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Orginal study

Pharmacodynamic Equivalence Study of Two Preparations of Eye Drops, Containing Dorzolamide in Healthy Volunteers

Emil M. Gatchev[1], Andrey D. Petrov[1], Russka W. Hristova[2], Irenna S. Demircheva[2], Ursula Thyroff-Friesinger[3], Wolfram H. Richter[4], Rossen K. Koytchev[4]

[1] Medical University of Sofia, Department of Clinical Pharmacology and Therapeutics, University Hospital "Tsaritsa Joanna-ISUL", Bulgaria
[2] Medical University of Sofia, Clinic of Ophthalmology, University Hospital "Tsaritsa Joanna-ISUL", Bulgaria
[3] Hexal AG, Holzkirchen, Germany
[4] Cooperative Clinical Drug Research and Development AG, Hoppegarten, Germany

SUMMARY

Introduction: Dorzolamide 20mg/ml eye drops (dorzolamide hydrochloride (CAS: 120279-96-1)) is a topical carbonic anhydrase inhibitor indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

The aim: The aim of the present study was to assess the pharmacodynamic equivalence of two preparations of eye drops containing 20 mg dorzolamide (CAS: 120279-96-1).

Method: The study was conducted as a monocentric, observer-blinded, randomized, single dose, single period study in thirty-six healthy volunteers. Each volunteer received in a random way after measurement of IOP intraocular pressure a single dose of 1 drop of the test product in the conjunctival sac of one eye and 1 drop of the reference drug in the conjunctival sac of the other eye. Measurement of intraocular pressure (IOP) of both eyes was performed on day 1 of each study period pre-dose and 2 h post dosing by means of Goldmann applanation tonometry. The two-sided 95% confidence interval was calculated for the difference of the primary target parameter (absolute decrease in intraocular pressure 2 h post dose).

Results: The statistical evaluation demonstrated a decrease in the IOP of 3.10 mmHg for the eye treated with the test formulation (dorzolamide 20mg/ml eye drops) and 3.23 mmHg for the eye treated with the reference formulation. The mean difference was -0.13 mmHg. The 95% confidence interval was between -0.65 and 0.40 mmHg and thus entirely within the pre-defined equivalence range (±1.5 mmHg).

Conclusion: Both formulations showed comparable results obtained at a time probably equal to the maximum effect concerning the primary target parameter lowering of intraocular pressure 2h post dose. The safety profile of both preparations showed

Corresponding author:
Prof Emil M. Gatchev, MD, PhD,
Specialist in Clinical Pharmacology
Medical University of Sofia, Department of Clinical Pharmacology and Therapeutics,
University Hospital "Tsaritsa Joanna-ISUL", Bulgaria
E-mail: emilgatchev@gmail.com

no difference.

Keywords: dorzolamide, eye drops, intraocular pressure

INTRODUCTION

Dorzolamide 20mg/ml eye drops (dorzolamide hydrochloride (CAS: 120279-96-1) is a topical carbonic anhydrase inhibitor indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension [1]. The drug decreases elevated intraocular pressure, whether or not associated with glaucoma, by reducing aqueous humor secretion. Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of glaucomatous field loss and optic nerve damage.

Dorzolamide hydrochloride is an inhibitor of human carbonic anhydrase II. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. Unlike miotics, dorzolamide reduces intraocular pressure without the common adverse effects of miotics such as night blindness, accommodative spasm and pupillary constriction. Unlike topical beta-blockers, dorzolamide has minimal or no effect on pulse rate or blood pressure. Unlike oral carbonic anhydrase inhibitors, topical administration of dorzolamide hydrochloride allows the drug to exert its effects directly in the eye at substantially lower doses and therefore with less systemic exposure [2]. In clinical studies, this resulted in a reduction in IOP without the acid-base disturbances or alterations in electrolytes characteristic of oral carbonic anhydrase inhibitors. The maximum effect has been observed approximately 2 h post dose. It has been demonstrated that the topical administration of dorzolamide reduces the intraocular pressure in healthy volunteers by 3.5 to 7 mmHg compared to pre-dose values [3]. The main pharmacodynamic effect of dorzolamide can be thus evaluated in healthy volunteers after administration of a single dose [4].

The aim of the present study was to assess the pharmacodynamic equivalence (lowering of intraocular pressure) of two preparations of eye drops containing 20 mg dorzolamide 1 ml eye drops.

SUBJECTS AND METHODS

Study Preparations

The test formulation in the present study (dorzolamide 20mg/ml eye drops) was manufactured by the company Hexal AG, Holzkirchen, Germany. Packaging and labeling was done according to the national and international requirements and GMP. The reference product (Trusopt®, Chibret Pharmaceutische GmbH) was purchased in a pharmacy.

Study Protocol

The pharmacodynamic study was performed in accordance with the relevant article of the Declaration of Helsinki (1964) as revised in Tokyo (1975), Venice (1983), Hong Kong (1989), Somerset West, RSA (1996) and Edinburgh (2000) and the "Note of Clarification on Paragraph 29" added by the WMA General Assembly, Washington (2002), the "Note of Clarification on Paragraph 30" added by the WMA General Assembly, Tokyo (2004), and in accordance with [5-9].

The study was reviewed and approved by the LEC (local ethics committee) of the University Hospital "Tsaritsa Joanna-ISUL", Bulgaria.

The study was performed at the Medical University of Sofia, Department of Clinical Pharmacology and Therapeutics and the Clinic of Ophthalmology, University Hospital "Tsaritsa Joanna-ISUL", Bulgaria.

The inclusion criteria pre-defined in the study protocol provided for the inclusion of thirty-eight male and female Caucasians (18 female/18 male) within the age range of 18 to 55 years, who were physically and mentally healthy as judged by means of a medical and standard laboratory examination, with intraocular pressure between 16 and 21 mmHg (mean value of 3 measurements) at screening with a normal body weight assessed by the

BMI (accepted range 19 to 27 kg/m^2).

Prior to being enrolled into the study, the volunteers gave their informed written consent to participate in the study in response to a complete written and verbal explanation of the nature, scope and possible consequences of the study, which was done by the clinical investigator.

All enrolled subjects met all inclusion and none of the exclusion criteria and were judged eligible for the study, based on medical history, demographic data, medication history, physical examination, vital signs and clinical laboratory tests.

A total number of 36 volunteers were enrolled in the study and all of them completed the study according to the protocol.

Study Design

The study was designed as a monocentric, observer-blinded, randomized, single-dose, single period study, with duration of hospitalization of approximately 6 h after dosing on day 1.

Study procedure

The volunteers were hospitalized for approximately 12 h overnight stay and further 6 h confinement on the day of dosing. After consumption of a standard breakfast in the morning on day 1 between 7:00 and 7:30 a.m., all volunteers received between 9:00 and 11:00 a.m. the study medication: a single dose of 1 drop eye drops containing 20 mg dorzolamide in 1 ml eye drops in the conjunctival sac of the right or the left eye. The allocation of test and reference product to the left or to the right eye was randomized. The sequence of randomized administration was the same for all volunteers: the right eye was dosed first, followed by the left eye.

The same investigator performed the study drug administration always for all volunteers, after the pre-dose measurement of intraocular pressure was completed. Measurement of intraocular pressure (IOP) of both eyes (by a blinded observer) was performed on day 1 two hours post dosing by means of Goldmann applanation tonometry.

The administration of study medication was related to the measurement of intraocular pressure. The administration was performed always by the same investigator for all volunteers after measurement of intraocular pressure was completed:

1. Administration of Alcaine® eye drops (a topical anesthetic ophthalmic solution containing proparacaine hydrochloride 0.5%, manufactured by Alcon Manufacturing, Ltd., Herts, UK and acquired at the local pharmacy) to the right eye, followed two minutes later by three consecutive measurements of intraocular pressure of the right eye.
2. Administration of Alcaine® eye drops, to the left eye, followed two minutes later by three consecutive measurements of intraocular pressure of the left eye.
3. Administration of study drugs (either 1 drop of the test formulation or 1 drop of the reference formulation in the conjunctival sac of the right eye) 15 minutes after Alcaine® administration to the right eye.
4. Administration of study drugs (either 1 drop of the test formulation or 1 drop of the reference formulation in the conjunctival sac of the left eye) 15 minutes after Alcaine® administration to the left eye.

Following sequence of procedures was followed:

- time 0 min: administration of ALCAINE® eye drops to the right eye
- time 2 min: first measurement of intraocular pressure of the right eye
- time 3 min: second measurement of intraocular pressure of the right eye
- time 4 min: third measurement of intraocular pressure of the right eye
- time 5 min: administration of ALCAINE® eye drops to the left eye
- time 7 min: first measurement of intraocular pressure of the left eye
- time 8 min: second measurement of intraocular pressure of the left eye
- time 9 min: third measurement of intraocular pressure of the left eye
- time 15 min: administration of study drug (1 drop in the conjunctival sac) to the right eye
- time 20 min: administration of study drug (1 drop in the conjunctival sac) to the left eye.

Ophthalmologic procedures

Measurement of intraocular pressure

Measurement of intraocular pressure (IOP): the intraocular pressure was measured by means of Goldmann applanation tonometry on both anesthetized eyes (between 9 a.m.

and 11 a.m.) at screening and on the right eye only on day 1 and at the final examination. Alcaine eye drops were used to anesthetize the cornea. The anesthetic was applied 2 min before the examination. The measurement of intraocular pressure was performed three times on each eye within 4 min, always by the same investigator and the same tonometer for the same volunteer. The mean value of the three measurements was taken for evaluation.

Additional ophthalmologic procedures

Eye motility: Saccades were assessed by having the volunteer move his eye quickly to a target at the far right, left, top and bottom. Slow tracking was assessed by the 'follow my finger' test, in which the examiner's finger traces an imaginary "H", which touches upon the six cardinal fields of gaze. This procedure is suitable to test the inferior, superior, lateral and medial rectus muscles of the eye, as well as the superior and inferior oblique muscles.

Pupil function: An examination of pupillary function includes inspecting the pupils for equal size (1 mm or less of difference may be normal), regular shape, reactivity to light, and direct and consensual accommodation. The results of the examination could be described as: pupils equal and regular; reactive to light; accommodate (direct and consensual). A swinging-flashlight test was used to evaluate the reactivity to light. In a normal reaction to the swinging-flashlight test, both pupils constrict when one is exposed to light. As the light is being moved from one eye to another, both eyes begin to dilate, but constrict again, when light has reached the other eye.

Visual acuity: Visual acuity is the eye's ability to detect fine details and is the quantitative measure of the eye's ability to see an in-focus image at a certain distance. Visual acuity was measured with a Snellen chart. The standard definition of normal visual acuity (20/20 or 6/6 vision) is the ability to resolve a spatial pattern separated by a visual angle of one minute of arc.

Slit lamp biomicroscopy: The evaluation of the anterior eye was performed by means of slit lamp biomicroscopy.

Evaluation of the fundus: The evaluation of the fundus was performed by means of the biomicroscope using corresponding lenses.

These additional ophthalmologic examinations were performed and evaluated by the investigator as "normal" or "abnormal"; in case of abnormal, the investigator had to comment. The tests were performed at entry (screening) visit for check of exclusion criterion and at the final visit.

Statistical analysis

In order to investigate the pharmacodynamic equivalence of both products, the 95% confidence interval was calculated for the difference (test-reference) of the primary target parameter absolute decrease in intraocular pressure 2 h post dose. The confidence intervals were determined by means of a parametric (ANOVA) statistical method. The ANOVA model included treatment, administration pattern, period and subject within pattern as factors. This confidence interval was then compared with the corresponding clinical acceptance range (±1.5 mmHg).

The secondary target parameter of the present study was to evaluate the relative (as percentage of baseline) decrease in intraocular pressure 2 h post dose of both products. In addition, the safety of both preparations was evaluated based on safety clinical and laboratory examinations and registration of local tolerability, vital signs (heart rate, blood pres-

Tabele 1. Results of the individual IOP measurements on day 1 (pre-dose and 2 h post dose)

	individual IOP [mmHg]			
	Test		Reference	
	pre-dose	2h	pre-dose	2h
Mean	17.514	14.394	17.421	14.194
SD	0.890	1.238	0.885	0.999
CV(inter)	5.08	8.60	5.08	7.04
Min.	16.000	12.333	15.000	12.167
Max.	19.500	17.000	19.500	16.167
Median	17.667	14.167	17.333	14.000
Geom.mean	17.492	14.342	17.399	14.161

sure), adverse events and/or adverse drug reactions.

RESULTS

A total number of 36 volunteers completed the study according to protocol. The results of the IOP measurements on day 1 (pre- dose and 2 h post dose) are presented in Table 1.

The primary and secondary target parameters of dorzolamide, administered as 1 drop in the conjunctival sac of the right or left eye of the test formulation or 1 drop in the conjunctival sac of the right or left eye of the reference formulation of the 36 volunteers who were subjected to pharmacodynamic and statistical evaluation are summarized in Table 2.

The mean value of the primary target parameter "absolute decrease in intraocular pressure 2 h post dose" was 3.10 ± 1.23 mmHg for the test formulation and 3.23 ± 1.15 mmHg for the reference formulation. The mean value of the secondary target parameter, relative decrease in intraocular pressure 2 h post was 17.65% ± 6.75% for the test formulation and 18.39% ± 5.96% for the reference formulation. A graphical presentation is given in Figure 1.

For the analysis of pharmacodynamic bioequivalence, the 2-sided 95% confidence interval was calculated for the difference (test-reference) of the absolute decrease in intraocular pressure 2 h post dose and then compared with the predefined acceptance range of ±1.5 mmHg. The difference observed has been 0.125 mmHg. The calculated confidence interval was between -0.65 - 0.40 mmHg and thus well within the acceptance range. The 95% confidence are presented in Table 3.

The local tolerability of both preparations was assessed on day 1 before dosing (before the IOP measurement) as well as 15 min, 1 h, 2 h (before the IOP measurement), and 6 h post dose in each eye by rating following symptoms: blurred vision, ocular burning, epiphora and hyperemia.

The two preparations were similarly well tolerated without any signs of clinically significant adverse effects. A to-

Vol Random No.	Absolute Decrease in IOP (mmHg)		Relative Decrease in IOP (% from baseline)	
	Test	Reference	Test	Reference
1.	1.167	2.500	6.422	14.019
2.	1.333	1.833	7.843	10.377
3.	0.667	1.833	4.000	11.111
4.	4.500	2.167	24.545	12.264
5.	2.333	2.500	12.500	13.393
6.	2.833	5.500	15.179	28.205
7.	1.333	3.167	8.163	19.388
8.	4.833	1.833	27.103	10.280
9.	1.333	6.500	7.547	34.821
10.	4.000	2.333	22.430	13.592
11.	4.500	5.500	24.324	29.730
12.	3.500	3.500	20.388	20.388
13.	3.833	3.000	21.101	17.308
14.	3.667	4.500	20.183	25.000
15.	3.667	4.833	18,803	25.893
16.	2.667	2.667	14.679	14.815
17.	2.500	4.167	13.636	22.124
18.	5.000	2.500	26.786	14.286
19.	1.333	1.167	8.000	6.863
20.	2.833	3.167	16.667	19.000
21.	3.333	3.167	20.408	18.627
22.	3.667	2.000	22.917	13.333
23.	3.500	3.167	21.429	18.812
24.	3.667	2.667	22.449	16.327
25.	3.333	3.000	19.231	17.308
26.	2.500	2.667	14.151	14.815
27.	3.333	3.333	19.048	19.231
28.	1.833	3.333	10.680	19.608
29.	3.667	3.000	20.755	17.308
30.	3.167	3.667	18.269	21.154
31.	5.833	3.500	32.110	20.388
32.	3.833	3.167	21.296	18.269
33.	4.000	3.833	22.430	21.495
34.	2.000	3.333	12.500	20.202
35.	1.833	2.333	11.458	14.583
36.	4.333	4.833	26.000	27.885
Mean	3.102	3.227	17.651	18.394
SD	1.225	1.152	6.751	5.957
CV(inter)	39.49	35.70	38.25	32.39
Min.	0.667	1.167	4.000	6.863
Max.	5.833	6.500	32.110	34.821
Median	3.333	3.167	19.139	18.448
Geom. mean	2.810	3.038	16.084	17.463

Tabele 2. Pharmacodynamic target parameters: Absolute Decrease in IOP (mmHg) and Relative Decrease in IOP (% from baseline) of dorzolamide 20mg/ml + timolol 5mg/ml eye drops – test formulation and reference formulation, after an single dose of 1 drop in the right eye (arithmetic mean ± SD, n=36)

Tabele 3. 95% confidence interval for the difference of the primary target parameter absolute decrease in intraocular pressure 2 h post dose (n=36)

Variable	point estimator	confidence limits
difference between means of absolute decrease of IOP	-0.125	-0.653 - 0.403

tal number of 22 non-serious adverse events were registered in 20 volunteers in the course of the study: 11 AEs were observed in the eye treated with the test formulation; 11 AEs were observed in the eye treated with the reference formulation. Seventeen AEs were of mild, three AEs of moderate and two AEs were of severe severity. Almost all AE fell into the category of localized ocular reactions (hyperemia of the eye, ocular burning). The results of clinical and laboratory screenings gave no indications for adverse events or adverse drug reactions. All AEs were followed by a complete restitution.

Figure 1. Comparative bar chart of absolute IOP decrease 2 h post dose

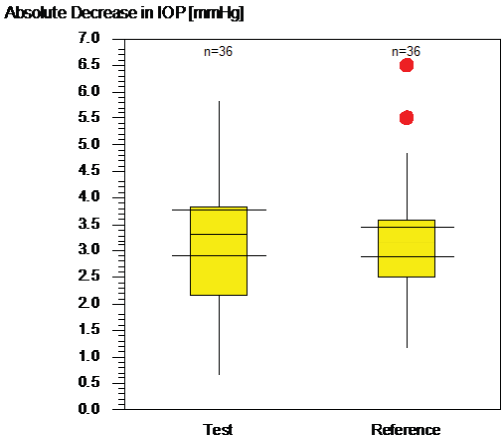
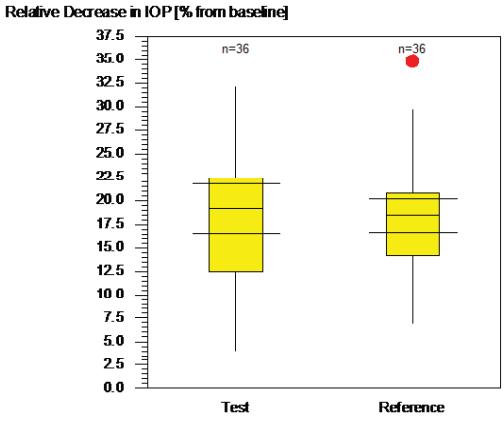


Figure 2. Comparative bar chart of relative IOP decrease 2 h post dose



DISCUSSION

It has been shown [10] that administration of topical carbonic anhydrase inhibitor in one of both eyes has practically no effect on the contralateral eye. A feasible alternative to a cross-over design was thus dosing of both eyes simultaneously: one of both eyes received the test drug and the other one the reference product.

The study was planned and conducted as a monocentric, observer- blinded, randomized, single-dose study in healthy volunteers.

The main objective of the present study was to assess the pharmacodynamic equivalence (lowering of intraocular pressure) of two formulations of eye drops containing 20 mg dorzolamide in 1 ml eye drops. The chosen design of the study was adequate to determine the pharmacodynamic target parameters of the test and reference formulation.

No changes to the protocol were done after the start of the study and no major deviations from the protocol were observed.

A total number of 36 volunteers completed the study according to the protocol. The results of all these volunteers were analyzed. The 95% confidence intervals are based on the data of 36 study completers.

All clinical work was performed according to GCP guidelines, local requirements and the current Declaration of Helsinki.

Both products caused a pronounced and almost identical decrease of the intraocular pressure: 3.10 ± 1.22 mmHg after administration of the test formulation and 3.23 ± 1.15 mmHg after administration of the reference formulation. These findings are well comparable to literature data. In [3] it has been demonstrated that the topical administration of dorzolamide reduces the intraocular pressure in healthy volunteers by 3.5 to 7 mmHg compared to pre-dose values.

For the analysis of pharmacodynamic bioequivalence, the 2-sided 95% confidence interval was calculated of the difference (test-reference) of the absolute decrease in intraocular pressure 2 h post dose and then compared with the predefined acceptance range of ±1.5 mmHg. The difference observed has been 0.125 mmHg. The calculated confidence interval was between -0.653 - 0.403 mmHg and thus well within the acceptance range. The equivalence limit of 1.5 mmHg was chosen as the largest medically justifiable deviation of the test formulation compared to the reference formulation based on a recommendation published in

[11]. The same equivalence limit was also used by other authors [4], [12] when comparing the efficacy of different formulations of timolol for the lowering of intraocular pressure. A difference of 1.5 mmHg can be therefore regarded as a generally accepted border of clinical significance in glaucoma research. The maximum effect was expected at 2 h post dose. Therefore, the assessment has been made at that time, considering that the sensitivity of the comparison would be the highest.

CONCLUSION

All findings regarding the pharmacodynamic parameter (lowering of intraocular pressure) are coherent and demonstrate the therapeutic equivalence of the test formulation (dorzolamide 20mg/ml eye drops) with the reference formulation.

Dorzolamide 20mg/ml eye drops can be considered as interchangeable with the reference formulation for the treatment of ocular hypertension.

The assessment of local tolerability together with the recording of vital signs and adverse events revealed no difference between the test and the reference formulation with respect to their safety profile. Both products were very well tolerated.

The test formulation dorzolamide 20mg/ml eye drops showed comparable results obtained at a time probably equal to the maximum effect concerning the primary target parameter lowering of intraocular pressure 2 h post dose and showed no difference concerning the safety profile and tolerability when compared to the reference formulation and is therefore considered to be therapeutically equivalent.

CONFLICT OF INTERESTS DISCLOSURE STATEMENT

The clinical study reported has been sponsored by Hexal AG, Holzkirchen, Germany.

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Farmakodinamska studija ekvivalencije dva preparata kapi za oči, koje sadrže dorzolamid kod zdravih ispitanika

Emil M. Gatchev[1], Andrey D. Petrov[1], Russka W. Hristova[2], Irenna S. Demircheva[2], Ursula Thyroff-Friesinger[3], Wolfram H. Richter[4], Rossen K. Koytchev[4]

[1] Odeljenje za kliničku farmakologiju, Univerzitetska bolnica "Tsaritsa Joanna-ISUL", Medicinski univerzitet Sofija, Bugarska
[2] Klinika za oftalmologiju, Univerzitetska bolnica "Tsaritsa Joanna-ISUL", Medicinski univerzitet Sofija, Bugarska
[3] Hexal AG, Holzkirchen, Nemačka
[4] Cooperative Clinical Drug Research and Development AG, Hoppegarten, Nemačka

KRATAK SADRŽAJ

Uvod: Dorzolamid kapi za oči 20mg/ml (dorzolamide hydrochloride (CAS: 120279-96-1)), lek iz grupe inhibitora karboanhidraze za lokalnu upotrebu, indikovan je za snižavanje povišenog intraokularnog pritiska (IOP) kod pacijenata sa glaukomom otvorenog ugla ili okularnom hipetenzijom.
Cilj studije: Cilj sprovedene studije bio je ispitivanje farmakodinamičke ekvivalencije dva preparata kapi za oči koji sadrže 20mg dorzolamida (CAS: 120279-96-1).
Metodologija: Sprovedena je monocentrična, posmatrač-slepa, randomizirana studija sa davanjem jedne doze leka u jednom posmatranom periodu kod trideset i šest zdravih ispitanika. Svakom ispitaniku je nakon merenja IOP-a metodom slučajnog izbora u konjunktivalnu kesu jednog oka aplikovana jedna doza (1 kap) test proizvoda, a u konjunktivalnu kesu drugog oka 1 doza (1 kap) referentnog leka. Merenje vrednosti IOP u oba oka obavljeno je na dan sprovođenja studije pre primene i 2h nakon primene leka Goldmann-ovom aplanacionom tonometrijom. Dvostrani 95% interval poverenja izračunat je za razliku vrednosti primarnog ciljnog parametra (apsolutno smanjenje vrednosti IOP-a 2h nakon primene leka).
Rezultati: Statističkom obradom podataka utvrđeno je snižavanje vrednosti IOP-a od 3.10 mmHg prilikom primene test formulacije (dorzolamid 20mg/ml kapi za oči), odnosno snižavanje od 3.23 mmHg prilikom primene referentnog leka. Srednja vrednost razlike IOP-a iznosila je -0.13 mmHg. Vrednost 95% intervala poverenja bila je između -0.65 and 0.40 mmHg, i stoga u potpunosti u okviru prethodno definisanog raspona ekvivalencije (±1.5 mmHg).
Zaključak: Ispitivane formulacije leka pokazale su slične rezultate u vremenskoj tačci koja se uzima kao najverovatnije vreme javljanja maksimalnog efekta - snižavanje vrednosti intraokularnog pritiska 2h nakon primene leka. Nisu zabeležene razlike u bezbednosnom profilu ispitivanih formulacija.

Ključne reči: dorzolamide, kapi, oči, intraokularni, očni pritisak

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