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Research Article

A COMPARATIVE STUDY ON THE QUALITY OF DIFFERENT OLMESARTAN TABLETS AVAILABLE IN THE ALBANIAN MARKET

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ABSTRACT

Objective: Olmesartan (OLM) is the latest molecule of registered and marketed in Albania for the treatment of arterial hypertension. This study aims to carry out a quality control (QC) test on all the alternatives available in the Albanian market and evaluate if there are any outstanding differences terms of quality as it is in terms of price.

Methods: There were carried out various QC pharmacopeias tests on a range of different productions of OLM 20 mg tablets. There have been carried out weight variation test, setting the diameter, thickness, friability, hardness, disintegration, and dissolution test. The pharmaceutical equivalents were compared to the reference product in terms of similar dissolution factor (f^2) of dissolution profiles and the dissolution efficiency. The dissolution test was carried out using Varian dissolution apparatus 2 (50 rpm, 37±0.5°C); Varian Prostar high-performance liquid chromatography was used to determine the OLM concentration at wavelength 250 nm; Varian hardness VK 200, Guoming BJ-2 disintegration apparatus were used for the respective tests.

Results: The study showed that although there is a consistent difference in market price, their quality is comparable. The dissolution profiles were very similar. All formulations met the standards of the United States Pharmacopoeia.

Conclusion: All tablets were within the pharmacopoeia limits. The present study confirmed that the difference in price not always represents a difference in terms of quality.

Keywords: Olmesartan medoxomil, Quality control, Pharmacopoeia standards.

INTRODUCTION

According to the data of Global Burden of Disease, arterial hypertension (AHT) is the second risk factor for all other kind of diseases in Albania for 2010 after the risk factors in connection with diet (Fig. 1) [1,2].

Olmesartan (OLM) is the latest molecule from the group of an antagonist of angiotensin inhibitor registered and marketed in Albania. It is one of the preferred preparations available for the treatment of AHT and part of the national reimbursement list. OLM medoxomil is 5-methyl-2-oxo-2*H*-1,3-dioxol-4-yl) methyl 4-(2-hydroxypropan-2-yl)-2-propyl-1-({4-[2-(2*H*-1,2,3,4-tetrazol-5-yl) phenyl] phenyl} methyl)-1*H*-imidazole-5-carboxylate (Fig. 2). It is a potent and selective angiotensin AT1 receptor blocker [3] which has been approved for the treatment of hypertension in the US, Japan, European countries, and Albania.

The drug contains a medoxomil ester moiety and is cleaved rapidly by an endogenous esterase to release the active metabolite OLM.

So, it was decided to carry out a quality control (QC) for different products OLM medoxomil sold in the Albanian pharmaceutical market. 4 generic drugs OLM medoxomil 20 mg were the subject of this study.

METHODS

Four different products OLM medoxomil purchased directly from pharmacies in Tirana, Albania (Table 1).

OLM medoxomil as reference standard; analytical balance APX-20 "Denver instrument; ph meter ultrabasic "Denver instrument"; It was conducted a United States Pharmacopoeia (USP) method for dissolution test; all chemicals and reagents were high-performance liquid chromatography (HPLC) grade, acetonitrile (9.8% pure); potassium phosphate monobasic (136.9 g/mol), phosphoric acid concentrated, a Varian ProStar HPLC system DAD detector, manual Rheodyne loop injection. The separation was performed on an analytical 250 × 4.6 mm Eurospher 100^{-5} C18 (5 µm, particle size) column. The wavelength was set at 250 nm. The mobile phase was a mixture of acetonitrile: Phosphate buffer (17:33) at pH 3.4 was selected a flow rate of 1.5 mL/min. The mobile phase was prepared daily and degassed by ultrasonication for 5 minutes before use.

The QC tests of tablets consisted of hardness, shape, diameter, thickness, disintegration, dissolution, percentage of content of the active ingredient.

Weight variation

20 tablets per each production of OLM medoxomil were weighted one after the other through an analytical balance, and it was calculated the average weight per each product. It was calculated as well the standard deviation (SD) [4].

Hardness

The hardness of 10 tablets per each product was measured using Varian VK200. Then, it was calculated the mean value and respective SD (Table 2) [5].

According to USP, the value of hardness of tablets should vary from 4 to 10 kgf.

Diameter and thickness

Diameter and thickness of 10 different tablets for each production are measured by Caliber WT. It is calculated the mean value of diameter and thickness along with the SD [6].

Disintegration

6 tablets of each sample were the subject to a disintegration test **using** Guoming BJ-2 apparatus set at 30 cycles/min, at 37±0.5°C, 1 L of distilled water as medium.

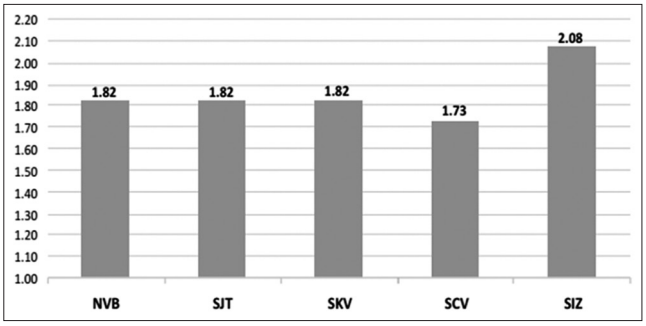

Fig. 1: The increase of death rate as a consequence of arterial hypertension in Albania from 1990 to 2010 [1]

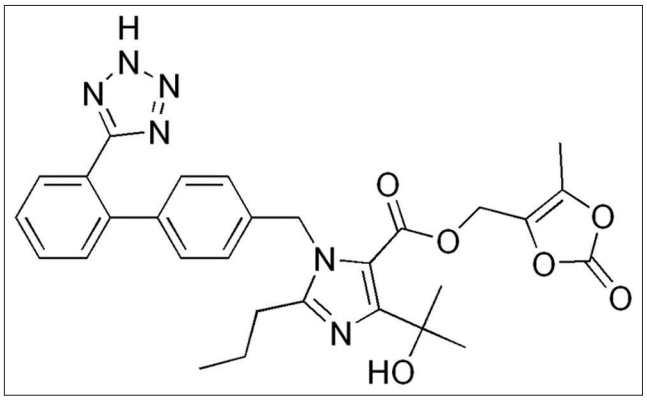

Fig. 2: Structure of olmesartan [3]

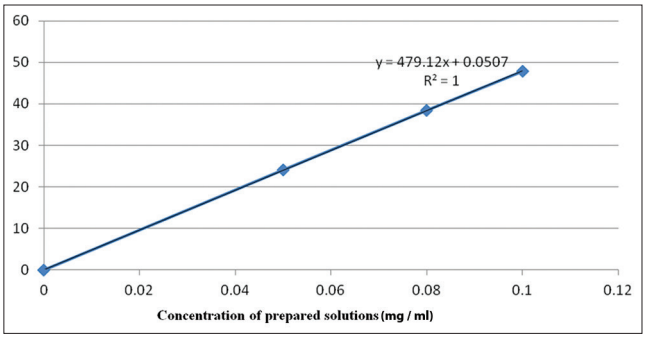

Fig. 3: Calibration curve

Table 1: These are doses and prices of subjects of this study

Name	Dose (mg)	Price (euro)/tab
Generic I	20	0.62
Generic II	20	0.45
Generic III	20	0.17
Generic IV	20	0.15

For each of the generics included in the study has been determined the mean time of disintegration (Table 2).

The test lasts 30 minutes for each formulation. According to USP, "the test is considered passed if all 6 tablets of the first series are disintegrated within the time limit. If only one of the tablets does not pass the test, it should be repeated with another series of 6 tablets [7]."

The active ingredient content test

The percentage of the content test has been based on the monography of OLM medoxomil described in the USP. According to USP, the OLM tablets should contain not <90% and not more than 110% OLM medoxomil, comparing to the quantity declared in the label. The results of this test are included in Table 3.

Calibration curve

The linearity of instrument standard response was determined for each compound with different concentration calibration standards ranging from 50 µg/ml; 80 µg/ml; 100 µg/ml for OLM. The calibration curve of OLM was constructed by plotting analyte peak area ratio as compared to the corresponding concentration and fitting these data in regression analysis.

Dissolution

Under the described chromatographic conditions, OLM peak was well resolved. The final results of the dissolution test on each tablet production are listed in Table 4. The Fig. 3 shows the dissolution profiles. Dissolution efficiency (DE), the area under a dissolution curve between defined time points, and the fit factors (f_1 and f_2) have been compared for the characterization of dissolution profiles. The DE of a pharmaceutical form (Khan and Rhodes 1972; Khan 1975) was defined as area under the dissolution curve up to a certain time, t, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time [8]. DE estimated the release of the active pharmaceutical substance into the absorptive medium. The determination has been done for every 6 vessels, and a mean value was obtained along with a confidence interval of 95%. It was used t test for a statistical reason to show any possible difference in the %DE 45 minutes of the generics compared to the reference III (significance difference *p<0.05).

Calculations in connection with DE [9,10] have been done according to formula (1) and (2) first developed by Moore and Flanner 1996.

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} \times 100 \quad (1)$$

$$f_2 = 50 + \log\left\{ \left(1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right) \right\}^{-0.5} \times 100 \quad (2)$$

R_t and T_t were percentages of drug release of the reference product and generic product in time t; n was the number of points were the samples of both reference and generic were released above 90%.

Table 2: Results of weight variation test, hardness, diameter, thickness, and disintegration time

Product	Weight (g) (mean) (%RSD)	Hardness (kgf) (mean±SD) (%RSD)	Diameter (mm) (mean±SD) (%RSD)	Thickness (mm) (mean±SD) (%RSD)	Disintegration (mean±SD) (%RSD)
Generic I	0.219 g (0.82)	11.6±6.4 (5.6)	8.64±0.005 (0.06)	3.74±0.004 (0.12)	15.17±0.4 (2.7)
Generic II	0.222 g (1.24)	8.4±3.7 (4.5)	8.66±0.004 (0.05)	3.86±0.005 (0.14)	15.17±0.14 (2.9)
Generic III	0.213 g (6.7)	10.5±6.7 (9.4)	8.54±0.005 (0.12)	3.62±0.004 (0.12)	15.0±0 (0)
Generic IV	0.216 g (2.09)	10.4±2.1 (2.06)	8.66±0.009 (0.1)	3.62±0.004 (0.12)	15.93±0.17 (1.09)

SD: Standard deviation, RSD: Relative standard deviation

RESULTS AND DISCUSSION

The main objective of any pharmacopeia is to provide the manufacturers of drugs and pharmaceutical dosage forms with a series of QC tests that ensures high quality of the final obtained dosage forms. There are in the market various productions of the same active ingredient and same pharmaceutical form dosage. These productions are considered as equivalents, and all of them are part of the reimbursement list. Thus, it is very important to see if there is a correlation between price and quality. This is what this study do, using the same methods of QC according to the same pharmacopoeia (USP), using the same instruments.

Weight variation

The results obtained from this test are listed in Table 2. As it can be noticed generic 3 has a relative SD (RSD) by 6.7%, while all other generics, from a statistical point of view, have a non-significant deviation. All tablets complied with the standards of the USP regarding weight variation [10].

Hardness

The results listed in Table 2, show that formulation II hardness value is within the range of USP while all 3 others have values upper than 10 kgf. Generic I has the highest deviation (RSD 5.6%).

Disintegration

The results of disintegration test are included in Table 2. It can be noticed that all productions are disintegrated within 30 minutes, so they pass this test.

Percentage of content of the active ingredient

The results of the determination of the content of the active ingredient are listed in Table 3. All tablets pass this test because they contain ≥99% of the active ingredient showed in the label (Fig. 3).

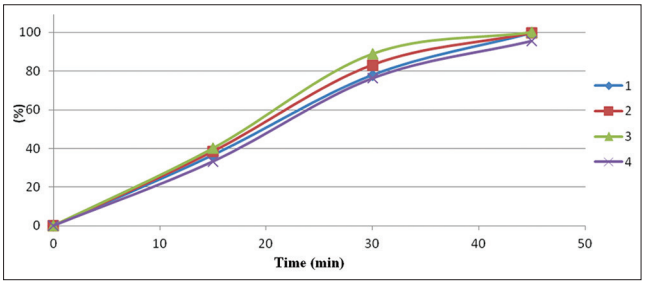

Fig. 4: Dissolution profiles of different olmesartan tablets 20 mg

Table 3: The content of active ingredient in %

Subjects of the study	% of active ingredient
Generic I	99.5
Generic II	99.0
Generic III	99.9
Generic IV	95.5

Table 4: Results of dissolution test of different OLM tablets expressed in percentage (%) drug release within 15, 30 and 45 minutes

Subjects of the study	Drug release % in 15'	Drug release % in 30'	Drug release % in 45'
Generic I	36.50	77.90	99.70
Generic II	38.40	83.20	99.74
Generic III	40.00	88.80	100.00
Generic IV	33.24	76.30	95.60

OLM: Olmesartan

Generic III has the highest value of the content of the active ingredient while all formulations are within the limits of USP for this test. Generic III contains 99.9% OLM medoxomil, Generic I 99.5%, Generic II 99.0%, and Generic IV only 95.5% OLM medoxomil.

Dissolution

The results of the dissolution test on each tablet are listed in Table 4. It can be noticed that all tablets dissolved within 30 minutes, on average more than 75% of the active ingredient.

From the data in the table, it can be said that at the end of 45 minutes all formulations release more than 95% of the active ingredient. Comparing these data, Generic III has the best dissolution profile. This result is expressed also in the Fig. 4.

Comparison of dissolution profiles

The brand patent is not registered in Albania. So, as long as the Generic III has the best dissolution profile, it was decided to compare the other 3 productions with it.

As it is shown in Table 5, the $t_{45\ minutes}$ values of generics are similar to the reference (*p<0.05), confirming a similarity in the dissolution process. DE (%$DE_{45\ minutes}$) values of the methods used in this study show no significant statistical difference between the reference and other generics (*p<0.05). The factors of similarity and difference demonstrate similarity since the f_1 values are within range 0-15, and the f_2 values are within 50-100.

The QC test showed that there is no significant difference between different generics of OLM medoxomil, marketed in Albania. Even other studies show that the QC tests, especially the dissolution test, may serve as tools for comparing the generics with a reference or just generics between them, through similarity factors and DE. In another step, they may serve as a tool for health authorities and specialists during the preparation of the drug reimbursement list.

CONCLUSIONS

Taking into account the results of QC tests carried out during this study, all different productions of OLM available in the Albanian market meet the requirements of USP. The average mass of the 20 tablets was within the limits of 85-115% of the average weight and the percentage RSD < 10%.

As a conclusion after the hardness test, it can be said that apart formulation II, the other formulations were harder by approximately 1% than the upper limit specified by USP. Regarding the diameter and thickness, there were no significant differences.

Comparing the time of disintegration of the tablets of OLM, it can be concluded that they are very similar, independently from the difference in hardness value.

Regarding the percentage of content of the active ingredient although Generic III has a low price 0.17 €/tab it contains 99.9% OLM medoxomil, whereas Generic I is the most expensive alternative in the National List of Reimbursement, costs 0.62 €/tab (quite 4 times more then Generic I) and contains 99.5% OLM medoxomil.

Table 5: Comparison of dissolution profiles and similarity/difference factors (f2 and f1)

Subjects of the study	t_{45} minutes (%)	Difference factor f1	Similarity factor f2
Reference III	100.00	-	-
Generic I	99.70	2.58	79.5
Generic II	99.74	6.32	63.1
Generic IV	95.60	10.3	53.3

OLM: Olmesartan

As a conclusion, it should be said that higher prices not always means higher quality. All four formulations are similar in quality, but different as far as it concerns the prices.

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