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PEER-REVIEW REPORT

Name of journal: *World Journal of Pharmacology*

Manuscript NO: 80095

Title: Pharmacokinetics/Pharmacodynamics study of Fixtral SB as compared to supra bioavailable Itraconazole and conventional Itraconazole

Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 00503176
Position: Editorial Board
Academic degree: MD, PhD
Professional title: Professor
Reviewer's Country/Territory: Croatia
Author's Country/Territory: India

Manuscript submission date: 2022-09-16

Reviewer chosen by: Dong-Mei Wang

Reviewer accepted review: 2022-10-21 14:30

Reviewer performed review: 2022-10-21 15:07

Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This study reports on what seems to be a formal BE study done for regulatory purposes. T product is a generic formulation (T) developed after an approved formulation of intraconazole that was designed in order to achieve improved absolute oral bioavailability (R2) - i.e., both T and R2 are "suprabioavailable" formulations of itraconazole, and T (generic) is compared to R2 (reference) in a formal single-dose, first-order cross-over study under fed conditions. The study includes also a further "Reference", which is a "conventional" oral formulation of itraconazole. The dose of T is 100 mg and is compared to 100 mg of R2 (i.e., two suprabioavailable formulations are compared on equivalent doses). The dose of R1 is 200 mg - i.e., suprabioavailable formulations (which has been previously shown for R2 formulation) are approximately twice more bioavailable, hence the approved dose is half the dose of the conventional formulation. With 3 treatments (T, R1, R2) - the study is hence 3 treatment 3 period cross over study. Generally, the addressed topic is of interest, but there are several flaws in this manuscript and it requires a major revision. 1. Some English polishing is needed. 2. Abstract is not straightforward to understand. It is a bit confusing. It mentions "3 treatments", but then mentions and reports only T vs. R2 results etc. _ it should be re-written in a way which will make it straightforwardly clear: There are 3 treatments, T is suprabioavailable and is tested for BE vs. a suprabioavailable reference (one referene treatment), There is another reference treatment - a conventional formualtion. T is NOT compared to thie reference for PK BE, but for a pharmacodynamic parameter AUC/MIC. 3. Figure 1 depicts subjects flaw and study design - but it is again confusing (a bit): a) if this was a 3 treatment 3 period single dose first-order cross-over, than it should have had

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6 sequences - and 54 subjects were randomized 9 to each sequence (Williams design for 3 treatments). This should be explicitly stated. 3. Concentration-time curves for the 3 treatments should be clearly graphically displayed. 4. A tabular or graphical representation of proportions achieving the "critical" AUC/MIC ratio per time points should be shown for T and R1. 5. In Results - this is a standard cross-over study. the so-called "period effect" or "sequence effect" or "significant treatment effect" - are irrelevant info. What matters is a) data summary; b) formal BE tests/ratios. I assume that - in line with the standards of cross over PK studies, subjects with pre-dose levels >5% of the previous period peak -were excluded (yes? should be stated explicitly). If so (and this is how it should be) - there is no carry-over - and one is not concerned with anything else. 6. Methods - clearly describe design (as mentioned), declare the rationale for the number of subjects; describe the bioanalytical method. While the method for the analysis of PK BE is rather clear (provide the proc mixed code), the method to analyze proportions is not really clear. The fact is - proportions from a cross-over design can also be analyzed just as the continuous outcome - a mixed model with subjects nested in sequence, with a binary distribution and a logit link (with treatment, period, sequence and subjects nested in sequence as fixed effects, or with subjects as a random effect). 7.IN BE studies, Cmax is a standard "primary outcome"..why not here? (i.e, T and R are BE if their peak (cmax) and total (AUCt) exposures are equivalent). 8. AUC0-t is not AUC from 0 to the last measurable concentration, but to the last sampling time. 9. First table in the mansucrtip should be one showing summary PK and PD data for T, R1, R2. 10. the next one should show formal BE tests, or comparisons in respect to the proportions. 11. Why compare AUC/MIC vs. "a conventional" formualation and not R2? 12. The current Table 1 and Table 2 seem to be discordant...the numbers do not seem to match - check it! 13. In Table 1, CIs for the Cmax GMR are erroneous - correct.

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Reviewer's code: 02192131
Position: Editorial Board
Academic degree: BSc, PhD

Professional title: Associate Professor, Honorary Research Fellow

Reviewer's Country/Territory: Australia

Author's Country/Territory: India

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Reviewer chosen by: Dong-Mei Wang

Reviewer accepted review: 2022-10-24 00:55

Reviewer performed review: 2022-10-24 03:36

Review time: 2 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The paper reports a bioequivalence study of a new formulation of itraconazole compared to an existing formulation. The study was performed using a three-way cross-over design in healthy volunteers and PK data was determined using non-compartmental calculations. Bioequivalence was assessed by ANOVA on the log-transformed AUC data. Thus, the study was carried out using standard methodology for this type of study and the derived parameters reported in a conventional manner. There are several issues with the report that require amendment / revision before the paper can be published. 1. The study appears to be a BE study for the purpose of drug registration. If this is the case, it should be noted in the Conflict-of-Interest statement at the end of the paper. 2. Somewhat surprisingly there is no mention of the methodology used for the determination of plasma drug and metabolite concentrations. This should report sample preparation, instrument(s) used, chemical methodology and the accuracy, precision, and detection limits of the assay method. 3. It is not clear why R1 was used in the study when the new formulation appears to have been established as bioequivalent to it. Would it have been better to report the data for R1 as dose corrected so that the reported values are comparable between test, R1 and R2? 4. Even though the authors report that the ratio of AUC/MIC was calculated for test (T) and reference (R1) at different levels of MIC up to maximum 16 mcg/mL, this data does not seem to appear anywhere in the paper. Furthermore, statistical comparisons between formulations are not reported other than the bare statement that the two formulations were equivalent. 5. With respect to the demographic data the number of males and females is not stated separately nor are their ages, weight

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etc reported. Perhaps a separate table reporting these demographic data is in order. If the weight and height are reported, is it necessary to report BMI, since it is not an independent variable or alternatively if BMI is reported then weight and height would seem superfluous. 6. The units for the value of Cmax are not stated in the text or in tables 2 and 3. In the absence of the assay methodology the reported precision of measurements is overstated. Indeed, it is doubtful if any analytical method has the precision implied by the reporting of the data, particularly at ng/ml levels. 7. Why was the data from one subject not included in the analysis?

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RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Pharmacology*

Manuscript NO: 80095

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Author's Country/Territory: India

Manuscript submission date: 2022-09-16

Reviewer chosen by: Yu-Jie Ma

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Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
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statements	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

I reviewed the revised manuscript. Comments. 1. In section of methods, it is stated that "treatment lasted 39 days..". What does this mean? This was a single-dose study with blood sampling over 96 hours post-dose and 14 days wash-out between periods 1 and 2 and 20 between periods 2 and 3. I suppose that authors wanted to state that the ENTIRE STUDY lasted 39 days, since first subject in to last subject out. This should be revised. 2. Tha part on sample size calculation should go to "methods" not to results. 3. In the methods, authors state that AUC/MIC ratios were calcualted and proportion of those achieving satisfactor levels were compared between T and R1 - but results do not metnion this outome: also, there is no tabular or graphical representation of these results - this should be added or this part should be completely removed from the manuscript. 4. The rationale for inclusion of R1 - is still not clearly explained. 5. As I already menioned - period, sequence etc. effects from ANOVA are irrelevant - the point is that with adequate wash-out carry-over was prevented. So - there is no need to report on this other things: what counts are summary PK data on primary and other outcomes and formal BE tests on primary outcomes.