Nintedanib: Drug information

(For additional information see "Nintedanib: Patient drug information")

For abbreviations and symbols that may be used in Lexicomp (show table)

Brand Names: US

Ofev

Brand Names: Canada

Ofev

Pharmacologic Category

Tyrosine Kinase Inhibitor

Dosing: Adult

Idiopathic pulmonary fibrosis (IPF): Oral: 150 mg every 12 hours (maximum: 300 mg/day)

Missed dose: If a dose is missed, the next dose should be taken at the next scheduled time. Do not make up a missed dose.

Dosing: Geriatric

Refer to adult dosing.

Dosing: Renal Impairment

CrCl ≥30 mL/minute: No initial dosage adjustment necessary.

CrCl <30 mL/minute and end-stage renal disease (ESRD): There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

Dosing: Hepatic Impairment

Hepatic impairment at baseline:

Mild impairment (Child-Pugh class A): 100 mg every 12 hours.

Moderate to severe impairment (Child-Pugh class B or C): Use is not recommended (exposure is increased in moderate impairment; has not been studied in severe impairment).

Hepatotoxicity during treatment:

US labeling:

AST or ALT >3 times to <5 times ULN (without signs of severe liver damage): Interrupt treatment or reduce dosage to 100 mg every 12 hours. Once liver enzymes have returned to baseline values after treatment interruption, reintroduce therapy at 100 mg every 12 hours; may be subsequently increased to 150 mg every 12 hours. If a patient does not tolerate 100 mg every 12 hours, consider treatment interruption or discontinue treatment to manage adverse

reactions.

AST or ALT >5 times ULN or >3 times ULN with signs or symptoms of severe liver damage: Discontinue therapy.

Canadian labeling:

AST or ALT >3 times ULN (without signs of severe liver damage): Interrupt treatment or reduce dosage to 100 mg every 12 hours and monitor closely. Once liver enzymes have returned to baseline values after treatment interruption, reintroduce therapy at 100 mg every 12 hours; may be subsequently increased to 150 mg every 12 hours. If a patient does not tolerate 100 mg every 12 hours, discontinue treatment.

AST or ALT >3 times ULN with signs or symptoms of severe liver damage: Discontinue therapy.

Dosing: Adjustment for Toxicity

Gastrointestinal toxicity (eg, diarrhea, nausea, vomiting) or other adverse reactions/toxicity: Dose reduction or temporary interruption may be needed. Treatment may be resumed at 150 mg every 12 hours or 100 mg every 12 hours, which may subsequently be increased to 150 mg every 12 hours. If a patient does not tolerate 100 mg every 12 hours, discontinue treatment.

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, Oral:

Ofev: 100 mg, 150 mg

Generic Equivalent Available (US)

No

Administration

Oral: Administer with food. Swallow capsules whole with liquid; do not chew or crush (bitter taste).

Hazardous Drugs Handling Considerations

Hazardous agent (meets NIOSH 2016 criteria). This medication is not on the NIOSH (2016) list; however, it meets the criteria for a hazardous drug. Drugs are classified as hazardous based on their properties; the properties of a hazardous drug include one or more of the following characteristics: carcinogenic, teratogenic (or other developmental toxicity), reproductive toxicity, organotoxic at low doses, genotoxic, and/or new agents with structural or toxicity profiles similar to existing hazardous agents.

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage. NIOSH recommends single gloving for administration of intact tablets or capsules (NIOSH 2016).

Use

Idiopathic pulmonary fibrosis: Treatment of idiopathic pulmonary fibrosis (IPF).

Medication Safety Issues

Sound-alike/look-alike issues:

Nintedanib may be confused with erlotinib, imatinib, nilotinib, vandetanib

Adverse Reactions

>10%:

Gastrointestinal: Diarrhea (62%), nausea (24%), abdominal pain (15%), vomiting (12%), decreased appetite (11%)

Hepatic: Increased liver enzymes (14%)

1% to 10%:

Cardiovascular: Hypertension (5%), arterial thrombosis (3%), myocardial infarction (2%)

Central nervous system: Headache (8%)

Endocrine & metabolic: Weight loss (10%), hypothyroidism (1%)

Hematologic and oncologic: Hemorrhage (10%)

Respiratory: Bronchitis (1%)

<1%, postmarketing, and/or case reports: Gastrointestinal perforation, major hemorrhage, pancreatitis, thrombocytopenia

Contraindications

There are no contraindications listed in the US manufacturer's labeling.

Canadian labeling: Hypersensitivity to nintedanib, peanut or soya or any component of the formulation; pregnancy

Warnings/Precautions

Concerns related to adverse effects:

• Bleeding: May increase the risk of bleeding. Use in patients with known risk of bleeding only if the benefit outweighs the risk.

• Cardiovascular effects: Arterial thromboembolic events, including MI, have been reported. Use caution in patients at high cardiovascular risk, including in patients with known coronary artery disease. Consider treatment interruption in patients who develop signs or symptoms of acute myocardial ischemia.

• Gastrointestinal effects: Diarrhea, nausea, and vomiting may occur. Diarrhea occurred in over 50% of nintedanib-treated patients, and was generally of mild to moderate intensity and occurred within the first 3 months of treatment. Treat with appropriate supportive care (eg, adequate hydration, antidiarrheals, antiemetics); dose reduction and/or treatment interruption may be required. If gastrointestinal effects do not resolve, discontinue treatment. In addition, nintedanib may increase the risk of gastrointestinal perforation; only use in patients at risk of perforation if the benefit outweighs the risk. Use caution in patients with recent abdominal surgery. The Canadian labeling recommends waiting at least 4 weeks following abdominal surgery before initiating therapy.

Discontinue if perforation develops.

• Hepatic effects: Elevations of ALT, AST, GGT, alkaline phosphatase, and bilirubin have occurred and were not associated with clinical signs or symptoms of liver injury; increases were reversible with dose modification/interruption. Obtain LFTs prior to treatment, monthly for 3 months, and every 3 months thereafter (or as clinically indicated).

Concurrent drug therapy issues:

• Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.

Special populations:

• Hepatic impairment: Nintedanib is primarily eliminated through biliary/fecal excretion; use is not recommended in patients with moderate or severe hepatic impairment. Dose reduction is recommended in patients with mild impairment; if adverse reactions occur, consider treatment interruption or discontinuation.

• Smokers: Smoking may decrease exposure to nintedanib; patients should stop smoking prior to treatment and avoid smoking during therapy.

Metabolism/Transport Effects

Substrate of CYP3A4 (minor), P-glycoprotein; **Note:** Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential

Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

Anticoagulants: May enhance the adverse/toxic effect of Nintedanib. Specifically, the risk for bleeding may be increased. *Risk C: Monitor therapy*

Combined Inducers of CYP3A4 and P-glycoprotein: May decrease the serum concentration of Nintedanib. *Risk X: Avoid combination*

Combined Inhibitors of CYP3A4 and P-glycoprotein: May increase the serum concentration of Nintedanib. *Risk C: Monitor therapy*

Lumacaftor: May decrease the serum concentration of P-glycoprotein/ABCB1 Substrates. Lumacaftor may increase the serum concentration of P-glycoprotein/ABCB1 Substrates. *Risk C: Monitor therapy*

P-glycoprotein/ABCB1 Inhibitors: May increase the serum concentration of P-glycoprotein/ABCB1 Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Pirfenidone: May decrease the serum concentration of Nintedanib. *Risk C: Monitor therapy*

Ranolazine: May increase the serum concentration of P-glycoprotein/ABCB1 Substrates. *Risk C: Monitor therapy*

Pregnancy Implications Based on the mechanism of action and adverse events observed in animal reproduction studies, nintedanib may be expected to cause fetal harm if used during pregnancy. Women of reproductive potential should use adequate contraception during therapy; pregnancy status should be obtained before treatment and pregnancy should be avoided; effective contraception should be used during therapy and for at least 3 months after the last dose. Based on animal studies, nintedanib may reduce female fertility.

Breast-Feeding Considerations It is not known if nintedanib is excreted in breast milk. Due to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended by the manufacturer.

Monitoring Parameters Obtain liver function tests prior to treatment, monthly for 3 months, and every 3 months thereafter (or as clinically indicated); obtain pregnancy test prior to treatment. Monitor for gastrointestinal events (eg, diarrhea, nausea, vomiting), arterial thromboembolic events, bleeding, and gastrointestinal perforation.

Mechanism of Action Inhibits multiple receptor tyrosine kinases (RTKs) and nonreceptor tyrosine kinases (nRTKs), including platelet-derived growth factor (PDGFR alpha and PDGFR beta); fibroblast growth factor receptor (FGFR1, FGFR2, FGFR3); vascular endothelial growth factor (VEGFR1, VEGFR2, and VEGFR3); and Fms-like tyrosine kinase-3 (FLT3). Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these receptors and blocks the intracellular signaling which is crucial for the proliferation, migration, and transformation of fibroblasts.

Pharmacodynamics/Kinetics

Absorption: Food increases exposure ~20% and delays absorption

Distribution: V_{ss}: 1050 L

Protein binding: ~98%

Metabolism: Hydrolytic cleavage by esterases to free acid moiety BIBF 1202; which is then glucuronidated by UGT 1A1, UGT 1A7, UGT 1A8, and UGT 1A10 to BIBF 1202 glucuronide; CYP 3A4 (minor).

Bioavailability: ~5%

Half-life elimination: 9.5 hours

Time to peak, plasma: 2 hours (4 hours with food)

Excretion: Feces (~93%); urine (<1%)

Pricing: US

Capsules (Ofev Oral)

100 mg (60): $10368.00

150 mg (60): $10368.00

Disclaimer: The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of

the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

International Brand Names Ofev (AT, CZ, DK, EE, ES, FR, GB, HK, HU, IS, JP, LT, LU, LV, MY, NO, PL, PT, SE, SG, SI, TH); Vargated (PT); Vargatef (AT, CZ, DE, DK, EE, ES, GB, HR, HU, IE, LT, LU, MT, NL, NO, PL, SE, SI, TH)

REFERENCES

1. *Ofev (nintedanib) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; February 2016.*
2. *Ofev (nintedanib) [product monograph]. Burlington, Ontario, Canada: Boehringer Ingelheim (Canada) Ltd; October 2015.*
3. *Richeldi L, du Bois RM, Raghu G, et al; INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2071-2082. doi: 10.1056/NEJMoa1402584. [PubMed 24836310]*
4. *US Department of Health and Human Services; Centers for Disease Control and Prevention; National Institute for Occupational Safety and Health. NIOSH list of antineoplastic and other hazardous drugs in healthcare settings 2016. http://www.cdc.gov/niosh/topics/antineoplastic/pdf/hazardous-drugs-list_2016-161.pdf. Updated September 2016. Accessed October 5, 2016.*

Topic 97640 Version 42.0