New Treatment Option for Idiopathic Pulmonary Fibrosis

Ofev® (nintedanib)

Boehringer Ingelheim Pharmaceuticals Inc.'s Ofev® (nintedanib) was approved by the FDA on October 15, 2014, for the treatment of idiopathic pulmonary fibrosis (IPF). Nintedanib—the first and only kinase inhibitor approved—was granted fast track, priority review, orphan product, and breakthrough designations by the agency.

Nintedanib is a small molecule that inhibits multiple receptor tyrosine kinases and nonreceptor tyrosine kinases. Research has shown that nintedanib blocks several growth factor receptors implicated in IPF—including the vascular endothelial growth factor receptor, fibroblast growth factor receptor, and platelet-derived growth factor receptor, according to a company news release announcing the drug's approval.

Nintedanib is associated with elevations in liver enzymes. Clinicians should conduct liver function tests prior to initiating treatment with nintedanib, monthly for 3 months, and every 3 months thereafter, and as clinically indicated. The recommended dosage of nintedanib is 150 mg twice daily administered approximately 12 hours apart, with food, and should be swallowed with liquid. The capsules should not be chewed or crushed because of a bitter taste. If a dose of nintedanib is missed, treatment should resume at the next scheduled time and at the recommended dose. The recommended maximum daily dose of 300 mg should not be exceeded.

In addition to symptomatic treatment, if applicable, the management of adverse reactions of nintedanib may require dose reduction or treatment interruption until the specific adverse reaction resolves to levels that allow continuation of therapy. Nintedanib may be resumed at the full dosage of 150 mg twice daily, or at the reduced dosage of 100 mg twice daily, which subsequently may be increased to the full dosage. If a patient does not tolerate 100 mg twice daily, discontinue treatment with nintedanib. Dose modifications or interruptions may be necessary for liver enzyme elevations. For aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 times to <5 times the upper limit of normal (ULN) without signs of severe liver damage, interrupt treatment or reduce nintedanib to 100 mg twice daily. Once liver enzymes have returned to baseline values, treatment with nintedanib may be reintroduced at a reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage (150 mg twice daily). Discontinue nintedanib for AST or ALT elevations >5 times ULN or >3 times ULN with signs or symptoms of severe liver damage.

The FDA approved nintedanib based on the results of the phase 2 TOMORROW [To Improve Pulmonary Fibrosis with BIBF 1120] and phase 3 INPULSIS-1 and INPULSIS-2 trials of 1231 patients with IPF. The trials were randomized, double-blind, placebo-controlled trials comparing nintedanib 150 mg twice daily to placebo for 52 weeks. All 3 trials demonstrated a consistent, statistically significant reduction in the annual rate of decline in forced vital capacity (FVC) with nintedanib versus placebo.

IPF is a rare and fatal lung disease in which the lungs become aggressively scarred over time. Most patients with IPF only live 2.5 to 3.5 years after diagnosis. Symptoms of IPF include shortness of breath, cough, rapid, shallow breathing, fatigue, aching muscles and joints, and clubbing. Current treatment options for IPF include medicines, oxygen therapy, pulmonary rehabilitation, and lung transplant, according to the National Heart, Lung, and Blood Institute.

PIVOTAL TRIALS

This *First Report Managed Care* Product Spotlight highlights the TOMORROW phase 2 trial and INPULSIS-1 and INPULSIS-2 phase 3 trials that assessed the efficacy and safety of nintedanib.

TOMORROW Trial

TOMORROW was a 12-month, randomized, double-blind, placebo-controlled, phase 2 trial that evaluated the efficacy and safety of 4 different doses of nintedanib compared with placebo in patients with IPF. Because nintedanib's approved dosage is 150 mg twice daily, *First Report Managed Care* provides the results from patients randomized to this treatment arm. Eligible patients, who were recruited from 92 sites in 25 countries, were ≥40 years of age with IPF that was consistent with criteria published by the American Thoracic Society and the European Respiratory Society and had received a diagnosis <5 years before screening. Patients were also required to have undergone high-resolution computed tomography (HRCT) of the chest <1 year before randomization with an FVC ≥50% of the predicted value and a carbon monoxide diffusing capacity (DLCO) 30% to 79% of the predicted value [*N Engl J Med*. 2011;365(12):1079-1087].

Of the 432 patients randomized to 1 of 4 doses of nintedanib or placebo, 32 received 150 mg nintedanib twice daily and 24 received placebo. The primary end point was the annual rate of decline in FVC. Secondary end points included acute exacerbations and quality of life (measured with the St. George's Respiratory Questionnaire [SGRQ]).

The results showed that annual rate of FVC in the nintedanib treatment arm declined by 0.06 L per year (95% confidence interval [CI], –0.14-–0.02) compared with 0.19 L per year in the placebo group (95% CI, –0.26-–0.12), a 68.4% reduction in the rate of loss with nintedanib 150 mg. This dose also resulted in a lower incidence of acute exacerbations compared with placebo (2.4 vs 15.7 per 100 patient-years, respectively; *P*=.02) and a small decrease in the SGRQ score (assessed on a scale of 0 to 100, with lower score indicating better quality of life) compared with an increase with placebo (–0.66 points vs 5.46 points, respectively; *P*=.007).

INPULSIS Trials

INPULSIS-1 and INPULSIS-2 were 2 replicate, randomized, double-blind,

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placebo-controlled, parallel group, phase 3 trials conducted at 205 sites in 24 countries that evaluated the efficacy and safety of 150 mg nintedanib twice daily in patients with IPF. Patients were eligible to participate in the 2 trials if they were ≥40 years of age and received a diagnosis of IPF within the previous 5 years. Additional eligibility criteria were an FVC ≥50% of the predicted value, a DLCO 30% to 79% of the predicted value, and HRCT of the chest performed within the previous 12 months. Concomitant therapy with up to 15 mg of prednisone per day, or the equivalent, was permitted if the dose had been stable for 8 or more weeks before screening [*N Engl J Med*. 2014;370(22):2071-2082].

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A total of 1066 patients were randomized 3:2 to nintedanib 150 mg twice daily or placebo. In INPULSIS-1, a total of 513 patients received at least 1 dose of the study medication (309 received nintedanib and 204 received placebo). For INPULSIS-2, a total of 548 patients received at least 1 dose of the study medication (329 received nintedanib and 219 received placebo). The primary end point was annual rate of decline in FVC. Key secondary end points were the time to first acute exacerbation and change from baseline in the total score on the SGRQ, both assessed over a 52-week period.

In both trials, the adjusted annual rate of change in FVC was significantly lower in the nintedanib group compared with the placebo group. In INPULSIS-1, the rate was –114.7 mL in the nintedanib group versus –239.9 mL per year in the placebo group, representing a difference of 125.3 mL per year (95% CI, 77.7-172.8; *P*<.001). In INPULSIS-2, the rate was –113.6 mL per year in the nintedanib group versus –207.3 mL per year in the placebo group, representing a difference of 93.7 mL per year (95% CI, 44.8-142.7; *P*<.001). The findings showed no significant difference between the nintedanib and placebo groups in INPULSIS-1 in the time to first acute exacerbation (hazard ratio [HR] with nintedanib, 1.15; 95% CI, 0.54-2.42; *P*=.67); in INPULSIS 2, there was a significant benefit with nintedanib versus placebo (HR, 0.38; 95% CI, 0.19-0.77; *P*=.005). In INPULSIS-1, there was no significant diffrence in the adjusted mean change in total SGRQ score from baseline to week 52 between the nintedanib and placebo groups (4.34 points vs 4.39 points, respectively; difference, –0.05; 95% CI, –2.50-2.40; *P*=.97); in INPULSIS-2, there was a significantly smaller increase in the total SGRQ score at week 52 (consistent with less deterioration in health-related quality of life) in the nintedanib group versus the placebo group (2.80 points vs 5.48 points, respectively; difference, –2.69; 95% CI, –4.95-–0.43; *P*=.02).

Safety Notes

The product's Prescribing Information notes nintedanib is not recommended in patients with moderate to severe liver problems. Clinicians should monitor ALT, AST, and bilirubin before and during treatment. Temporary dosage reductions or discontinuation may be required. Nintedanib is Pregnancy Category D. It can cause fetal harm when administered in pregnant women. If nintedanib is used during pregnancy, or if the patient becomes pregnant while taking nintedanib, the patient should be advised of the potential hazard to the fetus. Women of childbearing age should be advised to avoid becoming pregnant while receiving treatment with nintedanib and to use adequate contraception during treatment and at least 3 months after the last dose of nintedanib.

Arterial thromboembolic events have been reported in patients taking nintedanib. Clinicians should use caution when treating patients at higher cardiovascular risk including known coronary disease. Consider treatment interruption in patients who develop signs or symptoms of acute myocardial ischemia. In clinical trials, risks of bleeding have been reported with nintedanib. In patients with a known risk of bleeding, use nintedanib only if anticipated benefit outweighs the potential risk. Based on the mechanism of action, nintedanib may increase the risk of gastrointestinal (GI) perforation. Use nintedanib with caution when treating patients with recent abdominal surgery. Discontinue nintedanib in patients who develop GI perforation. Only use nintedanib in patients with known risk of GI perforation if the anticipated benefit outweighs the potential risk.

In clinical trials, the most commonly reported adverse reactions reported in ≥5% of nintedanib-treated patients and more commonly than in patients treated with placebo included diarrhea, nausea, abdominal pain, liver enzyme elevation, vomiting, decreased appetite, weight decrease, headache, and hypertension.

Nintedanib Facts

- Nintedanib—the first and only kinase inhibitor—was FDA approved on October 15, 2014, for the treatment of IPF.
- The FDA granted nintedanib fast track, priority review, orphan product, and breakthrough designations.
- The safety and efficacy of nintedanib was assessed in 3 clinical trials that enrolled 1231 patients.
- Nintedanib is marketed by Boehringer Ingelheim Pharmaceuticals, Inc.

Additional Resource

Prescribing Information for Ofev®: **http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing+Information/PIs/Ofev/ofev.pdf**