

Medicinal product no longer authorised

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dasatinib Accord 20 mg film-coated tablets
Dasatinib Accord 50 mg film-coated tablets
Dasatinib Accord 70 mg film-coated tablets
Dasatinib Accord 80 mg film-coated tablets
Dasatinib Accord 100 mg film-coated tablets
Dasatinib Accord 140 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Dasatinib Accord 20 mg film-coated tablets

Each film-coated tablet contains 20 mg dasatinib.

Excipient with known effect

Each film-coated tablet contains 27 mg of lactose (as monohydrate).

Dasatinib Accord 50 mg film-coated tablets

Each film-coated tablet contains 50 mg dasatinib.

Excipient with known effect

Each film-coated tablet contains 67.5 mg of lactose (as monohydrate).

Dasatinib Accord 70 mg film-coated tablets

Each film-coated tablet contains 70 mg dasatinib.

Excipient with known effect

Each film-coated tablet contains 94.5 mg of lactose (as monohydrate).

Dasatinib Accord 80 mg film-coated tablets

Each film-coated tablet contains 80 mg dasatinib.

Excipient with known effect

Each film-coated tablet contains 108 mg of lactose (as monohydrate).

Dasatinib Accord 100 mg film-coated tablets

Each film-coated tablet contains 100 mg dasatinib.

Excipient with known effect

Each film-coated tablet contains 135.0 mg of lactose (as monohydrate).

Dasatinib Accord 140 mg film-coated tablets

Each film-coated tablet contains 140 mg dasatinib.

Excipient with known effect

Each film-coated tablet contains 189 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Dasatinib Accord 20 mg film-coated tablets

White to off-white, round, 5.6 mm of diameter, coated tablets debossed on one side with "DAS" and "20" on the other side.

Dasatinib Accord 50 mg film-coated tablets

White to off-white, oval, 5.7 x 10.6 mm, coated tablets debossed on one side with "DAS" and "50" on the other side.

Dasatinib Accord 70 mg film-coated tablets

White to off-white, round, 8.7 mm of diameter, coated tablets debossed on one side with "DAS" and "70" on the other side.

Dasatinib Accord 80 mg film-coated tablets

White to off-white, triangle-shaped, 9.9 x 10.2 mm, coated tablets debossed on one side with "DAS" and "80" on the other side.

Dasatinib Accord 100 mg film-coated tablets

White to off-white, oval, 7.1 x 14.5 mm, coated tablets debossed on one side with "DAS" and "100" on the other side.

Dasatinib Accord 140 mg film-coated tablets

White to off-white, round, 11 mm of diameter, coated tablets debossed on one side with "DAS" and "140" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dasatinib Accord is indicated for the treatment of adult patients with:

- Ph+ acute lymphoblastic leukaemia (ALL) with resistance or intolerance to prior therapy.

Dasatinib Accord is indicated for the treatment of paediatric patients with:

- newly diagnosed Ph+ ALL in combination with chemotherapy.

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the diagnosis and treatment of patients with leukaemia.

Posology

Adult patients

The recommended starting dose for Ph+ ALL is 140 mg once daily (see section 4.4).

Paediatric population (Ph+ ALL)

Dosing for children and adolescents is on the basis of body weight (see Table 1). Dasatinib is administered orally once daily in the form of either Dasatinib Accord film-coated tablets or Dasatinib powder for oral suspension. The dose should be recalculated every 3 months based on changes in body weight, or more often if necessary. The tablet is not recommended for patients weighing less than 10 kg; the powder for oral suspension should be used for these patients. Dose increase or reduction is recommended based on individual patient response and tolerability. There is no experience with Dasatinib Accord treatment in children under 1 year of age.

Dasatinib Accord film-coated tablets and Dasatinib powder for oral suspension are not bioequivalent. Patients who are able to swallow tablets and who desire to switch from Dasatinib powder for oral suspension to Dasatinib Accord tablets or patients who are not able to swallow tablets and who desire to switch from tablets to oral suspension, may do so, provided that the correct dosing recommendations for the dosage form are followed.

The recommended starting daily dosage of Dasatinib Accord tablets in paediatric patients is shown in Table 1.

Table 1: Dosage of Dasatinib Accord tablets for paediatric patients with Ph+ ALL

Body weight (kg) ^a	Daily dose (mg)
10 to less than 20 kg	40 mg
20 to less than 30 kg	60 mg
30 to less than 45 kg	70 mg
at least 45 kg	100 mg

^a The tablet is not recommended for patients weighing less than 10 kg; the powder for oral suspension should be used for these patients.

Treatment duration

In clinical studies, treatment with dasatinib in adults with Ph+ ALL was continued until disease progression or until no longer tolerated by the patient. The effect of stopping treatment on long-term disease outcome after the achievement of a cytogenetic or molecular response [including complete cytogenetic response (CCyR), major molecular response (MMR) and MR4.5] has not been investigated.

In clinical studies, treatment with dasatinib in paediatric patients with Ph+ ALL was administered continuously, added to successive blocks of backbone chemotherapy, for a maximum duration of two years. In patients that receive a subsequent stem cell transplantation, dasatinib can be administered for an additional year post-transplantation. To achieve the recommended dose, Dasatinib Accord is available as 20 mg, 50 mg, 70 mg, 80 mg, 100 mg and 140 mg film-coated tablets. Dose increase or reduction is recommended based on patient response and tolerability.

Dose escalation

In clinical studies in adult Ph+ ALL patients, dose escalation to 180 mg once daily (Ph+ ALL) was allowed in patients who did not achieve a haematologic or cytogenetic response at the recommended starting dose.

Dose escalation is not recommended for paediatric patients with Ph+ ALL, as Dasatinib Accord is administered in combination with chemotherapy in these patients.

Dose adjustment for adverse reactions

Myelosuppression

In clinical studies, myelosuppression was managed by dose interruption, dose reduction, or discontinuation of study therapy. Platelet transfusion and red cell transfusion were used as appropriate. Haematopoietic growth factor has been used in patients with resistant myelosuppression. Guidelines for dose modifications in adults are summarised in Table 2. Guidelines for paediatric patients with Ph+ ALL treated in combination with chemotherapy are in a separate paragraph following the tables.

Table 2: Dose adjustments for neutropaenia and thrombocytopaenia in adults

Adults with Ph+ ALL (starting dose 140 mg once daily)	ANC < 0.5 x 10 ⁹ /L and/or platelets < 10 x 10 ⁹ /L	<ol style="list-style-type: none"> 1. Check if cytopaenia is related to leukaemia (marrow aspirate or biopsy). 2. If cytopaenia is unrelated to leukaemia, stop treatment until ANC ≥ 1.0 x 10⁹/L and platelets ≥ 20 x 10⁹/L and resume at the original starting dose. 3. If recurrence of cytopaenia, repeat step 1 and resume treatment at a reduced dose of 100 mg once daily (second episode) or 80 mg once daily (third episode).
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		4. If cytopaenia is related to leukaemia, consider dose escalation to 180 mg once daily.
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ANC: absolute neutrophil count

For paediatric patients with Ph+ ALL, no dose modification is recommended in cases of haematologic Grade 1 to 4 toxicities. If neutropaenia and/or thrombocytopaenia result in delay of the next block of treatment by more than 14 days, dasatinib should be interrupted and resumed at the same dose level once the next block of treatment is started. If neutropaenia and/or thrombocytopaenia persist and the next block of treatment is delayed another 7 days, a bone marrow assessment should be performed to assess cellularity and percentage of blasts. If marrow cellularity is <10%, treatment with dasatinib should be interrupted until ANC >500/ μ L (0.5×10^9 /L), at which time treatment may be resumed at full dose. If marrow cellularity is >10%, resumption of treatment with dasatinib may be considered.

Non-haematologic adverse reactions

If a moderate, grade 2, non-haematologic adverse reaction develops with dasatinib, treatment should be interrupted until the adverse reaction has resolved or returned to baseline. The same dose should be resumed if this is the first occurrence and the dose should be reduced if this is a recurrent adverse reaction. If a severe grade 3 or 4, non-haematologic adverse reaction develops with dasatinib, treatment must be withheld until the adverse reaction has resolved. Thereafter, treatment can be resumed as appropriate at a reduced dose depending on the initial severity of the adverse reaction. For patients with Ph+ ALL who received 140 mg once daily, dose reduction to 100 mg once daily with further reduction from 100 mg once daily to 50 mg once daily, if needed, is recommended. In Ph+ ALL paediatric patients with non-haematologic adverse reactions, if needed, one level of dose reduction should be followed, according to the dose reduction recommendations for haematologic adverse reactions that are described above.

Pleural effusion

If a pleural effusion is diagnosed, dasatinib should be interrupted until patient is examined, asymptomatic or has returned to baseline. If the episode does not improve within approximately one week, a course of diuretics or corticosteroids or both concurrently should be considered (see sections 4.4 and 4.8). Following resolution of the first episode, reintroduction of dasatinib at the same dose level should be considered. Following resolution of a subsequent episode, dasatinib at one dose level reduction should be reintroduced. Following resolution of a severe (grade 3 or 4) episode, treatment can be resumed as appropriate at a reduced dose depending on the initial severity of the adverse reaction.

Dose reduction for concomitant use of strong CYP3A4 inhibitors

The concomitant use of strong CYP3A4 inhibitors and grapefruit juice with Dasatinib Accord should be avoided (see section 4.5). If possible, an alternative concomitant medication with no or minimal enzyme inhibition potential should be selected. If Dasatinib Accord must be administered with a strong CYP3A4 inhibitor, consider a dose decrease to:

- 40 mg daily for patients taking Dasatinib Accord 140 mg tablet daily.
- 20 mg daily for patients taking Dasatinib Accord 100 mg tablet daily.
- 20 mg daily for patients taking Dasatinib Accord 70 mg tablet daily.

For patients taking Dasatinib Accord 60 mg or 40 mg daily, consider interrupting the dose of Dasatinib Accord until the CYP3A4 inhibitor is discontinued, or switching to a lower dose with the Dasatinib powder for oral suspension formulation (see Summary of Product Characteristics for Dasatinib powder for oral suspension). Allow a washout period of approximately 1 week after the inhibitor is stopped before reinitiating Dasatinib Accord.

These reduced doses of Dasatinib Accord are predicted to adjust the area under the curve (AUC) to the range observed without CYP3A4 inhibitors; however, clinical data are not available with these dose adjustments in patients receiving strong CYP3A4 inhibitors. If Dasatinib Accord is not tolerated after dose reduction, either discontinue the strong CYP3A4 inhibitor or interrupt Dasatinib Accord until the

inhibitor is discontinued. Allow a washout period of approximately 1 week after the inhibitor is stopped before the Dasatinib Accord dose is increased.

Special populations

Elderly

No clinically relevant age-related pharmacokinetic differences have been observed in these patients. No specific dose recommendation is necessary in elderly.

Hepatic impairment

Patients with mild, moderate or severe hepatic impairment may receive the recommended starting dose. However, Dasatinib Accord should be used with caution in patients with hepatic impairment (see section 5.2).

Renal impairment

No clinical studies were conducted with dasatinib in patients with decreased renal function. Since the renal clearance of dasatinib and its metabolites is < 4%, a decrease in total body clearance is not expected in patients with renal insufficiency.

Method of administration

Dasatinib Accord must be administered orally.

The film-coated tablets must not be crushed, cut or chewed in order to maintain dosing consistency and minimise the risk of dermal exposure; they must be swallowed whole. Film-coated tablets should not be dispersed as the exposure in patients receiving a dispersed tablet is lower than in those swallowing a whole tablet. Dasatinib powder for oral suspension is also available for paediatric Ph+ ALL patients, who cannot swallow tablets. Dasatinib Accord can be taken with or without a meal and should be taken consistently either in the morning or in the evening (see section 5.2). Dasatinib Accord should not be taken with grapefruit or grapefruit juice (see section 4.5).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Clinically relevant interactions

Dasatinib is a substrate and an inhibitor of cytochrome P450 (CYP) 3A4. Therefore, there is a potential for interaction with other concomitantly administered medicinal products that are metabolised primarily by or modulate the activity of CYP3A4 (see section 4.5).

Concomitant use of dasatinib and medicinal products or substances that potently inhibit CYP3A4 (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, telithromycin, grapefruit juice) may increase exposure to dasatinib. Therefore, in patients receiving dasatinib, coadministration of a potent CYP3A4 inhibitor is not recommended (see section 4.5).

Concomitant use of dasatinib and medicinal products that induce CYP3A4 (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or herbal preparations containing *Hypericum perforatum*, also known as St. John's Wort) may substantially reduce exposure to dasatinib, potentially increasing the risk of therapeutic failure. Therefore, in patients receiving dasatinib, coadministration of alternative medicinal products with less potential for CYP3A4 induction should be selected (see section 4.5).

Concomitant use of dasatinib and a CYP3A4 substrate may increase exposure to the CYP3A4 substrate. Therefore, caution is warranted when dasatinib is coadministered with CYP3A4 substrates of narrow therapeutic index, such as astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids (ergotamine, dihydroergotamine) (see section 4.5).

The concomitant use of dasatinib and a histamine-2 (H₂) antagonist (e.g. famotidine), proton pump inhibitor (e.g. omeprazole), or aluminium hydroxide/magnesium hydroxide may reduce the exposure to dasatinib. Thus, H₂ antagonists and proton pump inhibitors are not recommended and aluminium hydroxide/magnesium hydroxide products should be administered up to 2 hours prior to, or 2 hours following the administration of dasatinib (see section 4.5).

Special populations

Based on the findings from a single-dose pharmacokinetic study, patients with mild, moderate or severe hepatic impairment may receive the recommended starting dose (see section 5.2). Due to the limitations of this clinical study, caution is recommended when administering dasatinib to patients with hepatic impairment.

Important adverse reactions

Myelosuppression

Treatment with dasatinib is associated with anaemia, neutropaenia and thrombocytopaenia. Their occurrence is earlier and more frequent in patients with advanced phase CML or Ph+ ALL than in chronic phase CML. In adult patients with advanced phase CML or Ph+ ALL treated with dasatinib as monotherapy, complete blood counts (CBCs) should be performed weekly for the first 2 months, and then monthly thereafter, or as clinically indicated. In adult and paediatric patients with chronic phase CML, complete blood counts should be performed every 2 weeks for 12 weeks, then every 3 months thereafter or as clinically indicated. In paediatric patients with Ph+ ALL treated with dasatinib in combination with chemotherapy, CBCs should be performed prior to the start of each block of chemotherapy and as clinically indicated. During the consolidation blocks of chemotherapy, CBCs should be performed every 2 days until recovery (see sections 4.2 and 4.8). Myelosuppression is generally reversible and usually managed by withholding dasatinib temporarily or by dose reduction.

Bleeding

In patients with chronic phase CML (n=548), 5 patients (1%) receiving dasatinib had grade 3 or 4 haemorrhage. In clinical studies in patients with advanced phase CML receiving the recommended dose of dasatinib (n=304), severe central nervous system (CNS) haemorrhage occurred in 1% of patients. One case was fatal and was associated with Common Toxicity Criteria (CTC) grade 4 thrombocytopaenia. Grade 3 or 4 gastrointestinal haemorrhage occurred in 6% of patients with advanced phase CML and generally required treatment interruptions and transfusions. Other grade 3 or 4 haemorrhage occurred in 2% of patients with advanced phase CML. Most bleeding related adverse reactions in these patients were typically associated with grade 3 or 4 thrombocytopaenia (see section 4.8). Additionally, *in vitro* and *in vivo* platelet assays suggest that dasatinib treatment reversibly affects platelet activation.

Caution should be exercised if patients are required to take medicinal products that inhibit platelet function or anticoagulants.

Fluid retention

Dasatinib is associated with fluid retention. In the Phase III clinical study in patients with newly diagnosed chronic phase CML, grade 3 or 4 fluid retention was reported in 13 patients (5%) in the dasatinib-treatment group and in 2 patients (1%) in the imatinib-treatment group after a minimum of 60 months follow-up (see section 4.8). In all dasatinib treated patients with chronic phase CML, severe fluid retention occurred in 32 patients (6%) receiving dasatinib at the recommended dose (n=548). In clinical studies in patients with advanced phase CML or Ph+ ALL receiving dasatinib at the recommended dose (n=304), grade 3 or 4 fluid retention was reported in 8% of patients, including grade 3 or 4 pleural and pericardial effusion reported in 7% and 1% of patients, respectively. In these patients grade 3 or 4 pulmonary oedema and pulmonary hypertension were each reported in 1% of patients.

Patients who develop symptoms suggestive of pleural effusion such as dyspnoea or dry cough should be evaluated by chest X-ray. Grade 3 or 4 pleural effusion may require thoracentesis and oxygen therapy. Fluid retention adverse reactions were typically managed by supportive care measures that include diuretics and short courses of steroids (see sections 4.2 and 4.8). Patients aged 65 years and

older are more likely than younger patients to experience pleural effusion, dyspnoea, cough, pericardial effusion and congestive heart failure, and should be monitored closely. Cases of chylothorax have also been reported in patients presenting with pleural effusion (see section 4.8).

Pulmonary arterial hypertension (PAH)

PAH (pre-capillary pulmonary arterial hypertension confirmed by right heart catheterization) has been reported in association with dasatinib treatment (see section 4.8). In these cases, PAH was reported after initiation of dasatinib therapy, including after more than one year of treatment.

Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating dasatinib therapy. An echocardiography should be performed at treatment initiation in every patient presenting symptoms of cardiac disease and considered in patients with risk factors for cardiac or pulmonary disease. Patients who develop dyspnoea and fatigue after initiation of therapy should be evaluated for common etiologies including pleural effusion, pulmonary oedema, anaemia, or lung infiltration. In accordance with recommendations for management of non-haematologic adverse reactions (see section 4.2) the dose of dasatinib should be reduced or therapy interrupted during this evaluation. If no explanation is found, or if there is no improvement with dose reduction or interruption, the diagnosis of PAH should be considered. The diagnostic approach should follow standard practice guidelines. If PAH is confirmed, dasatinib should be permanently discontinued. Follow up should be performed according to standard practice guidelines. Improvements in haemodynamic and clinical parameters have been observed in dasatinib-treated patients with PAH following cessation of dasatinib therapy.

QT prolongation

In vitro data suggest that dasatinib has the potential to prolong cardiac ventricular repolarisation (QT Interval) (see section 5.3). In 258 dasatinib-treated patients and 258 imatinib-treated patients with a minimum of 60 months follow-up in the Phase III study in newly diagnosed chronic phase CML, 1 patient (< 1%) in each group had QTc prolongation reported as an adverse reaction. The median changes in QTcF from baseline were 3.0 msec in dasatinib-treated patients compared to 8.2 msec in imatinib-treated patients. One patient (< 1%) in each group experienced a QTcF > 500 msec. In 865 patients with leukaemia treated with dasatinib in Phase II clinical studies, the mean changes from baseline in QTc interval using Fridericia's method (QTcF) were 4 - 6 msec; the upper 95% confidence intervals for all mean changes from baseline were < 7 msec (see section 4.8).

Of the 2,182 patients with resistance or intolerance to prior imatinib therapy who received dasatinib in clinical studies, 15 (1%) had QTc prolongation reported as an adverse reaction. Twenty-one of these patients (1%) experienced a QTcF > 500 msec.

Dasatinib should be administered with caution to patients who have or may develop prolongation of QTc. These include patients with hypokalaemia or hypomagnesaemia, patients with congenital long QT syndrome, patients taking anti-arrhythmic medicinal products or other medicinal products which lead to QT prolongation, and cumulative high dose anthracycline therapy. Hypokalaemia or hypomagnesaemia should be corrected prior to dasatinib administration.

Cardiac adverse reactions

Dasatinib was studied in a randomised clinical study of 519 patients with newly diagnosed CML in chronic phase which included patients with prior cardiac disease. The cardiac adverse reactions of congestive heart failure/cardiac dysfunction, pericardial effusion, arrhythmias, palpitations, QT prolongation and myocardial infarction (including fatal) were reported in patients taking dasatinib. Cardiac adverse reactions were more frequent in patients with risk factors or a history of cardiac disease. Patients with risk factors (e.g. hypertension, hyperlipidaemia, diabetes) or a history of cardiac disease (e.g. prior percutaneous coronary intervention, documented coronary artery disease) should be monitored carefully for clinical signs or symptoms consistent with cardiac dysfunction such as chest pain, shortness of breath, and diaphoresis.

If these clinical signs or symptoms develop, physicians are advised to interrupt dasatinib administration and consider the need for alternative CML-specific treatment. After resolution, a functional assessment should be performed prior to resuming treatment with dasatinib. Dasatinib may

be resumed at the original dose for mild/moderate adverse reactions (\leq grade 2) and resumed at a dose level reduction for severe adverse reactions (\geq grade 3) (see section 4.2). Patients continuing treatment should be monitored periodically.

Patients with uncontrolled or significant cardiovascular disease were not included in the clinical studies.

Thrombotic microangiopathy (TMA)

BCR-ABL tyrosine kinase inhibitors have been associated with thrombotic microangiopathy (TMA), including individual case reports for dasatinib (see section 4.8). If laboratory or clinical findings associated with TMA occur in a patient receiving dasatinib, treatment with dasatinib should be discontinued and thorough evaluation for TMA, including ADAMTS13 activity and anti-ADAMTS13-antibody determination, should be completed. If anti-ADAMTS13-antibody is elevated in conjunction with low ADAMTS13 activity, treatment with dasatinib should not be resumed.

Hepatitis B reactivation

Reactivation of hepatitis B in patients who are chronic carriers of this virus has occurred after these patients received BCR-ABL tyrosine kinase inhibitors. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

Patients should be tested for HBV infection before initiating treatment with Dasatinib Accord. 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 (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with dasatinib should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy (see section 4.8).

Effects on growth and development in paediatric patients

In paediatric trials of dasatinib in imatinib-resistant/intolerant Ph+ CML-CP paediatric patients and treatment-naïve Ph+ CML-CP paediatric patients after at least 2 years of treatment, treatment-related adverse events associated with bone growth and development were reported in 6 (4.6%) patients, one of which was severe in intensity (Growth Retardation Grade 3). These 6 cases included cases of epiphyses delayed fusion, osteopaenia, growth retardation, and gynecomastia (see section 5.1). These results are difficult to interpret in the context of chronic diseases such as CML, and require long-term follow-up.

In paediatric trials of dasatinib in combination with chemotherapy in newly diagnosed Ph+ ALL paediatric patients after a maximum of 2 years of treatment, treatment-related adverse events associated with bone growth and development were reported in 1 (0.6%) patient. This case was a Grade 1 osteopenia.

Growth retardation has been observed in paediatric patients treated with dasatinib in clinical trials (see section 4.8). Monitoring of bone growth and development in paediatric patients is recommended.

Excipients

Lactose

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Isopropyl alcohol

This medicinal product contains isopropyl alcohol, as a residue of the manufacturing process.

4.5 Interaction with other medicinal products and other forms of interaction

Active substances that may increase dasatinib plasma concentrations

In vitro studies indicate that dasatinib is a CYP3A4 substrate. Concomitant use of dasatinib and medicinal products or substances which potentially inhibit CYP3A4 (e.g. ketoconazole, itraconazole,

erythromycin, clarithromycin, ritonavir, telithromycin, grapefruit juice) may increase exposure to dasatinib. Therefore, in patients receiving dasatinib, systemic administration of a potent CYP3A4 inhibitor is not recommended (see section 4.2).

At clinically relevant concentrations, binding of dasatinib to plasma proteins is approximately 96% on the basis of *in vitro* experiments. No studies have been performed to evaluate dasatinib interaction with other protein-bound medicinal products. The potential for displacement and its clinical relevance are unknown.

Active substances that may decrease dasatinib plasma concentrations

When dasatinib was administered following 8 daily evening administrations of 600 mg rifampicin, a potent CYP3A4 inducer, the AUC of dasatinib was decreased by 82%. Other medicinal products that induce CYP3A4 activity (e.g. dexamethasone, phenytoin, carbamazepine, phenobarbital or herbal preparations containing *Hypericum perforatum*, also known as St. John's Wort) may also increase metabolism and decrease dasatinib plasma concentrations. Therefore, concomitant use of potent CYP3A4 inducers with dasatinib is not recommended. In patients in whom rifampicin or other CYP3A4 inducers are indicated, alternative medicinal products with less enzyme induction potential should be used. Concomitant use of dexamethasone, a weak CYP3A4 inducer, with dasatinib is allowed; dasatinib AUC is predicted to decrease approximately 25% with concomitant use of dexamethasone, which is not likely to be clinically meaningful.

Histamine-2 antagonists and proton pump inhibitors

Long-term suppression of gastric acid secretion by H₂ antagonists or proton pump inhibitors (e.g. famotidine and omeprazole) is likely to reduce dasatinib exposure. In a single-dose study in healthy subjects, the administration of famotidine 10 hours prior to a single dose of dasatinib reduced dasatinib exposure by 61%. In a study of 14 healthy subjects, administration of a single 100 mg dose of dasatinib 22 hours following a 4 day, 40 mg omeprazole dose at steady state reduced the AUC of dasatinib by 43% and the C_{max} of dasatinib by 42%. The use of antacids should be considered in place of H₂ antagonists or proton pump inhibitors in patients receiving dasatinib therapy (see section 4.4).

Antacids

Non-clinical data demonstrate that the solubility of dasatinib is pH-dependent. In healthy subjects, the concomitant use of aluminium hydroxide/magnesium hydroxide antacids with dasatinib reduced the AUC of a single dose of dasatinib by 55% and the C_{max} by 58%. However, when antacids were administered 2 hours prior to a single dose of dasatinib, no relevant changes in dasatinib concentration or exposure were observed. Thus, antacids may be administered up to 2 hours prior to or 2 hours following dasatinib (see section 4.4).

Active substances that may have their plasma concentrations altered by dasatinib

Concomitant use of dasatinib and a CYP3A4 substrate may increase exposure to the CYP3A4 substrate. In a study in healthy subjects, a single 100 mg dose of dasatinib increased AUC and C_{max} exposure to simvastatin, a known CYP3A4 substrate, by 20 and 37% respectively. It cannot be excluded that the effect is larger after multiple doses of dasatinib. Therefore, CYP3A4 substrates known to have a narrow therapeutic index (e.g. astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids [ergotamine, dihydroergotamine]) should be administered with caution in patients receiving dasatinib (see section 4.4). *In vitro* data indicate a potential risk for interaction with CYP2C8 substrates, such as glitazones.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females

Both sexually active men and women of childbearing potential should use effective methods of contraception during treatment.

Pregnancy

Based on human experience, dasatinib is suspected to cause congenital malformations including neural tube defects, and harmful pharmacological effects on the foetus when administered during pregnancy. Studies in animals have shown reproductive toxicity (see section 5.3).

Dasatinib should not be used during pregnancy unless the clinical condition of the woman requires treatment with dasatinib. If dasatinib is used during pregnancy, the patient must be informed of the potential risk to the foetus.

Breast-feeding

There is insufficient/limited information on the excretion of dasatinib in human or animal breast milk. Physico-chemical and available pharmacodynamic/toxicological data on dasatinib point to excretion in breast milk and a risk to the breast-feeding child cannot be excluded. Breast-feeding should be stopped during treatment with dasatinib.

Fertility

In animal studies, the fertility of male and female rats was not affected by treatment with dasatinib (see section 5.3). Physicians and other healthcare providers should counsel male patients of appropriate age about possible effects of dasatinib on fertility, and this counseling may include consideration of semen deposition.

4.7 Effects on ability to drive and use machines

Dasatinib has minor influence on the ability to drive and use machines. Patients should be advised that they may experience adverse reactions such as dizziness or blurred vision during treatment with dasatinib. Therefore, caution should be recommended when driving a car or operating machines.

4.8 Undesirable effects

Summary of the safety profile

The data described below reflect the exposure to dasatinib as single-agent therapy at all doses tested in clinical studies (N=2,900), including 324 adult patients with newly diagnosed chronic phase CML, 2,388 adult patients with imatinib-resistant or -intolerant chronic or advanced phase CML or Ph+ ALL, and 188 paediatric patients.

In the 2,712 adult patients with either chronic phase CML, advanced phase CML or Ph+ ALL, the median duration of therapy was 19.2 months (range 0 to 93.2 months). In a randomized trial in patients with newly diagnosed chronic phase CML, the median duration of therapy was approximately 60 months. The median duration of therapy in 1,618 adult patients with chronic phase CML was 29 months (range 0 to 92.9 months). The median duration of therapy in 1,094 adult patients with advanced phase CML or Ph+ ALL was 6.2 months (range 0 to 93.2 months). Among 188 patients in paediatric studies, the median duration of therapy was 26.3 months (range 0 to 99.6 months). In the subset of 130 chronic phase CML dasatinib-treated paediatric patients, the median duration of therapy was 42.3 months (range 0.1 to 99.6 months).

The majority of dasatinib -treated patients experienced adverse reactions at some time. In the overall population of 2,712 dasatinib -treated adult subjects, 520 (19%) experienced adverse reactions leading to treatment discontinuation.

The overall safety profile of dasatinib in the paediatric Ph+ CML-CP population was similar to that of the adult population, regardless of formulation, with the exception of no reported pericardial effusion, pleural effusion, pulmonary oedema, or pulmonary hypertension in the paediatric population of the 130 dasatinib-treated paediatric subjects with CML-CP, 2 (1.5%) experienced adverse reactions leading to treatment discontinuation.

Tabulated list of adverse reactions

The following adverse reactions, excluding laboratory abnormalities, were reported in patients treated with dasatinib used as single-agent therapy in clinical studies and post-marketing experience (Table 3).

These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); not known (cannot be estimated from available post-marketing data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3: Tabulated summary of adverse reactions

Infections and infestations	
<i>Very common</i>	infection (including bacterial, viral, fungal, non-specified)
<i>Common</i>	pneumonia (including bacterial, viral, and fungal), upper respiratory tract infection/inflammation, herpes virus infection (including cytomegalovirus - CMV), enterocolitis infection, sepsis (including uncommon cases with fatal outcomes)
<i>Not known</i>	hepatitis B reactivation
Blood and lymphatic system disorders	
<i>Very common</i>	myelosuppression (including anaemia, neutropaenia, thrombocytopaenia)
<i>Common</i>	febrile neutropaenia
<i>Uncommon</i>	lymphadenopathy, lymphopaenia
<i>Rare</i>	aplasia pure red cell
Immune system disorders	
<i>Uncommon</i>	hypersensitivity (including erythema nodosum)
<i>Rare</i>	anaphylactic shock
Endocrine disorders	
<i>Uncommon</i>	hypothyroidism
<i>Rare</i>	hyperthyroidism, thyroiditis
Metabolism and nutrition disorders	
<i>Common</i>	appetite disturbances ^a , hyperuricaemia
<i>Uncommon</i>	tumour lysis syndrome, dehydration, hypoalbuminemia, hypercholesterolemia
<i>Rare</i>	diabetes mellitus
Psychiatric disorders	
<i>Common</i>	depression, insomnia
<i>Uncommon</i>	anxiety, confusional state, affect lability, libido decreased
Nervous system disorders	
<i>Very common</i>	headache
<i>Common</i>	neuropathy (including peripheral neuropathy), dizziness, dysgeusia, somnolence
<i>Uncommon</i>	CNS bleeding ^{a,b} , syncope, tremor, amnesia, balance disorder
<i>Rare</i>	cerebrovascular accident, transient ischaemic attack, convulsion, optic neuritis, VIIIth nerve paralysis, dementia, ataxia
Eye disorders	
<i>Common</i>	visual disorder (including visual disturbance, vision blurred, and visual acuity reduced), dry eye
<i>Uncommon</i>	visual impairment, conjunctivitis, photophobia, lacrimation increased
Ear and labyrinth disorders	
<i>Common</i>	tinnitus
<i>Uncommon</i>	hearing loss, vertigo
Cardiac disorders	
<i>Common</i>	congestive heart failure/cardiac dysfunction ^c , pericardial effusion*, arrhythmia (including tachycardia), palpitations
<i>Uncommon</i>	myocardial infarction (including fatal outcome)*, electrocardiogram QT prolonged*, pericarditis, ventricular arrhythmia (including ventricular tachycardia), angina pectoris, cardiomegaly, electrocardiogram T wave abnormal, troponin increased
<i>Rare</i>	cor pulmonale, myocarditis, acute coronary syndrome, cardiac arrest, electrocardiogram PR prolongation, coronary artery disease, pleuropericarditis
<i>Not Known</i>	atrial fibrillation/atrial flutter
Vascular disorders	

<i>Very common</i>	haemorrhage* ^d
<i>Common</i>	hypertension, flushing
<i>Uncommon</i>	hypotension, thrombophlebitis, thrombosis
<i>Rare</i>	deep vein thrombosis, embolism, livedo reticularis
<i>Not known</i>	thrombotic microangiopathy
Respiratory, thoracic and mediastinal disorders	
<i>Very common</i>	pleural effusion*, dyspnoea
<i>Common</i>	pulmonary oedema*, pulmonary hypertension*, lung infiltration, pneumonitis, cough
<i>Uncommon</i>	pulmonary arterial hypertension, bronchospasm, asthma, chylothorax*
<i>Rare</i>	pulmonary embolism, acute respiratory distress syndrome
<i>Not known</i>	interstitial lung disease
Gastrointestinal disorders	
<i>Very common</i>	diarrhoea, vomiting, nausea, abdominal pain
<i>Common</i>	gastrointestinal bleeding*, colitis (including neutropaenic colitis), gastritis, mucosal inflammation (including mucositis/stomatitis), dyspepsia, abdominal distension, constipation, oral soft tissue disorder
<i>Uncommon</i>	pancreatitis (including acute pancreatitis), upper gastrointestinal ulcer, oesophagitis, ascites*, anal fissure, dysphagia, gastroesophageal reflux disease
<i>Rare</i>	protein-losing gastroenteropathy, ileus, anal fistula
<i>Not known</i>	fatal gastrointestinal haemorrhage*
Hepatobiliary disorders	
<i>Uncommon</i>	hepatitis, cholecystitis, cholestasis
Skin and subcutaneous tissue disorders	
<i>Very common</i>	skin rash ^e
<i>Common</i>	alopecia, dermatitis (including eczema), pruritus, acne, dry skin, urticaria, hyperhidrosis
<i>Uncommon</i>	neutrophilic dermatosis, photosensitivity, pigmentation disorder, panniculitis, skin ulcer, bullous conditions, nail disorder, palmar-plantar erythrodysesthesia syndrome, hair disorder
<i>Rare</i>	leukocytoclastic vasculitis, skin fibrosis
<i>Not known</i>	Stevens-Johnson syndrome ^f
Musculoskeletal and connective tissue disorders	
<i>Very common</i>	musculoskeletal pain ^g
<i>Common</i>	arthralgia, myalgia, muscular weakness, musculoskeletal stiffness, muscle spasm
<i>Uncommon</i>	rhabdomyolysis, osteonecrosis, muscle inflammation, tendonitis, arthritis
<i>Rare</i>	epiphyses delayed fusion, ^h growth retardation ^h
Renal and urinary disorders	
<i>Uncommon</i>	renal impairment (including renal failure), urinary frequency, proteinuria
<i>Not known</i>	nephrotic syndrome
Pregnancy, puerperium and perinatal conditions	
<i>Rare</i>	abortion
Reproductive system and breast disorders	
<i>Uncommon</i>	gynecomastia, menstrual disorder
General disorders and administration site conditions	
<i>Very common</i>	peripheral oedema ⁱ , fatigue, pyrexia, face oedema ^j
<i>Common</i>	asthenia, pain, chest pain, generalised oedema* ^k , chills
<i>Uncommon</i>	malaise, other superficial oedema ^l
<i>Rare</i>	gait disturbance
Investigations	
<i>Common</i>	weight decreased, weight increased
<i>Uncommon</i>	blood creatine phosphokinase increased, gamma-glutamyltransferase increased
Injury, poisoning, and procedural complications	
<i>Common</i>	contusion

- ^a Includes decreased appetite, early satiety, increased appetite.
- ^b Includes central nervous system haemorrhage, cerebral haematoma, cerebral haemorrhage, extradural haematoma, haemorrhage intracranial, haemorrhagic stroke, subarachnoid haemorrhage, subdural haematoma, and subdural haemorrhage.
- ^c Includes brain natriuretic peptide increased, ventricular dysfunction, left ventricular dysfunction, right ventricular dysfunction, cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased and ventricular failure, left ventricular failure, right ventricular failure, and ventricular hypokinesia.
- ^d Excludes gastrointestinal bleeding and CNS bleeding; these adverse reactions are reported under the gastrointestinal disorders system organ class and the nervous system disorders system organ class, respectively.
- ^e Includes drug eruption, erythema, erythema multiforme, erythrosis, exfoliative rash, generalised erythema, genital rash, heat rash, milia, miliaria, pustular psoriasis, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin exfoliation, skin irritation, toxic skin eruption, urticaria vesiculosa, and vasculitic rash.
- ^f In the post-marketing setting, individual cases of Stevens-Johnson syndrome have been reported. It could not be determined whether these mucocutaneous adverse reactions were directly related to dasatinib or to concomitant medicinal product.
- ^g Musculoskeletal pain reported during or after discontinuing treatment.
- ^h Frequency reported as common in paediatric studies.
- ⁱ Gravitational oedema, localised oedema, oedema peripheral.
- ^j Conjunctival oedema, eye oedema, eye swelling, eyelid oedema, face oedema, lip oedema, macular oedema, oedema mouth, orbital oedema, periorbital oedema, swelling face.
- ^k Fluid overload, fluid retention, gastrointestinal oedema, generalised oedema, peripheral swelling, oedema, oedema due to cardiac disease, perinephric effusion, post procedural oedema, visceral oedema.
- ^l Genital swelling, incision site oedema, oedema genital, penile oedema, penile swelling, scrotal oedema, skin swelling, testicular swelling, vulvovaginal swelling.
- * For additional details, see section "Description of selected adverse reactions"

Description of selected adverse reactions

Myelosuppression

Treatment with dasatinib is associated with anaemia, neutropaenia and thrombocytopaenia. Their occurrence is earlier and more frequent in patients with advanced phase CML or Ph+ ALL than in chronic phase CML (see section 4.4).

Bleeding

Bleeding drug-related adverse reactions, ranging from petechiae and epistaxis to grade 3 or 4 gastrointestinal haemorrhage and CNS bleeding, were reported in patients taking dasatinib (see section 4.4).

Fluid retention

Miscellaneous adverse reactions such as pleural effusion, ascites, pulmonary oedema and pericardial effusion with or without superficial oedema may be collectively described as “fluid retention”. In the newly diagnosed chronic phase CML study after a minimum of 60 months follow-up, dasatinib-related fluid retention adverse reactions included pleural effusion (28%), superficial oedema (14%), pulmonary hypertension (5%), generalised oedema (4%), and pericardial effusion (4%). Congestive heart failure, cardiac dysfunction and pulmonary oedema were reported in < 2% of patients. The cumulative rate of dasatinib-related pleural effusion (all grades) over time was 10% at 12 months, 14% at 24 months, 19% at 36 months, 24% at 48 months and 28% at 60 months. A total of 46 dasatinib-treated patients had recurrent pleural effusions. Seventeen patients had 2 separate adverse reactions, 6 had 3 adverse reactions, 18 had 4 to 8 adverse reactions and 5 had > 8 episodes of pleural effusions.

The median time to first dasatinib-related grade 1 or 2 pleural effusion was 114 weeks (range: 4 to 299 weeks). Less than 10% of patients with pleural effusion had severe (grade 3 or 4) dasatinib-related pleural effusions. The median time to first occurrence of grade ≥ 3 dasatinib-related pleural effusion was 175 weeks (range: 114 to 274 weeks). The median duration of dasatinib-related pleural effusion (all grades) was 283 days (~40 weeks).

Pleural effusion was usually reversible and managed by interrupting dasatinib treatment and using diuretics or other appropriate supportive care measures (see sections 4.2 and 4.4). Among dasatinib-treated patients with drug-related pleural effusion (n=73), 45 (62%) had dose interruptions

and 30 (41%) had dose reductions. Additionally, 34 (47%) received diuretics, 23 (32%) received corticosteroids, and 20 (27%) received both corticosteroids and diuretics. Nine (12%) patients underwent therapeutic thoracentesis.

Six percent of dasatinib-treated patients discontinued treatment due to drug-related pleural effusion. Pleural effusion did not impair the ability of patients to obtain a response. Among the dasatinib-treated patients with pleural effusion, 96% achieved a cCCyR, 82% achieved a MMR, and 50% achieved a MR4.5 despite dose interruptions or dose adjustment.

See section 4.4 for further information on patients with chronic phase CML and advanced phase CML or Ph+ ALL.

Cases of chylothorax have been reported in patients presenting with pleural effusion. Some cases of chylothorax resolved upon dasatinib discontinuation, interruption, or dose reduction, but most cases also required additional treatment

Pulmonary arterial hypertension (PAH)

PAH (pre-capillary pulmonary arterial hypertension confirmed by right heart catheterization) has been reported in association with dasatinib exposure. In these cases, PAH was reported after initiation of dasatinib therapy, including after more than one year of treatment. Patients with PAH reported during dasatinib treatment were often taking concomitant medicinal products or had co-morbidities in addition to the underlying malignancy. Improvements in haemodynamic and clinical parameters have been observed in patients with PAH following discontinuation of dasatinib.

QT Prolongation

In the Phase III study in patients with newly diagnosed chronic phase CML, one patient (< 1%) of the dasatinib-treated patients had a QTcF > 500 msec after a minimum of 12 months follow-up (see section 4.4). No additional patients were reported to have QTcF > 500 msec after a minimum of 60 months follow-up.

In 5 Phase II clinical studies in patients with resistance or intolerance to prior imatinib therapy, repeated baseline and on-treatment ECGs were obtained at pre-specified time points and read centrally for 865 patients receiving dasatinib 70 mg twice daily. QT interval was corrected for heart rate by Fridericia's method. At all post-dose time points on day 8, the mean changes from baseline in QTcF interval were 4 - 6 msec, with associated upper 95% confidence intervals < 7 msec. Of the 2,182 patients with resistance or intolerance to prior imatinib therapy who received dasatinib in clinical studies, 15 (1%) had QTc prolongation reported as an adverse reaction. Twenty-one patients (1%) experienced a QTcF > 500 msec (see section 4.4).

Cardiac adverse reactions

Patients with risk factors or a history of cardiac disease should be monitored carefully for signs or symptoms consistent with cardiac dysfunction and should be evaluated and treated appropriately (see section 4.4).

Hepatitis B reactivation

Hepatitis B reactivation has been reported in association with BCR-ABL TKIs. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome (see section 4.4).

In the Phase III dose-optimisation study in patients with chronic phase CML with resistance or intolerance to prior imatinib therapy (median duration of treatment of 30 months), the incidence of pleural effusion and congestive heart failure/cardiac dysfunction was lower in patients treated with dasatinib 100 mg once daily than in those treated with dasatinib 70 mg twice daily.

Myelosuppression was also reported less frequently in the 100 mg once daily treatment group (see Laboratory test abnormalities below). The median duration of therapy in the 100 mg once daily group was 37 months (range 1-91 months). Cumulative rates of selected adverse reactions that were reported in the 100 mg once daily recommended starting dose are shown in Table 4a.

Table 4a: Selected adverse reactions reported in a phase 3 dose optimisation study (imatinib intolerant or resistant chronic phase CML)^a

	Minimum of 2 years follow up		Minimum of 5 years follow up		Minimum of 7 years follow up	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	Percent (%) of patients					
Diarrhoea	27	2	28	2	28	2
Fluid retention	34	4	42	6	48	7
Superficial oedema	18	0	21	0	22	0
Pleural effusion	18	2	24	4	28	5
Generalised oedema	3	0	4	0	4	0
Pericardial effusion	2	1	2	1	3	1
Pulmonary hypertension	0	0	0	0	2	1
Haemorrhage	11	1	11	1	12	1
Gastrointestinal bleeding	2	1	2	1	2	1

^a Phase 3 dose optimisation study results reported in recommended starting dose of 100 mg once daily (n=165) population

In the Phase III dose-optimisation study in patients with advanced phase CML and Ph+ ALL, the median duration of treatment was 14 months for accelerated phase CML, 3 months for myeloid blast CML, 4 months for lymphoid blast CML and 3 months for Ph+ ALL. Selected adverse reactions that were reported in the recommended starting dose of 140 mg once daily are shown in Table 4b. A 70 mg twice daily regimen was also studied. The 140 mg once daily regimen showed a comparable efficacy profile to the 70 mg twice daily regimen but a more favourable safety profile.

Table 4b: Selected adverse reactions reported in phase III dose-optimisation study: Advanced phase CML and Ph+ ALL^a

Preferred term	140 mg once daily n = 304	
	All grades	Grade 3/4
	Percent (%) of patients	
Diarrhoea	28	3
Fluid retention	33	7
Superficial oedema	15	<1
Pleural effusion	20	6
Generalised oedema	2	0
Congestive heart failure /cardiac dysfunction ^b	1	0
Pericardial effusion	2	1
Pulmonary hypertension	1	1
Haemorrhage	23	8
Gastrointestinal bleeding	8	6

^a Phase 3 dose optimisation study results reported at the recommended starting dose of 140 mg once daily (n=304) population at 2 year final study follow up.

^b Includes ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and ventricular failure.

In addition, there were two studies in a total of 161 paediatric patients with Ph+ ALL in which dasatinib was administered in combination with chemotherapy. In the pivotal study, 106 paediatric patients received dasatinib in combination with chemotherapy on a continuous dosing regimen. In a supportive study, of 55 paediatric patients, 35 received dasatinib in combination with chemotherapy on a discontinuous dosing regimen (two weeks on treatment followed by one to two weeks off) and 20 received dasatinib in combination with chemotherapy on a continuous dosing regimen. Among the 126 Ph+ ALL paediatric patients treated with dasatinib on a continuous dosing regimen, the median duration of therapy was 23.6 months (range 1.4 to 33 months).

Of the 126 Ph+ ALL paediatric patients on a continuous dosing regimen, 2 (1.6%) experienced adverse reactions leading to treatment discontinuation. Adverse reactions reported in these two paediatric studies at a frequency of $\geq 10\%$ in patients on a continuous dosing regimen are shown in Table 5. Of note, pleural effusion was reported in 7 (5.6%) patients in this group, and is therefore not included in the table.

Table 5: Adverse reactions reported in $\geq 10\%$ of paediatric patients with Ph+ ALL treated with dasatinib on a continuous dosing regimen in combination with chemotherapy (N=126)^a

Adverse reaction	Percent (%) of patients	
	All grades	Grade 3/4
Febrile neutropaenia	27.0	26.2
Nausea	20.6	5.6
Vomiting	20.6	4.8
Abdominal pain	14.3	3.2
Diarrhoea	12.7	4.8
Pyrexia	12.7	5.6
Headache	11.1	4.8
Decreased appetite	10.3	4.8
Fatigue	10.3	0

^a In the pivotal study, among 106 total patients, 24 patients received the powder for oral suspension at least once, 8 of whom received the powder for oral suspension formulation exclusively.

Laboratory test abnormalities

Haematology

In the Phase III newly diagnosed chronic phase CML study, the following grade 3 or 4 laboratory abnormalities were reported after a minimum of 12 months follow-up in patients taking dasatinib: neutropaenia (21%), thrombocytopaenia (19%), and anaemia (10%). After a minimum of 60 months follow-up, the cumulative rates of neutropaenia, thrombocytopaenia, and anaemia were 29%, 22% and 13%, respectively.

In dasatinib-treated patients with newly diagnosed chronic phase CML who experienced grade 3 or 4 myelosuppression, recovery generally occurred following brief dose interruptions and/or reductions and permanent discontinuation of treatment occurred in 1.6% of patients after a minimum of 12 months follow-up. After a minimum of 60 months follow-up the cumulative rate of permanent discontinuation due to grade 3 or 4 myelosuppression was 2.3%.

In patients with CML with resistance or intolerance to prior imatinib therapy, cytopenias (thrombocytopaenia, neutropaenia, and anaemia) were a consistent finding. However, the occurrence of cytopenias was also clearly dependent on the stage of the disease. The frequency of grade 3 and 4 haematological abnormalities is presented in Table 6.

Table 6: CTC grades 3/4 haematological laboratory abnormalities in clinical studies in patients with resistance or intolerance to prior imatinib therapy^a

	Chronic phase (n= 165) ^b	Accelerated phase (n= 157) ^c	Myeloid blast phase (n= 74) ^c	Lymphoid blast phase Ph+ALL (n= 168) ^c
Percent (%) of patients				
Haematology parameters				
Neutropaenia	36	58	77	76
Thrombocytopaenia	23	63	78	74
Anaemia	13	47	74	44

^a Phase 3 dose optimisation study results reported at 2 year study follow up.

^b CA180-034 study results in recommended starting dose of 100 mg once daily.

^c CA180-035 study results in recommended starting dose of 140 mg once daily.

CTC grades: neutropaenia (Grade 3 $\geq 0.5 - < 1.0 \times 10^9/l$, Grade 4 $< 0.5 \times 10^9/l$); thrombocytopaenia (Grade 3 $\geq 25 - < 50 \times 10^9/l$, Grade 4 $< 25 \times 10^9/l$); anaemia (haemoglobin Grade 3 $\geq 65 - < 80$ g/l, Grade 4 < 65 g/l).

Cumulative grade 3 or 4 cytopaenias among patients treated with 100 mg once daily were similar at 2 and 5 years including: neutropaenia (35% vs. 36%), thrombocytopaenia (23% vs. 24%) and anaemia (13% vs. 13%).

In patients who experienced grade 3 or 4 myelosuppression, recovery generally occurred following brief dose interruptions and/or reductions and permanent discontinuation of treatment occurred in 5% of patients. Most patients continued treatment without further evidence of myelosuppression.

Biochemistry

In the newly diagnosed chronic phase CML study, grade 3 or 4 hypophosphataemia was reported in 4% of dasatinib-treated patients, and grade 3 or 4 elevations of transaminases, creatinine, and bilirubin were reported in $\leq 1\%$ of patients after a minimum of 12 months follow-up. After a minimum of 60 months follow-up the cumulative rate of grade 3 or 4 hypophosphataemia was 7%, grade 3 or 4 elevations of creatinine and bilirubin was 1% and grade 3 or 4 elevations of transaminases remained 1%. There were no discontinuations of dasatinib therapy due to these biochemical laboratory parameters.

2 year follow-up

Grade 3 or 4 elevations of transaminases or bilirubin were reported in 1% of patients with chronic phase CML (resistant or intolerant to imatinib), but elevations were reported with an increased frequency of 1 to 7% of patients with advanced phase CML and Ph+ ALL. It was usually managed with dose reduction or interruption. In the Phase III dose-optimisation study in chronic phase CML, grade 3 or 4 elevations of transaminases or bilirubin were reported in $\leq 1\%$ of patients with similar low incidence in the four treatment groups. In the Phase III dose-optimisation study in advanced phase CML and Ph+ALL, grade 3 or 4 elevations of transaminases or bilirubin were reported in 1% to 5% of patients across treatment groups.

Approximately 5% of the dasatinib-treated patients who had normal baseline levels experienced grade 3 or 4 transient hypocalcaemia at some time during the course of the study. In general, there was no association of decreased calcium with clinical symptoms. Patients developing grade 3 or 4 hypocalcaemia often had recovery with oral calcium supplementation.

Grade 3 or 4 hypocalcaemia, hypokalaemia, and hypophosphataemia were reported in patients with all phases of CML but were reported with an increased frequency in patients with myeloid or lymphoid blast phase CML and Ph+ ALL. Grade 3 or 4 elevations in creatinine were reported in $< 1\%$ of patients with chronic phase CML and were reported with an increased frequency of 1 to 4% of patients with advanced phase CML.

Paediatric population

The safety profile of dasatinib administered as single-agent therapy in paediatric patients with Ph+ CML-CP was comparable to the safety profile in adults. The safety profile of dasatinib administered in combination with chemotherapy in paediatric patients with Ph+ ALL was consistent with the known safety profile of dasatinib in adults and the expected effects of chemotherapy, with the exception of a lower pleural effusion rate in paediatric patients as compared to adults.

In the paediatric CML studies, the rates of laboratory abnormalities were consistent with the known profile for laboratory parameters in adults.

In the paediatric ALL studies, the rates of laboratory abnormalities were consistent with the known profile for laboratory parameters in adults, within the context of an acute leukaemia patient receiving a background chemotherapy regimen.

Special population

While the safety profile of dasatinib in elderly was similar to that in the younger population, patients aged 65 years and older are more likely to experience the commonly reported adverse reactions such as fatigue, pleural effusion, dyspnoea, cough, lower gastrointestinal haemorrhage, and appetite disturbance and more likely to experience less frequently reported adverse reactions such as abdominal distention, dizziness, pericardial effusion, congestive heart failure, and weight decrease and should be monitored closely (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Experience with overdose of dasatinib in clinical studies is limited to isolated cases. The highest overdose of 280 mg per day for one week was reported in two patients and both developed a significant decrease in platelet counts. Since dasatinib is associated with grade 3 or 4 myelosuppression (see section 4.4), patients who ingest more than the recommended dose should be closely monitored for myelosuppression and given appropriate supportive treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors, ATC code: L01EA02

Pharmacodynamics

Dasatinib inhibits the activity of the BCR-ABL kinase and SRC family kinases along with a number of other selected oncogenic kinases including c-KIT, ephrin (EPH) receptor kinases, and PDGF β receptor. Dasatinib is a potent, subnanomolar inhibitor of the BCR-ABL kinase with potency at concentration of 0.6-0.8 nM. It binds to both the inactive and active conformations of the BCR-ABL enzyme.

Mechanism of action

In vitro, dasatinib is active in leukaemic cell lines representing variants of imatinib-sensitive and resistant disease. These non-clinical studies show that dasatinib can overcome imatinib resistance resulting from BCR-ABL overexpression, BCR-ABL kinase domain mutations, activation of alternate signalling pathways involving the SRC family kinases (LYN, HCK), and multidrug resistance gene overexpression. Additionally, dasatinib inhibits SRC family kinases at subnanomolar concentrations.

Clinical efficacy and safety

In the Phase I study, haematologic and cytogenetic responses were observed in all phases of CML and in Ph+ ALL in the first 84 patients treated and followed for up to 27 months. Responses were durable across all phases of CML and Ph+ ALL.

The efficacy of dasatinib is based on haematological and cytogenetic response rates. Durability of response and estimated survival rates provide additional evidence of dasatinib clinical benefit.

Ph+ ALL

An open-label, single-arm, multicentre study was conducted in patients with Ph+ ALL who were resistant or intolerant to prior imatinib therapy. A total of 46 patients with Ph+ ALL received dasatinib 70 mg twice daily (44 resistant and 2 intolerant to imatinib). The median time from diagnosis to start of treatment was 18 months. Median duration of treatment on dasatinib was 3 months with 7% of patients treated for > 24 months to date. The rate of major molecular response (all 25 treated patients with a CCyR) was 52% at 24 months. Further efficacy results are reported in Table 7. Of note, major

haematologic responses (MaHR) were achieved quickly (most within 55 days of first dasatinib administration for patients with Ph+ ALL).

Table 7: Efficacy in phase II dasatinib single-arm clinical studies^a

	Ph+ ALL (n= 46)
Haematologic response rate^b (%)	
MaHR (95% CI)	41% (27-57)
CHR (95% CI)	35% (21-50)
NEL (95% CI)	7% (1-18)
Duration of MaHR (%; Kaplan-Meier estimates)	
1 year	32% (8-56)
2 year	24% (2-47)
Cytogenetic response^c (%)	
MCyR (95% CI)	57% (41-71)
CCyR (95% CI)	54% (39-69)
Survival (%; Kaplan-Meier estimates)	
Progression-Free	
1 year	21% (9-34)
2 year	12% (2-23)
Overall	
1 year	35% (20-51)
2 year	31% (16-47)

Data described in this table are from studies using a starting dose of 70 mg twice daily. See section 4.2 for the recommended starting dose.

^a Numbers in bold font are the results of primary endpoints.

^b Haematologic response criteria (all responses confirmed after 4 weeks): Major haematologic response (MaHR)= complete haematologic response (CHR) + no evidence of leukaemia (NEL).

CHR (Ph+ ALL): WBC \leq institutional ULN, ANC \geq 1,000/mm³, platelets \geq 100,000/mm³, no blasts or promyelocytes in peripheral blood, bone marrow blasts \leq 5%, < 5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood < 20%, and no extramedullary involvement.

NEL: same criteria as for CHR but ANC \geq 500/mm³ and < 1,000/mm³, or platelets \geq 20,000/mm³ and \leq 100,000/mm³.

^c Cytogenetic response criteria: complete (0% Ph+ metaphases) or partial (> 0%-35%). MCyR (0%-35%) combines both complete and partial responses.

n/a = not applicable; CI = confidence interval; ULN = upper limit of normal range.

The outcome of patients with bone marrow transplantation after dasatinib treatment has not been fully evaluated.

Phase III clinical studies in patients with Ph+ ALL who were resistant or intolerant to imatinib

Two randomised, open-label studies were conducted to evaluate the efficacy of dasatinib administered once daily compared with dasatinib administered twice daily. Results described below are based on a minimum of 2 years and 7 years follow-up after the start of dasatinib therapy.

In the study in Ph+ ALL, the primary endpoint was MaHR. A total of 611 patients were randomised to either the dasatinib 140 mg once daily or 70 mg twice daily group. Median duration of treatment was approximately 6 months (range 0.03-31 months).

The once daily schedule demonstrated comparable efficacy (non-inferiority) to the twice daily schedule on the primary efficacy endpoint (difference in MaHR 0.8%; 95% confidence interval [-7.1% - 8.7%]); however, the 140 mg once daily regimen demonstrated improved safety and tolerability. Response rates are presented in Table 8.

Table 8: Efficacy of dasatinib in phase III dose-optimisation study: Ph+ ALL (2 year results)^a

	Ph+ALL (n= 40)
MaHR^b	38%
(95% CI)	(23-54)
CHR^b	33%
(95% CI)	(19-49)
NEL^b	5%
(95% CI)	(1-17)
MCyR^c	70%
(95% CI)	(54-83)
CCyR	50%
(95% CI)	(34-66)

^a Results reported in recommended starting dose of 140 mg once daily (see section 4.2).

^b Haematologic response criteria (all responses confirmed after 4 weeks): Major haematologic response (MaHR) = complete haematologic response (CHR) + no evidence of leukaemia (NEL).

CHR: WBC \leq institutional ULN, ANC \geq 1,000/mm³, platelets \geq 100,000/mm³, no blasts or promyelocytes in peripheral blood, bone marrow blasts \leq 5%, $<$ 5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood $<$ 20%, and no extramedullary involvement.

NEL: same criteria as for CHR but ANC \geq 500/mm³ and $<$ 1,000/mm³, or platelets \geq 20,000/mm³ and \leq 100,000/mm³.

^c MCyR combines both complete (0% Ph+ metaphases) and partial ($>$ 0%-35%) responses.

CI = confidence interval; ULN = upper limit of normal range.

In patients with Ph+ ALL treated with the 140 mg once daily regimen, the median duration of MaHR was 5 months the median PFS was 4 months, and the median overall survival was 7 months.

Paediatric population

Paediatric patients with ALL

The efficacy of dasatinib in combination with chemotherapy was evaluated in a pivotal study in paediatric patients over one year of age with newly diagnosed Ph+ ALL.

In this multicenter, historically-controlled Phase II study of dasatinib added to standard chemotherapy, 106 paediatric patients with newly diagnosed Ph+ ALL, of whom 104 patients had confirmed Ph+ ALL, received dasatinib at a daily dose of 60 mg/m² on a continuous dosing regimen for up to 24 months, in combination with chemotherapy. Eighty-two patients received dasatinib tablets exclusively and 24 patients received dasatinib powder for oral suspension at least once, 8 of whom received dasatinib powder for oral suspension exclusively. The backbone chemotherapy regimen was the same as used in the AIEOP-BFM ALL 2000 trial (chemotherapeutic standard multi-agent chemotherapy protocol). The primary efficacy endpoint was 3-year event-free survival (EFS), which was 65.5% (55.5, 73.7).

The minimal residual disease (MRD) negativity rate assessed by Ig/TCR rearrangement was 71.7% by the end of consolidation in all treated patients. When this rate was based on the 85 patients with evaluable Ig/TCR assessments, the estimate was 89.4%. The MRD negativity rates at the end of induction and consolidation as measured by flow cytometry were 66.0% and 84.0%, respectively.

5.2 Pharmacokinetic properties

The pharmacokinetics of dasatinib were evaluated in 229 adult healthy subjects and in 84 patients.

Absorption

Dasatinib is rapidly absorbed in patients following oral administration, with peak concentrations between 0.5-3 hours. Following oral administration, the increase in the mean exposure (AUC_{0-∞}) is approximately proportional to the dose increment across doses ranging from 25 mg to 120 mg twice daily. The overall mean terminal half-life of dasatinib is approximately 5-6 hours in patients.

Data from healthy subjects administered a single 100 mg dose of dasatinib 30 minutes following a high-fat meal indicated a 14% increase in the mean AUC of dasatinib. A low-fat meal 30 minutes prior to dasatinib resulted in a 21% increase in the mean AUC of dasatinib. The observed food effects do not represent clinically relevant changes in exposure. Dasatinib exposure variability is higher under fasted conditions (47% CV) compared to light-fat meal (39% CV) and high-fat meal (32% CV) conditions.

Based on the patient population PK analysis, variability in dasatinib exposure was estimated to be mainly due to inter-occasion variability in bioavailability (44% CV) and, to a lesser extent, due to inter-individual variability in bioavailability and inter-individual variability in clearance (30% and 32% CV, respectively). The random inter-occasion variability in exposure is not expected to affect the cumulative exposure and efficacy or safety.

Distribution

In patients, dasatinib has a large apparent volume of distribution (2,505 L), coefficient of variation (CV% 93%), suggesting that the medicinal product is extensively distributed in the extravascular space. At clinically relevant concentrations of dasatinib, binding to plasma proteins was approximately 96% on the basis of *in vitro* experiments.

Biotransformation

Dasatinib is extensively metabolised in humans with multiple enzymes involved in the generation of the metabolites. In healthy subjects administered 100 mg of [¹⁴C]-labelled dasatinib, unchanged dasatinib represented 29% of circulating radioactivity in plasma. Plasma concentration and measured *in vitro* activity indicate that metabolites of dasatinib are unlikely to play a major role in the observed pharmacology of the product. CYP3A4 is a major enzyme responsible for the metabolism of dasatinib.

Elimination

The mean terminal half-life of dasatinib is 3 hours to 5 hours. The mean apparent oral clearance is 363.8 L/hr (CV% 81.3%).

Elimination is predominantly in the faeces, mostly as metabolites. Following a single oral dose of [¹⁴C]-labelled dasatinib, approximately 89% of the dose was eliminated within 10 days, with 4% and 85% of the radioactivity recovered in the urine and faeces, respectively. Unchanged dasatinib accounted for 0.1% and 19% of the dose in urine and faeces, respectively, with the remainder of the dose as metabolites.

Hepatic and renal impairment

The effect of hepatic impairment on the single-dose pharmacokinetics of dasatinib was assessed in 8 moderately hepatic-impaired subjects who received a 50 mg dose and 5 severely hepatic-impaired subjects who received a 20 mg dose compared to matched healthy subjects who received a 70 mg dose of dasatinib. The mean C_{max} and AUC of dasatinib adjusted for the 70 mg dose were decreased by 47% and 8%, respectively, in subjects with moderate hepatic impairment compared to subjects with normal hepatic function. In severely hepatic-impaired subjects, the mean C_{max} and AUC adjusted for the 70 mg dose were decreased by 43% and 28%, respectively, compared to subjects with normal hepatic function (see sections 4.2 and 4.4).

Dasatinib and its metabolites are minimally excreted via the kidney.

Paediatric population

The pharmacokinetics of dasatinib have been evaluated in 104 paediatric patients with leukaemia or solid tumours (72 who received the tablet formulation and 32 who received the Dasatinib powder for oral suspension).

In a paediatric pharmacokinetics study, dose-normalized dasatinib exposure (C_{avg} , C_{min} and C_{max}) appears similar between 21 patients with CP-CML and 16 patients with Ph+ ALL.

Pharmacokinetics of the tablet formulation of dasatinib were evaluated for 72 paediatric patients with relapsed or refractory leukaemia or solid tumours at oral doses ranging from 60 to 120 mg/m² once daily and 50 to 110 mg/m² twice daily. Data was pooled across two studies and showed that dasatinib was rapidly absorbed. Mean T_{max} was observed between 0.5 and 6 hours and mean half-life ranged from 2 to 5 hours across all dose levels and age groups. Dasatinib PK showed dose proportionality with a dose-related increase in exposure observed in paediatric patients. There was no significant difference of dasatinib PK between children and adolescents. The geometric means of dose normalized dasatinib C_{max} , AUC (0-T), and AUC (INF) appeared to be similar between children and adolescents at different dose levels. A PPK model-based simulation predicted that the body weight tiered dosing recommendation described for the tablet, in section 4.2, is expected to provide similar exposure to a tablet dose of 60 mg/m². These data should be considered if patients are to switch from tablets to Dasatinib powder for oral suspension or vice versa.

5.3 Preclinical safety data

The non-clinical safety profile of dasatinib was assessed in a battery of *in vitro* and *in vivo* studies in mice, rats, monkeys, and rabbits.

The primary toxicities occurred in the gastrointestinal, haematopoietic, and lymphoid systems. Gastrointestinal toxicity was dose-limiting in rats and monkeys, as the intestine was a consistent target organ. In rats, minimal to mild decreases in erythrocyte parameters were accompanied by bone marrow changes; similar changes occurred in monkeys at a lower incidence. Lymphoid toxicity in rats consisted of lymphoid depletion of the lymph nodes, spleen, and thymus, and decreased lymphoid organ weights. Changes in the gastrointestinal, haematopoietic and lymphoid systems were reversible following cessation of treatment.

Renal changes in monkeys treated for up to 9 months were limited to an increase in background kidney mineralisation. Cutaneous haemorrhage was observed in an acute, single-dose oral study in monkeys but was not observed in repeat-dose studies in either monkeys or rats. In rats, dasatinib inhibited platelet aggregation *in vitro* and prolonged cuticle bleeding time *in vivo*, but did not invoke spontaneous haemorrhage.

Dasatinib activity *in vitro* in hERG and Purkinje fiber assays suggested a potential for prolongation of cardiac ventricular repolarisation (QT interval). However, in an *in vivo* single-dose study in conscious telemetered monkeys, there were no changes in QT interval or ECG wave form.

Dasatinib was not mutagenic in *in vitro* bacterial cell assays (Ames test) and was not genotoxic in an *in vivo* rat micronucleus study. Dasatinib was clastogenic *in vitro* to dividing Chinese Hamster Ovary (CHO) cells.

Dasatinib did not affect male or female fertility in a conventional rat fertility and early embryonic development study, but induced embryoletality at dose levels approximating human clinical exposures. In embryofoetal development studies, dasatinib likewise induced embryoletality with associated decreases in litter size in rats, as well as foetal skeletal alterations in both rats and rabbits. These effects occurred at doses that did not produce maternal toxicity, indicating that dasatinib is a selective reproductive toxicant from implantation through the completion of organogenesis.

In mice, dasatinib induced immunosuppression, which was dose-related and effectively managed by dose reduction and/or changes in dosing schedule. Dasatinib had phototoxic potential in an *in vitro* neutral red uptake phototoxicity assay in mouse fibroblasts. Dasatinib was considered to be

non-phototoxic *in vivo* after a single oral administration to female hairless mice at exposures up to 3-fold the human exposure following administration of the recommended therapeutic dose (based on AUC).

In a two-year carcinogenicity study, rats were administered oral doses of dasatinib at 0.3, 1, and 3 mg/kg/day. The highest dose resulted in a plasma exposure (AUC) level generally equivalent to the human exposure at the recommended range of starting doses from 100 mg to 140 mg daily. A statistically significant increase in the combined incidence of squamous cell carcinomas and papillomas in the uterus and cervix of high-dose females and of prostate adenoma in low-dose males was noted. The relevance of the findings from the rat carcinogenicity study for humans is not known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Hydroxypropyl cellulose
Cellulose, microcrystalline
Methacrylic acid – methacrylate copolymer (1:2)
Talc
Croscarmellose sodium
Magnesium stearate

Film-coating

Hypromellose (E464)
Titanium dioxide (E171)
Medium chain triglycerides

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

12 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Dasatinib Accord 20 mg, 50 mg and 70 mg film-coated tablets

Alu/Alu blisters (blisters or perforated unit dose blisters).

Carton containing 56 or 60 film-coated tablets in blisters.

Carton containing 56 x 1 or 60 x 1 film-coated tablet in perforated unit dose blisters.

Dasatinib Accord 80 mg, 100 mg and 140 mg film-coated tablets

Alu/Alu blisters (blisters or perforated unit dose blisters).

Carton containing 30 or 56 film-coated tablets in blisters.

Carton containing 30 x 1 or 56 x 1 film-coated tablet in perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The use of latex or nitrile gloves for appropriate disposal when handling tablets that are inadvertently crushed or broken is recommended, to minimise the risk of dermal exposure.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est, 6ª Planta,
08039 Barcelona,
Spain

8. MARKETING AUTHORISATION NUMBER(S)

Dasatinib Accord 20 mg film-coated tablets

EU/1/21/1540/001
EU/1/21/1540/002
EU/1/21/1540/003
EU/1/21/1540/004

Dasatinib Accord 50 mg film-coated tablets

EU/1/21/1540/005
EU/1/21/1540/006
EU/1/21/1540/007
EU/1/21/1540/008

Dasatinib Accord 70 mg film-coated tablets

EU/1/21/1540/009
EU/1/21/1540/010
EU/1/21/1540/011
EU/1/21/1540/012

Dasatinib Accord 80 mg film-coated tablets

EU/1/21/1540/013
EU/1/21/1540/014
EU/1/21/1540/015
EU/1/21/1540/016

Dasatinib Accord 100 mg film-coated tablets

EU/1/21/1540/017
EU/1/21/1540/018
EU/1/21/1540/019
EU/1/21/1540/020

Dasatinib Accord 140 mg film-coated tablets

EU/1/21/1540/021
EU/1/21/1540/022
EU/1/21/1540/023

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 March 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

Medicinal product no longer authorised

ANNEX II

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Pharmascience International Limited
1st Floor Iacovides Tower, 81-83 Griva Digeni Avenue
Nicosia, 1090
Cyprus

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

▪ Periodic safety update reports (PSURs)

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

▪ Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency,
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Medicinal product no longer authorised

ANNEX III
LABELLING AND PACKAGE LEAFLET

Medicinal product no longer authorised

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON FOR BLISTER PACK****1. NAME OF THE MEDICINAL PRODUCT**

Dasatinib Accord 20 mg film-coated tablets
dasatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 20 mg dasatinib.

3. LIST OF EXCIPIENTS

Excipients: contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

56 film-coated tablets
60 film-coated tablets
56 x 1 film-coated tablet
60 x 1 film-coated tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est, 6ª Planta,
08039 Barcelona,
Spain

12. MARKETING AUTHORISATION NUMBER(S)
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EU/1/21/1540/001
EU/1/21/1540/002
EU/1/21/1540/003
EU/1/21/1540/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dasatinib Accord 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Dasatinib Accord 20 mg tablets
dasatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON FOR BLISTER PACK****1. NAME OF THE MEDICINAL PRODUCT**

Dasatinib Accord 50 mg film-coated tablets
dasatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 50 mg dasatinib.

3. LIST OF EXCIPIENTS

Excipients: contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

56 film-coated tablets
60 film-coated tablets
56 x 1 film-coated tablet
60 x 1 film-coated tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est, 6ª Planta,
08039 Barcelona,
Spain

12. MARKETING AUTHORISATION NUMBER(S)
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EU/1/21/1540/005
EU/1/21/1540/006
EU/1/21/1540/007
EU/1/21/1540/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dasatinib Accord 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Dasatinib Accord 50 mg tablets
dasatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON FOR BLISTER PACK****1. NAME OF THE MEDICINAL PRODUCT**

Dasatinib Accord 70 mg film-coated tablets
dasatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 70 mg dasatinib.

3. LIST OF EXCIPIENTS

Excipients: contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

56 film-coated tablets
60 film-coated tablets
56 x 1 film-coated tablet
60 x 1 film-coated tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est, 6ª Planta,
08039 Barcelona,
Spain

12. MARKETING AUTHORISATION NUMBER(S)
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EU/1/21/1540/009
EU/1/21/1540/010
EU/1/21/1540/011
EU/1/21/1540/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dasatinib Accord 70 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Dasatinib Accord 70 mg tablets
dasatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON FOR BLISTER PACK****1. NAME OF THE MEDICINAL PRODUCT**

Dasatinib Accord 80 mg film-coated tablets
dasatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 80 mg dasatinib.

3. LIST OF EXCIPIENTS

Excipients: contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
56 film-coated tablets
30 x 1 film-coated tablet
56 x 1 film-coated tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est, 6ª Planta,
08039 Barcelona,
Spain

12. MARKETING AUTHORISATION NUMBER(S)
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EU/1/21/1540/013
EU/1/21/1540/014
EU/1/21/1540/015
EU/1/21/1540/016

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dasatinib Accord 80 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Dasatinib Accord 80 mg tablets
dasatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON FOR BLISTER PACK****1. NAME OF THE MEDICINAL PRODUCT**

Dasatinib Accord 100 mg film-coated tablets
dasatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg dasatinib.

3. LIST OF EXCIPIENTS

Excipients: contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
56 film-coated tablets
30 x 1 film-coated tablet
56 x 1 film-coated tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est, 6ª Planta,
08039 Barcelona,
Spain

12. MARKETING AUTHORISATION NUMBER(S)
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EU/1/21/1540/017
EU/1/21/1540/018
EU/1/21/1540/019
EU/1/21/1540/020

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dasatinib Accord 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Dasatinib Accord 100 mg tablets
dasatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON FOR BLISTER PACK****1. NAME OF THE MEDICINAL PRODUCT**

Dasatinib Accord 140 mg film-coated tablets
dasatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 140 mg dasatinib.

3. LIST OF EXCIPIENTS

Excipients: contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
56 film-coated tablets
30 x 1 film-coated tablet
56 x 1 film-coated tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est, 6ª Planta,
08039 Barcelona,
Spain

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/21/1540/021
EU/1/21/1540/022
EU/1/21/1540/023
EU/1/21/1540/024

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dasatinib Accord 140 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Dasatinib Accord 140 mg tablets
dasatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Medicinal product no longer authorised

Medicinal product no longer authorised

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Dasatinib Accord 20 mg film-coated tablets
Dasatinib Accord 50 mg film-coated tablets
Dasatinib Accord 70 mg film-coated tablets
Dasatinib Accord 80 mg film-coated tablets
Dasatinib Accord 100 mg film-coated tablets
Dasatinib Accord 140 mg film-coated tablets
dasatinib

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Dasatinib Accord is and what it is used for
2. What you need to know before you take Dasatinib Accord
3. How to take Dasatinib Accord
4. Possible side effects
5. How to store Dasatinib Accord
6. Contents of the pack and other information

1. What Dasatinib Accord is and what it is used for

Dasatinib Accord contains the active substance dasatinib. This medicine is used to treat Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL). It is used in adults who are not benefiting from previous therapies, as well as being combined with other cancer medicines in adolescents and children from 1 year of age with newly diagnosed Ph+ ALL. In people with ALL, white cells called lymphocytes multiply too quickly and live too long. Dasatinib Accord inhibits the growth of these leukaemic cells.

If you have any questions about how Dasatinib Accord works or why this medicine has been prescribed for you, ask your doctor.

2. What you need to know before you take Dasatinib Accord

Do not take Dasatinib Accord

- if you are **allergic** to dasatinib or any of the other ingredients of this medicine (listed in section 6).

If you could be allergic, ask your doctor for advice.

Warnings and precautions

Talk to your doctor or pharmacist before using Dasatinib Accord

- if you are taking **medicines to thin the blood** or prevent clots (see "Other medicines and Dasatinib Accord")
- if you have a liver or heart problem, or used to have one
- if you start **having difficulty breathing, chest pain, or a cough** when taking Dasatinib Accord: this may be a sign of fluid retention in the lungs or chest (which can be more common in patients aged 65 years and older), or due to changes in the blood vessels supplying the lungs

- if you have ever had or might now have a hepatitis B infection. This is because Dasatinib Accord could cause hepatitis B to become active again, which can be fatal in some cases. Patients will be carefully checked by their doctor for signs of this infection before treatment is started.
- if you experience bruising, bleeding, fever, fatigue and confusion when taking Dasatinib Accord, contact your doctor. This may be a sign of damage to blood vessels known as thrombotic microangiopathy (TMA).

Your doctor will regularly monitor your condition to check whether Dasatinib Accord is having the desired effect. You will also have blood tests regularly while you are taking Dasatinib Accord.

Children and adolescents

Do not give this medicine to children younger than one year of age. There is limited experience with the use of Dasatinib Accord in this age group. Bone growth and development will be closely monitored in children taking Dasatinib Accord.

Other medicines and Dasatinib Accord

Tell your doctor if you are taking, have recently taken or might take any other medicines.

Dasatinib Accord is mainly handled by the liver. Certain medicines may interfere with the effect of Dasatinib Accord when taken together.

These medicines are not to be used with Dasatinib Accord:

- ketoconazole, itraconazole - these are **antifungal medicines**
- erythromycin, clarithromycin, telithromycin - these are **antibiotics**
- ritonavir - this is an **antiviral medicine**
- phenytoin, carbamazepine, phenobarbital - these are treatments for **epilepsy**
- rifampicin - this is a treatment for **tuberculosis**
- famotidine, omeprazole - these are medicines that **block stomach acids**
- St. John's wort - a herbal preparation obtained without a prescription, used to treat **depression** and other conditions (also known as *Hypericum perforatum*)

Do not take medicines that neutralise stomach acids (**antacids** such as aluminium hydroxide or magnesium hydroxide) in the **2 hours before or 2 hours after taking Dasatinib Accord**.

Tell your doctor if you are taking **medicines to thin the blood** or prevent clots.

Dasatinib Accord with food and drink

Do not take Dasatinib Accord with grapefruit or grapefruit juice.

Pregnancy and breast-feeding

If you are pregnant or think you may be pregnant, **tell your doctor immediately. Dasatinib Accord is not to be used during pregnancy** unless clearly necessary. Your doctor will discuss with you the potential risk of taking Dasatinib Accord during pregnancy.

Both men and women taking Dasatinib Accord will be advised to use effective contraception during treatment.

If you are breast-feeding, tell your doctor. You should stop breast-feeding while you are taking Dasatinib Accord.

Driving and using machines

Take special care when driving or using machines in case you experience side effects such as dizziness and blurred vision.

Dasatinib Accord contains lactose

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Dasatinib Accord contains isopropyl alcohol

This medicine contains isopropyl alcohol, as a residue of the manufacturing process.

3. How to take Dasatinib Accord

Dasatinib Accord will only be prescribed to you by a doctor with experience in treating leukaemia. Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. Dasatinib Accord is prescribed for adults and children at least 1 year of age.

The starting dose recommended for adult patients with Ph+ ALL is 140 mg once a day.

Dosing for children with Ph+ ALL is on the basis of body weight.

Dasatinib Accord is administered orally once daily in the form of either Dasatinib Accord tablets or dasatinib powder for oral suspension. Dasatinib Accord tablets are not recommended for patients weighing less than 10 kg. The powder for oral suspension should be used for patients weighing less than 10 kg and patients who cannot swallow tablets. A change in dose may occur when switching between formulations (i.e., tablets and powder for oral suspension), so you should not switch from one to the other.

Your doctor will decide the right formulation and dose based on your weight, any side effects and response to treatment. The starting dose of Dasatinib Accord for children is calculated by body weight as shown below:

Body Weight (kg)^a	Daily Dose (mg)
10 to less than 20 kg	40 mg
20 to less than 30 kg	60 mg
30 to less than 45 kg	70 mg
at least 45 kg	100 mg

^a The tablet is not recommended for patients weighing less than 10 kg; the powder for oral suspension should be used for these patients.

There is no dose recommendation for Dasatinib Accord with children under 1 year of age.

Depending on how you respond to the treatment, your doctor may suggest a higher or lower dose, or even stopping treatment briefly. For higher or lower doses, you may need to take combinations of the different tablet strengths.

How to take Dasatinib Accord

Take your tablets at the same time every day. Swallow the tablets whole. **Do not crush, cut or chew them.** Do not take dispersed tablets. You cannot be sure you will receive the correct dose if you crush, cut, chew or disperse the tablets. Dasatinib Accord tablets can be taken with or without a meal.

Special handling instructions for Dasatinib Accord

It is unlikely that the Dasatinib Accord tablets will get broken. But if they do, persons other than the patient should use gloves when handling Dasatinib Accord.

How long to take Dasatinib Accord

Take Dasatinib Accord daily until your doctor tells you to stop. Make sure you take Dasatinib Accord for as long as it is prescribed.

If you take more Dasatinib Accord than you should

If you have accidentally taken too many tablets, talk to your doctor **immediately**. You may require medical attention.

If you forget to take Dasatinib Accord

Do not take a double dose to make up for a forgotten tablet. Take the next scheduled dose at the regular time.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

- **The following can all be signs of serious side effects:**
- if you have chest pain, difficulty breathing, coughing and fainting
- if you experience **unexpected bleeding or bruising** without having an injury
- if you find blood in your vomit, stools or urine, or have black stools
- if you get **signs of infections** such as fever, severe chills
- if you get fever, sore mouth or throat, blistering or peeling of your skin and/or mucous membranes

Contact your doctor immediately if you notice any of the above.

Very common side effects (may affect more than 1 in 10 people)

- **Infections** (including bacterial, viral and fungal)
- **Heart and lungs:** shortness of breath
- **Digestive problems:** diarrhoea, feeling or being sick (nausea, vomiting)
- **Skin, hair, eye, general:** skin rash, fever, swelling around the face, hands and feet, headache, feeling tired or weak, bleeding
- **Pain:** pain in the muscles (during or after discontinuing treatment), tummy (abdominal) pain
- **Tests may show:** low blood platelet count, low white blood cells count (neutropaenia), anaemia, fluid around the lungs

Common side effects (may affect up to 1 in 10 people)

- **Infections:** pneumonia, herpes virus infection (including cytomegalovirus - CMV), upper respiratory tract infection, serious infection of the blood or tissues (including uncommon cases with fatal outcomes)
- **Heart and lungs:** palpitations, irregular heartbeat, congestive heart failure, weak heart muscle, high blood pressure, increased blood pressure in the lungs, cough
- **Digestive problems:** appetite disturbances, taste disturbance, bloated or distended tummy (abdomen), inflammation of the colon, constipation, heartburn, mouth ulceration, weight increase, weight decrease, gastritis
- **Skin, hair, eye, general:** skin tingling, itching, dry skin, acne, inflammation of the skin, persistent noise in ears, hair loss, excessive perspiration, visual disorder (including blurred vision and disturbed vision), dry eye, bruise, depression, insomnia, flushing, dizziness, contusion (bruising), anorexia, somnolence, generalised oedema
- **Pain:** pain in joints, muscular weakness, chest pain, pain around hands and feet, chills, stiffness in muscles and joints, muscle spasm
- **Tests may show:** fluid around the heart, fluid in the lungs, arrhythmia, febrile neutropaenia, gastrointestinal bleeding, high uric acid levels in the blood

Uncommon side effects (may affect up to 1 in 100 people)

- **Heart and lungs:** heart attack (including fatal outcome), inflammation of the lining (fibrous sack) surrounding the heart, irregular heartbeat, chest pain due to lack of blood supply to the heart (angina), low blood pressure, narrowing of airway that may cause breathing difficulties, asthma, increased blood pressure in the arteries (blood vessels) of the lungs
- **Digestive problems:** inflammation of the pancreas, peptic ulcer, inflammation of the food pipe, swollen tummy (abdomen), tear in the skin of the anal canal, difficulty in swallowing, inflammation of the gallbladder, blockage of bile ducts, gastro-oesophageal reflux (a condition where acid and other stomach contents come back up into the throat)

- **Skin, hair, eye, general:** allergic reaction including tender, red lumps on the skin (erythema nodosum), anxiety, confusion, mood swings, lower sexual drive, fainting, tremor, inflammation of the eye which causes redness or pain, a skin disease characterized by tender, red, well-defined blotches with the sudden onset of fever and raised white blood cell count (neutrophilic dermatosis), loss of hearing, sensitivity to light, visual impairment, increased eye tearing, disturbance in skin colour, inflammation of fatty tissue under the skin, skin ulcer, blistering of the skin, nail disorder, hair disorder, hand-foot disorder, renal failure, urinary frequency, breast enlargement in men, menstrual disorder, general weakness and discomfort, low thyroid function, losing balance while walking, osteonecrosis (a disease of reduced blood flow to the bones, which can cause bone loss and bone death), arthritis, skin swelling anywhere in the body
- **Pain:** inflammation of vein which can cause redness, tenderness and swelling, inflammation of the tendon
- **Brain:** loss of memory
- **Tests may show:** abnormal blood test results and possibly impaired kidney function caused by the waste products of the dying tumour (tumour lysis syndrome), low levels of albumin in the blood, low levels of lymphocytes (a type of white blood cell) in the blood, high level of cholesterol in the blood, swollen lymph nodes, bleeding in the brain, irregularity of the electrical activity of the heart, enlarged heart, inflammation of the liver, protein in the urine, raised creatine phosphokinase (an enzyme mainly found in the heart, brain and skeletal muscles), raised troponin (an enzyme mainly found in the heart and skeletal muscles), raised gamma-glutamyltransferase (an enzyme mainly found in the liver), milky-appearing fluid around the lungs (chylothorax)

Rare side effects (may affect up to 1 in 1,000 people)

- **Heart and lungs:** enlargement of the right ventricle in the heart, inflammation of the heart muscle, collection of conditions resulting from blockage of blood supply to the heart muscle (acute coronary syndrome), cardiac arrest (stopping of blood flow from the heart), coronary (heart) artery disease, inflammation of the tissue covering the heart and lungs, blood clots, blood clots in the lungs
- **Digestive problems:** loss of vital nutrients such as protein from your digestive tract, bowel obstruction, anal fistula (an abnormal opening from the anus to the skin around the anus), impairment of kidney function, diabetes
- **Skin, hair, eye, general:** convulsion, inflammation of the optic nerve that may cause a complete or partial loss of vision, blue-purple mottling of the skin, abnormally high thyroid function, inflammation of the thyroid gland, ataxia (a condition associated with lack of muscular coordination), difficulty walking, miscarriage, inflammation of the skin blood vessels, skin fibrosis
- **Brain:** stroke, temporary episode of neurologic dysfunction caused by loss of blood flow, facial nerve paralysis, dementia
- **Immune system:** severe allergic reaction
- **Musculoskeletal and connective tissue:** delayed fusion of the rounded ends that form joints (epiphyses); slower or delayed growth

Other side effects that have been reported with frequency not known (cannot be estimated from the available data)

- Inflammation of the lungs
- Bleeding in the stomach or bowels that can cause death
- Recurrence (reactivation) of hepatitis B infection when you have had hepatitis B in the past (a liver infection)
- A reaction with fever, blisters on the skin, and ulceration of the mucous membranes
- Disease of the kidneys with symptoms including oedema and abnormal laboratory test results such as protein in the urine and low protein level in the blood
- Damage to blood vessels known as thrombotic microangiopathy (TMA), including decreased red blood cell count, decreased platelets, and formation of blood clots

Your doctor will check for some of these effects during your treatment.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Dasatinib Accord

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister or carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Dasatinib Accord contains

- The active substance is dasatinib. Each film-coated tablet contains 20 mg, 50 mg, 70 mg, 80 mg, 100 mg or 140 mg dasatinib.
- The other ingredients are:
 - *Tablet core*: lactose monohydrate (see section 2 "Dasatinib Accord contains lactose"); hydroxypropyl cellulose; cellulose, microcrystalline; methacrylic acid – methacrylate copolymer (1:2); talc; croscarmellose sodium; magnesium stearate
 - *Film-coating*: hypromellose (E464); titanium dioxide (E171); medium chain triglycerides

What Dasatinib Accord looks like and contents of the pack

Dasatinib Accord 20 mg: the film-coated tablet is white to off-white, round, 5.6 mm of diameter, coated tablets debossed on one side with "DAS" and "20" on the other side.

Dasatinib Accord 50 mg: the film-coated tablet is white to off-white, oval, 5.7 x 10.6 mm, coated tablets debossed on one side with "DAS" and "50" on the other side.

Dasatinib Accord 70 mg: the film-coated tablet is white to off-white, round, 8.7 mm of diameter, coated tablets debossed on one side with "DAS" and "70" on the other side.

Dasatinib Accord 80 mg: the film-coated tablet is white to off-white, triangle-shaped, 9.9 x 10.2 mm, coated tablets debossed on one side with "DAS" and "80" on the other side.

Dasatinib Accord 100 mg: the film-coated tablet is white to off-white, oval, 7.1 x 14.5 mm, coated tablets debossed on one side with "DAS" and "100" on the other side.

Dasatinib Accord 140 mg: the film-coated tablet is white to off-white, round, 11 mm of diameter, coated tablets debossed on one side with "DAS" and "140" on the other side.

Dasatinib Accord 20 mg, 50 mg or 70 mg film-coated tablets are available in cartons containing 56 or 60 film-coated tablets, and in cartons containing 56 x 1 or 60 x 1 film-coated tablets in perforated unit dose blisters.

Dasatinib Accord 80 mg, 100 mg or 140 mg film-coated tablets are available in cartons containing 30 or 56 film-coated tablets, and in cartons containing 30 x 1 or 56 x 1 film-coated tablets in perforated unit dose blisters.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>.

Medicinal product no longer authorised