LOSARTAN POTASSIUM HYDROCHLOROTHIAZIDE

xxxxxxxx-5343

CO-NORMOTEN DS

100 mg/25 mg
Film-Coated Tablet
Angiotensin II Receptor
Antagonist-Diuretic Combination

FORMULATION
Each film-coated tablet contains:
Losartan Potassium ..... 100 mg
Hydrochlorothiazide ..... 25 mg

PRODUCT DESCRIPTION
Losartan Potassium + Hydrochlorothiazide (Co-Normoten DS) 100 mg/25 mg is a yellow colored, oval shaped, biconvex film coated tablets with breakline on both sides.

CLINICAL PHARMACOLOGY

Mechanism of Action
Angiotensin II [formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kinase II)] is a potent vasoconstrictor, the primary vasoactive hormone of the renin angiotensin system and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II selectively blocking the binding of angiotensin II to the AT1 receptor found in the many tissues (e.g. Vascular smooth muscle, adrenal gland). There is also an AT2 receptor found in many tissues but it is not known to be associated with cardiovascular homeostasis. Both Losartan and its principal active metabolite do not exhibit any partial agonist activity at the AT1 receptor and much greater activity at the AT1 receptor and much have greater activity (about 1000 fold) at the AT1 receptor than for the AT2 receptor. In vitro binding studies indicate that Losartan is a reversible, competitive inhibitor of the AT1 receptor. The active metabolite is 10 to 40 times more potent by weight than Losartan and appears to be reversible, non-competitive inhibitor of the AT1 receptor. Neither Losartan not its active metabolite inhibits ACE (kinase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin); nor do they bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolytes reabsorption, directly increasing excretion of sodium and chloride in approximately equal amounts. Indirectly, the diuretic action of Hydrochlorothiazide reduces plasma volume, with consequent increase in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so co-administration of an angiotensin II antagonist tends to reverse the potassium loss associated with these diuretics.

Pharmacokinetics
LOSARTAN: Losartan is an orally active ingredient that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. It is converted, in part, to an active carboxylic acid metabolite that is responsible for most of the angiotensin II receptor antagonism that follows losartan treatment. The terminal half-life of Losartan is about 2 hours and of the metabolite is about 6 to 9 hours. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan doses up to 200 mg and do not change over time. Neither losartan nor its metabolite accumulate in plasma upon repeated once-daily dosing. Following oral administration, Losartan is well absorbed and undergoes substantial first-pass metabolism. The systemic bioavailabilty of Losartan is approximately 33%. About 14% of an orally administered dose of Losartan is converted to the active metabolite. Mean peak concentrations of Losartan and its metabolite are reached in 1 hour and 3-4 hours respectively. While maximum plasma concentrations of Losartan and its active metabolite are approximately equal, the AUC of the metabolite is about 4 times as great as that of Losartan.
A meal slows absorption of Losartan and decreases its Cmax but has only minor effects on Losartan AUC or on the AUC of the metabolite (about 10% decrease). Both Losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2% respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses. Studies in rats indicate that Losartan crosses the blood-brain barrier poorly, if at all. Losartan metabolites have been identified n human plasma and urine. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed. Following oral and intravenous administration of 14C-labeled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and its active metabolite. In vitro studies indicate that cytochrome P450 2C9 and 3A4 are involved in the biotransformation of Losartan to its metabolites. Minimal conversion of losartan to the active metabolite (less than 1% of the dose compared to 14% of the dose in normal subjects) was seen in about one percent of individuals studies. The volume of distribution of losartan is about 34 liters and of the active metabolite is about 12 liters. Total plasma clearance of losartan and the active metabolite is about 600 mL/min and 50 mL/min, respectively, with renal clerance of about 75 mL/min and 25 mL/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in urine and about 6% is excreted in urine as active metabolite. Biliary excretion contributes to the excretion of Losartan and its metabolites. Following oral 14C-labeled losartan, about 35% of radioactivity is recovered in the urine and about 60% in the feces Hydrohlorothiazide is well absorbed. The plasma half-life of Hydrochlorothiazide varies between 5.6 to 14.8 hours. Hydrochlorothiazide crosses the placenta but not the blood brain barrier. It is excreted in breast milk. Hydrochlorothiazide is eliminated primarily by renal pathways and 95% of the absorbed dose is excreted in the urine as unchanged drug.
Special Populations: Pediatric: Losartan pharmacokinetics have not been investigated in patients<18 years of age. **Geriatric and Gender:** Losartan pharmacokinetics have been investigated in the elderly (65 -75years) and in both genders. Plasma concentrations of Losartan and its active metabolite are similar in elderly and young hypertensives. Plasma concentrations of losartan were about twice as high in female hypertensives as in male hypertensives, but concentrations of the active metabolite are similar in males and females. **Renal Insufficiency:** Following oral administration of Losartan plasma concentrations and AUCs of losartan and its active metabolite are increased by 50-90% in patients with mild (creatinine clearance of 50 to 74 mL/min) or moderate (creatinine clearance 30 to 49 mL/min) renal insufficiency. In this study, renal clearance was reduced by 55 -85% for both losartan and its active metabolite in patients with mild to moderate renal insufficiency. Neither losartan nor its active metabolite can be removed by hemodialysis. Following administration of Hydrochlorothiazide, the AUC of hydrochlorothiazide is increased by 70 and 700% for patients with mild and moderate renal insufficiency, respectively. In this study, renal clearance of hydrochlorothiazide decreased by 45 and 85% in patients with mild and moderate renal impairment, respectively. The usual regimens of therapy with Losartan + Hydrochlorothiazide may be followed as long as the patients creatinine clearance is >30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred than thiazides, so Losartan + Hydrochlorothiazide is not recommended. Hepatic Insufficiency: Following oral administration in patients with mild than moderate alcoholic cirrhosis of the liver, plasma concentrations of Losartan and its active metabolite were, respectively, 5 times and about 1.7 times those in young male volunteers. Compared to normal subjects, the total plasma clearance of losartan in patients with hepatic insufficiency was about 50% lower, and the total bioavailability was about 2 times higher. The lower starting dose of losartan recommended for use in patients with hepatic therefore not recommended.

INDICATION
It is indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy of hypertension, except when hypertension is severe enough that the value of achieving prompt blood pressure control exceeds the risk of initiating combination therapy in these patients.

CONTRAINDICATIONS
It is contraindicated in patients who are hypersensitive to Losartan potassium or Hydrochlorothiazide. Because of Hydrochlorothiazide component, it is contraindicated in patients with anuria or hypersensitivity to other sulphonamide-derived drugs.

DOSAGE AND ADMINISTRATION
Hypertension: Dosing must be individualized. The usual starting dose of losartan is 50 mg once daily, with 25 mg recommended for patients with intravascular volume depletion (e.g. Patients treated with diuretics) and patients with a history of hepatic impairment. Losartan can be administered once or twice daily doses of 25 to 100 mg. If the antihypertensive effect measured at trough using once-a-day dosing is adequate, a twice-a-day regimen at the same total daily dose or an increase in dose may give a more satisfactory response. Hydrochlorothiazide is effective in doses of 12.5 to 50 mg once daily and can be given at doses of 12.5 mg to 25 mg.
To minimize dose-dependent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy. The side effects of losartan are generally rare and apparently independent of dose; those hydrochlorothiazide are a mixture of dose-dependent (primarily hypokalemia) and dose independent phenomena (e.g. Pancreatitis), the former much more common than the latter. Therapy with any combination of losartan and hydrochlorothiazide will be associated with both sets of dose-dependent side effects.
Replacement Therapy: The combination may be substituted for the titrated components. Dose Titration by Clinical Effect: A patient whose blood pressure is not adequately controlled with losartan monotherapy or hydrochlorothiazide alone, may be switched to Losartan Potassium + Hydrochlorothiazide 50 mg / 12.5 mg once daily. If blood pressure remains uncontrolled after about 3 weeks of therapy, the dose may be increased to two tablets of Losartan Potassium + Hydrochlorothiazide 50 mg / 12.5mg once daily or one tablet Losartan Potassium + Hydrochlorothiazide 100 mg / 25 mg once daily. A patient whose blood pressure is inadequately controlled by 25 mg once daily of hydrochlorothiazide, or is controlled but experiences hypokalemia with this regimen, may be switched to Losartan potassium + Hydrochlorothiazide 50 mg / 12.5 mg once daily, reducing the dose of hydrochlorothiazide without reducing the overall expected antihypertensive response. The clinical response to Losartan Potassium + Hydrochlorothiazide 50 mg / 12.5 mg should be subsequently evaluated, and if blood pressure remains uncontrolled after about 3 weeks of therapy, the dose may be increased to two tablets of Losartan Potassium + Hydrochlorothiazide 50 mg / 12.5 mg once daily or one tablet of Losartan Potassium + Hydrochlorothiazide 100 mg / 25 mg once daily
The usual dose of Losartan Potassium + Hydrochlorothiazide 50 mg / 12.5 mg is one table once daily. More than two tablets of Losartan Potassium + Hydrochlorothiazide 50 mg / 12.5 mg once daily or more than one tablet of Losartan Potassium + Hydrochlorothiazide 100 mg / 25 mg once daily is not recommended. The maximal antihypertensive effect is attained about 3 weeks after initiation of therapy. Use in Patients with renal Impairment: The usual regimens of therapy with Losartan Potassium + Hydrochlorothiazide may be followed as long as the patients creatinine clearance is >30 mL/min. Patients with Hepatic Impairment: Losartan Potassium + Hydrochlorothiazide is not recommended for titration in patients with hepatic impairment because the appropriate 25 mg starting dose of losartan cannot be given. Severe Hypertension: The starting dose for initial treatment of severe hypertension is one tablet of Losartan Potassium + Hydrochlorothiazide 50 mg / 12.5 mg once daily. For patients who do not respond adequately with Losartan Potassium + Hydrochlorothiazide 50 mg / 12.5 mg after 2 to 4 weeks of therapy, the dosage may be increased to one tablet of Losartan Potassium + Hydrochlorothiazide 50 mg / 25 mg once daily. The maximum dose is one tablet of Losartan Potassium + Hydrochlorothiazide 50 mg / 12.5 mg once daily.

ADVERSE EFFECTS
No side effects peculiar to this combination have been observed. Side effects have been limited to those that were reported previously with Losartan Potassium and /or Hydrochlorothiazide.
Losartan is generally well tolerated in a controlled clinical trial in hypertensive patients with left ventricular hypertrophy. The most common drug-related side-effects were dizziness, asthenia/fatigue and vertigo. The following adverse reactions have been reported: Hypersensitivity: Anaphylactic reactions, angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue have been reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Vasculitis, including Henoch-Schlonlein purpura, has been reported rarely. Gastro-Intestinal: Hepatitis (reported rarely), diarrhea, liver function abnormalities. Hematologic : Anemia Musculoskeletal: Mylagia, arthralgia. Nervous System / Psychiatric : Migraine Respiratory: Cough Skin: Urticaria, pruritus, rash.
Hydrochlorothiazide side effects: Body as a whole: weakness; Digestive: pancreatitis, jaundice (intrahepatic cholestatic janudice) sialadenitis, cramping, gastric irritations; Hematologic: aplastic anemia, agranulocytois, leukopenia, hemolytic anemia, thrombocytopenia; Hypersensitivity: purpura, photosensitivity, urticaria, necrotizingganglitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema; Metabolic: hyperglycemia, glycosuria, hyperuricemia; Musculoskeletal: muscle spasm; Nervous System /Psychiatric: restlessness; Renal: renal failure, renal dysfunction, interstitial nephritis; Skin: erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxicepiderma necrolysis; Special Sense: transient blurred vision; xanthopsia.
"For suspected adverse drug reaction, report to FDA: www.fda.gov.ph or to TORRENT: www.torrentpharma.com".
Patient to seek medical attention immediately at the first sign of any adverse drug reaction shall appear.

WARNINGS
Fetal / Neonatal / Morbidity and Mortality: Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, Losartan Potassium + Hydrochlorothiazide should be discontinued as soon as possible. The use of drugs that act directly on the renin-angiotensin system during the second or third trimester of pregnancy has been associated with fetal or 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 conctractures, 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. Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.
Hypotension - Volume Depleted Patients: In patients who are intravascularly volume-depleted (e.g those treated with diuretics) symptomatic hypotension may occur after initiation of therapy and this condition should be corrected prior to administration.
Impaired Hepatic Function: It is not recommended for patients with hepatic impairment who require titration with losartan. The lower starting dose of losartan recommended for use in patients with hepatic impairment cannot be given using losartan potassium + Hydrochlorothiazide. Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte imbalance may precipitate hepatic coma.
Hypersensitivity reactions: Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without history of allergy or bronchial asthma, but are more likely in patients with such a history.
Systemic Lupus Erythematosus: Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.
Lithium Interaction: Lithium should not be generally given with thiazide.

PRECAUTIONS
Pregnancy and Lactation: Female patients of childbearing age should be told about the consequences of second and third- trimester exposure to drugs that act on the renin-angiotensin system, and they should be told that these consequences does not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physician as soon as possible.

DRUG INTERACTIONS
Losartan potassium does not affect the pharmaceutics or pharmacodynamic of a single dose of Warfarin and also intravenous or oral digoxin. Coadministration of Losartan potassium and cimetidine leads to an increase of about 18% in AUC of Losartan potassium but does not affect the pharmacokinetics of its active metabolite. There is no pharmacokinetic interaction between Losartan Potassium and hydrochlorothiazide. When administered concomitantly the drugs, which may interact are: Alcohol, barbiturates or narcotics, antidiabetic drugs, other antihypertensive drugs, cholestyramine and colestipol resins, corticosteroids, pressor amines (e.g. norepinephrine) skeletal muscle relaxants, lithium, Non-Steroidal Anti-inflammatory Drugs (NSAIDS).

OVERDOSAGE
Losartan Potassium - Significant lethality was observed on mice and rats, after oral administration of 1000mg/kg and 2000mg/kg of Losartan potassium respectively about 44 and 170 times the maximum. recommended human dose on a mg/m^2 basis The most likely manifestation of overdosage will be hypotension and tachycardia, bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension occurs, supportive treatment should be instituted.
Hydrochlorothiazide - The oral LD_{50} of Hydrochlorothiazide is greater than 10g/kg in both mice and rats. The most common signs and symptoms are those caused by electrolyte depletion, such as hypokalemia, hypochloremia, hyponatremia and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia might accentuate cardiac arrhytmias, The degree to which Hydrochlorothiazide is removed by hemodialysis has not been established.

STORAGE
Store at temperatures not exceeding 30°C.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

AVAILABILITY
Losartan Potassium + Hydrochlorothiazide (Co-Normoten DS) 100 mg/ 25 mg Film-Coated Tablet- Alu-Alu Blister Pack x 10's (Box of 30's) – DRP-2686

DATE OF FIRST AUTHORIZATION
July 30, 2009

DATE OF REVISION
November, 2016

torrent PHARMA

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
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Imported and Distributed by :
TORRENT PHARMA PHILIPPINES INC.
Units 3 & 4, 34th Floor, Zuellig Building
Makati Avenue Corner Paseo de Roxas
Makati City, PHILIPPINES

PRODUCT NAME	:	Co-Normoten DS	**COUNTRY :** Philippines	**LOCATION :** Chhatral	**Supersedes A/W No.:**		
ITEM / PACK	:	Insert	**NO. OF COLORS:** 1	**REMARK : Folded Size 30 mm**			
DESIGN STYLE	:	-	**PANTONE SHADE NOS.:**	**SUBSTRATE :**			
CODE	:	xxxxxxxx-5343	Black	**Activities**	**Department**	**Name**	**Signature**	**Date**
DIMENSIONS (MM)	:	150 x 200		Prepared By	**Pkg.Dev**			
ART WORK SIZE	:	S/S		Reviewed By	**Pkg.Dev**			
DATE	:	15-11-2016		Approved By	**Quality**			