**Summary of product characteristics**

## 1.Name of the medicinal product

DIUTOR INJECTION

## 2.Qualitative and quantitative composition

Each ml contains:
Torsemide USP..... 10mg
For the full list of excipients, see section 6.1

## 3.Pharmaceutical form

Injection

A clear colorless solution.

## 4.Clinical particulars

### 4.1 Therapeutic indications

DIUTOR injection is indicated for the treatment of edema associated with congestive heart failure, renal disease, or hepatic disease. Use of torsemide has been found to be effective for the treatment of edema associated with chronic renal failure.

### 4.2 Posology and method of administration

**Posology**

Adults

Oedema: The usual dose is 5mg. once daily. If necessary, the dose can be increased stepwise up to 20mg once daily.
In individual cases, as much as 40 mg torasemide/day has been administered.

Elderly

No special dosage adjustments are necessary.

Children

There is no experience of torasemide in children.

Congestive Heart Failure

The usual initial dose is 10 mg or 20 mg of once-daily intravenous Diutor. If the diuretic response is inadequate, the dose should be titrated upward by approximately doubling until the desired diuretic response is obtained. Single doses higher than 200 mg have not been adequately studied.

Chronic Renal Failure

The usual initial dose of Diutor is 20 mg of once-daily intravenous Diutor. If the diuretic response is inadequate, the dose should be titrated upward by approximately doubling until the desired diuretic response is obtained. Single doses higher than 200 mg have not been adequately studied.

Hepatic Cirrhosis

The usual initial dose is 5 mg or 10 mg of once-daily intravenous Diutor, administered together with an aldosterone antagonist or a potassium-sparing diuretic. If the diuretic response is inadequate, the dose should be titrated upward by approximately doubling until the desired diuretic response is obtained. Single doses higher than 40 mg have not been adequately studied.
Chronic use of any diuretic in hepatic disease has not been studied in adequate

and well-controlled trials.
Hypertension
The usual initial dose is 5 mg once daily. If the 5 mg dose does not provide adequate reduction in blood pressure within 4 to 6 weeks, the dose may be increased to 10 mg once daily. If the response to 10 mg is insufficient, an additional antihypertensive agent should be added to the treatment regimen.
**Method of administration:**

Intravenous use only
Diutor intravenous injection should be administered either slowly as a bolus over a period of 2 minutes or administered as a continuous infusion.
If Diutor is administered through an IV line, it is recommended that, as with other IV injections, the
IV line be flushed with Normal Saline (Sodium Chloride Injection, USP) before and after administration. Diutor injection is formulated above pH 8.3. Flushing the line is recommended to avoid the potential for incompatibilities caused by differences in pH which could be indicated by color change, haziness or the formation of a precipitate in the solution.

## 4.3 Contraindications
Hypersensitivity to the active substances or to any of the excipients.
Cardiac arrhythmias, simultaneous therapy with aminoglycosides or cephalosporins, or renal dysfunction due to drugs which cause renal damage.

## 4.4 Special warnings and precautions for use

Hypokalaemia, hyponatraemia, hypovolaemia and disorders of micturition must be corrected before treatment.
On long-term treatment with torasemide, regular monitoring of the electrolyte balance, glucose, uric acid, creatinine and lipids in the blood, is recommended.
Careful monitoring of patients with a tendency to hyperuricaemia and gout is recommended. Carbohydrate metabolism in latent or manifest diabetes mellitus should be monitored.
As for other drugs which produce changes in blood pressure, patients taking torasemide should be warned not to drive or operate machinery if they experience dizziness or related symptoms.
Patients with rare hereditary problems of glucose intolerance, the Lapp lactase deficiency of glucose-galactose malabsorption should not take this medication.
**Difficulty with micturition**
Particular caution is required in patients with difficulty with micturition including prostatic hypertrophy because they have an increased risk of developing acute urinary retention and require careful close monitoring

## 4.5 Interaction with other medicinal products and other forms of interaction
When used simultaneously with cardiac glycosides, a potassium and/or magnesium deficiency may increase sensitivity of the cardiac muscle to such drugs.
The kaliuretic effect of mineralo-and glucocorticoids and laxatives may be increased.
As with other diuretics, the effect of antihypertensive drugs given concomitantly may be potentiated.
Torasemide, especially at high doses, may potentiate the toxicity of aminoglycoside antibiotics, cisplatin preparations, the nephrotoxic effects of cephalosporins, and

the cardioand neurotoxic effect of lithium. The action of curare-containing muscle relaxants and of theophylline can be potentiated. In patients receiving high doses of salicylates, salicylate toxicity may be increased. The action of anti-diabetic drugs may be reduced.
Sequential or combined treatment, or starting a new co-medication with an ACE inhibitor may result in transient hypotension. This may be minimised by lowering the starting dose of the ACE inhibitor and/or reducing or stopping temporarily the dose of torasemide. Torasemide may decrease arterial responsiveness to pressor agents e.g. adrenaline, noradrenaline.
Non-steroidal anti-inflammatory drugs (eg. Indometacin) and probenecid may reduce the diuretic and hypotensive effect of torasemide.

## 4.6 Fertility, pregnancy and lactation

Pregnancy
This drug should be used during pregnancy only if clearly needed.
Breast-feeding
This drug should be used during breast feeding only if clearly needed.
Fertility
There are no data from experience in humans of the effect of torasemide on the embryo and foetus. Whilst studies in the rat have shown no teratogenic effect, malformed foetuses have been observed after high doses in pregnant rabbits.

## 4.7 Effects on ability to drive and use machines

As for other drugs which produce changes in blood pressure, patients taking torasemide should be warned not to drive or operate machinery if they experience dizziness or related symptoms.

## 4.8 Undesirable effects

Adverse reactions listed below are classified according to frequency and system organ class (SOC). Frequency categories are defined according to the following convention: 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), and not known (cannot be estimated from the available data).

**Blood and lymphatic system disorders**
Frequency not known: Thrombocytopenia, Leukopenia, Anaemia

**Immune system disorders**
Very rare: Allergic skin reactions (e.g. Pruritus, Exanthema), Photosensitivity reaction
Frequency not known: Serious skin reactions (e.g. Stevens-Johnson syndrome, Toxic epidermal necrolysis)

**Metabolism and nutrition disorders**
Common: Metabolic alkalosis, Fluid and electrolyte imbalance (e.g. Hypovolaemia, Hyponatraemia)

**Nervous system disorders**
Common: Headache, Dizziness
Frequency not known: Cerebral ischaemia, Parenthesis, Confusional state

**Eye disorders**
Frequency not known: Visual impairment

**Ear and labyrinth disorders**
Frequency not known: Tinnitus, Deafness

**Cardiac disorders**

Frequency not known: Acute myocardial infarction, Myocardial ischaemia, Angina pertoris, Syncope,

**Hypotension Vascular disorders**

Frequency not known: Embolism

**Gastrointestinal disorders**

Common: Gastrointestinal disorder (e.g. Loss of appetite, Abdominal pain upper Nausea, Vomiting, Diarrhoea, Constipation)

Frequency not known: Dry mouth, Pancreatitis

**Hepatobiliary disorders**

Uncommon: Hepatic enzyme increased (e.g. Gamma-glutamyltransferase increased)

**Skin and subcutaneous tissue disorders**

Very rare: Allergic skin reactions (e.g. Pruritus, Exanthema), Photosensitivity reaction Frequency not known: Serious skin reactions (e.g. Stevens-Johnson syndrome, Toxic epidermal necrolysis)

**Musculoskeletal and connective tissue disorders**

Common: Muscle spasms

**Renal and urinary disorders**

Uncommon: Urinary retention, Bladder dilatation Rare: Blood urea increased, Blood creatinine increased

**General disorders and administration site conditions**

Common: Fatigue, Asthenia

**Investigations**

Uncommon: Blood uric acid increased, Blood glucose increased, Lipids increased (Blood triglycerides increased, Blood cholesterol increased).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

***Symptoms and signs***

No typical picture of intoxication is known. If overdosage occurs, then there may be marked diuresis with the danger of loss of fluid and electrolytes which may lead to somnolence, confusion, hypotension, hyponatremia, hypokalemia, hypochloremic alkalosis, hemoconcentration dehydration and circulatory collapse. Gastrointestinal disturbances may occur.

***Treatment***

No specific antidote is known. Symptoms and signs of overdosage require the reduction of the dose or withdrawal of torasemide, and simultaneous replacement of fluid and electrolytes.

**Reporting of suspected adverse reactions:**

Reporting suspected adverse reactions after authorisation of the medicinal product is important as it allows continued monitoring of the benefit–risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions to the marketing authorisation holder or, where applicable, via the national reporting system

## 4.9 Overdose

There is no human experience with overdoses of torsemide, but the signs and symptoms of overdosage can be anticipated to be those of excessive pharmacologic

effect: dehydration, hypovolemia, hypotension, hyponatremia, hypokalemia, hypochloremic alkalosis, and hemoconcentration. Treatment of overdosage should consist of fluid and electrolyte replacement.
Laboratory determinations of serum levels of torsemide and its metabolites are not widely available. No data are available to suggest physiological maneuvers (eg, maneuvers to change the pH of the urine) that might accelerate elimination of torsemide and its metabolites. Torsemide is not dialyzable, so hemodialysis will not accelerate elimination.

## 5.Pharmacological properties

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: High ceiling diuretics, sulphonamide monodrugs, ATC code: C03CA04.
Torasemide is a loop diuretic. However, at low doses its pharmacodynamic profile resembles that of the thiazide class regarding the level and duration of diuresis. At higher doses, torasemide induces a brisk diuresis in a dose dependant manner with a high ceiling of effect.
Torasemide acts as a salidiuretic by inhibition of renal sodium and chloride reabsorption in the ascending limb of the loop of Henle.
In healthy subjects an increase in dose results in a linear increase in urine excretion corresponding to the logarithm of the dose (high-ceiling activity) within the 5 to 100 mg dose range. An increase in diuresis may also take place if other diuretics are no longer active, eg in the presence of impaired renal function.
In renal failure endogenous organic acids compete with loop diuretics for the acid secretion mechanism in the proximal tubule. Therefore, the torasemide dose has to be adequately increased in order to achieve effective amounts of drug at the site of action.
Torasemide leads to a gentle removal of edema and especially to an improvement of the working condition of the heart failure by reducing the preload and afterload.
In patients with severe to endstage chronic renal failure there is a reduction of aterial blood pressure in addition to removal of edema and maintenance of residual diuresis

### 5.2 Pharmacokinetic properties

Absorption
Torasemide is absorbed rapidly and almost completely after administration, and peak serum levels are reached after one to two hours.
Distribution
The apparent distribution volume is 16 litres.

Metabolism
Torasemide is metabolised to three metabolites, M1, M3 and M5 by stepwise oxidation, hydroxylation or ring hydroxylation. Further metabolites (M2 and M4) have been found in animal experiments, but not in humans.
Elimination
The terminal half-life of torasemide and its metabolites is three to four hours in healthy subjects. Total clearance of torasemide is 40ml/min and renal clearance about 10ml/min. About 80% of the dose administered is excreted as torasemide and metabolites into the renal tubule - torasemide 24%, M1 12%, M3 3%, M5 41%.
In patients with congestive heart failure and disorders of liver fnction, the elimination hal-lives of torasemide and metabolite M5 are only slightly increased compared with those in healthy volunteers. The amounts of torasemide and metabolites excreted in the urine are similar to those in healthy subjects; therefore

no accumulation is to be expected.
In the presence of renal failure, elimination half-life of torasemide is unchanged.

**5.3 Preclinical safety data**

**Acute toxicity**

Very low toxicity.

**Chronic toxicity**

The changes observed in toxicity studies in dogs and rats at high doses are attributable to an excess pharmacodynamic action (diuresis). Changes observed were weight reduction, increases in creatinine and urea and renal alterations such as tubular dilatation and interstitial nephritis. All drug induced changes were shown to be reversible.

**Teratogenicity**

Reproduction toxicology studies in the rat have shown no teratogenic effect, but malformed foetuses have been observed after high doses in pregnant rabbits. No effects on fertility have been seen. Torasemide showed no mutagenic potential. Carcinogenicity studies in rats and mice showed no tumourigenic potential.

**6.Pharmaceutical particulars**

**6.1 List of excipients**

Water for injection

**6.2 Incompatibilities**

Not applicable

**6.3 Shelf life**

24 months

**6.4 Special precautions for storage**

- Store at 15 ˚C to 30˚C.
- Do not freeze.
- Keep out of the reach and sight of children.
- Do not use Diutor injection after the expiry date printed on the pack.

**6.5 Nature and contents of container**

2 ml ampoule x 5's

**6.6 Special precautions for disposal and other handling**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**7.Marketing authorisation holder**

Krishna Chemists Ltd
Manufactured by:
ARMEIN PHARMACEUTICALS PVT. LTD.
Survey # 494, Khambhat - Petlad Road,
Bamanva- 388580, Ta- Khambhat, Dist- Anand,
Gujarat, India

**8.Marketing authorisation number(s)**

H2024/CTD10910/23874

**9.Date of first authorisation/renewal of the authorization**

2029 March 25

**10. Date of revision of the text**

2029 March 25