SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE PRODUCT

Onato® (Amlodipine Besylate) 5mg Tablets

Onato® (Amlodipine Besylate) 10mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Onato® 5mg Tablets	**Onato® 10mg Tablets**
Each tablet contains:	Each tablet contains:
Amlodipine Besylate Ph. Eur.	Amlodipine Besylate Ph. Eur.
equivalent to Amlodipine.....5mg	equivalent to Amlodipine.....10mg

3. PHARMACEUTICAL FORM

Tablet

Appearance:

Onato® 5mg Tablets: White color, oval shaped tablets, having break line on one side while other side is plain.

Onato® 10mg Tablets: Pink to reddish pink color, capsular shaped tablets, engraved "SAMI" on one side and a break line on the other side.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

- Hypertension
- Chronic stable angina pectoris
- Vasospastic (Prinzmetal's) angina

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:

Posology:

Adults: For both hypertension and angina, the usual initial dose is 5mg of **Onato®** once daily which may be increased to a maximum dose of 10mg depending on the individual patient's response. In hypertensive patients, **Onato®** has been used in combination with a thiazide diuretic, alpha-blocker, beta-blocker, or an angiotensin-converting enzyme inhibitor. For angina, **Onato®** may be used as monotherapy or in combination with other antianginal medicinal products in patients with angina that is refractory to nitrates and/or to adequate doses of beta blockers. No dose adjustment of **Onato®** is required upon concomitant administration of thiazide diuretics, beta-blockers, and angiotensin-converting enzyme inhibitors.

Special populations:

Elderly: **Onato®** used at similar doses in elderly or younger patients is equally well tolerated. Normal dosage regimens are recommended in the elderly, but an increase of the dosage should take place with care.

Hepatic impairment: Dosage recommendations have not been established in patients with mild to moderate hepatic impairment; therefore, dose selection should be cautious and should start at the lower end of the dosing range. The pharmacokinetics of amlodipine have not been studied in severe hepatic impairment. Amlodipine should be initiated at the lowest dose and titrated slowly in patients with severe hepatic impairment.

Renal impairment: Changes in amlodipine plasma concentrations are not correlated with the degree of renal impairment, therefore the normal dosage is recommended. Amlodipine is not dialysable.

Paediatric population: Children and adolescents with hypertension from 6 years to 17 years of age. The recommended antihypertensive oral dose in paediatric patients ages 6-17 years is 2.5mg once daily as a starting dose, up-titrated to 5mg once daily if the blood pressure goal is not achieved after 4 weeks. Doses in excess of 5mg daily have not been studied in paediatric patients. Doses of amlodipine 2.5mg are not possible with this medicinal product.

Children under 6 years old: No data are available.

Method of administration:

For oral administration.

4.3. CONTRAINDICATIONS:

Amlodipine is contraindicated in patients with:

- Hypersensitivity to dihydropyridine derivatives, amlodipine, or to any of the excipients.
- Severe hypotension.
- Shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g., high-grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

The safety and efficacy of amlodipine in hypertensive crisis has not been established.

Patients with cardiac failure: Patients with heart failure should be treated with caution. In a long-term, placebo-controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group. Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Use in patients with impaired hepatic function: The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.

Use in elderly patients: In the elderly increase of the dosage should take place with care.

Use in renal failure: Amlodipine may be used in such patients at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTIONS:

Effects of other medicinal products on amlodipine:

CYP3A4 inhibitors: Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

CYP3A4 inducers: There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g., rifampicin, hypericum perforatum) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers. Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Dantrolene (infusion): Due to the risk of hyperkalemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Effects of amlodipine on other medicinal products:

The blood pressure-lowering effects of amlodipine add to the blood pressure-lowering effects of other medicinal products with antihypertensive properties. In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin, or ciclosporin.

4.6. FERTILITY, PREGNANCY AND LACTATION:

Fertility: Clinical data are insufficient regarding the potential effect of amlodipine on fertility.

Pregnancy: The safety of amlodipine in human pregnancy has not been established. Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

Breast-feeding: It is not known whether amlodipine is excreted in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with amlodipine should be made taking into account the benefit of breast-feeding to the child and the benefit of amlodipine therapy to the mother.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue, or nausea the ability to react may be impaired. Caution is recommended especially at the start of treatment.

4.8. UNDESIRABLE EFFECTS:

The following adverse reactions have been observed and reported during treatment with amlodipine with the following frequencies: 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); very rare (≤1/10,000).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Blood and lymphatic system disorders: ***Very rare:*** Leukocytopenia, thrombocytopenia.

Immune system disorders: ***Very rare:*** Allergic reactions

Metabolism and nutrition disorders: ***Very rare:*** Hyperglycemia

Psychiatric disorders: ***Uncommon:*** Insomnia, mood changes (including anxiety), depression. ***Rare:*** Confusion.

Nervous system disorders: ***Common:*** Somnolence, dizziness, headache (especially at the beginning of the treatment). ***Uncommon:*** Tremor, dysgeusia, syncope, hypoesthesia, paraesthesia. ***Very rare:*** Hypertonia, peripheral neuropathy.

SUMMARY OF PRODUCT CHARACTERISTICS

Eye disorders: ***Uncommon:*** Visual disturbance (including diplopia).
Ear and labyrinth disorders: ***Uncommon:*** Tinnitus.
Cardiac disorders: ***Common:*** Palpitations. ***Very rare:*** Myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia, and atrial fibrillation).
Vascular disorders: ***Common:*** Flushing. ***Uncommon:*** Hypotension. ***Very rare:*** Vasculitis
Respiratory, thoracic, and mediastinal disorders: ***Uncommon:*** Dyspnoea, rhinitis. ***Very rare:*** Cough.
Gastrointestinal disorders: ***Common:*** Abdominal pain, nausea. ***Uncommon:*** Vomiting, dyspepsia, altered bowel habits (including diarrhea and constipation), dry mouth. ***Very rare:*** Pancreatitis, gastritis, gingival hyperplasia.
Hepatobiliary disorders: ***Very rare:*** Hepatitis, jaundice, hepatic enzymes increased*.
Skin and subcutaneous tissue disorders: ***Uncommon:*** Alopecia, purpura, skin discoloration, hyperhidrosis, pruritus, rash, exanthema. ***Very rare:*** Angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity.
Musculoskeletal and connective tissue disorders: ***Common:*** Ankle swelling. ***Uncommon:*** Arthralgia, myalgia, muscle cramps, back pain.
Renal and urinary disorders: ***Uncommon:*** Micturition disorder, nocturia, increased urinary frequency.
Reproductive system and breast disorders: ***Uncommon:*** Impotence, gynecomastia.
General disorders and administration site conditions: ***Common:*** Oedema, fatigue. ***Uncommon:*** Chest pain, asthenia, pain, malaise.
Investigations: ***Uncommon:*** Weight increase, weight decrease.
*Mostly consistent with cholestasis.
Exceptional cases of extrapyramidal syndrome have been reported.

4.9. OVERDOSE:
In humans experience with intentional overdose is limited.
Symptoms: Available data suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.
Treatment: Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10mg has been shown to reduce the absorption rate of amlodipine. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES:
Pharmacotherapeutic group: Calcium channel blockers, selective calcium channel blockers with mainly vascular effects. **ATC Code:** C08CA01.
Mechanism of action: Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces total ischemic burden by the following two actions:
1. Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.
2. The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

5.2. PHARMACOKINETICS:
Absorption: After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post-dose. Absolute bioavailability has been estimated to be between 64 and 80%.
Distribution: The volume of distribution is approximately 21 L/kg. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins. The bioavailability of amlodipine is not affected by food intake.
Metabolism: Amlodipine is extensively metabolized by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.
Elimination: The terminal plasma elimination half-life is about 35-50 hours and is consistent with once-daily dosing.

5.3. PRECLINICAL SAFETY DATA:
Reproductive toxicology: Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labor, and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.
Impairment of fertility: There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10mg/kg/day (8 times* the maximum recommended human dose of 10mg on a mg/m^2 basis). In another rat study in which male rats were treated with amlodipine besylate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.
Carcinogenesis, mutagenesis: Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10mg on a mg/m^2 basis) was close to the maximum tolerated dose for mice but not for rats. Mutagenicity studies revealed no drug-related effects at either the gene or chromosome levels.
*Based on patient weight of 50kg

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:
Onato® 5mg Tablets: ● Maize starch ● Lactose spray dried ● Microcrystalline cellulose ● Magnesium stearate
Onato® 10mg Tablets: ● Maize starch ● Lactose spray dried ● Microcrystalline cellulose ● Magnesium stearate ● Red iron oxide color

6.2. INCOMPATIBILITIES:
Not applicable.

6.3. SHELF LIFE:
See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:
Avoid exposure to heat, light and humidity. Store between 15 to 30°C. Improper storage may deteriorate the medicine.
Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:
Onato® 5mg Tablets: Alu/PVC blister, pack size 30's.
Onato® 10mg Tablets: Alu/PVC blister, pack size 30's.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:
Any unused product or waste material should be disposed of in accord.

6.7. DRUG PRODUCT SPECIFICATIONS:
USP Specs.

7. MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, Off Hub River Road, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com
Mfg. Lic. No. 000072

8. MARKETING AUTHORISATION NUMBER(S)

Onato® 5mg Tablets: 027777
Onato® 10mg Tablets: 024499

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Onato® 5mg Tablets: 14th May, 2002
Onato® 10mg Tablets: 14th March, 2002

10. DATE OF REVISION OF THE TEXT

اُناٹو ٹیبلٹ

(ایملوڈیپین بیسیلیٹ)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں

بچوں کی پہنچ سے دور رکھیں

دوا کو دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ

کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی