Pharmacokinetic Properties of a Fixed-Dose Combination of Bisoprolol and Amlodipine

Ulrike Gottwald-Hostalek and Sumedh Gaikwad*

Merck KGaA, Darmstadt, Germany

***Corresponding Author:** Sumedh Gaikwad, RD-EVQ-Q Established Products Department, Merck KGaA, Darmstadt, Germany.*

Abstract

For the treatment of hypertension, a fixed dose combination (FDC) tablet of bisoprolol and amlodipine in four strengths was developed for patients, whose blood pressure can be adequately controlled by simultaneously given amlodipine and bisoprolol of the same doses.

For this third-line or substitution treatment, bioequivalence between the free and the fixed-dose could be demonstrated in three bioequivalence studies, two with the highest dose of 10 mg/10 mg carried out in Canada and Brazil, and one with the lowest dose of 5 mg/5 mg done in China. A dose interaction study could clearly show that there is no relevant interaction between the two compounds, bisoprolol and amlodipine. In none of the PK studies, any severe or serious adverse event was documented, neither any clinically significant deviations in vital signs, ECG or laboratory data.

Keywords: Pharmacokinetic Properties; Bisoprolol; Amlodipine

Introduction

Evidence suggests that most hypertensive patients will require two or more antihypertensive agents to reach specified blood pressure (BP) targets. Combining two drugs from different classes has the potential to target different aspects of hypertension, which may result in additional BP decreases compared with either agent used alone [1,2].

Thus, combination therapy has an important place in the routine management of hypertension. Combination therapy offers many potential advantages. The use of two drugs with different mechanisms of action can produce greater antihypertensive efficacy and higher response rates than can be achieved with monotherapy. Furthermore, combination therapy allows the drugs to be given in low doses, thereby reducing the risk of adverse effects, and, thus, increasing patient adherence. As a result, current management guidelines recommend the use of combination therapy.

ß1-selective beta-blocker (BB) and calcium channel blockers (CCB) are both used as first-line therapy in hypertension. The vasodilatation effects of CCB are additive to those of beta-blockers, namely blocking the sympathetic nervous system and decreasing renin release. Therefore, the combination of beta-adrenergic-blocking and calcium-entry-blocking drugs have a positive influence on three pathomechanisms of hypertension.

The 2013 ESH/ESC guidelines [3] explicitly recommend a combination of beta-blockers and CCB in hypertensive patients with concomitant ischemic heart disease.

For the treatment of hypertension, a fixed dose combination (FDC) tablet of the highly selective ß1 beta-blocker bisoprolol and the calcium channel blocker amlodipine in the strengths of 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg was developed for patients, whose blood pressure can be adequately controlled by simultaneously given amlodipine and bisoprolol of the same doses.

For this third-line or substitution treatment, bioequivalence between the free and the fixed-dose combination needs to be demonstrated.

BE study in Canada

The first bioequivalence (BE) study was done in Canada comparing the fixed combination tablet of bisoprolol and amlodipine (10 mg/10 mg) with the single compounds 10 mg amlodipine besilate and 10 mg bisoprolol fumarate tablets given concomitantly [4].

It was a single centre, randomized, single dose, laboratory-blinded, two-way, crossover comparative bioavailability study conducted under fasting conditions on twenty-eight healthy male subjects. The rate and extent of absorption of amlodipine and bisoprolol were measured and compared. Main pharmacokinetic parameters were the maximum serum concentration (C_{max}), the area under the curve $(AUC)_{0-t}$, and $AUC_{0-\infty}$ for bisoprolol and amlodipine. Criteria for bioequivalence were 90% CIs for the ratios of geometric means of the primary endpoints between the FDC and the comparators within 80 - 125%.

As all bioequivalence criteria C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were met, the bioequivalence between the free and the fixed-dose combination could be demonstrated.

As this fixed-dose combination is planned to be marketed globally, another bioequivalence study with the FDC was done in Brazilian patients, and a third one in Chinese patients [5,6].

BE study in Brazil

The Brazilian study [5] also assessed the bioequivalence between the FDC 10 mg/10 mg and one tablet of bisoprolol 10 mg and one tablet of amlodipine 10mg given concomitantly in a single centre, open, randomized, single dose, two-way, two-sequences crossover study. Main pharmacokinetic parameters were C_{max}, and AUC_{0-t}, for bisoprolol and amlodipine. Criteria for bioequivalence were Criteria for bioequivalence were 90% CIs for the ratios of geometric means of the primary endpoints between the FDC and the comparators within 80 - 125% (see tables 1 and 2 and figures 1 and 2).

Parameter N = 28	Ratio test/reference (%)	90% CI limits	CV (intra) (%)	Power (%)
C_{max} (ng/ml)	111.206	102.397 - 120.773	18.254	99.631
AUC_{0-t} (ngxh/ml)	103.059	97.777 - 108.625	11.578	100.000
AUC $0-\infty$(ngxh/ml)	103.120	98.013 - 108.494	11.178	100.00

Table 1: *Bioequivalence results for bisoprolol [5].*

Parameter N=28	Ratio test/reference (%)	90% CI limits	CV (intra) (%)	Power (%)
C_{max} (ng/ml)	105.462	99.532 - 111.744	12.745	99.998
AUC_{0-t} (ngxh/ml)	102.140	95.429 - 109.324	14.993	99.969
AUC $0-\infty$(ngxh/ml)	101.003	95.728 - 106.568	11.806	99.999

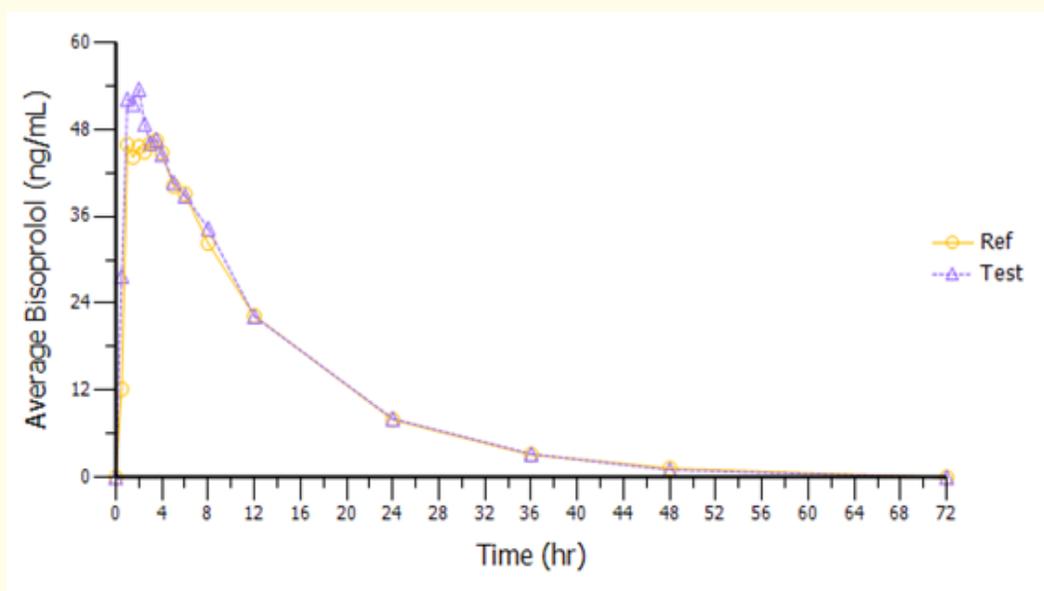***Table 2:*** *Bioequivalence results for amlodipine [5].*

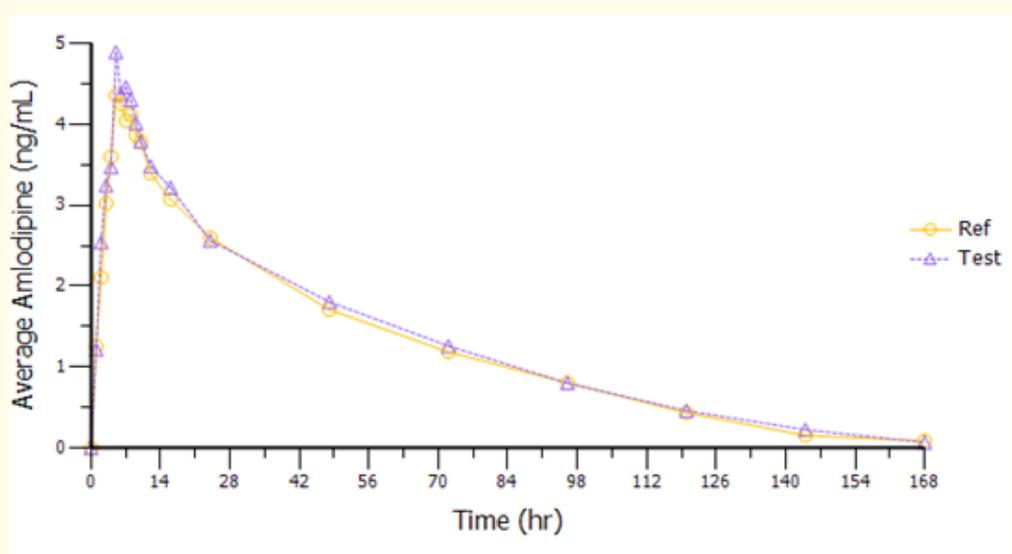***Figure 1:*** *Serum levels of bisoprolol [5].*

Figure 2: *Serum levels of amlodipine [5].*

Secondary parameters included a descriptive analysis of other pharmacokinetic parameters such as t_{max}, $t_{1/2}$, K_{el}, $AUC_{0-\infty}$, and AUC_{extra} of the test and reference drugs and safety and tolerability by means of adverse event, vital signs, ECG, and laboratory data reporting.

As all bioequivalence criteria were met, the results of the bioequivalence study confirmed the fact, that the proposed fixed-dose combination tablets and the co-administration of the two reference medicinal products as free combination are bioequivalent.

There were 39 adverse events recorded in 15 of the 28 subjects, thereof 21 adverse events in 11 subjects under the test, and 18 adverse events in 12 subjects under the reference medication. 27 out of the 39 adverse events were rated as possibly related to the study medication. The most frequent adverse event was headache. 35 of the 39 adverse events were mild and four were moderate. There was no severe or serious adverse event. In addition, no clinically significant deviations were observed in vital signs, ECG or laboratory data.

BE study in China

The Chinese BE study was a randomized, two-period crossover trial examining bioequivalence of the FDC 5 mg/5 mg tablets versus bisoprolol 5 mg tablets and amlodipine 5 mg tablets given concomitantly in healthy subjects, this time in fasting and fed state [6].

The primary target parameters included AUC_{0-t} and C_{max} of bisoprolol and amlodipine. Secondary PK endpoints included t_{max}, $t_{1/2}$, λ_z, $AUC_{0-\infty}$, $AUC_{extra\%}$, $CL_{/f}$, $V_z/_f$, frequency and severity of adverse events (AEs), vital signs, ECG, biochemistry, hematology, urinalysis, and physical examination. Criteria for bioequivalence were 90% CIs for the ratios of geometric means of the primary endpoints between the FDC and the comparators within 80 - 125%.

Results of BE evaluation for bisoprolol and amlodipine under fasted condition are presented in the tables 3 and 4 and figures 3 and 4 below.

Fasting conditions

Parameter N = 16	Treatment	Geometric LS Mean	95% CI of Geometric LS Mean	Ratio test/ reference (%)	90% CI limits
C_{max} (ng/ml)	A	26.1	(23.5, 28.9)	97.85	92.29 - 103.74
	B	26.6	(24.0, 29.6)		
AUC_{0-t} (ngxh/ml)	A	294	(265, 326)	99.46	93.25 - 106.09
	B	295	(267, 327)		
$AUC_{0-\infty}$ (ngxh/ml)	A	306	(276, 338)	99.98	93.61 - 106.79
	B	306	(276, 338)		

Table 3: *Statistical comparison of bisoprolol plasma pharmacokinetic parameters AUCs and C$_{max}$ between treatment A and treatment B under fasting condition – pharmacokinetic analysis set [6].*

CI: Confidence Interval; LS: Least-Squares. Results based on a mixed-effects model with sequence, treatment, and period as fixed effects and subject nested within sequence as a random effect.
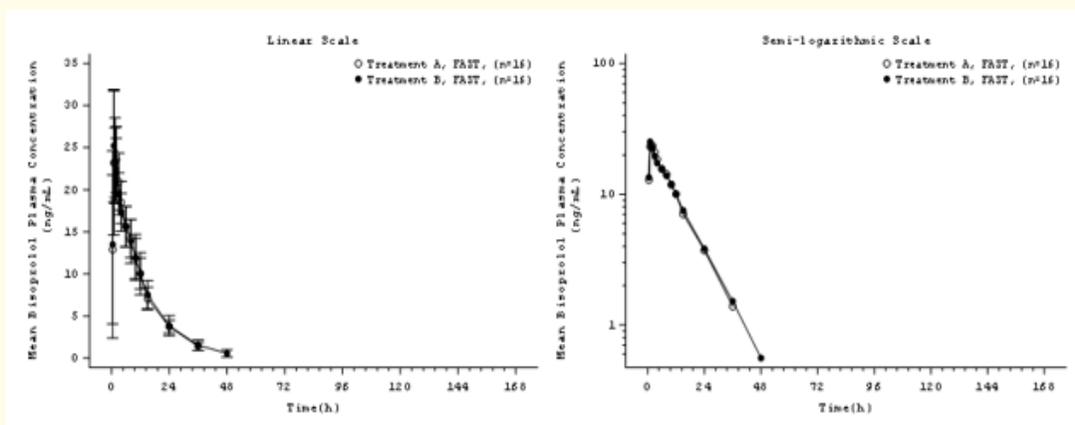
Treatment A = 5 mg/5 mg bisoprolol-amlodipine FDC tablet administered as a single dose. Treatment B = 5 mg bisoprolol tablet (Concor) and 5 mg amlodipine tablet (Norvasc) administered concomitantly as a single dose.

| Parameter N = 16	Treatment	Geometric LS Mean	95% CI of Geometric LS Mean	Ratio of test/reference (%)	90% CI limits
C_{max} (ng/ml)	A	4.17	(3.66, 4.74)	100.03	94.37 - 106.03
	B	4.17	(3.66, 4.74)		
AUC_{0-t} (ngxh/ml)	A	205	(172, 245)	96.76	92.95 - 100.73
	B	212	(178, 253)		
$AUC_{0-\infty}$ (ngxh/ml)	A	232	(193, 278)	98.68	93.38 - 104.28
	B	235	(196, 282)		

***Table 4:** Statistical comparison of amlodipine plasma pharmacokinetic parameters AUCs and C_{max} between treatment A and treatment B under fasting condition – pharmacokinetic analysis set [6].*

CI: Confidence Interval; LS: Least-Squares. Results based on a mixed-effects model with sequence, treatment, and period as fixed effects and subject nested within sequence as a random effect.

Treatment A = 5 mg/5 mg bisoprolol-amlodipine combination tablet (Concor AM) administered as a single dose. Treatment B = 5 mg bisoprolol tablet (Concor) and 5 mg amlodipine tablet (Norvasc) administered concomitantly as a single dose.

***Figure 3:** Arithmetic mean (±SD) bisoprolol plasma concentration-time profiles for treatment A and treatment B in fasting group on linear and semi logarithmic scales - pharmacokinetic analysis set [6]. Treatment A = 5 mg/5 mg bisoprolol-amlodipine FDC tablet administered as a single dose. Treatment B = 5mg bisoprolol tablet (Concor) and 5 mg amlodipine tablet (Norvasc) administered concomitantly as a single dose.*
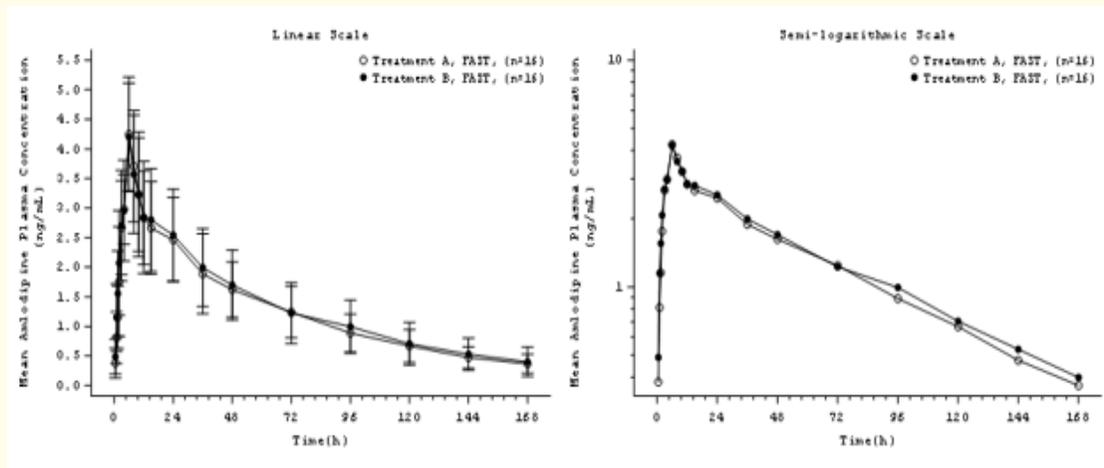
Figure 4: *Arithmetic mean (±SD) amlodipine plasma concentration-time profiles for treatment A and treatment B in fasting group on linear and semi-logarithmic scales - pharmacokinetic analysis set [6]. Treatment A = 5 mg/5 mg bisoprolol-amlodipine combination tablet (Concor AM) administered as a single dose. Treatment B = 5 mg bisoprolol tablet (Concor) and 5mg amlodipine tablet (Norvasc) administered concomitantly as a single dose.*

Based on C_{max} and AUC_{0-t}, bisoprolol and amlodipine exposure between Treatment A and Treatment B was comparable under fasted condition, with point estimates for all target parameters close to 100% and their 90% CIs contained within the 80 - 125% BE criterion.

Fed conditions

Results of BE evaluation for bisoprolol and amlodipine under fed condition are described in the tables 5 and 6 and figures 5 and 6 below.

Parameter N = 13 for a, N = 14 for B	Treatment	Geometric LS Mean	95% CI of Geometric LS Mean	Ratio of test/reference (%)	90% CI limits
C_{max} (ng/ml)	A	20.5	(17.9, 23.6)	93.87	84.56 - 104.20
	B	21.9	(19.1, 25.0)		
AUC_{0-t} (ngxh/ml)	A	272	(237, 312)	98.95	90.02 - 108.76
	B	275	(240, 314)		
$AUC_{0-\infty}$ (ngxh/ml)	A	283	(247, 324)	98.52	89.75 - 108.15
	B	287	(251, 328)		

Table 5: *Statistical comparison of bisoprolol plasma pharmacokinetic parameters AUCs and Cmax between treatment A and treatment B under fed condition – pharmacokinetic analysis set [6].*
Note: CI: Confidence Interval; LS: Least-Squares.
Results based on a mixed-effects model with sequence, treatment, and period as fixed effects and subject nested within sequence as a random effect.
Treatment A = 5 mg/5 mg bisoprolol-amlodipine combination tablet administered as a single dose.
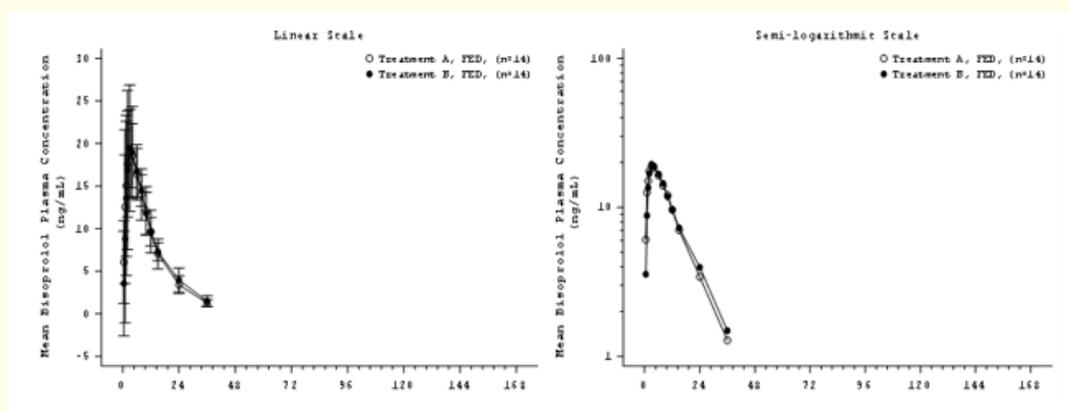*Treatment B = 5 mg bisoprolol tablet (Concor) and 5 mg amlodipine tablet (Norvasc) administered concomitantly as a single dose.*

| Parameter N = 13 for a, N = 14 for B	Treatment	Geometric LS Mean	95% CI of Geometric LS Mean	Ratio of test/ reference (%)	90% CI limits
C_{max} (ng/ml)	A	3.40	(2.90, 3.99)	106.56	97.82 - 116.08
	B	3.19	(2.73, 3.74)		
AUC_{0-t} (ng·h/ml)	A	173	(145, 206)	103.07	95.53 - 111.20
	B	167	(141, 200)		
$AUC_{0-\infty}$ (ng·h/ml)	A	190	(158, 228)	104.06	96.11 - 112.66
	B	182	(152, 219)		

Table 6: *Statistical comparison of amlodipine plasma pharmacokinetic parameters AUCs and Cmax between treatment A and treatment B under fed condition – pharmacokinetic analysis set [6].*

Note: CI: Confidence Interval; LS: Least-Squares. Results based on a mixed-effects model with sequence, treatment, and period as fixed effects and subject nested within sequence as a random effect.

Treatment A = 5 mg/5 mg bisoprolol-amlodipine combination tablet (Concor AM) administered as a single dose. Treatment B = 5 mg bisoprolol tablet (Concor) and 5mg amlodipine tablet (Norvasc) administered concomitantly as a single dose.

Figure 5: *Arithmetic mean (±SD) bisoprolol plasma concentration-time profiles for treatment A and treatment B in fed group on linear and semi logarithmic scales - pharmacokinetic analysis set [6]. Treatment A = 5 mg/5 mg bisoprolol-amlodipine combination tablet (Concor AM) administered as a single dose. Treatment B = 5 mg bisoprolol tablet (Concor) and 5 mg amlodipine tablet (Norvasc) administered concomitantly as a single dose.*
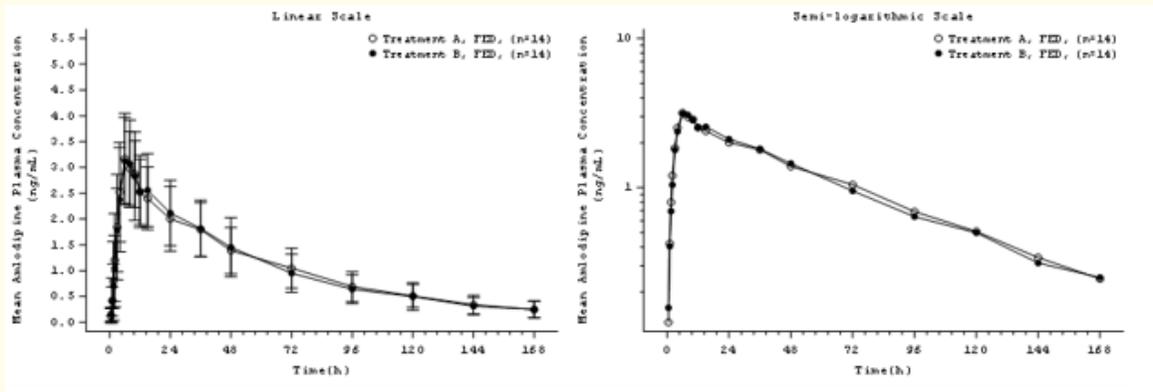
Figure 6: *Arithmetic mean (±SD) amlodipine plasma concentration-time profiles for treatment A and treatment B in fed group on linear and semi logarithmic scales - pharmacokinetic analysis set [6]. Treatment A = 5 mg/5 mg bisoprolol-amlodipine combination tablet (Concor AM) administered as a single dose. Treatment B = 5 mg bisoprolol tablet (Concor) and 5mg amlodipine tablet (Norvasc) administered concomitantly as a single dose.*

Based on C_{max} and AUC_{0-t}, bisoprolol and amlodipine exposure between Treatment A and Treatment B was comparable under fed condition, with point estimates for all target parameters close to 100% and their 90% CIs contained within the 80 - 125% BE criterion.

Overall, single doses of Concor AM (test product), administered in a crossover design with bisoprolol and amlodipine given concomitantly as a single dose (reference product) in healthy subjects were safe and well tolerated. There were total 2 subjects withdrawn from the trial for reasons not regarding safety.

Throughout the course of this study, none of the subjects participating in the trial reported treatment-emergent adverse events (TEAE), severe adverse events (SAE), or death. None of the safety laboratory showed any relevant mean or median changes after treatment. As can be expected as the IMPs are antihypertensive drugs, vital signs regarding blood pressure and pulse rate, or electrocardiogram (ECG) parameters, were altered. Individual abnormal values were observed but none was considered clinically significant.

Drug-drug interaction study

Although the FDC is currently only approved for substitution indication, Egis recently conducted an open label, multiple-dose, single-sequence drug-drug interaction study in 22 health volunteers [7] to assess the pharmacokinetic drug-drug interaction of bisoprolol and amlodipine ($AUC_{\tau,ss}$, $C_{max,ss}$) in 22 volunteers.

The geometric LSmeans $AUC_{\tau,ss}$, $C_{max,ss}$, and $C_{min,ss}$ ratios for Treatment 3 (bisoprolol and amlodipine) versus Treatment 1 (bisoprolol alone) for bisoprolol were 108.90%, 109.22%, and 116.04%, respectively. These results suggest that following multiple doses of the treatments, the bioavailability of bisoprolol is slightly increased (approximately 9% for $AUC_{\tau,ss}$ and $C_{max,ss}$ and 16% for $C_{min,ss}$) when administered concomitantly with amlodipine.

The geometric LSmeans $AUC_{\tau,ss}$, $C_{max,ss}$ and $C_{min,ss}$ ratios for Treatment 3 (bisoprolol and amlodipine) versus Treatment 2 (amlodipine alone) for amlodipine were 105.61%, 109.10% and 106.85%, respectively. Again, the results suggest that following multiple doses of the treatments, the bioavailability of amlodipine is slightly increased (approximately 6% for $AUC_{\tau,ss}$, 9% for $C_{max,ss}$ and 7% for $C_{min,ss}$) when administered concomitantly with bisoprolol.

No significant difference was observed for $T_{max,ss}$ between both treatments (p-value > 0.05) for bisoprolol and amlodipine.

A slight increase was observed in C_{max} and AUC for bisoprolol and amlodipine when both drugs were administered concomitantly. As the 90% confidence intervals were within the range of 80 - 125% for the target parameters, bisoprolol and amlodipine, when administered alone or concomitantly, were bioequivalent.

Discussion

Currently, the FDC of bisoprolol and amlodipine that is available in four different strengths, 5 mg/5 mg, 10 mg/5 mg, 5 mg/10 mg, and 10 mg/10 mg is authorized in 42 countries worldwide for a third line or substitution indication. That means that the FDC can replace a free combination of bisoprolol and amlodipine at the same strengths of the mono-components. For a such a substitution indication, a positive bioequivalence study is required according to international guidelines [8,9]. In case of different strengths of the FDC, the BE study is generally done with the highest strengths and for the other strengths a waiver is applied for. With the positive BE results of totally three BE studies, bioequivalence data are available for even two strengths of the FDC, namely the lowest and highest ones, 5 mg/5 mg and 10 mg/10 mg, and for the lowest strength even in fasted and fed state. This gives the physician the assurance that a free combination of bisoprolol and amlodipine can be easily replaced by the FDC. Due to the fact that the four FDC strengths cover all potential doses of the free combination, the flexibility of the physician to select the right doses of both mono-components is not limited. The advantage of the FDC is the expected better adherence of the patient that may improve clinical outcome [10].

Although in general not needed for a substitution indication, the results of the DDI study clearly show that their no relevant interaction between the components of the FDC, bisoprolol and amlodipine. This becomes important as soon as the FDC may be submitted for second line indication [8,9].

Conclusion

The available PK data for the FDC of bisoprolol and amlodipine demonstrate that the FDC is bioequivalent to the free combination of bisoprolol and amlodipine, and that there is no relevant drug-drug interaction between bisoprolol and amlodipine. This data confirms the use of the FDC in the labelled indication.

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