Post Marketing Bioequivalence Study of Six Brands of Ciprofloxacin HCl in Egypt Market and Evaluation as a Treatment of Human Periodontal Pockets

Mona El Assal

Associat Professor of Pharmaceutics at Pharmaceutics and Pharmaceutical Technology department at FUE University.

Abstract

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Research Article
Post Marketing Bioequivalence Study of Six Brands of Ciprofloxacin HCL in Egyptian Market and Evaluation as a Treatment of Human Periodontal Pockets
Mai M.I.1, Mona I. El Assal2*, Mohamed A.K.3
1Military Medical Academy, Cairo, Egypt.
2Department of pharmaceutical technology, faculty of pharmaceutical science and pharmaceutical industries, Future University in Egypt.
3Department of Pharmaceutics, faculty of Pharmacy, Cairo University, Cairo, Egypt.
ABSTRACT
The availability of numerous brands of ciprofloxacin HCl in our drug market today places clinicians and pharmacists in a difficult situation of choice of a suitable brand or the possibility of alternative use. The aim of the present study was to evaluate physical standards of six brands of ciprofloxacin HCl tablets marketed in Egypt using in-vitro tests and then in vivo bioequivalence of best two brands of ciprofloxacin HCL, finally their evaluation in treatment of human periodontal pockets. The in-vitro dissolution study was carried out on six brands of ciprofloxacin HCl tablets using basket method according to US pharmacopoeia guidelines. Other general quality assessment tests like Weight variation, hardness, friability, drug content uniformity y and disintegration were also determined. Then brands of ciprofloxacin HCl were subjected to in-vivo efficacy studies in treatment of human periodontal pockets. Significant results were obtained with respect to both microbiological and clinical parameters. For evaluation of bioequivalence of best two brands of ciprofloxacin HCl, blood samples were taken, plasma concentration of ciprofloxacin HCl brands were determined by simple HPLC method. The pharmacokinetic parameters, Including peak plasma concentrations and time needed to reach the peak were obtained directly from plasma concentration–time profiles. The area under the curve was calculated using noncompartmental methods. Statistical analysis of in-vitro and in-vivo studies shows that ciprofloxacin brands are effective in treating periodontal pockets in order of ciprobay, cipromax, mifoxin, ciprocin, rancif and ciprofar. Statistical analysis of main parameters confirm the bioequivalence of the ciprofloxacin formulations in terms of pharmacokinetic characteristic, the results from this study demonstrate that Ciprobay and Cipromax

are interchangeable in the clinical setting.
Keywords: Bioequivalence, ciprofloxacin, periodontal pocket, Dissolution
QR Code for Mobile Users
Address for Correspondence:
Mona I. El Assal
Department of pharmaceutical technology, faculty of pharmaceutical science and pharmaceutical industries, Future University in Egypt.
Email: drmona_2012@hotmail.com
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INTRODUCTION:
Post-market surveillance or monitoring involves all activities undertaken to obtain more data and information about a product after it had been granted marketing authorization and made available for public use. The data and information so obtained

could be employed for product improvement, development of standards and regulations. Regulatory agencies rely on limited information obtained during clinical trials and to some extent scientific literature as guides to granting marketing authorization of medicines for public use. It is therefore imperative to conduct post-market surveillance or monitoring of approved medicines in order to adequately assess the quality, therapeutic effectiveness and safety of medicines for the larger public Post-market monitoring ought not to be a one off event rather it should be a continuous event throughout the life of a drug product. Activities of post market monitoring of a drug have been identified to include: review of product's condition of approved study; evaluation and investigation of reported drug complaints; inspection of manufacturer's processes and procedures for production and complaint handling; market surveys of technical and clinical documentation; review of product claims/labeling; public access to information taken and reported to the regulatory agency(ies); and in vitro testing of products for compliance to Standards (Garcia J, 2006). In vitro testing or quality control of drugs is a set of studies or experiments undertaken during production and occasionally ought to be undertaken post production by regulatory agencies and researchers. Routine laboratory testing of drugs in the market is crucial to protect public health especially in developing countries where counterfeit and substandard drugs have become a major challenge to health care services. Counterfeit and substandard medicines are a major cause of morbidity, mortality and loss of public confidence in drugs and health structures (Cockburn et al.,2005). Bioequivalence has been described as the absence of a significant difference in the rate and extent to which the active ingredient or moiety in pharmaceutical equivalents or pharmaceutical alternatives become availabl e at the site of drug action (that is ,a significant difference in the bioavailability of the 2 drug products) when they are administered at the same molar dose under similar conditions in an appropriately designed study (FDA,2003). Generic substitution

could be considered when a generic copy of a reference drug contains identical amounts of the same active ingredient in the same dose formulation and route of administration as well as meet standards for strength, purity, quality and identity (Meredith, 2003). Bioequivalence studies may involve both in vivo and in vitro studies. In vitro Dissolution testing, a surrogate marker for bioequivalence test and may be vital in assessing in vivo performance. Dissolution testing also serves as a tool to distinguish between acceptable and unacceptable drug products (Ochekpe et al., 2006). In the present study the bioequivalence of two ciprofloxacin brands was evaluated in vivo by comparing the pharmacokinetic parameters derived from serum ciprofloxacin concentration-time profiles. Periodontal infection results either from the penetration of pathogenic microorganisms in the tissues, or even the activation of already existing germs, but not pathogenic under normal condition. This responsible flora is polymorphic, gram negative and microaerophilic or strictly anaerobic. Only ten or twenty species, regarded as pathogens, play a role in the pathogenesis of periodontal destruction (Darby et al, 2001). These poly¬microbial infections involve bacteria called periodontal pathogens, most of them gram-negative and strictly anaerobic, which act in synergy. Among these species, the most important are Aggregatibacter actinomycetem¬comitans, Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola, Fusobacterium nucleatum, Prevotella intermedia ,Prevotella nigrescens , Campylobacter rectus , Eikenella corrodens and Peptostreptococcus micros (Feng Z et al, 2006) . Ciprofloxacin is effective against several periodontal pathogens, including A. actinomycetemcomitans (Slots J et al, 1990). This antibiotic effectively penetrates the diseased periodontal tissues and can reach higher concentrations in the crev¬icular fluid than in the serum .Ciprofloxacin-metronidazole (500 mg of each, twice daily for 8 days) is indicated for periodontitis involving a mixture of enteric gram-negative facultative rods and anaerobic bacteria (Slots J, 2004).

EXPERIMENTAL

1. Materials

1.1. In vivo evaluation:

6 different brands of ciprofloxacin as shown in Table 1 were purchased from different companies in Egypt pharmacies. The reagents utilized include hydrochloric acid and ferric chloride.

Drug

Average Weight variation (mg)

Average Hardness (kg/cm3)

Friability %

Average Drug Content (mg)

Average Disintegration (min)

ciprobay

781.4
9.3
0.19
500.02
3.1
Mifoxin
859.5
14.1
0.062
495.2
5.1
Cipromax
768.1
16.2
0.006
483.5
6.3
Ciprocin
634.8
16.9
0.014
475.01
6.9
Rancif
748.7
17.5
0.341
462.2
7.2
Ciprofar
930.6
29.7
0
458.9
8.2

Table 1: The quality control tests undertaken on six brands of ciprofloxacin

1.1.1 Determination of uniformity of weight

10 tablets from each of the 6 brands were weighed individually with an analytical weighing balance (Mettler). The average weights for each brand were obtained.

1.1.2 Hardness test

The crushing strength was determined with a tablet hardness tester(Shital scientific, England). 4 tablets were randomly selected from each brand and the pressure at which each tablet crushed was recorded.

1.1.3 Friability test

10 tablets of each brand were weighed and subjected to abrasion by employing a Roche friabilator (Erweka Gmbh, Germany) at 25 rev/min for 4 min. The tablets were then weighed and compared with their initial weights and percentage friability

was obtained.

1.1.4 Assay

A solution of 1% w/v ferric chloride was freshly prepared as well as100 mcg/ml of pure ciprofloxacin. 5 tablets from each brand were crushed and 100 mg of the powdered samples were weighed,dissolved in 100 ml 0.1N hydrochloric acid (HCl) and further dilution was made to obtain 100 mcg/ml for each brand. To 5 ml of each brand and the pure sample, 1 ml of ferric chloride was added and made up to 50 ml with 0.1N HCl. The absorbance of each sample was taken at 438 nm against the blank reagent (1 ml ferric chloride solution made up to 50 ml with 0.1N HCl) with an ultraviolet spectrophotometer (Jenway, UK). The percentage content was calculated for each brand.

1.1.5 Disintegration test

6 tablets from each brand were employed for the test in a freshly prepared medium, 0.1 N HCl at 37°C using Educational Sciences Disintegration Apparatus (Es Eagle Scientific Limited, Nottingham,UK). The disintegration time was taken to be the time no particle remained on the basket of the system.

1.1.6 Dissolution test

The dissolution test was undertaken using USP apparatus I (basket method) in 6 replicates for each brand. The dissolution medium was 1000 ml 0.1N HCl which was maintained at 37 ± 0.5°C. In all the experiments, 5 ml of dissolution sample was withdrawn at 0, 3, 8,15, 25, 35, 45 and 60 min and replaced with equal volume to maintain sink condition. Samples were filtered and assayed by ultraviolet spectrophotometry at 277nm. The concentration of each sample was determined from a calibration curve obtained from pure samples of ciprofloxacin.

Data analysis

The uniformity of weight, hardness test, friability test, drug content, disintegration test, dissolution test were analyzed with simple statistics using one way analysis of variance (ANOVA) and Dunnett's test.

2. In vivo bioequivalence study

2.1 Study Design

12 Egyptian healthy male volunteers aged between 20 and 34 years (22.7 ± 3.6 years) and weighed from 51 to 93 kg (70.7 ± 10.3 kg) were enrolled in this study after providing written informed consent. The volunteers were examined and assessed for their eligibility to participate in the present study.The examinations and tests included medical history, physical examination, and measurement of weight, height and vital signs(heart rate and blood pressure). This study was a single-dose,randomized, open label, crossover. The 2 phases of study were separated by a 1 week washout period. The washout period was determined based on 5–7 times of the elimination half life (T 1/2) of ciprofloxacin . After an overnight fast for 12 h, the volunteers received 500 mg of either formulation of ciprofloxacin i.e ciprobay and cipromax, taken with 200 mL of water.5 mL of blood samples were obtained just before drug administration and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12 hr after that. The plasma was separated by centrifugation at 10 000 rpm for 5 min at room temperature (20 °C), followed

by direct transfer into polypropylene tubes and storage at − 20 °C until analysis.
2.2 HPLC method
In the present study plasma concentrations of ciprofloxacin were analyzed using a sensitive and selective HPLC method with ultraviolet detector. The HPLC instrumentation was manufactured by Knauer, Germany. 1 mL of sample was first deproteinized with an aqueous solution of trichloroacetic acid (10 % v/v). The mixture was vortexed for 10 s and centrifuged for 15 min. 20 μL of clear supernatant was injected onto the HPLC column. Short-term stability studies showed that CPR is stable in acidic media at least for 12 h at room temperature. The mobile phase consisted of 0.025 M phosphoric acid (pH = 3), acetonitrile, and triethylamine (88:12:0.1, v/v). Analytical column used for chromatographic separations was 5 μm Eurosphere C8 (150 × 4.5 mm) with a Eurosphere C8 (5 μm, 4.6 × 10 mm) guard column. The flow rate was 1 ml/min and the detector wavelength was set at 278 nm. Under these conditions the retention time for ciprofloxacin was 10 min. The method used was validated for specificity, precision and sensitivity. Validation parameters were according to the recommendation of the Center for Drug Evaluation and Research (CDER) and International Conference on Harmonisation (ICH) guidelines (Zakeri-Milani P, et al.2012). The precision, as the measure of intra-day repeatability,was expressed as the coeffi cient of variance (CV %) of 6 identically prepared and measured calibration samples during 1 day measurement series. Inter-day precision (reproducibility) was performed as a CV (%) of 6 consecutive days' measurements of plasma samples (Valizadeh H, et al. 2010).The pharmacokinetic parameters for test and reference formulations were evaluated. The C max and the corresponding time of peak plasma concentration (T max) were taken directly from the individual plasma data. The elimination rate constant (k e) was estimated as the slope of the semi logarithmic plot of the 3–4 last points of the plasma concentration vs. time curve. The area under the plasma concentration vs. time curve, AUC 0–t, was calculated by linear trapezoidal method. T 1/2 was calculated as ln2/k e. For the purpose of bioequivalence analysis AUC 0–t, AUC 0–∞
and C max were considered as the primary variables. The values of AUC 0–t, AUC 0–∞ and C max were analyzed statistically using an analysis of variance (ANOVA).
3. In vivo efficacy study
3.1 Clinical procedure
Thirty-five patients were enrolled in this study. Patients' dental and medical histories were obtained. The patients had no systematic diseases such as diabetes, blood pressure, and hematologic, cardiovascular or renal disorders. None of them had taken any antibiotics or used any kind of mouth rinses in the previous 3 months and had mild to moderate chronic periodontitis with pocket depths of 3-5 mm. The clinical indices of patients were recorded at baseline: attachment level, pocket depth (by William's probe) and gingival bleeding (Ainano and Bay's method). (Newman MG, et al. 2002)
3.2 Microbiological Studies
3.2.1 Determination of MIC by agar plate dilution method
Preparation of sterile stock solutions of Ciprofloxacin brands
Weigh 102.4 mg of each brand placed in 10 ml volumetric flask and completed to

10 ml with distelled water to get conc of 10.24 mg/ml (10240 ug/ml). All stock solution were sterilized by filtration with Millipore bacterial filters (0.22 u Membrane Syringe Filter) and transferred into sterile tube with rubber cap, and stored away of light.

Preparation of working dilutions for agar susceptibility tests:

In 50 ml sterile falcon tube, using sterile pipettes, 1ml volume of the prepared dilution series added to 19 ml of sterile molten agar (Mueller-Hinton agar with 10% horse blood), mix thoroughly, and pour into 90 mm sterile Petri dishes to get final concentration in medium of (0.03-512 ug/ml).

Bacterial Growth Inhibition Assay (Agar dilution susceptibility method)

Two µl of staphylococcus aureus suspension was inoculated on agar plates containing different concentrations of drug. After 72 hrs of incubation, 37C, microaerobic atmosphere, the plates were examined visually, and the lowest concentration of antibiotics showing complete inhibition of bacterial growth was recorded as the MIC for each drug calculated by (ug/ml).

3.2.2 Evaluation of drug therapeutic effects on bacteria before and after treatment

Each brand of ciprofloxacin has been given to six patients 500 mg twice daily for eight days

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(Slots J, et al. 2002) and dental samples were taken before and after treatment.

Sample Collection

The samples were collected aseptically the supra gingival plaque was removed with the help of a Sterile Cotton Swap.With the help of paper point (No: 38) the sub gingival plaque was collected, by inserting the paper point into the deepest periodontal pockets for 20 seconds (Mane A.K., et al. 2009).The paper points were transferred into reduced Thioglycollate broth. The paper points were transported to the Microbiology Laboratory in reduced Thioglycollate broth. The bottle containing the paper point was shaken to dislodge the adhered bacteria on the paper point. Using standard loop technique culture was put on blood agar plate containing Hemin and Vitamin K (Slots J, et al. 1983). The plates were incubated in anaerobic jar Gas Pack for 6 days. The bacteria were identified based on Colony morphology, Gram Staining, pigment formation and biochemical tests (Baron E.J., et al. 1997).

Probable pocket depth

Probable pocket depth of the selected teeth was noted using Williams probe to the nearest mm at the baseline.

Relative attachment level

Sites of deepest pockets were selected for relative attachment level measurements. Williams probe was used to measure the relative attachment level to nearest mm.

Plaque index

Plaque was assessed on labial, buccal and lingual surfaces. Scoring criteria were followed as 0 for no plaque, 1 for separate flecks of plaque at the cervical margin of the tooth, 2 for a thin continous band (up to 1 mm) of plaque at the cervical margin of the tooth, 3 for a band of plaque wider than 1 mm, but covering less than one third of the crown of tooth and 4 for plaque covering at least one third, but less than

two third of the crown of the tooth. The plaque index was calculated as:
Plaque index = total score/ number of surfaces examined (F.J. Vander Quderaa. 1991).

Gingival index

All the tooth were examined on all four surfaces i.e., buccal, lingual/palatal, distobuccal, mesiobuccal and the amount of gingival inflammation was assessed by clinically examining the color, consistency and size of the gingival tissue, scoring criteria were followed as 1 for mild inflammation, slight edema, no bleeding on probing, 2 for moderate inflammation, redness, edema, bleeding on probing and 3 for severe inflammation, marked redness, edema, ulcerations and spontaneous bleeding. The gingival index was calculated as:
Gingival index= [total score/number of tooth examined] x 4 (R.A. Seymour, et al.1995)

Statistical analysis

The obtained data was analyzed using different tests as T test, Paired Samples test, Crosstabs.

RESULTS AND DISCUSSION

As shown in Table I, all the brands complied with the compendia specification for uniformity of weight which states that for tablets weighing more than 324 mg, weights of not more than 2 tablets should not differ from the average weight by more than 5%. While all the brands complied with the USP specification for assay, brands ciprofar, ciprocin and rancif did not meet British pharmacopoeia (BP) standard. The USP specification is that the content of ciprofloxacin hydrochloride should not be less than 90% and not more than 110% while BP specifies that the content should not be less than 95% and not more than 105%. However, the result ascertains the presence of USP compendia quantity of ciprofloxacin hydrochloride in all the brands and so could not be judged as counterfeits without APIs.

The hardness or crushing strength assesses the ability of tablets to withstand handling without fracturing or chipping. It can also influence friability and disintegration. The harder a tablet, the less friable and the more time it takes to disintegrate. As shown in Table I, brand Ciprobay required the least pressure before fracture (9.3 kg/cm3) while brand ciprofar break at (29.7 kg/cm3) with Monsanto hardness tester while the other brands were in between. A force of about 4 kg is the minimum requirement for a satisfactory tablet (Allen et al., 2004) . Hence the tablets of all brands were satisfactory. Friability test is used to evaluate the tablets resistance to abrasion, the compendia specification for friability is 1% . Friability for all the brands was below 1%.

Disintegration could be directly related to dissolution and subsequent bioavailability of a drug. A drug incorporated in a tablet is released rapidly as the tablet disintegrates; a crucial step for immediate release dosage forms because the rate of disintegration affects the dissolution and subsequently the

therapeutic efficacy of the medicine. As shown in Table I, all the brands were film coated and

complied with the compendia specifications for disintegration. The BP specification is that
Table 2: Dunnett’s test on the six brands at 0.05 level (two-tailed)
Mean difference is obtained by substracting mean % dissolved of brand ciprobay (reference)from mean % dissolved of other brands (test products).
uncoated tablets should disintegrate within 15 min and film coated in 30 min while USP specifies that uncoated and film coated tablets should disintegrate within 30 min The USP and BP specifies that the amount of drug released (dissolution) should not be less than 80% of the labeled amount at 30 min. All brands complied except brand ciprofar which had 71% at 35 min as shown in Figure 1. Ciprofloxacin is a class III drug (Wu and Benet, 2005; Kasim et al., 2004) and from Figure 1, brand ciprobay released as much as 94% at 15 min and so it is envisaged that it will not have any bioavailability problems, brand cipromax released as much as 91%.The amounts released by the other brands were below 85%.
Figure 1: Dissolution profiles of six brands of ciprofloxacin Hcl tablets
The percentage dissolved was tested statistically to ascertain differences among brands using Dennett's test. The analyses were undertaken for time points 25 and 35 min. These time points were chosen because at least 5brands had released over 90% at these times. The results of Dennett's test as shown in Table 2 indicate that at 25 min and 35 min there is none significance difference between ciprobay and each of cipromax, mifoxin, rancif while there is significant difference between ciprobay and ciprofar. However brands rancif and ciprofar show the least departure from ciprobay at two time points.
Bioequivalence is a comparison of the bioavailability of two or more drug product. The two chosen drugs containing the same active ingredient are bioequivalent if their rates and extents of absorption don’t show a significant difference. The mean plasma profiles of ciprobay and cipromax were

visually very similar in shape and pattern as shown in (Figure. 2).

Figure 2: Main plasma concentration time curve of ciprofloxacin following administration of ciprobay and cipromax to six volunteers

Figure 3: Bacterial growth inhibition assay (the last conc. for each brand after which growth inhibition is obtained)

The parameters AUC 0–∞ and T max were related to the extent and rate of drug absorption respectively, while C max was related to both of these processes (Valizadeh H, et al. 2010). After administration of ciprofloxacin the mean Cmax of 55.75 ± 0.65ng/ml and 46.36±0.99 were attained in about 2 hr for both of ciprobay and cipromax respectively. In the present study the mean value of AUC 0–t were 275.2 ± 23.01and 270.9 ± 1 6.06 ng.hr/mL and AUC0–∞ values were 339.61±48.7 and 304.04±40.37 ng.hr/mL for both ciprobay and cipromax respectively and as shown in Table III, Mann-Witney test statistical analysis for these parameters showed no statistically significant difference between two brands. Therefore confirming the bioequivalence of both brands of

Time (min)	Pair comparison	Mean difference	Significance
25	Cipromax vs ciprobay	-1.27	0.785
	Mifoxin vs ciprobay	-4.73	0.194
	Rancif vs ciprobay	-2.00	0.081
	Ciprocin vs ciprobay	-3.37	0.075
	Ciprofar vs ciprobay	-54.97	0.016
35	Cipromax vs ciprobay	-0.23	0.926
	Mifoxin vs ciprobay	1.03	0.575
	Rancif vs ciprobay	-1.83	0.468
	Ciprocin vs ciprobay	2.7	0.078
	Ciprofar vs ciprobay	-23.8	0

ciprofloxacin. For evaluation of drug therapeutic effects on bacteria each brand of ciprofloxacin has been given to six patients 500mg twice daily for eight days (Slots J, et al. 2002) and dental samples were taken before and after treatment. As shown in Table V, regarding pocket depth there is a significant decline in pocket depth between before and after drug administration for each of ciprobay, cipromax, mifoxin, ciprocin and rancif at $p \leq 0.05$,regarding attachment level there is a significant decline for each of ciprobay, cipromax, mifoxin and rancif at $p \leq 0.05$,regarding plaque index there is a significant decline for each of ciprobay, cipromax, mifoxin, , and ciprofar at $p \leq 0.05$, regarding gingival index there is significant decline for each of ciprobay, cipromax, mifoxin , ciprocin and rancif at $p \leq 0.05$. Microbiological studies also include determination of the lowest concentration of each drug showing complete inhibition of bacterial growth which recorded as the MIC as shown in Table IV, the MIC of rancif and ciprofar were higher than the other brands (2 μgm/ml).

Table 3: Mann- Whitney test statistical analysis of two brands of ciprofloxacin HCl

Table 4: Comparison of antibacterial activities of different brands of Ciprofloxacin

Drugs	Dose	Tmax	Cmax	Kel	T½el	AUC0-12	Auc0-end	Vd	CLtot
ciprobay	N	6"	6	6	6	6	6	6	6
	Mean	5.0000	2.0000	55.7533	0.1642	4.2367	275.1650	339.6117	

10.1833
1.6683
Std. Deviation
0.00000
0.00000
0.65430
0.01203
0.29978
23.01198
48.68775
1.36144
0.21104
Median
5.0000
2.0000
55.4900
0.1618
4.2800
271.9950
338.3050
10.2500
1.7350
Minimum
500.00
2.00
55.27
0.15
3.78
248.37
278.94
8.61
1.41
Maximum
500.00
2.00
56.98
0.18
4.55
300.76
412.05
12.28
1.88
Cipromax
N
6
6
6

6
6
6
6
6
6
Mean
5.0000
2.0000
46.3600
0.1535
4.6450
270.9700
304.0467
9.9750
1.4950
Std. Deviation
0.00000
0.00000
0.99874
0.02632
0.92531
16.06535
40.37101
2.15675
0.21296
Median
5.0000
2.0000
46.2600
0.1599
4.3400
272.8600
288.9300
9.0900
1.4800
Minimum
500.00
2.00
45.00
0.11
3.85
242.68
265.66
7.93
1.21
Maximum

500.00
2.00
47.65
0.18
6.32
288.96
353.86
13.00
1.79
P value
1.000
1.000
0.104
0.631
0.631
0.749
0.109
0.631
0.128
Drug
Conc ug/ ml (MIC) No growth
Ciprobay
1
Mifoxin
1
Cipromax
1
Ciprocin
1
Rancif
2
Ciprofar
2
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Table 5: T-Test statistical analysis of six brands of ciprofloxacin HCL in treatment of periodontal pockets
CONCLUSION
Post-market monitoring is very crucial for effective clinical outcome and this study has emphasized that all the brands of ciprofloxacin complied with the official specification for uniformity of weight, hardness, friability and disintegration. Drug content and in vitro dissolution studies among other tests are important pointers to the quality of drugs. This research shows that six brands can be used interchangeably with innovator brand ciprobay
Drugs

pocket depth(mm) before
pocket depth(mm) after
attachment level(mm)before
attachment level(mm) after
plaque indexbefore
plaque indexafter
gingival index before
gingival index after
ciprobay
N
6.00
6.00
6.00
6.00
6.00
6.00
6.00
6.00
Mean
4.67
3.00
6.50
4.33
4.50
3.00
2.83
0.03
Std. Deviation
0.82
0.00
0.55
0.52
0.55
0.00
0.00
0.00
Median
4.50
3.00
6.50
4.00
4.50
3.00
4.00
3.00
Minimum
4.00

3.00
6.00
4.00
4.00
3.00
2.00
3.00
Maximum
6.00
3.00
7.00
5.00
5.00
3.00
4.00
3.00
Pair diff
P value
0.001
0.002
0.016
0.005
cipromax
N
6.00
6.00
6.00
6.00
6.00
6.00
6.00
6.00
Mean
5.50
3.50
6.50
3.50
3.67
3.00
2.5
1.17
Std. Deviation
0.84
0.84
0.55
0.55
0.52

0.00
0.00
1.03
Median
5.00
3.00
6.50
3.50
4.00
3.00
3.50
2.50
Minimum
5.00
3.00
6.00
3.00
3.00
3.00
1.50
1.00
Maximum
6.00
5.00
7.00
4.00
4.00
3.00
3.50
8.00
Pair diff
P value
0.004
0.034
0.006
0.016
mifoxin
N
6.00
6.00
6.00
6.00
6.00
6.00
6.00
6.00
Mean

4.33
3.33
4.83
3.83
4.67
3.00
2.00
1.00
Std. Deviation
0.52
0.52
0.75
0.75
0.52
0.00
0.00
1.03
Median
4.00
3.00
5.00
4.00
5.00
3.00
1.5
1.00
Minimum
4.00
3.00
4.00
3.00
4.00
3.00
1.50
1.00
Maximum
5.00
4.00
6.00
5.00
5.00
3.00
3.50
2.50
Pair diff
P value
0.005

0.002
0.010
0.005
ciprocin
N
6.00
6.00
6.00
6.00
6.00
6.00
6.00
6.00
Mean
4.83
3.50
5.17
3.83
3.33
3.00
3.00
1.00
Std. Deviation
0.75
0.84
0.75
0.41
0.52
0.00
0.00
0.82
Median
5.00
3.00
5.00
4.00
3.00
3.00
3.00
1.00
Minimum
4.00
3.00
4.00
3.00
3.00
3.00

2.00
0.00
Maximum
6.00
5.00
6.00
4.00
4.00
3.00
3.00
2.00
Pair diff
P value
0.001
0.317
0.233
0.012
rancif
N
6.00
6.00
6.00
6.00
6.00
6.00
6.00
6.00
Mean
4.83
3.50
6.33
3.33
3.50
3.00
1.83
0.00
Std. Deviation
0.75
0.84
0.52
0.52
0.55
0.00
0.00
1.10
Median
5.00

3.00
6.00
3.00
3.50
3.00
2.30
1.00
Minimum
4.00
3.00
6.00
3.00
3.00
3.00
1.00
0.00
Maximum
6.00
5.00
7.00
4.00
4.00
3.00
2.50
1.00
Pair diff
P value
0.014
0.022
0.359
0.001
ciprofar
N
6.00
6.00
6.00
6.00
6.00
6.00
6.00
6.00
Mean
3.83
3.50
3.33
3.33
4.50

3.00
2.5
2.5
Std. Deviation
0.75
0.84
0.52
0.52
0.55
0.00
0.00
1.03
Median
4.00
3.00
3.00
3.00
4.50
3.00
2.00
2.00
Minimum
3.00
3.00
3.00
3.00
4.00
3.00
2.00
2.00
Maximum
5.00
5.00
4.00
4.00
5.00
3.00
3.00
3.00
Pair diff
P value
0.325
0.247
0.002
0.184
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in order of cipromax, mifoxin, ciprocin, rancif and ciprofar respectively.Statistical analysis of main parameters confirm the bioequivalence of the ciprofloxacin formulations in terms of pharmacokinetic characteristics in healthy volunteers after a single 500mg dose, the results from this study demonstrate that Ciprobay and Cipromax are bioequivalence and interchangeable in the clinical setting.
Clinical studies indicated an improvement in the probable pocket depth, relative attachment level, gingival index and plaque index. Statistical analysis proved that ciprofloxacin brands are found to be effective in treating periodontal pockets in order of ciprobay, cipromax, mifoxin, ciprocin, rancif and ciprofar
REFERENCES:
1. Allen LV, Popovich NG, Ansel HC (2004), "Ansel's pharmaceutical dosage forms and drug delivery systems" in, 8th Edition edn, Lippincott Williams & Wilkins, Philadelphia, p. 236.
2. Baron E.J., Citron D.M., Anaerobic infection flowchart using minimal laboratory resources, Clinical infectious Diseases, 25(2), 143-146(1997).
3. Cockburn R, Newton PN, Agyarko EK, Akunyili D, White NJ (2005). The Global Threat of Counterfeit Drugs: Why Industry and Governments Must Communicate the Dangers. PLoS Med. 2 (4): e100.
4. Darby, I.M. Curtis, 2001. Microbiology of periodontal disease in children and young adults. Periodontology, 26: 33-53.
5. F.J. Vander Quderaa, Anti-plaque agents: rationale and prospects of prevention of gingivitis and periodontal disease, J.Clin.Periodontol. 18(1991) 449-454.
6. Feng Z, Weinberg A. Role of bacteria in health and disease of peri¬odontal tissues. Periodontol 2000 2006; 40:50–76.
7. Garcia J (2006) Post-Market Surveillance: A Product Regulator's View. Australian Government, Department of Health Therapeutic Goods Administration.
8. Kasim NA, Whitehouse M, Ramachandran C, Bermejo M, Lennernas H, Hussain AS, Junginger HE, Stavchansky SA, Midha KK, Shah VP, Amidon GL (2004). Molecular Properties of WHO Essential Drugs and Provisional Biopharmaceutical Classification. Mol. Pharm. 1(1): 85-96.
9. Mane A.K., Karmarkar A.R., Bharadwaj RS.,., Anaerobic bacteria in subjects with chronic periodontitis and in Periodontal health. J. of Oral health Community Dentistry, 3(3) 49-51 (2009).
10. Meredith P (2003). Bioequivalence and other unresolved issues in generic drug substitution. Clin. Ther. 25 (11): 2875-2890.
11. Newman MG, Taki HH, Carranza FA,Carranza's Clinical Periodontology: WB Saunders Co. Philadelphia: USA, 2002: 96-100
12. Ochekpe NA, Ngwuluka NC, Owolayo H, Fashedemi T (2006) Dissolution profiles of three brands of Lamivudine and Zidovudine combinations in the Nigerian market. Dissolution Tech., 13(4): 12-17.
13. R.A. Seymour, P.A. Heasman, Tetracyclines in the management of periodontal diseases, J.Clin. Periodontol. 22 (1995) 22-35.
14. Slots J. Systemic antibiotics in periodontics. J Periodontol. 2004:75;1553-1565.
15. Slots J, Feik D, Rams TE. In vitro antimicrobial sensitivity of enteric rods and pseudomonads from advanced adult periodontitis. Oral Microbiol Immunol 1990;

5(5):298–301.
16. Slots J., Rosling B.G., Genco R.J., Suppression of pencillin resistant oral Actinobacillus actinomycetomcomitans with tetracycline, consideration on endocarditis prophylaxis journal of Periodontology, 54 193-196 (1983).
17. US Food and Drug Administration, Center for Drug Evaluation and Research (2003). Guidance for industry: Bioavailability and bioequivalence studies for orally administered drug products—general considerations.
18. Valizadeh H , Nemati M , Hallaj-Nezhadi S et al. Single dose bioequivalence study of alpha methyldopa tablet formulations using a modified HPLC method . Arzneimittel-Forschung/Drug Research 2010 ; 60 (10):607 – 611
19. Wu C, Benet LZ (2005). Predicting Drug Disposition via Application of BCS: Transport/Absorption/ Elimination Interplay and Development of a Biopharmaceutics Drug Disposition Classification System. Pharm. Res. 22 (1): 11-23.
20. Zakeri-Milani P , Ghanbarzadeh S , Valizadeh H . Comparative in vitro Dissolution and in vivo Bioequivalence of 2 Pentoxifylline Sustained Release Formulations . Drug Research (Arzneimittelforschung) 2012 ;62 : in press

- *2014, January*