LACIPIL™

lacidipine

QUALITATIVE AND QUANTITATIVE COMPOSITION

- Lacidipine, 2 mg - round shaped white engraved on one face.
- Lacidipine, 4 mg - oval white with break line on both faces.
- Lacidipine, 6 mg - oval white biconvex.

PHARMACEUTICAL FORM

Film-coated tablets.

CLINICAL PARTICULARS

Indications

As a treatment of hypertension either alone or in combination with other antihypertensive agents, e.g. beta-blockers, diuretics and ACE inhibitors.

Dosage and Administration

The initial dosage is 2 mg once daily. It should be taken at the same time each day, preferably in the morning, with or without food.

The treatment of hypertension should be adapted to the severity of the condition, and according to individual response.

The dose may be increased to 4 mg and if necessary to 6 mg, after adequate time has been allowed for the full pharmacological effect to occur. In practice this should not be less than three to four weeks, unless the clinical condition requires a more rapid upward titration.

Treatment may be continued indefinitely.

- **Hepatic impairment**

  No dose modification is required in patients with mild or moderate hepatic impairment**.** Insufficient data are available to make a recommendation for patients with severe hepatic impairment (see Warnings and Precautions).

- **Renal impairment**

As lacidipine is not excreted by the kidneys the dose does not require modification in patients with renal impairment.

- **Children**

No experience has been gained with lacidipine in children.

- **Elderly**

No dose modification is required.

Contraindications

– Hypersensitivity to any component of the preparation.

– As with other dihydropyridines, *LACIPIL* is contraindicated in patients with severe aortic stenosis.

Warnings and Precautions

In specialised studies lacidipine has been shown not to affect the spontaneous function of the SA node or to cause prolonged conduction within the AV node. However the theoretical potential for a calcium antagonist to affect the activity of the SA and AV nodes should be noted, and therefore *LACIPIL* should be used with caution in patients with pre-existing abnormalities in the activity of the SA and AV nodes.

As has been reported with other dihydropyridine calcium channel antagonists, *LACIPIL* should be used with caution in patients with congenital or documented acquired QT prolongation. *LACIPIL* should also be used with caution in patients treated concomitantly with medications known to prolong the QT interval such as, class I and III antiarrhythmics, tricyclic antidepressants, some antipsychotics, antibiotics (e.g. erythromycin) and some antihistamines (e.g. terfenadine).

As with other calcium antagonists, *LACIPIL* should be used with caution in patients with poor cardiac reserve.

As with other dihydropyridine calcium antagonists *LACIPIL* should be used with care in patients with unstable angina pectoris.

LACIPIL should be used with caution in patients after recent myocardial infarction.

LACIPIL should be used with caution in patients with impaired liver function because antihypertensive effect may be increased.

There is no evidence that *LACIPIL* impairs glucose tolerance or alters diabetic control.

Interactions

Co-administration of *LACIPIL* with other agents recognised to have a hypotensive effect, including anti-hypertensive agents, (e.g. diuretics, beta-blockers, or ACE inhibitors), may

have an additive hypotensive effect. However, no specific interaction problems have been identified in studies with common antihypertensive agents (e.g. beta-blockers and diuretics) or with digoxin, tolbutamide or warfarin.

The plasma level of *LACIPIL* may be increased by simultaneous administration of cimetidine.

LACIPIL is highly protein bound (more than 95 %) to albumin and alpha-1- glycoprotein.

As with other dihydropyridines, *LACIPIL* should not be taken with grapefruit juice as bioavailability may be altered.

In clinical studies in patients with a renal transplant treated with cyclosporin, *LACIPIL* reversed the decrease in renal plasma flow and glomerular filtration rate induced by cyclosporin.

Lacidipine is known to be metabolised by cytochrome CYP3A4 and, therefore, significant inhibitors and inducers of CYP3A4 administered concurrently may interact with the metabolism and elimination of lacidipine.

Pregnancy and Lactation

There are no data on the safety of *LACIPIL* in human pregnancy.

Animal studies have shown no teratogenic effects or growth impairment.

LACIPIL should only be used in pregnancy when the potential benefits for the mother outweigh the possibility of adverse effects in the foetus or neonate.

The possibility that *LACIPIL* can cause relaxation of the uterine muscle at term should be considered.

Milk transfer studies in animals have shown that lacidipine (or its metabolites) are likely to be excreted into breast milk.

LACIPIL should only be used during lactation when the potential benefits for the mother outweigh the possibility of adverse effects in the foetus or neonate.

Effects on Ability to Drive and Use Machines

None reported.

Adverse Reactions

Data from large clinical trials (internal and published) were used to determine the frequency of very common to uncommon adverse reactions.

The following convention has been used for the classification of frequency:- very common ≥ 1/10, common ≥ 1/100 and <1/10, uncommon ≥ 1/1000 and <1/100, rare ≥ 1/10000 and < 1/1000, very rare <1/10000.

LACIPIL is usually well tolerated. Some individuals may experience minor side-effects which are related to its known pharmacological action of peripheral vasodilation. Such effects, indicated by a hash (#), are usually transient and usually disappear with continued administration of *LACIPIL* at the same dosage.

Psychiatric disorders

Very rare	Depression

Nervous system disorders

Common	#Headache, #dizziness
Very rare	Tremor

Cardiac disorders

Common	#Palpitation, tachycardia
Uncommon	Aggravation of underlying angina, syncope, hypotension

As with other dihydropyridines aggravation of underlying angina has been reported in a small number of individuals, especially at the start of treatment. This is more likely in patients with symptomatic ischaemic heart disease.

Vascular disorders

Common	#Flushing

Gastrointestinal disorders

Common	Stomach discomfort, nausea
Uncommon	Gingival hyperplasia

Skin and subcutaneous tissue disorders

Common	Skin rash (including erythema and itching)
Rare	Angioedema, urticaria

Renal and urinary disorders

Common	Polyuria

General disorders and administration site conditions

Common	Asthenia, #oedema

Investigations

Common	Reversible increase in alkaline phosphatase (clinically significant increases are uncommon)

Overdose

There have been no recorded cases of *LACIPIL* overdosage.

The most likely problem would be prolonged peripheral vasodilation associated with hypotension and tachycardia.

Bradycardia or prolonged AV conduction could theoretically occur.

There is no specific antidote. Standard general measures for monitoring cardiac function and appropriate supportive and therapeutic measures should be used.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Lacidipine is a specific and potent calcium antagonist, with a predominant selectivity for calcium channels in the vascular smooth muscle.

Its main action is to dilate peripheral arterioles, reducing peripheral vascular resistance and lowering blood pressure.

Following the oral administration of 4 mg *LACIPIL* to volunteer subjects, a minimal prolongation of QTc interval has been observed.

Pharmacokinetics

Absorption

Lacidipine is rapidly but poorly absorbed from the gastrointestinal tract following oral dosing and undergoes extensive first-pass metabolism in the liver. Absolute bioavailability averages about 10 %. Peak plasma concentrations are reached between 30 and 150 min.

Metabolism

There are four principal metabolites which possess little, if any pharmacodynamic activity. The drug is eliminated primarily by hepatic metabolism (involving P450 CYP3A4). There is no evidence that lacidipine causes either induction or inhibition of hepatic enzymes.

Elimination

Approximately 70 % of the administered dose is eliminated as metabolites in the faeces and the remainder as metabolites in the urine.

The average terminal half-life of lacidipine ranges from between 13 and 19 h at steady state.

Pre-clinical Safety Data

No additional data of relevance.

PHARMACEUTICAL PARTICULARS

List of Excipients

Tablet core

Lactose
Povidone K30
Magnesium stearate.

Film-coat

As registered locally.

Incompatibilities

None reported.

Shelf Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

LACIPIL tablets should be stored below 30°C.

LACIPIL tablets should be protected from light and therefore should not be removed from their foil pack until required for administration.

If the dosage schedule means that half a 4 mg tablet should be taken, the unused half must be kept in the original foil pack and used within 48 h.

Keep out of reach of children.

Nature and Contents of Container

Double foil blister pack or child-resistant foil blister pack.

Instructions for Use/Handling

Do not remove from foil pack until required for administration.

Not all presentations are available in every country.

Manufactured by Glaxo Wellcome S.A., Aranda de Duero, Spain

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[GlaxoSmithKline logo]