For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory Only

DASHORI

1. **Generic Name**

Dasatinib Tablets

2. Qualitative and quantitative composition

DASHORI 20

Each film-coated tablet contains:

Dasatinib …….20 mg

Excipients……...q.s.

Colour: Titanium Dioxide I.P.

The excipients used are Lactose Monohydrate, Microcrystalline Cellulose, Croscarmellose Sodium, Hydroxyproyl Cellulose, Magnesium Stearate, Hypromellose, Triacetin, Titanium Dioxide and Talc.

DASHORI 50

Each film-coated tablet contains:

Dasatinib …….50 mg

Excipients……...…..q.s.

Colour: Titanium Dioxide I.P.

The excipients used are Lactose Monohydrate, Microcrystalline Cellulose, Croscarmellose Sodium, Hydroxyproyl Cellulose, Magnesium Stearate, Hypromellose, Triacetin, Titanium Dioxide and Talc.

DASHORI 70

Each film-coated tablet contains:

Dasatinib …….70 mg

Excipients……...…..q.s.

Colour: Titanium Dioxide I.P.

The excipients used are Lactose Monohydrate, Microcrystalline Cellulose, Croscarmellose Sodium, Hydroxyproyl Cellulose, Magnesium Stearate, Hypromellose, Triacetin, Titanium Dioxide and Talc.

DASHORI 100

Each film-coated tablet contains:

Dasatinib …….100 mg

Excipients……...…..q.s.

Colour: Titanium Dioxide I.P.

The excipients used are Lactose Monohydrate, Microcrystalline Cellulose, Croscarmellose Sodium, Hydroxyproyl Cellulose, Magnesium Stearate, Hypromellose, Triacetin, Titanium Dioxide and Talc.

3. Dosage form and strength

Dosage Form: Film coated tablet

Strengths: 20mg, 50mg, 70mg and 100mg

4. Clinical particulars

4.1 Therapeutic indication

20mg, 50mg, 70mg & 100mg

For the treatment of adults with chronic accelerated or myeloid or lymphoid blast phase chronic myeloid leukaemia (CML).

20mg, 50mg & 70mg

Treatment of newly Diagnosed Adults with Chronic Myeloid Leukaemia (CML) in Chronic Phase.

4.2 Posology and Method of administration

The recommended starting dosage of Dasatinib for chronic phase CML in adults is 100 mg administered orally once daily. The recommended starting dosage of dasatinib for accelerated phase CML, myeloid or lymphoid blast phase CML, in adults is 140 mg administered orally once daily.

Tablets should not be crushed, cut, or chewed; they should be swallowed as whole.

Dasatinib can be taken with or without a meal, either in the morning or in the evening.

Dose Modification

Strong CYP3A4 Inducers

Avoid the use of concomitant strong CYP3A4 inducers and St. John's wort. If patients must be coadministered a strong CYP3A4 inducer, consider a *Dasatinib* dose increase. If the dose of dasatinib is increased, monitor the patient carefully for toxicity.

Strong CYP3A4 Inhibitors

Avoid the use of concomitant strong CYP3A4 inhibitors and grapefruit juice. Recommend selecting an alternate concomitant medication with no or minimal enzyme inhibition potential, if possible. If dasatinib must be administered with a strong CYP3A4 inhibitor, consider a dose decrease to:

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

For patients taking Dasatinib 60 mg or 40 mg daily, consider interrupting Dasatinib until the inhibitor is discontinued. Allow a washout period of approximately 1 week after the inhibitor is stopped before reinitiating Dasatinib.

These reduced doses of Dasatinib 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 is not tolerated after dose reduction, either discontinue the strong CYP3A4 inhibitor or interrupt Dasatinib until the inhibitor is discontinued. Allow a washout period of approximately 1 week after the inhibitor is stopped before the Dasatinib dose is increased.

Dose Adjustment for Adverse Reactions

Myelosuppression

In clinical studies, myelosuppression was managed by dose interruption, dose reduction, or discontinuation of study therapy. Hematopoietic growth factor has been used in patients with resistant myelosuppression. Guidelines for dose modifications for adult patients are summarized in below table:

Dose Adjustments for Neutropenia and Thrombocytopenia in Adults

Chronic Phase CML (starting dose 100 mg once daily)	ANC* $<0.5 \times 10^9$/L or Platelets $<50 \times 10^9$/L	1. Stop Dasatinib until ANC $\geq 1.0 \times 10^9$/L and platelets $\geq 50 \times 10^9$/L. 2. Resume treatment with *Dasatinib* at the original starting dose if recovery occurs in ≤7 days. 3. If platelets $<25 \times 10^9$/L or recurrence of ANC $<0.5 \times 10^9$/L for >7 days, repeat Step 1 and resume Dasatinib at a reduced dose of 80 mg once daily for second episode. For third episode, further reduce dose to 50 mg once daily (for newly diagnosed patients) or discontinue dasatinib (for patients resistant or intolerant to prior therapy including imatinib).

Non-Hematologic Adverse Reactions

For adults with Ph+ CML, if a severe non hematologic adverse reaction develops with dasatinib use, treatment must be withheld until the event has resolved or improved. Thereafter, treatment can be resumed as appropriate at a reduced dose depending on the severity and recurrence of the event.

Duration of Treatment

In reported clinical studies, treatment with dasatinib in adults and in pediatric patients with chronic phase CML 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 response (including complete cytogenetic response [CCyR]) or major molecular response (MMR and MR4.5) has not been established.

Dasatinib is an antineoplastic product. Follow applicable special handling and disposal procedures.

4.3 Contraindications

Hypersensitivity to the active substance.

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.

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.

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.

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).

The concomitant use of dasatinib and a histamine-2 (H_2) antagonist (e.g. famotidine), proton pump inhibitor (e.g. omeprazole), or aluminium hydroxide/magnesium hydroxide may reduce the exposure to dasatinib. Thus, H_2 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.

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. 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, neutropenia and thrombocytopenia. Their occurrence is earlier and more frequent in patients with advanced phase chronic myelogenous leukaemia (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. Myelosuppression is generally reversible and usually managed by withholding dasatinib temporarily or by dose reduction. 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.

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 thrombocytopenia. 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 thrombocytopenia. 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 thoracocentesis and oxygen therapy. Fluid retention adverse reactions were typically managed by supportive care measures that include diuretics and short courses of steroids. 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.

Pulmonary arterial hypertension (PAH)

PAH (pre-capillary pulmonary arterial hypertension confirmed by right heart catheterization) has been reported in association with dasatinib treatment. 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 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

Reported in vitro data suggest that dasatinib has the potential to prolong cardiac ventricular repolarisation (QT Interval). 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.

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

In a reported data, 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 (≤ grade 2) and resumed at a dose level reduction for severe adverse reactions (≥ grade 3). 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. 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. 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.

Effects on growth and development in paediatric patients

In reported paediatric trials of dasatinib in imatinib-resistant/intolerant Ph+ CML in chronic phase (Ph+ CML-CP) paediatric patients and treatment-naive 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, osteopenia, growth retardation, and gynecomastia. These results are difficult to interpret in the context of chronic diseases such as CML, and require long-term follow-up.

In reported 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.

Excipients

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 medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Active substances that may increase dasatinib plasma concentrations

Reported in vitro studies indicate that dasatinib is a CYP3A4 substrate. Concomitant use of dasatinib and medicinal products or substances which potently 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.

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 H_2 antagonists or proton pump inhibitors (e.g. famotidine and omeprazole) is likely to reduce dasatinib exposure. In a reported 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 H_2 antagonists or proton pump inhibitors in patients receiving dasatinib therapy.

Antacids

Reported 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.

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.

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 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

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. The reported studies in animals have shown reproductive toxicity.

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 suckling child cannot be excluded.

Breast-feeding should be stopped during treatment with Dasatinib.

Fertility

In reported animal studies, the fertility of male and female rats was not affected by treatment with dasatinib. Physicians and other healthcare providers should counsel male patients of appropriate age about possible effects of Dasatinib fertility, and this counselling 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 reported 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 reported 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. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to

< 1/100); rare (≥ 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.

Infections and infestations

Very common: infection (including bacterial, viral, fungal, and non-specified)

Common: 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)

Not known: hepatitis B reactivation

Blood and lymphatic system disorders

Very common: myelosuppression (including anaemia, neutropenia, and thrombocytopenia)

Common: febrile neutropenia

Uncommon: lymphadenopathy, lymphopenia

Rare: aplasia pure red cell

Immune system disorders

Uncommon: hypersensitivity (including erythema nodosum)

Rare: anaphylactic shock

Endocrine disorders

Uncommon: Hypothyroidism

Rare: hyperthyroidism, thyroiditis

Metabolism and nutrition disorders

Common: appetite disturbances[a], hyperuricaemia

Uncommon: tumour lysis syndrome, dehydration, hypoalbuminemia, hypercholesterolemia

Rare: diabetes mellitus

Psychiatric disorders

Common: depression, insomnia

Uncommon: anxiety, confusional state, affect lability, libido decreased

Nervous system disorders

Very Common: Headache

Common: neuropathy (including peripheral neuropathy), dizziness, dysgeusia, somnolence

Uncommon: CNS bleeding[b], syncope, tremor, amnesia, balance disorder

Rare: cerebrovascular accident, transient ischaemic attack, convulsion, optic neuritis, VIIth nerve paralysis, dementia, ataxia

Eye disorders

Common: visual disorder (including visual disturbance, vision blurred, and visual acuity reduced), dry eye

Uncommon: visual impairment, conjunctivitis, photophobia, lacrimation increased

Ear and labyrinth disorders

Common: Tinnitus

Uncommon: hearing loss, vertigo

Cardiac disorders

Common: congestive heart failure/cardiac dysfunction[c], pericardial effusion, arrhythmia (Including tachycardia), palpitations

Uncommon: myocardial infarction (including fatal outcome), electrocardiogram QT prolonged, pericarditis, ventricular arrhythmia (including ventricular tachycardia), angina pectoris, cardiomegaly, electrocardiogram T wave abnormal, troponin increased

Rare: cor pulmonale, myocarditis, acute coronary syndrome, cardiac arrest, electrocardiogram PR prolongation, coronary artery disease, pleuropericarditis

Not known: atrial fibrillation/atrial flutter

Vascular disorders

Very Common: haemorrhage[d]

Common: hypertension, flushing

Uncommon: hypotension, thrombophlebitis, thrombosis

Rare: deep vein thrombosis, embolism, livedo reticularis

Not known: thrombotic microangiopathy

Respiratory, thoracic and mediastinal disorders

Very Common: pleural effusion, dyspnoea

Common: pulmonary oedema, pulmonary hypertension, lung infiltration, pneumonitis, cough

Uncommon: pulmonary arterial hypertension, bronchospasm, asthma

Rare: pulmonary embolism, acute respiratory distress syndrome

Not known: interstitial lung disease

Gastrointestinal disorders

Very Common: diarrhoea, vomiting, nausea, abdominal pain

Common: gastrointestinal bleeding, colitis (including neutropenic colitis), gastritis, mucosal inflammation (including mucositis/stomatitis), dyspepsia, abdominal distension, constipation, oral soft tissue disorder

Uncommon: pancreatitis (including acute pancreatitis), upper gastrointestinal ulcer, oesophagitis, ascites, anal fissure, dysphagia, gastroesophageal reflux disease

Rare: protein-losing gastroenteropathy, ileus, anal fistula

Not known: fatal gastrointestinal haemorrhage

Hepatobiliary disorders

Uncommon: hepatitis, cholecystitis, cholestasis

Skin and subcutaneous tissue disorders

Very common: skin rash[e]

Common: alopecia, dermatitis (including eczema), pruritus, acne, dry skin, urticaria, hyperhidrosis

Uncommon: neutrophilic dermatosis, photosensitivity, pigmentation disorder, panniculitis, skin ulcer, bullous conditions, nail disorder, palmar-plantar erythrodysesthesia syndrome, hair disorder

Rare: leukocytoclastic vasculitis, skin fibrosis

Not known: Stevens-Johnson syndrome[f]

Musculoskeletal connective tissue and bone disorders

Very Common: musculoskeletal pain[g]

Common: arthralgia, myalgia, muscular weakness, musculoskeletal stiffness, muscle spasm

Uncommon: rhabdomyolysis, osteonecrosis, muscle inflammation, tendonitis, arthritis

Rare: epiphyses delayed fusion,[h] growth retardation[h]

Renal and urinary disorders

Uncommon: renal impairment (including renal failure), urinary frequency, proteinuria

Unknown: nephrotic syndrome

Pregnancy, puerperium and perinatal conditions

Uncommon: gynecomastia, menstrual disorder

Reproductive system and breast disorders

Unknown: Gynaecomastia

General disorders and administration site conditions

Very common: peripheral oedema[i], fatigue, pyrexia, face oedema[j]

Common: asthenia, pain, chest pain, generalised oedema[k], chills

Uncommon: malaise, other superficial oedema[l]

Rare: gait disturbance

Investigations

Common: weight decreased, weight increased

Uncommon: blood creatine phosphokinase increased, gamma-glutamyl transferase increased

Injury, poisoning, and procedural complications

Common: Confusion

[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 psoriaisis, 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.

Reporting of suspected adverse reactions

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting

4.9 Overdose

In a reported clinical study studies, experience with overdose of dasatinib 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, patients who ingest more than the recommended dose should be closely monitored for myelosuppression and given appropriate supportive treatment.

5. Pharmacological Properties

5.1 Mechanism of action

In a reported study, in vitro, dasatinib is active in leukaemic cell lines representing variants of imatinib-sensitive and resistant disease. These reported 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.

5.2 Pharmacodynamic properties

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 PDGFβ 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.

5.3 Pharmacokinetic properties

Absorption

In a reported study, 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 (AUCτ) 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.

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.

Metabolism:

Dasatinib is extensively metabolised in humans with multiple enzymes involved in the generation of the metabolites. In healthy subjects administered 100 mg of [^{14}C]-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.

Excretion:

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 [^{14}C]-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.

<u>Hepatic and renal impairment</u>

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.

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 powder for oral suspension).

In a paediatric pharmacokinetics study, dose-normalized dasatinib exposure (C_{avg}, C_{mm} 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/m^2 once daily and 50 to 110 mg/m^2 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 is expected to provide similar exposure to a tablet dose of 60 mg/m^2. These data should be considered if patients are to switch from tablets to powder for oral suspension or vice versa.

6. Nonclinical Properties

6.1 Animal Toxicology or Pharmacology

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.

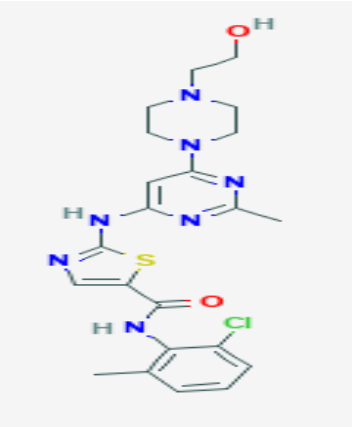
Dasatinib did not affect male or female fertility in a conventional rat fertility and early embryonic development study, but induced embryo lethality at dose levels approximating human clinical exposures. In embryofoetal development studies, dasatinib likewise induced embryolethality with associated 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 photo toxicity 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.

7. Description

Dasatinib is N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-yl]amino]-1,3-thiazole-5-carboxamide having molecular formula as $C_{22}H_{26}ClN_7O_2S$ and molecular weight as 488 g/mol with the chemical structure as below:



DASHORI 20mg, 50mg, 70mg & 100mg

Dasatinib Tablets are white colored, circular shaped, film coated tablets plain on both sides. The excipients used are Lactose Monohydrate, Microcrystalline Cellulose, Croscarmellose Sodium, Hydroxyproyl Cellulose, Magnesium Stearate, Hypromellose, Triacetin, Titanium Dioxide and Talc.

8. Pharmaceutical Particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than date of expiry

8.3 Packing Information

DASHORI 20, 50 & 70 is available in bottle of 60 tablets.

DASHORI 100 is available in bottle of 30 tablets.

8.4 Storage and handling instructions

- Store at a temperature not exceeding 30^0C. Protect from moisture.
- Keep out of reach of children.
- Keep the container tightly closed.
- Do not use if seal over bottle opening is broken or missing.
- Dispense in original container.

9. Patient Counselling Information

Advise the patient to read the approved patient labelling (Patient Information).

Bleeding

Inform patients of the possibility of serious bleeding and to report immediately any signs or symptoms suggestive of hemorrhage (unusual bleeding or easy bruising).

Myelosuppression

Inform patients of the possibility of developing low blood cell counts. Advise patients to immediately report fever particularly in association with any suggestion of infection.

Fluid Retention

Patients should be informed of the possibility of developing fluid retention (swelling, weight gain, dry cough, chest pain on respiration, or shortness of breath) and advised to seek medical attention promptly if those symptoms arise.

Pulmonary Arterial Hypertension

Inform patients of the possibility of developing pulmonary arterial hypertension (dyspnea, fatigue, hypoxia, and fluid retention) and advise them to seek medical attention promptly if those symptoms arise.

Tumor Lysis Syndrome

Inform patients to immediately report and seek medical attention for any symptoms such as nausea, vomiting, weakness, edema, and shortness of breath, muscle cramps, and seizures, which may indicate tumor lysis syndrome.

Growth and Development in Pediatric Patients

Inform pediatric patients and their caregivers of the possibility of developing bone growth abnormalities, bone pain, or gynecomastia and advise them to seek medical attention promptly if those symptoms arise.

Embryo-Fetal Toxicity

- Advise pregnant women of the potential risk to a fetus.
- Advise females of reproductive potential to avoid pregnancy, which may include use of effective contraception during treatment with Dasatinib and for 30 days after the final

dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking Dasatinib.

Lactation

Advise women that breastfeeding is not recommended during treatment with Dasatinib and for 2 weeks after the final dose.

Gastrointestinal Complaints

Inform patients that they may experience nausea, vomiting, or diarrhea with Dasatinib. Advise patients to seek medical attention if these symptoms are bothersome or persistent.

Advise patients using antacids to avoid taking Dasatinib and antacids less than 2 hours apart.

Pain

Inform patients that they may experience headache or musculoskeletal pain with Dasatinib. Advise patients to seek medical attention if these symptoms are bothersome or persistent.

Fatigue

Inform patients that they may experience fatigue with Dasatinib. Advise patients to seek medical attention if this symptom is bothersome or persistent.

Rash

Inform patients that they may experience skin rash with Dasatinib. Advise patients to seek medical attention if this symptom is bothersome or persistent.

Lactose

Inform patients that Dasatinib contains 135 mg of lactose monohydrate in a 100-mg daily dose and 189 mg of lactose monohydrate in a 140-mg daily dose.

Missed Dose

Advise patients that if they miss a dose of Dasatinib, they should take the next scheduled dose at its regular time. The patient should not take two doses at the same time.

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.

What is in this leaflet?

9.6.Contents of the pack and other information

9.1. What DASHORI Tablet is and what it is used for

DASHORI 20mg, 50mg, 70mg & 100mg contains Dasatinib as active ingredient, used to treat adults who have chronic accelerated or myeloid or lymphoid blast phase chronic myeloid leukemai (CML).

DASHORI 20mg, 50mg & 70mg is used for treatment of newly Diagnosed Adults with Chronic Myeloid Leukaemia (CML) in Chronic Phase.

9.2. What you need to know before you take DASHORI Tablet

Before you take DASHORI, tell your healthcare provider if you:

- have problems with your immune system
- have liver problems
- have heart problems
- are lactose intolerant
- Have any other medical conditions.
- Are pregnant or planning to become pregnant. DASHORI may harm your unborn baby. Women should not become pregnant while taking DASHORI. Talk to your healthcare provider right away, if you are pregnant or plan to become pregnant.
- Are breastfeeding or plan to breastfeed? It is not known if DASHORI passes into your breast milk or if it can harm your baby. You and your healthcare provider should decide if you will take DASHORI or breastfeed. You should not do both.

  Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, antacids, and herbal supplements.

  Especially tell your healthcare provider if you take:

  Medicines that increase the amount of DASHORI **in your bloodstream such as:**

  Ketoconazole, Nefazodone, itraconazole, Saquinavir, ritonavir, telithromycin, atazanavir sulfate, erythromycin, indinavir, clarithromycin. Nelfinavir.

  Medicines that decrease the amount of DASHORI in **your bloodstream such as:** dexamethasone, rifampin, phenytoin, phenobarbital. Carbamazepine,

  Medicines whose blood levels might change by taking DASHORI **such as:**

  Cyclosporine, sirolimus, alfentanil, tacrolimus, fentanyl, ergotamine. Pimozide.

  DASHORI is best absorbed from your stomach into your bloodstream in the presence of stomach acid. You should avoid taking medicines that reduce stomach acid such as:

  Cimetidine, pantoprazole sodium, famotidine, esomeprazole, ranitidine, rabeprazole, omeprazole, lansoprazole.

  Medicines that neutralize stomach acid, such as aluminum hydroxide/magnesium hydroxide, calcium carbonate, or calcium carbonate and magnesia may be taken up to 2 hours before or 2 hours after DASHORI.

  Since DASHORI therapy may cause bleeding, tell your healthcare provider if you are using blood thinner medicine, such as warfarin sodium or aspirin.

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

Warnings

Patients should be informed of the possibility of serious bleeding and to report immediately any signs or symptoms suggestive of following conditions.

- Unusual bleeding or easy bruising
- Low blood cell counts
- Fever
- Swelling, weight gain, or shortness of breath
- Dasatinib may cause fetal harm when administered to a pregnant woman. Women should be advised of the potential hazard to the fetus and to avoid becoming pregnant.
- Nausea, vomiting, or diarrhea
- Headache or musculoskeletal pain, fatigue
- Skin rash

9.3. How to take DASHORI Tablet

Take DASHORI exactly **as prescribed by your healthcare provider.**

- Take DASHORI with or without food. Try to take DASHORI at the same time each day.
- Swallow DASHORI tablets whole. Do not break, cut, or crush the tablets.
- You should not drink grapefruit juice while taking DASHORI.

Your healthcare provider may:

- **change your dose of** DASHORI **or**
- **Tell you to temporarily stop taking DASHORI.**

- Do not change your dose or stop taking DASHORI without first talking with your healthcare provider.
- If you miss a dose of DASHORI, take your next scheduled dose at its regular time. Do not take two doses at the same time. Call your healthcare provider or pharmacist if you are not sure what to do.
- If you take too much DASHORI, call your healthcare provider or go to the nearest hospital emergency room right away.

9.4. Possible side effects

DASHORI may cause serious side effects, including:

Low Blood Cell Counts: DASHORI may cause low red blood cell counts (anemia), low white blood cell counts (neutropenia), and low platelet counts (thrombocytopenia). Your healthcare provider will do blood tests to check your blood cell counts regularly during your treatment with DASHORI. Call your healthcare provider right away if you have a fever or any signs of an infection while taking DASHORI.

Bleeding: DASHORI may cause severe bleeding that can lead to death. Call your healthcare provider right away if you have:

- unusual bleeding or bruising of your skin
- bright red or dark tar-like stools
- a decrease in your level of consciousness, headache, or change in speech.

Your body may hold too much fluid (fluid retention): In severe cases, fluid may build up in the lining of your lungs, the sac around your heart, or your stomach cavity. Call your healthcare provider right away if you get any of these symptoms during treatment with DASHORI:

- swelling all over your body
- weight gain
- Shortness of breath and cough.

Heart problems. DASHORI may cause an abnormal heart rate, heart problems or a heart attack. Your healthcare provider will monitor the potassium and magnesium levels in your blood, and your heart function.

Other common side effects of DASHORI therapy include:

- diarrhea
- tiredness
- headache
- vomiting
- cough
- muscle pain
- skin rash
- weakness
- Fever
- infections
- nausea

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of DASHORI. For more information, ask your healthcare provider or pharmacist.

Reporting of suspected adverse reactions

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting

9.5. How to store DASHORI Tablet

- Store at a temperature not exceeding 30°C. Protect from moisture.
- Keep out of reach of children.

- Keep the container tightly closed.
- Do not use if seal over bottle opening is broken or missing.
- Dispense in original container.

9.6. Contents of the pack and other information

DASHORI 20, 50 & 70 is available in bottle of 60 tablets.

DASHORI 100 is available in bottle of 30 tablets.

10. Details of manufacturer

Manufactured in India by:

Hetero Labs Limited (Unit-I)

Village: Kalyanpur, Chakkan Road, Tehsil: Baddi,

Distt.: Solan, Himachal Pradesh – 173205, INDIA**.**

11. Details of permission or licence number with date

Mfg Lic No. MNB/06/328 issued on 21.01.2021

12. Date of revision

FEB, 2021

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/DASHORI 20,50,70,100 mg/FEB-21/02/PI