Summary of Key Safety Recommendations for Tasigna® (nilotinib)

NOVARTIS

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Introduction

The purpose of this brochure is to provide health care professionals prescribing Tasigna® (nilotinib) with the potential serious adverse reactions that may occur with Tasigna therapy and provide information on how to proactively prevent and/or reduce these events.

Tasigna is indicated for

- The treatment of adult and pediatric patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) in the chronic phase (CP).
- The treatment of adult patients with CP and accelerated phase (AP) Ph+ CML with resistance or intolerance to at least one prior therapy, including imatinib.
- The treatment of pediatric patients with CP Ph+ CML with resistance or intolerance to prior therapy, including imatinib.

The recommended dose of Tasigna for Ph+ CML is:

- 300 mg twice daily for newly diagnosed adult patients in CP.
- 400 mg twice daily for imatinib-resistant or imatinib–intolerant adult patients in CP or AP.
- 230 mg/m^2 twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg) for newly diagnosed or prior TKI-resistant or intolerant pediatric patients in CP (see Table 1).

Table 1: Dosing scheme of Tasigna 230 mg/m^2 twice daily in pediatric patients

Body Surface Area (BSA)	Dose in mg (twice daily)
Up to 0.32 m^2	50 mg
0.33 – 0.54 m^2	100 mg
0.55 – 0.76 m^2	150 mg
0.77 – 0.97 m^2	200 mg
0.98 – 1.19 m^2	250 mg
1.20 – 1.41 m^2	300 mg
1.42 – 1.63 m^2	350 mg
≥1.64 m^2	400 mg

QT prolongation

- Tasigna may prolong the QT interval.
- Prolongation of the QT interval may occur when Tasigna is inappropriately taken with food and/or strong CYP3A4 inhibitors and/or medicinal products known to prolong QT. The presence of hypokalemia and hypomagnesaemia may also further prolong the QT interval.
- Avoid its co-administration with food and concomitant use with strong CYP3A4 inhibitors and/or avoid medicinal products with a known potential to prolong QT.
- Monitor for hypokalaemia and hypomagnesaemia and correct deficiencies.
- Administer Tasigna with caution in patients who are at significant risk of developing QTc prolongation or with long QT syndrome, uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina, or clinically significant bradycardia, or patients taking concomitant antiarrhythmic medicines (including, but not limited to, amiodarone, disopyramide, procainamide, quinidine, and sotalol) or other drugs that may prolong the QT interval (including, but not limited to, chloroquine, halofantrine, clarithromycin, haloperidol, methadone, and moxifloxacin).

Cardiovascular events

- Evaluate the cardiovascular status of patients and actively monitor and manage cardiovascular risk factors during Tasigna therapy according to standard guidelines.
- Advise patients to seek immediate medical attention if they experience acute signs or symptoms of cardiovascular events.

Uncontrolled or significant cardiac disease/cardiac failure

- A baseline ECG is recommended prior to initiating therapy with Tasigna and repeated as clinically indicated.
- Use Tasigna with caution in patients with risk factors for cardiac/coronary heart disease and/or history of uncontrolled or significant cardiac disease. Monitor patient for signs or symptoms consistent with cardiac dysfunction and treat appropriately.

Fluid retention

- Carefully investigate unexpected, rapid weight gain. If signs of

severe fluid retention (such as cardiac failure or pulmonary oedema) appear during treatment with Tasigna, evaluate the etiology and treat patients accordingly.

Hepatoxicity

- Elevations in bilirubin and hepatic transaminase levels have been reported very commonly in pediatric and adult patients.
- Bilirubin and hepatic transaminase levels should be tested monthly or as clinically indicated.

Hepatic impairment

- Hepatic impairment has a modest effect on the pharmacokinetics of Tasigna. Therefore, use with caution in patients with hepatic impairment.

Pancreatitis

- Elevations of lipase and amylase have been observed in patients taking Tasigna. Use with caution in patients with a history of pancreatitis.

Blood glucose increased

- Increases in blood glucose levels have been reported with Tasigna therapy.

Blood cholesterol increased

- Increases in blood cholesterol levels have been reported with Tasigna therapy.

Interaction with food

- Prolongation of the QT interval may occur when nilotinib is inappropriately taken with food. Therefore Tasigna must **NOT** be taken with food. [see QT prolongation]
- Advise patients to avoid food for 2 hours before and at least 1 hour after taking Tasigna.
- Avoid grapefruit juice or other foods that are known to inhibit CYP3A4 while on Tasigna.

Drug interaction with strong CYP3A4 inhibitors

- Tasigna undergoes metabolism by CYP3A4, and concomitant use of strong CYP3A4 inhibitors (including, but not limited to,

ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, and ritonavir) can increase the Tasigna serum concentration.

- Should treatment with any of these agents be required, Tasigna therapy should be interrupted if possible. If transient interruption of treatment with Tasigna is not possible, close monitoring of the patient for prolongation of the QT interval is indicated. [see QT prolongation]
- Avoid foods that are known to inhibit CYP3A4, such as grapefruit and grapefruit products, as these may also increase serum concentrations of Tasigna.

Drug interaction with strong CYP3A4 inducers

- Tasigna undergoes metabolism by CYP3A4, and concomitant use of medicinal products that are potent inducers of CYP3A4 may reduce Tasigna serum concentration.
- In patients for whom CYP3A4 inducers (e.g., phenytoin, rifampicin, carbamazepine, phenobarbital, and St. John's Wort) are indicated, consider alternative agents with less enzyme-induction potential.

Interaction with sensitive CYP3A4 substrates

- Monitor patient and dose adjust as needed for drugs that are CYP3A4 substrates and have narrow therapeutic index (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, quinidine, sirolimus and tacrolimus) when co-administered with Tasigna.

Reproductive toxicity/pregnancy

- Tasigna should not be used during pregnancy. If given during pregnancy, the patient must be informed of the potential risk to the fetus.
- Advise women of childbearing potential to use highly effective contraceptives during Tasigna treatment and for up to 2 weeks after treatment.

Special monitoring of Ph+ CML-CP patients who have achieved a sustained deep molecular response

Eligibility for discontinuation of treatment

- Discontinuation of Tasigna should be initiated by a physician experienced in the treatment of patients with CML. Eligible patients who are confirmed to express the typical BCR-ABL transcripts, e13a2/b2a2 or e14a2/b3a2, can be considered for treatment discontinuation. Patients must have typical BCR-ABL transcripts to allow quantitation of BCR-ABL levels, evaluation of the depth of molecular response, and determination of a possible loss of molecular remission after Tasigna treatment discontinuation.

Monitoring of patients who have discontinued therapy

- Frequent monitoring of BCR-ABL transcript levels in patients eligible for treatment discontinuation must be performed with a quantitative diagnostic test validated to measure molecular response levels with a sensitivity of at least MR4.5. BCR-ABL transcript levels must be assessed prior to and during treatment discontinuation.

Treatment discontinuation in Ph+ CML-CP patients who have achieved a sustained deep molecular response

- After discontinuation of Tasigna therapy within the framework of attempting treatment-free remission (TFR), patients may experience musculoskeletal symptoms more frequently than before treatment discontinuation, e.g., myalgia, pain in extremity, arthralgia, bone pain, spinal pain, or musculoskeletal pain.

Pediatric patients

- There is no experience in pediatric patients below 2 years of age or in pediatric patients with Philadelphia chromosome positive CML in accelerated phase or blast crisis. The long-term effects of prolonged treatment with Tasigna in children are unknown.

Please see full prescribing information.

References: 1. TASIGNA® (nilotinib) Core Data Sheet. Basel, Switzerland: Novartis Pharma AG; version 1.8. **2.** TASIGNA® (nilotinib) Summary of Product Characteristics. Basel, Switzerland: Novartis Pharma AG; November 2017.

TASIGNA® (nilotinib) 50mg and 200mg Hard Capsules

PRESENTATION: 50mg and 200mg Hard Capsules. **INDICATIONS:** TASIGNA is indicated for adult and paediatric patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in the chronic phase. Adult patients with chronic phase and accelerated phase Philadelphia chromosome positive CML with resistance or intolerant to prior therapy including imatinib. Paediatric patients with chronic phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib. **DOSAGE AND ADMINISTRATION:** Treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs. The recommended dose of TASIGNA is 300mg twice daily in newly diagnosed patients with CML in the chronic phase. 400 mg twice daily in patients with chronic or accelerated phase CML with resistance or intolerance to prior therapy. In paediatric patients, the recommended dose of nilotinib is 230 mg/m^2 twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg). There is no experience with treatment of paediatric patients below 2 years of age. *For patients on first line treatment with Tasigna,* discontinuation of treatment may be considered in eligible Philadelphia chromosome positive (Ph+) CML patients in chronic phase who have been treated with Tasigna at 300 mg twice daily for a minimum of 3 years if a deep molecular response is sustained for a minimum of one year immediately prior to discontinuation of therapy.*For patients being treated with Tasigna following prior imatinib therapy,*discontinuation of treatment may be considered in eligible Philadelphia chromosome positive (Ph+) CML patients in chronic phase who have been treated with Tasigna for a minimum of 3 years if a deep molecular response is sustained for a minimum of one year immediately prior to discontinuation of therapy. Tasigna may need to be temporarily withheld and/or dose reduced for haematological toxicities (neutropenia, thrombocytopenia) that are not related to the underlying leukaemia. Consult the full SmPC for information about dose adjustments. The safety and efficacy of Tasigna in paediatric patients with Philadelphia chromosome positive CML in chronic phase from 2 to less than 18 years of age have been established. TASIGNA should be taken twice daily approximately 12 hours apart and should not be taken with food. The capsules should be swallowed whole with water. No food should be consumed for 2 hours before the dose is taken and no food should be consumed for at least one hour after the dose is taken.. If a dose is missed the patient should not take an additional dose, but take the usual prescribed next dose. Increases in serum cholesterol and blood glucose levels have been reported with Tasigna therapy. See the full SPC for full prescribing information for 50mg and 200mg doses. **CONTRAINDICATIONS:** Known hypersensitivity to nilotinib or to any of the excipients. **WARNINGS/PRECAUTIONS:** ♦Treatment with TASIGNA is associated with thrombocytopenia, neutropenia and anaemia (NCI CTC Grade 3/4). Occurrence is more frequent in patients with imatinib-resistant or intolerant CML, in particular patients with accelerated phase CML. Complete blood counts should be performed every two weeks for the first 2 months and then monthly thereafter, or as clinically indicated. ♦TASIGNA should be used with caution in patients who have or who are at significant risk of developing prolongation of the QT interval. Close monitoring for an effect on the QT interval is advisable and a baseline ECG is recommended prior to initiating therapy with Tasigna. Hypokalaemia or hypomagnesaemia should be corrected prior to TASIGNA administration and monitored periodically during therapy. ♦It is recommended that the glucose levels be assessed before initiating treatment with Tasigna and monitored during treatment, as clinically indicated. If test results warrant therapy, physicians should follow their local standards of practice and treatment guidelines. ♦Uncommon cases (0.1 to 1%) of sudden deaths have been reported in patients with imatinib-resistant or intolerant CML in chronic phase or accelerated phase receiving Tasigna with a past medical history of cardiac disease or significant cardiac risk factors. Co-morbidities in addition to the underlying malignancy were also frequently present as were concomitant medicinal products. Ventricular repolarisation abnormalities may have been contributory factors. ♦Women of childbearing potential have to use highly effective contraception during treatment with Tasigna, up to 2 weeks after treatment cessation. ♦Severe forms of fluid retention were uncommonly observed in a Phase III study of newly diagnosed CML patients and in post-marketing reports. Unexpected, rapid weight gain should be carefully investigated. If signs of severe fluid retention appear during treatment with nilotinib, the aetiology should be evaluated and patients treated accordingly. ♦Cardiovascular events were reported in a randomised Phase III study in newly diagnosed CML patients and observed in post-marketing reports. Patients should be advised to seek immediate medical attention if they experience acute signs or symptoms of cardiovascular events. The cardiovascular status of patients should be evaluated and cardiovascular risk factors monitored and actively managed during Tasigna therapy according to standard guidelines. Appropriate therapy should be prescribed to manage cardiovascular risk factors. ♦TASIGNA is not recommended for patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption. ♦Patients should be tested for HBV infection before initiating treatment with Tasigna. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B serology and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with Tasigna should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. ♦ It is recommended that the lipid profiles be determined before initiating treatment with Tasigna, assessed at month 3 and 6 after initiating therapy and at least yearly during chronic therapy. ♦ Metabolism of nilotinib is mainly hepatic. Patients with hepatic impairment might therefore have increased exposure to nilotinib and should be treated with caution. ♦ Elevation in serum

lipase has been observed. Caution is recommended in patients with previous history of pancreatitis. ♦ The bioavailability of nilotinib might be reduced in patients with total gastrectomy, more frequent follow-up is recommended. ♦ Due to possible occurrence of tumour lysis syndrome (TLS) correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiating therapy with Tasigna. ♦ Laboratory abnormalities of mild to moderate transient elevations of aminotransferases and total bilirubin have been observed in children at a higher frequency than in adults, indicating a higher risk of hepatotoxicity in the paediatric population – monitor liver function. **INTERACTIONS:** Tasigna may be given in combination with haematopoietic growth factors such as erythropoietin or granulocyte colony-stimulating factor (G-CSF) if clinically indicated. It may be given with hydroxyurea or anagrelide if clinically indicated. The administration of TASIGNA with agents that are strong CYP3A4 inhibitors (including but not limited to, ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir) should be avoided. Alternative concomitant treatment with no or minimal CYP3A4 inhibition should be considered ♦The concomitant administration of other medications that induce CYP3A4 (e.g. phenytoin, carbamazepine, phenobarbital, and St. John's Wort) may reduce exposure to nilotinib. Rifampicin (a potent CYP3A4 inducer) and nilotinib should not be used concomitantly. In patients for whom CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be considered. Caution should be exercised when co-administering TASIGNA with substrates of these enzymes (CYP3A4, CYP2C8, CYP2C9, and CYP2D6) that have a narrow therapeutic index. In CML patients, nilotinib administered at 400 mg twice daily for 12 days increased the systemic exposure of oral midazolam (a substrate of CYP3A4). Nilotinib is a moderate CYP3A4 inhibitor. As a result, the systemic exposure of other drugs primarily metabolised by CYP3A4 (e.g. certain HMG-CoA reductase inhibitors) may be increased when co-administered with nilotinib. Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided. **ADVERSE REACTIONS:** Non-haematological adverse reactions include for newly diagnosed CML-CP: Very common: headache, nausea, upper abdominal pain, rash, pruritis, alopecia, myalgia, fatigue. Common: decreased appetite, constipation, diarrhoea, abdominal pain, dyspepsia, dry skin, erythema, muscle spasms, arthralgia, bone pain, pain in extremity, asthenia, peripheral oedema. For Imatinib-resistant or intolerant CML-CP and CML-AP – very common: Headache, nausea, constipation, diarrhoea, vomiting, rash, pruritis, myalgia, fatigue. Common: decreased appetite, upper abdominal pain, abdominal pain, dyspepsia, alopecia, dry skin, erythema, muscle spasms, arthralgia, bone pain, pain in extremity, asthenia, peripheral oedema. Please refer to the SPC for a full list of all adverse reactions reported including laboratory abnormalities. **LEGAL CATEGORY**: POM. **MARKETING AUTHORISATION HOLDER**: Novartis Europharm Limited, Frimley Business Park, Camberley, GU16 7SR United Kingdom. **MARKETING AUTHORISATION NUMBER**: EU/1/07/422/008, EU/1/07/422/015.

Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma Services, P.O. Box 4, MRS 1000, Marsa, Malta. Tel +356 21222872.

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Any suspected adverse reactions and medication errors can be reported via the national Adverse Drug Reactions (ADRs) reporting system. Report forms can be downloaded from http://www.medicinesauthority.gov.mt/adrportal and posted to:

Medicines Authority Post-licensing Directorate,
Sir Temi Zammit Buildings,
Malta Life Sciences Park,
San Gwann. SGN 3000.

Or sent by e-mail to postlicensing.medicinesauthority@gov.mt.

Healthcare Professionals may also report any adverse events suspected to be associated with the use of Tasigna to Novartis Pharma Services Inc., Representative Office, Malta, by phone on +356 21222872, by fax on +356 22487219 or e-mail at drug_safety.malta@novartis.com.

Marketing Authorisation Holder: Novartis Europharm Limited, Frimley Business Park, Camberley GU16 7S4, United Kingdom.

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