Public Assessment Report

Decentralised Procedure

Zanidip Novum 8mg Film Coated Tablets
Zanidip Novum 16mg Film Coated Tablets

UK/H/0132/003-004/DC

Licence nos: PL 04595/0022-23

Recordati Industria Chimica e Farmaceutica S.p.A.
LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Recordati Industria Chimica Farmaceutica Marketing Authorisations (licences) for the medicinal products Zanidip Novum 8mg and 16mg Tablets. These are prescription-only medicines (POM). These medicines are used to treat high blood pressure, also known as hypertension.

This medicine contains the active ingredient, lercanidipine hydrochloride. Lercanidipine reduces blood pressure by its actions on the blood vessels and the heart.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Zanidip Novum 8mg and 16mg tablets outweigh the risks; hence Marketing Authorisations have been granted.
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## Module 1

| Product Name                | Zanidip Novum 8mg Film Coated Tablets  
<table>
<thead>
<tr>
<th></th>
<th>Zanidip Novum 16mg Film Coated Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Application</td>
<td>Known Active Substance, Article 8.3</td>
</tr>
<tr>
<td></td>
<td>(Line extension)</td>
</tr>
<tr>
<td>Active Substance</td>
<td>Lercanidipine hydrochloride</td>
</tr>
<tr>
<td>Form</td>
<td>Film Coated Tablets</td>
</tr>
<tr>
<td>Strength</td>
<td>8mg</td>
</tr>
<tr>
<td></td>
<td>16mg</td>
</tr>
</tbody>
</table>
| MA Holder                   | Recordati Industria Chimica e Farmaceutica S.p.A  
|                            | via Matteo Civitali, 1, 20148 – Milan, Italy |
| RMS                         | UK                                     |
| CMS                         | Austria, Belgium, Germany, Denmark, Greece, Spain, Finland,  
|                            | Italy, Luxembourg, The Netherlands, Portugal and Sweden |
| Procedure Number            | UK/H/0132/003-004/DC                   |
| End of Procedure            | 2nd February 2010                      |
MODULE 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Zanidip Novum 8 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains as active ingredient lercanidipine 7.55 mg (present as lercanidipine hydrochloride 8 mg).

Excipients: one film-coated tablet contains 45 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Yellow, circular, biconvex tablet.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Zanidip Novum is indicated for the treatment of mild to moderate essential hypertension.

4.2 Posology and method of administration
Zanidip Novum 8 mg film-coated tablets is bioequivalent to Zanidip 10 mg film-coated tablets.

The recommended dosage of Zanidip Novum is 8 mg orally once a day at least 15 minutes before meals; the dose may be increased to 16 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 Zanidip Novum 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 of lercanidipine hydrochloride is steep with a plateau close to the higher recommended dose, it is unlikely that efficacy will be improved by doses of Zanidip Novum higher than 16 mg 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 and adolescents: Zanidip Novum is not recommended for use in children and adolescent below age 18 due to a lack of data on safety and efficacy (see section 5.1 and 5.2). There is no experience in children (see section 4.4 and 5.2).

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 16 mg daily of Zanidip Novum 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.

Zanidip Novum is not recommended for use in patients with severe hepatic impairment or in patients with severe renal impairment (creatinine clearance < 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),
- cyclosporin (see section 4.5),
- grapefruit juice (see section 4.5).

4.4 Special warnings and precautions for use
Special care should be exercised when Zanidip Novum 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 Zanidip Novum 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 16 mg daily of Zanidip Novum
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.
Zanidip Novum is not recommended for use in patients with severe hepatic impairment or in patients
with severe renal impairment (creatinine clearance < 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).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-
galactose malabsorption should not take Zanidip Novum.

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 Zanidip Novum 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 Cmax for
the eutomer S-lercanidipine).

Cyclosporin and lercanidipine should not be administered together (see section 4.3).
Increased plasma levels of both lercanidipine and cyclosporin have been observed following concomitant
administration. A study in young healthy volunteers has shown that when cyclosporin was administered
3 hours after lercanidipine intake, the plasma levels of lercanidipine did not change, while the AUC of
cyclosporin increased by 27%. However, the co-administration of lercanidipine HCl with cyclosporin has caused a 3-fold increase of the plasma levels of lercanidipine and a 21% increase of the cyclosporin 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 lercanidipine HCl was concomitantly administered 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 Zanidip Novum is co-prescribed with other substrates of CYP3A4, like terfenadine, astemizole, class III antiarrhythmic drugs such as amiodarone, quinidine.

Co-administration of Zanidip Novum 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 HCl was co-administered with metoprolol, a $\beta$-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 $\beta$-blockers and may therefore occur with other drugs of this class. Consequently, Zanidip Novum 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 lercanidipine HCl in patients chronically treated with $\beta$-methylidyldigoxin showed no evidence of pharmacokinetic interaction. Healthy volunteers treated with digoxin following dosing with lercanidipine HCl 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 lercanidipine HCl 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 $\beta$-hydroxycacid by 28%. It is unlikely that such changes are of clinical relevance. No interaction is expected when Zanidip Novum is administered in the morning and simvastatin in the evening, as indicated for such drug.

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

Lercanidipine HCl 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, Zanidip Novum 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
Zanidip Novum has minor or moderate influence on the ability to drive and use machines because dizziness, asthenia, fatigue and rarely somnolence may occur.
No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects
About 1.8% of patients treated with lercanidipine HCl 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.

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Frequency</th>
<th>Preferred Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune System Disorders</td>
<td>Very rare (&lt;1/10,000)</td>
<td>hypersensitivity</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Rare (≥1/10,000 to &lt;1/1000)</td>
<td>somnolence</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Uncommon (≥1/1000 to &lt;1/100)</td>
<td>headache; dizziness</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>Rare (≥1/10,000 to &lt;1/1000)</td>
<td>angina pectoris</td>
</tr>
<tr>
<td></td>
<td>Uncommon (≥1/1000 to &lt;1/100)</td>
<td>tachycardia; palpitations</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>Uncommon (≥1/1000 to &lt;1/100)</td>
<td>flushing</td>
</tr>
<tr>
<td></td>
<td>Very rare (&lt;1/10,000)</td>
<td>syncope</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Rare (≥1/10,000 to &lt;1/1000)</td>
<td>nausea; dyspepsia; diarrhoea; abdominal pain; vomiting</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Rare (≥1/10,000 to &lt;1/1000)</td>
<td>rash</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>Rare (≥1/10,000 to &lt;1/1000)</td>
<td>myalgia</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td>Rare (≥1/10,000 to &lt;1/1000)</td>
<td>Polyuria</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Uncommon (≥1/1000 to &lt;1/100)</td>
<td>oedema peripheral</td>
</tr>
<tr>
<td></td>
<td>Rare (≥1/10,000 to &lt;1/1000)</td>
<td>asthenia; fatigue</td>
</tr>
</tbody>
</table>

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).
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 ± SD diastolic blood pressure of 114.5 ± 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 HCl.
In a double-blind, randomized, controlled study versus placebo in patients with isolated systolic hypertension lercanidipine HCl 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
Absorption:
Zanidip Novum 8 mg and 16 mg tablets are bioequivalent to Zanidip 10 and 20 mg tablets respectively. Similar lercanidipine Cmax and AUC are obtained. No significant differences in Tmax which occurs at about 1.0-1.5 hours (as median) after dosing are observed.
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 HCl orally administered to healthy volunteers under fasting conditions is about 3.3%. When Zanidip Novum is administered immediately after a high fat meal compared to being administered during fasting conditions, $C_{\text{max}}$ and AUC are increased 1.8- and 1.9-fold respectively.

Distribution:
Distribution of lercanidipine 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.

Biotransformation:
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 Zanidip Novum is not expected at therapeutic doses.

Elimination:
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.

Linearity/non linearity:
Oral administration of lercanidipine HCl leads to plasma levels not directly proportional to dosage (non-linear kinetics). After administration of lercanidipine HCl 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.

Characteristics in patients:
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 HCl, 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

Tablet core:
Lactose monohydrate
Microcrystalline cellulose
Povidone K30
Sodium starch glycolate
Silica colloidal anhydrous
Poloxamer 407
Magnesium stearate

Film coating:
Hypermellose
Talc
Titanium dioxide (E171)
Macrogol 6000
Iron oxide (E172)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container
Opaque PVC/PE/PVDC - Aluminium blisters.
Packs of 7, 14, 28, 35, 50, 56, 98 and 100 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.
Any unused product or waste material should be disposed of in accordance with the local requirements.

7 MARKETING AUTHORISATION HOLDER

RECORDATI Industria Chimica e Farmaceutica S.p.A.
Via Matteo Civitali, 1
20148 Milan (Italy)

8 MARKETING AUTHORISATION NUMBER(S)

PL 04595/0022

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/02/2010

10 DATE OF REVISION OF THE TEXT

22/02/2010
1 NAME OF THE MEDICINAL PRODUCT
Zanidip Novum 16 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains as active ingredient lercanidipine 15.10 mg (present as lercanidipine hydrochloride 16 mg).

Excipients: one film-coated tablet contains 80 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Pink, circular, biconvex tablet.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Zanidip Novum is indicated for the treatment of mild to moderate essential hypertension.

4.2 Posology and method of administration
Zanidip Novum 16 mg film-coated tablets is bioequivalent to Zanidip 20 mg film-coated tablets.

The recommended dosage of Zanidip Novum is 8 mg orally once a day at least 15 minutes before meals; the dose may be increased to 16 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 Zanidip Novum 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 of lercanidipine hydrochloride is steep with a plateau close to the higher recommended dose, it is unlikely that efficacy will be improved by doses of Zanidip Novum higher than 16 mg 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 and adolescents: Zanidip Novum is not recommended for use in children and adolescent below age 18 due to a lack of data on safety and efficacy (see section 5.1 and 5.2). There is no experience in children (see section 4.4 and 5.2).

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 16 mg daily of Zanidip Novum 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.

Zanidip Novum is not recommended for use in patients with severe hepatic impairment or in patients with severe renal impairment (creatinine clearance < 30 ml/min).

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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),
cyclosporin (see section 4.5),
grapefruit juice (see section 4.5).

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Special care should be exercised when Zanidip Novum 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 Zanidip Novum 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).

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Zanidip Novum is not recommended for use in patients with severe hepatic impairment or in patients with severe renal impairment (creatinine clearance < 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).
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Zanidip Novum.

4.5 Interaction with other medicinal products and other forms of interaction
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Co-prescription of Zanidip Novum 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).
Cyclosporin and lercanidipine should not be administered together (see section 4.3).
Increased plasma levels of both lercanidipine and cyclosporin have been observed following concomitant administration. A study in young healthy volunteers has shown that when cyclosporin was administered 3 hours after lercanidipine intake, the plasma levels of lercanidipine did not change, while the AUC of cyclosporin increased by 27%. However, the co-administration of lercanidipine HCl with cyclosporin has caused a 3-fold increase of the plasma levels of lercanidipine and a 21% increase of the cyclosporin 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 lercanidipine HCl was concomitantly administered 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 Zanidip Novum is co-prescribed with other substrates of CYP3A4, like terfenadine, astemizole, class III antiarrhythmic drugs such as amiodarone, quinidine.

Co-administration of Zanidip Novum 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 HCl was co-administered with metoprolol, a $\beta$-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 $\beta$-blockers and may therefore occur with other drugs of this class. Consequently, Zanidip Novum 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 lercanidipine HCl in patients chronically treated with $\beta$-methyldigoxin showed no evidence of pharmacokinetic interaction. Healthy volunteers treated with digoxin following dosing with lercanidipine HCl 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 lercanidipine HCl 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 $\beta$-hydroxyacid by 28%. It is unlikely that such changes are of clinical relevance. No interaction is expected when Zanidip Novum is administered in the morning and simvastatin in the evening, as indicated for such drug.

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

Lercanidipine HCl 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, Zanidip Novum 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**

Zanidip Novum has minor or moderate influence on the ability to drive and use machines because dizziness, asthenia, fatigue and rarely somnolence may occur. No studies on the effects on the ability to drive and use machines have been performed.
4.8 Undesirable effects

About 1.8% of patients treated with lercanidipine HCl 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.

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Frequency</th>
<th>Preferred Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune System Disorders</td>
<td>Very rare (&lt;1/10,000)</td>
<td>hypersensitivity</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Rare (≥1/10,000 to &lt;1/1000)</td>
<td>somnolence</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Uncommon (≥1/1000 to &lt;1/100)</td>
<td>headache; dizziness</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>Rare (≥1/10,000 to &lt;1/1000)</td>
<td>angina pectoris</td>
</tr>
<tr>
<td></td>
<td>Uncommon (≥1/1000 to &lt;1/100)</td>
<td>tachycardia; palpitations</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>Uncommon (≥1/1000 to &lt;1/100)</td>
<td>flushing</td>
</tr>
<tr>
<td></td>
<td>Very rare (&lt;1/10,000)</td>
<td>syncope</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Rare (≥1/10,000 to &lt;1/1000)</td>
<td>nausea; dyspepsia; diarrhoea; abdominal pain; vomiting</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Rare (≥1/10,000 to &lt;1/1000)</td>
<td>rash</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>Rare (≥1/10,000 to &lt;1/1000)</td>
<td>myalgia</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td>Rare (≥1/10,000 to &lt;1/1000)</td>
<td>Polyuria</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Uncommon (≥1/1000 to &lt;1/100)</td>
<td>oedema peripheral</td>
</tr>
<tr>
<td></td>
<td>Rare (≥1/10,000 to &lt;1/1000)</td>
<td>asthenia; fatigue</td>
</tr>
</tbody>
</table>

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).
<table>
<thead>
<tr>
<th>Dosage</th>
<th>Symptoms</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 mg + undefined amount of alcohol</td>
<td>Sleepiness</td>
<td>Gastric lavage, Active charcoal, Recovered</td>
</tr>
<tr>
<td>280 mg + 5.6 mg moxonidine</td>
<td>Cardiogenic shock, Severe myocardial ischaemia, Mild renal failure</td>
<td>High-dose catecholamines, Furosemide, Digitalis, Parenteral plasma expanders, Recovered</td>
</tr>
<tr>
<td>800 mg</td>
<td>Emesis, Hypotension</td>
<td>Active charcoal, Cathartics, Dopamine i.v., Recovered</td>
</tr>
</tbody>
</table>

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 ± SD diastolic blood pressure of 114.5 ± 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 HCl.
In a double-blind, randomized, controlled study versus placebo in patients with isolated systolic hypertension lercanidipine HCl 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
Absorption:
Zanidip Novum 8 mg and 16 mg tablets are bioequivalent to Zanidip 10 and 20 mg tablets respectively. Similar lercanidipine C<sub>max</sub> and AUC are obtained. No significant differences in T<sub>max</sub> which occurs at about 1.0-1.5 hours (as median) after dosing are observed.
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 HCl orally administered to healthy volunteers under fasting conditions is about 3.3%. When Zanidip Novum is administered immediately after a high fat meal compared to being administered during fasting conditions, Cmax and AUC are increased 1.8- and 1.9-fold respectively.

Distribution:
Distribution of lercanidipine 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.

Biotransformation:
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 Zanidip Novum is not expected at therapeutic doses.

Elimination:
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.

Linearity/non linearity:
Oral administration of lercanidipine HCl leads to plasma levels not directly proportional to dosage (non-linear kinetics). After administration of lercanidipine HCl 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.

Characteristics in patients:
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 HCl, 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

Tablet core:
- Lactose monohydrate
- Microcrystalline cellulose
- Povidone K30
- Sodium starch glycolate
- Silica colloidal anhydrous
- Poloxamer 407
- Magnesium stearate

Film coating:
- Hypromellose
- Talc
- Titanium dioxide (E171)
- Macrogol 6000
- Iron oxide (E172)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container
Opaque PVC/PE/PVDC - Aluminium blisters.
Packs of 7, 14, 28, 35, 50, 56, 98 and 100 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.
Any unused product or waste material should be disposed of in accordance with the local requirements.

7 MARKETING AUTHORISATION HOLDER
RECORDATI Industria Chimica e Farmaceutica S.p.A.
Via Matteo Civitali, 1
20148 Milan (Italy)

8 MARKETING AUTHORISATION NUMBER(S)
PL 04595/0023

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
22/02/2010

10 DATE OF REVISION OF THE TEXT
22/02/2010
MODULE 3
PRODUCT INFORMATION LEAFLET

Zanidip Novum 8 mg & 16 mg Film Coated Tablets

1. WHAT ZANIDIP NOVUM IS AND WHAT IT IS USED FOR

Zanidip Novum 8 mg & 16 mg Film Coated Tablets (containing zanidepine citrate) is a type of medication that helps lower blood pressure. It is used to treat hypertension, which is a condition where the blood pressure is too high.

2. BEFORE YOU TAKE ZANIDIP NOVUM AND TELL YOUR DOCTOR IF:

- You are allergic to zaneprone or any other ingredients in Zanidip Novum tablets.
- You have had a liver disease or kidney disease.
- You have taken certain medicines recently (check with your doctor).
- You have diabetes, kidney disease, or hypertension.
- You are taking any other medicines (check with your doctor).
- You have had a liver disease.
- You have had a kidney disease.
- You have any other medical conditions.

3. HOW TO TAKE ZANIDIP NOVUM

Take Zanidip Novum by mouth. Follow the instructions on the container or those provided by your doctor. Take the tablets at the same time each day, preferably in the morning. Do not crush or break the tablets.

4. POSSIBLE SIDE EFFECTS

Some possible side effects of Zanidip Novum include:
- Headache
- Dizziness
- Fatigue
- Nausea
- Constipation
- Diarrhea
- Increased appetite
- Weight gain
- Dry mouth
- Blurred vision
- Muscle weakness
- Dizziness
- Nervousness
- Insomnia
- Mood changes

5. HOW TO STORE ZANIDIP NOVUM

Store Zanidip Novum at room temperature (5°C to 30°C). Keep it in a tight container, away from heat and direct sunlight.

6. FURTHER INFORMATION

If you have any further questions or concerns about Zanidip Novum, please consult your doctor or pharmacist.

PREGNANCY AND BREAST FEEDING

It is not known whether Zanidip Novum can cause harm to the unborn baby. If you are pregnant or planning to become pregnant, discuss the benefits and risks with your doctor.

DRIVING AND USING MACHINERY

Driving and using machinery while taking Zanidip Novum is generally safe. However, if you experience symptoms such as dizziness or confusion, you should avoid driving or operating machinery.

INFORMATION ABOUT SOME INGREDIENTS OF ZANIDIP NOVUM

Zanidepine citrate is a type of medication that helps to lower blood pressure. It is not known whether Zanidip Novum can cause harm to the unborn baby. If you are pregnant or planning to become pregnant, discuss the benefits and risks with your doctor.

3. HOW TO TAKE ZANIDIP NOVUM

You should take Zanidip Novum as directed by your doctor. Follow all instructions carefully. You should take the tablets at the same time each day, preferably in the morning. If you miss a dose, take it as soon as you remember. You should not take double doses.

7. REPORTING SUSPECTED ADVERSE REACTIONS

If you suspect an adverse reaction to Zanidip Novum, contact your doctor or pharmacist immediately. They will be able to provide you with the necessary advice.

8. COMPLAINTS AND FEEDBACK

If you have any complaints or feedback about Zanidip Novum, contact your doctor or pharmacist.

9. RESERVATION OF PATIENTS’ RIGHTS

Your doctor or pharmacist may reserve the right to refuse to prescribe Zanidip Novum if they feel it is not appropriate for your condition.
Patients with liver or kidney problems: Special care is needed in starting treatment. In these patients, an increase in daily dose to 16 mg should be approached with caution.

Children: This medicine should not be used in children under 10 years of age.

If you have any further questions on the use of this product ask your doctor.

5. HOW TO STORE ZANIDIP NOVUM

Keep out of the reach and sight of children.

Do not use Zanidip Novum after the expiry date which is stated on the blister pack and also on the blister strip. The expiry date refers to the last day of that month.

Store in the original package to protect from light and moisture. The original package should be kept in a dry place.

Medicines should not be disposed of via household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. FURTHER INFORMATION

WHAT ZANIDIP NOVUM CONTAINS

- Each tablet of Zanidip Novum 8 mg contains as active ingredient: 755 mg of levamlodipine (equal to levamlodipine hydrochloride 8 mg) and is equivalent to, gives the same concentrations of active substance in blood, to a tablet of Zanidip 10 mg.
- Each tablet of Zanidip Novum 16 mg contains as active ingredient: 1,510 mg of levamlodipine (equal to levamlodipine hydrochloride 16 mg) and is equivalent to, gives the same concentrations of active substance in blood, to a tablet of Zanidip 20 mg.

The other ingredients are:
- Corn soda, lactose monohydrate, microcrystalline cellulose, Povidone Sodium starch glycolate, calcium chloride anhydrous, Polacar A, Magnesium stearate.
- Film coating: Hydroxypropyl, polyethylene glycol 6000, iron oxide (E172), Titanium dioxide (E171), Macrogol 1000, (E1520), iron oxide (E171).

WHAT ZANIDIP NOVUM LOOKS LIKE AND CONTENTS OF THE PACK

Zanidip Novum 8 mg yellow, circular, coated, prolong release, Zanidip Novum 16 mg, orange-coated, prolong release.
Zanidip Novum is available in blister packs of 7, 14, 28, 35, 56, 98, 160 tablets. Not all pack sizes may be marketed.

MARKETING AUTHORIZATION-HOLDER AND MANUFACTURER

Marketing Authorisation Holder:
RESEARCH Indiva Pharma S.p.A. - Via Matteo Cialdi 1 - 20161 Milan Italy

Pharmaceutical:
Pfizer Italia S.r.l., Via Carbone, 19, 00189 Roma, Italy or
RESEARCH Indiva Pharma S.p.A. - Via Matteo Cialdi 1 - 20161 Milan Italy

This medicinal product is authorised in the following Member State of the EEA:

Austria
Belgium
Germany
Denmark
Greece
Ireland
Italy
Luxembourg
Netherlands
Portugal
Sweden
United Kingdom

Date of last revision of the text 02/24/19
Module 4
Labelling

Carton
MODULE 5

SCIENTIFIC DISCUSSION DURING INITIAL PROCEDURE

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Zanidip Novum 8mg & 16 mg Film Coated Tablets, in the treatment of mild to moderate essential hypertension, is approvable.

This application was submitted via the decentralised procedure in accordance with Article 8(3) of Directive 2001/83/EC and is for the addition of new strengths of the known active substance lercanidipine hydrochloride, as line extensions to the existing marketing authorisations for Zanidip 10mg & 20mg film-coated Tablets.

The applicant argues that this application is a line extension of the already marketed product. As there is no experience in children with the marketed formulation the new formulation will not be developed for paediatric use. A paediatric development plan therefore was not conducted with the new formulation.

Recordati is the Marketing Authorisation holder for the originator products, Zanidip 10 and 20 mg film-coated tablets, registered in the UK since March 1996 and August 2002 respectively. Both originator products have been marketed worldwide in European and non-European countries.

The applicant claims that the new strength of 8mg (Zanidip Novum 8mg) is bioequivalent to Zanidip 10mg and that the new strength of 16mg (Zanidip Novum 16mg) is bioequivalent to Zanidip 20mg, both from Recordati, marketed worldwide.

Zanidip Novum is an antihypertensive drug containing lercanidipine (as lercanidipine hydrochloride) as the active ingredient. Lercanidipine is a third generation 1,4-dihydropyridine calcium antagonist with a potent vascular selective calcium entry blocking activity without any negative inotropic activity. It has been used for the treatment of hypertension for many years.

Lercanidipine exists as a racemate, with anti-hypertensive activity residing primarily in the S-enantiomer. The R-enantiomer and S-enantiomers show similar plasma profiles. No interconversion of the enantiomers occurs in vivo.

These products are indicated for the treatment of mild to moderate essential hypertension.

A new formulation containing 8 and 16mg lercanidipine hydrochloride has been developed to improve bioavailability of the active principle and lower food effect. The indication remains the same as for currently licensed lercanidipine hydrochloride 10mg and 20mg tablets.

The application is in accordance with Article 8.3 of Directive 2001/83/EC as amended. The submitted documentation in relation to the proposed product is of sufficient quality and is consistent with the current EU regulatory requirements. Satisfactory quality, pre-clinical and clinical overviews have been submitted.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

A formal Environment Assessment was not submitted. This is acceptable as no increase in environmental risk is to be expected compared to that of the reference product.
Since a literature review has been presented for the Non-clinical Overview, it is not known whether the studies cited were conducted in accordance with the GLP regulations. However, it is assumed that the studies conducted by the innovator would have been in compliance with the standards prevailing at the time.

**Pharmacovigilance system**
The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provided adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

**Risk Management Plan**
A risk management plan has been submitted and was deemed acceptable on the basis that the drug substance’s and class of drugs’ safety profile is well known. The possibility of confusing the new product with the old product should be adequately resolved by using a suffix to the product name and thus there are no other steps that need be taken to avoid confusion.

### II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Zanidip Novum 8mg Film Coated Tablets  
| | Zanidip Novum 16mg Film Coated Tablets |
| Name(s) of the active substance(s) (INN) | Lercanidipine hydrochloride |
| Pharmacotherapeutic classification (ATC code) | Selective calcium channel blockers C08CA13 |
| Pharmaceutical form and strength(s) | Film-coated tablets, 8mg, 16mg |
| Reference numbers for the Decentralised Procedure | UK/H/0132/003-004/DC |
| Reference Member State | United Kingdom |
| Member States concerned | Austria, Belgium, Germany, Denmark, Greece, Spain, Finland, Italy, Luxembourg, The Netherlands, Portugal and Sweden |
| Marketing Authorisation Number(s) | PL 04595/0022-23 |
| Name and address of the authorisation holder | Recordati Industria Chimica e Farmaceutica S.p.A via Matteo Civitali, 1, 20148 – Milan, Italy |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

3.2.S.1.1 Nomenclature

INN Name: Lercanidipine hydrochloride

Chemical Names:
- 2-[(3,3-diphenylpropyl)methylamino]-1,1-dimethyl-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenoxy)-3,5-pyridinedicarboxylate hydrochloride.
- 1,1-dimethyl-2-[N-(3,3-diphenylpropyl)-N-methylamino]ethylmethyl-2,6-dimethyl-4-(3-nitrophenoxy)-1,4-dihydropyridine-3,5-dicarboxylate hydrochloride.
- 1,1-dimethyl-2-[N-(3,3-diphenylpropyl)-N-methylamino]ethyl-2,6-dimethyl-5-methoxycarbonyl-4-(3-nitrophenoxy)-1,4-dihydropyridine-3-carboxylate hydrochloride.
- 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenoxy)-3,5-pyridinedicarboxylic acid 2-[(3,3-diphenylpropyl)methylamino]-1,1-dimethylethyl methyl ester hydrochloride.
- 3,5-pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenoxy)-2-[(3,3-diphenylpropyl)methylamino]-1,1-dimethylethyl methyl ester hydrochloride.

The CAS numbers for Lercanidipine base and salt are: [132866-11-6] and [100427-26-7] respectively.

Structural formula:

![Structural formula of Lercanidipine hydrochloride]

Molecular formula: C_{36}H_{41}N_{3}O_{6}.HCl

Molecular weight: 648.205

General Properties

Physical form: A yellow powder (crystalline form)
Solubility: Soluble in methanol and practically insoluble in water.

Lercanidipine hydrochloride complies with in-house specifications.
Manufacture
An Active Substance Master File (ASMF) has been provided covering the manufacture and control of the drug substance lercanidipine hydrochloride.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the drug substance.

An appropriate specification is provided for lercanidipine hydrochloride, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specifications.

Satisfactory specifications and certificates of analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Suitable certificates of analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing lercanidipine hydrochloride to be physically and chemically stable drug, and supporting an appropriate retest period.

DRUG PRODUCT
Other ingredients
Other ingredients inside the tablet core are pharmaceutical excipients, namely lactose monohydrate, microcrystalline cellulose, povidone K30, sodium starch glycolate, silica colloidal anhydrous, poloxamer 407 and magnesium stearate.

The tablet film-coating consists of pharmaceutical excipients, namely hypromellose, talc, titanium dioxide (E171), macrogol 6000 and iron oxide (E172). All excipients comply with their relevant Ph Eur monographs. Satisfactory Certificates of Analysis have been provided for all excipients. An appropriate justification for the inclusion of each excipient has been provided.

With the exception of lactose monohydrate, none of the excipients used contain material of animal or human origin. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as those intended for human consumption.

No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development
The aim was to develop two formulations containing lercanidipine hydrochloride which were chemically stable solid dosage forms under normal and accelerated conditions with most favourable physical attributes enabling at least 20% dose reduction but possessing essentially
equal in vivo performance compared to the reference product Zanedip tablets, marketed by Recordati.

A satisfactory, detailed pharmaceutical development has been provided. For all studied formulations appropriate description of the composition, dissolution profiles and physical attributes of tablets manufactured (hardness and disintegration time) has been provided in support of each decision taken.

The development of the product focused on improving the dissolution rate by enhancing the drug solubility.

**Dissolution profiles**
The dissolution profiles of the drug products have been extensively studied during the formulation trials with comparative in vitro and in vivo tests. These are satisfactory.

**Manufacture**
A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Supporting data have been provided from three pilot-scale batches of each strength of the finished product and the results appear satisfactory. The applicant commits to place the first three commercial batches produced under stability testing. This is satisfactory.

**Manufacturing process**
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. In-process controls are appropriate considering the nature of the product and the method of manufacture.

**Finished product specification**
The finished product specifications are satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis for all working standards used have been provided and are satisfactory.

**Container Closure System**
The product is packaged in blisters composed of polyvinylchloride/polyethylene/polyvinylidenechloride/aluminium (PVC/PE/PVdC/Al). Specifications and a Certificate of Analysis for the package types used have been provided. All primary product packaging complies with EU legislation regarding contact with food. The product is packaged in blister packs of 7, 14, 28, 35, 50, 56, 98 and 100 tablets. The product is then packed into a cardboard box. Not all pack sizes may be marketed. The Marketing Authorisation Holder (MAH) has committed to submitting mock-ups for all packaging for assessment before those pack sizes are commercially marketed.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. The precautions “Store in the original package in order to protect from light and moisture” is considered acceptable.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL),
Labels
The SmPC, PIL and labelling are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with
target patient groups (“user testing”), in accordance with Article 59 of Council Directive
2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and
organised, easy to understand and written in a comprehensive manner. The test shows that
the patients/users are able to act upon the information that it contains.

MAA form
The MAA form is pharmaceutically acceptable.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is
a suitable summary of the pharmaceutical dossier.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.

III.2 PRE-CLINICAL ASPECTS
The pharmacodynamic, pharmacokinetic and toxicological properties of lercanidipine
hydrochloride are well known. As lercanidipine is a widely used, well-known active
substance, the applicant has not provided additional studies and further studies are not
required. Overview based on literature review is, thus, appropriate. The present applications
are for a suprabioavailable formulation, of which the 8mg and 16mg strengths are stated to be
bioequivalent to the currently available Zanidip 10mg and 20mg strengths, respectively. In
this event, no increased toxicity is expected from use of the new formulations and no new
non-clinical data are required.

The non-clinical overview has been written by a qualified pharmacist. The report refers to 49
publications up to year 2003.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and
toxicology is adequate.

A suitable justification for the absence of an environmental risk assessment has been
provided.

Conclusions
There are no objections to approval of Zanidip Novum 8mg & 16mg film-coated Tablets
from a non-clinical point of view.

III.3 CLINICAL ASPECTS
Pharmacokinetics
The applicant has presented 3 bioequivalence studies: 2 in fasting state with 8mg and 16mg
Zanidip Novum. In addition another study with Zanidip Novum 16mg tablet has been
submitted to demonstrate food effect.
Biowaiver
The applicant has conducted fed state bioequivalence study only with Zanidip Novum 16 mg tablet and has argued a biowaver for the lower strength. This is acceptable as the tablets are recommended for administration in the fasting state.

Assessor's comment:
The biowaver for fed study with lower strength Zanidip Novum 8mg is accepted. Food effect is more than adequately demonstrated in the study performed with the higher strength. This can be extrapolated to the lower strength tablet.

Pharmacokinetic studies
As stated above 3 bioequivalence studies have been submitted; single dose fasting studies with Zanidip Novum 8mg (Study AA 44452) and 16mg (Study AA 70948) and a single dose fed study with Zanidip Novum 16 mg (Study AA 74542)

STUDY AA 44452 (Fasting study, 8mg)

Methods
Study design
This was a randomised, comparative, single-dose, 2-way crossover bioequivalence study of the proposed product 8mg Lercanidipine Hydrochloride tablet and the reference product 10mg Lercanidipine Hydrochloride tablet. The tablets were administered in a fasting state to healthy volunteers.

Assessor's comment: The study design is acceptable. The washout and sampling period were adequate. The drug is intended to be administered in a fasting state hence this study is appropriate.

Test and reference products

Test Product - A:
Lercanidipine HCl 8mg

Reference Product - B:
ZANEDIP® 10MG*

* Lercanidipine HCl 10mg

Assessor's comment: The reference product chosen for the bioequivalence study is appropriate.

Population(s) studied
A total of 80 healthy volunteers (52 males and 28 females) were recruited, 78 completed the study. Two subjects were withdrawn/discontinued from the study (1 due to positive cocaine screen and 1 due to subject cancelling period 2).

Assessor's comment: The number of subjects was more than adequate. With this sample size, 2 drop outs would not have made much difference to the results. The study report clearly explains the reason for dropout.
Analytical methods
Both S and R enantiomers were determined using a fully validated chiral HPLC/MS/MS method.

Assessor's comment: The study was conducted in accordance with GLP guidance. The analytical method was acceptable and was validated pre-study.

Pharmacokinetic Variables
The pharmacokinetic variables investigated were AUC0-t, AUC0-inf, AUC0-τ/AUC0-inf, Cmax, tmax, Kel and τ½. These parameters were measured for S- and R-lercanidipine.

Assessor's comment: The pharmacokinetic variables chosen were appropriate.

Statistical methods
For the concentration and pharmacokinetic data, arithmetic means, standard deviation (SD), coefficients of variation (CV%), geometric means, median, minimum and maximum values were calculated. ANOVA were performed on the ln-transformed AUC0-t, AUC0-inf and Cmax. Ratio of LSM were calculated from the ln-transformed AUC0-t, AUC0-inf and Cmax for both S- and R-lercanidipine. 90% confidence interval were derived. Non-parametric analysis was used for Tmax.

Assessor's comment: Statistical methods chosen were appropriate.

Results
The confidence interval for Cmax and AUC from this study are shown in the table below.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>S-lercanidipine 8mg lercanidipine HCl tablets (A) Vs. 10mg lercanidipine HCl tablets (Zanedip®) (B)</th>
<th>R-lercanidipine 8mg lercanidipine HCl tablets (A) Vs. 10mg lercanidipine HCl tablets (Zanedip®) (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-t</td>
<td>0.92 (0.87 – 0.97)</td>
<td>0.92 (0.87 – 0.98)</td>
</tr>
<tr>
<td>AUC0-inf</td>
<td>0.91 (0.86 – 0.97)</td>
<td>0.92 (0.86 – 0.98)</td>
</tr>
<tr>
<td>Cmax</td>
<td>0.91 (0.84 – 1.00)</td>
<td>0.92 (0.84 – 1.00)</td>
</tr>
</tbody>
</table>

Assessor's comment: The bioequivalence of 8mg Zanidip Novum tablets in fasting state has been shown. It can safely be concluded that Zanidip Novum 8mg is equivalent to Recordati lercanidipine 10mg tablets.

STUDY AA 70948 (Fasting study 16mg)

Methods

Study design
This was a randomised, comparative, single-dose, 2-way crossover bioequivalence study of the proposed product, 16mg Lercanidipine Hydrochloride tablet and the reference product,
20mg Lercanidipine Hydrochloride tablet. The tablets were administered in a fasting state to healthy volunteers. The washout period was 14 days and the sampling period was up to 36 hours post-dose. The study was conducted according to GCP.

**Assessor's comment:** The study design is acceptable. The washout and sampling period were adequate. The drug is intended to be administered in a fasting state hence this study is appropriate.

**Test and reference products**

**Test Product - A:**
Lercanidipine HCl- 16mg

**Reference Product - B:**
ZANEDIP® 20MG (Lercanidipine HCl 20mg)

**Assessor's comment:** The reference product chosen for the study is appropriate.

**Population studied**
A total of 80 healthy volunteers (50 males and 30 females) were recruited, all completed the study.

**Assessor's comment:** The number of subjects in the study was more than adequate.

**Analytical methods**
Both S and R enantiomers were determined using a fully validated chiral HPLC/MS/MS method. Analysis were performed according to GLP.

**Assessor's comment:** The study was conducted in accordance with GLP guidance. The analytical method was acceptable and was in validated pre-study.

**Pharmacokinetic Variables**
The pharmacokinetic variables investigated were AUC0-t, AUC0-inf, AUC0-inf/AUC0-inf, Cmax, tmax, Kel and t½. These parameters were measured for S- and R-lercanidipine.

**Assessor's comment:** The pharmacokinetic variables chosen were appropriate.

**Statistical methods**
For the concentration and pharmacokinetic data, arithmetic means, standard deviation (SD), coefficients of variation (CV%), geometric means, median, minimum and maximum values were calculated. ANOVA were performed on the ln-transformed AUC0-t, AUC0-inf and Cmax. Ratio of LSM were calculated from the ln-transformed AUC0-t, AUC0-inf and Cmax for both S- and R-lercanidipine. 90% confidence interval were derived. Non-parametric analysis was used for Tmax.

**Assessor's comment:** Statistical methods chosen were appropriate.
Results

The confidence interval for Cmax and AUC for Zanidip Novum 16mg tablets from this study are shown in the table below.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>S-lercanidipine 16mg lercanidipine HCl tablets (A) Vs. 20mg lercanidipine HCL tablets (Zanedip®) (B)</th>
<th>R-lercanidipine 16mg lercanidipine HCl tablets (A) Vs. 20mg lercanidipine HCL tablets (Zanedip®) (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(0-t)</td>
<td>1.02 (0.98 – 1.06)</td>
<td>1.03 (0.99 – 1.08)</td>
</tr>
<tr>
<td>AUC(0-\infty)</td>
<td>1.03 (0.99 – 1.07)</td>
<td>1.04 (1.00 – 1.09)</td>
</tr>
<tr>
<td>C(\text{max})</td>
<td>0.97 (0.91 – 1.04)</td>
<td>0.97 (0.91 – 1.04)</td>
</tr>
</tbody>
</table>

Assessor’s comments: Assessor concurs with the conclusions that the Zanidip Novum 16mg tablets are bioequivalent to reference product 20mg tablets. The bioequivalence of Zanidip Novum 16mg tablet has been shown.

Study AA 74542 (Fed, 16mg tablet)

Study design
This was a randomised, comparative, single-dose, 2-cohort, 2-way crossover bioequivalence study to compare the food effect between proposed product, 16mg Lercanidipine Hydrochloride tablet and reference product, 20mg Lercanidipine Hydrochloride tablet. The tablets were administered in a fasting and fed state to healthy volunteers. The washout period was 14 days and the sampling period was up to 36 hours post-dose. The study was conducted according to GCP.

Assessor's comment: The study design to observe food effect is acceptable. The washout and sampling period were adequate. As food increases bioavailability the innovator is recommended to be administered in a fasting state. Same recommendation has been followed here.

Test and reference products

Test Product:  
Lercanidipine HCl 16mg

Reference Product:  
ZANEDIP® 20MG*

Assessor's comment: The reference product chosen for the study is appropriate.

Population studied
A total of 76 healthy volunteers were recruited in the study, 70 (45 males and 25 females) completed the clinical phase of the study.
Assessor's comment: The number of subjects in the study was acceptable.

Analytical methods
Both S and R enantiomers were determined using a fully validated chiral HPLC/MS/MS method.

Assessor's comment: The study was conducted in accordance with GLP guidance. The analytical method was acceptable and was in validated pre-study.

Pharmacokinetic Variables
The pharmacokinetic variables investigated were AUC_{0-t}, AUC_{0-inf}, AUC_{0-t}/AUC_{0-inf}, C_{max}, t_{max}, Kel and t_{1/2}. These parameters were measured for S- and R-lercanidipine.

Assessor's comment: The pharmacokinetic variables chosen were appropriate.

Statistical methods
For the concentration and pharmacokinetic data, arithmetic means, standard deviation (SD), coefficients of variation (CV%), geometric means, median, minimum and maximum values were calculated. ANOVA were performed on the ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max}. Ratio of LSM were calculated from the ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} for both S- and R-lercanidipine. 90% confidence interval were derived. Non-parametric analysis was used for T_{max}.

The primary assessment in this study was the difference in food effects between the reference and the test formulations based on the logarithmic LSM for both AUC_{0-t} and C_{max}.

Assessor's comment: Statistical methods chosen were appropriate.

Results
In this study subjects were into two cohorts for dosing (Cohort 1: subject nos. 1-38 and Cohort 2: subject nos. 39-76)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>S-lercanidipine 16mg lercanidipine HCl tablets under fed conditions Vs. 16mg lercanidipine HCl tablets under fasting conditions</th>
<th>R-lercanidipine 16mg lercanidipine HCl tablets under fed conditions Vs. 16mg lercanidipine HCl tablets under fasting conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0-t}</td>
<td>1.89 (1.67 – 2.14)</td>
<td>1.85 (1.60 – 2.14)</td>
</tr>
<tr>
<td>AUC_{0-inf}</td>
<td>1.88 (1.65 – 2.13)</td>
<td>1.84 (1.58 – 2.14)</td>
</tr>
<tr>
<td>C_{max}</td>
<td>1.80 (1.57 – 2.07)</td>
<td>1.80 (1.54 – 2.10)</td>
</tr>
</tbody>
</table>
Study AA74542. Ratio of LSM (90% Confidence Intervals)- Cohort 2 (Subject Nos. 39 – 76)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>S-lercanidipine 20mg lercanidipine HCl tablets (Zanedip®) under fed conditions Vs. 20mg lercanidipine HCl tablets (Zanedip®) under fasting conditions</th>
<th>R-lercanidipine 20mg lercanidipine HCl tablets (Zanedip®) under fed conditions Vs. 20mg lercanidipine HCl tablets (Zanedip®) under fasting conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;0-4t&lt;/sub&gt;</td>
<td>2.31 (2.07 – 2.58)</td>
<td>2.23 (2.01 – 2.48)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt;</td>
<td>2.31 (2.07 – 2.57)</td>
<td>2.23 (2.01 – 2.48)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>3.15 (2.60 – 3.82)</td>
<td>3.06 (2.53 – 3.70)</td>
</tr>
</tbody>
</table>

Assessor's comment: Although the food effect exists for Zanidip Novum the magnitude is less compared to reference product lercanidipine 20mg tablets. The recommendation to take Zanidip Novum before meal stands.

Pharmacokinetic conclusion
Based on the submitted bioequivalence studies Zanidip Novum 8mg and 16mg tablet is considered bioequivalent with reference products, lercanidipine 10mg and 20mg tablet.

Pharmacodynamic studies
No new data has been submitted and none is required. Lercanidipine is a known product and has been in clinical use for many years.

Additional data
None.

Expert Report
The clinical expert report has been written by an appropriately qualified expert and is a suitable summary of the clinical aspects of the dossier. The report refers to 29 publications up to year 2007. The CV of the expert has been supplied.

Post marketing experience
No post-marketing data is available. The medicinal product has not been marketed in any country.

Benefit-Risk assessment
The bioequivalence study conducted in fasting state shows that Zanidip Novum 8mg and 16mg tablets are bioequivalent with Lercanidipine 10mg and 20mg tablets (Recordati). The safety and efficacy profile of lercanidipine is well known. Approval is recommended from the clinical point of view.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labelling are medically acceptable.
MAA form
The MAA form is medically acceptable.

CONCLUSIONS
The efficacy and safety of the product is satisfactory for the grant of these product licences.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Zanidip Novum 8mg and 16mg Film Coated Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
The bioequivalence study conducted in fasting state shows that Zanidip Novum 8mg and 16mg tablets are bioequivalent with Lercanidipine 10mg and 20mg tablets (Recordati). No new or unexpected safety concerns arise from this application.

The SmPC, PIL and labels are satisfactory and are consistent with that for the reference products.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with lercanidipine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
**MODULE 6**

**STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY**

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
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