

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

TELDAY AM
(Telmisartan and Amlodipine Tablets)

COMPOSITION:

Each uncoated bilayered tablet contains:

Telmisartan I.P. 40 mg

Amlodipine Besilate I.P. equivalent to Amlodipine 5 mg

Colour: Red Oxide of Iron

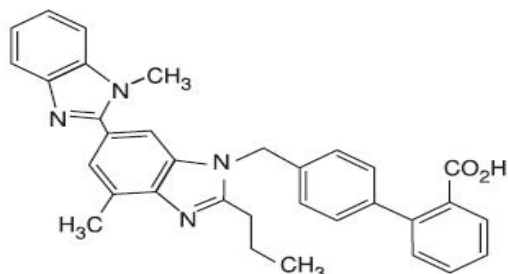
WARNING: FETAL TOXICITY

When pregnancy is detected, discontinue the product as soon as possible.

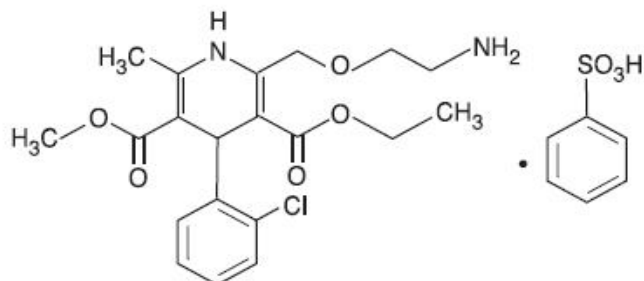
Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus

DESCRIPTION:

Telday AM is a combination of telmisartan, an orally active angiotensin II receptor blocker (ARB) acting on the AT₁ receptor subtype and amlodipine besilate is a long acting dihydropyridine calcium channel-blocking agent. Telmisartan, a nonpeptide molecule, is chemically described as 4'-[[4-Methyl- 6-(1-methyl-1*H*-benzimidazol-2-yl)-2-propyl-1*H*-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid. It has empirical formula C₃₃H₃₀N₄O₂ and molecular weight is 514.6. The chemical structure of Telmisartan is:



The Amlodipine Besilate molecule, is chemically described as 3-ethyl-5-methyl(4*RS*)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzene sulphonate. Its empirical formula is C₂₆H₃₁ClN₂O₈S its molecular weight is 567.1. The chemical structure of Amlodipine Besilate is:



CLINICAL PHARMACOLOGY:

Pharmacodynamics:

Telmisartan

Telmisartan is a nonpeptide angiotensin II receptor antagonist which selectively and insurmountably inhibits angiotensin II AT₁ receptor subtype without affecting other systems involved in cardiovascular regulation. Telmisartan blocks the vasoconstrictor and aldosterone secretion effect of angiotensin II by selectively blocking the binding of angiotensin II to the AT₁ receptor in many tissues. Its action is therefore independent of the pathways for angiotensin II synthesis.

AT₂ receptor is found in many tissues, but AT₂ is not known to be associated with cardiovascular homeostasis. Telmisartan has greater affinity (>3,000 fold) for the AT₁ receptor than for the AT₂ receptor. Telmisartan has a higher octanol/ buffer partition coefficient and thus is more lipophilic than candesartan, irbesartan, valsartan and active metabolite of losartan. The drug dissociates slowly from AT₁ receptors, with dissociation half-life (t_{1/2}) of 5.9 hours.

Because telmisartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Telmisartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of telmisartan on blood pressure.

Telmisartan reduces blood pressure and left ventricular mass index in patients with hypertension and mild to moderate Left Ventricular (LV) hypertrophy. It has been shown to be effective in reducing arterial stiffness in hypertensive patients with type 2 diabetes and may potentially have beneficial effects on cardiovascular outcomes, beyond blood pressure lowering effects in this patient group.

Amlodipine

Amlodipine is a dihydropyridine calcium channel-blocking agent structurally related to nifedipine. The mechanism of action of amlodipine is similar to that of other calcium channel-blocking agents. Amlodipine inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Amlodipine binds to both dihydropyridine and non dihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through

specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells.

Unlike nifedipine and other dihydropyridines, amlodipine is ionized at physiologic pH. Its binding to calcium channel receptors is increased (tighter binding) at low pH such as that seen under ischemic conditions. Amlodipine has a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure. At therapeutic doses, amlodipine does not exert negative inotropic effects.

In patients with exertional angina, amlodipine reduces the total peripheral resistance (afterload) against which the heart works and reduces the rate pressure product, and thus myocardial oxygen demand, at any given level of exercise. In vasospastic angina, amlodipine inhibits coronary spasm and restores blood flow in coronary arteries and arterioles.

Pharmacokinetics:

Absorption:

Telmisartan:

The oral bioavailability of telmisartan is dose dependent (40-60 %). Telmisartan may be taken with or without food. Following oral administration, peak concentrations (C_{max}) of telmisartan are reached in 0.5-1 hour (T_{max}) after dosing. Food slightly reduces the bio-availability.

Amlodipine:

Oral amlodipine appears to be well absorbed with bioavailability of 64-90%. Maximum concentrations (C_{max}) are produced at 6 to 12 hours (T_{max}) after oral administration. Food does not have any effect on the absorption of amlodipine.

Distribution:

Telmisartan:

Telmisartan is extensively distributed to the tissues (mean apparent volume of distribution at steady state was 460 to 510 L in healthy male volunteers) and is highly bound to plasma proteins (> 99.5%). Steady plasma concentrations were achieved after approximately 5 to 7 days of administration and this appears to be little potential for drug accumulation with prolonged administration of telmisartan.

Amlodipine:

Amlodipine has high tissue affinity, as evidenced by a large volume of distribution. The drug displays an unusually slow rate of association and dissociation in isolated vascular or cardiac tissue, unlike other dihydropyridines plasma protein binding of amlodipine is 93-98%.

Metabolism and Excretion:

Telmisartan:

Telmisartan is metabolized by conjugation to form a pharmacologically inactive acylglucuronide. The cytochrome P450 isoenzymes are not involved in the metabolism of

telmisartan. The primary route of elimination of telmisartan and its metabolite is biliary-faecal excretion. More than > 97% of 40 mg single oral or intravenous dose of [¹⁴C] telmisartan was excreted within 120 hours in healthy male volunteers, while <1% was recovered in urine. Telmisartan shows bi-exponential decay kinetics with a terminal elimination half-life of approximately 24 hours. Total Plasma clearances is > 800 ml/min.

Amlodipine:

Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism. Amlodipine is metabolized by oxidation to the pyridine analogue, with subsequent oxidative deamination of the 2- aminoethoxymethyl side chain or de-esterification at the 5-methoxycarbonyl group. Rate of oxidation of amlodipine may be slower, as suggested by less extensive and variable first-pass metabolism and a longer half-life compared to other dihydropyridines.

Approximately 60% of an administered dose is excreted in the urine; with 5- 10% appearing as unchanged drug and 20-25% of the administered dose is excreted in the faeces. The plasma elimination half- life is 35-50 hours.

Special populations:

Age and sex:

There was no clinically relevant effect of age or sex on the pharmacokinetics of Telmisartan. Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40-60%, and a lower initial dose of amlodipine may be required.

Renal insufficiency:

No dosage adjustment is necessary in patients with decreased renal function. Telmisartan is not removed from blood by hemofiltration. Renal impairment has no influence on the pharmacokinetics of amlodipine; thus, dose adjustment in patients with renal dysfunction is not necessary.

Hepatic insufficiency:

In patients with hepatic insufficiency, plasma concentrations of telmisartan are increased and telmisartan should be initiated under close medical supervision in such patients. Absolute bioavailability approaches 100 %. Amlodipine is extensively metabolized in the liver, which results in a slight reduction of clearance in the presence of hepatic impairment. Dosage adjustments may be required in patients with liver disease start with a low initial dose.

Pregnancy:

Pregnancy categories C (first trimester) and D (second and third trimesters). Drugs acting directly on the renin-angiotensin-aldosterone system are documented to cause fetal or neonatal injury or death when used during second or third trimester of pregnancy. Exposure to drug limited to the first trimester has not been associated with fetal or neonatal injury. Use of Telday AM is contraindicated in pregnant women.

Nursing Mothers:

Telday AM is contraindicated in lactating females.

Pediatric Use:

Safety and effectiveness in pediatric patients have not been established.

INDICATIONS AND USAGE:

Telday AM is indicated for the treatment of essential hypertension in adults.

DOSAGE AND ADMINISTRATION:

Telday AM should be administered once daily with or without food. Telday AM may be administered with other antihypertensive agents. The combination may be substituted for the titrated components.

Patients with Renal Impairment:

No dosage adjustment is necessary in patients with mild or moderate renal impairment.

Patients with Hepatic Impairment:

Dosage adjustments may be required in patients with liver disease. Telday AM is not recommended for patients with severe hepatic impairment.

CONTRAINDICATIONS:

1. Prior hypersensitivity to telmisartan
2. Prior hypersensitivity to amlodipine or other Calcium channel blockers
3. Patients with anuria
4. Pregnant and lactating females
5. Hereditary or idiopathic angioedema

PRECAUTIONS AND WARNINGS:

When pregnancy is detected, Telmisartan should be discontinued as soon as possible as it can cause injury and even death to the developing fetus, when used in pregnancy during second and third trimesters of pregnancy. Fetal and neonatal morbidity and mortality:

Telmisartan:

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug. When pregnancy is detected, Telday AM should be discontinued as soon as possible.

Hypotension in volume and salt depleted Patients:

Initiation of antihypertensive therapy in patients whose renin-angiotensin system is activated such as patients who are intravascular volume-or sodium-depleted, e.g., in patients treated vigorously with diuretics, should only be approached cautiously. These conditions should be corrected prior to administration of Telday AM. Treatment should be started under close medical supervision. If hypotension occurs, the patients should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline.

Amlodipine:

Since the vasodilation induced by amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration of amlodipine. Caution should be exercised while administering amlodipine with any other peripheral vasodilator particularly in patients with severe aortic stenosis. A transient hypotensive response is not a contraindication to further treatment which usually can be continued without difficulty once the blood pressure has stabilized.

Hyperkalemia:

Telmisartan:

Hyperkalemia has been rarely reported with the use of ARB therapy Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ARB therapy.

Increased Angina and/or Myocardial Infarction:

Amlodipine:

Patients with severe obstructive coronary artery disease can develop increased frequency, duration and/or severity of angina or acute myocardial infarction with calcium channel blocker therapy.

Patients with Congestive Heart Failure:

In general, calcium channel blockers should be used with caution in patients with heart failure.

Patients with Impaired Hepatic Function:

Telmisartan:

As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Initiate telmisartan at low doses and titrate slowly in these patients.

Amlodipine:

Amlodipine is extensively metabolized by the liver and the plasma elimination half-life ($t_{1/2}$) is 56 hours in patients with impaired hepatic function. Since patients with hepatic impairment have decreased clearance of amlodipine, start amlodipine or add amlodipine at 2.5 mg in patients with hepatic impairment. The lowest dose of TELDAY AM is 40/5 mg; therefore, initial therapy with TELDAY AM tablets is not recommended in hepatically impaired patients.

Renal Function Impairment:

Telmisartan:

As a consequence of inhibiting the renin-angiotensin-aldosterone system, anticipate changes in renal function in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure or renal dysfunction), treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with telmisartan. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long term use of telmisartan in patients with unilateral or bilateral renal artery stenosis, but anticipate an effect similar to that seen with ACE inhibitors.

Dual Blockade of the Renin-Angiotensin-Aldosterone System:

Dual Blockade of the Renin-Angiotensin-Aldosterone System

Dual blockade of the RAS with angiotensin-receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy.

The reported ONTARGET trial enrolled 25,620 patients ≥ 55 years old with atherosclerotic disease or diabetes with end-organ damage, randomizing them to telmisartan only, ramipril only, or the combination, and followed them for a median of 56 months. Patients receiving the combination of telmisartan and ramipril did not obtain any additional benefit compared to monotherapy, but experienced an increased incidence of renal dysfunction (e.g., acute renal failure) compared with groups receiving telmisartan alone or ramipril alone.

In most patients no benefit has been associated with using two RAS inhibitors concomitantly. In general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function, and electrolytes in patients on telmisartan and other agents that affect the RAS.

Do not co-administer aliskiren with telmisartan in patients with diabetes. Avoid concomitant use of aliskiren with telmisartan in patients with renal impairment ($\text{GFR} < 60 \text{ mL}/\text{min}/1.73 \text{ m}^2$).

Heart Failure:

Amlodipine:

Closely monitor patients with heart failure. Amlodipine (5-10 mg per day) has been studied in a placebo-controlled trial of 1153 patients with NYHA Class III or IV heart failure on stable doses of ACE inhibitor, digoxin, and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by lifethreatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure). Amlodipine has been compared to placebo in four 812 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsening of heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF. In the PRAISE-2 study, 1654 patients with NYHA class III

(80%) or IV (20%) heart failure without evidence of underlying ischemic disease, on stable doses of ACE inhibitor (99%), digitalis (99%), and diuretics (99%) were randomized 1:1 to receive placebo or amlodipine and followed for a mean of 33 months. While there was no statistically significant difference between amlodipine and placebo in the primary endpoint of all cause mortality (95% confidence limits from 8% reduction to 29% increase on amlodipine), there were more reports of pulmonary edema in the patients on amlodipine.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:

Telmisartan:

There was no evidence of carcinogenicity when telmisartan was administered in the diet to mice and rats for up to 2 years. The highest doses administered to mice (1000 mg/kg/day) and rats (100 mg/kg/day) are, on a mg/m² basis, about 59 and 13 times, respectively, the maximum recommended human dose (MRHD) of telmisartan. Genotoxicity assays did not reveal any telmisartan-related effects at either the gene or chromosome level. No drug-related effects on the reproductive performance of male and female rats were noted at 100 mg/kg/day (the highest dose administered), about 13 times, on a mg/m² basis, the MRHD of telmisartan.

Amlodipine:

No evidence of carcinogenicity was observed in studies conducted in rats and mice. No evidence of mutagenicity was observed in mutagenicity tests. No evidence of reproductive toxicity was seen in fertility studies conducted in animals.

DRUG INTERACTIONS:

Telmisartan:

Telmisartan is not metabolized by any cytochrome P450 (CYP) isoenzymes hence has low potential to interfere with metabolism of drugs, metabolized through this system, except for possible inhibitor of the metabolism of drug metabolized by CYP2C19.

Digoxin:

Plasma concentration was altered during co-administration of telmisartan. However no interaction was reported in a large well designed study of telmisartan in heart failure in which more than one-third of patients were taking digoxin. Nonetheless, serum digoxin concentrations should be monitored and dosage of digoxin adjusted accordingly when therapy with telmisartan is introduced.

Warfarin:

Telmisartan had a small effect on plasma warfarin concentration in 12 healthy volunteers, but there were no statistically significant changes in international normalized ratio (INR) after introduction of telmisartan.

Lithium:

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists including telmisartan. Therefore, monitor serum lithium levels during concomitant use.

Ramipril and Ramiprilat:

Co-administration of telmisartan 80 mg once daily and ramipril 10 mg once daily to healthy subjects increases steady-state C_{max} and AUC of ramipril 2.3- and 2.1-fold, respectively, and C_{max} and AUC of ramiprilat 2.4- and 1.5-fold, respectively. In contrast, C_{max} and AUC of telmisartan decrease by 31% and 16%, respectively. When co-administering telmisartan and ramipril, the response may be greater because of the possibly additive pharmacodynamic effects of the combined drugs, and also because of the increased exposure to ramipril and ramiprilat in the presence of telmisartan. Co-administration of telmisartan and ramipril is not recommended.

Other Drugs:

Co-administration of telmisartan had no effect on steady state pharmacokinetics of amlodipine, glibenclamide, ibuprofen, paracetamol, hydrochlorothiazide, simvastatin and glyburide.

Amlodipine:

Amlodipine had no effect on the protein binding of drugs tested (digoxin, phenytoin, warfarin, and indomethacin). Amlodipine had no clinically significant pharmacokinetic interaction with cimetidine, antacid, sildenafil, digoxin, warfarin or ethanol. In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

ADVERSE REACTIONS:***Telmisartan:***

Adverse events are generally mild and no more frequent than those experienced in patients treated with placebo. Discontinuation due to adverse events is less common with telmisartan than with placebo. Most commonly reported adverse events with Telmisartan are upper respiratory tract infection, back pain, sinusitis, diarrhea and pharyngitis. Less commonly reported adverse events include:

Autonomic Nervous System: impotence, increased sweating, flushing; **Body as a Whole:** allergy, fever, leg pain, malaise;

Cardiovascular: palpitation, dependent edema, angina pectoris, tachycardia, leg edema, abnormal ECG; **CNS:** insomnia, somnolence, migraine, vertigo, paresthesia, involuntary muscle contractions, hypoesthesia;

Gastrointestinal: flatulence, constipation, gastritis, vomiting, dry mouth, hemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache, nonspecific gastrointestinal disorders; ***Metabolic:*** gout, hypercholesterolemia, diabetes mellitus;

Musculoskeletal: arthritis, arthralgia, leg cramps; **Psychiatric:** anxiety, depression, nervousness;

Resistance Mechanism: infection, fungal infection, abscess, otitis media; ***Respiratory:*** asthma, bronchitis, rhinitis, dyspnea, epistaxis;

Skin: dermatitis, rash, eczema, pruritus;

Urinary: micturition frequency, cystitis;

Vascular: cerebrovascular disorder; and Special Senses: abnormal vision, conjunctivitis, tinnitus, earache.

Amlodipine:

Amlodipine is generally well tolerated. Adverse events seen are mild and transient. Commonly reported adverse events are: headache, peripheral oedema, fatigue, dizziness, flushing, palpitations, nausea and somnolence.

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis;

Central and Peripheral Nervous System: hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo; **Gastrointestinal:** anorexia, constipation, dyspepsia,** dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia, change of bowel habit; **General:** allergic reaction, asthenia,** back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease; **Musculoskeletal System:** arthralgia, arthrosis, muscle cramps,** myalgia;

Psychiatric: sexual dysfunction (male** and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization, mood change;

Respiratory System: dyspnea,** epistaxis; **Skin and Appendages:** angioedema, erythema multiforme, pruritus,** rash,** rash erythematous, rash maculopapular; **Special Senses:** abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus;

Urinary System: micturition frequency, micturition disorder, nocturia; **Autonomic Nervous System:** dry mouth, sweating increased;

Metabolic and Nutritional: hyperglycemia, thirst;

Hemopoietic: leukopenia, purpura, thrombocytopenia. **These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies. The following events occurred in <0.1% of patients: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia.

OVERDOSAGE:

Telmisartan:

Limited data are available with respect to over dosage in human beings. The most likely manifestations due to over dosage of Telmisartan can be hypotension, dizziness and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic, hypotension should involve supportive treatment. Telmisartan is not removed by hemodialysis.

Amlodipine:

Few cases of overdosage with amlodipine have been reported. Overdosage can cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In the event of an overdose, symptomatic and supportive measures should be employed. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) who was hospitalized underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A case of accidental drug overdose has been documented in a 19- month-old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae was noted. If hypotension occurs, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. Administration of vasopressors (such as phenylephrine) should be considered in unresponsive hypotension. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

EXPIRY DATE:

Do not use later than expiry date.

STORAGE:

Store at a temperature not exceeding 30°C, protected from light and moisture.
Keep out of reach of children.

PRESENTATION:

Telday AM is available in strip of 10 tablets.

MARKETED BY



TORRENT PHARMACEUTICALS LTD.

Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA

IN/TELDAY AM/40,5mg/Feb-15/02/PI