CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215358Orig1s000
215358Orig2s000

RISK ASSESSMENT AND RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	215358
PDUFA Goal Date	02/24/2022
OSE RCM #	2021-664
Reviewer Name(s)	Ingrid N. Chapman, Pharm.D., BCPS
Team Leader	Naomi Boston, Pharm.D.
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	10/28/2021
Subject	Evaluation of Need for a REMS
Established Name	Asciminib
Trade Name	Scemblix
Name of Applicant	Novartis Pharmaceuticals Corporation
Therapeutic Class	ABL/BCR-ABL1 tyrosine kinase inhibitor
Formulation(s)	20 mg and 40 mg film-coated tablets for oral administration
Dosing Regimen	Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP): 80 mg PO Qday or 40 mg PO BID Ph+ CML in CP harboring the T315I mutation: 200 mg PO BID

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME), Scemblix (asciminib) is necessary to ensure the benefits outweigh its risks. Novartis Pharmaceuticals Corporation submitted a New Drug Application (NDA) 215358 for asciminib with the proposed indication: for the treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP) and Ph+ CML in CP harboring the T315I mutation.

The FDA approved indication will be: 1) for the treatment of adult patients with Ph+ CML in CP, previously treated with two or more tyrosine kinase inhibitors (TKIs) and 2) for the treatment of adult patients with Ph+ CML in CP with the T315I mutation.

Asciminib meets the accelerated approval criteria for the treatment of Ph+ CML in CP in adult patients previously treated with two or more TKIs by having the potential to address an unmet medical need in a serious condition based on the endpoint, major molecular response (MMR) at 24 weeks and supporting evidence of improved cytogenetic response rate at 24 weeks, MMR at 48 weeks, and other prespecified time points, durability of response and subgroup analyses. Additionally, regular approval is recommended for asciminib in patients with Ph+ CML in CP with the T315I mutation.

The Division of Risk Management (DRM) and the Division of Hematologic Malignancies 1 (DHM1) agree that a REMS is not needed to ensure the benefits of asciminib outweigh its risks. The Applicant did not submit a proposed REMS or risk management plan with this application. The serious risks determined to be associated with asciminib include myelosuppression, pancreatic toxicity, hypertension, hypersensitivity, cardiovascular toxicity, and embryo-fetal toxicity. These risks are similar to other BCR-ABL tyrosine kinase inhibitors. Prescribers (hematologists and oncologists) are likely to be familiar with and able to appropriately monitor for these risks. Additionally, these risks will be addressed in the Warnings and Precautions section of the asciminib label.

1 Introduction

This review evaluates whether a REMS for the NME, Scemblix (asciminib) is necessary to ensure the benefits outweigh its risks.[a] Novartis Pharmaceuticals Corporation submitted NDA 215358 for asciminib with the proposed indication: for the treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP) and Ph+ CML in CP harboring the T315I mutation.[1] The FDA approved indication will be: 1) for the treatment of adult patients with Ph+ CML in CP, previously treated with two or more TKIs and 2) for the treatment of adult patients with Ph+ CML in CP with the T315I mutation.[2]

This application is under review in the DHM1. The Applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

2.1 PRODUCT INFORMATION

Scemblix (asciminib), an NME, is an ABL/BCR-ABL1 tyrosine kinase inhibitor (TKI) proposed for the treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors and Ph+ CML in CP harboring the T315I mutation. Asciminib is proposed as 20 mg and 40 mg film-coated tablets for oral administration.

The proposed dose is as follows:[2]

- Ph+ CML in CP: 80 mg orally once daily or 40 mg orally twice daily
- Ph+ CML in CP with the T315I mutation: 200 mg orally twice daily

Treatment is continued as long as clinical benefit is observed or until unacceptable toxicity occurs.[2,b] Asciminib is not currently approved in any jurisdiction. If approved, asciminib will be the 6th BCR-ABL TKI with the indication to treat Ph+ CML in CP and the 2nd BCR-ABL TKI to treat Ph+ CML in CP with the T315I mutation. None of the FDA-approved BCR-ABL TKIs include a REMS.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 215358 relevant to this review:

- 02/27/2017: Orphan Drug Designation granted to asciminib under IND 119257 for the treatment of CML.
- 08/24/2020: Fast Track Designation granted to asciminib under IND 119257.
- 02/02/2021: Breakthrough Therapy Designation granted to asciminib (ABL001) under IND 119257 for the treatment of adult patients with Ph+ CML in CP, previously treated with two or more tyrosine kinase inhibitors (TKIs) and for the treatment of adult patients with Ph+ CML in CP harboring the T315I mutation.
- 06/24/2021: NDA 215358 submission for asciminib received.
- 09/17/2021: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for asciminib.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

CML is a myeloproliferative neoplasm characterized by the dysregulated production and uncontrolled proliferation of mature and maturing granulocytes with fairly normal differentiation.[3] CML accounts for 10% – 15% of leukemias with the incidence being approximately 1 – 1.5 in 100,000 persons.[c] In 95% of cases, CML is associated with the Philadelphia chromosome t(9;22)(q34;q11) and the BCR-ABL1 fusion gene, which produces a constitutively active BCR-ABL1 tyrosine kinase.[4] It is this deregulated tyrosine

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*
[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

kinase that is implicated in the development of CML.[5] CML presents as a triphasic clinical course: chronic phase (CP), accelerated phase, and blastic/crisis phase. CP, referred to as the indolent phase, is typically present at the time of diagnosis in 85% - 95% of patients. Patients may be asymptomatic or present with fatigue, malaise, weight loss, excessive sweating, abdominal fullness, and bleeding episodes due to platelet dysfunction.[3] The life expectancy of those with CML approaches the general population now that BCR-ABL 1 tyrosine kinase inhibitors have been incorporated into the initial treatment of CML.[3,d]

3.2 Description of Current Treatment Options

Initial treatment considerations for patients diagnosed with CML in CP include comorbidities, patient preference, toxicity profile of the TKI, drug interactions, and the patient's risk score. Imatinib (400 mg by mouth daily) and second-generation TKIs (bosutinib [400 mg by mouth daily], dasatinib [100 mg once by mouth daily], and nilotinib [300 mg by mouth twice daily]) are all appropriate options for first-line TKI therapy for patients with CML in CP cross all risk scores.[6] Second-generation TKIs are associated with lower risk of disease progression than imatinib and are therefore preferred for patients with an intermediate- or high-risk Sokal or Euro score.[e]

For patients with an inadequate response to dasatinib, nilotinib, or bosutinib, switching to an alternate TKI (not imatinib) is an option, although there is no clear evidence that the switch would improve long-term clinical outcomes. Ponatinib is an option for patients with a T315I mutation and for those with disease that has not responded to several TKIs. However, ponatinib use is limited in those with cardiovascular risk factors due to the Boxed Warning for vascular occlusion, heart failure, and hepatoxicity. Omacetaxine is a treatment option for patients with CP-CML resistant or intolerant to ≥ 2 TKIs including patients with a T315I mutation although the response rates and survival outcomes were substantially lower than that observed with ponatinib in the PACE trial.[f] See Table 1 in the appendix for further details on drug therapy in adult patients with Ph+ CML in CP and Ph+ CML in CP with the T315I mutation.

4 Benefit Assessment

The efficacy of asciminib for the treatment of Ph+ CML in CP previously treated with two or more TKIs was demonstrated in ASCEMBL (NCT03106779) while the efficacy of asciminib in Ph+ CML in CP with the T315I mutation was demonstrated in CABL001X2101 (NCT02081378).[2]

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.*

[e] Sokal score: based on the patient's age, spleen size on clinical exam, platelet count, and percentage of blasts in the peripheral blood; Euro score: includes eosinophils and basophils in the peripheral blood in addition to the same clinical variables used in the Sokal score

[f] PACE Trial: Pivotal Phase 2 Ponatinib Ph+ ALL and CML Evaluation (PACE) trial valuated efficacy and safety of ponatinib at a starting dose of 45 mg once daily in 449 patients with chronic myeloid leukemia (CML) or Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL) resistant/intolerant to dasatinib or nilotinib, or with BCR-ABL1^{T315I}

4.1 PH+ CML IN CP TREATED WITH TWOR OR MORE TKIS

Study ASCEMBL (NCT03106779) was a multi-center, active-controlled, open-label, randomized study of oral asciminib versus bosutinib in adult patients with CML-CP, previously treated with at least two TKIs.[2] In this study 233 patients were randomized in a 2:1 ratio and stratified according to major cytogenetic response (MCyR) status to receive either asciminib 40 mg by mouth twice daily (n = 157) or bosutinib 500 mg by mouth daily (n = 76).

The primary endpoint was major molecular response (MMR) at 24 weeks (MMR ≤ 0.1% of BCR-ABL1 ratio on the International Scale).[g] The key secondary endpoint was MMR at 96 weeks. Subjects were to receive treatment for up to 96 weeks after the last patient received the first study dose or up to 48 weeks after the last patient had switched to asciminib treatment whichever was longer unless patients had discontinued study treatment earlier. Results showed that the MMR rate at Week 24 was 25% in the asciminib arm compared to 13% in the bosutinib arm. The treatment difference was statistically significant at 12% (95% CI: 2.2, 22, two-sided p-value: 0.029, stratified by MCyR status at baseline).[7] At each scheduled time point, the MMR rate was improved in the asciminib arm, with meaningful improvement starting at the 12-week assessment. Median time to MMR was 12.7 weeks in the asciminib arm and 14.3 weeks in bosutinib arm. With a median duration of follow-up of 20 months (range: 1 day to 36 months), the median duration of response had not yet been reached for patients with MMR at any time. Additionally, the key secondary endpoint, MMR at 96 weeks was not analyzed due to immaturity of data.[7]

The FDA review team recommends accelerated approval for asciminib for the treatment of Ph+ CML in CP previously treated with two or more TKIs.[7]

4.2 PH+ CML IN CP WITH THE T315I MUTATION

Study CABL001X2101 (NCT02081378) was a multicenter, open-label study that evaluated patients harboring the T315I mutation. For the purpose of this NDA, Study CABL001X2101 provides the following:[7] the efficacy of asciminib in patients with CML in CP harboring the T315I mutation based on data from the cohort of CML-CP patients with the T315I mutation (N = 45) who received asciminib 200 mg by mouth twice daily.

The primary endpoint of the study was the incidence of dose limiting toxicities and secondary efficacy endpoints included MMR by and at scheduled timepoints, duration of MMR, and time to MMR, cytogenetic response, and hematologic response. Results showed cumulative MMR was achieved by 24 weeks in 42% (95% CI: 28, 58) of the 45 patients treated with asciminib. MMR was achieved by 96 weeks in 49% (95% CI: 34, 64). The median duration of treatment was 108 weeks (range, 2 to 215 weeks).[7]

Of the 45 patients in the efficacy population with T315I mutations treated at 200 mg twice daily, all had received at least one prior BCR-ABL TKI; however, 26/45 (58%) had prior ponatinib treatment, and 19/45 (42%) did not have prior ponatinib treatment which is the only other TKI with activity in the T315I

[g] Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

mutation. Of the 26 patients with prior ponatinib treatment, the cumulative MMR rate by 24 weeks was 30.8% (90% CI: 16.3%-48.7%), and the MMR rate at week 24 was 26.9% (90% CI: 13.4, 44.7). Of the 19 patients without prior ponatinib treatment, the cumulative MMR rate by 24 weeks was 57.9% (90% CI: 36.8%-77.0%), and the MMR rate at Week 24 was 52.6% (90% CI: 32.0, 72.6).[7]

The FDA review team recommends regular approval for asciminib for the treatment of Ph+ CML in CP with the T315I mutation.[7]

5 Risk Assessment & Safe-Use Conditions

The safety profile of asciminib was derived from the pooled population of 356 patients enrolled in two clinical trials: 1) Patients with Ph+ CML in CP receiving asciminib as monotherapy (ASCEMBL), and 2) Patients receiving asciminib who have the T351I mutation in study CABL001X2101. These pooled analyses reflect exposure to asciminib with doses between 10 mg to 200 mg orally twice daily. The median duration of exposure to asciminib was 89 weeks (0.1 to 342 weeks).[2]

The serious risks determined to be associated with asciminib include myelosuppression, pancreatic toxicity, hypertension, hypersensitivity, cardiovascular toxicity, and embryo-fetal toxicity.[7,h] The Warnings and Precautions section of the asciminib proposed label includes these risks and will be discussed below along with the deaths that occurred.[2]

5.1 MYELOSUPPRESSION

Thrombocytopenia, neutropenia, and anemia have occurred in patients receiving asciminib.[2] Thrombocytopenia occurred in 98 of 356 (28%) patients receiving asciminib, with Grade 3 or 4 thrombocytopenia reported in 24 (7%) and 42 (12%) of patients, respectively. Neutropenia occurred in 69 (19%) patients receiving asciminib, with Grade 3 and 4 neutropenia reported in 27 (8%) and 29 (8%) patients, respectively. Anemia occurred in 45 (13%) patients receiving asciminib, with Grade 3 anemia occurring in 19 (5%) patients. The Warnings and Precautions section of the proposed label states, "Based on the severity of thrombocytopenia and/or neutropenia, the asciminib dose should be reduced, temporarily withheld, or permanently discontinued as described in Table 2." Table 2 is in the Dosage and Administration section of the label.

5.2 PANCREATIC TOXICITY

Pancreatitis occurred in 9 of 356 (2.5%) patients receiving asciminib, with Grade 3 pancreatitis occurring in 4 (1.1%) patients. Asymptomatic elevation of serum lipase and amylase occurred in 76 of 356 (21%) patients receiving asciminib, with Grade 3 and Grade 4 pancreatic enzyme elevations occurring in 36 (10%) and 8 (2.2%) patients, respectively. Both the Warnings and Precautions and Dosage and Administration sections of the proposed label address pancreatic toxicity. Serum lipase and amylase should be monitored. Based on severity, asciminib should be interrupted then resumed at a lower dose or discontinued. Patients should also be evaluated for pancreatitis when lipase elevation is accompanied by abdominal symptoms.[2]

[h] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

5.3 HYPERTENSION

Hypertension occurred in 66 of 356 (19%) patients receiving asciminib, with Grade 3 or 4 hypertension reported in 31 (9%) and 1 (0.3%) patients, respectively. The Warnings and Precautions section of the proposed label advises to monitor blood pressure and manage hypertension as clinically indicated. It also recommends to interrupt, dose reduce, or stop asciminib if hypertension is not medically controlled.[2]

5.4 HYPERSENSITIVITY

Hypersensitivity occurred in 113 of 356 (32%) patients receiving asciminib, with Grade 3 or 4 hypersensitivity reported in 6 (1.7%) patients. The Warnings and Precautions section of the proposed label advises to monitor patients for signs and symptoms and initiate appropriate treatment as clinically indicated.[2]

5.5 CARDIOVASCULAR TOXICITY

Cardiovascular toxicity (including ischemic cardiac and CNS conditions, arterial thrombotic and embolic conditions) and cardiac failure occurred in 46 (13%) and in 8 (2.2%) of 356 patients receiving asciminib, respectively. Grade 3 cardiovascular toxicity was reported in 12 (3.4%) patients, while grade 3 cardiac failure was observed in 4 (1.1%) patients. Grade 4 cardiovascular toxicity occurred in 2 (0.6%) patients with fatalities occurring in 3 (0.8%) patients. Asciminib was permanently discontinued in 3 (0.8%) of patients due to cardiovascular toxicity and in 1 (0.3%) patient due to cardiac failure, respectively. These toxicities occurred in patients with pre-existing cardiovascular conditions or risk factors and/or patients that had prior exposure to multiple TKIs. Arrhythmia, including QTc prolongation, occurred in 23 of 356 (7%) of patients receiving asciminib, with Grade 3 arrhythmia reported in 7 (2%) of patients. QTc prolongation alone occurred in 3 of 356 (0.8%) patients. Grade 3 QTc prolongation was reported in only one (0.3%) patient. The Warnings and Precautions section of the proposed label advises to monitor patients with history of cardiovascular risk factors for cardiovascular signs and symptoms and to initiate appropriate treatment as clinically indicated.[2] For cardiovascular events Grade 3 or higher, recommendations are to temporarily withhold, reduce the dose, or permanently discontinue asciminib depending on the persistence of cardiovascular toxicity.

5.6 EMBRYO-FETAL TOXICITY

Based on findings from animal studies and its mechanism of action, asciminib can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of asciminib to pregnant rats and rabbits during the period organogenesis caused adverse developmental outcomes including embryo-fetal mortality and malformations at maternal exposures (AUC) equivalent to or less than those in patients at the recommended doses. The Warnings and Precautions section of the proposed label states to advise females of reproductive potential of the potential risk to a fetus and to use effective contraception.[2]

5.7 DEATHS

Overall, death occurred in 8 (2.2%) of 356 patients receiving asciminib within 30 days after the last dose. Three of the eight deaths were attributed to their respective study indication. Two of the deaths, arterial embolism and ischemic stroke, occurred in Study CABL001A2301. The Applicant determined

both of these cases had confounding factors and neither was suspected to be related to study treatment. The remaining three deaths, cardiac arrest, completed suicide, and abnormal general physical condition, occurred in Study CABL001X2101. The Applicant also determined these deaths were not suspected to be related to study treatment. The FDA agrees with the Applicant's assessment based on the investigator's assessment of causality of death due to AE.[7]

6 Expected Postmarket Use

Asciminib will be prescribed primarily in the outpatient setting. The likely prescribers include hematologists and oncologists who are familiar with managing patients with CML. These prescribers should be familiar with managing the adverse effects associated with asciminib and other kinase inhibitors, including myelosuppression, pancreatic toxicity, hypertension, hypersensitivity, cardiovascular toxicity, and embryo-fetal toxicity.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities beyond labeling and routine pharmacovigilance for asciminib. If approved, asciminib would be subject to postmarketing requirements including:[7]

1. PMR#1: To conduct clinical study CABL001A2301 (ASCEMBL), A Phase 3, Multi-center, Open-label, Randomized Study of Oral ABL001 Versus Bosutinib in Patients with Chronic Myelogenous Leukemia in Chronic Phase (CML-CP), Previously Treated With 2 or More Tyrosine Kinase Inhibitors and provide the interim report with at least 24 months (96 weeks) follow-up of all patients to describe and confirm the clinical benefit of asciminib. The rationale is that data cutoff for the CABL001A2301 provides less than 24 months of follow-up data, (b) (4)
2. PMR #2: To provide 24 months of follow-up data from the CABL001A2301 trial. (b) (4)
3. PMR #3: To conduct a clinical trial to determine the appropriate dose of asciminib and to assess safety, tolerability, pharmacokinetics, and pharmacodynamics of asciminib in pediatric patients with Ph+ CML-CP previously treated with one or more tyrosine kinase inhibitors, ages ≥1 to <18 years and provide the core study report with at least 12 months (52 weeks) data for all patients. They should include at least 15 patients ≥1 to <12 years old and 15 patients ≥12 to <18 years old. The rational is that the agreed is for asciminib has a waiver for children <1 year and a deferral for children ≥1 year to < (b) (4) years. FDA requested a PREA PMR for their pediatric PK study in children aged ≥1 year to < (b) (4) years.

8 Discussion of Need for a REMS

The review team recommends accelerated approval for asciminib for the treatment of Ph+ CML in CP previously treated with two or more TKIs and regular approval for asciminib for the treatment of Ph+ CML in CP with a T315I mutation.

CML is a myeloproliferative neoplasm that accounts for 10% – 15% of leukemias with the incidence being approximately 1 – 1.5 in 100,000 persons. At the time of diagnosis, 85% - 95% of patients present in chronic phase (indolent phase). There is no cure for CML, however, there are five FDA-approved BCR-ABL TKIs for Ph+ CML in CP. Asciminib offers an additional agent for patients with Ph+ CML in CP that have been previously treated with at least two TKIs, and in patients Ph+ CML in CP with the T315I mutation.

The risks associated with asciminib include myelosuppression, pancreatic toxicity, hypertension, hypersensitivity, cardiovascular toxicity, and embryo-fetal toxicity. The likely prescribers, hematologists and oncologists, should be familiar with managing the adverse effects associated with asciminib and other tyrosine kinase inhibitors. Additionally, these risks will be addressed in the Warnings and Precautions section of the label for asciminib. This reviewer recommends that, should asciminib be approved, a REMS is not necessary to ensure its benefits outweigh its risk.

9 Conclusion & Recommendations

Based on the available data, DRM and DHM1 agree that a REMS is not necessary for asciminib to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 References

1. Novartis Pharmaceuticals Corporation. Scemblix (asciminib). NDA 215358. Prescribing Information, draft. June 24, 2021.
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7. Food and Drug Administration. Division of Hematologic Malignancies I. Scemblix (asciminib). NDA 215358. Multi-disciplinary Review and Evaluation, draft. October 26, 2021.
8. Drug Facts and Comparisons. Wolters Kluwer Health, Inc. Riverwoods, IL. . http://fco.factsandcomparisons.com/lco/action/home. Accessed October 26, 2021.

10.2 TABLE 1:[8] FDA-APPROVED THERAPIES FOR PH+ CML IN CP AND PH+ CML IN CP WITH THE T315I MUTATION

Drug (Approval Date)	**Important Safety & Tolerability Issues**	**Risk Management Approaches**
Gleevec – imatinib (05/10/2001)	**Warnings and Precautions** Fluid retention/edema Bone marrow suppressions Cardiovascular effects Hepatotoxicity Hemorrhage Gastrointestinal toxicity Dermatologic reactions Thyroid disease Tumor lysis syndrome Nephrotoxicity Gastric surgery Appropriate Use	Labeling – Warnings and Precautions
Sprycel – dasatinib (06/28/2006)	**Warnings and Precautions** Bone marrow suppression Hemorrhage Fluid retention QT prolongation Cardiovascular adverse events Pulmonary arterial hypertension Dermatologic toxicity Tumor lysis syndrome Drug-drug interactions • Anticoagulants or antiplatelets • CYP3A4 inducers/inhibitors • Drugs that affect gastric pH	Labeling – Warnings and Precautions
Tasigna – nilotinib (10/29/2007)	**Warnings and Precautions** Bone marrow suppression QT prolongation/sudden death Cardiovascular Hepatotoxicity Pancreatitis Electrolyte imbalance Tumor lysis syndrome Hemorrhage Gastrectomy Lactose Fluid retention	Labeling – Warnings and Precautions

	Appropriate administration BCR-ABL transcript monitoring Polymorphisms	
Bosulif – bosutinib (09/04/2012)	**Warnings and Precautions** Gastrointestinal toxicity Bone marrow suppression Fluid retention/edema Hepatotoxicity Cardiovascular toxicity Hypersensitivity	Labeling – Warnings and Precautions
Iclusig – pONATinib (12/14/2012)	**Boxed Warning** Arterial occlusive events Heart failure Hepatotoxicity Venous thromboembolic events **Warnings and Precautions** Includes Boxed Warning Risks and Hypertension Pancreatitis CML in CP (newly diagnosed) Neuropathy Ocular toxicity Hemorrhage Fluid retention Arrhythmias Bone marrow suppression Tumor lysis syndrome Reversible posterior leukoencephalopathy syndrome Would healing impairment Gastrointestinal perforation	Labeling – Boxed Warning and Warnings and Precautions
Synribo – omacetaxine (10/26/2012)	**Warnings and Precautions** Bone marrow suppression Glucose intolerance	Labeling – Warnings and Precautions

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