CADTH CDEC FINAL RECOMMENDATION

NINTEDANIB
(Ofev — Boehringer Ingelheim Canada Ltd.)
Indication: Idiopathic Pulmonary Fibrosis

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that nintedanib be listed for the treatment of idiopathic pulmonary fibrosis (IPF), if the following clinical criteria and conditions are met:

Clinical Criteria:
- Forced vital capacity (FVC) greater than or equal to 50% of predicted.
- Treatment with nintedanib should be discontinued if absolute FVC declines by ≥ 10% within any 12-month period while receiving therapy.

Conditions:
- Under the care of a specialist with experience in the diagnosis and management of IPF.
- Drug plan cost for nintedanib must not exceed the drug plan cost for pirfenidone.

Reasons for the Recommendation:
1. Two double-blind, randomized controlled trials (RCTs) (INPULSIS-1 [N = 515] and INPULSIS-2 [N = 551]) demonstrated that nintedanib 150 mg twice daily resulted in statistically significant improvements in FVC compared with placebo.
2. At the submitted price ($27.18 per 100 mg tablet and $54.36 per 150 mg tablet), the annual cost of treatment with nintedanib ($39,683 per year) is less than the cost of treatment with pirfenidone ($41,983 in the first year and $42,804 in subsequent years).

Of Note:
CDEC noted the following:
- Nintedanib should not be used in combination with pirfenidone.
- There is no evidence addressing the use of nintedanib in patients who have failed treatment with pirfenidone; therefore, CDEC was unable to make a recommendation addressing this patient population.
- All other causes of restrictive lung disease (e.g., collagen vascular disorders or hypersensitivity pneumonitis) should be excluded before initiating treatment.

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Background:
Nintedanib is an inhibitor of multiple tyrosine kinases, including fibroblast growth factor receptor 1-3, platelet-derived growth factor alpha and beta, and vascular endothelial growth factor receptor 1-3. Nintedanib is indicated for the treatment of IPF and is available as 100 mg and 150 mg oral capsules. The recommended dose is 150 mg twice daily, administered approximately 12 hours apart with food.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs and pivotal studies of nintedanib, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to patients with IPF.

Patient Input Information
Four patient groups provided their perspectives: The Lung Association of Saskatchewan, The Ontario Lung Association, The Canadian Pulmonary Fibrosis Foundation, and The British Columbia Lung Association and Lung Groups. Surveys conducted in 2015 and 2014 were used by two groups to collect perspectives of patients with IPF and caregivers, including a total of 28 respondents who had used nintedanib. Other associations drew on the expertise of staff with direct and regular contact with IPF patients.

The following is a summary of information provided by the four patient groups:

- IPF is a progressive and life-threatening condition that has no cure. Patients with IPF often experience breathlessness, fatigue, loss of energy, reduced physical activity, and a chronic cough. Additional symptoms can also include chest pain or tightness, rapid weight loss, leg swelling, wheezing, and difficulty fighting infections. In addition to the symptoms, patients and caregivers have to manage psychosocial issues associated with IPF. The stress of the diagnosis and prognosis greatly affects patients' quality of life and mental well-being, even among those with mild disease and minimal symptoms.
- There are few supportive treatments available to manage symptoms of IPF. Patients have reported using oxygen, N-acetylcysteine, prednisone, azathioprine, and pulmonary rehabilitation. These treatments were somewhat effective in some patients but the drug therapies were often accompanied by unwanted side effects (such as weight gain, mood swings, confusion, difficulty sleeping, and bowel issues) that added to their stress.
- Patients realize that nintedanib is not a cure for IPF and hope that it may offer them an alternate medication choice, with potentially increased tolerability, if current treatment is not well tolerated. Patients are also hopeful that nintedanib will slow the progression of IPF and, at least partially, address their most problematic symptoms. Patients are willing to cope with side effects as long as they are not worse than what they are currently experiencing, and are not irreversible.

Clinical Trials
The CDR systematic review included two 52-week, placebo-controlled, double-blind, phase 3 RCTs: INPULSIS-1 (N = 515) and INPULSIS-2 (N = 551). Patients were randomized (3:2) to receive nintedanib 150 mg twice daily or placebo. In the case of adverse events, the dosage of nintedanib could be reduced to 100 mg twice daily at the request of the investigator. Both trials enrolled patients who were at least 40 years of age with a diagnosis of IPF within the past five

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years according to the most recent American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association guidelines with baseline FVC ≥ 50% predicted and carbon monoxide diffusion capacity (DLCO) of 30% to 79% predicted.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Mortality — evaluated using survival analyses for time to death, time to death due to respiratory cause (adjudicated), and time to on-treatment death.
- Lung-transplantation or death — A patient was considered to qualify for a lung transplant if that patient had FVC < 45% predicted or DLCO < 30% predicted or oxygen saturation of peripheral blood (SpO_2) < 88% at rest. Transplantation was evaluated as composite outcomes using survival analyses for time to death or lung transplant and time to death or lung transplant or qualifying for lung transplant, all over 52 weeks.
- FVC — volume of air that can be forcibly exhaled from the lungs after taking in the deepest breath possible. FVC was evaluated using the following measures:
  - Annual rate of decline in FVC
  - Absolute change from baseline in FVC
  - Absolute change from baseline in per cent predicted FVC
  - Proportion of patients with an absolute decline in per cent predicted FVC of no greater than 5% or 10% and with an FVC evaluation at 52 weeks.
- St. George's Respiratory Questionnaire (SGRQ) — a self-administered 50-item instrument used to assess impaired health and perceived well-being in respiratory disease. The SGRQ is divided into three dimensions: symptoms, activity, and impacts. Total SGRQ scores range from 0 to 100, with higher values indicating lower health-related quality of life. A minimal clinically important difference in the SGRQ total score in IPF has been reported to be 6 to 13. The SGRQ was evaluated using the following measures:
  - Change from baseline in domain scores and total score
  - Proportion of SGRQ responders (defined as absolute change from baseline at 52 weeks in SGRQ total score ≤ −4 points)
  - Change from baseline in an IPF-specific version of the SGRQ (SGRQ-I) total score.

The primary efficacy end point in both INPULSIS trials was the adjusted rate of decline in FVC over 52 weeks. The two key secondary end points were the change from baseline to 52 weeks in the SGRQ total score and the time to first investigator-reported acute IPF exacerbation.

Efficacy

- There were no statistically significant differences between nintedanib and placebo for time to death, time to death due to respiratory cause, time to on-treatment death, time to death or lung transplant, and time to death or lung transplant or qualifying for lung transplant. The hazard ratios from the pooled analyses of INPULSIS-1 and INPULSIS-2 were:
  - Time to death: 0.70 (95% confidence interval [CI], 0.43 to 1.12); *P* = 0.1399
  - Time to death due to respiratory cause: 0.74 (95% CI, 0.41 to 1.34); *P* = 0.3435
  - Time to on-treatment death: 0.68 (95% CI, 0.39 to 1.19); *P* = 0.1599
  - Time to death or lung transplant: 0.70 (95% CI, 0.44 to 1.10); *P* = 0.1185
  - Time to death or lung transplant or qualifying for lung transplant: 0.80 (95% CI, 0.60 to 1.06); *P* = 0.1233.

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- The adjusted rate of decline in FVC over 52 weeks was statistically significantly lower in the nintedanib groups compared with the placebo groups in both trials. The adjusted rate differences were:
  - INPULSIS-1: 125.26 mL per year (95% CI, 77.68 to 172.84); $P < 0.0001$
  - INPULSIS-2: 93.73 mL per year (95% CI, 44.78 to 142.68); $P = 0.0002$
  - Pooled: 109.94 mL per year (95% CI, 75.85 to 144.03); $P < 0.0001$.
- The absolute change from baseline in FVC and in FVC per cent predicted over 52 weeks was statistically significantly lower in the nintedanib-treated groups compared with the placebo-treated groups in both INPULSIS-1 and INPULSIS-2. The adjusted mean differences in FVC and per cent predicted FVC (respectively) were:
  - INPULSIS-1: 109.93 mL (95% CI, 71.27 to 148.59) and 3.22 (95% CI, 2.11 to 4.33)
  - INPULSIS-2: 109.77 mL (95% CI, 70.92 to 148.62) and 3.06 (95% CI, 1.87 to 4.25).
- In both INPULSIS trials, a statistically significantly greater proportion of nintedanib-treated patients (52.75% and 53.19%) had a decline in FVC of ≤ 5% compared with placebo-treated patients (38.24% and 39.27%). A statistically significant difference was also observed for the proportion of patients with a decline in FVC of ≤ 10% in INPULSIS-1; however, there was no significant difference in INPULSIS-2. The odds ratios for achieving a decline of ≤ 5% or ≤ 10% in FVC, respectively, were:
  - INPULSIS-1: 1.85 (95% CI, 1.28 to 2.66) and 1.914 (95% CI, 1.32 to 2.79)
  - INPULSIS-2: 1.79 (95% CI, 1.26 to 2.55) and 1.286 (95% CI, 0.89 to 1.86).
- In INPULSIS-2, there was a statistically significant difference between nintedanib and placebo in the total SGRQ score; however, there was no statistically significant difference in INPULSIS-1 and in the pooled analysis. The differences in adjusted mean change from baseline to week 52 were:
  - INPULSIS-1: −0.05 (95% CI, −2.50 to 2.40); $P = 0.9657$
  - INPULSIS-2: −2.69 (95% CI, −4.95 to −0.43); $P = 0.0197$
  - Pooled: −1.43 (95% CI, −3.09 to 0.23); $P = 0.2081$.
- In INPULSIS-2, there was a statistically significant decrease in the time to the first acute exacerbation (investigator-reported) in the nintedanib group compared with the placebo group; however, there was no statistically significant difference in INPULSIS-1 or in the pooled analysis:
  - INPULSIS-1: 1.15 (95% CI, 0.54 to 2.42); $P = 0.6728$
  - INPULSIS-2: 0.38 (95% CI, 0.19 to 0.77); $P = 0.005$
  - Pooled: 0.64 (95% CI, 0.39 to 1.05); $P = 0.0823$.
- The proportion of patients who received a lung transplant was low across all treatment groups in the INPULSIS trials (i.e., 0% to 1.3% with nintedanib and 0.5% to 0.9% with placebo).
- Patients identified symptoms and the severity of symptoms as important outcomes for IPF. There were no statistically significant differences observed between treatment groups in any of the patient-report outcomes used to measure symptoms in either INPULSIS-1 or INPULSIS-2.

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Harms (Safety and Tolerability)

- Across both treatment groups, the most frequent serious adverse event in both the nintedanib and placebo groups was IPF. The proportions of patients who experienced at least one serious adverse event were:
  - INPULSIS-1: 31.1% with nintedanib and 27.0% with placebo
  - INPULSIS-2: 29.8% with nintedanib and 32.9% with placebo.
- The most frequently reported adverse event in the nintedanib groups was diarrhea (61.5% and 63.2%) when compared with the placebo groups (18.6% and 18.3%). Similarly, other gastrointestinal adverse events (e.g., nausea, decreased appetite, vomiting, and weight loss) occurred more frequently with nintedanib. The proportions of patients who experienced at least one adverse event were:
  - INPULSIS-1: 96.4% with nintedanib and 88.7% with placebo
  - INPULSIS-2: 94.5% with nintedanib and 90.4% with placebo.
- The proportions of patients who withdrew as a result of adverse events were:
  - INPULSIS-1: 21.0% with nintedanib and 10.8% with placebo
  - INPULSIS-2: 17.6% with nintedanib and 15.1% with placebo.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing nintedanib plus best supportive care (BSC) versus BSC alone. BSC included patient monitoring, oxygen, and concomitant therapies (e.g., proton pump inhibitors, bronchodilators, and antitussive treatments) and was assumed to be represented by the control groups of the INPULSIS trials. Comparisons with pirfenidone and N-acetylcysteine in adult patients with IPF were also performed over a lifetime horizon (approximately 30 years) from a public-payer perspective. The risks of death, exacerbations, and loss of lung function for patients receiving BSC were obtained from the TOMORROW and INPULSIS trials, and mathematical models were used to estimate long-term efficacy. A manufacturer-conducted network meta-analysis (NMA) was used to estimate relative efficacy and harms among treatments. Quality of life was assigned for each per cent predicted FVC category by compiling data from the INPULSIS trials.

CDR identified a number of limitations with the manufacturer's pharmacoeconomic submission:

- One-year clinical trial data from the BSC groups were modelled over a lifetime horizon (~30 years). While best fit was assessed during this one-year period, and face validity was assessed by comparing modelled survival with observational data, alternate parametric models led to significant differences in survival.
- The reference case model used the point estimate of survival, which was not statistically significant in either the clinical trials or the NMA.
- The manufacturer assumed that differences in outcomes that were observed in short-term RCTs (e.g., 12 months) can be extrapolated to a lifetime horizon.

In the base case, the manufacturer reported that nintedanib compared with BSC results in an incremental cost-utility ratio (ICUR) of $248,186 per quality-adjusted life-year (QALY). When compared with pirfenidone, nintedanib dominates pirfenidone due to a lower drug acquisition cost (i.e., $9 less per day). The ICURs in the CDR reference case increase dramatically when direct evidence is used to inform the model, and when nintedanib is assumed to result in similar survival compared with BSC ($315,000 to $1,300,000 per QALY). There is limited comparative

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clinical information for nintedanib and pirfenidone and there is significant uncertainty in the model, particularly with the long-term risk of death.

At the recommended daily dose of nintedanib (150 mg twice daily), nintedanib ($109 per day) is less costly than pirfenidone ($117 per day); therefore, when comparing only drug costs, treatment with nintedanib results in modest cost savings compared with pirfenidone.

Other Discussion Points:

CDEC noted the following:

- Nintedanib and pirfenidone have different mechanisms of action; however, there is no evidence evaluating the efficacy and safety of their combined usage. There is potential for these two products to be used in combination, which could be associated with significant costs for the CDR-participating drug plans.
- Two indirect comparisons suggested similar efficacy between nintedanib and pirfenidone; however, due to heterogeneity across the included RCTs, CDEC concluded that there remains uncertainty regarding the comparative safety and efficacy for these two treatments.
- The two INPULSIS trials did not exclude people with normal lung function, while the ASCEND trial comparing pirfenidone against placebo imposed an upper limit on FVC. This resulted in a clinically meaningful difference in baseline per cent predicted FVC between the INPULSIS and ASCEND trials and suggested that patients in ASCEND may have had more advanced disease. This difference in baseline disease severity may have influenced the number of mortality events in the trials and impacted the ability to observe a mortality benefit with nintedanib.
- The twice-daily dosing schedule for nintedanib is more convenient than the dosing schedule for pirfenidone (i.e., three capsules taken three times daily).
- CDEC noted that patients who are intolerant to pirfenidone could be considered for treatment with nintedanib.

Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- There are no studies directly comparing nintedanib against pirfenidone for the treatment of patients with IPF.
- There is no evidence addressing the use of nintedanib in patients who have failed treatment with pirfenidone.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

September 16, 2015 Meeting

Regrets:

None

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Conflicts of Interest:

None

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