Clinical Study Synopsis

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1. **Title page**

**Title:** Effects of Adalat LA 30 mg and Coracten XL 30 mg on nifedipine plasma concentration, plasma catecholamines, blood pressure response, and heart rate in fed mild to moderate hypertensive subject.

**Test drug:** Adalat LA
Coracten XL

**Indication:** Adalat LA
Coracten XL

**Sponsor’s name and address:** Bayer Inc.
77 Belfield Road
Toronto, Ontario
M9W 1G6

**Study number(s):** 100128

**MRR number:** 00124

**Development phase:** Phase IV

**Study dates:** 17 Dec 2003 to 19 Aug 2004

**Investigator(s):** Dr. Morris Jonathan Brown
See Section 16.1.4 for details.

**GCP compliance statement:** See Sections 5.2 and 9.6 of the report

**Date:**

**Signatures:** *I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.*

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2. **Study synopsis**

<table>
<thead>
<tr>
<th><strong>Title of the study:</strong></th>
<th>Effects of Adalat LA 30 mg and Coracten XL 30 mg on nifedipine plasma concentration, plasma catecholamines, blood pressure response, and heart rate in fed mild to moderate hypertensive subjects.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigator(s):</strong></td>
<td>Dr. Morris Jonathan Brown Principal/Coordinating Investigator (for details see Section 16.1.4):</td>
</tr>
<tr>
<td><strong>Study center(s):</strong></td>
<td>This study was conducted at 1 center in Canada.</td>
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<tr>
<td><strong>Publications (references):</strong></td>
<td>None</td>
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<tr>
<td><strong>Period of study:</strong></td>
<td>17 Dec 2003 to 19 Aug 2004 (first subject’s first visit to last subject’s last visit)</td>
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<td><strong>Clinical phase:</strong></td>
<td>Phase IV</td>
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<tr>
<td><strong>Objectives:</strong></td>
<td>To compare the effect of Adalat LA (nifedipine GITS) 30 mg with that of Coracten XL 30 mg on drug pharmacokinetics as well as changes in plasma catecholamines, blood pressure and heart rate in fed mild to moderate hypertensive subjects.</td>
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<td><strong>Primary objective</strong></td>
<td>To compare the maximum change in plasma norepinephrine response to nifedipine GITS 30 mg daily and Coracten 30 mg daily in the fed state from dose administration to within 6 hours after the first dose.</td>
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<tr>
<td><strong>Secondary objectives</strong></td>
<td>To compare the responses in plasma epinephrine, systolic and diastolic blood pressure, and heart rate to nifedipine GITS 30 mg daily and Coracten XL 30 mg daily in the fed state at trough and peak plasma drug concentrations after first dose.</td>
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<td></td>
<td>To compare the responses in plasma norepinephrine and epinephrine, systolic and diastolic blood pressure, and heart rate to nifedipine GITS 30 mg daily and Coracten XL 30 mg daily in the fed state at trough and peak plasma drug concentrations after 2 weeks treatment.</td>
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<td></td>
<td>To compare the responses in plasma norepinephrine and</td>
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Epinephrine, systolic and diastolic blood pressure, and heart rate in multi-dose nifedipine GITS subjects switched to Coracten XL and multi-dose Coracten XL subjects switched to nifedipine GITS.

To describe the plasma concentration time profile of nifedipine after an initial dose of nifedipine GITS 30 mg and Coracten XL 30 mg administered in the fed state.

<table>
<thead>
<tr>
<th>Methodology (design of study):</th>
<th>A single-centre, open label, randomized, 3-period crossover study under fed conditions.</th>
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<tbody>
<tr>
<td>Number of subjects:</td>
<td>Forty-five subjects were enrolled and 43 were randomized. Twenty-one subjects were randomized to receive nifedipine GITS, Coracten XL, and then nifedipine GITS (Sequence 1). Twenty-two subjects were randomized to receive Coracten XL, nifedipine GITS, and then Coracten XL (Sequence 2). Twenty-one subjects completed Sequence 1 and 21 subjects completed Sequence 2. All randomized subjects were valid for intent-to-treat (ITT), per protocol (PP), and safety analyses.</td>
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<tr>
<td>Diagnosis and main criteria for inclusion:</td>
<td>Male or female subjects from 18-75 years of age; newly diagnosed or previously diagnosed mild to moderate essential hypertensives. Previously diagnosed subjects with controlled blood pressure for at least 1 month on therapy with sitting diastolic blood pressure (DBP) &lt; 90 mmHg and/or systolic blood pressure (SDB) &lt; 140 mmHg.</td>
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<tr>
<td>Test product, dose, and mode of administration, batch number:</td>
<td>Adalat LA, 30 mg tablets, administered orally, Batch: BXB96PA.</td>
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<tr>
<td>Duration of treatment:</td>
<td>In each Sequence, subjects received the first drug for 14 days, the second for 14 days, and the third for 1 day.</td>
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<td>Reference therapy, dose, and mode of administration, batch number:</td>
<td>Coracten XL, 30 mg capsules, administered orally, Batch: BX01E1P.</td>
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<td>Criteria of evaluation:</td>
<td>Efficacy: The measurements used for determination of the primary and secondary drug efficacy objectives were systolic and diastolic blood pressure, heart rate, and plasma nifedipine,</td>
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</table>
norepinephrine, and epinephrine levels.

**Safety:**
Observations used for determination of drug safety were adverse events, medical conditions, and physical findings.

**Drug pharmacodynamics:**
Plasma nifedipine measurements were made pre-dose and 13 times during the 6-hour post-dose period.

<table>
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<th><strong>Statistical methods:</strong></th>
<th><strong>Efficacy:</strong></th>
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<td></td>
<td>The primary objective of the study is to compare the efficacy of nifedipine GITS at the 30 mg daily dose to the 30 mg daily dose of Coracten XL with food on the effect of plasma norepinephrine after the first dose. The median change in plasma norepinephrine from trough to peak drug concentration was compared between the 2 treatments. The hypothesis of no difference in norepinephrine between the nifedipine GITS and Coracten XL was tested using a Wilcoxon Rank Sum Test. This test protects against substantial deviation from normality while preserving the power of the study. The secondary study objectives were as follows: First Dose: the trough to peak drug concentration change in epinephrine, systolic and diastolic blood pressure, and heart rate; and plasma nifedipine concentration time profile including ( C_{\text{max}} ) and ( t_{\text{max}} ) under fed conditions for single dose at Day 1. Multi-Dose: the trough to peak drug concentration (from last day of 2 weeks treatment) change in norepinephrine, epinephrine, systolic and diastolic blood pressure, and heart rate; and plasma nifedipine concentration time profile including ( C_{\text{max}} ) and ( t_{\text{max}} ) under fed conditions after 2 weeks treatment. The multi-dose objective was in fact a 2-period crossover. The hypothesis of no difference in the norepinephrine and no difference in epinephrine between the treatment arms were both analyzed using a Wilcoxon Signed Rank Test. Switch: the trough to peak drug concentration change in norepinephrine, epinephrine, systolic and diastolic blood pressure, and heart rate; and plasma nifedipine concentration time profile including ( C_{\text{max}} ) and ( t_{\text{max}} ) under fed conditions compared between subjects’ multi-dose nifedipine GITS (week 2 and week 4) to subject’s first dose switched to Coracten XL (2 weeks plus 1 day and 4 weeks plus 1 day).</td>
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</table>
The switch objective was also a 2-period crossover. The hypothesis of no difference between multi-dose nifedipine GITS and switch to Coracten XL was analyzed using the Wilcoxon Signed Rank Test. The change in epinephrine was also analyzed using a Wilcoxon Signed Rank test. The switch objective was also analyzed for subjects switching from Coracten to nifedipine GITS.

Confidence intervals for the change in norepinephrine and epinephrine were also calculated. In general, a log transformation and other possible distributional assumptions were explored to improve any confidence interval estimations. If no appropriate transformation was determined, then non-parametric methods for the confidence interval were used. The pattern of norepinephrine over time was presented graphically by treatment and period for first dose, multi-dose, and switch using the chosen summary measure.

The plasma nifedipine concentration time profile variables, t\(_{\text{max}}\) and C\(_{\text{max}}\), were summarized by treatment arm and period using the mean and standard deviation for first dose, multi-dose and switch.

Washout subject demographics were summarized by treatment using the mean and standard deviation (normally distributed data), the median and interquartile range (non-normally distributed data), or frequency counts and percentages (categorical data) to ensure adequate balance in the randomization. Measures of blood pressure, heart rate and adverse events results were also presented by treatment arm and period using means and standard deviations or rates as appropriate for first dose, multi-dose and switch. No statistical comparisons were made.

Safety:

Adverse events were tabulated by treatment and type (MedDRA term). Vital signs were summarized by treatment and period.

All analyses were done by Bayer Inc. All statistical tests were conducted using a 2-sided \(\alpha=0.05\) level of significance. The test of the primary hypothesis was the only one considered in terms of the experiment-wise error.
Summary and conclusions:

Summary of efficacy: After an initial dose, nifedipine GITS was associated with a decrease and Coracten XL with an increase in mean norepinephrine concentration ($p = 0.0028$) From nifedipine trough level to nifedipine peak concentration time ($t_{\text{max}}$). During the 6 hours following drug administration, mean norepinephrine levels were lower for nifedipine GITS than for Coracten XL.

After multiple dosing, nifedipine GITS produced a decrease in mean norepinephrine concentration while Coracten XL produced an increase ($p = 0.005$). There was no statistically significant difference between drugs in median epinephrine response.

Median and mean SBP were lowered to a statistically significantly greater degree by Coracten XL than by nifedipine GITS ($p = 0.020$ and $p = 0.011$, respectively). There was no statistically significant difference in lowering of mean or median DBP by nifedipine GITS or Coracten XL.

Median heart rate was lowered to a greater degree by nifedipine GITS than by Coracten XL ($p = 0.045$). There was no statistically significant difference in mean heart rate response to the two drugs.

Coracten XL 30 mg produced higher mean and median nifedipine C_{\text{max}} at a shorter $t_{\text{max}}$ than nifedipine GITS 30mg.

At after-switch visits, catecholamine concentrations were lower for nifedipine GITS than for Coracten XL ($p = 0.042$). Mean norepinephrine levels over the 6 hours collection period following switches were consistently lower for nifedipine GITS than for Coracten XL.

Summary of safety: Nifedipine itself, rather than the 2 preparations of nifedipine that were administered, was the subject of safety evaluation. Twenty-eight (65.1%) subjects experienced an adverse event. Twenty (46.5%) subjects had a drug-related treatment emergent adverse event. One subject (2.3%) discontinued treatment due to a drug-related treatment emergent adverse event. There were no deaths or other serious adverse events.

Nifedipine was found to be safe and well tolerated, in either nifedipine GITS or Coracten XL formulation.

Summary of After initial administration Coracten XL 30 mg produced higher mean and median nifedipine C_{\text{max}} at a shorter $t_{\text{max}}$ than
### Pharmacokinetics

Nifedipine GITS 30 mg. For nifedipine GITS and Coracten XL, respectively, mean and median were $C_{\text{max}}$ 16.9 and 57.2, and 16.2 and 47.8, and $t_{\text{max}}$ were 5.1 and 3.0, and 5.3 and 4.0.

### Conclusions

This Phase IV, single-centre, open label, randomized, 3-period crossover study in 45 subjects with mild to moderate hypertension demonstrated that nifedipine GITS brought about a decrease in both plasma norepinephrine and plasma epinephrine concentrations while Coracten XL brought about an increase in plasma norepinephrine and a decrease in plasma epinephrine concentrations. The study was not designed to compare the relative blood pressure lowering by the 2 study preparations; however, it found that, under study conditions, Coracten XL lowered SBP significantly more than nifedipine GITS while there was no significant difference between the amounts by which the 2 agents decreased DBP. Nifedipine GITS lowered median heart rate while Coracten XL increased it, with the difference being significant. Nifedipine $C_{\text{max}}$ was greater and nifedipine $t_{\text{max}}$ was lower with Coracten XL than with nifedipine GITS.

Nifedipine GITS 30 mg and Coracten XL 30 mg were both found to be safe and well tolerated.

The study demonstrated that nifedipine GITS did not cause activation of the sympathetic nervous system, as evidenced by decreases in norepinephrine and epinephrine concentrations and heart rate associated with lowering of blood pressure. Coracten XL appears to activate the sympathetic nervous system as evidenced by an increase in plasma norepinephrine concentration and heart rate associated with lowering of blood pressure.

Subjects exposed to nifedipine GITS either after initial dosing or short term use show no activation of the sympathetic nervous system. However, subjects exposed to Coracten XL after initial use or switching form nifedipine GITS show an activation of the sympathetic nervous system. This may present a concern in those subjects with compromised coronary vessels, or small cerebral vessel due to atherosclerosis who may be placed at risk when they are switched to Coracten XL from nifedipine GITS and a vasoconstriction occurs in these vessels as a result of sympathetic activation. Accordingly, subjects should not be switched between preparations of nifedipine without adequate medical supervision.