were elevated to 10 U/mL or higher in 79 of 245 patients (32%) receiving axitinib and in 25 of 232 patients (11%) receiving sorafenib.

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Thyroid function should be monitored before therapy begins and periodically throughout treatment. Hypothyroidism and hyperthyroidism should be treated according to standard medical practice to maintain a euthyroid state.

Wound-healing complications. Axitinib’s effect on wound healing has not been studied. Axitinib should be stopped at least 24 hours before scheduled surgery. The decision to resume axitinib therapy after surgery should be based on clinical judgment of adequate wound healing.

Reversible posterior leukoencephalopathy syndrome. In a controlled clinical study of patients with RCC, reversible posterior leukoencephalopathy syndrome (RPLS) was reported in one patient receiving axitinib and in no patients receiving sorafenib. In other clinical trials with axitinib, there were two additional reports of RPLS.

RPLS, a neurological disorder, can be manifested as headaches, seizures, lethargy, confusion, blindness, and other visual and neurological disturbances. Mild-to-severe hypertension may be present. If RPLS develops, axitinib should be discontinued. It is unclear whether it is safe to restart axitinib therapy in patients who previously experienced RPLS.

Proteinuria. In a controlled clinical study of RCC, proteinuria was reported in 39 of 359 axitinib patients (11%) and in 26 of 355 patients (7%) receiving sorafenib. Grade 3 proteinuria was reported in 11 patients (3%) receiving axitinib and in six patients (2%) receiving sorafenib. Monitoring for proteinuria is recommended before axitinib is initiated and periodically throughout treatment. If moderate-to-severe proteinuria develops, the dose of axitinib should be reduced or treatment should be temporarily interrupted.

Elevated liver enzymes. In a controlled clinical study, alanine aminotransferase (ALT) elevations of all grades occurred in 22% of patients receiving both axitinib and sorafenib. Grade 3 or 4 events developed in fewer than 1% of axitinib patients and in 2% of sorafenib patients. ALT, aspartate aminotransferase (AST), and bilirubin levels should be monitored before treatment with axitinib begins and periodically throughout treatment.

Hepatic impairment. Systemic exposure to axitinib was higher in subjects with moderate hepatic impairment (Child–Pugh class B) than in those with normal hepatic function. A decrease in dosage is recommended for patients with moderate hepatic impairment (Child–Pugh class B). Axitinib has not been studied in patients with severe hepatic impairment (Child–Pugh class C).

Pregnancy. Because of its mechanism of action, axitinib can cause fetal harm in pregnant women. No adequate or well-controlled studies of axitinib have been conducted during pregnancy. In developmental toxicity studies in mice, axitinib was teratogenic, embryotoxic, and fetotoxic at maternal exposures that were lower than human exposures at the recommended clinical dose. Women of childbearing age should avoid pregnancy during axitinib therapy. If a woman becomes pregnant while using this drug, she should be apprised of the potential hazard to the fetus.

Dosage and Administration: The recommended starting oral dose of axitinib is 5 mg twice daily. Doses should be taken approximately 12 hours apart with or without food. Tablets should be swallowed whole with a glass of water. 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.

Commentary: Axitinib (Inlyta) was evaluated in a randomized, open-label clinical study of 723 patients whose disease had progressed during or after treatment with one previous systemic therapy. Results showed a median progression-free survival of 6.7 months with axitinib compared with 4.7 months with sorafenib, a standard treatment.

Axitinib is the seventh drug approved to treat metastatic or advanced RCC since 2005. Other FDA-approved agents for RCC include sorafenib (2005), sunitinib (2006), temsirolimus (2007), everolimus (2009), bevacizumab (2009), and pazopanib (2010). Such an unprecedented degree of drug development within this time period has significantly altered the treatment paradigm of metastatic kidney cancer and offers patients multiple treatment options.

The recommended dose of Prostaglandin analogues are often used as
Lucinactant is indicated for the prevention of
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www.fda.gov; www.pmlive.com; www.discovery-
Some premature infants are born with an
of the four active components are as follows:
2° to 8°C (36°–46°F). It becomes a free-flowing suspension
white to off-white opaque gel-like product is a suspension at
Indication: Macular edema has been reported during
treatment with prostaglandin F₂ analogues. Tafluprost should
be used with caution in aphakic patients, in pseudophakic
patients with a torn posterior lens capsule, or in patients with
risk factors for macular edema.
Dosage and Administration: The recommended dose of
tafluprost ophthalmic solution is 1 drop in the conjunctival sac
of the affected eye in the evening. The dose should not be taken
more than once daily. More frequent administration of prosta-
glandin analogues may lessen the IOP-lowering effect.
Reduction of IOP starts approximately 2 to 4 hours after the first
administration, and the maximum effect is achieved after 12 hours.
Meanwhile, tafluprost may be used with other topical ophthalmic drugs
to reduce IOP. If more than one topical ophthalmic product is
used, each product should be given at least 5 minutes apart.
The solution from one individual unit should be used imme-
diately after it is opened. Sterility cannot be maintained after
the individual unit is opened; therefore, the remaining contents
should be discarded immediately after administration.
Commentary: Prostaglandin analogues are often used as
a first-line treatment to decrease IOP in patients with open-
angle glaucoma. Tafluprost (Zioptan) is the first preservative-
free prostaglandin analogue.
The FDA’s approval of tafluprost was based on results from
five controlled clinical studies of up to 2 years in duration in 905
patients. Once-daily administration of tafluprost in the evening
lowered IOP at 3 and 6 months by 6 to 8 mm Hg and 5 to 8 mm
Hg respectively, from a baseline IOP of 23 to 26 mm Hg.
Sources: www.fda.gov; www.merck.com/product/usa/pi_circulars/z/zioptan/zioptan_pi.pdf
Lucinactant Intratracheal Suspension (Surfaxin)
Manufacturer: Discovery Laboratories, Warrington, Pa.
Indication: Lucinactant is indicated for the prevention of
respiratory distress syndrome (RDS) in premature infants
at high risk for this condition.
Drug Class: Lucinactant is a synthetic formulation that
consists of phospholipids, a fatty acid, and sinapultide (KL₄, pep-
tide), a 21-amino acid hydrophobic synthetic peptide. The
white to off-white opaque gel-like product is a suspension at
2° to 8°C (36°–46°F). It becomes a free-flowing suspension
after it is warmed up for 15 minutes in a dry block heater set
at 44°C (111°F). The chemical names and empirical formulas
of the four active components are as follows:
Sinapultide (KL₄, acetate)
Chemical name: L-Lysyl-L-leucyl-L-leucyl-L-leucyl-
L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-
L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-
L-leucyl-L-lysine, acetate
Empirical formula: C₁₁₂H₂₅₁N₁₃O₁₁₂
Molecular weight: 2469.46
DPPC
Chemical name: 1,2-dipalmitoyl-sn-glycero-3-
phosphocholine
Empirical formula: C₄₀H₇₆O₁₀P
Molecular weight: 734.06
Uniqueness of Drug: Lucinactant is the first synthetic, pep-
tide-containing surfactant approved for use in neonatal medi-
ne. It is a sterile, non-pyrogenic pulmonary surfactant
intended for intratracheal use only.
Warnings and Precautions:
Acute changes in lung compliance. Infants receiving
lucinactant should be evaluated frequently so that oxygen and
ventilatory support can be adjusted to respond to any changes
in respiratory status.
Adverse reactions. If an adverse drug reaction (e.g., brady-
cardia, oxygen desaturation, reflux of the suspension into the
endotracheal tube, airway obstruction, or endotracheal tube
obstruction) occurs during lucinactant administration, therapy
should be interrupted and the infant’s clinical condition should
be evaluated and stabilized. Suctioning of the endotracheal
tube or re-intubation may be necessary if airway obstruction
persists or is severe.
Adverse reactions in adults with acute RDS. In a two-part
clinical trial in adults with ARDS, compared with the standard
of care, patients who received lucinactant via segmental bron-
choscopic lavage experienced an increased incidence of death,
multiorgan failure, sepsis, anoxic encephalopathy, renal failure,
hypoxia, pneumothorax, hypotension, and pulmonary embolism.
Lucinactant is not indicated for patients with acute RDS.
Dosage and Administration: Lucinactant should be given
by the intratracheal route and only by clinicians experienced
in intubation, ventilator management, and the general care of
premature infants. The recommended dose is 5.8 mL/kg of the
infant’s birth weight. Up to four doses can be given in the first
48 hours of life, but doses should be given no more frequently
than every 6 hours. No data are available for doses above 5.8
mL/kg of birth weight, the effects of more than four doses, or
dosing more frequently than every 6 hours.
Commentary: Some premature infants are born with an
insufficient amount of pulmonary surfactant, a substance that
is produced naturally in the lungs and is essential for breath-
ing. Approximately 90,000 premature infants in the U.S. are
treated annually with animal-derived surfactant-replacement
therapy along with mechanical ventilation. The approval of
lucinactant (Surfaxin) is an important advancement for the
neonatology community and parents of preterm infants.
Lucinactant is the fifth drug in the U.S. to be approved to
treat RDS in premature infants. FDA-approved animal-based
surfactants include beractant (Survanta, Abbott), poractant
alpha (Curosurf, Cornerstone/Chiesi), and calfactant (Infa-
surf, Ony, Inc.). Colfosceirl palmitate (Exosurf, Glaxo-
SmithKline/Burroughs Wellcome) is no longer marketed.
Sources: www.fda.gov; www.pmlive.com; www.discovery-
labs.com; www.drugs.com/surfaxin.html □