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OPEN PEER REVIEW

Pharmacokinetics and Bioequivalence of Two Formulations of Apixaban Tablets: A Double-Blind, Single-Dose, Crossover Study in Healthy Subjects

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1 Original submission

1 comment · 9 Dec 2024

Sima Sadrai Reviewer

MINOR REVISION 9 Dec 2024

Dear Author
Please add the results for tmax to table 3.
Discuss a possible lag time because the tmax values differ by 0.5 h.
In Fig 3, a smaller label size would be better.

2

Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

We would like to express our sincerest gratitude for reviewing our manuscript and the valuable feedback you provided. We have carefully considered each of your comments to revise our manuscript, and they have been highly insightful. We believe our revisions effectively address your concerns and strengthen the manuscript.

 # Reviewer 1

1- The study is well designed, written and discussed. It is suggested to add your reference in quality control section.

In response to the reviewer's valuable suggestion, we have included additional references in the quality control section.

References "Wang CC, Chen YL, Lu TC, Lee C, Chang YC, Chan YF, et al. Design and evaluation of oral formulation for apixaban. *Heliyon*. 2023;**9**(8)." and "Jain HK NV. Formulation development and stability indicating HPLC assay of tablets of apixaban. *Int J Pharm Pharm Sci*. 2017;**9**:24-32." were added to the Content Assay section in the text (Page 4, line 87) and supplementary file (Page 1, line 9).

Reference "Pharmacopeia US. < 905 > Uniformity of Dosage Units. Rockville, MD: United States Pharmacopeial Convention; 2024" was added to the Content Uniformity section in the text (Page 5, line 95) and supplementary file (Page 2, line 29).

Reference "Wang CC, Chen YL, Lu TC, Lee C, Chang YC, Chan YF, et al. Design and evaluation of oral formulation for apixaban. *Heliyon*. 2023;**9**(8)" was added to the *In Vitro* Dissolution Testing section in the text (Page 5, line 98) and supplementary file (Page 2, line 35).

 # Reviewer 2

1- Please add results of tmax in table 3

In bioequivalence studies, the parameters AUC and C_{max} are analyzed and statistically compared to assess the bioequivalence of test and reference products (1, 2). Additionally, non-parametric statistical analyses are employed to compare the T_{max} values of the test and reference groups (3-5). In response to the reviewer's insightful comment, we performed a non-parametric analysis based on the Wilcoxon test for T_{max} in Table 3. The results showed a p-value of 0.923 for this comparison, indicating no significant difference between the Tmax of the test and reference groups. In addition, non-parametric analyses using the Friedman and Kruskal-Wallis tests yielded similar results, with p-values of 0.808 and 0.682, respectively.

Table 3 has been changed as below:

"Table 3. Bioequivalence analysis of C_{max} and AUC and nonparametric test of T_{max} between the test and reference apixaban tablets in healthy subjects

Parameters	**T/R GMR (%)**	**90% CI (%)**
C_{max} (ng/mL)	94.2	87.1-101.9
$AUC_{0\text{-}t}$ (ng.h/mL)	98.4	91.4-105.9
$AUC_{0-\infty}$ (ng.h/mL)	99.8	92.9-106.9
	Reference	**Test**
T_{max} [a] (h)	2.43 (0.10)	2.41 (0.14)

T/R GMR, geometric mean ratio of (test/reference); 90% CI, 90% confidence intervals; [a] Values of T_{max} are shown as Mean (SEM) "

These changes have been in the supplementary file (Page 6, line 117).

"T_{max} was analyzed by the Wilcoxon signed-rank test. A significance level of $P < 0.05$ was considered to indicate statistical significance."

Furthermore, the T_{max} analysis result was included in the results section (Page 9, lines 174 and 175) in response to the reviewer's request as below:

“3.5. Bioequivalence of the Generic Product

The 90% CI for the geometric mean ratio of log-transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of the test product to the reference product, respectively, were 87.1-101.9, 91.4-105.9, and 92.9-106.9. The results fell within the permitted 80-125% range (1, 2), showing that the test product and the reference product are bioequivalent (Table 3). Also, Wilcoxon's non-parametric test for T_{max} showed no significant difference between the two formulations (P = 0.923).”

2-Discuss a possible lag time because tmax have 0.5 h difference

In bioequivalence studies, the T_{max} parameters are reported as median values along with their minimum and maximum range, as shown in Table 2 of the present study. The average T_{max} for the test and reference samples is 2.41 and 2.43, respectively (The mean data has been added to Table 3). Statistical comparisons using non-parametric tests (Wilcoxon, Friedman, and Kruskal-Wallis) indicated that there is no significant difference between the test and reference groups. Therefore, the slight variation between the samples (T_{max} values for each individual are summarized in the table below) can be attributed to inter- and intra-subject variations primarily due to variations in the motility of the gastrointestinal tract, differences in the acidity of digestive juices, or the extent of absorption (6, 7). Furthermore, the T_{max} analysis result was included in the results section (Page 9, lines 174 and 175) in response to the reviewer's request as below:

“3.5. Bioequivalence of the Generic Product

The 90% CI for the geometric mean ratio of log-transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of the test product to the reference product, respectively, were 87.1-101.9, 91.4-105.9, and 92.9-106.9. The

results fell within the permitted 80-125% range (1, 2), showing that the test product and the reference product are bioequivalent (Table 3). Also, Wilcoxon's non-parametric test for T_{max} showed no significant difference between the two formulations (P = 0.923).”

T_{max} values for each individual:

	T_{max}	
	Reference	Test
Subject 1	2	2.5
Subject 2	2	2.5
Subject 3	2.5	2.5
Subject 4	2.5	2.5
Subject 5	1	1.5
Subject 6	2.5	2
Subject 7	2.5	1.5
Subject 8	2	3
Subject 9	2.5	2.5
Subject 10	2	2
Subject 11	2.5	3
Subject 12	2.5	4
Subject 13	2.5	3
Subject 14	3	2
Subject 15	2	2
Subject 16	2	3
Subject 17	3.5	2.5
Subject 18	3	2.5
Subject 19	2.5	2.5
Subject 20	2.5	2
Subject 21	3	4
Subject 22	2.5	1.5
Subject 23	3.5	1.5
Subject 24	2	2

3-In Fig 3 smaller size for label is better

In response to the reviewer's valuable suggestion, we have made the requested changes in Figure 3.

References:

1. Research CfDEa. Statistical Approaches to Establishing Bioequivalence: U.S. Food and Drug Administration; 2020 [updated 2020/04/29/Wed, - 14:03. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/statistical-approaches-establishing-bioequivalence.
2. Research CfDEa. Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations: U.S. Food and Drug Administration; 2020 [updated 2020/04/29/Wed, - 16:30. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bioavailability-and-bioequivalence-studies-submitted-ndas-or-inds-general-considerations.
3. Zuo X, Zhao X, Shi J, Zhang T. Pharmacokinetics and bioequivalence evaluation of two oral formulations of cotrimoxazole tablets in healthy Chinese volunteers under fasting conditions. BMC Pharmacol Toxicol. 2024;25(1):23.
4. Jalali RK, Rasaily D. Chapter 20 - Generic Drug and Bioequivalence Studies. In: Vohora D, Singh G, editors. Pharmaceutical Medicine and Translational Clinical Research. Boston: Academic Press; 2018. p. 327-39.
5. Zhai Y, Wu L, Zheng Y, Wu M, Huang Y, Huang Q, et al. Bioequivalence Study of Amitriptyline Hydrochloride Tablets in Healthy Chinese Volunteers Under Fasting and Fed Conditions. Drug Des Devel Ther. 2020;14:3131-42.
6. Karalis V, Macheras P, Van Peer A, Shah VP. Bioavailability and bioequivalence: focus on physiological factors and variability. Pharmaceutical research. 2008;25:1956-62.
7. Vinarov Z, Abdallah M, Agundez JA, Allegaert K, Basit AW, Braeckmans M, et al. Impact of gastrointestinal tract variability on oral drug absorption and pharmacokinetics: An UNGAP review. European Journal of Pharmaceutical Sciences. 2021;162:105812.

2 Revision 1

1 comment · 9 Feb 2025

Sima Sadrai Reviewer

ACCEPT 9 Feb 2025

Dear Author,
Overall, it is OK.
The labels in the figure comparing the test and reference can also be smaller.