Pharmacokinetic Properties of a Combination of Bisoprolol and Amlodipine

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The duration of action of bisoprolol and amlodipine exceeds 24 hours after dosing. The bisoprolol and amlodipine components of the single-tablet combination meet formal criteria for bioequivalence with a co-administered combination of leading proprietary formulations of these agents. This simplifies a switch from a co-administered bisoprolol and amlodipine combination to the single-tablet formulation. Overall, bisoprolol and amlodipine have complementary pharmacokinetic properties consistent with inclusion in a combination tablet.

General pharmacokinetics of bisoprolol and amlodipine

Table 1 provides an overview of key pharmacokinetic parameters for bisoprolol and amlodipine [1–4]. Both drugs are extensively absorbed,
and have a plasma half-life consistent with once-daily dosing, with the
duration of action of amlodipine being especially long, consistent with its
large volume of distribution and extensive binding to plasma proteins.
Neither drug is susceptible to clinically significant first-pass metabolism,
and neither generates active metabolites.

The balanced renal/hepatic elimination of bisoprolol has clinical
significance. For example, the elimination half-life of bisoprolol was in-
creased by 1.96 fold in patients with versus without severe renal dysfunc-
tion, with similar plasma levels of bisoprolol in patients with severe renal
dysfunction or receiving renal dialysis [4]. Therefore, it is unlikely that
severe accumulation of the drug would occur in this setting (Chapter 8
of this book addresses the safety and tolerability of this combination).
Amlodipine should be used with caution in the setting of hepatic impair-
ment consistent with the liver being its principal site of metabolism; no
dose adjustments are required for renal dysfunction, however.

The pharmacokinetic profiles of these agents suggests that they are
suitable for co-administration (duration of action is consistent with
once-daily dosing, and there are no major restrictions according to re-
nal or hepatic function). However, regulatory requirements mean that
dedicated studies need to be conducted to ensure that bisoprolol and
amlodipine, delivered by a combination tablet, are bioequivalent with

<table>
<thead>
<tr>
<th></th>
<th>Bisoprolol</th>
<th>Amlodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>90%</td>
<td>60–65%</td>
</tr>
<tr>
<td>Elimination</td>
<td>Balanced between hepatic</td>
<td>Mainly hepatic</td>
</tr>
<tr>
<td></td>
<td>metabolism and renal</td>
<td>metabolism with 5%</td>
</tr>
<tr>
<td></td>
<td>excretion as unchanged</td>
<td>excreted as unchanged</td>
</tr>
<tr>
<td></td>
<td>drug</td>
<td>drug</td>
</tr>
<tr>
<td>Active metabolites?</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>First pass metabolism</td>
<td>Very low/absent</td>
<td>Very low/absent</td>
</tr>
<tr>
<td>Time to peak plasma</td>
<td>2 hours</td>
<td>6–8 hours</td>
</tr>
<tr>
<td>concentration after dosing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elimination half life</td>
<td>10–11 hours</td>
<td>30–50 hours</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>3.5 L</td>
<td>21 L</td>
</tr>
<tr>
<td>Recommended dosing</td>
<td>Once daily</td>
<td>Once daily</td>
</tr>
<tr>
<td>schedule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>30%</td>
<td>98%</td>
</tr>
</tbody>
</table>

Table 1 Overview of the pharmacokinetics of bisoprolol and amlodipine [1–4].

Compiled from information presented in references [1–4].
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marketed formulations of these agents. This chapter summarises the results of these studies.

**Pharmacokinetic evaluation of a single-tablet combination of bisoprolol and amlodipine**

**Overview of pharmacokinetic studies**

Four pharmacokinetic studies, (three bioequivalence studies and one drug-drug interaction study, Table 2), have evaluated the bisoprolol-amlodipine combination tablet in comparison with proprietary reference formulations of bisoprolol (Concor™, Merck Healthcare KGaA) and amlodipine (Norvasc®, Pfizer) [5]. All were randomised, crossover studies conducted in healthy volunteers. Three studies (A, B and C in Table 2), compared a bisoprolol 10 mg/amlodipine 10 mg tablet with the respective monotherapies, either after a single dose or after 5 days of dosing. The fourth study (D in Table 2), compared single administrations of the bisoprolol 5 mg/amlodipine 5 mg combination tablet with a co-administered combination of the corresponding proprietary reference products. The studies took place in Canada, China and Brazil in order to confirm the results of the studies in different populations.

**Bioequivalence studies in fasted subjects**

The mean maximal plasma concentration (C_{\text{max}}), mean area under the concentration-time curve over the 24-hour dosing interval (AUC), and the time to C_{\text{max}} of each drug after ingestion (T_{\text{max}}) are shown in Table 3. Within each study, these parameters were similar for bisoprolol and amlodipine proprietary reference products and the combination tablet. C_{\text{max}} and AUC were higher for the multiple-dose study (study C), compared with the single-dose study (study A). This would be expected as these drugs have durations of action that exceed 24 hours. Plasma concentrations of drugs started at zero at the time of drug administration in the single-dose study, whereas the last administration of drug in the multiple-dose study added to the steady-state trough drug concentration.
Table 2 Pharmacokinetic evaluations of a single-tablet combination of bisoprolol and amlodipine [5]*.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Subjects</th>
<th>Treatments</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (Canada)</td>
<td>R, X, OL</td>
<td>28</td>
<td>Healthy male or female volunteers (fasted)</td>
<td>Amlodipine 10 mg&lt;sup&gt;a&lt;/sup&gt; Amlodipine 10 mg&lt;sup&gt;b&lt;/sup&gt; Amlodipine 10 mg/bisoprolol 10 mg combination tablet</td>
<td>Single dose</td>
</tr>
<tr>
<td>B (Brazil)</td>
<td>R, X, OL, SB</td>
<td>28</td>
<td>Healthy male volunteers (fasted)</td>
<td>Amlodipine 10 mg&lt;sup&gt;a&lt;/sup&gt; Amlodipine 10 mg/bisoprolol 10 mg combination tablet</td>
<td>Single dose</td>
</tr>
<tr>
<td>C (Canada)</td>
<td>R, X, OL</td>
<td>22</td>
<td>Healthy male or female volunteers (fasted)</td>
<td>Amlodipine 10 mg&lt;sup&gt;a&lt;/sup&gt; Amlodipine 10 mg/bisoprolol 10 mg combination tablet</td>
<td>5 days</td>
</tr>
<tr>
<td>D (China)</td>
<td>R, X, OL</td>
<td>32</td>
<td>Healthy male or female volunteers (fasted and fed)</td>
<td>Amlodipine 5 mg&lt;sup&gt;a&lt;/sup&gt; Amlodipine 5 mg/bisoprolol 5 mg combination tablet</td>
<td>Single dose</td>
</tr>
</tbody>
</table>

OL: open-label; R: randomised; SB: single (laboratory) blind; X: crossover.
Proprietary reference formulations: <sup>a</sup>Novasc® (Pfizer); <sup>b</sup>Concor™ (Merck Healthcare KGaA), or equivalent local brands.
*Also includes information from original clinical study reports (Merck Healthcare KGaA).

Table 3 Key pharmacokinetic evaluation of the bisoprolol 10 mg/amlodipine 10 mg combination tablet in fasted subjects compared with proprietary reference formulations of the individual components [5]*.

|                | Mean C<sub>max</sub> [ng/mL (CV(%) | Mean AUC<sub>τ</sub> [ng·h/mL (CV(%) | Median T<sub>max</sub> (hours)
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Single dose (Study A)</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisoprolol 10 mg (combination tablet)</td>
<td>43.4 (19.0)</td>
<td>719.0 (19.2)</td>
<td>2.5</td>
</tr>
<tr>
<td>Bisoprolol 10 mg (reference)</td>
<td>42.8 (17.7)</td>
<td>703.6 (21.1)</td>
<td>2.0</td>
</tr>
<tr>
<td>Amlodipine 10 mg (combination tablet)</td>
<td>5.9 (25.9)</td>
<td>315.5 (29.6)</td>
<td>8.0</td>
</tr>
<tr>
<td>Amlodipine 10 mg (reference)</td>
<td>5.5 (28.3)</td>
<td>286.1 (34.9)</td>
<td>8.0</td>
</tr>
<tr>
<td><strong>Multiple doses (5 days, Study C)</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisoprolol 10 mg (combination tablet)</td>
<td>58.5 (8.7)</td>
<td>838.7 (10.7)</td>
<td>2.50</td>
</tr>
<tr>
<td>Bisoprolol 10 mg (reference)</td>
<td>53.6 (9.7)</td>
<td>771.0 (11.7)</td>
<td>2.75</td>
</tr>
<tr>
<td>Amlodipine 10 mg (combination tablet)</td>
<td>28.6 (18.7)</td>
<td>534.4 (16.1)</td>
<td>8.0</td>
</tr>
<tr>
<td>Amlodipine 10 mg (reference)</td>
<td>26.2 (18.2)</td>
<td>506.7 (16.6)</td>
<td>7.0</td>
</tr>
</tbody>
</table>

AUC<sub>τ</sub>: mean area under the concentration-time curve over a 24-hour dosing interval; C<sub>max</sub>: mean maximal plasma drug concentration; CV: coefficient of variation; T<sub>max</sub>: time to maximal plasma drug concentration after ingestion.
*See Table 2 for details of studies and proprietary reference products; studies B and D did not provide data for arithmetic means for these parameters and are thus omitted here.
*Also includes information from original clinical study reports (Merck Healthcare KGaA).
in each case. This can be seen clearly in Figure 1, where the concentrations of bisoprolol and amlodipine at time zero of the last day of the multiple-dose study were about 15 ng/mL and 18 ng/ML, respectively. Values of $T_{\text{max}}$ were also similar for bisoprolol or amlodipine from the proprietary or combination tablets, and similar to published values (Table 1).

The formal demonstration of bioequivalence requires geometric mean ratios of pharmacokinetic parameters, and their 90% confidence intervals (90% CI), determined after administration of the test versus reference drug to lie between 80% and 125% [6]. Figure 2 shows the data on bioequivalence from the three studies in fasted volunteers. The geometric mean ratios and their 90% CI for both bisoprolol and amlodipine were well within the 80–125% criteria. This applied to single-dose administration (Studies A, B and D), multiple-dose administration (Study C), and to administration of combination tablet strengths of 5 mg/5 mg (Study D) and 10 mg/10 mg (Studies A, B and C). Therefore,

![Figure 1](image_url)

*Figure 1 Plasma concentrations of bisoprolol and amlodipine during a 24-hour dosing interval from a crossover study in healthy volunteers treated once daily for 5 days with amlodipine 10 mg or bisoprolol 10 mg monotherapy, or a single-tablet combination containing these treatments [5].

*Also includes information from original clinical study reports (Merck Healthcare KGaA). Proprietary reference products were as per Table 1. h: hour.
the bisoprolol-amlodipine combination tablet is fully bioequivalent with previously marketed formulations of these agents.

**Effects of food on the pharmacokinetics of the single-tablet combination of bisoprolol and amlodipine**

Study D evaluated the effects of food on the pharmacokinetics of bisoprolol and amlodipine delivered from the combination tablet or from a co-administered combination of proprietary reference products. Mean $C_{\text{max}}$ (Figure 3a) and mean $\text{AUC}_{0-t}$ (Figure 3b) were slightly lower in fed versus fasted subjects, but not to a clinically significant extent. Importantly, bioequivalence was maintained between the formulations irrespective of fed or fasted status (Figure 3c). Accordingly, the combination tablet can be taken with food.
Figure 3  Effects of food on the pharmacokinetics of the bisoprolol 5 mg/amlodipine 5 mg combination tablet (Study D) [5]*.

a) $C_{\text{max}}$

b) $\text{AUC}_{0-t}$

c) Geometric mean ratios of $C_{\text{max}}$ and $\text{AUC}_{0-t}$ in fed and fasted conditions

AUC$_{0-t}$: mean area under the concentration-time curve from 0 to t hours; CI: confidence interval; $C_{\text{max}}$: mean maximal plasma drug concentration; CV: coefficient of variation.

*Also includes information from original clinical study reports (Merck Healthcare KGaA).

Bars in panel (a) represent CV (%).
**Physical properties of the bisoprolol-amlodipine combination tablet**

**Solubility**

The dissolution of the combination tablets in aqueous medium was assessed according to a priori quality control criteria set by the European and United States (US) regulators and the pharmaceutical sponsor of the treatment. On average, ≥85% of the bisoprolol content and ≥75% of the bisoprolol and amlodipine content, respectively, were required to be released within 30 minutes, with no individual findings of <70% (bisoprolol) or <65% (amlodipine) active ingredient release [7]. The average release ranged between 98.4–101.6% for bisoprolol and 95.9–101.9% for amlodipine; corresponding minimum amounts were ≥86.1% and ≥82.4%. The combination tablet therefore exceeded the minimum standards required for dissolution in an aqueous medium.

**Breaking combination tablets for flexibility of dosage and administration**

The bisoprolol-amlodipine combination tablet is scored to facilitate breaking the tablet in half, whether to provide a lower dosage or to reduce the size of the tablet for easier ingestion. It is important to establish
that tablets broken to halve the dose provide consistent dosages of the active ingredients, as it is possible that tablets may break unevenly. This was tested in an analytical study on samples from three batches each of the amlodipine/bisoprolol 5/5 mg and 5/10 mg tablet strengths [7]. Both the mass of each half of broken tablet, and the amount of active ingredient contained within each half, passed criteria set by the European [8] and the US Pharmacopeia [9].

These findings are important for the routine administration of this combination tablet. Some physicians have preferred to start bisoprolol at a dosage below the lower adult dose of 5 mg/day, especially for vulnerable populations [10]. The scored tablet containing bisoprolol 5 mg provides flexibility to do this. In addition, difficulty swallowing tablets is an important cause of poor adherence to therapy, and halved tablets are easier for patients to swallow [11].

**Conclusions**

The bisoprolol and amlodipine components of the single-tablet combination met formal criteria for bioequivalence with a co-administered combination of leading proprietary formulations of these agents. Accordingly, a switch from a co-administered bisoprolol and amlodipine combination to the combination tablet can be made at equivalent doses, thereby simplifying the regimen without expectation of a marked change in antihypertensive effect. Alternatively, intensification of the regimen by using the combination tablet in place of either of the components would be expected to provide additional antihypertensive efficacy. The analytical data on the solubility of the tablet is consistent with the findings on bioequivalence. In addition, the analytical data on the effective dose delivered by halved tablets adds to the flexibility of dosing with the combination tablet, where the physician wishes to administer bisoprolol at a dose of 2.5 mg. Overall, bisoprolol and amlodipine have complementary pharmacokinetic properties consistent with their inclusion in a combination tablet for the management of hypertension.
References


