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Effectiveness and tolerability of fixed dose combination of amlodipine/valsartan in treatment of hypertension in the real-life setting among Egyptian patients

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Introduction: Many hypertension international guidelines recommend the use of fixed-dose combination of antihypertensive therapies as a first- line in high-risk hypertensive patients, in whom more rapid and pronounced blood pressure (BP) control is desired. The aim of this study was to evaluate the effectiveness, safety and tolerability of the single-pill combination of amlodipine/valsartan among Egyptian patients with arterial hypertension in a real-life setting.

Method: This prospective, open-label, multi-center, non-comparative post-marketing surveillance study enrolled adults with arterial hypertension (systolic BP >140 mmHg and/or diastolic BP >90 mmHg) treated with single-pill combination (SPC) of amlodipine/valsartan; 5/160 mg or 10/160 mg once daily dose. Patients were observed over a 3-months period with approximately monthly intervals between clinic visits. Primary objectives were comparison of systolic and diastolic blood pressure and heart rate at study start and after 12 weeks of therapy. Secondary objectives were evaluation of the blood pressure lowering effect in terms of response rates, evaluation of safety and tolerability of study medication.

Results: A total of 2489 patients were enrolled and 2357 completed the study. Mean age was 54 years and 85% of patients had received prior antihypertensive therapy. At study end, a significant mean BP reduction of −39.4/−21.7 mmHg (baseline: 171.5/103.4 mmHg; $p < 0.001$) was seen in the overall population. The corresponding mean BP reduction for patients on amlodipine/valsartan 5/160 mg was −34.6/−19.2 mmHg (baseline: 166/101 mmHg; $p < 0.001$) and for patients on amlodipine/valsartan 10/160 mg was −47.1/−24.3 mmHg (baseline: 178.6/106.4 mmHg; $p < 0.001$). In a post-hoc analysis for subgroups with important co-morbid conditions, the corresponding mean BP reductions were: patients with diabetes; −41.1/−21.6 mmHg (baseline 173.2/103.5 mmHg; $p = 0.00001$), patients with history of heart failure; −45.2/−22.8 mmHg (baseline 175.9/104.6 mmHg; $p = 0.00001$), patients with history of coronary heart diseases; −43/22.7 mmHg (baseline: 175.8/105 mmHg; $p = 0.00001$). A small change in the heart rate was noticed (82 bpm at baseline and 78.4 bpm at the end of study; $p < 0.001$). 70.3% of patients had their blood pressure controlled (BP <140/90 mmHg). Subjective investigators assessment as "excellent to very good" for amlodipine/valsartan SPC was 97.3% for effectiveness and 96.8% for tolerability. The corresponding investigators and patients assessment for compliance was 96.6% and 93.3% respectively. Adverse events were reported in 4.4% of patients mainly due to edema in 3.6%. Amlodipine/valsartan SPC was generally well tolerated.

Conclusion: The Results of this study showed that Single-pill combination of amlodipine/valsartan effectively reduced BP among Egyptian hypertensive patients with high tolerability profile and provided evidence that most of hypertensive patients may benefit from this combination.

Introduction: High blood pressure is the most common cause of death estimated to affect at least 25% of all adults. The risk of cardiovascular disease doubles with every increase of 20/10 mmHg above a normal blood pressure. Antihypertensive medications not only lower blood pressure, but also reduce the risk of stroke or Cardiovascular diseases. Despite the availability of a wide range of antihypertensive medications, about 70% of hypertensive patients fail to achieve a blood pressure control target of less than 140/90 mmHg.[1,2]Data from different national and regional surveys show that hypertension is common in developing countries, and the rates of awareness, treatment, and control are low. The increased prevalence in developing countries possibly caused by urbanization, ageing of population, changes of dietary habits, and social stress. Almost three-quarters of people with hypertension (639 million people) live in developing countries with limited health resources and where people have a very low awareness of hypertension and poor blood pressure control.[3]

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In Egypt, Patients aware of their disease accounts only for 37.5% of which 23.9% are treated and 8% only are controlled.[3]

The guidelines acknowledge that most patients with hypertension require 2 or more antihypertensive medications to achieve blood pressure control. Accordingly, initiation of therapy with 2 drugs is recommended in patients whose blood pressure is more than 20/10 mmHg above goal, either as separate agents or in a fixed-dose combination. One of the combinations recommended by the ESH/ESC guidelines is the combination of a calcium channel blocker with an angiotensin receptor blocker.[2]

Fixed dose combination of Valsartan plus Amlodipine is an effective and well tolerated antihypertensive medication. Data showed that the two complementary mechanisms of action of calcium channel blocker and angiotensin receptor blocker helped more patients to reach their recommended blood pressure goals.[4]

Furthermore, a recent study conducted on 8336 patients to evaluate the effectiveness and safety of amlodipine/valsartan single pill combination (SPC) showed that an optimal blood pressure (BP) reduction was achieved for all hypertension grades, including patients with isolated systolic hypertension. The treatment was well tolerated with few adverse events (AEs).[5]

Due to the fact of limited available data on Egyptian hypertensive patients, this study was planned to be conducted on large number of patients to show the results in real-life setting.

Methods: Study design Multicenter, observational, Post Marketing Surveillance (PMS) study. The total duration of treatment with SPC of amlodipine/valsartan 5/160 and 10/160 in this study was 12 weeks. In accordance with the definition of non-intervention studies, therapy was prescribed in terms of the marketing authorization. The assignment of patient to therapy was decided based on clinical evaluation and was separated from the decision to include the patient in the study. The dose of SPC of amlodipine/valsartan prescribed by the treating physician was recorded at the initial visit. Concomitant medications, including antihypertensive medications were allowed in the study. Patients were observed over a 3-months period. Patients could discontinue participation in the study for any reason. In the event of premature discontinuation, the investigators were requested to document the reason for discontinuation

Patients: Males or females, >18 years of age, with hypertension (SBP/DBP >140/90 mmHg), for whom an antihypertensive therapy with the SPC of Valsartan 160 mg and Amlodipine 5 or 10 mg once daily is clinically recommended, were included in the study. All patients were asked to provide written informed consent before participating in the study. Women who were pregnant, intending to become pregnant or breastfeeding, patients with severe medical condition(s) that in the view of the investigator prohibits participation in the study e.g. severe renal or hepatic impairment and hypersensitivity to valsartan, amlodipine or any of the components in the formulation were excluded from the study. Independent ethical committee approval was obtained before the study initiation as per the local regulations.

Study procedures: At baseline, patients were assessed for demographic details, history, concomitant diseases, previous antihypertensive medications, blood pressure, and heart rate. Suitable dose of amlodipine/valsartan SPC was studied. The dose was adjusted during the follow up visits by the treating physician. Patients were monitored closely for change in SBP/DBP and heart rate during follow up visits for 12 weeks. Safety and tolerability assessments included the recording of adverse events (AEs) and serious adverse events (SAEs) throughout the study, irrespective to suspected relation to study medication. No additional diagnostic or monitoring procedures were performed. Primary end point was comparison of systolic and diastolic blood pressure and heart rate at study start and after 12 weeks of therapy with amlodipine/valsartan 5/160 mg or amlodipine/valsartan 10/160 mg. Secondary endpoint was evaluation of the blood pressure lowering effect in terms of response rates and evaluation of AEs and SAEs. Investigators entered the required patients' data in the Case Report Form (CRF). It was entered anonymously into the study database, validated and analyzed.

Statistical analysis: A total of 2489 patients were enrolled and 2357 completed the study (Intent To Treat population). Analysis of results included descriptive statistics of the demographic data as well as efficacy and safety data. To determine statistical significance of efficacy and safety data, chi square test has been used to compare categorical results, while t-test has been used to compare two means and ANOVA for comparison of more than 2 means. Statistical significance limit was taken to be 0.05. Patients were analyzed as one group and were also divided into clinically relevant groups. In post-hoc analysis, patients were divided according to the prescribed dosage into 4 groups (up and down-titration were the decision of the treating physician); **Group 1:** Started amlodipine/valsartan 5/160 in V1 and maintained on amlodipine/valsartan 5/160 to V4 (33% of patients; $n = 789$), **Group 2:** Started amlodipine/valsartan 5/160 in V1 and increased to amlodipine/valsartan 10/160 in V2 or V3 (23% of patients; $n = 535$), **Group 3:** Started amlodipine/valsartan 10/160 at V1 and maintained on amlodipine/valsartan 10/160 to V4 (27% of patients; $n = 630$), **Group 4:** Started amlodipine/valsartan 10/160 at V1 and decreased to amlodipine/valsartan 5/160 to V4 (15% of patients; $n = 344$).

Results: Total of 2489 patients were enrolled in the study 2357 patients completed the four visits of the study and were evaluable for efficacy analysis. The baseline demographic details are shown in Table 1.

51.4% ($n = 1212$) of patients were on other concomitant medications. The leading concomitant diseases for which concomitant medications were indicated were: Diabetes (27.3%), Hypertension (13%), Hypercholesterolemia (11.8%), Ischemic Heart Diseases (11.7%),

Table 1
Demographic and baseline characteristics ($n = 2357$).

Age (Y)	Mean	54.06
	SD	9.68
Age group-*n*	<40 years	200
	41–50 years	672
	51–60 years	933
	>60 years	539
Weight (Kg)	Mean	87.2
	SD	13.8
Smoker-n	Smoker	683
	Non-smoker	1660
Hypertension duration (Y)	Mean	6.94
	SD	5.62
Diabetes – %	Diabetics	25%
	Non-Diabetics	75%

Table 2
Antihypertensive therapy taken before switching to study medication.

Antihypertensive medications (*n*,%)	Beta blockers	954	27.3%
	ACE Inhibitors	861	24.7%
	Diuretics	783	22.4%
	Calcium channel blockers	499	14.3%
	ARBs	358	10.3%
	Others	34	1.0%