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

CORVADIL-A

1. Generic Name
Amlodipine & Atenolol Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each uncoated bilayered tablet contains:
Amlodipine Besilate I.P. equivalent to Amlodipine…….5 mg
Atenolol I.P. ……...50 mg
Colour: Red Oxide of Iron

The excipients used are Starch, Dibasic Calcium, Magnesium Stearate, Talc, Sodium Lauryl Sulphate, Sodium Carboxymethyl Cellulose, Ferric Oxide Red, Sodium Starch Glycolate, and Microcrystalline Cellulose.

3. DOSAGE FORM AND STRENGTH
Dosage Form: Uncoated Bilayered Tablets
Strength: Amlodipine…….5 mg, Atenolol……..50mg

4. CLINICAL PARTICULARS
4.1 Therapeutic Indication
For the treatment of Mild to moderate hypertension.

4.2 Posology and Method of Administration
Dose: As directed by the Physician.

Elderly
Dosage requirements may be reduced, especially in patients with impaired renal function.

Paediatric population
There is no paediatric experience with Corvadil-A, for this reason, it is not recommended for use in children.

Renal impairment
Since Atenolol is excreted via the kidneys, the dosage should be adjusted in cases of severe impairment of renal function.

As per reported data, no significant accumulation of Atenolol occurs in patients who have a creatinine clearance greater than 35 ml/min/1.73 m^2 (normal range is 100–150 ml/min/1.73 m^2).

For patients with a creatinine clearance of 15–35 ml/min/1.73 m^2 (equivalent to serum creatinine of 300–600 micromol/litre), the oral dose should be 50 mg daily.

For patients with a creatinine clearance of less than 15 ml/min/1.73 m^2 (equivalent to serum creatinine of greater than 600 micromol/litre), the oral dose should be 25 mg daily or 50 mg on alternate days.

Patients on haemodialysis should be given 50 mg orally after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

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 Corvadil-A have not been studied in severe hepatic impairment. Corvadil-A should be initiated at the lowest dose and titrated slowly in patients with severe hepatic impairment

Method of administration
For administration by the oral route.

4.3 Contraindications

- Hypersensitivity to dihydropyridine derivatives, amlodipine, atenolol or to any of the excipients of this product
- 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
- Uncontrolled heart failure
- Sick sinus syndrome
- Second-or third-degree heart block
- Untreated phaeochromocytoma
- Metabolic acidosis
- Bradycardia (<45 bpm)
- Severe peripheral arterial circulatory disturbances.

4.4 Special Warnings and Precautions for Use

Amlodipine Besylate
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 reported 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.

Atenolol
Atenolol as with other beta-blockers:

- Should not be withdrawn abruptly. The dosage should be withdrawn gradually over a period of 7–14 days, to facilitate a reduction in beta-blocker dosage. Patients should be followed during withdrawal, especially those with ischaemic heart disease.
- When a patient is scheduled for surgery, and a decision is made to discontinue beta-blocker therapy, this should be done at least 24 hours prior to the procedure. The risk-benefit assessment of stopping beta-blockade should be made for each patient. If treatment is continued, an anaesthetic with little negative inotropic activity should be selected to minimise the risk of myocardial depression. The patient may be protected against vagal reactions by intravenous administration of atropine.
- Although contraindicated in uncontrolled heart failure, may be used in patients whose signs of heart failure have been controlled. Caution must be exercised in patients whose cardiac reserve is poor.
- May increase the number and duration of angina attacks in patients with Prinzmetal's angina due to unopposed alpha-receptor mediated coronary artery vasoconstriction. Atenolol is a $beta_1$-selective beta-blocker; consequently, its use may be considered although utmost caution must be exercised.
- Although contraindicated in severe peripheral arterial circulatory disturbances, may also aggravate less severe peripheral arterial circulatory disturbances.
- Due to its negative effect on conduction time, caution must be exercised if it is given to patients with first-degree heart block.
- May mask the symptoms of hypoglycaemia, in particular, tachycardia.
- May mask the signs of thyrotoxicosis.
- Will reduce heart rate as a result of its pharmacological action. In the rare instances when a treated patient develops symptoms which may be attributable to a slow heart rate and the pulse rate drops to less than 50–55 bpm at rest, the dose should be reduced.
- May cause a more severe reaction to a variety of allergens when given to patients with a history of anaphylactic reaction to such allergens. Such patients may be unresponsive to the usual doses of adrenaline (epinephrine) used to treat the allergic reactions.
- May cause a hypersensitivity reaction including angioedema and urticaria.
- Should be used with caution in the elderly, starting with a lesser dose.

Since Atenolol is excreted via the kidneys, dosage should be reduced in patients with a creatinine clearance of below 35 ml/min/1.73 m^2.

Although cardioselective ($beta_1$) beta-blockers may have less effect on lung function than non-selective beta-blockers, as with all beta-blockers, these should be avoided in patients with reversible obstructive airways disease, unless there are compelling clinical reasons for their use. Where such reasons exist, Atenolol may be used with caution. Occasionally, some increase in airways resistance may occur in asthmatic patients however, and this may usually be reversed by commonly used dosage of bronchodilators such as salbutamol or isoprenaline. The label and patient information leaflet for this product state the following warning: "If you have ever had asthma or wheezing, you should not take this medicine unless you have discussed these symptoms with the prescribing doctor".

As with other beta-blockers, in patients with a phaeochromocytoma, an alpha-blocker should be given concomitantly.

4.5 Drugs Interactions

Amlodipine Besylate

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)

As per reported data, 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 reported clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin or warfarin.

Atenolol

Combined use of beta-blockers and calcium channel blockers with negative inotropic effects, e.g. verapamil and diltiazem, can lead to an exaggeration of these effects particularly in patients with impaired ventricular function and/or sinoatrial or atrioventricular conduction abnormalities. This may result in severe hypotension, bradycardia and cardiac failure. Neither the beta-blocker nor the calcium channel blocker should be administered intravenously within 48 hours of discontinuing the other.

Concomitant therapy with dihydropyridine, e.g. nifedipine, may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency.

Digitalis glycosides, in association with beta-blockers, may increase atrioventricular conduction time.

Beta-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are co-administered, the beta-blocker should be withdrawn several days before discontinuing clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta-blockers should be delayed for several days after clonidine administration has stopped. (See also prescribing information for clonidine.)

Class I anti-arrhythmic drugs (e.g. disopyramide) and amiodarone may have a potentiating effect on atrial-conduction time and induce negative inotropic effect.

Concomitant use of sympathomimetic agents, e.g. adrenaline (epinephrine), may counteract the effect of beta-blockers.

Concomitant use with insulin and oral antidiabetic drugs may lead to the intensification of the blood sugar lowering effects of these drugs. Symptoms of hypoglycaemia, particularly tachycardia, may be masked.

Concomitant use of prostaglandin synthetase-inhibiting drugs, e.g. ibuprofen and indomethacin, may decrease the hypotensive effects of beta-blockers.

Caution must be exercised when using anaesthetic agents with Atenolol. The anaesthetist should be informed and the choice of anaesthetic should be an agent with as little negative inotropic activity as possible. Use of beta-blockers with anaesthetic drugs may result in attenuation of the reflex tachycardia and increase the risk of hypotension. Anaesthetic agents causing myocardial depression are best avoided.

4.6 Use in Special Populations (Such as Pregnant Women, Lactating Women, Paediatric Patients, Geriatric Patients Etc.)

Amlodipine Besylate

Pregnancy

The safety of amlodipine in human pregnancy has not been established.
In reported animal studies, reproductive toxicity was observed at high doses.
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

Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3-7%, with a maximum of 15%. The effect of amlodipine on infants is unknown. 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.

Fertility

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Reported clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one reported rat study, adverse effects were found on male fertility.

Atenolol

Caution should be exercised when Atenolol is administered during pregnancy or to a woman who is breast-feeding.

Pregnancy

Atenolol crosses the placental barrier and appears in the cord blood. No studies have been performed on the use of Atenolol in the first trimester and the possibility of foetal injury cannot be excluded. Atenolol has been used under close supervision for the treatment of hypertension in the third trimester. Administration of Atenolol to pregnant women in the management of mild to moderate hypertension has been associated with intra-uterine growth retardation.

The use of Atenolol in women who are, or may become, pregnant requires that the anticipated benefit be weighed against the possible risks, particularly in the first and second trimesters, since beta-blockers, in general, have been associated with a decrease in placental perfusion which may result in intra-uterine deaths, immature and premature deliveries.

Breast-feeding

There is significant accumulation of Atenolol in breast milk.
Neonates born to mothers who are receiving Atenolol at parturition or breast-feeding may be at risk of hypoglycaemia and bradycardia.

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

Summary of the safety profile

The most commonly reported adverse reactions during treatment are somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue.

Tabulated list of adverse reactions

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); not known (cannot be estimated from the available data).

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

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Rare	Thrombocytopenia, purpura
	Very rare	Leukocytopenia
Immune system disorders	Very rare	Allergic reactions
Metabolism and nutrition disorders	Very rare	Hyperglycaemia
Psychiatric disorders	Uncommon	Depression, mood changes (including anxiety), insomnia/Sleep disturbances of the type noted with other beta-blockers
	Rare	Nightmares, confusion, psychoses and hallucinations
Nervous system disorders	Common	Somnolence, dizziness, headache (especially at the beginning of the treatment)
	Uncommon	Tremor, dysgeusia, syncope, hypoaesthesia, paraesthesia
	Very rare	Hypertonia, peripheral neuropathy
Eye disorders	Common	Visual disturbance (including diplopia)
	Rare	Dry Eyes
Ear and labyrinth disorders	Uncommon	Tinnitus
Cardiac disorders	Common	Palpitations, bradycardia
	Uncommon	Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)
	Rare	Heart failure deterioration, precipitation of heart block
	Very rare	Myocardial infarction
Vascular disorders	Common	Flushing, cold extremities
	Uncommon	Hypotension
	Very rare	Vasculitis
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
	Uncommon	Cough, rhinitis
	Rare	Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints
Gastrointestinal disorders	Common	Abdominal pain, nausea, dyspepsia, altered bowel habits (including diarrhoea and constipation)
	Uncommon	Vomiting, dry mouth

	Very rare	Pancreatitis, gastritis, gingival hyperplasia
Hepatobiliary disorders	Uncommon	hepatic enzyme increased*
	Very rare	Hepatitis, jaundice
Skin and subcutaneous tissue disorders	Uncommon	Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, exanthema, urticaria
	Rare	Psoriasiform skin reactions, exacerbation of psoriasis,
	Very rare	Angioedema, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity
	Not known	Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Common	Ankle swelling, muscle cramps
	Uncommon	Arthralgia, myalgia, back pain
	Not known	Lupus-like syndrome
Renal and urinary disorders	Uncommon	Micturition disorder, nocturia, increased urinary frequency
Reproductive system and breast disorders	Uncommon	Impotence, gynaecomastia
General disorders and administration site conditions	Very common	Oedema
	Common	Fatigue, asthenia
	Uncommon	Chest pain, pain, malaise
Investigations	Uncommon	Weight increased, weight decreased
	Very Rare	An increase in ANA (Antinuclear Antibodies) has been observed, however the clinical relevance of this is not clear

*mostly consistent with cholestasis
Exceptional cases of extrapyramidal syndrome have been reported.

Discontinuance of the drug should be considered if, according to clinical judgement, the well-being of the patient is adversely affected by any of the above reactions.

- **Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist 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

Symptoms

Available data suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia or bradycardia, acute cardiac insufficiency and bronchospasm. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Treatment

General treatment should include: close supervision; treatment in an intensive care ward; the use of gastric lavage; activated charcoal and a laxative to prevent absorption of any drug still present in the gastrointestinal tract; the use of plasma or plasma substitutes to treat hypotension and shock. The possible uses of haemodialysis or haemoperfusion may be considered.

Excessive bradycardia can be countered with atropine 1–2 mg intravenously and/or a cardiac pacemaker. If necessary, this may be followed by a bolus dose of glucagon 10 mg intravenously. If required, this may be repeated or followed by an intravenous infusion of glucagon 1–10 mg/hour depending on response. If no response to glucagon occurs or if glucagon is unavailable, a beta-adrenoceptor stimulant such as dobutamine 2.5 to 10 micrograms/kg/minute by intravenous infusion may be given. Dobutamine, because of its positive inotropic effect could also be used to treat hypotension and acute cardiac insufficiency. It is likely that these doses would be inadequate to reverse the cardiac effects of beta-blocker blockade if a large overdose has been taken. The dose of dobutamine should therefore be increased if necessary to achieve the required response according to the clinical condition of the patient.

Clinically significant hypotension due to 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.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

Bronchospasm can usually be reversed by bronchodilators.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

Amlodipine Besylate

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 ischaemic 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 ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

Atenolol

Atenolol is a beta-blocker which is $beta_1$-selective, (i.e. acts preferentially on $beta_1$-adrenergic receptors in the heart). Selectivity decreases with increasing dose.

Atenolol is without intrinsic sympathomimetic and membrane-stabilising activities and as with other beta-blockers, has negative inotropic effects (and is therefore contraindicated in uncontrolled heart failure).

As with other beta-blockers, the mode of action of atenolol in the treatment of hypertension is unclear.

It is probably the action of atenolol in reducing cardiac rate and contractility which makes it effective in eliminating or reducing the symptoms of patients with angina.

It is unlikely that any additional ancillary properties possessed by S (-) atenolol, in comparison with the racemic mixture, will give rise to different therapeutic effects.

5.2 Pharmacodynamic Properties

Amlodipine Besylate

Pharmacotherapeutic group: Calcium channel blockers, selective calcium channel blockers with mainly vascular effects. ATC Code: C08CA01.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24-hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1 mm ST segment depression, and decreases both angina attack frequency and glyceryl trinitrate tablet consumption.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.
The long-term effects of amlodipine on growth, puberty and general development have not been studied. The long-term efficacy of amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood has also not been established.

Atenolol

Pharmacotherapeutic group: Beta-blocking agents, plain, selective, ATC code: CO7A B03**.**

Clinical efficacy and safety

Atenolol is effective and well-tolerated in most ethnic populations although the response may be less in black patients.

Atenolol is effective for at least 24 hours after a single oral dose. The drug facilitates compliance by its acceptability to patients and simplicity of dosing. The narrow dose range and early patient response ensure that the effect of the drug in individual patients is quickly demonstrated. Atenolol is compatible with diuretics, other hypotensive agents and antianginals. Since it acts preferentially on beta-receptors in the heart, Atenolol may, with care, be used successfully in the treatment of patients with respiratory disease, who cannot tolerate non-selective beta-blockers.

5.3 Pharmacokinetic Properties

Amlodipine Besylate

Absorption, distribution, plasma protein binding***:*** 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%. 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.

Biotransformation/elimination

The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

Hepatic impairment

Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40-60%.

Elderly population

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.

Paediatric population

As per reported data, a population PK study has been conducted in 74 hypertensive children aged from 1 to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 L/hr respectively in males and 16.4 and 21.3 L/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years is limited.

Atenolol

Absorption

Absorption of atenolol following oral dosing is consistent but incomplete (approximately 40–50%) with peak plasma concentrations occurring 2–4 hours after dosing. The atenolol blood levels are consistent and subject to little variability. There is no significant hepatic metabolism of atenolol and more than 90% of that absorbed reaches the systemic circulation unaltered.

Distribution

Atenolol penetrates tissues poorly due to its low lipid solubility and its concentration in brain tissue is low. Plasma protein binding is low (approximately 3%).

Elimination

The plasma half-life is about 6 hours but this may rise in severe renal impairment since the kidney is the major route of elimination.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

Reproductive toxicology

Reported reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour 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 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis). In another reported rat study in

which male rats were treated with amlodipine besilate 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 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m^2 basis) was close to the maximum tolerated dose for mice but not for rats.

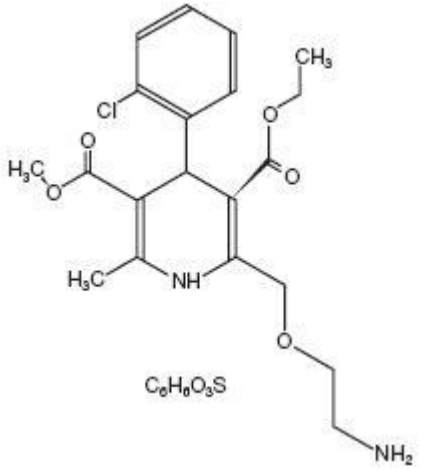
Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

*Based on patient weight of 50 kg

7. DESCRIPTION

Amlodipine Besylate

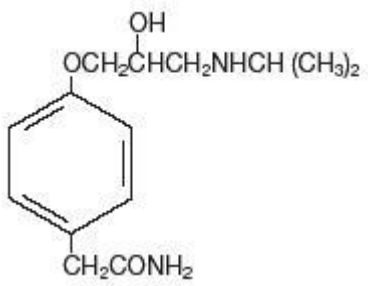
Amlodipine besylate is chemically described as 3-Ethyl-5-methyl (±)-2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzene-sulphonate. Its molecular formula is $C_{20}H_{25}ClN_2O_5 \bullet C_6H_6O_3S$, and its structural formula is:



Amlodipine besylate is a white or almost white powder with a molecular weight of 567.1. it is freely soluble in methanol; sparingly soluble in ethanol (95 percent); slightly soluble in 2-propanol and in water.

Atenolol

Atenolol is (RS)-4-(2-hydroxy-3-isopropylaminopropoxy) phenylacetamide. Atenolol has a molecular weight of 266.34 and its empirical formula is $C_{14}H_{22}N_2O_3$. The chemical structure is:



Atenolol is a white or almost white powder, soluble in ethanol; sparingly soluble in water; slightly soluble in dichloromethane; practically insoluble in ether.

Amlodipine & Atenolol Tablets are Pink and white, uncoated, bilayered, flat tablets with break-line on one side. The excipients used are Starch, Dibasic Calcium, Magnesium Stearate, Talc, Sodium Lauryl Sulphate, Sodium Carboxymethyl Cellulose, Ferric Oxide Red, Sodium Starch Glycolate and Microcrystalline Cellulose.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than date of expiry

8.3 Packaging information

CORVADIL-A is available in blister pack of 15 tablets.

8.4 Storage and Handing Instructions

Store in a dry place at a temperature not exceeding 30°C, protected from light.

Keep all medicines out of reach of children.

9. PATIENT COUNSELLING INFORMATION

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, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1. What Corvadil-A is and what it is used for

Corvadil A is combination of a calcium antagonist (Amlodipine Besylate) and Atenolol (beta-blockers).

It works by making your heart beat more slowly and with less force. In patients with high blood pressure, this medicine works by relaxing blood vessels, so that blood passes through them more easily.

Corvadil-A is used for the treatment of Mild to moderate hypertension.

9.2. What you need to know before you take Corvadil-A

Do not take Corvadil-A

- If you are allergic (hypersensitive) to amlodipine, atenolol or any of the other ingredients of this medicine or to any other calcium antagonists. This may be itching, reddening of the skin or difficulty in breathing.
- If you have severe low blood pressure (hypotension).
- If you have narrowing of the aortic heart valve (aortic stenosis) or cardiogenic shock (a condition where your heart is unable to supply enough blood to the body).
- Heart failure which is not under control (this usually makes you breathless and causes your ankles to swell)
- Second- or third-degree heart block (a condition which may be treated by a pacemaker)
- Very slow or very uneven heart beats or very poor circulation
- If you have a tumour called phaeochromocytoma that is not being treated. This is usually near your kidney and can cause high blood pressure. If you are being treated for phaeochromocytoma, your doctor will give you another medicine, called an alpha-blocker, to take as well as Corvadil-A.
- If you have been told that, you have higher than normal levels of acid in your blood (metabolic acidosis).

Do not take Corvadil-A if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Corvadil-A.

Warnings and precautions

Talk to your doctor or pharmacist before taking Corvadil-A.

You should inform your doctor if you have or have had any of the following conditions:

- Recent heart attack
- Heart failure
- Severe increase in blood pressure (Hypertensive crisis)
- Liver disease
- You are elderly and your dose needs to be increased
- You have asthma, wheezing or any other similar breathing problems, or you get allergic reactions, for example to insect stings. If you have ever had asthma o wheezing, do not take this medicine without first checking with your doctor
- You have a type of chest pain (angina) called Prinzmetal's angina
- You have poor blood circulation or controlled heart failure
- You have first-degree heart block
- You have diabetes. Your medicine may change how you respond to having low blood sugar. You may feel your heart beating faster
- You have thyrotoxicosis (a condition caused by an overactive thyroid gland). Your medicine may hide the symptoms of thyrotoxicosis
- You have problems with your kidneys. You may need to have some check-ups during your treatment

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking Corvadil-A.

Children and adolescents
Corvadil-A has not been studied in children under the age of 6 years. Corvadil-A should only be used for hypertension in children and adolescents from 6 years to 17 years of age. For more information, talk to your doctor.

Other medicines and Corvadil-A

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines that you buy without a prescription and herbal medicines.
This is because Tenormin can affect the way some other medicines work and some medicines can have an effect on Corvadil-A.

Corvadil-A may affect or be affected by other medicines, such as:
- Ketoconazole, itraconazole (anti-fungal medicines)
- Ritonavir, indinavir, nelfinavir (so called protease inhibitors used to treat hiv)
- Rifampicin, erythromycin, clarithromycin (antibiotics)
- Hypericum perforatum (st. John's wort)
- Verapamil, diltiazem, nifedipine (for high blood pressure or chest pain)
- Dantrolene (infusion for severe body temperature abnormalities)
- Tacrolimus, sirolimus, temsirolimus, and everolimus (medicines used to alter the way your immune system works)
- Simvastatin (cholesterol lowering medicine)
- Cyclosporine (an immunosuppressant)
- Clonidine (for high blood pressure or migraine). If you are taking clonidine and Corvadil-A together, do not stop taking clonidine unless your doctor tells you to do so. If you have to stop taking clonidine, your doctor will give you careful instructions about how to do it.
- Disopyramide, quinidine or amiodarone (for an uneven heart beat)
- Digoxin (for heart problems)
- Adrenaline, also known as epinephrine (a medicine that stimulates the heart).
- Ibuprofen or indometacin (for pain and inflammation).
- Insulin or medicines that you take by mouth for diabetes
- Medicines to treat nose or sinus congestion or other cold remedies (including those you can buy in the pharmacy)

Corvadil-A may lower your blood pressure even more if you are already taking other medicines to treat your high blood pressure.

Corvadil-A with food and drink
Grapefruit juice and grapefruit should not be consumed by people who are taking Corvadil-A. This is because grapefruit and grapefruit juice can lead to an increase in the blood levels of the active ingredient amlodipine, which can cause an unpredictable increase in the blood pressure lowering effect of Corvadil-A.

Operations
If you go into hospital to have an operation, tell the anaesthetist or medical staff that you are taking Corvadil-A. This is because you can get low blood pressure (hypotension) if you are given certain anaesthetics while you are taking Tenormin.

Pregnancy and breast-feeding

Pregnancy

The safety of amlodipine in human pregnancy has not been established. If you think you might be pregnant, or are planning to get pregnant, you must tell your doctor before you take Corvadil-A.

Breast-feeding

Amlodipine has been shown to pass into breast milk in small amounts. If you are breast-feeding or about to start breast-feeding, you must tell your doctor before taking Corvadil-A.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Corvadil-A may affect your ability to drive or use machines. If the tablets make you feel sick, dizzy or tired, or give you a headache, do not drive or use machines and contact your doctor immediately.

9.3. How to take Corvadil-A

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

- Your doctor will tell you how many tablets to take each day and when to take them. Read the label on the carton to remind you what the doctor said.
- Swallow your Tenormin tablet whole with a drink of water.
- Try to take your tablet at the same time each day.

Dose: As directed by physician.

This medicine can be used before or after food and drinks. You should take this medicine at the same time each day with a drink of water. Do not take Corvadil-A with grapefruit juice.

Elderly

If you are an elderly person, your doctor may decide to give you a lower dose, particularly if you have problems with your kidneys.

People with severe kidney problems

If you have severe kidney problems, your doctor may decide to give you a lower dose.

Use in Children

This medicine must not be given to children.

If you take more Corvadil-A than you should

Taking too many tablets may cause your blood pressure to become low or even dangerously low. You may feel dizzy, lightheaded, faint or weak. If blood pressure drop is severe, enough shock can occur. Your skin could feel cool and clammy and you could lose consciousness. Seek immediate medical attention if you take too many Corvadil-A tablets.

If you forget to take Corvadil-A

Do not worry. If you forget to take a tablet, leave out that dose completely. Take your next dose at the right time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Corvadil-A

Your doctor will advise you how long to take this medicine. Your condition may return if you stop using this medicine before you are advised.

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

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

Visit your doctor immediately if you experience any of the following side effects after taking this medicine.

Allergic reactions:
If you have an allergic reaction, see a doctor straight away. The signs may include raised lumps on your skin (weals), or swelling of your face, lips, mouth, tongue or throat.

- Sudden wheeziness, chest pain, shortness of breath or difficulty in breathing
- Swelling of eyelids, face or lips
- Swelling of the tongue and throat which causes great difficulty breathing
- Severe skin reactions including intense skin rash, hives, reddening of the skin over your whole body, severe itching, blistering, peeling and swelling of the skin, inflammation of mucous membranes (Stevens Johnson Syndrome, toxic epidermal necrolysis) or other allergic reactions
- Heart attack, abnormal heart beat
- Inflamed pancreas which may cause severe abdominal and back pain accompanied with feeling very unwell

The following **very common side effect** has been reported. If this causes you problems or if it **lasts for more than one week**, you should **contact your doctor.**

Very common: may affect more than 1 in 10 people

- Oedema (fluid retention)

The following **common side effects** have been reported. If any of these cause you problems or if they **last for more than one week**, you should **contact your doctor.**

Common: may affect up to 1 in 10 people
- Headache, dizziness, sleepiness (especially at the beginning of treatment)
- Palpitations (awareness of your heart beat), flushing
- Abdominal pain, feeling sick (nausea)
- Altered bowel habits, diarrhoea, constipation, indigestion
- Tiredness, weakness
- Visual disturbances, double vision
- Muscle cramps
- Ankle swelling
- You may notice that your pulse rate becomes slower while you are taking the tablets. This is normal, but if you are concerned please tell your doctor about it.
- Cold hands and feet.
- Diarrhoea.
- Feeling tired.

Other side effects that have been reported include the following list. If any of these get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Uncommon: may affect up to 1 in 100 people

- Mood changes, anxiety, depression, sleeplessness
- Trembling, taste abnormalities, fainting
- Numbness or tingling sensation in your limbs, loss of pain sensation
- Ringing in the ears
- Low blood pressure
- Sneezing/running nose caused by inflammation of the lining of the nose (rhinitis)
- Cough
- Dry mouth, vomiting (being sick)
- Hair loss, increased sweating, itchy skin, red patches on skin, skin discolouration
- Disorder in passing urine, increased need to urinate at night, increased number of times of passing urine
- Inability to obtain an erection, discomfort or enlargement of the breasts in men
- Pain, feeling unwell
- Joint or muscle pain, back pain
- Weight increase or decrease
- Disturbed sleep.

Rare: may affect up to 1 in 1,000 people

- Confusion
- Heart block (which can cause dizziness, abnormal heart beat, tiredness or fainting).
- Numbness and spasm in your fingers which is followed by warmth and pain (Raynaud's disease).
- Nightmares.
- Feeling confused.
- Changes in personality (psychoses) or hallucinations.
- Dry eyes.
- Skin rash.
- Reduced numbers of platelets in your blood (this may make you bruise more easily).
- Purplish marks on your skin.
- Jaundice (causing yellowing of your skin or the whites of your eyes).

Very rare: may affect up to 1 in 10,000 people

- Decreased numbers of white blood cells
- Excess sugar in blood (hyperglycaemia)
- Swelling of the gums
- Abdominal bloating (gastritis)
- Abnormal liver function, inflammation of the liver (hepatitis), yellowing of the skin (jaundice), liver enzyme increase which may have an effect on some medical tests
- Increased muscle tension
- Inflammation of blood vessels, often with skin rash
- Sensitivity to light
- Disorders combining rigidity, tremor, and/or movement disorders

- Changes to some of the cells or other parts of your blood. Your doctor may take blood samples every so often to check whether Tenormin has had any effect on your blood

Not known (frequency cannot be estimated from the available data)
Lupus-like syndrome (a disease where the immune system produces antibodies that attacks mainly skin and joints).

Conditions that may get worse
If you have any of the following conditions, they may get worse when you start to take your medicine. This happens rarely affecting less than 1 in 1,000 people.

- Psoriasis (a skin condition)
- Being short of breath or having swollen ankles (if you have heart failure)
- Asthma or breathing problems
- Poor circulation.

- **Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist 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 Corvadil-A

Store in a dry place at a temperature not exceeding 30°C, protected from light.
Keep all medicines out of reach of children.

9.6. Contents of the pack and other information

The active substance in Corvadil-A are amlodipine 5mg (as besilate) and Atenolol I.P 50 mg.
Colour: Red Oxide of Iron

The excipients used are Starch, Dibasic Calcium, Magnesium Stearate, Talc, Sodium Lauryl Sulphate, Sodium Carboxymethyl Cellulose, Ferric Oxide Red, Sodium Starch Glycolate and Microcrystalline Cellulose.

Corvadil-A is available in blister pack of 15 tablets.

10. DETAILS OF MANUFACTURER

Torrent Pharmaceuticals Ltd.
32 No. Middle Camp, NH-10, East District, Gangtok. Sikkim-737 135.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Mfg Licence No.: M/563/2010 issued on 12.03.2019

12. DATE OF REVISION

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/CORVADIL-A 5, 50mg/NOV-19/01/PI