

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205832Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: September 11, 2014

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Drug Name(s): Nintedanib (Ofev)

Therapeutic Class: tyrosine kinase inhibitor

Dosage and Route: 150 mg twice daily by mouth

Application Type/Number: NDA 205832

Applicant/Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc

OSE RCM #: 2014-952, 980

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for the new molecular entity, nintedanib. The Agency received NDA 205832 from Boehringer Ingelheim Pharmaceuticals, Inc (BIPI) for nintedanib on May 2, 2014. The proposed indication is for the treatment of idiopathic pulmonary fibrosis (IPF) [REDACTED] (b) (4). BIPI did not propose a REMS for nintedanib.

Nintedanib has been granted orphan, fast track, and breakthrough designation and is under priority review. There are no approved treatment options for IPF at this time;¹ therefore, there is a clear medical need for effective treatment options for IPF, a disease that is fatal within a relatively short time frame. Based on the available safety information, addressing the risks identified with nintedanib through labeling is consistent with the risk management approach for other tyrosine kinase inhibitors (TKIs). Based on the currently available data, a REMS is not necessary to ensure the benefits outweigh the risks for nintedanib.

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for the new molecular entity, nintedanib. The Agency received NDA 205832 from Boehringer Ingelheim Pharmaceuticals, Inc (BIPI) for nintedanib on May 2, 2014. BIPI did not propose a REMS or submit a risk management plan; rather, a two-page “Sponsor rationale on REMS” was provided.

Nintedanib has been granted orphan, fast track, and breakthrough designation and is under priority review. Nintedanib is not approved in any country.

1.1 PRODUCT BACKGROUND

Nintedanib is a small molecule receptor tyrosine kinase inhibitor for platelet-derived growth factor receptor (PDGFR) α and β , fibroblast growth factor receptor (FGFR) 1-3, and vascular endothelial growth factor receptor (VEGFR) 1-3. In addition, nintedanib inhibits FLT-3, Lck, Lyn, and Src kinases.

The proposed indication is “for the treatment of idiopathic pulmonary fibrosis (IPF) [REDACTED] (b) (4)” Among those receptors, FGFR, PDGFR, and VEGFR have been implicated in IPF pathogenesis. Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these receptors and blocks the intracellular signaling which is necessary for the proliferation, migration, and transformation of fibroblasts. These pathways have been proposed as essential mechanisms in IPF pathology.

Nintedanib is an oral capsule with a proposed recommended dose of 150 mg twice daily.

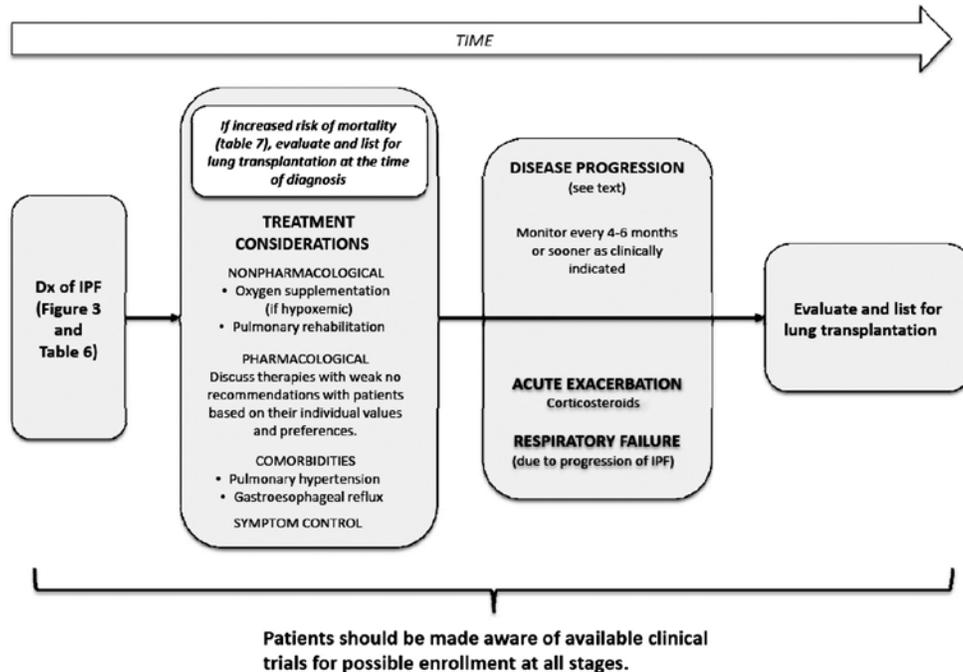
¹ Pirfenidone is currently under review for FDA approval. The anticipated action date is October 1, 2014.

1.2 DISEASE BACKGROUND

According to the Official ATS/ERS/JRS/ALAT² Statement on the “evidence-based guidelines for diagnosis and management” of on IPF published in 2011³, IPF is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown causes, occurring primarily in older adults (50-70 years old) and limited to the lungs. It is characterized by progressive worsening of dyspnea and lung function resulting in death. Definitive survival and/or mortality data are not available but several articles cite a similar range of median survival anywhere from 2 to 5 years from the time of diagnosis. In one study published in 2007 using the most rigorous definition of IPF, the mortality rate in the United States in 2003 was 61.2 deaths per 1,000,000 in men and 54.5 per 1,000,000 in women; making the mortality burden attributable to IPF higher than some cancers (e.g., acute myeloid leukemia, multiple myeloma and bladder cancer).⁴

THE ATS/ERS/JRS/ALAT committee “did not find sufficient evidence to support the use of any specific pharmacologic therapy for patients with IPF.” Pharmacological treatment options evaluated in the guideline included: corticosteroid monotherapy, colchicine, cyclosporine, combined corticosteroid and immune modulator therapy, interferon γ 1b, bosentan, etanercept, combined acetylcysteine+azathioprine+prednisone, acetylcysteine monotherapy, anticoagulants, pirfenidone, sildenafil, and imatinib.

The clinical management of patients with IPF is depicted in the following figure:³



² America Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Association (ALAT).

³ Raghu G, et al. Am J Respir Crit Care Med. 2011; 183:788-824.

⁴ Olson AL, et al. Am J Respir Crit Care Med, 2007;176:277-284.

As such, there are no FDA-approved treatment options for IPF.

2 REGULATORY HISTORY

- June 29, 2011: Orphan designation granted
- May 31, 2013: Fast track designation granted
- October 31, 2013: pre-NDA meeting
 - BIPI stated they did not intend to submit a REMS with the application and posed the following question: “Does the FDA have any comment or guidance to offer BI to assure that all discussions relating to a REMS be covered during the review period?” In the preliminary meeting comments, Agency stated “We acknowledge your proposal not to submit a REMS. If we determine a REMS to be necessary, we will work with you during the review period.”
- May 2, 2014: BIPI submitted the NDA for nintedanib.
 - The submission did not include a REMS; submission included rationale for why a REMS was not necessary for nintedanib.
- July 15, 2014: Breakthrough designation granted
- August 26, 2014: Midcycle meeting communication
 - The Agency’s determination on need for a REMS was not mentioned in this communication.

3 MATERIALS REVIEWED

- Paterniti MO. NDA 205832 clinical review. Signed in DARRTS September 3, 2014 by Paterniti MO and Karimi Shah BA.
- FDA. Draft labeling for nintedanib, dated September 2, 2014.
- Paterniti MO. August 6, 2014. Midcycle meeting slides.
- Boehringer Ingelheim. May 2, 2014 NDA 205832.
 - Proposed nintedanib labeling (1.14.1.3)
 - Sponsor rationale on REMS (1.16)
 - Clinical overview (2.5)
 - Summary of clinical safety (2.7.4.)

4 RESULTS OF REVIEW

4.1 OVERVIEW OF CLINICAL PROGRAM

The phase 3 development program for nintedanib consisted of two trials, 1199.32 and 1199.34. Both trials were randomized, double-blind, placebo-controlled trials comparing nintedanib 150 mg twice daily to placebo for 52 weeks. The primary outcome measure was annual rate of decline in forced vital capacity (FVC). Secondary endpoints included time to first acute IPF exacerbation and change from baseline in Saint George's Respiratory Questionnaire (SGRQ) total score at 52 weeks.

The medical officer also evaluated Study 1199.30 as a “pivotal study” which was a phase 2 dose-ranging study of a similar design to the phase 3 studies.

According to the medical officer’s clinical review, in total there were 723 patients randomized to nintedanib and 508 to placebo.

The majority of patients were male (~79%) and the mean age was 67 years (range: 42 to 89).

All three studies achieved statistical significance for the primary endpoint in favor of nintedanib. The treatment difference was as follows:

Study	Annual rate of decline in FVC Treatment difference (nintedanib – placebo)
1199.34	94 mL/year
1199.32	125 mL/year
1199.30	131 mL/year

The statistical review confirmed the efficacy results through various sensitivity analyses.

4.2 SAFETY CONCERNS

The primary safety evaluation is derived from the phase 3 trials described in Section 4.1 of this review. Supportive safety information was also provided from a phase 2 dose ranging study (N= 85 nintedanib), two phase 2 open-label studies, and a phase 2 study stratified by pirfenidone. In addition, data from non-IPF studies for nintedanib was also provided (e.g., non-small cell lung cancer, multi-cancer, ovarian cancer, and healthy volunteers (n=5390)).

According to the Sponsor, based on pooled data from all 7 IPF trials, the maximum treatment duration was 66.8 months (i.e., about 5.5 years). The overall treatment exposure in IPF trials was 2298 patient-years.

According to the medical officer’s midcycle meeting presentation, approximately 80% of patients completed the studies. Rates of serious adverse events were similar between groups except for gastrointestinal and liver enzymes elevations. Upon further review, the medical officer’s final review states that the three serious adverse events that were reported more frequently in the nintedanib group were myocardial infarction (1.1% nintedanib, 0.4% placebo), diarrhea (0.7% nintedanib, 0.2% placebo), and transient ischemic attack (0.4% nintedanib, 0% placebo).

Adverse events leading to discontinuation were slightly more frequent in the nintedanib-treated patients (20.6%) compared to placebo (15.0%). Diarrhea was the most common reason for discontinuation (5.3% nintedanib vs. 0.2% placebo). The next most frequent adverse events leading to discontinuation more frequently in the nintedanib-treated

patients compared to placebo-treated patients were nausea, decreased appetite, and weight decreased.

Overall, there were numerically fewer deaths in the nintedanib treated patients (5.3%) compared to placebo-treated patients (8.5%). The most common AE leading to death was IPF (4.1% placebo vs. 2.5% nintedanib), followed by pneumonia (0.6% placebo vs. 0.7% nintedanib).

Sections 4.2.1 through 4.2.5 highlight the risks of interest presented during the August 6, 2014 internal midcycle meeting and the medical officer's final review.⁵

4.2.1 Liver abnormalities

Sponsor Summary

Nintedanib has not been studied in patients with moderate or severe hepatic impairment. Administration of nintedanib was associated with elevations of liver enzymes (ALT, AST, ALKP, GGT) and bilirubin with a potentially higher risk for female patients. Liver enzyme elevations were reported as adverse events in 13.6% of nintedanib-treated patients compared to 2.6% of placebo-treated patients. Liver enzyme elevations were reported as serious 0.6%. The Sponsor characterizes the liver enzyme increases as reversible and not associated with clinical signs or symptoms of liver injury.

The Sponsor proposes to include liver enzyme and bilirubin elevations in the Warnings and Precautions section. The Sponsor recommends liver tests (liver enzymes and bilirubin levels) prior to treatment with nintedanib, periodically thereafter, and as clinically indicated.

DPARP Assessment: There were more patients in the nintedanib treated arm who experienced liver enzyme abnormalities across all parameters. Four patients each had ALT or AST of eight times the upper limit of normal compared to one patient in the placebo group.

Liver enzyme elevations led to more frequent early discontinuations (2.1% nintedanib vs. 0.4% placebo), and permanent dose reductions (1.5% nintedanib vs. 0.2% placebo) in nintedanib treated patients compared to placebo treated patients. These increases were reversible with dose modification or interruption and not associated with clinical signs or symptoms of liver injury. The majority of elevated liver enzymes and bilirubin events were $\leq 3x$ ULN and $\leq 1.5x$ ULN, respectively.

Bilirubin increased	Nintedanib	Placebo
All AEs	1.1%	0.2%
SAEs	0	0

⁵ Percentages and numbers may differ in this section from the Sponsor analysis as the information included reflects the Division of Pulmonary Allergy and Rheumatology Product's analysis of the application.

AE leading to death	0	0
Liver enzyme elevation		
All AEs	14.4%	2.6%
SAEs	0.7%	0.2%
AE leading to death	0	0

DRISK Comment: The monitoring regimen implemented in the clinical trials appears adequate to detect enzyme elevations and make appropriate adjustments to nintedanib.

4.2.2 Arterial thromboembolism

Sponsor Summary

Based on the mechanism of action, BIPI states that nintedanib may increase the risk of thromboembolic events.

Patients with a recent history of myocardial infarction or stroke were excluded from the trials. According to the Sponsor, a higher percentage of patients experienced myocardial infarctions in the nintedanib group (1.6%) compared to the placebo group (0.5%). Arterial thromboembolic events were reported in 2.5% of patients in the nintedanib group and 0.7% of patients in the placebo group. This difference was attributed to myocardial infarction events. Events were characterized as serious in 2% in the nintedanib group compared to 0.7% placebo. Adverse events related to ischemic heart disease were reported in 4.2% of patients in the nintedanib group and 4.0% of patients in the placebo group.

The Sponsor proposes to include arterial thromboembolism in the Warnings and Precautions section.

DPARP Assessment

The medical officer noted the following during the midcycle meeting:

Arterial Thromboembolism	Nintedanib	Placebo
All AEs	2.5%	0.8%
SAEs	2.1%	0.6%
AE leading to death	0.3%	0.2%

Based on the revised labeling under discussion (as of September 2, 2014), DPARP recommends addressing arterial thromboembolism in the Warnings and Precautions section along with a cautionary statement about not using nintedanib in patients at higher cardiovascular risk.

DRISK Comment: There are several kinase inhibitors that target some of the same receptors as nintedanib that include thromboembolism and/or myocardial infarction in the Warnings and Precautions section of their label. This risk is not an unexpected adverse event for a TKI.

4.2.3 Venous thromboembolism

Sponsor Summary

In the clinical trials, BIPI reports that no increased risk of venous thromboembolism was observed in nintedanib treated patients (1.2% nintedanib vs 1.1% placebo).

The Sponsor proposes to include this risk in the Warnings and Precautions of the label.

DPARP Assessment: DPARP recommends removing venous thromboembolism from the Warnings and Precautions section.

DRISK Comment: The clinical trial experience as assessed by the review division does not demonstrate a signal that would require additional risk management measures to be considered.

4.2.4 Gastrointestinal disorders

Sponsor Summary

Based on the mechanism of action, nintedanib may increase the risk of gastrointestinal perforation. No patients in the IPF clinical trials were reported to have a perforation.

BIPI notes the most common adverse reactions are gastrointestinal disorders including diarrhea (62.4% compared to 18.4% placebo), nausea (24.5% vs 6.6% placebo), vomiting (11.6% vs 2.6% placebo), abdominal pain, decreased weight, and decreased appetite. Nintedanib was discontinued due to these adverse events in 4.4% (diarrhea), 2% (nausea), and 0.8% (vomiting) of patients, respectively. The Sponsor characterizes these as mild to moderate intensity, non-serious, and managed by symptomatic treatment or temporary nintedanib interruption or dose reduction.

The Sponsor proposes to include diarrhea, nausea and vomiting, and gastrointestinal perforation in the Warnings and Precautions section.

DPARP Assessment: The medical officer notes that the majority of the most common adverse reactions in patients treated with nintedanib were gastrointestinal in nature (e.g., diarrhea, nausea, abdominal pain, vomiting). In the clinical trials, gastrointestinal perforation was reported in 0.3% of patients treated with nintedanib, compared to no cases in placebo-treated patients.

Gastrointestinal (combined)	Nintedanib	Placebo
SAEs	3.2%	1.4%
AE leading to death	0.1%	0
Diarrhea		
SAEs	0.7%	0.2%

Gastrointestinal perforation		
All AEs	0.3%	0
SAEs	0.3%	0
AE leading to death	0	0

DRISK Comment: Gastrointestinal disorders specifically perforation, is a risk associated with several kinase inhibitors and listed in the Warnings and Precautions section of their respective labels.

4.2.5 Bleeding

Sponsor Summary

The Sponsor states that “no relevant bleeding risk was observed in patients treated with nintedanib. However, “patients with inherited predisposition to bleeding or patients receiving a full dose of anticoagulation treatment” were excluded from the trials.

Bleeding was more frequently reported in patients treated with nintedanib (10.3%) than in those receiving placebo (7.8%). Non-serious epistaxis and contusion represented the most frequent bleeding events. Serious bleeding events occurred with similar incidences in the two treatment groups (placebo: 1.4%; nintedanib: 1.3%); fatal bleeding occurred in 1 nintedanib patient (0.2%) and no placebo patient.

The Sponsor proposes to include risk of bleeding in the Warnings and Precautions section.

DPARP Assessment: Patients with known bleeding risk were excluded. Serious adverse events occurred at the same rate in the placebo and nintedanib treated patients.

Bleeding	Nintedanib	Placebo
All AEs	9.5%	7.3%
SAEs	1.2%	1.2%
AE leading to death	0.1% (1 patient)	0

DRISK Comment: Bleeding is another known risk associated with kinase inhibitors and none of these drugs are approved with a REMS to address the risk of bleeding. The clinical trial experience as assessed by the review division does not demonstrate a signal that would require additional risk management measures to be considered given the serious adverse events related to bleeding were balanced between the treatment groups.

4.2.6 Other Safety Concerns

The following safety signal was identified and further evaluated by DPARP:

- **Neoplasm:** Carcinogenicity studies showed no evidence of carcinogenic potential for nintedanib. However, the medical officer noted an imbalance of neoplasms leading to death (6 in nintedanib and 1 in placebo). Therefore, a malignancy analysis was performed. The difference was driven by Study 1199.30 and no difference was demonstrated in the phase 3 trials. The medical officer notes that the imbalance is small, inconsistent, and not likely to be clinically relevant.

The most current version of the label mentions neoplasm in the Adverse Reactions section.

DRISK Comment: The clinical trial experience as assessed by the review division does not demonstrate a signal that would require additional risk management measures to be considered given the medical officer’s conclusion that the imbalance is not likely to be clinically relevant. .

The following safety concern was identified by DRISK:

- **Embryofetal toxicity:** The Sponsor states that nintedanib can cause fetal harm due to its mechanism of action and findings from animal studies. The Sponsor’s proposed labeling includes a (b) (4) Pregnancy Category (b) (4).

DPARP Assessment: The revisions to the label include Pregnancy Category D (b) (4).

DRISK Comment: While this is an important risk, it must be put in context with the treated population whose median age exceeds 60s years old. Therefore, most patients are not of reproductive potential. Further, the majority of patients appear to be male. In considering the potential for off-label use, most clinical trial investigation has been focused in oncology. There are many chemotherapeutic agents that are known or suspected teratogens and this risk for most oncology products is communicated through professional labeling only.

5 SPONSOR’S PROPOSED RISK MANAGEMENT APPROACH

BIPI states that the “proposed nintedanib labeling and routine reporting requirements are sufficient to mitigate risks and preserve benefits in the treatment of IPF.” BIPI does not propose a Boxed Warning in the labeling. They do propose a “patient information” document.

6 DISCUSSION

6.1 BENEFIT

IPF is characterized by progressive worsening of dyspnea and lung function resulting in death with median survival estimated to be 2 to 5 years from the time of diagnosis. The current treatment guideline from ATS/ERS/JRS/ALAT states that there are no known effective pharmacologic therapies available.

If approved, nintedanib will be the first drug approved in the United States to treat IPF because it demonstrated statistically significant improvement in annual rate of decline of FVC.

6.2 RISKS AND RISK MANAGEMENT APPROACHES

Adverse events of interest based on DPARP review of nintedanib include liver abnormalities, arterial thromboembolism, and gastrointestinal disorders.

- **Liver:** The majority of elevated liver enzymes and bilirubin events were $\leq 3x$ ULN and $\leq 1.5x$ ULN, respectively. Four patients had ALT or AST of eight times the upper limit of normal compared to one patient in the placebo group. These increases were reversible with dose modification or interruption and not associated with clinical signs or symptoms of liver injury. While these events are concerning, the clinical trial experience does not reflect reports of life-threatening or fatal outcomes which would increase the level of concern with this risk.
- **Arterial Thrombosis:** There were 2.1% of patients treated with nintedanib experienced a serious adverse arterial thromboembolic event compared to 0.6% in the placebo arm. However, fatal outcomes were similar between the treatment groups (0.3% of patients died as a result of this adverse event compared to 0.2% in the placebo arm).
- **Gastrointestinal:** In the clinical trials, gastrointestinal perforation was reported in 0.3% of patients treated with nintedanib, compared to no cases in placebo-treated patients. The majority of the most common adverse reactions in patients treated with nintedanib were gastrointestinal in nature (e.g., diarrhea, nausea, abdominal pain, vomiting).

With these risks in mind, DRISK considered the safety profiles and risk management approach for approved kinase inhibitors and REMS that address these risks.

- **Liver:** Hepatotoxicity is a known risk with tyrosine kinase inhibitors (TKIs) and the Agency has required a REMS to address this risk for one TKI. Votrient (pazopanib) was initially approved with a REMS consisting of a Medication Guide. The REMS was released on April 21, 2011 and the Medication Guide remains required as part of labeling. Stivarga (regorafenib) also has patient labeling but not a Medication Guide. Both these kinase inhibitors target some of the same receptors as nintedanib and both include a Boxed Warning for hepatotoxicity. The Boxed Warning cites serious and fatal events reported in the clinical trials; however none of the hepatic adverse events associated with nintedanib in the trials resulted in death.

There are a number of approved drugs across a variety of therapeutic areas associated with hepatotoxicity that rely on labeling alone to communicate this risk. Correspondingly, there are relatively few drugs with a REMS approved to address liver abnormalities and/or hepatotoxicity to balance the benefit-risk

- profile for the individual product. Of the drugs with a REMS to address this risk⁶, the rationale for requiring a REMS is summarized as follows:
- Most of the labels include a Boxed Warning for hepatotoxicity. At this time a Boxed Warning is not being considered for nintedanib.
 - The labeling for only two of these products (Tracleer, Multaq) includes reports of serious clinical outcomes (e.g., liver failure, cirrhosis, transplantation) in the setting of pulmonary arterial hypertension and atrial fibrillation, respectively. However, it is important to note that two other products (Juxtapid, Kynamro) were approved based on extremely small clinical development programs with “clinical studies unlikely to detect adverse outcomes given their size and duration”⁷, serious hepatic concerns, and substantial concern for much broader use beyond the indicated population which collectively affected the decision to require a REMS.
 - With regard to the type of REMS approved to address hepatotoxicity, three (Juxtapid, Kynamro, Tracleer) include elements to assure safe use that require, at minimum, prescriber certification and pharmacy certification. The other two REMS programs consist of a Communication Plan (Actemra, Multaq).
- Arterial Thrombosis: There have been six different drugs approved with a REMS to address the risk of thromboembolism or, more specifically, myocardial infarction; one of these (ponatinib) is also a tyrosine kinase inhibitor.
 - Iclusig (ponatinib) is a tyrosine kinase inhibitor with activity against ABL, and T315I mutant ABL and VEGFR, PDGFR, FGFR, EPH, Src, KIT, RET, ITE2, and FLT3. Ponatinib is approved for the treatment of T315I-positive chronic myeloid leukemia or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia. The REMS addresses the approved indication and the risk of vascular occlusion and thromboembolism through a communication plan.

At the time of initial approval, serious arterial thrombosis events which included cardiovascular, cerebrovascular, and peripheral vascular thrombosis, including fatal myocardial infarction and stroke, occurred in 8% of Iclusig-treated patients, and venous thromboembolic events occurred in 3% of patients. The label included a Boxed Warning to

⁶ Juxtapid and Kynamro (homozygous familial hypercholesterolemia / REMS - hepatotoxicity, appropriate monitoring, restrict access to the indicated population), Tracleer (pulmonary arterial hypertension / REMS - hepatotoxicity, teratogenicity), Multaq (reduce the risk of hospitalization for atrial fibrillation in patients in sinus rhythm with a history of paroxysmal or persistent AF / REMS - appropriate patient selection, cardiovascular death, liver injury/hepatic failure (including acute liver failure requiring transplant has been reported)), Actemra (rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis / REMS - serious infections, gastrointestinal perforations, hypersensitivity reactions, anaphylaxis, changes in liver function, decreases in peripheral neutrophil counts, platelet counts, elevations in lipids, demyelinating disorders, malignancy).

⁷ Juxtapid [package insert]. Cambridge, MA: Aegerion; 2014. Kynamro [package insert]. Cambridge, MA: Genzyme Corporation; 2013.

address this risk (along with hepatotoxicity). Post approval, the Agency became aware of new clinical trial and spontaneous post marketing reports indicating an increase of arterial and venous occlusions now reported in 27% of all patients and subsequently required a REMS. These events include fatal and life threatening myocardial infarction and stroke, distal extremity necrosis and gangrene requiring amputation, urgent revascularization procedures (cerebrovascular, coronary, peripheral arterial), visual loss, blindness, and retinal vein occlusion.

Of the other drugs with a REMS to address this risk,⁸

- Four of the five drugs include a Boxed Warning for this risk. A Boxed Warning is not being considered for nintedanib.
 - All of them, at present, have a REMS that consists of a communication plan.
- **Gastrointestinal:** Gastrointestinal disorders specifically perforation, is a risk associated with several kinase inhibitors and listed in the Warnings and Precautions section of their respective labels. None of these drugs have a REMS to address gastrointestinal perforation. The clinical trial experience as assessed by the review division does not demonstrate a signal that would require additional risk management measures to be considered given the small difference compared to placebo.

We concluded that discussing the safety profiles of other drugs to treat IPF was of limited value given the lack of effective options. However, we do note that several of the drugs

⁸ There are two Factor Xa inhibitors (Eliquis, Xarelto) approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Both were approved with a REMS consisting of a Communication Plan (dear healthcare professional and society letters) to address the increased risk of thrombotic events in the indicated population when discontinuing the Xa inhibitor without introducing an adequate alternative anticoagulant. Both drugs included a Boxed Warning to address the risk.

Entereg, a peripherally acting opioid receptor antagonist, is approved to accelerate the time to upper and lower gastrointestinal recovery following surgeries that include partial bowel resection with primary anastomosis. The label includes a Boxed Warning regarding the potential risk of myocardial infection with long-term use. The REMS consists of an ETASU to limit Entereg distribution to hospital pharmacies that are specially certified. Those hospital pharmacies agree to dispense no more than 15 doses in an inpatient settings.

Omontys (peginesatide) carries a Boxed Warning for increases risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access and tumor progression or recurrence. The REMS addresses the potentially fatal cardiovascular and /or thromboembolic adverse events and the increased risk of these events in non-dialysis patients. The REMS consists of a communication plan (DHCP and society letter).

Rosiglitazone, a thiazolidinedione, approved for the treatment of type 2 diabetes *had* a REMS with ETASU to address the potential increased risk of myocardial infarction. Based on data re-adjudication, the REMS was modified to remove the ETASU and inform prescribers about the most up to date cardiovascular information. At the time the REMS was modified, the Boxed Warning was revised to remove the myocardial infarction risk.

that may be tried despite their lack of efficacy (and endorsement by an international collaboration of professional organizations) are immunosuppressants and/or immune modulators that have important and significant safety profiles. Therefore, practitioners who treat IPF should have experience with treating patients with drugs with serious safety considerations.

6.3 SUMMARY

There are several FDA-approved TKIs, most of which are approved for the treatment of various malignancies. Of these approved TKIs, each one targets a different compilation of receptors. Therefore, there are similarities and differences in grossly comparing the adverse event profile across the class. Many of these products include Boxed Warnings and/or Warnings and Precautions regarding hemorrhage, gastrointestinal perforation, compromised wound healing, thromboembolic events, liver enzyme elevations, hepatotoxicity, and hypertension. In most instances, these risks are communicated through the product's labeling and have not been required to implement a REMS.

There is a clear medical need for effective treatment options for IPF, a disease that is fatal within a relatively short time frame. Based on the available safety information, addressing the risks identified with nintedanib through labeling is consistent with the risk management approach for other TKIs. The observed safety profile in the clinical studies for nintedanib is no more concerning than the known safety profile for other TKIs and the medical officer is not recommending a Boxed Warning to highlight any of the identified risks at this time. While the majority of TKIs are approved for oncology indications, IPF is a similarly serious and fatal disease for which disease management necessitates frequent interaction with healthcare professionals.

It seems prudent to require patient labeling or a Medication Guide to educate patients on signs and symptoms of the serious risks associated with nintedanib to be aware of in effort to prevent or mitigate serious sequelae and reinforce the importance of periodic monitoring.

7 CONCLUSION AND RECOMMENDATION

In conclusion, risk mitigation measures beyond professional labeling are not warranted for nintedanib. The efficacy of nintedanib for the treatment of IPF has been demonstrated based on annual rate of FVC decline. The serious risks of concern associated with nintedanib include liver abnormalities, arterial thromboembolic events, and gastrointestinal disorders. Based on the available data, the benefit-risk profile is acceptable and a REMS is not necessary for nintedanib to ensure the benefits outweigh the risks.

If new safety information becomes available that changes the benefit risk profile, this recommendation can be reevaluated.

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