CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

NINTEDANIB (OFEV — BOEHRINGER INGELHEIM CANADA INC.)
Indication: Chronic fibrosing interstitial lung diseases

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that nintedanib be reimbursed for the treatment of chronic fibrosing interstitial lung diseases with a progressive phenotype only if the following conditions are met.

Conditions for Reimbursement
Initiation criteria
1. The patient has a diagnosis of chronic fibrosing interstitial lung disease with a progressive phenotype confirmed by a specialist in interstitial lung diseases.
2. The patient has a forced vital capacity greater than or equal to 45% of predicted.

Renewal criteria
1. The patient must not experience a more severe progression of disease, defined as an absolute decline in percent predicted forced vital capacity of 10% or greater over the preceding year of treatment with nintedanib.
2. The patient's clinical status should be evaluated every 12 months.

Prescribing conditions
1. The patient's condition has been assessed by a specialist with experience in the diagnosis and management of interstitial lung diseases.
2. Concurrent treatment of nintedanib with pirfenidone should not be reimbursed.

Pricing conditions
A reduction in price.

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Indication: Chronic fibrosing interstitial lung diseases

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that nintedanib be reimbursed for the treatment of chronic fibrosing interstitial lung diseases with a progressive phenotype only if the following conditions are met.

Conditions for Reimbursement

Initiation criteria

1. The patient has a diagnosis of chronic fibrosing interstitial lung disease with a progressive phenotype confirmed by a specialist in interstitial lung diseases.
2. The patient has a forced vital capacity (FVC) greater than or equal to 45% of predicted.

Renewal criteria

1. The patient must not experience a more severe progression of disease, defined as an absolute decline in percent predicted FVC of 10% or more during the preceding year of treatment with nintedanib.
2. The patient's clinical status should be evaluated every 12 months.

Prescribing conditions

1. The patient's condition has been assessed by a specialist with experience in the diagnosis and management of interstitial lung diseases.
2. Concurrent treatment of nintedanib with pirfenidone should not be reimbursed.

Pricing conditions

1. A reduction in price.

Reasons for the Recommendation

1. In one double-blind, randomized controlled trial (RCT) (INBUILD, N = 663) treatment with nintedanib was associated with a slower annual rate of decline in FVC, the primary outcome in the study, compared with placebo in patients with chronic fibrosing interstitial lung disease with a progressive phenotype. The adjusted mean difference between groups in FVC at 52 weeks was 107 mL per year (95% confidence interval [CI], 65 to 149 mL per year). As well, fewer patients treated with nintedanib experienced an absolute decline in percent predicted FVC values of 10% or greater (28% versus 37% for placebo; odds ratio of 0.68; 95% CI, 0.49 to 0.95).
2. Based on a CADTH reanalysis of the sponsor-submitted economic model, the incremental cost-effectiveness ratio (ICER) for nintedanib with best supportive care (BSC) compared with BSC alone is $154,688 per quality-adjusted life-year (QALY) gained. A price reduction of more than 77% for nintedanib would be required to achieve an ICER of $50,000 per QALY. This estimate is associated with significant uncertainty associated with the clinical inputs (including extrapolated survival benefit and the regression model used to predict decreases in percent predicted FVC over time). In an analysis that does not include a survival benefit, CADTH's estimate of the ICER is $317,832 per QALY.

Implementation Considerations

- Clinical experts indicated that chronic fibrosing interstitial lung diseases with a progressive phenotype is frequently difficult to distinguish from interstitial pulmonary fibrosis. Although the INBUILD trial required quantification of the degree of fibrosis on high resolution computed tomography, the clinical experts indicated that this is not a routine measurement in clinical practice and would not be feasible to implement as a nintedanib initiation criterion. CDEC concluded that limiting prescribing to specialists with experience in the management of interstitial lung diseases would be appropriate for identifying patients in whom treatment with nintedanib should be reimbursed.

- CDEC noted that patient access to a specialist with experience in the diagnosis and management of interstitial lung diseases may be limited across Canada. In such circumstances, consultation between the treating physician and a specialist in interstitial lung diseases would be considered adequate.

Discussion Points

- Patient group input to CADTH identified an unmet need in the treatment of chronic fibrosing interstitial lung diseases with a progressive phenotype that, CDEC concluded, could potentially be met by nintedanib.
- Although decreases in percent predicted FVC are correlated with mortality in patients with interstitial lung diseases, it is unclear whether the mean difference of 107 mL between groups in the annual rate of decline in FVC that was observed in INBUILD is clinically meaningful. CDEC noted that the effect on percent predicted FVC was similar to that observed in anti-fibrotic therapy of patients with idiopathic pulmonary fibrosis.
- There was no statistically significant decrease in mortality between nintedanib and placebo (hazard rate [HR] 0.94; 95% CI, 0.47 to 1.86) or in the combined end point of acute interstitial lung disease exacerbation or death (HR 0.80, 95% CI, 0.48 to 1.34) in INBUILD, although few deaths occurred during the 52-week study (5% in each study group). Mortality was extrapolated in the economic model using survival analyses. The difference in mortality is a key driver of the results in the sponsor's economic model. In the CADTH base case reanalysis, the majority (greater than 99%) of the incremental QALYs estimated for nintedanib plus BSC occurred during the extrapolated period and this was attributed to the modelled survival benefit for nintedanib. In a scenario analysis where no survival benefit for nintedanib was assumed, the ICER for nintedanib plus BSC versus BSC was found to increase to $317,832 per QALY gained.
- Secondary end point analyses in INBUILD suggested benefits in dyspnea and cough with nintedanib versus placebo, but no statistically significant differences in health-related quality of life were observed.
- Time to first non-elective hospitalization or death over 52 weeks was an exploratory outcome in INBUILD and no difference was demonstrated between nintedanib and placebo with this outcome.
- Chronic fibrosing interstitial lung disease with a progressive phenotype is a heterogenous classification consisting of a number of diseases. The available evidence does not identify a subset of patients who are more likely to benefit from treatment with nintedanib.
- Gastrointestinal effects, particularly diarrhea, were common in the nintedanib group (67% versus 24% with placebo) and led to a higher percentage of patients who discontinued treatment (7% with nintedanib versus less than 1% with placebo). The frequent occurrence of diarrhea may also have led to unblinding of some patients in INBUILD. A higher percentage of patients treated with nintedanib also experienced elevated liver enzymes, increased bilirubin, and serious drug-induced liver injury.

Background

Nintedanib has a Health Canada indication for treatment of other chronic fibrosing interstitial lung diseases with a progressive phenotype (also known as progressive fibrosing interstitial lung disease). Nintedanib is a multikinase inhibitor. It is available as capsules in strengths of 100 mg and 150 mg. The Health Canada–approved dosage is 150 mg every 12 hours. Dose reduction to 100 mg every 12 hours is recommended to manage adverse effects from nintedanib.

Submission History

Nintedanib was previously reviewed for the treatment of idiopathic pulmonary fibrosis and received a recommendation of list with criteria (see CDEC Final Recommendation, October 15, 2015).

Summary of Evidence Considered by CDEC

CDEC considered the following information prepared by CADTH: a systematic review of double-blind randomized controlled trials of nintedanib and a critique of the sponsor's pharmacoeconomic evaluation. CDEC also considered input from clinical experts with experience in treating patients with interstitial lung disease, and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

Four groups (British Columbia Lung Association, Canadian Pulmonary Fibrosis Foundation, Scleroderma Canada, and the Lung Health Foundation) provided input for this submission. Patient perspectives were obtained from surveys, interviews, focus groups, and patient experience. The following is a summary of key input from the perspective of the patient groups:

- Patients describe progressive fibrosing interstitial lung disease as a debilitating and fatal disease characterized by a progressive burden of symptoms including shortness of breath, chronic cough, fatigue, weight loss, and appetite loss. Patients cite breathing difficulties as the most debilitating, which often leaves them unable to carry out activities of daily living and requiring assistance from caregivers. Patients' physical deterioration and the resulting limits on activity also cause a significant impact on emotional and mental health.
- Multiple drugs are used to manage their condition; however, none meet the needs of patients. Notably, patients seek a drug that halts or delays progression of their disease, as none of the currently available drugs do this.
- Patients look forward to a drug that can control symptoms (fatigue, shortness of breath, cough), and most importantly, a drug that can either slow or halt disease progression.

Clinical Trials

The systematic review included one double-blind, randomized, placebo-controlled trial of patients with progressive fibrosing interstitial lung disease. INBUILD was a 52-week study that compared nintedanib 150 mg twice daily to matched placebo in 663 patients. There were 24% of patients in the nintedanib group and 15% of patients in the placebo group who discontinued study medication and 5% of nintedanib patients and 6% of placebo patients who did not complete the 52-week observation time.

Limitations of the included trial were the large number of patients who discontinued treatment in the nintedanib group (20%) compared with the placebo group (10%) by week 52. Additionally, although the intention was to continue to perform assessments on all patients, this was not accomplished. None of the outcomes outside of the primary outcome were adjusted for multiple statistical comparisons. The 52-week study duration was not long enough to assess the impact of nintedanib on mortality, hospitalizations, and health-related quality of life, key outcome for patients.

Outcomes

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

- Mortality
- Change in pulmonary function was assessed using FVC, following American Thoracic Society/European Thoracic Society 2005 guidelines. The annual rate of decline in FVC over 52 weeks was the primary outcome of INBUILD. Progression was defined as a 10% or greater decline in FVC.
- Health-related quality of life was assessed using King's Brief Interstitial Lung Disease questionnaire (K-BILD), a 15-item questionnaire that assesses three domains: breathlessness and activities, psychological, and chest symptoms. Each domain has its own score and there is also a total score, with a range from 0 to 100, with higher scores indicating better health status. No minimally important difference has been established in progressive fibrosing interstitial lung disease.
- Symptoms were assessed using the Living with Pulmonary Fibrosis (L-PF) questionnaire, which consists of 44 items with two modules, symptoms (23 items) and impact (21 items). The symptoms module contains three domains (dyspnea, cough, and fatigue) and the impact module has a single score. These modules are combined to give a total score, ranging from 0 to 100, with higher scores indicating greater impairment. There is no established minimally important difference in progressive fibrosing interstitial lung disease.
- Health care resource utilization (e.g., hospitalizations)
- Acute exacerbations were defined as previous or concurrent diagnosis of interstitial lung disease, acute worsening or new dyspnea within the past month, computed tomography with new bilateral ground-glass cages superimposed, and clinical worsening not explained by cardiac causes.
- Adverse events

Efficacy

The annual rate of decline in FVC over 52 weeks was the primary outcome of INBUILD. FVC was reduced from baseline to 52 weeks in both the nintedanib and placebo groups (adjusted mean difference between nintedanib and placebo of 106.96 mL [95% CI, 65.42, 148.50], P < 0.0001). Sensitivity analyses, including tipping point analyses, were consistent with that of the primary analysis. FVC declined in both groups, but the decline was slower with nintedanib than with placebo.

Over the 52 weeks, 5% of patients died in each of the nintedanib and placebo groups, and 3% of patients in the nintedanib group and 4% of patients in the placebo group died due to a respiratory cause. The lack of difference in mortality despite the slowed decline in pulmonary function may reflect the small number of events accrued over a relatively short 52-week treatment period.

K-BILD scores were similar between groups (adjusted mean difference between groups of 1.34 [95% CI, –0.31, 2.98], P = 0.1115). Symptoms like dyspnea worsened in both groups, but less with nintedanib than with placebo, while cough improved with nintedanib and worsened with placebo.

The percentage of patients with an event of first non-elective hospitalization or death over 52 weeks was 26% in the nintedanib and 28% in the placebo group. There were 8% of nintedanib-treated patients and 10% of those in the placebo group who had an event of acute interstitial lung disease exacerbation or death over 52 weeks. Over the 52 weeks, 26% of patients in the nintedanib group and 38% of patients in the placebo group either progressed (defined as a 10% or greater absolute decline in percent predicted FVC) or died.

Harms (Safety)

There were 96% of nintedanib-treated and 89% of placebo-treated patients with at least one adverse event in the study. The most common adverse event was diarrhea (67% nintedanib and 24% placebo), followed by nausea (29% nintedanib and 9% placebo), vomiting (18% nintedanib and 5% placebo), abdominal pain (10% nintedanib and 2% placebo) and abdominal pain upper (9% nintedanib and 2% placebo).

Serious adverse events occurred in 32% of nintedanib and 33% of placebo patients across the 52 weeks. Pneumonia was the most common serious adverse event in the nintedanib group, occurring in 4% of nintedanib and 3% of placebo patients.

There were 20% of nintedanib-treated and 10% of placebo-treated patients who discontinued treatment due to an adverse event. The most common adverse event leading to treatment discontinuation in either group was diarrhea in 7% of nintedanib patients versus less than 1% of the placebo group.

Liver injury was a notable harm. With respect to liver enzymes, increased alanine aminotransferase occurred in 13% of nintedanib patients and 4% placebo, increased aspartate aminotransferase in 11% of nintedanib and 4% placebo, increased gamma glutamyl transferase in 6% nintedanib and 2% placebo, and abnormal hepatic function in 6% nintedanib and 1% placebo. Drug-induced liver injury was categorized as a serious adverse event in 2% of patients in the nintedanib group and in no patients in the placebo group. Bleeding was another harm of interest, and this occurred in 11% of nintedanib and 13% placebo. Thrombotic events such as arterial thromboembolism occurred in 1% of patients in each group, venous thromboembolism in 1% of nintedanib patients and 2% placebo, pulmonary embolism in less than 1% of nintedanib patients and 1% placebo, deep vein thrombosis in 1% of nintedanib and less than 1% placebo. Myocardial infarction occurred in 1% of patients in each group and stroke occurred in less than 1% of nintedanib patients and 1% of placebo patients.

Indirect Treatment Comparisons

No indirect treatment comparisons were submitted by the sponsor and none were found in the literature.

Cost and Cost-Effectiveness

At the sponsor's submitted prices of $28.42 per 100 mg capsule and $56.83 per 150 mg capsule, the annual cost of nintedanib is $41,517 per patient based on the recommended dosage for chronic fibrosing interstitial lung disease with a progressive phenotype.

The sponsor submitted a cost-utility analysis comparing nintedanib plus BSC versus BSC alone for the treatment of patients with chronic fibrosing interstitial lung disease with a progressive phenotype. BSC was assumed to consist of immunosuppressant therapy. The analysis was conducted from the perspective of the Canadian publicly funded health care system over a lifetime time horizon (25 years) with the cycle length of one month. In the nintedanib plus BSC, [redacted]% of patients were assumed to be treated with the 150 mg strength and [redacted]% with the 100 mg strength. The submitted microsimulation model generated patients with unique health profiles using the distribution of baseline characteristics observed within the INBUILD trial. Both the patient's characteristics and their history of prior events could influence their percent predicted FVC level. percent predicted FVC was assumed to worsen progressively (i.e., only decrease in value was possible) and was re-calculated at the end of each model cycle. Once an absolute decline of greater than or equal to 10% in percent predicted FVC compared with baseline occurred, the patient was assumed to have progressed, resulting in a permanent utility decrement. When a decrease to less than or equal to 40% in percent predicted FVC occurred, the patient was assumed to have died. In addition, for patients on nintedanib plus BSC, the model re-assessed at the end of each cycle whether they would remain on nintedanib plus BSC or discontinue nintedanib and exclusively receive BSC. All patients who remained alive could experience an acute exacerbation that was dependent on whether they received nintedanib plus BSC or BSC, resulting in different reductions in percent predicted FVC (nintedanib plus BSC = –4.03%; BSC = –6.95%). Patients could transition at any time to the death health state, with the risk of death being treatment-dependent.

CADTH identified the following key limitations with the sponsor's submitted economic analysis:

- Overall survival was informed by fitting parametric extrapolations of data from INBUILD which predicted a substantial survival benefit for nintedanib plus BSC. However, this trial was not powered to demonstrate a statistically significant reduction in mortality over 52 weeks.
- Clinical experts consulted by CADTH noted that that the selected distribution for the time to treatment discontinuation underestimated the likelihood of remaining on nintedanib.
- Disease progression was modelled according to reduction in percent predicted FVC with different covariates selected within nintedanib plus BSC and BSC alone prediction models. No justification was provided for why covariates within the model would differ and the sponsor's selected prediction models likely overestimated total expected QALYs for nintedanib plus BSC.
- Validity of percent predicted FVC-based cut-offs to define disease progression (i.e., 10% decline in percent predicted FVC from baseline) and immediate death (absolute percent predicted FVC ≤ 40%) remains unclear.

CADTH undertook reanalyses to address limitations relating to the extrapolations of overall survival by selecting a gamma function, which estimated more clinically plausible net survival benefits; modified the extrapolation of time to the discontinuation of nintedanib to a lognormal function to reflect what clinical experts considered to be more clinically plausible; and, selected an alternate prediction model for change in percent predicted FVC for BSC based on one that applied the same covariates as those used for the nintedanib plus BSC prediction model. The ICER for nintedanib plus BSC compared with BSC alone was $154,688 per QALY gained. A reduction of 77% in the price of nintedanib was required to improve its cost-effectiveness relative to BSC and generate an ICER less than $50,000 per QALY.

As CADTH was unable to validate the survival benefit modelled and the regression model used to predict decreases in percent predicted FVC over time, the results of the CADTH reanalyses remain uncertain. In a CADTH scenario analysis where no survival benefit for nintedanib was assumed, the ICER for nintedanib plus BSC versus BSC increased to $317,832 per QALY gained. Given a lack of studies reporting the measurement properties of percent predicted FVC in patients with chronic fibrosing interstitial lung disease with a progressive phenotype, CADTH was unable to incorporate an evidence-based percent predicted FVC cut-off to define disease progression.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Dr. Kerry Mansell, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

January 20, 2021 Meeting

Regrets

None

Conflicts of Interest

None