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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lercanidipine Hydrochloride 10 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Lercanidipine Hydrochloride 10 mg film-coated tablets
One film-coated tablet contains 10 mg lercanidipine hydrochloride, which is equivalent to 9.4 mg lercanidipine.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Lercanidipine Hydrochloride 10 mg film-coated tablets
Yellow, round shaped biconvex, film-coated tablets with break-line on one side and plain on the other side.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lercanidipine Hydrochloride film-coated tablets are indicated for the treatment of mild to moderate, essential hypertension.

4.2 Posology and method of administration

The recommended dosage is 10 mg orally once a day at least 15 minutes before meals; the dose may be increased to 20 mg depending on the individual patient's response.

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Dose titration should be gradual, because it may take about 2 weeks before the maximal antihypertensive effect is apparent.

Some individuals, not adequately controlled on a single antihypertensive agent, may benefit from the addition of lercanidipine to therapy with a beta-adrenoceptor blocking drug (atenolol), a diuretic (hydrochlorothiazide) or an angiotensin converting enzyme inhibitor (captopril or enalapril).

Since the dose-response curve is steep with a plateau at doses between 20 - 30 mg, it is unlikely that efficacy will be improved by higher doses; whereas side effects may increase.

Use in the elderly:

Although the pharmacokinetic data and clinical experience suggest that no adjustment of the daily dosage is required, special care should be exercised when initiating treatment in the elderly.

Use in children:

Since there is no clinical experience in patients under the age of 18 years, use in children is not currently recommended.

Use in renal or hepatic dysfunction:

Special care should be exercised when treatment is commenced in patients with mild to moderate renal or hepatic dysfunction. Although the usually recommended dose schedule may be tolerated by these subgroups, an increase in dose to 20 mg daily must be approached with caution. The antihypertensive effect may be enhanced in patients with hepatic impairment and consequently an adjustment of the dosage should be considered.

Lercanidipine is not recommended for use in patients with severe hepatic impairment or in patients with severe renal impairment (GFR < 30 ml/min).

4.3 Contraindications

- Hypersensitivity to the active substance lercanidipine, to any dihydropyridine or to any of the excipients of the medicinal product.
- Pregnancy and lactation (see section 4.6).
- Women of child-bearing potential unless effective contraception is used.
- Left ventricular outflow tract obstruction.

- Untreated congestive cardiac failure.

- Unstable angina pectoris.
- Severe renal or hepatic impairment.
- Within 1 month of a myocardial infarction.
- Co-administration with:
  - strong inhibitors of CYP3A4 (see section 4.5),
  - ciclosporin (see section 4.5),
  - grapefruit juice (see section 4.5).

4.4 Special warnings and precautions for use

Special care should be exercised when lercanidipine is used in patients with sick sinus syndrome (if a pacemaker is not in situ). Although hemodynamic controlled studies revealed no impairment of ventricular function, care is also required in patients with LV dysfunction. It has been suggested that some short-acting dihydropyridines may be associated with increased cardiovascular risk in patients with ischaemic heart disease. Although lercanidipine is long-acting caution is required in such patients.

Some dihydropyridines may rarely lead to precordial pain or angina pectoris. Very rarely patients with pre-existing angina pectoris may experience increased frequency, duration or severity of these attacks. Isolated cases of myocardial infarction may be observed (see section 4.8).

Use in renal or hepatic dysfunction:

Special care should be exercised when treatment is commenced in patients with mild to moderate renal or hepatic dysfunction. Although the usually recommended dose schedule may be tolerated by these subgroups, an increase in dose to 20 mg daily must be approached with caution. The antihypertensive effect may be enhanced in patients with hepatic impairment and consequently an adjustment of the dosage should be considered.

Lercanidipine is not recommended for use in patients with severe hepatic impairment or in patients with severe renal impairment (GFR < 30 ml/min) (see section 4.2).

Alcohol should be avoided since it may potentiate the effect of vasodilating antihypertensive drugs (see section 4.5).

Inducers of CYP3A4 like anticonvulsants (e.g. phenytoin, carbamazepine) and rifampicin may reduce lercanidipine's plasma levels and therefore the efficacy of lercanidipine may be less than expected (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

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Lercanidipine is known to be metabolised by the CYP3A4 enzyme and, therefore, inhibitors and inducers of CYP3A4 administered concurrently may interact with the metabolism and elimination of lercanidipine.

Co-prescription of lercanidipine with inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir, erythromycin, troleandomycin) should be avoided (see section 4.3).
An interaction study with a strong CYP3A4 inhibitor, ketoconazole, has shown a considerable increase in plasma levels of lercanidipine (a 15-fold increase of the AUC and an 8-fold increase of the C_{max} for the eutomer S-lercanidipine).

Ciclosporin and lercanidipine should not be administered together (see section 4.3).
Increased plasma levels of both lercanidipine and ciclosporin have been observed following concomitant administration. A study in young healthy volunteers has shown that when ciclosporin was administered 3 hours after the lercanidipine intake, the plasma levels of lercanidipine did not change, while the AUC of ciclosporin increased by 27%. However, the co-administration of lercanidipine with ciclosporin has caused a 3-fold increase of the plasma levels of lercanidipine and a 21% increase of the ciclosporin AUC.

Lercanidipine should not be taken with grapefruit juice (see section 4.3).
As for other dihydropyridines, lercanidipine is sensitive to inhibition of metabolism by grapefruit juice, with a consequent rise in its systemic availability and increased hypotensive effect.

When concomitantly administered at a dose of 20 mg with midazolam p.o. to elderly volunteers, lercanidipine's absorption was increased (by approximately 40%) and the rate of absorption was decreased (t_{max} was delayed from 1.75 to 3 hours). Midazolam concentrations were not modified.

Caution should be exercised when lercanidipine is co-prescribed with other substrates of CYP3A4, like terfenadine, astemizole, class III antiarrhythmic drugs such as amiodarone, quinidine.

Co-administration of lercanidipine with CYP3A4 inducers like anticonvulsants (e.g.

phenytoin, carbamazepine) and rifampicin should be approached with caution since the

antihypertensive effect may be reduced and blood pressure should be monitored more frequently than usual.

When lercanidipine was co-administered with metoprolol, a β-blocker eliminated mainly by the liver, the bioavailability of metoprolol was not changed while that of lercanidipine was reduced by 50%. This effect may be due to the reduction in the hepatic blood flow caused by β-blockers and may therefore occur with other drugs of this class. Consequently, lercanidipine may be safely administered with beta-adrenoceptor blocking drugs, but dose adjustment may be required.

An interaction study with fluoxetine (an inhibitor of CYP2D6 and CYP3A4), conducted in volunteers of an age of 65 ± 7 years (mean ± s.d.), has shown no clinically relevant modification of the pharmacokinetics of lercanidipine.

Concomitant administration of cimetidine 800 mg daily does not cause significant modifications in plasma levels of lercanidipine, but at higher doses caution is required since the bioavailability and the hypotensive effect of lercanidipine may be increased.

Co-administration of 20 mg lercanidipine in patients chronically treated with ß-methyldigoxin showed no evidence of pharmacokinetic interaction. Healthy volunteers treated with digoxin following dosing with 20 mg lercanidipine given fasted showed a mean increase of 33% in digoxin C_{max}, while AUC and renal clearance were not significantly modified. Patients on concomitant digoxin treatment should be closely monitored clinically for signs of digoxin toxicity.

When a dose of 20 mg of lercanidipine was repeatedly co-administered with 40 mg of simvastatin, the AUC of lercanidipine was not significantly modified, while simvastatin's AUC increased by 56% and that of its active metabolite β-hydroxyacid by 28%. It is unlikely that such changes are of clinical relevance. No interaction is expected when lercanidipine is administered in the morning and simvastatin in the evening, as indicated for such drug.

The co-administration of 20 mg lercanidipine to healthy volunteers given fasted did not alter the pharmacokinetics of warfarin.

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Lercanidipine has been safely administered with diuretics and ACE inhibitors.

Alcohol should be avoided since it may potentiate the effect of vasodilating antihypertensive drugs (see section 4.4).

4.6 Pregnancy and lactation

Data for lercanidipine provide no evidence of a teratogenic effect in the rat and the rabbit and reproductive performance in the rat was unimpaired. Nevertheless, since there is no clinical experience with lercanidipine in pregnancy and lactation, and other dihydropyridine compounds have been found teratogenic in animals, lercanidipine should not be administered during pregnancy or to women with child-bearing potential unless effective contraception is used. Because of high lipophilicity of lercanidipine, distribution in milk may be expected. Therefore, it should not be administered to nursing mothers.

4.7 Effects on ability to drive and use machines

Clinical experience with lercanidipine indicates that it is unlikely to impair a patient's ability to drive or use machinery. However, caution should be exercised because dizziness, asthenia, fatigue and rarely somnolence may occur.

4.8 Undesirable effects

About 1.8% of treated patients experienced adverse reactions.

The table below shows the incidence of adverse drug reactions, at least possibly causally related, grouped by MedDRA System Organ Class classification, and ranked by frequency (uncommon, rare).

As shown in the table, the most commonly occurring adverse drug reactions reported in controlled clinical trials are headache, dizziness, peripheral oedema, tachycardia, palpitations, flushing, each occurring in less than 1% of patients.

MedDRA System Organ Class	*Frequency*	*Preferred Terms*
Immune system disorders	Very rare (<1/10,000)	Hypersensitivity
Psychiatric disorders	Rare (>1/10,000 <1/1000)	Somnolence

Nervous system disorders	Uncommon (>1/1000 <1/100)	Headache; dizziness

Cardiac disorders	Uncommon (>1/1000 <1/100)	Tachycardia; palpitations
	Rare (>1/10,000 <1/1000)	Angina pectoris
Vascular disorders	Uncommon (>1/1000 <1/100)	Flushing
	Very rare (<1/10,000)	Syncope
Gastrointestinal disorders	Rare (>1/10,000 <1/1000)	Nausea; dyspepsia; diarrhoea; abdominal pain; vomiting
Skin and subcutaneous tissue disorders	Rare (>1/10,000 <1/1000)	Rash
Musculoskeletal, connective tissue and bone disorders	Rare (>1/10,000 <1/1000)	Myalgia
Renal and urinary disorders	Rare (>1/10,000 <1/1000)	Polyuria
General disorders and administration site conditions	Uncommon (>1/1000 <1/100)	Oedema peripheral
	Rare (>1/10,000 <1/1000)	Asthenia; fatigue

In post-marketing experience, from spontaneous reports the following undesirable effects were reported very rarely (<1/10,000): gingival hypertrophy, reversible increases in serum levels of hepatic transaminases, hypotension, urinary frequency and chest pain.
Some dihydropyridines may rarely lead to precordial pain or angina pectoris. Very rarely patients with pre-existing angina pectoris may experience increased frequency, duration or severity of these attacks. Isolated cases of myocardial infarction may be observed.
Lercanidipine does not appear to influence adversely blood sugar or serum lipid levels.

4.9 Overdose

In the post-marketing experience, three cases of overdose were reported (150 mg, 280 mg and 800 mg of lercanidipine, respectively, ingested in an attempt to commit suicide).

Dose level	*Sign/Symptoms*	*Management*	*Outcome*
150 mg + undefined amount of alcohol	Sleepiness	Gastric lavage Active charcoal	Recovered

280 mg + 5.6 mg moxonidine	Cardiogenic shock Severe myocardial ischemia Mild renal failure	High-dose catecholamines Furosemide Digitalis	Recovered

		Parenteral plasma expanders	
800 mg	Emesis Hypotension	Active charcoal Cathartics Dopamine i.v.	Recovered

As with other dihydropyridines, overdosage might be expected to cause excessive peripheral vasodilatation with marked hypotension and reflex tachycardia. In case of severe hypotension, bradycardia and unconsciousness, cardiovascular support could be helpful, with intravenous atropine for bradycardia.

In view of the prolonged pharmacological effect of lercanidipine, it is essential that the cardiovascular status of patients who take an overdose is monitored for 24 hours at least. There is no information on the value of dialysis. Since the drug is highly lipophilic, it is most probable that plasma levels are no guide to the duration of the period of risk and dialysis may not be effective.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Selective calcium channel blockers with mainly vascular effects

ATC code: C08CA13

Lercanidipine is a calcium antagonist of the dihydropyridine group and inhibits the transmembrane influx of calcium into cardiac and smooth muscle. The mechanism of its antihypertensive action is due to a direct relaxant effect on vascular smooth muscle thus lowering total peripheral resistance. Despite its short pharmacokinetic plasma half-life, lercanidipine is endowed with a prolonged antihypertensive activity because of its high membrane partition coefficient, and is devoid of negative inotropic effects due to its high vascular selectivity.

Since the vasodilatation induced by lercanidipine is gradual in onset, acute hypotension with reflex tachycardia has rarely been observed in hypertensive patients.

As for other asymmetric 1,4-dihydropyridines, the antihypertensive activity of lercanidipine is mainly due to its (S)-enantiomer.

In addition to the clinical studies conducted to support the therapeutic indications, a further small uncontrolled but randomised study of patients with severe hypertension (mean $\pm$ SD diastolic blood pressure of 114.5 $\pm$ 3.7 mmHg) showed that blood pressure

was normalised in 40% of the 25 patients on 20 mg once daily dose and in 56% of 25

patients on 10 mg twice daily doses of lercanidipine. In a double-blind, randomized, controlled study versus placebo in patients with isolated systolic hypertension lercanidipine was efficacious in lowering systolic blood pressure from mean initial values of 172.6 ± 5.6 mmHg to 140.2 ± 8.7 mmHg.

5.2 Pharmacokinetic properties

Lercanidipine is completely absorbed after 10 - 20 mg oral administration and peak plasma levels, 3.30 ng/ml ± 2.09 s.d. and 7.66 ng/ml ± 5.90 s.d. respectively, occur about 1.5 - 3 hours after dosing.

The two enantiomers of lercanidipine show a similar plasma level profile: the time to peak plasma concentration is the same, the peak plasma concentration and AUC are, on average, 1.2-fold higher for the (S) enantiomer and the elimination half-lives of the two enantiomers are essentially the same. No "*in vivo*" interconversion of enantiomers is observed.

Due to the high first pass metabolism, the absolute bioavailability of lercanidipine orally administered to patients under fed conditions is around 10%, although it is reduced to 1/3 when administered to healthy volunteers under fasting conditions.
Oral availability of lercanidipine increases 4-fold when lercanidipine is ingested up to 2 hours after a high fat meal. Accordingly, lercanidipine should be taken before meals.

Distribution from plasma to tissues and organs is rapid and extensive.
The degree of serum protein binding of lercanidipine exceeds 98%. Since plasma protein levels are reduced in patients with severe renal or hepatic dysfunction, the free fraction of the drug may be increased.

Lercanidipine is extensively metabolised by CYP3A4; no parent drug is found in the urine or the faeces. It is predominantly converted to inactive metabolites and about 50% of the dose is excreted in the urine.

"In vitro" experiments with human liver microsomes have demonstrated that lercanidipine shows some degree of inhibition of CYP3A4 and CYP2D6, at concentrations 160- and 40-fold, respectively, higher than those reached at peak in the

plasma after the dose of 20 mg.

Moreover, interaction studies in humans have shown that lercanidipine did not modify the plasma levels of midazolam, a typical substrate of CYP3A4, or of metoprolol, a typical substrate of CYP2D6. Therefore, inhibition of biotransformation of drugs metabolised by CYP3A4 and CYP2D6 by lercanidipine is not expected at therapeutic doses.

Elimination occurs essentially by biotransformation**.**

A mean terminal elimination half life of 8 - 10 hours was calculated and the therapeutical activity lasts for 24 hours because of its high binding to lipid membrane. No accumulation was seen upon repeated administration.

Oral administration of lercanidipine leads to plasma levels of lercanidipine not directly proportional to dosage (non-linear kinetics). After 10, 20 or 40 mg, peak plasma concentrations observed were in the ratio 1:3:8 and areas under plasma concentration-time curves in the ratio 1:4:18, suggesting a progressive saturation of first pass metabolism. Accordingly, availability increases with dosage elevation.

In elderly patients and in patients with mild to moderate renal dysfunction or mild to moderate hepatic impairment the pharmacokinetic behaviour of lercanidipine was shown to be similar to that observed in the general patient population; patients with severe renal dysfunction or dialysis-dependent patients showed higher levels (about 70%) of the drug. In patients with moderate to severe hepatic impairment, the systemic bioavailability of lercanidipine is likely to be increased since the drug is normally metabolised extensively in the liver.

5.3 Preclinical safety data

Safety pharmacological studies in animals have shown no effects on the autonomic nervous system, the central nervous system or on gastrointestinal function at antihypertensive doses.

The relevant effects which have been observed in long-term studies in rats and dogs were related, directly or indirectly, to the known effects of high doses of Ca-antagonists,

predominantly reflecting exaggerated pharmacodynamic activity.

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Lercanidipine was not genotoxic and showed no evidence of carcinogenic hazard.

Fertility and general reproductive performance in rats were unaffected by treatment with lercanidipine.

There was no evidence of any teratogenic effect in rats and rabbits; however, in rats, lercanidipine at high dose levels induced pre- and post- implantation losses and delay in foetal development.

Lercanidipine hydrochloride, when administered at high dose (12 mg/kg/day) during labour, induced dystocia.

The distribution of lercanidipine and/or its metabolites in pregnant animals and their excretion in breast milk have not been investigated.

Metabolites have not been evaluated separately in toxicity studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lercanidipine Hydrochloride 10 mg film-coated tablets

Core:

Maize starch
Sodium starch glycolate (type A)
Silica, colloidal anhydrous
Cellulose, microcrystalline
Poloxamer 188
Sodium stearyl fumarate
Macrogol 6000

Film-coating:

Hypromellose
Macrogol 6000
Iron oxide yellow (E 172)

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Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Lercanidipine Hydrochloride 10 mg film-coated tablets

3 years.

6.4 Special precautions for storage

Store in the original carton in order to protect from light.

6.5 Nature and contents of container

Lercanidipine Hydrochloride 10 mg film-coated tablets

PVC–Al or PVC/PVdC-Al blister packs of 28 film-coated tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Torrent Pharma (UK) Ltd.
Unit 4, Charlwood Court
County Oak Way, Crawley
West Sussex, RH11 7XA
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PL 36687/0012

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/04/2010

10 DATE OF REVISION OF THE TEXT

08/2011

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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lercanidipine Hydrochloride 20 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Lercanidipine Hydrochloride 20 mg film-coated tablets
One film-coated tablet contains 20 mg lercanidipine hydrochloride, which is equivalent to 18.8 mg lercanidipine.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Lercanidipine Hydrochloride 20 mg film-coated tablets
Pink, round shaped biconvex, film-coated tablets with break-line on one side and plain on the other side.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lercanidipine Hydrochloride film-coated tablets are indicated for the treatment of mild to moderate, essential hypertension.

4.2 Posology and method of administration

The recommended dosage is 10 mg orally once a day at least 15 minutes before meals; the dose may be increased to 20 mg depending on the individual patient's response.

Dose titration should be gradual, because it may take about 2 weeks before the maximal antihypertensive effect is apparent.

Some individuals, not adequately controlled on a single antihypertensive agent, may benefit from the addition of lercanidipine to therapy with a beta-adrenoceptor blocking drug (atenolol), a diuretic (hydrochlorothiazide) or an angiotensin converting enzyme inhibitor (captopril or enalapril).

Since the dose-response curve is steep with a plateau at doses between 20 - 30 mg, it is unlikely that efficacy will be improved by higher doses; whereas side effects may increase.

Use in the elderly:

Although the pharmacokinetic data and clinical experience suggest that no adjustment of the daily dosage is required, special care should be exercised when initiating treatment in the elderly.

Use in children:

Since there is no clinical experience in patients under the age of 18 years, use in children is not currently recommended.

Use in renal or hepatic dysfunction:

Special care should be exercised when treatment is commenced in patients with mild to moderate renal or hepatic dysfunction. Although the usually recommended dose schedule may be tolerated by these subgroups, an increase in dose to 20 mg daily must be approached with caution. The antihypertensive effect may be enhanced in patients with hepatic impairment and consequently an adjustment of the dosage should be considered.

Lercanidipine is not recommended for use in patients with severe hepatic impairment or in patients with severe renal impairment (GFR < 30 ml/min).

4.3 Contraindications

- Hypersensitivity to the active substance lercanidipine, to any dihydropyridine or to any of the excipients of the medicinal product.
- Pregnancy and lactation (see section 4.6).
- Women of child-bearing potential unless effective contraception is used.
- Left ventricular outflow tract obstruction.

- Untreated congestive cardiac failure.

- Unstable angina pectoris.
- Severe renal or hepatic impairment.
- Within 1 month of a myocardial infarction.
- Co-administration with:
  - strong inhibitors of CYP3A4 (see section 4.5),
  - ciclosporin (see section 4.5),
  - grapefruit juice (see section 4.5).

4.4 Special warnings and precautions for use

Special care should be exercised when lercanidipine is used in patients with sick sinus syndrome (if a pacemaker is not in situ). Although hemodynamic controlled studies revealed no impairment of ventricular function, care is also required in patients with LV dysfunction. It has been suggested that some short-acting dihydropyridines may be associated with increased cardiovascular risk in patients with ischaemic heart disease. Although lercanidipine is long-acting caution is required in such patients.

Some dihydropyridines may rarely lead to precordial pain or angina pectoris. Very rarely patients with pre-existing angina pectoris may experience increased frequency, duration or severity of these attacks. Isolated cases of myocardial infarction may be observed (see section 4.8).

Use in renal or hepatic dysfunction:

Special care should be exercised when treatment is commenced in patients with mild to moderate renal or hepatic dysfunction. Although the usually recommended dose schedule may be tolerated by these subgroups, an increase in dose to 20 mg daily must be approached with caution. The antihypertensive effect may be enhanced in patients with hepatic impairment and consequently an adjustment of the dosage should be considered.

Lercanidipine is not recommended for use in patients with severe hepatic impairment or in patients with severe renal impairment (GFR < 30 ml/min) (see section 4.2).

Alcohol should be avoided since it may potentiate the effect of vasodilating antihypertensive drugs (see section 4.5).

Inducers of CYP3A4 like anticonvulsants (e.g. phenytoin, carbamazepine) and rifampicin may reduce lercanidipine's plasma levels and therefore the efficacy of lercanidipine may be less than expected (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Lercanidipine is known to be metabolised by the CYP3A4 enzyme and, therefore, inhibitors and inducers of CYP3A4 administered concurrently may interact with the metabolism and elimination of lercanidipine.

Co-prescription of lercanidipine with inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir, erythromycin, troleandomycin) should be avoided (see section 4.3).
An interaction study with a strong CYP3A4 inhibitor, ketoconazole, has shown a considerable increase in plasma levels of lercanidipine (a 15-fold increase of the AUC and an 8-fold increase of the C_{max} for the eutomer S-lercanidipine).

Ciclosporin and lercanidipine should not be administered together (see section 4.3).
Increased plasma levels of both lercanidipine and ciclosporin have been observed following concomitant administration. A study in young healthy volunteers has shown that when ciclosporin was administered 3 hours after the lercanidipine intake, the plasma levels of lercanidipine did not change, while the AUC of ciclosporin increased by 27%. However, the co-administration of lercanidipine with ciclosporin has caused a 3-fold increase of the plasma levels of lercanidipine and a 21% increase of the ciclosporin AUC.

Lercanidipine should not be taken with grapefruit juice (see section 4.3).
As for other dihydropyridines, lercanidipine is sensitive to inhibition of metabolism by grapefruit juice, with a consequent rise in its systemic availability and increased hypotensive effect.

When concomitantly administered at a dose of 20 mg with midazolam p.o. to elderly volunteers, lercanidipine's absorption was increased (by approximately 40%) and the rate of absorption was decreased (t_{max} was delayed from 1.75 to 3 hours). Midazolam concentrations were not modified.

Caution should be exercised when lercanidipine is co-prescribed with other substrates of CYP3A4, like terfenadine, astemizole, class III antiarrhythmic drugs such as amiodarone, quinidine.

Co-administration of lercanidipine with CYP3A4 inducers like anticonvulsants (e.g.

phenytoin, carbamazepine) and rifampicin should be approached with caution since the

antihypertensive effect may be reduced and blood pressure should be monitored more frequently than usual.

When lercanidipine was co-administered with metoprolol, a β-blocker eliminated mainly by the liver, the bioavailability of metoprolol was not changed while that of lercanidipine was reduced by 50%. This effect may be due to the reduction in the hepatic blood flow caused by β-blockers and may therefore occur with other drugs of this class. Consequently, lercanidipine may be safely administered with beta-adrenoceptor blocking drugs, but dose adjustment may be required.

An interaction study with fluoxetine (an inhibitor of CYP2D6 and CYP3A4), conducted in volunteers of an age of 65 ± 7 years (mean ± s.d.), has shown no clinically relevant modification of the pharmacokinetics of lercanidipine.

Concomitant administration of cimetidine 800 mg daily does not cause significant modifications in plasma levels of lercanidipine, but at higher doses caution is required since the bioavailability and the hypotensive effect of lercanidipine may be increased.

Co-administration of 20 mg lercanidipine in patients chronically treated with ß-methyldigoxin showed no evidence of pharmacokinetic interaction. Healthy volunteers treated with digoxin following dosing with 20 mg lercanidipine given fasted showed a mean increase of 33% in digoxin C_{max}, while AUC and renal clearance were not significantly modified. Patients on concomitant digoxin treatment should be closely monitored clinically for signs of digoxin toxicity.

When a dose of 20 mg of lercanidipine was repeatedly co-administered with 40 mg of simvastatin, the AUC of lercanidipine was not significantly modified, while simvastatin's AUC increased by 56% and that of its active metabolite β-hydroxyacid by 28%. It is unlikely that such changes are of clinical relevance. No interaction is expected when lercanidipine is administered in the morning and simvastatin in the evening, as indicated for such drug.

The co-administration of 20 mg lercanidipine to healthy volunteers given fasted did not alter the pharmacokinetics of warfarin.

Lercanidipine has been safely administered with diuretics and ACE inhibitors.

Alcohol should be avoided since it may potentiate the effect of vasodilating antihypertensive drugs (see section 4.4).

4.6 Pregnancy and lactation

Data for lercanidipine provide no evidence of a teratogenic effect in the rat and the rabbit and reproductive performance in the rat was unimpaired. Nevertheless, since there is no clinical experience with lercanidipine in pregnancy and lactation, and other dihydropyridine compounds have been found teratogenic in animals, lercanidipine should not be administered during pregnancy or to women with child-bearing potential unless effective contraception is used. Because of high lipophilicity of lercanidipine, distribution in milk may be expected. Therefore, it should not be administered to nursing mothers.

4.7 Effects on ability to drive and use machines

Clinical experience with lercanidipine indicates that it is unlikely to impair a patient's ability to drive or use machinery. However, caution should be exercised because dizziness, asthenia, fatigue and rarely somnolence may occur.

4.8 Undesirable effects

About 1.8% of treated patients experienced adverse reactions.
The table below shows the incidence of adverse drug reactions, at least possibly causally related, grouped by MedDRA System Organ Class classification, and ranked by frequency (uncommon, rare).
As shown in the table, the most commonly occurring adverse drug reactions reported in controlled clinical trials are headache, dizziness, peripheral oedema, tachycardia, palpitations, flushing, each occurring in less than 1% of patients.

MedDRA System Organ Class	*Frequency*	*Preferred Terms*
Immune system disorders	Very rare (<1/10,000)	Hypersensitivity
Psychiatric disorders	Rare (>1/10,000 <1/1000)	Somnolence

Nervous system disorders	Uncommon (>1/1000 <1/100)	Headache; dizziness

Cardiac disorders	Uncommon (>1/1000 <1/100)	Tachycardia; palpitations
	Rare (>1/10,000 <1/1000)	Angina pectoris
Vascular disorders	Uncommon (>1/1000 <1/100)	Flushing
	Very rare (<1/10,000)	Syncope
Gastrointestinal disorders	Rare (>1/10,000 <1/1000)	Nausea; dyspepsia; diarrhoea; abdominal pain; vomiting
Skin and subcutaneous tissue disorders	Rare (>1/10,000 <1/1000)	Rash
Musculoskeletal, connective tissue and bone disorders	Rare (>1/10,000 <1/1000)	Myalgia
Renal and urinary disorders	Rare (>1/10,000 <1/1000)	Polyuria
General disorders and administration site conditions	Uncommon (>1/1000 <1/100)	Oedema peripheral
	Rare (>1/10,000 <1/1000)	Asthenia; fatigue

In post-marketing experience, from spontaneous reports the following undesirable effects were reported very rarely (<1/10,000): gingival hypertrophy, reversible increases in serum levels of hepatic transaminases, hypotension, urinary frequency and chest pain.
Some dihydropyridines may rarely lead to precordial pain or angina pectoris. Very rarely patients with pre-existing angina pectoris may experience increased frequency, duration or severity of these attacks. Isolated cases of myocardial infarction may be observed.
Lercanidipine does not appear to influence adversely blood sugar or serum lipid levels.

4.9 Overdose

In the post-marketing experience, three cases of overdose were reported (150 mg, 280 mg and 800 mg of lercanidipine, respectively, ingested in an attempt to commit suicide).

Dose level	*Sign/Symptoms*	*Management*	*Outcome*
150 mg + undefined amount of alcohol	Sleepiness	Gastric lavage Active charcoal	Recovered

280 mg + 5.6 mg moxonidine	Cardiogenic shock Severe myocardial ischemia Mild renal failure	High-dose catecholamines Furosemide Digitalis	Recovered

		Parenteral plasma expanders	
800 mg	Emesis Hypotension	Active charcoal Cathartics Dopamine i.v.	Recovered

As with other dihydropyridines, overdosage might be expected to cause excessive peripheral vasodilatation with marked hypotension and reflex tachycardia. In case of severe hypotension, bradycardia and unconsciousness, cardiovascular support could be helpful, with intravenous atropine for bradycardia.

In view of the prolonged pharmacological effect of lercanidipine, it is essential that the cardiovascular status of patients who take an overdose is monitored for 24 hours at least. There is no information on the value of dialysis. Since the drug is highly lipophilic, it is most probable that plasma levels are no guide to the duration of the period of risk and dialysis may not be effective.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Selective calcium channel blockers with mainly vascular effects

ATC code: C08CA13

Lercanidipine is a calcium antagonist of the dihydropyridine group and inhibits the transmembrane influx of calcium into cardiac and smooth muscle. The mechanism of its antihypertensive action is due to a direct relaxant effect on vascular smooth muscle thus lowering total peripheral resistance. Despite its short pharmacokinetic plasma half-life, lercanidipine is endowed with a prolonged antihypertensive activity because of its high membrane partition coefficient, and is devoid of negative inotropic effects due to its high vascular selectivity.

Since the vasodilatation induced by lercanidipine is gradual in onset, acute hypotension with reflex tachycardia has rarely been observed in hypertensive patients.

As for other asymmetric 1,4-dihydropyridines, the antihypertensive activity of lercanidipine is mainly due to its (S)-enantiomer.

In addition to the clinical studies conducted to support the therapeutic indications, a further small uncontrolled but randomised study of patients with severe hypertension (mean $\pm$ SD diastolic blood pressure of 114.5 $\pm$ 3.7 mmHg) showed that blood pressure

was normalised in 40% of the 25 patients on 20 mg once daily dose and in 56% of 25

patients on 10 mg twice daily doses of lercanidipine. In a double-blind, randomized, controlled study versus placebo in patients with isolated systolic hypertension lercanidipine was efficacious in lowering systolic blood pressure from mean initial values of 172.6 ± 5.6 mmHg to 140.2 ± 8.7 mmHg.

5.2 Pharmacokinetic properties

Lercanidipine is completely absorbed after 10 - 20 mg oral administration and peak plasma levels, 3.30 ng/ml ± 2.09 s.d. and 7.66 ng/ml ± 5.90 s.d. respectively, occur about 1.5 - 3 hours after dosing.

The two enantiomers of lercanidipine show a similar plasma level profile: the time to peak plasma concentration is the same, the peak plasma concentration and AUC are, on average, 1.2-fold higher for the (S) enantiomer and the elimination half-lives of the two enantiomers are essentially the same. No "*in vivo*" interconversion of enantiomers is observed.

Due to the high first pass metabolism, the absolute bioavailability of lercanidipine orally administered to patients under fed conditions is around 10%, although it is reduced to 1/3 when administered to healthy volunteers under fasting conditions.
Oral availability of lercanidipine increases 4-fold when lercanidipine is ingested up to 2 hours after a high fat meal. Accordingly, lercanidipine should be taken before meals.

Distribution from plasma to tissues and organs is rapid and extensive.
The degree of serum protein binding of lercanidipine exceeds 98%. Since plasma protein levels are reduced in patients with severe renal or hepatic dysfunction, the free fraction of the drug may be increased.

Lercanidipine is extensively metabolised by CYP3A4; no parent drug is found in the urine or the faeces. It is predominantly converted to inactive metabolites and about 50% of the dose is excreted in the urine.

"In vitro" experiments with human liver microsomes have demonstrated that lercanidipine shows some degree of inhibition of CYP3A4 and CYP2D6, at concentrations 160- and 40-fold, respectively, higher than those reached at peak in the

plasma after the dose of 20 mg.

Moreover, interaction studies in humans have shown that lercanidipine did not modify the plasma levels of midazolam, a typical substrate of CYP3A4, or of metoprolol, a typical substrate of CYP2D6. Therefore, inhibition of biotransformation of drugs metabolised by CYP3A4 and CYP2D6 by lercanidipine is not expected at therapeutic doses.

Elimination occurs essentially by biotransformation**.**

A mean terminal elimination half life of 8 - 10 hours was calculated and the therapeutical activity lasts for 24 hours because of its high binding to lipid membrane. No accumulation was seen upon repeated administration.

Oral administration of lercanidipine leads to plasma levels of lercanidipine not directly proportional to dosage (non-linear kinetics). After 10, 20 or 40 mg, peak plasma concentrations observed were in the ratio 1:3:8 and areas under plasma concentration-time curves in the ratio 1:4:18, suggesting a progressive saturation of first pass metabolism. Accordingly, availability increases with dosage elevation.

In elderly patients and in patients with mild to moderate renal dysfunction or mild to moderate hepatic impairment the pharmacokinetic behaviour of lercanidipine was shown to be similar to that observed in the general patient population; patients with severe renal dysfunction or dialysis-dependent patients showed higher levels (about 70%) of the drug. In patients with moderate to severe hepatic impairment, the systemic bioavailability of lercanidipine is likely to be increased since the drug is normally metabolised extensively in the liver.

5.3 Preclinical safety data

Safety pharmacological studies in animals have shown no effects on the autonomic nervous system, the central nervous system or on gastrointestinal function at antihypertensive doses.

The relevant effects which have been observed in long-term studies in rats and dogs were related, directly or indirectly, to the known effects of high doses of Ca-antagonists,

predominantly reflecting exaggerated pharmacodynamic activity.

Lercanidipine was not genotoxic and showed no evidence of carcinogenic hazard.

Fertility and general reproductive performance in rats were unaffected by treatment with lercanidipine.

There was no evidence of any teratogenic effect in rats and rabbits; however, in rats, lercanidipine at high dose levels induced pre- and post- implantation losses and delay in foetal development.

Lercanidipine hydrochloride, when administered at high dose (12 mg/kg/day) during labour, induced dystocia.

The distribution of lercanidipine and/or its metabolites in pregnant animals and their excretion in breast milk have not been investigated.

Metabolites have not been evaluated separately in toxicity studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lercanidipine Hydrochloride 20 mg film-coated tablets

Core:

Cellulose, microcrystalline

Maize starch

Sodium starch glycolate (type A)

Silica, colloidal anhydrous

Povidone K 30

Sodium stearyl fumarate

Film-coating:

Hypromellose

Macrogol 6000

Iron oxide yellow (E 172)

Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Lercanidipine Hydrochloride 20 mg film-coated tablets

3 years.

6.4 Special precautions for storage

Store in the original carton in order to protect from light.

6.5 Nature and contents of container

Lercanidipine Hydrochloride 20 mg film-coated tablets

PVC–Al or PVC/PVdC-Al blister packs of 28 film-coated tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Torrent Pharma (UK) Ltd.
Unit 4, Charlwood Court
County Oak Way, Crawley
West Sussex, RH11 7XA
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PL 36687/0013

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

10/2010