CORVADIL

To be sold by retail on the prescription of R.M.P. only

Abbreviated Prescribing information for **CORVADIL** (Amlodipine Tablets I.P.)

[Please refer the complete prescribing information available at www.torrentpharma.com]

PHARMACOLOGICAL PROPERTIES:

Mechanism of action: Carvedilol: 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. 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.

DOSAGE AND ADMINISTRATION: As directed by the Physician.

CONTRAINDICATION: 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.

WARNINGS & PRECAUTIONS: 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. **Patients with hepatic impairment**: 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. **Elderly patients**: In the elderly increase of the dosage should take place with care. **Patients with renal impairment**: Amlodipine may be used in such patients at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialysable.

DRUG INTERACTION: 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 resulting in an increased risk of hypotension. 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:* Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, hypericum perforatum). 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)*: In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene. Due to 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 adds to the blood pressure-lowering effects of other medicinal products with antihypertensive properties. *Tacrolimus:* There is a risk of increased tacrolimus blood levels when co-administered with amlodipine but the pharmacokinetic mechanism of this interaction is not fully understood. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate. *Mechanistic Target of Rapamycin (mTOR) Inhibitors*: mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors. *Cyclosporine*: No drug interaction studies have been conducted with cyclosporine and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases (average 0% - 40%) of cyclosporine were observed. Consideration should be given for monitoring cyclosporine levels in renal transplant patients on amlodipine, and cyclosporine dose reductions should be made as necessary. *Simvastatin:* Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily. In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin or warfarin

ADVERSE REACTIONS: Leukocytopenia, thrombocytopenia, Allergic reactions, Hyperglycaemia, Depression, mood changes (including anxiety), insomnia, Confusion, Somnolence, dizziness, headache (especially at the beginning of the treatment), Tremor, dysgeusia, syncope, hypoaesthesia, paraesthesia, Hypertonia, peripheral neuropathy, Visual disturbance (including diplopia), Tinnitus, Palpitations, Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation), Myocardial infarction, Flushing, Hypotension, Vasculitis, Dyspnoea, Cough, rhinitis, Abdominal pain, nausea, dyspepsia, altered bowel habits (including diarrhoea and constipation), Vomiting, dry mouth, Pancreatitis, gastritis, gingival hyperplasia, Hepatitis, jaundice, hepatic enzyme increased, Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, exanthema, urticarial, Angioedema, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity, Toxic epidermal necrolysis, Ankle swelling, muscle cramps, Arthralgia, myalgia, back pain, Micturition disorder, nocturia, increased urinary frequency, Impotence, gynaecomastia, Oedema, Fatigue, asthenia, Chest pain, pain, malaise, Weight increased, weight decreased

Manufactured by:

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IN/ CORVADIL 2.5, 5 mg/JAN-22 /01/ABPI
(Additional information is available on request)