Chapter 5

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 increased by 1.96 fold in patients with versus without severe renal dysfunction, 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 impairment 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 renal 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 1 Overview of the pharmacokinetics of bisoprolol and amlodipine [1–4].

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

Compiled from information presented in references [1–4].

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_{max}), mean area under the concentration-time curve over the 24-hour dosing interval (AUC), and the time to C_{max} of each drug after ingestion (T_{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_{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]*.

Study	Design	N	Subjects	Treatments	Duration
A (Canada)	R, X, OL	28	Healthy male or female volunteers (fasted)	Amlodipine 10 mg[a] Bisoprolol 10 mg[b] Amlodipine 10 mg/bisoprolol 10 mg combination tablet	Single dose
B (Brazil)	R, X, OL, SB	28	Healthy male volunteers (fasted)	Amlodipine 10 mg[a] Bisoprolol 10 mg[b] Amlodipine 10 mg/bisoprolol 10 mg combination tablet	Single dose
C (Canada)	R, X, OL	22	Healthy male or female volunteers (fasted)	Amlodipine 10 mg[a] Bisoprolol 10 mg[b] Amlodipine 10 mg/bisoprolol 10 mg combination tablet	5 days
D (China)	R, X, OL	32	Healthy male or female volunteers (fasted and fed)	Amlodipine 5 mg[a] Bisoprolol 5 mg[b] Amlodipine 5 mg/bisoprolol 5 mg combination tablet	Single dose

OL: open-label; R: randomised; SB: single (laboratory) blind; X: crossover.
Proprietary reference formulations: [a]Novasc® (Pfizer); [b]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]*.

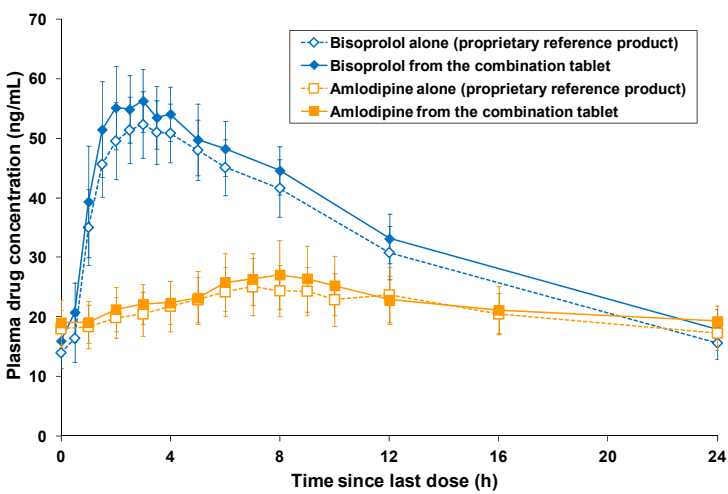
	Mean C_{max} [ng/mL (CV(%)]	Mean AUC_{τ} [ng·h/mL (CV(%)]	Median T_{max} (hours)
Single dose (Study A)[a]			
Bisoprolol 10 mg (combination tablet)	43.4 (19.0)	719.0 (19.2)	2.5
Bisoprolol 10 mg (reference)	42.8 (17.7)	703.6 (21.1)	2.0
Amlodipine 10 mg (combination tablet)	5.9 (25.9)	315.5 (29.6)	8.0
Amlodipine 10 mg (reference)	5.5 (28.3)	286.1 (34.9)	8.0
Multiple doses (5 days, Study C)[a]			
Bisoprolol 10 mg (combination tablet)	58.5 (8.7)	838.7 (10.7)	2.50
Bisoprolol 10 mg (reference)	53.6 (9.7)	771.0 (11.7)	2.75
Amlodipine 10 mg (combination tablet)	28.6 (18.7)	534.4 (16.1)	8.0
Amlodipine 10 mg (reference)	26.2 (18.2)	506.7 (16.6)	7.0

AUC_{τ}: mean area under the concentration-time curve over a 24-hour dosing interval; C_{max}: mean maximal plasma drug concentration; CV: coefficient of variation; T_{max}: time to maximal plasma drug concentration after ingestion.
[a]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_{max} were also similar for bisoprolol or amlodipine from the proprietary or combination tablets, and similar to published values (Table 1).

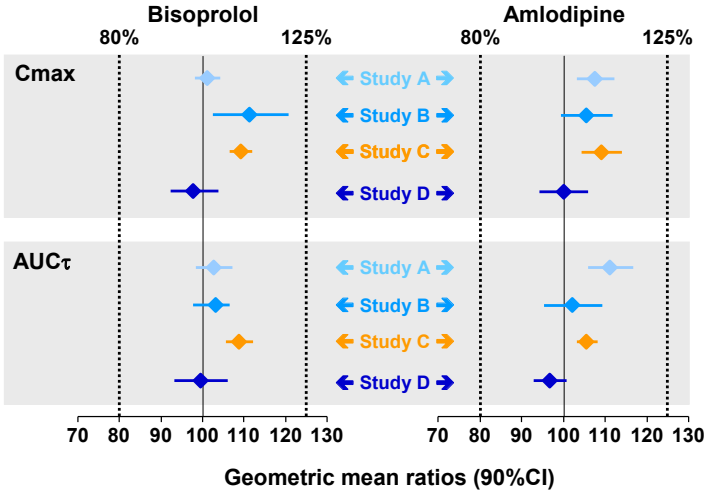
The formal demonstration of bioequivalence requires geometric mean ratios of pharmacokinetic parameters, and their 90% confidence intervals (90% CI), determined after administration of the test versus reference drug to lie between 80% and 125% [6]. Figure 2 shows the data on bioequivalence from the three 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 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.

Figure 2 Demonstration of bioequivalence between the bisoprolol and amlodipine components of a combination tablet and proprietary reference formulations of these agents [5]*.



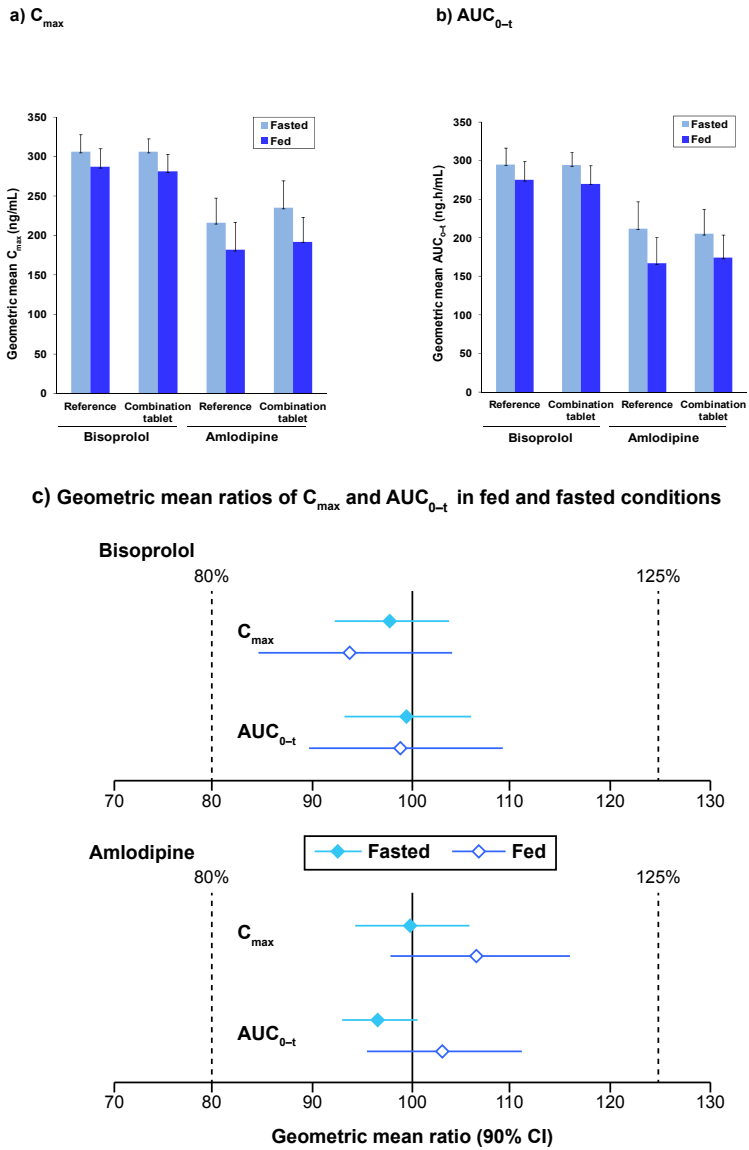
AUC_τ: mean area under the concentration-time curve over a 24-hour dosing interval; CI: confidence interval; C_{max}: mean maximal plasma drug concentration.
*Also includes information from original clinical study reports (Merck Healthcare KGaA).
Formal bioequivalence is demonstrated when the geometric mean ratios and their 90% CI for C_{max} or AUC fall between 80% and 125%.
Studies A, C and D were single-dose studies; Study C was a multiple-dose study.

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_{max} (Figure 3a) and mean 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]*.



AUC_{0-t}: mean area under the concentration-time curve from 0 to t hours; CI: confidence interval; C_{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 (%).

T_{max} for bisoprolol was 1.0 hour (95% CI, 1.0 to 3.0 for combination tablet and 0.5 to 2.0 for co-administration) for both formulations in the fasted state and was 3.0 hours (95% CI, 1.0 to 6.0 for combination tablet and 2.0 to 6.0 for co-administration) for both formulations in the fed state. Corresponding T_{max} values for amlodipine were 6.0 hours (95% CI, 4.0 to 8.0 for combination tablet and 4.0 to 12.0 for co-administration) and 6.0 hours (95% CI, 4.0 to 15.0 for combination tablet and 4.0 to 10.0 for co-administration) for both formulations. T_{max} was minimally affected by food, apart from the possibility of a slight delay to absorption of bisoprolol with food.

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.

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