CERTIFICATE OF PROMOTIONAL MATERIAL

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Job Name: Lacipil PI for Health.GSK

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CERTIFICATION
It is certified that this promotional material has been examined in its final form and is believed to be in compliance with relevant local laws & regulations, good ethical practices and standards established in the GSK Promotion and Marketing Code, PHAP Code of Pharmaceutical Marketing Practices and to be consistent with the Certificate of Product Registration (CPR) and Prescribing Information (PI), and is a fair, truthful and balanced presentation of the facts about the product(s).

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Lacidipine
Lacipil®

PRODUCT DESCRIPTION
Lacidipine (*Lacipil*®) *2mg tablet:* white, film-coated, round tablet engraved "2" on one face and plain on the other side. Each tablet contains Lacidipine 2mg.
Lacidipine (*Lacipil*®) *4mg tablet:* white, film-coated, oval biconvex tablet with break line on both sides, engraved with "GS" on one side and "3MS" on the other side. Each tablet contains Lacidipine 4mg.
Lacidipine (*Lacipil*®) *6mg tablet:* white, film-coated, oval biconvex tablet engraved "GXCX3" on one side and plain on the other side. Each tablet contains Lacidipine 6mg.

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 Lacidipine (*Lacipil*®) to volunteer subjects, a minimal prolongation of QTc interval has been observed.
In the four-year randomised double-blind ELSA (European Lacidipine Study on Atherosclerosis) trial, the primary efficacy parameter for atherosclerosis was the measurement of carotid intima-media thickness (IMT) by ultrasonography. The results in the patients treated with Lacidipine (*Lacipil*®) showed significant effects on IMT variables, consistent with an anti-atherogenic effect.
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
The only significant toxicological findings with lacidipine were reversible and consistent with the known pharmacological effects of calcium channel antagonists at high doses - decreased myocardial contractility and gingival hyperplasia in rats and dogs, and constipation in rats.
No evidence of developmental toxicity was seen following administration of lacidipine to pregnant rats or rabbits. In a fertility and reproductive study in rats, embryotoxicity was seen at maternally toxic doses and, consistent with the expected pharmacological activity of a calcium channel antagonist on the myometrium, increased duration of gestation and difficulties during parturition were seen at high doses. Calcium channel antagonists are known to interfere pharmacologically with the normal function of the myometrium during parturition, leading to decreased contractility.
Lacidipine was not genotoxic in a battery of in vitro and in vivo tests. There was no evidence of carcinogenic potential in mice. Consistent with other calcium channel antagonists, there was an increase in benign interstitial cell tumours in the testis in a carcinogenicity study in rats. However, the endocrine mechanisms believed to be involved in the production of interstitial cell hyperplasia and adenomas in the rat are not relevant to humans.

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, Lacidipine (*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 Lacidipine (*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, Lacidipine (*Lacipil*®) should be used with caution in patients with congenital or documented acquired QT prolongation. Lacidipine (*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, Lacidipine (*Lacipil*®) should be used with caution in patients with poor cardiac reserve.

As with other dihydropyridine calcium antagonists Lacidipine (*Lacipil*®) should be used with care in patients with unstable angina pectoris.

Lacidipine (*Lacipil*®) should be used with caution in patients after recent myocardial infarction.

Lacidipine (*Lacipil*®) should be used with caution in patients with impaired liver function because antihypertensive effect may be increased.

There is no evidence that Lacidipine (*Lacipil*®) impairs glucose tolerance or alters diabetic control.

Effects on Ability to Drive and Use Machines

None reported.

DRUG INTERACTIONS

Co-administration of Lacidipine (*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 Lacidipine (*Lacipil*®) may be increased by simultaneous administration of cimetidine.

Lacidipine (*Lacipil*®) is highly protein bound (more than 95 %) to albumin and alpha-1- glycoprotein.

As with other dihydropyridines, Lacidipine (*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, Lacidipine (*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 Lacidipine (*Lacipil*®) in human pregnancy.

Animal studies have shown no teratogenic effects or growth impairment (see Pre-clinical Safety Data).

Lacidipine (*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 Lacidipine (*Lacipil*®) can cause relaxation of the uterine muscle at term should be considered (see Pre-clinical Safety Data).

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

Lacidipine (*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.

ADVERSE EFFECTS

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.

Lacidipine (*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 Lacidipine (*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)

OVERDOSAGE AND TREATMENT
There have been no recorded cases of Lacidipine (*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.

STORAGE CONDITIONS
Lacidipine (*Lacipil*®) tablets should be stored at temperatures not exceeding 30°C.
Lacidipine (*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.

INSTRUCTIONS FOR USE AND HANDLING
Do not remove from foil pack until required for administration

AVAILABILITY
- Lacidipine (*Lacipil*®) 2 mg Film-coated Tablet: 7 tablets per Alu/Alu Blister (Box of 56's)
- Lacidipine (*Lacipil*®) 4 mg Film-coated Tablet: 7 tablets per Alu/Alu Blister (Box of 56's)
- Lacidipine (*Lacipil*®) 6 mg Film-coated Tablet: 7 tablets per Alu/Alu Blister (Box of 28's)

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
Keep all medicines out of reach of children.

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GlaxoSmithKline

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