1.4 PRODUCT INFORMATION

1.4.1 Prescribing information (Summary of Product Characteristics)

Enclosed herewith

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF MEDICINAL PRODUCT

Trade Name: BRANTA

Generic Name: Losartan potassium USP + Amlodipine Besilate Ph.Eur Tablets 50 mg/ 5 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film coated tablet contains:
Losartan Potassium USP…….....50mg
Amlodipine Besilate equivalent to Amlodipine Ph.Eur. ..…5 mg
Colors: Lake of Sunset Yellow and Titanium dioxide

3. PHARMACEUTICAL FORM

Orange colored round biconvex film coated tablets with break line on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BRANTA is indicated in treatment of mild to moderate hypertension. It is also indicated in treatment of hypertension associated with ischaemic heart disease and diabetes mellitus.

4.2 Posology and method of administration

The recommended dose of BRANTA is one tablet once daily taken with or without food.
Method of administration:
Oral use
Swallow whole tablet. Do not crush or chew.

4.3 *Contraindications*

BRANTA is contraindicated in patients allergic to angiotensin receptor blocker or dihydropyridine calcium channel antagonist. Patients with a history of angioedema or any other adverse effect related to previous treatment with an angiotensin receptor blocker or calcium channel antagonist.

4.4 Special warnings and precautions for Use

WARNINGS
Hypotension: Losartan Potassium can cause symptomatic hypotension. Symptomatic hypotension is most likely to occur in patients who have been volume and/ or salt-depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume and/ or salt depletion should be corrected before initiating therapy with Losartan Potassium and Amlodipine combination.
Hepatic Failure: Rarely, angiotensin receptor inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients

receiving this combination who develop jaundice or marked elevations of hepatic enzymes should discontinue the therapy and receive appropriate medical follow-up.

PRECUATION

Impaired Liver Function: Losartan Potassium and Amlodipine combination should be given with caution in patients with impaired hepatic function since the half life of amlodipine is prolonged in patients with impaired liver function.

Impaired Renal patients: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the reninangiotensin-
aldosterone system, treatment with angiotensin receptor blocker may be associated with oliguria and/ or progressive azotemia and (rarely) with acute renal failure and/ or death.

4.5 Interactions with other medicinal products and other forms of interaction

Losartan Potassium

Losartan Potassium administered for 12 days, did not affect the pharmacokinetics or pharmacodynamics of a single dose of warfarin. Losartan Potassium did not affect the pharmacokinetics of oral and intravenous digoxin. Co administration of Losartan Potassium and cimetidine led to an increase of about 18% in AUC of Losartan Potassium but did not affect the pharmacokinetics of E3174. Co administration of Losartan Potassium and phenobarbital led to reduction of about 20% in the AUC of Losartan Potassium and E3174. There is no pharmacokinetic interaction between Losartan Potassium and Hydrochlorothiazide.Inhibitors of Cytochrome P34A are unlikely to have significant drug interactions while potent inducers of Cytochrome P34A might cause a significant interaction.

As with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium.

Amlodipine

Amlodipine has been safely administered with thiazide diuretics, beta adrenoceptor blocking drugs, angiotensin converting enzyme inhibitors, long acting nitrates, sublingual glyceryl trinitrate, nonsteroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic agents. Co administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers. Co administration of cimetidine did not alter the pharmacokinetics of amlodipine.

In healthy volunteers, co administration of amlodipine did not significantly alter the effect of warfarin on prothrombin time. The introduction of amlodipine is not likely to result in the need for modification of an established warfarin regimen.

4.6 Fertility, Pregnancy and Lactation

Pregnancy: There is no clinical experience with BRANTA in pregnancy or lactation. So, BRANTA should not be administered during pregnancy or lactation or to women of childbearing potential unless effective contraception is ensured.

Nursing Mothers: Women receiving BRANTA should not breast-feed.

Use in children: Since there is no clinical experience of BRANTA, use of this product is not currently recommended for children and adolescents of less than 18 years of age.

4.7 Effects on Ability to Drive and use Machines

There are no data available on the effect on driving vehicles.

4.8 Undesirable Effects

Losartan Potassium
In general, treatment with Losartan Potassium was well tolerated. Following adverse events, whether or not attributed to the treatment, occurring in at least 1% of patients treated with Losartan Potassium and that were more frequent in Losartan Potassium than placebo.
Digestive: Diarrhea, dyspepsia.
Musculoskeletal: Muscle cramp, myalgia, back pain, leg pain.
Nervous System/Psychiatric: Dizziness, insomnia.
Respiratory: Nasal congestion, cough, upper respiratory tract infection, sinus disorder, sinusitis.
The following adverse events were also reported at a rate 1% or greater in patients treated with Losartan, but were as, or more frequent, in the placebo group: asthenia/fatigue, oedema/ swelling, abdominal pain, chest pain, nausea, headache, pharyngitis.

Amlodipine
The most commonly observed side effects are edema, flushing, palpitation, fatigue, headache, somnolence, abdominal pain and dizziness.
The following events occurred in <1% but >0.1% of patients in controlled clinical trials: (Use capital letter or follow the same system as for losartan)

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, and vertigo.

Gastrointestinal: Anorexia, constipation, dyspepsia, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia.
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.

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.

4.9 Overdose

Losartan

Symptom: The most likely manifestation of overdosage would be hypotension and tachycardia. Bradycardia could occur from parasympathetic (vagal) stimulation.
Treatment: If symptomatic hypotension occurs, supportive treatment should be instituted. Neither Losartan Potassium nor E-3174 can be removed by haemodialysis.

Amlodipine

Symptoms: Available data suggests that the gross over dosage could result in excessive peripheral vasodilation with marked and probably prolonged hypotension and possibly a reflex tachycardia.
Treatment: Since absorption of amlodipine is slow, gastric lavage should be performed. Active cardiovascular support including monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output should be given. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. A vasoconstrictor agent may be helpful in restoring vascular tone and blood pressure provided that there is no contraindication to its use. Since Amlodipine is highly protein bound, dialysis is unlikely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 *Pharmacodynamic Properties*

Pharmacotherapeutic group: Angiotension II receptor blocker (ARBs) and Calcium Channel Blockers
ATC code: C09DB06

Losartan

It is an angiotensin II receptor (type AT1) antagonist. Angiotensin II is a potent vasoconstrictor and an important component in the pathophysiology of hypertension. Losartan Potassium blocks the vasoconstrictor and aldosterone secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland).

Amlodipine

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. The contractile process of cardiac muscle and

vascular smooth muscle are dependent upon movement of extra cellular calcium ions into these cells through specific ion channels. By inhibiting calcium ion influx, it directly dilates vascular smooth muscle, resisting hypertension. The mechanism of relieve angina pectoris with amlodipine is not yet determined completely, but it is clear that this product can abate myocardial ischemia through the following functions:
1. Dilate the peripheral small artery, decreasing peripheral resistance, causing the reduction of energy consumption and oxygen requirement of cardiac muscle.
2. Dilate the coronary artery and the small coronary artery at normal and ischaemic areas, increasing the oxygen supply of cardiac muscle in patients with coronary spasm.

5.2 Pharmacokinetic Properties

Losartan Potassium
The pharmacokinetics of Losartan Potassium and its active metabolite (E3174) are linear with oral doses up to 200mg and do not change over the time. Neither Losartan, nor its metabolite accumulates in plasma upon repeated once a day dosing. Following oral administration, Losartan Potassium has a systemic bioavailability of around 33%. Losartan Potassium 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 Potassium treatment. About 14% of an orally administered dose is converted to the active metabolite. After oral administration Losartan Potassium is rapidly absorbed, reaching peak plasma concentrations within an hour. Losartan Potassium and E3174 have been reported to reach peak plasma concentration of 296 ng/ml and 249 ng/ml in 1.0 and 4.1 hours respectively after single oral dose of 50mg in healthy volunteers. The area under the plasma concentration time curve (AUC) for E-3174 is approximately 4 fold greater than for Losartan Potassium (1915 vs. 476 ng.h/ml). Absorption is slowed and Cmax reduced by food. Losartan Potassium and E3174 are highly protein bound (98.7% and 99.8 %) with volumes of distribution of 34L and 12L respectively. Approximately 35% of the drug is eliminated in the urine and approximately 60% is excreted in the feces. Losartan Potassium and E3174 have elimination half-lives of 2.1 and 6.4 hours respectively. The rate of renal clearance of Losartan Potassium and E3174 is 4.3 and 1.6L/h.

Amlodipine
After oral administration of therapeutic doses of amlodipine, absorption occurs gradually with peak plasma concentration occurring between 6 and 9 hours. The median Tmax reported for amlodipine was 8.00 hours respectively after single oral dose of 5mg in healthy volunteers. Absolute bioavailability has been estimated to be between 64 and 90%. The bioavailability of amlodipine is not altered by the presence of food. Amlodipine has a large volume of distribution (Vd) of 21L/Kg and is highly plasma protein bound (95%). Amlodipine undergoes extensive, but slow hepatic metabolism. The dihydropyridine moiety is oxidized to the pyridine analogue during initial biotransformation, with minimal first-pass or presystemic metabolism. Metabolites have no significant activity. Less than 10% of an oral dose is excreted unchanged. Following oral administration 60% of oral dose is recovered in the urine mainly as metabolites and 20 to 25% in the faeces. The elimination half-life of Amlodipine is in the range of 35 to 50 hours in healthy subjects.

5.3 Preclinical Safety Data

No data of therapeutic relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Dibasic Calcium Phosphate Anhydrous
Starch (Maize Starch)
Sodium Starch Glycollate
Polyvinyl pyrrolidone (K-30)
Isopropyl alcohol
Microcrystalline Cellulose (Avicel PH 102)
Colloidal Silicon Dioxide
Magnesium Stearate
Hydroxypropyl methyl cellulose 6 cps
Polyethylene Glycol 6000
Titanium Dioxide (E-171)
Talc
Lake of Sunset Yellow (E-110)
Purified Water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months from the date of manufacturing

6.4 Special Precautions for Storage

Store below 30°C.

6.5 Nature and Contents of Container

It is packed in Alu-Alu blister pack using a CFB foil sealed with printed Aluminium foil. Each Alu-Alu blister strip contains 10 Tablets.

6.6 Special Precautions for Disposal and other Handling

Not applicable

7. MARKETING AUTHORIZATION HOLDER

Torrent Pharmaceuticals Ltd.,
"Torrent House",
Off Ashram Road,
Ahmedabad – 380 009
INDIA.
Tel. No.: 91-79-6583060 / 6585090

Fax. No.: 91-79-6582100

8. MARKETING AUTHORIZATION NUMBER

H2014/CTD1396/162

9. DATE OF AUTHORIZATION OR OF THE LAST RENEWAL OF THE AUTHORIZATION

NOT APPLICABLE

10. DATE OF REVISION OF TEXT

NOT APPLICABLE

1.4.2 Container Labelling

Enclosed herewith

PRODUCT NAME	:	Branta	COUNTRY : Kenya	LOCATION : Indrad		Supersedes A/W No.:	Nil	
ITEM / PACK	:	Blister	NO. OF COLORS: 3	REMARK :				
DESIGN STYLE	:	Reverse Tuck	PANTONE SHADE NOS.:	SUBSTRATE : 0.025x138 HTPAF				
CODE	:	8049776-6712	[redacted] 2645 C	Activities	Department	Name	Signature	Date
DIMENSIONS (MM)	:	138	[redacted] 273 C	Prepared By	Pkg.Dev	[redacted]	[redacted]	21/7/2014
ART WORK SIZE	:	S/S		Reviewed By	Pkg.Dev	[redacted]	[redacted]	21/07/14
DATE	:	19-06-2014	[redacted] Black	Reviewed By	RA	Ram Shamler	[redacted]	22/07/14
				Approved By	CQA	Dr Parth Shah	[redacted]	24/07/14

This colour proof is not colour binding. Follow Pantone shade reference for actual colour matching.

3527

108 mm Advance

138 mm Foil Width

BRANTA **TORRENT**

LOSARTAN POTASSIUM AND AMLODIPINE BESILATE TABLETS 50 MG+5 MG

[redacted] BRANTA

Each film coated tablet contains :
Losartan Potassium U.S.P. 50 mg
Amlodipine Besilate Ph.Eur. equivalent to Amlodipine 5 mg
Colours : Lake of Sunset Yellow & Titanium Dioxide
Dose : As directed by the Physician

torrent PHARMA

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721,
Dist. Mehsana, INDIA.

STORE BELOW 30°C

Mfg. Lic. No. : G/926

8049776-6712

BRANTA TORRENT

BRANTA **TORRENT**

LOSARTAN POTASSIUM AND AMLODIPINE BESILATE TABLETS 50 MG+5 MG

[redacted] BRANTA

Each film coated tablet contains :
Losartan Potassium U.S.P. 50 mg
Amlodipine Besilate Ph.Eur. equivalent to Amlodipine 5 mg
Colours : Lake of Sunset Yellow & Titanium Dioxide
Dose : As directed by the Physician

torrent PHARMA

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721,
Dist. Mehsana, INDIA.

STORE BELOW 30°C

Mfg. Lic. No. : G/926

8049776-6712

BRANTA TORRENT

BRANTA **TORRENT**

LOSARTAN POTASSIUM AND AMLODIPINE BESILATE TABLETS 50 MG+5 MG

[redacted] BRANTA

Each film coated tablet contains :
Losartan Potassium U.S.P. 50 mg
Amlodipine Besilate Ph.Eur. equivalent to Amlodipine 5 mg
Colours : Lake of Sunset Yellow & Titanium Dioxide
Dose : As directed by the Physician

torrent PHARMA

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721,
Dist. Mehsana, INDIA.

STORE BELOW 30°C

Mfg. Lic. No. : G/926

8049776-6712

BRANTA TORRENT

Web Advance Direction

1.4.3 Patient information leaflet (PIL)

Enclosed herewith

1391

PRODUCT NAME	: Branta	COUNTRY : Kenya	LOCATION : Indrad	Supersedes A/W No. :	N11
ITEM / PACK	: Insert	NO. OF COLOURS : 1	REMARK :		
DESIGN STYLE	: Front-Back	PANTONE SHADE NOS :	SUBSTRATE : 55 gsm, Maplitho Paper		
CODE	: 8049779-6713	Black	Activities	Department	Name	Signature	Date
DIMENSIONS (MM)	: 150 x 240		Prepared By	Pkg. Dev	Dhara Gaur		21/7/14
THERAPEUTIC RANGE	: Anti-Infective		Reviewed By	Pkg. Dev	Jagruti Nayak		21/7/14
ART WORK SIZE	: S/S			RA	Ram Gomber		22/7/14
DATE	: 19-06-2014		Approved By	COA	Dr. Rizvi		24/7/14

This colour proof is not colour binding. Follow Pantone shade reference for actual colour matching.

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory 8049779-6713

BRANTA

(Losartan Potassium and Amlodipine Besilate Tablets 50 mg+5 mg)

COMPOSITION

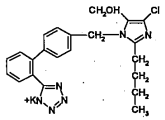
Each film coated tablet contains:

Losartan Potassium U.S.P.	50 mg
Amlodipine Besilate Ph.Eur. equivalent to Amlodipine	5 mg

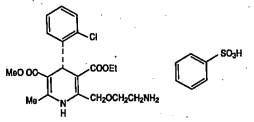
Colours : Lake of Sunset Yellow & Titanium Dioxide

PROPERTIES

Losartan Potassium is the first of a new class of antihypertensive. It is an angiotensin II receptor (type AT_1) antagonist. It is white to light yellow crystalline powder soluble in water, methanol and ethanol and insoluble in chloroform. Losartan is the potassium salt of 2 n butyl 4 chloro 1 [2' (tetrazol 5 yl) 1,1'biphenyl–4 ylmethyl]–1H–imidazole–5 methanol. Its empirical formula is $C_{22}H_{22}ClKN_6O$ and the molecular weight is 461. The structure of Losartan Potassium is:



Amlodipine Besylate is a white crystalline powder with a molecular weight of 567.1. It is slightly soluble in water and sparingly soluble in ethanol. Chemically it is described as (R.S.) 3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5- pyridinedicarboxylate benzenesulphonate. Its empirical formula is $C_{20}H_{25}ClN_2O_5{\cdot}C_6H_6O_3S$, and its



PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Losartan

It is an angiotensin II receptor (type AT_1) antagonist. Angiotensin II is a potent vasoconstrictor and an important component in the pathophysiology of hypertension. Losartan Potassium blocks the vasoconstrictor and aldosterone secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland).

Amlodipine

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. The contractile process of cardiac muscle and vascular smooth muscle are dependent upon movement of extra cellular calcium ions into these cells through specific ion channels. By inhibiting calcium ion influx, it directly dilates vascular smooth muscle, resisting hypertension. The mechanism of relieve angina pectoris with amlodipine is not yet determined completely, but it is clear that this product can abate myocardial ischemia through the following functions:

1. Dilate the peripheral small artery, decreasing peripheral resistance, causing the reduction of energy consumption and oxygen requirement of cardiac muscle.
2. Dilate the coronary artery and the small coronary artery at normal and ischaemic areas, increasing the oxygen supply of cardiac muscle in patients with coronary spasm.

Pharmacokinetics

Losartan Potassium

The pharmacokinetics of Losartan Potassium and its active metabolite (E3174) are linear with oral doses up to 200mg and do not change over the time. Neither Losartan, nor its metabolite accumulates in plasma upon repeated once a day dosing. Following oral administration, Losartan Potassium has a systemic bioavailability of around 33%.

Losartan Potassium 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 Potassium treatment. About 14% of an orally administered dose is converted to the active metabolite. After oral administration Losartan Potassium is rapidly absorbed, reaching peak plasma concentrations within an hour. Losartan Potassium and E3174 have been reported to reach peak plasma concentration of 296 ng/ml and 249 ng/ml in 1.0 and 4.1 hours respectively after single oral dose of 50mg in healthy volunteers. The area under the plasma concentration time curve (AUC) for E-3174 is approximately 4 fold greater than for Losartan Potassium (1915 vs. 478 ng.h/ml). Absorption is slowed and Cmax reduced by food. Losartan Potassium and E3174 are highly protein bound (98.7% and 99.8 %) with volumes of distribution of 34L and 12L respectively. Approximately 35% of the drug is eliminated in the urine and approximately 60% is excreted in the feces. Losartan Potassium and E3174 have elimination half-lives of 2.1 and 6.4 hours respectively. The rate of renal clearance of Losartan Potassium and E3174 is 4.3 and 1.6L/h.

Amlodipine

After oral administration of therapeutic doses of amlodipine, absorption occurs gradually with peak plasma concentration occurring between 6 and 9 hours. The median Tmax reported for amlodipine was 8.00 hours respectively after single oral dose of 5mg in healthy volunteers.. Absolute bioavailability has been estimated to be between 64 and 90%. The bioavailability of amlodipine is not altered by the presence of food. Amlodipine has a large volume of distribution (Vd) of 21L/Kg and is highly plasma protein bound (95%).

Amlodipine undergoes extensive, but slow hepatic metabolism. The dihydropyridine moiety is oxidized to the pyridine analogue during initial biotransformation, with minimal first-pass or presystemic metabolism. Metabolites have no significant activity.

Less than 10% of an oral dose is excreted unchanged. Following oral administration 60% of oral dose is recovered in the urine mainly as metabolites and 20 to 25% in the feces.

The elimination half-life of Amlodipine is in the range of 35 to 50 hours in healthy subjects.

INDICATION

BRANTA is indicated in treatment of mild to moderate hypertension.

CONTRAINDICATIONS

BRANTA is contraindicated in patients allergic to angiotensin receptor blocker or dihydropyridine calcium channel antagonist. Patients with a history of angioedema or any other adverse effect related to previous treatment with an angiotensin receptor blocker or calcium channel antagonist.

PRECAUTIONS

Impaired Liver Function: Losartan Potassium and Amlodipine combination should be given with caution in patients with impaired hepatic function since the half life of amlodipine is prolonged in patients with impaired liver function.

Impaired Renal patients: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin receptor blocker may be associated with oliguria and/ or progressive azotemia and (rarely) with acute renal failure and/ or death.

WARNINGS

Hypotension: Losartan Potassium can cause symptomatic hypotension. Symptomatic hypotension is most likely to occur in patients who have been volume and/ or salt-depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume and/ or salt depletion should be corrected before initiating therapy with Losartan Potassium and Amlodipine combination.

Hepatic Failure: Rarely, angiotensin receptor inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood.

Patients receiving this combination who develop jaundice or marked elevations of hepatic enzymes should discontinue the therapy and receive appropriate medical follow-up.

USE IN PREGNANCY, NURSING MOTHERS AND CHILDREN

Pregnancy: There is no clinical experience with BRANTA in pregnancy or lactation. So, BRANTA should not be administered during pregnancy or lactation or to women of childbearing potential unless effective contraception is ensured.

Nursing Mothers: Women receiving BRANTA should not breast-feed.

Use in children: Since there is no clinical experience of BRANTA, use of this product is not currently recommended for children and adolescents of less than 18 years of age.

SIDE EFFECTS

Losartan Potassium

In general, treatment with Losartan Potassium was well tolerated. Following adverse events, whether or not attributed to the treatment, occurring in at least 1% of patients treated with Losartan Potassium and that were more frequent in Losartan Potassium than placebo.

Digestive: Diarrhea, dyspepsia.

Musculoskeletal: Muscle cramp, myalgia, back pain, leg pain.

Nervous System/Psychiatric: Dizziness, insomnia.

Respiratory: Nasal congestion, cough, upper respiratory tract infection, sinus disorder, sinusitis.

The following adverse events were also reported at a rate 1% or greater in patients treated with Losartan, but were as, or more frequent, in the placebo group: asthenia/fatigue, oedema/ swelling, abdominal pain, chest pain, nausea, headache, pharyngitis.

Amlodipine

The most commonly observed side effects are edema, flushing, palpitation, fatigue, headache, somnolence, abdominal pain and dizziness.

The following events occurred in <1% but >0.1% of patients in controlled clinical trials: (Use capital letter or follow the same system as for losartan)

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, and vertigo.

Gastrointestinal: Anorexia, constipation, dyspepsia, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia.

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.

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.

DRUG INTERACTIONS

Losartan Potassium

Losartan Potassium administered for 12 days, did not affect the pharmacokinetics or pharmacodynamics of a single dose of warfarin. Losartan Potassium did not affect the pharmacokinetics of oral and intravenous digoxin. Co administration of Losartan Potassium and cimetidine led to an increase of about 18% in AUC of Losartan Potassium but did not affect the pharmacokinetics of E3174. Co administration of Losartan Potassium and phenobarbital led to reduction of about 20% in the AUC of Losartan Potassium and E3174. There is no pharmacokinetic interaction between Losartan

Potassium and Hydrochlorothiazide.Inhibitors of Cytochrome P34A are unlikely to have significant drug interactions while potent inducers of Cytochrome P34A might cause a significant interaction.

As with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium.

Amlodipine

Amlodipine has been safely administered with thiazide diuretics, beta adrenoceptor blocking drugs, angiotensin converting enzyme inhibitors, long acting nitrates, sublingual glyceryl trinitrate, nonsteroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic agents.

Co administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers. Co administration of amlodipine did not alter the pharmacokinetics of amlodipine.

In healthy volunteers, co administration of amlodipine did not significantly alter the effect of warfarin on prothrombin time. The introduction of amlodipine is not likely to result in the need for modification of an established warfarin regimen.

DOSAGE AND ADMINISTRATION

The recommended dose of BRANTA is one tablet once daily taken with or without food.

DIRECTION FOR USE

SWALLOW WHOLE TABLET. DO NOT CRUSH OR CHEW.

OVER DOSAGE

Losartan

Symptom: The most likely manifestation of overdosage would be hypotension and tachycardia. Bradycardia could occur from parasympathetic (vagal) stimulation.

Treatment: If symptomatic hypotension occurs, supportive treatment should be instituted. Neither Losartan Potassium nor E-3174 can be removed by haemodialysis.

Amlodipine

Symptoms: Available data suggests that the gross over dosage could result in excessive peripheral vasodilation with marked and probably prolonged hypotension and possibly a reflex tachycardia.

Treatment: Since absorption of amlodipine is slow, gastric lavage should be performed. Active cardiovascular support including monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output should be given. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. A vasoconstrictor agent may be helpful in restoring vascular tone and blood pressure provided that there is no contraindication to its use. Since amlodipine is highly protein bound, dialysis is unlikely to be of benefit.

STORAGE

Store below 30°C

PRESENTATION

BRANTA is available in blister strip of 10 Tablets.

torrent PHARMA

Manufactured by:
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist. Mehsana, INDIA

1.4.4 Mock-ups and specimens

Enclosed herewith

PRODUCT NAME	:	Branta	COUNTRY : Kenya	LOCATION : Indrad		Supersedes A/W No.:	Nil	
ITEM / PACK	:	Carton, 1 x 10	NO. OF COLORS: 2	REMARK :				
DESIGN STYLE	:	Reverse Tuck	PANTONE SHADE NOS.:	SUBSTRATE :	300 gsm FBB			
CODE	:	8049778-6711		Activities	Department	Name	Signature	Date
DIMENSIONS (MM)	:	136 x 22 x 54	273 C	Prepared By	Pkg.Dev			21/7/14
ART WORK SIZE	:	S/S	273 C Screen of 40%	Reviewed By	Pkg.Dev			21/07/14
DATE	:	19-06-2014	Black	Reviewed By	RA	Ram Shanker		22/07/14
				Approved By	CQA	Dr. Rikesh		24/07/14

This colour proof is not colour binding. Follow Pantone shade reference for actual colour matching.

1041

1 x 10 TABLETS

BRANTA

LOSARTAN POTASSIUM AND
AMLODIPINE BESILATE TABLETS
50 MG + 5 MG

BRANTA

1 BLISTER STRIP OF 10 TABLETS

8049778-6711

BRANTA

1 x 10 TABLETS

torrent PHARMA

Each film coated tablet contains :
Losartan Potassium U.S.P. 50 mg
Amlodipine Besilate Ph.Eur.
equivalent to Amlodipine 5 mg
Colours : Lake of Sunset Yellow & Titanium Dioxide
Dose : As directed by the Physician

torrent PHARMA

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist. Mehsana, INDIA.

STORE BELOW 30°C
Mfg. Lic. No. : G/926
Registration No. : CTD 1396
Legal category: POM

Batch No. :
Mfg. :
Exp. :

GTIN: XXXXXXXXXXXXX
Sr. No.: YYYYYYYYYYYYYYYYY

Over stamp

Varnish Free

PRODUCT NAME	:	Branta	COUNTRY : Kenya	LOCATION : Indrad		Supersedes A/W No.:	Nil	
ITEM / PACK	:	Carton, 3 x 10	NO. OF COLORS: 2	REMARK :				
DESIGN STYLE	:	Reverse Tuck	PANTONE SHADE NOS.:	SUBSTRATE : 300 gsm PSB				
CODE	:	8049777-6711		Activities	Department	Name	Signature	Date
DIMENSIONS (MM)	:	136 x 24 x 54	273 C	Prepared By	Pkg.Dev			21/7/14
ART WORK SIZE	:	S/S	273 C Screen of 40%	Reviewed By	Pkg.Dev			21/07/14
DATE	:	19-06-2014	Black	Reviewed By	RA	Ram Shanker		22/07/14
				Approved By	CQA			24/07/14

1040

This colour proof is not colour binding. Follow Pantone shade reference for actual colour matching.

3 x 10 TABLETS

BRANTA

BRANTA

3 x 10 TABLETS

torrent PHARMA

LOSARTAN POTASSIUM AND
AMLODIPINE BESILATE TABLETS
50 MG + 5 MG

BRANTA

3 BLISTER STRIPS OF 10 TABLETS EACH

8049777-6711

Each film coated tablet contains :
Losartan Potassium U.S.P. 50 mg
Amlodipine Besilate Ph.Eur.
equivalent to Amlodipine - 5 mg
Colours : Lake of Sunset Yellow & Titanium Dioxide
Dose : As directed by the Physician

torrent PHARMA

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist. Mehsana, INDIA.

STORE BELOW 30°C
Mfg. Lic. No. : G/926
Registration No. : CTD 1396
Legal category: POM

Batch No. :
Mfg. :
Exp. :

GTIN: XXXXXXXXXXXXX
Sr. No.: YYYYYYYYYYYYYYYYY

Over stamp

Varnish Free