



# ***FAST RESPONSE MATTERS:***

The journey toward long-term outcomes starts with early molecular response (EMR)

## **Importance of Early Molecular Response**

### **INDICATIONS for TASIGNA® (nilotinib) Capsules**

#### **Adult Patients With Newly Diagnosed Ph+ CML-CP**

TASIGNA® (nilotinib) capsules is indicated for the treatment of adults with newly diagnosed Philadelphia chromosome–positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP).

#### **Adult Patients With Resistant or Intolerant Ph+ CML-CP and CML-AP**

TASIGNA is indicated for the treatment of adult patients with CP and accelerated phase (AP) Ph+ CML resistant or intolerant to prior therapy that included imatinib.

### **IMPORTANT SAFETY INFORMATION for TASIGNA® (nilotinib) Capsules**

#### **WARNING: QT PROLONGATION AND SUDDEN DEATHS**

- TASIGNA prolongs the QT interval. Prior to TASIGNA administration and periodically, monitor for hypokalemia or hypomagnesemia and correct deficiencies. Obtain ECGs to monitor the QTc at baseline, 7 days after initiation, and periodically thereafter, and following any dose adjustments
- Sudden deaths have been reported in patients receiving TASIGNA. Do not administer TASIGNA to patients with hypokalemia, hypomagnesemia, or long QT syndrome
- Avoid use of concomitant drugs known to prolong the QT interval and strong CYP3A4 inhibitors
- Avoid food 2 hours before and 1 hour after taking the dose

### **CONTRAINDICATIONS**

Do not use in patients with hypokalemia, hypomagnesemia, or long QT syndrome.

Please see Important Safety Information, including **Boxed WARNING**, on pages 4-6, and [click here](#) for full Prescribing Information.



# FAST RESPONSE MATTERS: EMR is the first leg on the treatment journey

3-month early milestone is an important prognostic indicator of long-term outcomes

EMR has been demonstrated to predict

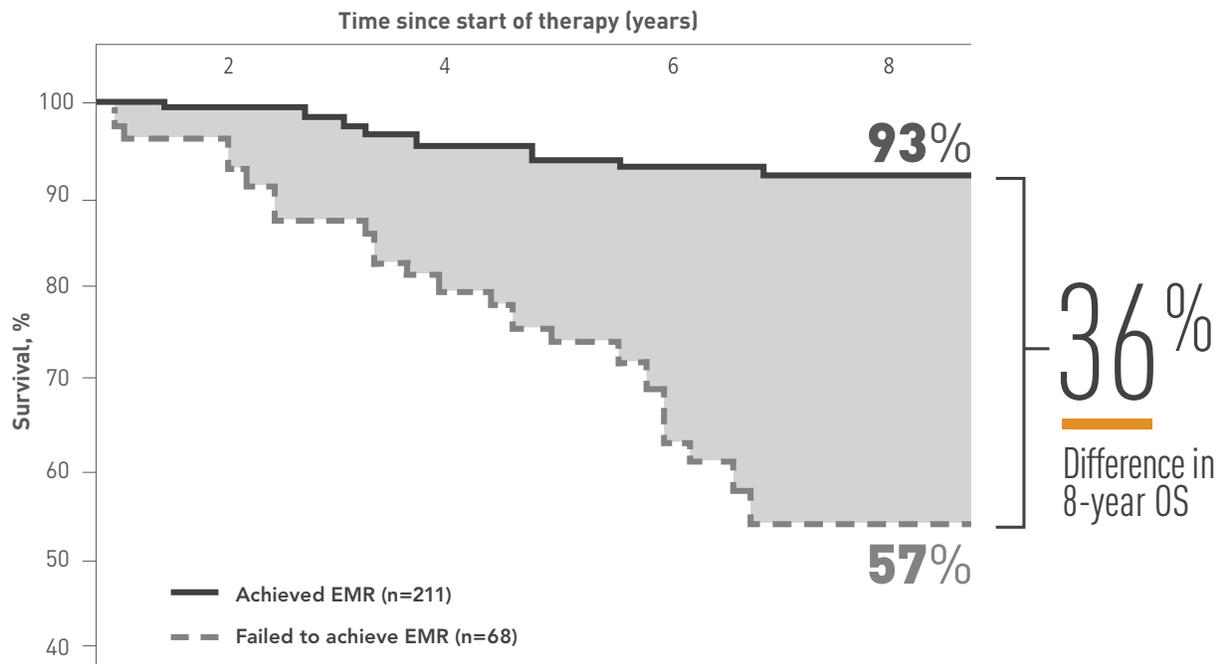


- Future MMR and MR4.5<sup>1</sup>
- Reduced risk of progression to AP/BC<sup>1</sup>
- Improved OS<sup>2</sup>

EMR is defined as BCR-ABL1 ≤10% IS at 3 months.

Measuring response at 3 months is the most accurate method to assess long-term prognosis and allows for earlier clinical intervention<sup>2</sup>

EMR has been demonstrated to predict long-term OS<sup>2</sup>



BC, blast crisis; IS, International Scale.

Based on a retrospective analysis of newly diagnosed patients on TKI therapy.

## IMPORTANT SAFETY INFORMATION for TASIGNA® (nilotinib) Capsules WARNINGS AND PRECAUTIONS

**Myelosuppression:** Treatment with TASIGNA® (nilotinib) capsules can cause Grade 3/4 thrombocytopenia, neutropenia, and anemia. Perform complete blood counts every 2 weeks for the first 2 months and then monthly thereafter, or as clinically indicated. Myelosuppression was generally reversible and usually managed by withholding TASIGNA temporarily or dose reduction.

**QT Prolongation:** TASIGNA prolongs the QT interval. ECGs should be performed at baseline, 7 days after initiation, periodically as clinically indicated, and following dose adjustments. Correct hypokalemia or hypomagnesemia prior to administration and monitor periodically.

Please see Important Safety Information, including **Boxed WARNING**, on pages 4-6, and [click here](#) for full Prescribing Information.

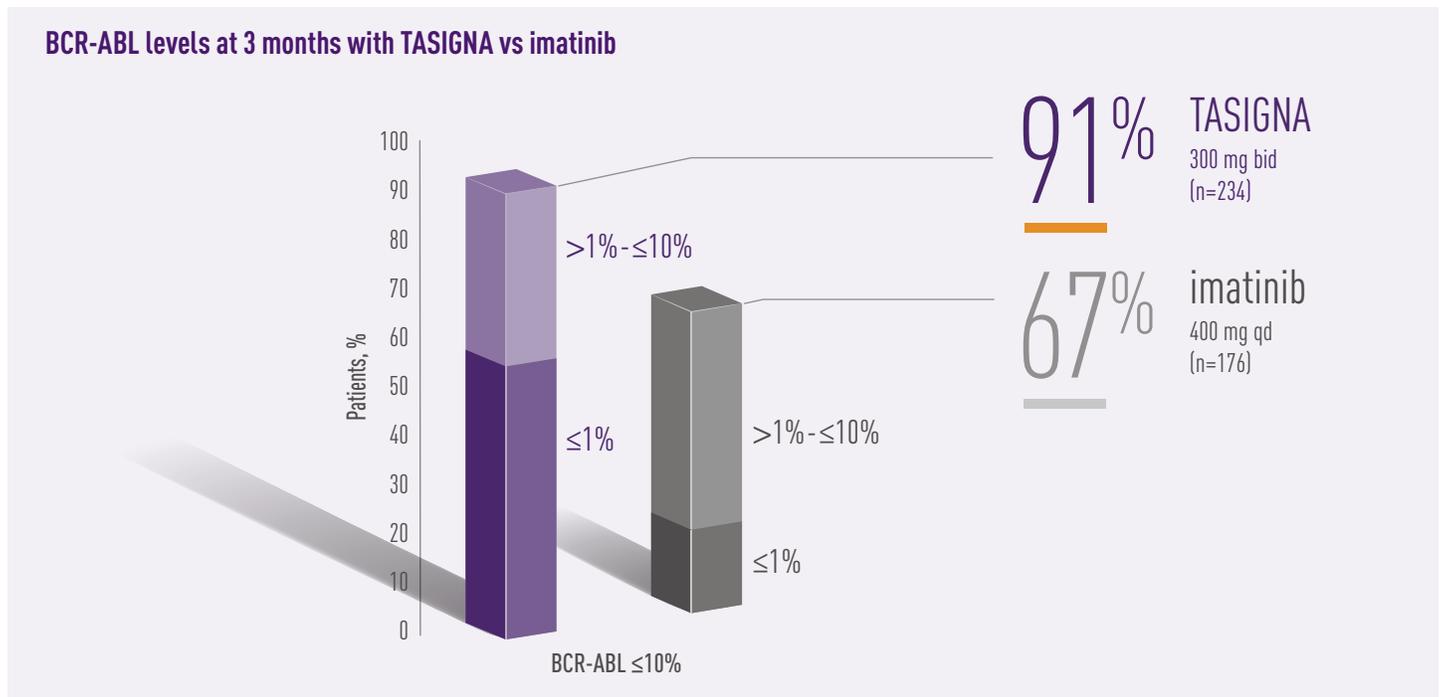


# START TASIGNA:

## Aim toward EMR for your patients

Primary end point: TASIGNA® (nilotinib) capsules doubled the rate of MMR at 1 year compared with imatinib: 44% (n=282; 95% CI, 38%-50%;  $P < .0001$ ) vs 22% (n=283; 95% CI, 18%-28%)<sup>3,4</sup>

## More patients achieved EMR with TASIGNA<sup>1</sup>



**3-MONTH ANALYSIS:** A descriptive analysis of patients receiving TASIGNA 300 mg bid (n=258) or imatinib 400 mg qd (n=264) in ENESTnd with typical b2a2 and/or b3a2 BCR-ABL1 transcripts and evaluable RQ-PCR samples at 3 months. Data were grouped based on BCR-ABL1 transcript levels at 3 months: 1%, >1% to 10%, and >10%. At 3 months, 24 patients in the TASIGNA arm and 19 patients in the imatinib arm had unevaluable BCR-ABL1 transcript levels (atypical transcripts at baseline, missing RQ-PCR samples, or discontinued therapy) and were excluded from the analysis.<sup>1</sup>

- By 5 years, 77% of patients on TASIGNA had achieved MMR vs 60% with imatinib, and 54% of patients on TASIGNA had achieved MR4.5 vs 31% with imatinib<sup>3</sup>
- Two patients on TASIGNA progressed to AP/BC while 12 patients on imatinib progressed to AP/BC at 5 years<sup>3</sup>
- Estimated survival rate at 5 years was 93.7% with TASIGNA vs 91.7% with imatinib. Median OS was not reached in either arm<sup>3</sup>

CCyR, complete cytogenetic response; MMR, major molecular response; OS, overall survival.

### IMPORTANT SAFETY INFORMATION for TASIGNA® (nilotinib) Capsules (cont)

**QT Prolongation (cont):** Significant prolongation of the QT interval may occur when TASIGNA is inappropriately taken with food and/or strong CYP3A4 inhibitors and/or medicinal products with a known potential to prolong QT. Therefore, co-administration with food must be avoided and concomitant use with strong CYP3A4 inhibitors and/or medicinal products with a known potential to prolong QT should be avoided. The presence of hypokalemia and hypomagnesemia may further enhance this effect.

Please see Important Safety Information, including **Boxed WARNING**, on pages 4-6, and [click here](#) for full Prescribing Information.



# IMPORTANT SAFETY INFORMATION for TASIGNA® (nilotinib) Capsules

## WARNING: QT PROLONGATION AND SUDDEN DEATHS

- **TASIGNA prolongs the QT interval. Prior to TASIGNA administration and periodically, monitor for hypokalemia or hypomagnesemia and correct deficiencies. Obtain ECGs to monitor the QTc at baseline, 7 days after initiation, and periodically thereafter, and following any dose adjustments**
- **Sudden deaths have been reported in patients receiving TASIGNA. Do not administer TASIGNA to patients with hypokalemia, hypomagnesemia, or long QT syndrome**
- **Avoid use of concomitant drugs known to prolong the QT interval and strong CYP3A4 inhibitors**
- **Avoid food 2 hours before and 1 hour after taking the dose**

## CONTRAINDICATIONS

Do not use in patients with hypokalemia, hypomagnesemia, or long QT syndrome.

## WARNINGS AND PRECAUTIONS

### Myelosuppression

Treatment with TASIGNA® (nilotinib) capsules can cause Grade 3/4 thrombocytopenia, neutropenia, and anemia. Perform complete blood counts every 2 weeks for the first 2 months and then monthly thereafter, or as clinically indicated. Myelosuppression was generally reversible and usually managed by withholding TASIGNA temporarily or dose reduction.

### QT Prolongation

TASIGNA prolongs the QT interval. ECGs should be performed at baseline, 7 days after initiation, periodically as clinically indicated, and following dose adjustments. Correct hypokalemia or hypomagnesemia prior to administration and monitor periodically.

Significant prolongation of the QT interval may occur when TASIGNA is inappropriately taken with food and/or strong CYP3A4 inhibitors and/or medicinal products with a known potential to prolong QT. Therefore, co-administration with food must be avoided and concomitant use with strong CYP3A4 inhibitors and/or medicinal products with a known potential to prolong QT should be avoided. The presence of hypokalemia and hypomagnesemia may further enhance this effect.

### Sudden Deaths

Sudden deaths have been reported in patients with Ph+ CML treated with TASIGNA. The relatively early occurrence of some of these deaths relative to the initiation of TASIGNA suggests the possibility that ventricular repolarization abnormalities may have contributed to their occurrence.

### Cardiac and Arterial Vascular Occlusive Events

Cardiovascular events, including arterial vascular occlusive events, were reported in a randomized, clinical trial in patients with newly diagnosed Ph+ CML and observed in the postmarketing reports of patients receiving TASIGNA therapy. Cases of cardiovascular events included ischemic heart disease-related events, peripheral arterial occlusive disease, and ischemic cerebrovascular events.

If acute signs or symptoms of cardiovascular events occur, advise patients to seek immediate medical attention. The cardiovascular status of patients should be evaluated and cardiovascular risk factors should be monitored and actively managed during TASIGNA therapy according to standard guidelines.

### Pancreatitis and Elevated Serum Lipase

TASIGNA can cause increases in serum lipase. Patients with a previous history of pancreatitis may be at greater risk of elevated serum lipase. If lipase elevations are accompanied by abdominal symptoms, interrupt dosing and consider appropriate diagnostics to exclude pancreatitis. Test serum lipase levels monthly or as clinically indicated.

Please see Important Safety Information, including **Boxed WARNING**, on pages 4-6, and [click here](#) for full Prescribing Information.

# IMPORTANT SAFETY INFORMATION for TASIGNA<sup>®</sup> (nilotinib) Capsules (cont)

## Hepatotoxicity

TASIGNA may result in hepatotoxicity as measured by elevations in bilirubin, AST/ALT, and alkaline phosphatase. Grade 3-4 elevations of bilirubin, AST, and ALT were reported at a higher frequency in pediatric patients than in adults. Monitor hepatic function tests monthly or as clinically indicated.

## Electrolyte Abnormalities

The use of TASIGNA can cause hypophosphatemia, hypokalemia, hyperkalemia, hypocalcemia, and hyponatremia. Correct electrolyte abnormalities prior to initiating TASIGNA and monitor these electrolytes periodically during therapy.

## Tumor Lysis Syndrome

Tumor lysis syndrome cases have been reported in patients taking TASIGNA who have resistant or intolerant Ph+ CML. Malignant disease progression, high white blood cell counts, and/or dehydration were present in most of these cases. Maintain adequate hydration and correct uric acid levels prior to initiating therapy with TASIGNA.

## Hemorrhage

Serious hemorrhage, including fatal events, from any site, including the GI tract, was reported in patients with Ph+ CML receiving TASIGNA. Monitor patients for signs and symptoms of bleeding and medically manage as needed.

## Total Gastrectomy

Since the exposure of TASIGNA is reduced in patients with total gastrectomy, perform more frequent monitoring of these patients. Consider dose increase or alternative therapy in patients with total gastrectomy.

## Lactose

Since the capsules contain lactose, TASIGNA is not recommended for patients with rare hereditary problems of galactose intolerance, severe lactase deficiency with a severe degree of intolerance to lactose-containing products, or of glucose-galactose malabsorption.

## Monitoring Laboratory Tests

Complete blood counts should be performed every 2 weeks for the first 2 months and then monthly thereafter. Perform chemistry panels, including electrolytes, calcium, magnesium, liver enzymes, lipid profile, and glucose prior to therapy and periodically. ECGs should be obtained at baseline, 7 days after initiation, and periodically thereafter, as well as following dose adjustments.

Monitor lipid profiles and glucose periodically during the first year of TASIGNA therapy and at least yearly during chronic therapy. Assess glucose levels before initiating treatment with TASIGNA and monitor during treatment as clinically indicated. If test results warrant therapy, physicians should follow their local standards of practice and treatment guidelines.

## Fluid Retention

Grade 3/4 fluid retention including pleural effusion, pericardial effusion, ascites, and pulmonary edema have been reported in patients with Ph+ CML receiving TASIGNA. Monitor patients for signs of severe fluid retention (eg, unexpected rapid weight gain or swelling) and for symptoms of respiratory or cardiac compromise (eg, shortness of breath); evaluate etiology and treat patients accordingly.

## Effects on Growth and Development in Pediatric Patients

Adverse reactions associated with growth and development can occur in pediatric patients receiving BCR-ABL tyrosine kinase inhibitors (TKIs). The long-term effects of prolonged treatment with BCR-ABL TKIs on growth and development in pediatric patients are unknown. Monitor growth and development in pediatric patients receiving BCR-ABL TKI treatment.

## Embryo-Fetal Toxicity

TASIGNA can cause fetal harm. Advise females to inform their doctor if they are pregnant or become pregnant. Inform female patients of the risk to the fetus and potential for loss of the pregnancy. Advise females of reproductive potential to use effective contraception during treatment and for 14 days after receiving the last dose of TASIGNA. Advise lactating women not to breastfeed during treatment with TASIGNA and for at least 14 days after the last dose.

# IMPORTANT SAFETY INFORMATION for TASIGNA<sup>®</sup> (nilotinib) Capsules (cont)

## Monitoring of BCR-ABL Transcript Levels

Monitor BCR-ABL transcript levels in patients eligible for treatment discontinuation using an FDA-authorized test validated to measure molecular response (MR) levels with a sensitivity of at least MR4.5. In patients who discontinue TASIGNA<sup>®</sup> (nilotinib) capsules therapy, assess BCR-ABL transcript levels monthly for 1 year, then every 6 weeks for the second year, and every 12 weeks thereafter during treatment discontinuation.

Following a loss of MMR (first line/second line) or confirmed loss of MR4 (2 consecutive measures separated by at least 4 weeks showing loss of MR4 in second line), patients should reinitiate TASIGNA within 4 weeks of when the loss of remission is known to have occurred.

Monitor CBC and BCR-ABL transcripts in patients who reinitiate treatment with TASIGNA due to loss of MR quantitation every 4 weeks until MMR is reestablished and then every 12 weeks.

For patients who fail to achieve MMR after 3 months of treatment reinitiating, BCR-ABL kinase domain mutation testing should be performed.

## ADVERSE REACTIONS

The most commonly reported nonhematologic adverse reactions ( $\geq 20\%$ ) in adult and pediatric patients receiving TASIGNA were nausea, rash, headache, fatigue, pruritus, vomiting, diarrhea, cough, constipation, arthralgia, nasopharyngitis, pyrexia, and night sweats.

Hematologic adverse drug reactions (all grades) include myelosuppression: thrombocytopenia, neutropenia, and anemia.

Musculoskeletal symptoms (eg, myalgia, pain in extremity, arthralgia, bone pain, spinal pain, or musculoskeletal pain) have been reported in eligible patients who discontinued TASIGNA therapy after attaining a sustained MR4.5. The rate of new musculoskeletal symptoms (all grades) generally decreased from the first year (34%-48%) to the second year (9%-15%) after treatment discontinuation.

## DOSE ADJUSTMENTS OR MODIFICATIONS

TASIGNA may need to be temporarily withheld and/or dose reduced for QT prolongation, hepatic impairment, hematologic toxicities that are not related to underlying leukemia, clinically significant moderate or severe nonhematologic toxicities, laboratory abnormalities (lipase, bilirubin, or hepatic transaminase elevations) or concomitant use of strong CYP3A4 inhibitors.

## DRUG INTERACTIONS

Avoid concomitant use of strong CYP3A4 inhibitors with TASIGNA, or reduce TASIGNA dose if co-administration cannot be avoided.

Avoid concomitant use of strong CYP3A4 inducers with TASIGNA. Use short-acting antacids or H2 blockers as an alternative to proton pump inhibitors.

Please see additional Important Safety Information, including **Boxed WARNING**, on pages 4 and 5, and [click here](#) for full Prescribing Information.

## REFERENCES

1. Hughes TP, Saglio G, Kantarjian HM, et al. Early molecular response predicts outcomes in patients with chronic myeloid leukemia in chronic phase treated with frontline nilotinib or imatinib. *Blood*. 2014;123(9):1353-1360.
2. Marin D, Ibrahim AR, Lucas C, et al. Assessment of BCR-ABL1 transcript levels at 3 months is the only requirement for predicting outcome for patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors. *J Clin Oncol*. 2012;30(3):232-238.
3. Tasigna [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2018.
4. Saglio G, Kim D-W, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2010;362(24):2251-2259.

