PRODUCT NAME	:	TORVAL H	**COUNTRY :** Philippines		**LOCATION :** INDRAD		**Supersedes A/W No.:**
ITEM / PACK	:	Insert	**NO. OF COLORS:** 1		**REMARK :**		
DESIGN STYLE	:	Front/Back	**PANTONE SHADE NOS.:**		**SUBSTRATE :**		
CODE	:	xxxxxxxx-5343	**Activities**	**Department**	**Name**	**Signature**	**Date**
DIMENSIONS (MM)	:	150 x 260	Prepared By	**Pkg.Dev**			
ART WORK SIZE	:	S/S	Reviewed By	**Pkg.Dev**			
DATE	:	08-08-2016	Approved By	**Quality**			

xxxxxxxx-5343

VALSARTAN + HYDROCHLOROTHIAZIDE

TORVAL H 80 / 12.5
TORVAL H 160 / 12.5
TORVAL H 160 / 25

80mg / 12.5mg Film-Coated Tablet
160mg / 12.5mg Film-Coated Tablet
160mg / 25mg Film-Coated Tablet
Antihypertensive

FORMULATION:
Each film-coated tablet contains:
Valsartan, USP ……..…. 80 mg
Hydrochlorothiazide ……..…12.5 mg
Each film-coated tablet contains:
Valsartan, USP ……...……160 mg
Hydrochlorothiazide ……..…12.5 mg
Each film-coated tablet contains:
Valsartan, USP ……..…… 160 mg
Hydrochlorothiazide ……..……..…… 25 mg

PRODUCT DESCRIPTION:
Valsartan + Hydrochlorothiazide (Torval H 80/12.5) 80 mg / 12.5 mg is a white to off white colored, oval shaped, beveled edge, biconvex film coated tablet debossed with "1071" on one side and plain on other side.
Valsartan + Hydrochlorothiazide (Torval H 160/12.5) 160 mg / 12.5 mg is a pink colored, oval shaped, beveled edge, biconvex film coated tablet debossed with "1072" on one side and plain on other side.
Valsartan + Hydrochlorothiazide (Torval H 160/25) 160 mg / 25 mg is a yellow colored, oval shaped, beveled edge, biconvex film coated tablet with breakline on both sides

CLINICAL PHARMACOLOGY:
Valsartan is a nonpeptide, orally active and specific angiotensin II antagonist acting on the AT1 receptor subtype. Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland.
Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma rennin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The rennin-aldosterone link is mediated by angiotensin II, so co-administration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics. The mechanism of the antihypertensive effect of thiazides is unknown.

PHARMACOKINETICS:
Valsartan is rapidly absorbed following oral administration, with a bioavailability of about 23%. Peak plasma concentrations of Valsartan occur 2 to 4 hours after an oral dose. It is between 94 and 97% bound to plasma proteins. Valsartan is not significantly metabolized and is excreted mainly via the bile as unchanged drug. The terminal elimination half-life is about 5 to 9 hours. Following an oral dose of about 83% is excreted in the feces and about 13% in urine.
Hydrochlorothiazide is rapidly absorbed from the gastrointestinal tract. It is reported to have a bioavailability of about 65 to 70%. It has been estimated to have a plasma half-life of between about 5 and 15 hours and appears to be preferentially bound to red blood cells. It is excreted mainly unchanged in the urine. Hydrochlorothiazide crosses the placental barrier and is distributed into breast milk.

INDICATIONS:
Valsartan and hydrochlorothiazide is indicated for the treatment of hypertension. This fixed-dose combination is not indicated for initial therapy.

CONTRAINDICATIONS:
Valsartan and Hydrochlorothiazide is contraindicated in patients with known hypersensitivity to any of its components. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS:
Valsartan
Fetal/Neonatal Morbidity and Mortality
Valsartan cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting enzyme inhibitors. There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction when pregnant women have inadvertently taken valsartan. When pregnancy is detected, Valsartan and hydrochlorothiazide should be discontinued as soon as possible. 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.
Hydrochlorothiazide
Impaired Hepatic Function
Thiazide diuretics should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
Hypersensitivity Reaction
Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a 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 generally should not be given with thiazides (see PRECAUTIONS, Drug Interactions, Hydrochlorothiazide, Lithium).

PRECAUTIONS:
Hypertensives:
Patients taking combination of Valsartan and Hydrochlorothiazide may develop hypokalemia, hyperkalemia, decrease in serum potassium. Thus, periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.
Valsartan
Valsartan should be used with caution in patients with hepatic impairment, cirrhosis, or biliary obstruction. Valsartan is excreted in urine and in bile and in reduced doses may therefore be required in patients with renal impairment and should be considered in patients with hepatic impairment. Patients with volume depletion (for example those who have received high-dose diuretic therapy) may experience hypotension; volume depletion should be corrected before starting therapy, or a low initial dose should be used. Since hyperkalemia may occur, serum-potassium concentrations should be monitored, especially in the elderly and patients with renal impairment, and the concomitant use of potassium-sparing diuretics should generally be avoided.
Hydrochlorothiazide
All diuretics produce changes in fluid and electrolyte balance. They should be used with caution in patients with existing fluid and electrolyte disturbances or who are at risk from changes in fluid and electrolyte balance, such as the elderly. They should be avoided in patients with severe hepatic impairment, in whom encephalopathy may be precipitated. Patients with hepatic cirrhosis are also most likely to develop hypokalemia. Hyponatremia may occur in patients with severe heart failure who are very edematous, particularly with large doses of thiazides and restricted salt intake. Thiazides should not be given to patients with Addison's disease.
Should also be given with caution in renal impairment since they can further reduce renal function. Most thiazides are not effective in patients with a creatinine clearance of less than 30mL/minute. They should not be used in patients with severe renal impairment or anuria.
Thiazides may precipitate attacks of gout in susceptible patients. They may cause hyperglycemia and aggravate or unmask diabetes mellitus. Thiazides can reduce urinary excretion of calcium, sometimes resulting in mild hypercalcemia; they should not be given to patients with pre-existing hypercalcemia.

ADVERSE REACTIONS:
Valsartan
The most common adverse effects include headache, dizziness, vertigo, fatigue, diarrhea, abdominal pain, muscle cramps, dry cough, hypotension, nausea, pruritus, rash, constipation, dry mouth, impotence. Other reported events seen less frequently include chest pain, syncope, anorexia, vomiting, and angioedema.
Hydrochlorothiazide
Hydrochlorothiazide and other thiazide diuretics may cause a number of metabolic disturbances especially at high doses. They may provoke hyperglycemia and glycosuria in diabetic and other susceptible patients. They may cause hyperuricemia and precipitate attacks of gout in some patients. Administration of thiazide diuretics may be associated with electrolyte imbalances including hypochloraemic alkalosis, hyponatremia, and hypokalemia.
Signs of electrolyte imbalance include dry mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain and cramps, seizures, oliguria, hypotension, and gastrointestinal disturbances.
Other side effects include anorexia, gastric irritation, nausea, vomiting, constipation, diarrhea, sialadenitis, headache, dizziness, photosensitivity reactions, orthostatic hypotension, paraesthesia, impotence, and yellow vision. Hypersensitivity reactions include skin rashes, fever, pulmonary edema, pneumonitis, anaphylaxis, and toxic epidermal necrolysis. Cholestatic jaundice, pancreatitis and blood dyscrasias including thrombocytopenia and, more rarely, granulocytopenia, leucopenia, and aplastic and haemolytic anemia have been reported.
"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.

DRUG INTERACTIONS:
Valsartan
No clinically significant pharmacokinetic interactions were observed when Valsartan was co-administered with amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin. The valsartan-atenolol combination was more antihypertensive than either component, but it did not lower the heart rate more than atenolol alone. Co-administration of Valsartan and warfarin did not change the pharmacokinetics of Valsartan or the time-course of the anticoagulant properties of warfarin. CYP 450 Interactions: The enzyme(s) responsible for Valsartan metabolism have not been identified but do not seem to be CYP 450 isoenzymes. The inhibitory or induction potential of Valsartan on CYP 450 is also unknown.
Hydrochlorothiazide
When administered concurrently the following drugs may interact with thiazide diuretics:
Alcohol, barbiturates, or narcotics - Potentiation of orthostatic hypotension may occur.
Antidiabetic drugs (oral agents and insulin) Dosage adjustment of the antidiabetic drug may be required.
Other antihypertensive drugs - Additive effect or potentiation.
Cholestyramine and colestipol resins - Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43% respectively.
Corticosteroids, ACTH - Intensified electrolyte depletion, particularly hypokalemia. Pressor amines (e.g., norepinephrine) - Possible decreased response to pressor amines but not sufficient to preclude their use.
Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine) - Possible increased responsiveness to the muscle relaxant. Lithium - Should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with valsartan and hydrochlorthiazide.
Non-steroidal anti-inflammatory Drugs - In some patients, the administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when Valsartan and hydrochlorothiazide and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

DOSAGE AND ADMINISTRATION:
The recommended starting dose of Valsartan is 80 mg or 160 mg once daily when used as monotherapy in patients who are not volume depleted. Patients requiring greater reductions may be started at the higher dose. Valsartan may be used over a dose range of 80 mg to 320 mg daily, administered once-a day. 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 as valsartan and hydrochlorothiazide. To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.
Dose titration: A patient whose blood pressure is not adequately controlled with valsartan monotherapy may add hydrochlorothiazide by switching to Valsartan and Hydrochlorothiazide (Valsartan 80 mg/hydrochlorothiazide 12.5 mg or valsartan 160 mg/hydrochlorothiazide 12.5 mg) once daily. If blood pressure remains uncontrolled after about 3-4 weeks of therapy, either valsartan or both components may be increased depending on clinical response. A patient whose blood pressure is inadequately controlled by 25 mg once daily of hydrochlorothiazide, or is controlled but who experiences hypokalemia with this regimen, may be switched to valsartan and hydrochlorothiazide (valsartan 80 mg/hydrochlorothiazide 12.5 mg or valsartan 160 mg/hydrochlorothiazide 12.5 mg) once daily, reducing the dose of hydrochlorothiazide without reducing the overall expected antihypertensive response. The clinical response to valsartan and hydrochlorothiazide should be subsequently evaluated and if blood pressure remains uncontrolled after 3-4 weeks of therapy, the dose may be titrated up to valsartan 160 mg/hydrochlorothiazide 25 mg. The maximal antihypertensive effect is attained about 4 weeks after initiation of therapy.
Patients with Renal Impairment: The usual regimens of therapy with valsartan and hydrochlorothiazide may be followed as long as the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so valsartan and hydrochlorothiazide is not recommended.
Patients with Hepatic Impairment: Care should be exercised with dosing of valsartan and hydrochlorothiazide in patients with hepatic impairment.
No initial dosage adjustment is required for elderly patients. Valsartan and hydrochlorothiazide may be administered with other antihypertensive agents. Valsartan and hydrochlorothiazide may be administered with or without food.

STORAGE CONDITION:
Store at temperatures not exceeding 30°C. Protect from moisture.

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

AVAILABILITY:
Valsartan + Hydrochlorothiazide (Torval H 80 / 12.5) 80mg + 12.5mg Film-Coated Tablet - Alu-Alu Blister Pack of 10's (Box of 30's and 100's) - DRP-3956
Valsartan + Hydrochlorothiazide (Torval H 160 / 12.5) 160mg + 12.5mg Film-Coated Tablet - Alu-Alu Blister Pack of 10's (Box of 30's and 100's) - DRP-3953
Valsartan + Hydrochlorothiazide (Torval H 160 / 25) 160mg + 25mg Film-Coated Tablet - Alu-Alu Blister Pack of 10's (Box of 30's and 100's) - DRP-3954

DATE OF FIRST AUTHORIZATION
May 17, 2012

DATE OF REVISION
August 2016

torrent PHARMA

Manufactured by :
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