BOSUTINIB - bosutinib tablet, film coated
Alembic Pharmaceuticals Limited

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BOSUTINIB TABLETS safely and effectively. See full prescribing information for BOSUTINIB TABLETS.

BOSUTINIB tablets, for oral use
Initial U.S. Approval: 2012

INDICATIONS AND USAGE

Bosutinib is a kinase inhibitor indicated for the treatment of:
• adult patients with chronic phase Ph+ chronic myelogenous leukemia (CML), newly-diagnosed or resistant or intolerant to prior therapy. (1)
• adult patients with accelerated, or blast phase Ph+ CML with resistance or intolerance to prior therapy. (1)

DOSAGE AND ADMINISTRATION

• Adult patients with chronic, accelerated, or blast phase Ph+ CML with resistance or intolerance to prior therapy: 500 mg orally once daily with food. (2.1)
• Consider dose escalation by increments of 100 mg once daily to a maximum of 600 mg daily in adult patients who do not reach complete hematologic, cytogenetic, or molecular response and do not have Grade 3 or greater adverse reactions. (2.2)
• Adjust dosage for toxicity and organ impairment (2)

DOSAGE FORMS AND STRENGTHS

Tablets: 100 mg and 500 mg. (3).

CONTRAINDICATIONS

Hypersensitivity to bosutinib tablets. (4)

WARNINGS AND PRECAUTIONS

• Gastrointestinal Toxicity: Monitor and manage as necessary. Withhold, dose reduce, or discontinue bosutinib tablets. (2.3, 5.1)
• Myelosuppression: Monitor blood counts and manage as necessary. Withhold, dose reduce or discontinue bosutinib tablets (2.4, 5.2)
• Hepatic Toxicity: Monitor liver enzymes at least monthly for the first 3 months and as needed. Withhold, dose reduce, or discontinue bosutinib tablets. (2.3, 5.3)
• Cardiovascular Toxicity: Monitor and manage as necessary. Interrupt, dose reduce, or discontinue bosutinib tablets. (5.4)
• Fluid Retention: Monitor patients and manage using standard of care treatment. Interrupt, dose reduce, or discontinue bosutinib tablets. (2.3, 5.5)
• Renal Toxicity: Monitor patients for renal function at baseline and during therapy with bosutinib tablets. (5.6)
• Embryo-Fetal Toxicity: Bosutinib tablets can cause fetal harm. Advise female patients of reproductive potential of potential risk to a fetus and to use effective contraception. (5.7)

ADVERSE REACTIONS

• Most common adverse reactions (≥20%), in adult patients with CML are diarrhea, abdominal pain, vomiting, nausea, rash, fatigue, hepatic dysfunction, headache, pyrexia, and respiratory tract infection. The most common laboratory abnormalities (≥20%) in adult patients are creatinine increased, hemoglobin decreased, lymphocyte count decreased, platelets decreased, ALT increased, calcium decreased, white blood cell count decreased, AST increased, absolute neutrophil count decreased, glucose increased, phosphorus decreased, urate increased, alkaline phosphatase increased, lipase increased, creatine kinase increased, and amylase increased. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

• Strong and Moderate CYP3A Inhibitors: Avoid concomitant use with bosutinib tablets. (7.1)
• Strong CYP3A Inducers: Avoid concomitant use with bosutinib tablets. (7.1)
• Proton Pump Inhibitors: Use short-acting antacids or H2 blockers as an alternative to proton pump inhibitors. (7.1)

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed. (8.2)

Pediatric use information is approved for PF PRISM CV's BOSULIF® (bosutinib) tablets. However, due to PF PRISM CV's marketing exclusivity rights, this drug product is not labeled with that information.
See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.
Revised: 3/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Bosutinib tablets are indicated for the treatment of:

• Adult patients with chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML), resistant or intolerant to prior therapy *[see Clinical Studies (14.2)].*
• Adult patients with accelerated phase (AP), or blast phase (BP) Ph+ CML with resistance or intolerance to prior therapy *[see Clinical Studies (14.2)]*.

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2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage is taken orally once daily with food. Swallow tablets whole. Do not cut, crush, break or chew tablets. Continue treatment with bosutinib tablets until disease progression or intolerance to therapy.

If a dose is missed beyond 12 hours, the patient should skip the dose and take the usual

prescribed dose on the following day.

Dosage in Adult Patients with CP, AP, or BP Ph+ CML with Resistance or Intolerance to Prior Therapy
The recommended dosage of bosutinib tablet is 500 mg orally once daily with food.

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2.2 Dose Escalation

In clinical studies of adult patients with Ph+ CML, dose escalation by increments of 100 mg once daily to a maximum of 600 mg once daily was allowed in patients who did not achieve or maintain a hematologic, cytogenetic, or molecular response and who did not have Grade 3 or higher adverse reactions at the recommended starting dosage.

The maximum dose in adult patients is 600 mg once daily.

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2.3 Dosage Adjustments for Non-Hematologic Adverse Reactions

Elevated liver transaminases: If elevations in liver transaminases greater than 5×institutional upper limit of normal (ULN) occur, withhold bosutinib tablets until recovery to less than or equal to 2.5×ULN and resume at 400 mg once daily thereafter. If recovery takes longer than 4 weeks, discontinue bosutinib tablets. If transaminase elevations greater than or equal to 3×ULN occur concurrently with bilirubin elevations greater than 2×ULN and alkaline phosphatase less than 2×ULN (Hy's law case definition), discontinue bosutinib tablets *[see Warnings and Precautions (5.3)].*

Diarrhea: For National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade 3 to 4 diarrhea (increase of greater than or equal to 7 stools/day over baseline/pretreatment), withhold bosutinib tablets until recovery to Grade less than or equal to 1. Bosutinib tablets may be resumed at 400 mg once daily *[see Warnings and Precautions (5.1)]*.

For other clinically significant, moderate or severe non-hematological toxicity, withhold bosutinib tablets until the toxicity has resolved, then consider resuming bosutinib tablets at a dose reduced by 100 mg taken once daily. If clinically appropriate, consider re-escalating the dose of bosutinib tablets to the starting dose taken once daily.

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2.4 Dosage Adjustments for Myelosuppression

Dose reductions for severe or persistent neutropenia and thrombocytopenia are described below (Table 3).

Table 3: Dose Adjustments for Neutropenia and Thrombocytopenia in Adult Patients

ANC[a] less than 1000 $x10^6$/L or Platelets less than 50,000 $x10^6$/L	Withhold bosutinib tablets until ANC greater than or equal to 1000$x10^6$/ L and platelets greater than or equal to 50,000$x10^6$/L. Resume treatment with bosutinib tablets at the same dose if recovery occurs within 2 weeks. If blood counts remain low for greater than 2 weeks, upon recovery, reduce dose by 100 mg and resume treatment. If cytopenia recurs, reduce dose by an additional 100 mg upon recovery and resume treatment.

[a] Absolute Neutrophil Count

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2.5 Dosage Adjustments for Renal Impairment or Hepatic Impairment

The recommended starting doses for patients with renal and hepatic impairment are described in Table 4 below.

Table 4: Dose Adjustments for Renal and Hepatic Impairment in Adult Patients

	Recommended Starting Dosage
	Chronic, accelerated, or blast phase Ph+ CML with resistance or intolerance to prior therapy
Normal	500 mg daily
Renal impairment	
Creatinine clearance 30 to 50 mL/min	400 mg daily
Creatinine clearance less than 30 mL/min	300 mg daily
Hepatic impairment	
Mild (Child-Pugh A), Moderate (Child-Pugh B) or severe (Child-Pugh C)	200 mg daily

[see Use in Specific Populations (8.6, 8.7) and Clinical Pharmacology (12.3)].

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3 DOSAGE FORMS AND STRENGTHS

• 100 mg are yellow colored, oval shaped, biconvex, film coated tablet, debossed with L603 on one side and plain on other side.
• 500 mg are red colored, oval shaped, biconvex, film coated tablet debossed with L604 on one side and plain on the other.

4 CONTRAINDICATIONS

Bosutinib tablet is contraindicated in patients with a history of hypersensitivity to bosutinib. Reactions have included anaphylaxis *[see Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Gastrointestinal Toxicity

Diarrhea, nausea, vomiting, and abdominal pain occur with bosutinib tablets treatment. Monitor and manage patients using standards of care, including antidiarrheals, antiemetics, and fluid replacement.

Among 546 adult patients in a single-arm study in patients with CML who were resistant or intolerant to prior therapy, the median time to onset for diarrhea (all grades) was 2 days and the median duration per event was 2 days. Among the patients who experienced diarrhea, the median number of episodes of diarrhea per patient during treatment with bosutinib tablets was 3 (range 1 to 268).

To manage gastrointestinal toxicity, withhold, dose reduce, or discontinue bosutinib tablets as necessary *[see Dosage and Administration (2.3) and Adverse Reactions (6)]*.

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5.2 Myelosuppression

Thrombocytopenia, anemia and neutropenia occur with bosutinib tablets treatment. Perform complete blood counts weekly for the first month of therapy and then monthly thereafter, or as clinically indicated. To manage myelosuppression, withhold, dose reduce, or discontinue bosutinib tablets as necessary *[see Dosage and Administration (2.4) and Adverse Reactions (6)]*.

5.3 Hepatic Toxicity

Bosutinib may cause elevations in serum transaminases (alanine aminotransferase [ALT], aspartate aminotransferase [AST]).

Two cases consistent with drug induced liver injury (defined as concurrent elevations in ALT or AST greater than or equal to 3×ULN with total bilirubin greater than 2×ULN and alkaline phosphatase less than 2×ULN) have occurred without alternative causes. This represented 2 out of 1711 patients in bosutinib tablets clinical trials.

Among the 546 adult patients in a single-arm study in patients with CML who were resistant or intolerant to prior therapy, the incidence of increased ALT was 53.3% and AST elevation was 46.7%. Sixty percent of the patients experienced an increase in either ALT or AST. Most cases of transaminase elevations in this study occurred early in treatment; of patients who experienced increased transaminase of any grade, more than 81% experienced their first increase within the first 3 months. The median time to onset of increased ALT and AST was 22 and 29 days, respectively, and the median duration for each was 21 days.

Perform hepatic enzyme tests monthly for the first 3 months of bosutinib tablets treatment and as clinically indicated. In patients with transaminase elevations, monitor liver enzymes more frequently. Withhold, dose reduce, or discontinue bosutinib tablets as necessary *[see Dosage and Administration (2.3) and Adverse Reactions (6)]*.

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5.4 Cardiovascular Toxicity

Bosutinib can cause cardiovascular toxicity including cardiac failure, left ventricular dysfunction, and cardiac ischemic events. Cardiac failure events occurred more frequently in previously treated patients and were more frequent in patients with advanced age or risk factors, including previous medical history of cardiac failure. Cardiac ischemic events occurred in previously treated patients and were more common in patients with coronary artery disease risk factors, including history of diabetes, body mass index greater than 30, hypertension, and vascular disorders.

In a single-arm study in adult patients with CML who were resistant or intolerant to prior therapy, cardiac failure was observed in 5.3% of patients and cardiac ischemic events were observed in 5.1% of patients treated with bosutinib.

Monitor patients for signs and symptoms consistent with cardiac failure and cardiac ischemia and treat as clinically indicated. Interrupt, dose reduce, or discontinue bosutinib as necessary *[see Dosage and Administration (2.3)and Adverse Reactions (6)].*

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5.5 Fluid Retention

Fluid retention occurs with bosutinib tablets and may manifest as pericardial effusion, pleural effusion, pulmonary edema, and/or peripheral edema.

Among 546 adult patients in a single-arm study in patients with Ph+ CML who were resistant or intolerant to prior therapy, Grade 3 or 4 fluid retention was reported in 30 patients (6%). Some patients experienced more than one fluid retention event. Specifically, 24 patients experienced Grade 3 or 4 pleural effusions, 9 patients experienced Grade 3 or Grade 4 pericardial effusions, and 6 patients experienced Grade

3 edema.

Monitor and manage patients using standards of care. Interrupt, dose reduce or discontinue bosutinib tablets as necessary *[see Dosage and Administration (2.3) and Adverse Reactions (6)]*.

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5.6 Renal Toxicity

An on-treatment decline in estimated glomerular filtration rate (eGFR) has occurred in patients treated with bosutinib tablets. Table 6 identifies the shift from baseline to lowest observed eGFR during bosutinib tablets therapy for patients in the pooled leukemia studies regardless of line of therapy. The median duration of therapy with bosutinib tablets was approximately 24 months (range, 0.03 to 155) for patients in these studies.

Table 6: Shift From Baseline to Lowest Observed eGFR Group During Treatment Safety Population in Clinical Studies (N=1372)*

Baseline		**Follow-Up**					
Renal Function Status	**N**	**Normal n (%)**	**Mild n (%)**	**Mild to Moderate n (%)**	**Moderate to Severe n (%)**	**Severe n (%)**	**Kidney Failure n (%)**
Normal	527	115 (21.8)	330 (62.6)	50 (9.5)	23 (4.4)	3 (0.6)	5 (0.9)
Mild	672	10 (1.5)	259 (38.5)	271 (40.3)	96 (14.3)	26 (3.9)	6 (0.9)
Mild to Moderate	137	0	6 (4.4)	40 (29.2)	66 (48.2)	24 (17.5)	1 (0.7)
Moderate to Severe	33	0	1 (3)	1 (3)	8 (24.2)	19 (57.6)	4 (12.1)
Severe	1	0	0	0	0	0	1 (100)
Total	1370	125 (9.1)	596 (43.5)	362 (26.4)	193 (14.1)	72 (5.2)	17 (1.2)

Abbreviations: eGFR=estimated glomerular filtration rate; N/n=number of patients.
Notes: eGFR was calculated using Modification in Diet in Renal Disease method (MDRD).
Notes: Grading is based on Kidney Disease Improving Global Outcomes (KDIGO) Classification by eGFR: Normal: greater than or equal to 90, Mild: 60 to less than 90, Mild to Moderate: 45 to less than 60, Moderate to Severe: 30 to less than 45, Severe: 15 to less than 30, Kidney Failure: less than 15 ml/min/1.73 m^2.
*Among the 1372 patients, eGFR was missing in 7 patients at baseline or on-therapy. There were no patients with kidney failure at baseline.

Monitor renal function at baseline and during therapy with bosutinib tablets, with particular attention to those patients who have preexisting renal impairment or risk factors for renal dysfunction. Consider dose adjustment in patients with baseline and treatment emergent renal impairment *[see Dosage and Administration (2.5)]*.

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5.7 Embryofetal Toxicity

Based on findings from animal studies and its mechanism of action, bosutinib tablets can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies conducted in rats and rabbits, oral administration of bosutinib during organogenesis caused adverse developmental outcomes, including structural abnormalities, embryo-fetal mortality, and alterations to growth at maternal exposures (AUC) as low as 1.2 times the human exposure at the dose of 500 mg/day. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential

to use effective contraception during treatment and for 2 weeks after the last dose *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Gastrointestinal toxicity *[see Warnings and Precautions (5.1)]*.
- Myelosuppression *[see Warnings and Precautions (5.2)]*.
- Hepatic toxicity *[see Warnings and Precautions (5.3)]*.
- Cardiovascular toxicity *[see Warnings and Precautions (5.4)].*
- Fluid retention *[see Warnings and Precautions (5.5)]*.
- Renal toxicity *[see Warnings and Precautions (5.6)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common adverse reactions, in ≥20% of adults with resistance or intolerance to prior therapy (N=814) were diarrhea (80%), rash (44%), nausea (44%), abdominal pain (43%), vomiting (33%), fatigue (33%), hepatic dysfunction (33%), respiratory tract infection (25%), pyrexia (24%), and headache (21%).

The most common laboratory abnormalities that worsened from baseline in ≥20% of adults were creatinine increased (93%), hemoglobin decreased (90%), lymphocyte count decreased (72%), platelets decreased (69%), ALT increased (58%), calcium decreased (53%), white blood cell count decreased (52%), absolute neutrophils count decreased (50%), AST increased (50%), glucose increased (46%), phosphorus decreased (44%), urate increased (41%), alkaline phosphatase increased (40%), lipase increased (36%), creatine kinase increased (29%), and amylase increased (24%).

Adverse Reactions in Adult Patients With Imatinib-Resistant or-Intolerant Ph+ CP, AP, and BP CML

The single-arm clinical trial enrolled patients with Ph+ CP, AP and BP CML and with resistance or intolerance to prior therapy *[see Clinical Studies (14.2)].* The safety population (received at least 1 dose of bosutinib tablets) included 546 CML patients:

• two hundred eighty-four (284) patients with CP CML previously treated with imatinib only who had a median duration of bosutinib tablets treatment of 26 months (range: 0.2 to 155 months), and a median dose intensity of 437 mg/day.
• one hundred and nineteen (119) patients with CP CML previously treated with both imatinib and at least 1 additional tyrosine kinase inhibitor (TKI) who had a median duration of bosutinib tablets treatment of 9 months (range: 0.2 to 148 months), and a median dose intensity of 427 mg/day.
• one hundred forty three (143) patients with advanced phase (AdvP) CML including 79 patients with AP CML and 64 patients with BP CML. In the patients with AP CML and BP CML, the median duration of bosutinib tablets treatment was 10 months (range: 0.1 to 140 months) and 3 months (range: 0.03 to 71 months), respectively. The median dose intensity was 406 mg/day, and 456 mg/day, in the AP CML and BP CML cohorts, respectively.

Serious adverse reactions occurred in 30% of patients in the safety population of the single-arm trial in patients with CML (N=546) who were resistant or intolerant to prior therapy. Serious adverse reactions reported in >2% of patients included pneumonia (7%), pleural effusion (6%), pyrexia (3.7%), coronary artery disease (3.5%), dyspnea (2.6%), rash (2.2%), thrombocytopenia (2%), abdominal pain (2%), and diarrhea (2%). Fatal adverse reactions occurred in 12 patients (2.2%) due to coronary artery disease (0.9%), pneumonia (0.4%), respiratory failure (0.4%), gastrointestinal hemorrhage (0.2%), acute kidney injury (0.2%), and acute pulmonary edema (0.2%).

Permanent discontinuation of bosutinib due to an adverse reaction occurred in 22% of patients with CML who were resistant or intolerant to prior therapy. Adverse reactions which resulted in permanent discontinuation in >2% of patients included

thrombocytopenia (6%), hepatic dysfunction (3.3%), and neutropenia (2%).

Dose modifications (dose interruption or reductions) of bosutinib due to an adverse reaction occurred in 66% of patients with CML who were resistant or intolerant to prior therapy. Adverse reactions which required dose interruptions or reductions in >5% of patients included thrombocytopenia (24%), diarrhea (14%), rash (13%), hepatic dysfunction (10%), neutropenia (9%), pleural effusion (8%), vomiting (7%), anemia (6%), and abdominal pain (6%).

The most common adverse reactions, in ≥20% of patients in the safety population of the single-arm trial in patients with CML (N=546) who were resistant or intolerant to prior therapy were diarrhea (83%), nausea (47%), rash (46%), abdominal pain (45%), vomiting (39%), fatigue (33%), pyrexia (28%), hepatic dysfunction (27%), respiratory tract infection (24%), cough (23%), and headache (21%).

The most common laboratory abnormalities that worsened from baseline in ≥20% were creatinine increased (93%), hemoglobin decreased (91%), lymphocyte decreased (80%), platelets decreased (69%), absolute neutrophil count (54%), ALT increased (53%), calcium decreased (53%), white blood cell count decreased (52%), urate increased (48%), AST increased (47%), phosphorus decreased (39%), alkaline phosphatase increased (39%), lipase increased (28%), magnesium increased (25%), potassium decreased (24%), potassium increased (23%). See Table 10 for Grade 3/4 laboratory abnormalities.

Table 9 identifies adverse reactions greater than or equal to 10% for All Grades and Grades 3 or 4 for the Phase 1/2 CML safety population based on long-term follow-up.

Table 9: Adverse Reactions (10% or Greater) in Patients With CML Who Were Resistant or Intolerant to Prior Therapy in Single-Arm Trial*

System Organ Class	Preferred Term	CP CML N=403		AdvP CML N=143	
		All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Gastrointestinal disorders	Diarrhea	85	10	76	4
	Abdominal pain[a]	49	2	36	7
	Nausea	47	1	48	2
	Vomiting	38	3	43	3
	Constipation	15	<1	17	1
Skin and subcutaneous tissue disorders	Rash[e]	48	9	42	5
	Pruritus	12	1	7	0
General disorders and administration-site conditions	Fatigue	35	3	27	6
	Pyrexia	25	1	37	3
	Edema[c]	19	<1	17	1
	Chest pain[g]	8	1	12	1
Hepatobiliary disorders	Hepatic dysfunction[h]	29	11	21	10
Infections and infestations	Respiratory tract infection[f]	27	<1	17	0
	Influenza[i]	11	1	3	0

	Pneumonia[d]	10	4	18	12
Respiratory, thoracic, and mediastinal disorders	Cough	24	0	22	0
	Pleural effusion	14	4	9	4
	Dyspnea	12	2	20	6
Nervous system disorders	Headache	21	1	18	4
	Dizziness	11	0	14	1
Musculoskeletal and connective tissue disorders	Arthralgia	19	1	15	0
	Back pain	14	1	8	1
Metabolism and nutrition disorders	Decreased appetite	14	1	14	0
Vascular disorders	Hypertension[b]	11	3	8	3

ADR Definition
* Based on Minimum of 105 Months of Follow-up.
Adverse drug reactions are based on all-causality treatment-emergent adverse events.
The commonality stratification is based on 'All Grades' under Total column.
'Grade 3', 'Grade 4' columns indicate maximum toxicity
[a] Abdominal pain includes the following preferred terms: Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Dyspepsia, Epigastric discomfort, Gastrointestinal pain, Hepatic pain.
[g] Chest pain includes the following preferred terms: Chest discomfort, Chest pain.
[h] Hepatic dysfunction includes the following preferred terms: Alanine aminotransferase increased, Aspartate aminotransferase increased, Bilirubin conjugated increased, Blood alkaline phosphatase increased, Blood bilirubin increased, Blood bilirubin unconjugated increased, Gamma-glutamyltransferase increased, Hepatic enzyme increased, Hepatic function abnormal, Hepatic steatosis, Hepatitis toxic, Hepatomegaly, Hepatotoxicity, Hyperbilirubinemia, Liver disorder, Liver function test abnormal, Liver function test increased, Transaminases increased.
[b] Hypertension* includes the following preferred terms: Blood pressure increased, Blood pressure systolic increased, Essential hypertension, Hypertension, Hypertensive crisis, Retinopathy hypertensive.
[i] Influenza includes the following preferred terms: H1N1 influenza, Influenza.
[c] Edema includes the following preferred terms: Eye edema, Eyelid edema, Face edema, Generalized edema, Localized edema, Edema, Edema peripheral, Penile edema, Periorbital edema, Periorbital swelling, Peripheral swelling, Scrotal edema, Scrotal swelling, Swelling, Swelling face, Swelling of eyelid, Testicular edema, Tongue edema.
[d] Pneumonia includes the following preferred terms: Atypical pneumonia, Lower respiratory tract congestion, Lower respiratory tract infection, Pneumonia, Pneumonia aspiration, Pneumonia bacterial, Pneumonia fungal, Pneumonia necrotising, Pneumonia streptococcal.
[e] Rash includes the following preferred terms: Acarodermatitis, Acne, Angular cheilitis, Blister, Dermatitis, Dermatitis acneiform, Dermatitis psoriasiform, Drug eruption, Eczema, Eczema asteatotic, Erythema, Erythema annulare, Exfoliative rash, Lichenoid keratosis, Palmar erythema, Photosensitivity reaction, Pigmentation disorder, Psoriasis, Pyoderma gangrenosum, Pyogenic granuloma, Rash, Rash erythematous, Rash generalised, Rash macular, Rash maculo-papular, Rash pruritic, Rash pustular, Seborrhoeic dermatitis, Seborrhoeic keratosis, Skin depigmentation, Skin discoloration, Skin disorder, Skin exfoliation, Skin hyperpigmentation, Skin hypopigmentation, Skin irritation, Skin lesion, Skin plaque, Skin toxicity, Stasis dermatitis.
[f] Respiratory tract infection includes the following preferred terms: Nasopharyngitis, Respiratory tract congestion, Respiratory tract infection, Respiratory tract infection viral, Upper respiratory tract infection, Viral upper respiratory tract infection.
* ADR identified post-marketing

In the single-arm study in patients with CML who were resistant or intolerant to prior therapy, 2 patients (0.4%) experienced QTcF interval of greater than 500 milliseconds. Patients with uncontrolled or significant cardiovascular disease including QT interval

prolongation were excluded by protocol.

Table 10 identifies the clinically relevant or severe Grade 3/4 laboratory test abnormalities for the safety population of the study in patients with CML who were resistant or intolerant to prior therapy based on long-term follow-up.

Table 10: Number (%) of Patients With Clinically Relevant All Grade or Grade 3/4 Laboratory Test Abnormalities in the Safety Population of the Study of Patients With CML Who Were Resistant or Intolerant to Prior Therapy*

	CP CML N=403 %		AdvP CML N=143 %	
	All grade	**Grade 3/4**	**All grade**	**Grade 3/4**
Hematology Parameters				
Platelet Count decreased	66	26	80	57
Absolute Neutrophil Count decreased	50	16	66	39
Hemoglobin decreased	89	13	97	38
Lymphocyte decreased	79	14	82	21
White Blood Cell Count decreased	51	7	57	27
Biochemistry Parameters				
SGPT/ALT increased	58	11	39	6
SGOT/AST increased	50	5	37	3.5
Lipase increased	32	12	19	6
Phosphorus decreased	41	8	33	7
Total Bilirubin increased	16	0.7	22	2.8
Creatinine increased	95	3	87	1.4
Alkaline Phosphatase increased	39	0	39	1.4
Glucose increased	42	2.7	39	6
Sodium increased	23	0.5	11	0
Sodium decreased	18	2.2	27	6
Calcium decreased	55	4.7	45	3.5
Urate increased	49	6	43	6
Magnesium increased	27	7	18	4.9
Potassium decreased	22	1.7	29	4.9
Potassium increased	25	2.7	19	2.1

* Based on Minimum of 105 Months of Follow-up.
Abbreviations: AdvP=advanced phase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CML=chronic myelogenous leukemia; CP=chronic phase; N/n=number of patients; SGPT=serum glutamate-pyruvate transaminase; SGOT=serum

glutamate-oxaloacetate aminotransferase; ULN=upper limit of normal.

Additional Adverse Reactions From Multiple Clinical Trials
The following adverse reactions were reported in patients in clinical trials with bosutinib tablets (less than 10% of bosutinib tablets-treated patients). They represent an evaluation of the adverse reaction data from all 1372 patients with leukemia who received at least 1 dose of single-agent bosutinib tablets. These adverse reactions are presented by system organ class and are ranked by frequency. These adverse reactions are included based on clinical relevance and ranked in order of decreasing seriousness within each category.

Blood and Lymphatic System Disorders: *0.1% and less than 1%* - Febrile neutropenia
Cardiac Disorders: *1% and less than 10%* - Cardiac ischemia (includes Acute coronary syndrome, Acute myocardial infarction, Angina pectoris, Angina unstable, Arteriosclerosis coronary artery, Coronary artery disease, Coronary artery occlusion, Coronary artery stenosis, Myocardial infarction, Myocardial ischemia, Troponin increased), Pericardial effusion, Cardiac failure (includes Cardiac failure, Cardiac failure acute, Cardiac failure chronic, Cardiac failure congestive, Cardiogenic shock, Cardiorenal syndrome, Ejection fraction decreased, Left ventricular failure); *0.1% and less than 1%* - Pericarditis
Ear and Labyrinth Disorders: *1% and less than 10%* - Tinnitus
Endocrine Disorders: *1% and less than 10%* - Hypothyroidism; *0.1% and less than 1%* - Hyperthyroidism
Gastrointestinal Disorders: *1% and less than 10%* - Gastritis, Pancreatitis (includes Edematous pancreatitis, Pancreatic enzymes increased, Pancreatitis, Pancreatitis acute, Pancreatitis chronic), Gastrointestinal hemorrhage (includes Anal hemorrhage, Gastric hemorrhage, Gastrointestinal hemorrhage, Intestinal hemorrhage, Lower gastrointestinal hemorrhage, Rectal hemorrhage, Upper gastrointestinal hemorrhage)
General Disorders and Administrative Site Conditions: *1% and less than 10%* - Pain
Immune System Disorders: *1% and less than 10%* - Drug hypersensitivity; *0.1% and less than 1%* - Anaphylactic shock
Infections and Infestations: *1% and less than 10%* - Bronchitis
Investigations: *1% and less than 10%* - Electrocardiogram QT prolonged (includes Electrocardiogram QT prolonged, Long QT syndrome)
Metabolism and Nutrition Disorders: *1% and less than 10%* - Dehydration
Musculoskeletal and Connective Tissue Disorders: *1% and less than 10%* - Myalgia
Nervous System Disorders: *1% and less than 10%* - Dysgeusia
Renal and Urinary Disorders: *1% and less than 10%* - Acute kidney injury, Renal impairment, Renal failure
Respiratory, Thoracic and Mediastinal Disorders: *1% and less than 10%* - Pulmonary hypertension (includes Pulmonary hypertension, Pulmonary arterial hypertension, Pulmonary arterial pressure increased); *0.1% and less than 1%* - Acute pulmonary edema (includes Acute pulmonary edema, Pulmonary edema), Interstitial lung disease, Respiratory failure
Skin and Subcutaneous Disorders: *0.1% and less than 1%* - Erythema multiforme, Cutaneous vasculitis

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6.2 Postmarketing Experience

The following additional adverse reactions have been identified during post-approval use of bosutinib tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Blood and Lymphatic System Disorders: Thrombotic microangiopathy
Skin and Subcutaneous Tissue Disorders: Stevens-Johnson syndrome

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on Bosutinib Tablets

Strong or Moderate CYP3A Inhibitors
Avoid the concomitant use of strong or moderate CYP3A inhibitors with bosutinib tablets. Bosutinib is a CYP3A substrate. Concomitant use with a strong or moderate CYP3A inhibitor increases bosutinib C_{max} and AUC *[see Clinical Pharmacology (12.3)]* which may increase the risk of toxicities.

Strong CYP3A Inducers
Avoid the concomitant use of strong CYP3A inducers with bosutinib tablets. Bosutinib is a CYP3A substrate. Concomitant use with a strong CYP3A inducer decreases bosutinib C_{max} and AUC *[see Clinical Pharmacology (12.3)]* which may reduce bosutinib tablets efficacy.

Proton Pump Inhibitors (PPI)
As an alternative to PPIs, use short-acting antacids or H2 blockers and separate dosing by more than 2 hours from bosutinib tablets dosing. Bosutinib displays pH dependent aqueous solubility, Concomitant use with a PPI decreases bosutinib C_{max} and AUC *[see Clinical Pharmacology (12.3)]* which may reduce bosutinib tablets efficacy.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, bosutinib tablets can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*.

There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies conducted in rats and rabbits, oral administration of bosutinib during organogenesis caused adverse developmental outcomes, including structural abnormalities, embryo-fetal mortality, and alterations to growth at maternal exposures (AUC) as low as 1.2 times the human exposure at the dose of 500 mg/day *(see Data)*. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies are 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In a rat fertility and early embryonic development study, bosutinib was administered orally to female rats for approximately 3 to 6 weeks, depending on day of mating (2 weeks prior to cohabitation with untreated breeder males until gestation day [GD] 7). Increased embryonic resorptions occurred at greater than or equal to 10 mg/kg/day of bosutinib (1.6 and 1.2 times the human exposure at the recommended doses of 400 or 500 mg/day, respectively), and decreased implantations and reduced number of viable embryos at 30 mg/kg/day of bosutinib (3.4 and 2.5 times the human exposure at the recommended doses of 400 or 500 mg/day, respectively).

In an embryo-fetal development study conducted in rabbits, bosutinib was administered orally to pregnant animals during the period of organogenesis at doses of 3, 10 and 30 mg/kg/day. At the maternally-toxic dose of 30 mg/kg/day of bosutinib, there were fetal anomalies (fused sternebrae, and 2 fetuses had various visceral observations), and an approximate 6% decrease in fetal body weight. The dose of 30 mg/kg/day resulted in exposures (AUC) approximately 5.1 and 3.8 times the human exposures at the recommended doses of 400 and 500 mg/day, respectively.

Fetal exposure to bosutinib-derived radioactivity during pregnancy was demonstrated in a placental-transfer study in pregnant rats. In a rat pre-and postnatal development study, bosutinib was administered orally to pregnant animals during the period of organogenesis through lactation day 20 at doses of 10, 30, and 70 mg/kg/day. Reduced number of pups born occurred at greater than or equal to 30 mg/kg/day bosutinib (3.4 and 2.5 times the human exposure at the recommended doses of 400 or 500 mg/day, respectively), and increased incidence of total litter loss and decreased growth of offspring after birth occurred at 70 mg/kg/day bosutinib (6.9 and 5.1 times the human exposure at the recommended doses of 400 or 500 mg/day, respectively).

8.2 Lactation

Risk Summary

No data are available regarding the presence of bosutinib or its metabolites in human milk or its effects on a breastfed child or on milk production. However, bosutinib is present in the milk of lactating rats. Because of the potential for serious adverse reactions in a nursing child, breastfeeding is not recommended during treatment with bosutinib tablets and for 2 weeks after the last dose.

Animal Data

After a single radiolabeled bosutinib dose to lactating rats, radioactivity was present in the plasma of suckling offspring for 24 to 48 hours.

8.3 Females and Males of Reproductive Potential

Based on findings from animal studies, bosutinib tablets can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy
Females of reproductive potential should have a pregnancy test prior to starting treatment with bosutinib tablets.

Contraception

Females

Advise females of reproductive potential to use effective contraception (methods that result in less than 1% pregnancy rates) during treatment with bosutinib tablets and for 2 weeks after the last dose.

Infertility

The risk of infertility in females or males of reproductive potential has not been studied in humans. Based on findings from animal studies, bosutinib tablets may cause reduced fertility in females and males of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of bosutinib tablets in pediatric patients younger than 1 year of age with newly diagnosed CP Ph+ CML, pediatric patients younger than 1 year of age with CP Ph+ CML that is resistant or intolerant to prior therapy, and pediatric patients with AP Ph+ CML or BP Ph+ CML have not been established.

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8.5 Geriatric Use

In the single-arm study in patients with CML who were resistant or intolerant to prior therapy of bosutinib tablets in patients with Ph+ CML, 20% were age 65 and over, 4% were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

Reduce the bosutinib tablets starting dose in patients with moderate (creatinine clearance [CL_{cr}] 30 to 50 mL/min, estimated by Cockcroft-Gault (C-G)) and severe (CL_{cr} less than 30 mL/min, C-G) renal impairment at baseline. For patients who have declining renal function while on bosutinib tablets who cannot tolerate the starting dose, follow dose adjustment recommendations for toxicity *[see Dosage and Administration (2.3, 2.5) and Clinical Pharmacology (12.3)]*. Bosutinib tablet has not been studied in patients undergoing hemodialysis.

8.7 Hepatic Impairment

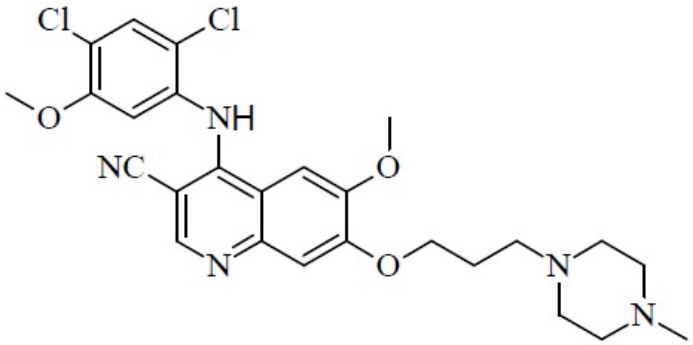
Reduce the bosutinib tablets dosage in patients with hepatic impairment (Child-Pugh A, B, or C) *[see Dosage and Administration (2.3, 2.5) and Clinical Pharmacology (12.3)].*

10 OVERDOSAGE

Experience with bosutinib tablets overdose in clinical studies was limited to isolated cases. There were no reports of any serious adverse events associated with the overdoses. Patients who take an overdose of bosutinib tablets should be observed and given appropriate supportive treatment.

11 DESCRIPTION

Bosutinib tablet contains bosutinib, a kinase inhibitor. The chemical name for bosutinib is 3-Quinolinecarbonitrile, 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-methyl-1-piperazinyl) propoxy]. Its chemical formula is $C_{26}H_{29}Cl_2N_5O_3$; its molecular weight is 530.45. Bosutinib has the following chemical structure:



Bosutinib is a white to yellowish-tan powder. Bosutinib is freely soluble in dimethyl sulfoxide, very slightly soluble in ethyl acetate and practically insoluble in water.

Bosutinib tablets are supplied for oral administration in two strengths: 100 mg and 500 mg. Each strength reflects the equivalent amount of bosutinib content (on anhydrous basis). The tablets contain the following inactive ingredients: croscarmellose sodium, hypromellose, iron oxide red (for 500 mg tablet), iron oxide yellow (for 100 mg tablet), magnesium stearate, microcrystalline cellulose, poloxamer 188, polyethylene glycol 6000, povidone K-25, talc (for 500 mg tablet) and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Bosutinib is a TKI. Bosutinib inhibits the BCR-ABLkinase that promotes CML; it is also an inhibitor of Src-family kinases including Src, Lyn, and Hck. Bosutinib inhibited 16 of 18 imatinib-resistant forms of BCR-ABL kinase expressed in murine myeloid cell lines. Bosutinib did not inhibit the T315I and V299L mutant cells.

12.2 Pharmacodynamics

A greater likelihood of response and a greater likelihood of safety events were observed with higher bosutinib exposure in clinical studies. The time course of bosutinib pharmacodynamic response has not been fully characterized.

Cardiac Electrophysiology
At a single oral dose of 500 mg bosutinib tablet with ketoconazole (a strong CYP3A inhibitor), bosutinib tablets does not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

Bosutinib pharmacokinetics were assessed following oral dosing with food in adult patients with CML and were presented as geometric mean (CV%), unless otherwise specified.

Bosutinib exhibits dose proportional increases in C_{max} and AUC over the oral dose range

of 200 to 800 mg (0.33 to 1.3 times the maximum approved recommended dosage of 600 mg). Bosutinib steady state C_{max} was 127 ng/mL (31%), C_{trough} was 68 ng/mL (39%) and AUC was 2370 ng•h/mL (34%) following multiple oral doses of bosutinib tablets 400 mg; Bosutinib steady state C_{max} was 171 ng/mL (38%),C_{trough} was 91 ng/mL (42%) and AUC was 3150 ng•h/mL (38%) following multiple oral doses of bosutinib tablets 500 mg. No clinically significant differences in the pharmacokinetics of bosutinib were observed following administration of either the tablet or capsule dosage forms of bosutinib at the same dose, under fed conditions.

Absorption

The median bosutinib (minimum, maximum) time-to-C_{max} (t_{max}) was 6 (6, 6) hours following oral administration of a single oral dose of bosutinib tablets 500 mg with food. The absolute bioavailability was 34% in healthy subjects.

Effect of Food

Bosutinib C_{max} increased 1.8-fold and AUC increased 1.7-fold when bosutinib tablets were given with a high fat meal to healthy subjects compared to administration under fasted condition. The high-fat meal (800 to 1000 total calories) consisted of approximately 150 protein calories, 250 carbohydrate calories, and 500 to 600 fat calories.

Distribution

The mean (SD) apparent bosutinib volume of distribution is 6080 (1230) L after an oral dose of 500 mg of bosutinib. Bosutinib protein binding is 94% *in vitro* and 96% ex vivo, and is independent of concentration.

Elimination

The mean (SD) bosutinib terminal phase elimination half-life ($t_{½}$) was 22.5 (1.7) hours, and the mean (SD) apparent clearance was 189 (48) L/h following a single oral dose of bosutinib tablets.

Metabolism

Bosutinib is primarily metabolized by CYP3A4.

Excretion

Following a single oral dose of [^{14}C] radiolabeled bosutinib without food, 91.3% of the dose was recovered in feces and 3.3% of the dose recovered in urine.

Specific Populations

Patients with Renal Impairment

Bosutinib AUC increased 1.4-fold in subjects with moderate renal impairment (CL_{cr}: 30 to 50 mL/min, estimated by Cockcroft-Gault (C-G)) and increased 1.6-fold in subjects with severe renal impairment (CL_{cr} less than 30 mL/min) following a single oral dose of bosutinib tablets 200 mg (0.33 times the maximum approved recommended dosage of 600 mg). No clinically significant difference in the pharmacokinetics of bosutinib was observed in subjects with mild renal impairment (CL_{cr}: 51 to 80 mL/min, C-G). Bosutinib tablets has not been studied in patients undergoing hemodialysis.

Patients with Hepatic Impairment

Bosutinib C_{max} increased 2.4-fold, 2-fold, and 1.5-fold, and AUC increased 2.3-fold, 2-fold, and 1.9-fold in hepatic impairment Child-Pugh A, B, and C, respectively, following a single oral dose of bosutinib tablet 200 mg (0.33 times the maximum approved recommended dosage of 600 mg).

Drug Interaction Studies

Clinical Studies

Strong CYP3A Inhibitors: Bosutinib C_{max} increased 5.2-fold and AUC increased 8.6-fold following a single dose of bosutinib tablets 100 mg (0.17 times the maximum approved recommended dosage) without food when used concomitantly with 400 mg ketoconazole (a strong CYP3A inhibitor) administered over multiple daily doses.

Moderate CYP3A Inhibitors: Bosutinib C_{max} increased 1.5-fold and AUC increased 2.0-fold following a single dose of bosutinib tablet 500 mg with food when administered concomitantly with 125 mg aprepitant (a moderate CYP3A inhibitor).

Strong CYP3A Inducers: Bosutinib C_{max} decreased by 86% and AUC decreased by 94% following a single dose of bosutinib tablet 500 mg with food administered concomitantly with multiple daily doses of 600 mg of rifampin (a strong CYP3A inducer).

Proton Pump Inhibitors: Lansoprazole decreased bosutinib C_{max} by 46% and AUC by 26% following a single oral dose of bosutinib tablet 400 mg without food when used concomitantly with lansoprazole 60 mg (proton pump inhibitor) administered over multiple daily doses. Bosutinib displays pH-dependent aqueous solubility, in vitro *[see Description (11)].*

P-gp Substrates: No clinically significant differences in bosutinib pharmacokinetics were observed when used concomitantly with dabigatran etexilate mesylate (a P-glycoprotein (P-gp) substrate).

In Vitro Studies

Transporters Systems:

Bosutinib inhibits breast cancer resistance protein (BCRP) but, does not inhibit organic anion transporting polypeptide (OATP)1B1, OATP1B3, organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)1, and OCT2.

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13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Bosutinib was not carcinogenic in rats or transgenic mice. The rat 2-year carcinogenicity study was conducted at bosutinib oral doses up to 25 mg/kg in males and 15 mg/kg in females. Exposures at these doses were approximately 1.5 times (males) and 3.1 times (females) the human exposure at the 400 mg dose and 1.2 times (males) and 2.4 times (females) exposure in humans at the 500 mg dose. The 6-month RasH2 transgenic mouse carcinogenicity study was conducted at bosutinib oral doses up to 60 mg/kg.

Bosutinib was not mutagenic or clastogenic in a battery of tests, including the bacteria reverse mutation assay (Ames Test), the *in vitro* assay using human peripheral blood lymphocytes and the micronucleus test in orally treated male mice.

In a rat fertility study, drug-treated males were mated with untreated females, or untreated males were mated with drug-treated females. Females were administered the drug from pre-mating through early embryonic development. The dose of 70 mg/kg/day of bosutinib resulted in reduced fertility in males as demonstrated by 16% reduction in the number of pregnancies. There were no lesions in the male reproductive organs at this dose. This dose of 70 mg/kg/day resulted in exposure (AUC) in male rats approximately 1.5 times and equal to the human exposure at the recommended doses of 400 and 500 mg/day, respectively. Fertility (number of pregnancies) was not affected when female rats were treated with bosutinib. However, there were increased embryonic resorptions at greater than or equal to 10 mg/kg/day of bosutinib (1.6 and 1.2 times the human exposure at the recommended doses of 400 and 500 mg/day, respectively), and decreased implantations and reduced number of viable embryos at 30 mg/kg/day of bosutinib (3.4 and 2.5 times the human exposure at the recommended doses of 400 or 500 mg/day, respectively).

14 CLINICAL STUDIES

14.2 Adult Patients with Imatinib-Resistant or -Intolerant Ph+ CP, AP, and BP

CML

Study 200 (NCT00261846), a single-arm open-label, multicenter study in patients with CML who were resistant or intolerant to prior therapy was conducted to evaluate the efficacy and safety of bosutinib tablets 500 mg once daily in patients with imatinib-resistant or -intolerant CML with separate cohorts for CP, AP, and BP disease previously treated with 1 prior TKI (imatinib) or more than 1 TKI (imatinib followed by dasatinib and/or nilotinib). The definition of imatinib resistance included (1) failure to achieve or maintain any hematologic improvement within 4 weeks; (2) failure to achieve a CHR by 3 months, cytogenetic response by 6 months or major cytogenetic response (MCyR) by 12 months; (3) progression of disease after a previous cytogenetic or hematologic response; or (4) presence of a genetic mutation in the BCR-ABL gene associated with imatinib resistance. Imatinib intolerance was defined as inability to tolerate imatinib due to toxicity, or progression on imatinib and inability to receive a higher dose due to toxicity. The definitions of resistance and intolerance to both dasatinib and nilotinib were similar to those for imatinib. The protocol was amended to exclude patients with a known history of the T315I mutation after 396 patients were enrolled in the trial.

The efficacy endpoints for patients with CP CML previously treated with 1 prior TKI (imatinib) were the rate of attaining MCyR by Week 24 and the duration of MCyR. The efficacy endpoints for patients with CP CML previously treated with both imatinib and at least 1 additional TKI were the cumulative rate of attaining MCyR by Week 24 and the duration of MCyR. The efficacy endpoints for patients with previously treated AP and BP CML were confirmed CHR and overall hematologic response (OHR).

The study enrolled 546 patients with CP, AP or BP CML. Of the total patient population 73% were imatinib resistant and 27% were imatinib intolerant. In this trial, 53% of patients were males, 65% were Caucasian, and 20% were 65 years old or older. Of the 546 treated patients, 506 were considered evaluable for cytogenetic or hematologic efficacy assessment. Patients were evaluable for efficacy if they had received at least 1 dose of bosutinib tablets and had a valid baseline efficacy assessment. Among evaluable patients, there were 262 patients with CP CML previously treated with 1 prior TKI (imatinib), 112 patients with CP CML previously treated with both imatinib and at least 1 additional TKI, and 132 patients with advanced phase CML previously treated with at least 1 TKI.

Median duration of bosutinib tablets treatment was 26 months in patients with CP CML previously treated with 1 TKI (imatinib), 9 months in patients with CP CML previously treated with imatinib and at least 1 additional TKI, 10 months in patients with AP CML previously treated with at least imatinib, and 3 months in patients with BP CML previously treated with at least imatinib.

The 24 week efficacy and MCyR at any time results are summarized in Table 14.

Table 14: Efficacy Results in Patients with Ph+ CP CML With Resistance to or Intolerance to Imatinib

	Prior Treatment With Imatinib Only (N=262 evaluable) n (%)	**Prior Treatment With Imatinib and Dasatinib or Nilotinib (N=112 evaluable) n (%)**
By Week 24 MCyR (95% CI)	 105 (40.1) (34.1, 46.3)	 29 (25.9) (18.1, 35)
MCyR any time	156 (59.5) (53.3, 65.5)	45 (40.2) (31, 49.9)

Abbreviations: CI=confidence interval; CML=chronic myelogenous leukemia; CP=chronic phase; MCyR=major cytogenetic response; N/n=number of patients; Ph+=Philadelphia chromosome positive.

The long-term follow-up data analysis was based on a minimum of 60 months for patients with CP CML treated with 1 prior TKI (imatinib) and a minimum of 48 months for patients with CP CML treated with imatinib and at least 1 additional TKI. For the 59.5% of patients with CP CML treated with 1 prior TKI (imatinib) who achieved a MCyR at any time, the median duration of MCyR was not reached. Among these patients, 65.4% and 42.9% had a MCyR lasting at least 18 and 54 months, respectively. For the 40.2% of patients with CP CML treated with imatinib and at least 1 additional TKI who achieved a

MCyR at any time, the median duration of MCyR was not reached. Among these patients, 64.4% and 35.6% had a MCyR lasting at least 9 and 42 months, respectively. Of the 403 treated patients with CP CML, 20 patients had confirmed disease transformation to AP or BP while on treatment with bosutinib tablets.

The 48-week efficacy results in patients with accelerated and blast phases CML previously treated with at least imatinib are summarized in Table 15.

Table 15: Efficacy Results in Patients With Accelerated Phase and Blast Phase CML Previously Treated With at Least Imatinib

	AP CML (N=72 evaluable) (n%)	**BP CML (N=60 evaluable) n (%)**
CHR[a] by Week 48 (95% CI)	22 (30.6) (20.2, 42.5)	10 (16.7) (8.3, 28.5)
OHR[a] by Week 48 (95% CI)	41 (56.9) (44.7, 68.6)	17 (28.3) (17.5, 41.4)

Abbreviations: AP=accelerated phase; BP=blast phase; CHR=complete hematologic response; CI=confidence interval; CML=chronic myelogenous leukemia; CI=confidence interval, OHR=overall hematologic response, CHR=complete hematologic response, N/n=number of patients

[a.] Overall hematologic response (OHR) = major hematologic response (complete hematologic response + no evidence of leukemia) or return to chronic phase (RCP). All responses were confirmed after 4 weeks. Complete hematologic response (CHR) for AP and BP CML: WBC less than or equal to institutional ULN, platelets greater than or equal to 100,000/mm^3 and less than 450,000/mm^3, absolute neutrophil count (ANC) greater than or equal to 1×10^9 /L, no blasts or promyelocytes in peripheral blood, less than 5% myelocytes + metamyelocytes in bone marrow, less than 20% basophils in peripheral blood, and no extramedullary involvement. No evidence of leukemia (NEL): Meets all other criteria for CHR except may have thrombocytopenia (platelets greater than or equal to 20,000/mm^3 and less than 100,000/mm^3) and/or neutropenia (ANC greater than or equal to 0.5×10^9 /L and less than 1×10^9 /L). Return to chronic phase (RCP) = disappearance of features defining accelerated or blast phases but still in chronic phase.

The long-term follow-up data analysis was based on a minimum of 48 months for patients with AP CML and BP CML. Of the 79 treated patients with AP CML, 3 patients had confirmed disease transformation to BP while on bosutinib tablets treatment.

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16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Bosutinib tablets are available in the following packaging configurations with a child-resistant (CR) closure. Bottle contains desiccants.

Bosutinib tablets 100 mg are yellow colored, oval shaped, biconvex, film coated tablet, debossed with L603 on one side and plain on other side.
NDC 46708-311-35 bottle of 120 tablets

Bosutinib tablets 500 mg are red colored, oval shaped, biconvex, film coated tablet debossed with L604 on one side and plain on the other.

NDC 46708-312-30 bottle of 30 tablets

Storage
Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Handling and Disposal
Procedures for proper disposal of anticancer drugs should be considered. Touching or handling crushed or broken tablets is to be avoided. Any unused product or waste material should be disposed of in accordance with local requirements, or drug take back programs.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

• **Dosage and Administration**
Instruct patients to take bosutinib tablets exactly as prescribed, not to change their dose or to stop taking bosutinib tablets unless they are told to do so by their doctor. If patients miss a dose beyond 12 hours, they should be advised to take the next scheduled dose at its regular time. A double dose should not be taken to make up for any missed dose. Advise patients to take bosutinib tablets with food. Patients should be advised: “Swallow tablets whole. Do not crush, break, or cut tablet. Do not touch or handle crushed or broken tablets.”

• **Gastrointestinal Toxicity**
Advise patients that they may experience diarrhea, nausea, vomiting, abdominal pain, or blood in their stools with bosutinib tablets and to seek medical attention promptly for these symptoms *[see Warnings and Precautions (5.1)].*

• **Myelosuppression**
Advise patients of the possibility of developing low blood cell counts and to immediately report fever, any suggestion of infection, or signs or symptoms suggestive of bleeding or easy bruising *[see Warnings and Precautions (5.2)].*

• **Hepatic Toxicity**
Advise patients of the possibility of developing liver function abnormalities and to immediately report jaundice *[see Warnings and Precautions (5.3)].*

• **Cardiovascular Toxicity**
Advise patients that cardiac failure, left ventricular dysfunction, and cardiac ischemic events have been reported. Advise patients to seek immediate medical attention if any symptoms suggestive of cardiac failure and cardiac ischemia occur, such as shortness of breath, weight gain, or fluid retention *[see Warnings and Precautions (5.4)].*

• **Fluid Retention**
Advise patients of the possibility of developing fluid retention (swelling, weight gain, or shortness of breath) and to seek medical attention promptly if these symptoms arise *[see Warnings and Precautions (5.5)].*

• **Renal Toxicity**
Advise patients of the possibility of developing renal problems and to immediately report frequent urination, polyuria or oliguria *[see Warnings and Precautions (5.6)].*

• **Adverse Reactions**
Advise patients that they may experience other adverse reactions such as respiratory tract infections, rash, fatigue, headache, dizziness, back pain, arthralgia, or pruritus with bosutinib tablets and to seek medical attention if symptoms are significant. There is a possibility of anaphylactic shock *[see Contraindications (4) and Adverse Reactions (6)].*

• **Embryo-Fetal Toxicity**
Advise females to inform their healthcare provider if they are pregnant or become pregnant. Advise female patients of the risk to a fetus and potential loss of the pregnancy *[see Use in Specific Populations (8.1)]*.

Advise females of reproductive potential, to use effective contraception during treatment and for 2 weeks after receiving the last dose of bosutinib tablets *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.1, 8.3)].*

Advise lactating women not to breastfeed during treatment with bosutinib tablets and for 2 weeks after the last dose *[see Use in Specific Populations (8.2)].*

• **Drug Interactions**
Advise patients that bosutinib tablets and certain other medicines, including over the counter medications or herbal supplements (such as St. John’s wort) can interact with each other and may alter the effects of bosutinib tablets *[see Drug Interactions (7)].*

Manufactured by:
Alembic Pharmaceuticals Limited

Formulations Division II,
Panelav 389350, Gujarat, India

Revised: 03/2026

PATIENT INFORMATION
BOSUTINIB (boe sue' ti nib) TABLETS

What is bosutinib tablet?
Bosutinib tablet is a prescription medicine used to treat:
• adults who have a certain type of leukemia called chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML) who no longer benefit from or did not tolerate other treatment.
• adults with accelerated phase (AP), or blast phase (BP) Ph+ CML who can no longer benefit from or did not tolerate other treatment.
It is not known if bosutinib tablets are safe and effective in children less than 1 year of age with CP Ph+ CML who are newly-diagnosed or no longer benefit from or did not tolerate other treatment or in children with AP Ph+ CML or BP Ph+ CML.

Do not take bosutinib tablets if you are allergic to bosutinib or any of the ingredients in bosutinib tablets. See the end of this leaflet for a complete list of ingredients of bosutinib tablets.

Before taking bosutinib tablets, tell your doctor about all of your medical conditions, including if you:
• have liver problems
• have heart problems
• have kidney problems
• have high blood pressure
• have diabetes
• are pregnant or plan to become pregnant. Bosutinib tablets can harm your unborn baby. Females who are able to become pregnant should have a pregnancy test before starting treatment with bosutinib tablets. Tell your doctor right away if you become pregnant during treatment with bosutinib tablets.
o **Females** who are able to become pregnant should use effective birth control (contraception) during treatment with bosutinib tablets and for 2 weeks after the last dose. Talk to your doctor about birth control methods that may be right for you.
• are breastfeeding or plan to breastfeed. It is not known if bosutinib passes into your breast milk or if it can harm your baby. Do not breastfeed during treatment with bosutinib tablets and for 2 weeks after the last dose.
Tell your doctor about all the medicines you take, including prescription medicines, over-the-counter medicines, vitamins, and herbal supplements. When taken together, bosutinib tablets and certain other medicines can affect each other.
Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new medicine.

How should I take bosutinib tablets?
• Take bosutinib tablets exactly as prescribed by your doctor.
• Do not change your dose or stop taking bosutinib tablets without first talking with your doctor.
• Take bosutinib tablets with food.
• Swallow bosutinib tablets whole. Do not crush, break, chew or cut bosutinib tablets. Do not touch or handle crushed or broken bosutinib tablets.
• If you take an antacid or H2 blocker medicine, take it at least 2 hours before or 2 hours after bosutinib tablets. If you take a Proton Pump Inhibitor (PPI) medicine, talk to your doctor or pharmacist.
• You should avoid grapefruit, grapefruit juice, and supplements that contain grapefruit extract during treatment with bosutinib tablets. Grapefruit products increase the amount of bosutinib tablets in your body.
• If you miss a dose of bosutinib tablets, take it as soon as you remember. If you miss a dose by more than 12 hours, skip that dose and take your next dose at your regular time. Do not take 2 doses at the same time.
• If you take too much bosutinib tablets, call your doctor or go to the nearest hospital emergency room right away.

What are the possible side effects of bosutinib tablets?
Bosutinib tablets may cause serious side effects, including:
• **Stomach problems.** Bosutinib tablets may cause stomach (abdomen) pain, nausea, diarrhea, vomiting, or blood in your stools. Get medical help right away for any stomach problems.

• **Low blood cell counts**. Bosutinib tablets may cause low platelet counts (thrombocytopenia), low red blood cell counts (anemia) and low white blood cell counts (neutropenia). Your doctor should do blood tests to check your blood cell counts regularly during your treatment with bosutinib tablets. Call your doctor right away if you have unexpected bleeding or bruising, blood in your urine or stools, fever, or any signs of an infection.
• **Liver problems**. Your doctor should do blood tests to check your liver function regularly during your treatment with bosutinib tablets. Call your doctor right away if your skin or the white part of your eyes turns yellow (jaundice) or you have dark "tea color" urine.
• **Heart problems.** Bosutinib tablets may cause heart problems, including heart failure and decreased blood flow to the heart which can lead to heart attack. Get medical help right away if you get shortness of breath, weight gain, chest pain, or swelling in your hands, ankles or feet.
• **Your body may hold too much fluid (fluid retention).** Fluid may build up in the lining of your lungs, the sac around your heart, or your stomach cavity. Get medical help right away if you get any of the following symptoms during your treatment with bosutinib tablets:

- shortness of breath and cough
- chest pain
- swelling in your hands, ankles, or feet
- swelling all over your body
- weight gain

• **Kidney problems**. Your doctor should do tests to check your kidney function when you start treatment with bosutinib tablets and during your treatment. Call your doctor right away if you get any of the following symptoms during your treatment with bosutinib tablets:

- you urinate more often than normal
- you urinate less often than normal
- you make a much larger amount of urine than normal
- you make a much smaller amount of urine than normal

The most common side effects of bosutinib tablets in adults with CML include:

• diarrhea
• stomach (abdominal) pain
• vomiting
• nausea
• rash
• tiredness
• liver problems
• headache
• fever
• respiratory tract infections (infections in nose, throat or lungs)
• changes in certain blood tests. Your doctor may do blood tests during treatment with bosutinib tablets to check for changes

Tell your doctor or get medical help right away if you get respiratory tract infections, loss of appetite, headache, dizziness, back pain, joint pain, rash or itching while taking bosutinib tablets. These may be symptoms of a severe allergic reaction.
Your doctor may change your dose, temporarily stop, or permanently stop treatment with bosutinib tablets if you have certain side effects.
Bosutinib tablets may cause fertility problems in females and males. This may affect your ability to have a child. Talk to your doctor if this is a concern for you.
Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of bosutinib tablets.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store bosutinib tablets?
• Store bosutinib tablets at room temperature between 68°F to 77°F (20°C to 25°C).
• The bosutinib tablets bottle has a child-resistant closure.
• The bosutinib tablets bottle contain desiccants to help keep your medicine dry (protect it from moisture). Keep the desiccants in the bottle. **Do not eat the desiccant.**
• Ask your doctor or pharmacist about the right way to throw away outdated or unused bosutinib tablets.
Keep bosutinib tablets and all medicines out of the reach of children.

General information about the safe and effective use of bosutinib tablets.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use bosutinib tablets for a condition for which it is not prescribed. Do not give bosutinib tablets to other people even if they have the same symptoms you have. It may harm them. You can ask your doctor or pharmacist for information about bosutinib tablets that is written for health professionals.

What are the ingredients in bosutinib tablets?
Active ingredient: bosutinib.

Inactive ingredients: croscarmellose sodium, hypromellose, iron oxide red (for 500 mg tablet), iron oxide yellow (for 100 mg tablet), magnesium stearate, microcrystalline cellulose, poloxamer 188, polyethylene glycol 6000, povidone K-25, talc (for 500 mg tablet) and titanium dioxide.

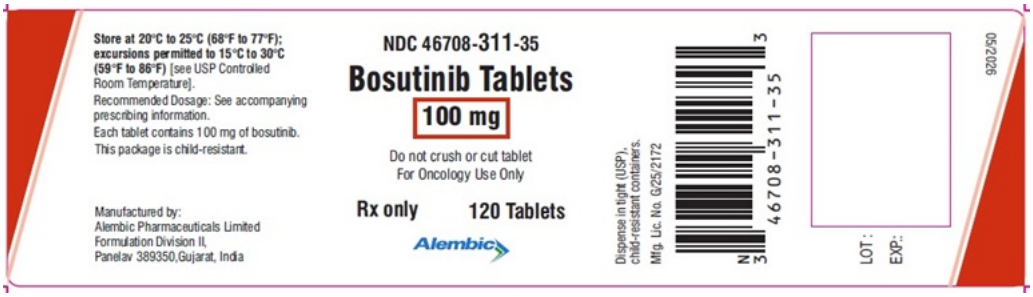
Pediatric use information is approved for PF PRISM CV's BOSULIF® (bosutinib) tablets. However, due to PF PRISM CV's marketing exclusivity rights, this drug product is not labeled with that information.

Manufactured by:
Alembic Pharmaceuticals Limited
Formulations Division II,
Panelav 389350, Gujarat, India

This Patient Information has been approved by the U.S. Food and Drug Administration.
Revised: 03/2026

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL 100 mg

NDC 46708-311-35
Bosutinib Tablets
100 mg
Do not crush or cut tablet
For Oncology Use Only
Rx only **120 Tablets**
Alembic



PACKAGE LABEL.PRINCIPAL DISPLAY PANEL 500 mg

NDC 46708-312-30
Bosutinib Tablets
500 mg
Do not crush or cut tablet
For Oncology Use Only
Rx only **30 Tablets**
Alembic

BOSUTINIB
bosutinib tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:46708-311

Route of Administration	ORAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
BOSUTINIB (UNII: 5018V4AEZ0) (BOSUTINIB - UNII:5018V4AEZ0)	BOSUTINIB	100 mg

Inactive Ingredients

Ingredient Name	Strength
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
POLOXAMER 188 (UNII: LQA7B6G8JG)	
POVIDONE K25 (UNII: K0KQV10C35)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
POLYETHYLENE GLYCOL 6000 (UNII: 30IQX730WE)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	

Product Characteristics

Color	YELLOW	**Score**	no score
Shape	OVAL	**Size**	11mm
Flavor		**Imprint Code**	L603
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:46708-311-35	120 in 1 BOTTLE; Type 0: Not a Combination Product	05/19/2026	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA209543	05/19/2026	

BOSUTINIB

bosutinib tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:46708-312
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
BOSUTINIB (UNII: 5018V4AEZ0) (BOSUTINIB - UNII:5018V4AEZ0)	BOSUTINIB	500 mg

Inactive Ingredients

Ingredient Name	Strength
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
POLOXAMER 188 (UNII: LQA7B6G8JG)	
POVIDONE K25 (UNII: K0KQV10C35)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
POLYETHYLENE GLYCOL 6000 (UNII: 30IQX730WE)	
TALC (UNII: 7SEV7J4R1U)	

FERRIC OXIDE RED (UNII: 1K09F3G675)	

Product Characteristics			
Color	RED	**Score**	no score
Shape	OVAL	**Size**	18mm
Flavor		**Imprint Code**	L604
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:46708-312-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	05/19/2026	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA209543	05/19/2026	

Labeler - Alembic Pharmaceuticals Limited (650574663)

Establishment

Name	Address	ID/FEI	Business Operations
Alembic Pharmaceuticals Limited		675480402	MANUFACTURE(46708-311, 46708-312)

Revised: 5/2026 Alembic Pharmaceuticals Limited