Bioequivalence Study of Vildagliptin and Metformin Fixed Dose Combinations in Healthy Volunteers

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The Indian Practitioner; Vol. 72 No. 12. December 2019; 21-25. (Article was not published online since the inaccuracies were brought into notice during the usual interval between print and online publishing).

The above print article has been retracted by agreement with the authors, journal Executive Editor, and Blockdale Media LLP (publishers of The Indian Practitioner) on initiative taken by the authors. A revised version of the article has been published after successful peer-review and editorial scrutiny in the current (Vol.73 No.1 January 2020; 28-33) issue of The Indian Practitioner.

Author's Statement:

We, the authors, are retracting the above mentioned article because of multiple inaccuracies in the information presented in the original article which can significantly alter the interpretation of our research. We deeply regret this situation and apologize for any inconvenience to readers of The Indian Practitioner. We submit to the readers a revised version of the retracted article with due corrections made in the current (Vol.73 No.1 January 2020; 28-33) issue of The Indian Practitioner.

Summary of Changes in the Revised Article:

1. General Changes- Author Sequence

Text in Original Manuscript

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Pratip Sen[2],
Shalmali Ambekar[3],
Rajendra Agarwal[4]

Text in Revised Manuscript to be Read As

Pratip Sen[1],
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Rajendra Agarwal[3],
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2. General Changes- Test product representation throughout manuscript

Text in Original Manuscript

Vildamet®

Text in Revised Manuscript to be Read As

Vildamac-M®

3. Abstract: Methods- Last line:

Text in Original Manuscript

The study compared oral bioavailability of two formulations Vildamet® versus Eucreas® as two tablets in single dose administered in fed condition.

Text in Revised Manuscript to be Read As

The study compared oral bioavailability of two formulations Vildamac-M® versus Eucreas® as one tablet in single dose administered in fed condition.

4. Abstract: Results

Text in Original Manuscript

The 90% confidence intervals for the ratio (Test/Reference) of C_{max} and AUC_{0-48} for Vildamet® were within the acceptable limits of bioequivalence 80.00% - 125.00%. Ratio (T/R) for C_{max} found to be 101.99%. The highest intra subject C.V. for Vildamet® combination was observed to be 8.95%

Text in Revised Manuscript to be Read As

The 90% confidence intervals for the ratio (Test/Reference) of C_{max} and AUC_{0-48} for **Vildamac-M®** were within the acceptable limits of bioequivalence 80.00% - 125.00%. Ratio (T/R) for C_{max} and AUC_{0-48} found to be 101.99% and **105.61% for metformin respectively and 97.27% and 101.05% for vildagliptin respectively.** The highest intra subject C.V. was observed to be 8.95% **for metformin and 15.85% for vildagliptin**

5. Materials and Methods: Formulations in the study-Reference Drug

Text in Original Manuscript:

Eucreas® (Vildagliptin and Metformin hydrochloride 50 mg/1000 mg) tablet: manufactured by **Novartis Pharma, India**.

Text in Revised Manuscript to be Read As

Eucreas® (Vildagliptin and Metformin hydrochloride 50 mg/1000 mg) tablet: manufactured by **Novartis Pharmaceuticals Ltd., UK.**

6. Materials and Methods: Study Design

Text in Original Manuscript:

The study was conducted at BA/BE facility after approval from an independent ethics committee.

Text in Revised Manuscript to be Read As

The study was conducted at BA/BE facility of **Macleods Pharmaceuticals Limited, India** after approval from an independent ethics committee.

7. Materials and Methods: LC-MS/MS Method for Estimation of Vildagliptin and Metformin Fixed Dose Combination in Human Plasma Samples

Text in Original Manuscript:

Method for Estimation of Vildagliptin and Metformin Fixed Dose Combination in Human **serum** Samples

Text in Revised Manuscript to be Read As

Method for Estimation of Vildagliptin and Metformin Fixed Dose Combination in Human **Plasma** Samples

8. Results: Second Paragraph

Text in Original Manuscript:

This study was performed to evaluate the bioequivalence of fixed dose combination of Vildamet® of Macleods Pharmaceutical Limited) with Eucreas® of **Novartis Pharma India.**

Text in Revised Manuscript to be Read As

This study was performed to evaluate the bioequivalence of fixed dose combination of **Vildamac-M®** of Macleods Pharmaceutical Limited) with Eucreas® of **Novartis Pharmaceuticals Ltd., UK.**

9. Results: Third Paragraph

Text in Original Manuscript:

The comparative pharmacokinetic profiles of both test and reference products are shown in Table-1A, Table-1B and Figure-1.

Text in Revised Manuscript to be Read As

The comparative pharmacokinetic profiles of both test and reference products are shown in Table-1A, Table-1B, Table 1C, **Table 1D, Table-2A, Table-2B, Figure-1A and Figure 1B.**

10. Results: Fourth Paragraph

Text in Original Manuscript:

The C_{max} was found to be 1630.97 ng/mL in test formulation compared to 1589.45 ng/mL in reference formulation.

Text in Revised Manuscript to be Read As

The **mean** C_{max} was found to be **1630.97 ng/mL for metformin in test formulation compared to 1589.45 ng/mL in reference formulation. Similarly, the C_{max} was found to be 167.17 ng/mL for vildagliptin in test formulation compared to 169.36 ng/mL in reference formulation.**

11. Results: Fourth Paragraph

Text in Original Manuscript:

The AUC_{0-48} was 18248.30 ng*hrs/mL in test formulation compared to 17316.10 ng*hrs/mL

Text in Revised Manuscript to be Read As

The **mean** AUC_{0-48} **for metformin was 18248.30 ng*hrs/mL in test formulation compared to 17316.10 ng*hrs/mL in reference formulation. The AUC_{0-48} for vildagliptin was 1060.07 ng*hrs/mL in test formulation compared to 1054.14 ng*hrs/mL in reference formulation.**

12. Results: Fourth Paragraph

Text in Original Manuscript:

The T_{max} was found to be 5.62 hrs in test formulation compared to 5.77 hrs in reference formulation.

Text in Revised Manuscript to be Read As

The median T_{max} **of metformin was found to be 5.75 hrs in test formulation compared to 6.00 hrs in reference formulation. The median T_{max} of vildagliptin was found to be 4.00 hrs in test formulation compared to 3.84 hrs in reference formulation.**

13. Results: Fifth Paragraph

Text in Original Manuscript:

The 90% confidence interval (CI) of geometric mean of C_{max} and AUC_{0-48} for test and reference products were 87.87 (90% CI 86.57-109.29) and 99.92 (90% CI 95-107.49) respectively. There was no statistical significant difference observed in pharmacokinetic parameters between test and reference products. Ratio (T/R) for C_{max} found to be 101.99%. The highest intra subject C.V. for Vildagliptin and Metformin combination was observed to be 8.95% (Table-2).

Text in Revised Manuscript to be Read As

The T/R ratio (90% confidence interval) for Test/Reference of C_{max} and AUC_{0-48} of metformin in test and reference products were 101.99% (95.46-108.96%) and 105.61% (102.13-109.21%) respectively. The T/R ratio (90% confidence interval) for Test/Reference of C_{max} and AUC_{0-48} of vildagliptin were 97.27% (86.57-109.29%) and 101.05% (95.00 -107.49%) respectively. The highest intra subject C.V. for Metformin and Vildagliptin was observed to be 8.95% and 15.85%. The power of C_{max} and AUC_{0-48} for Metformin was observed to be 99.85% and 100.00% respectively. Similarly C_{max} and AUC_{0-48} for Vildagliptin was observed to be 87.87% and 99.92% respectively.

Legends for following tables are modified in revised manuscript

Table-1A: Comparative Mean Pharmacokinetic Data of Metformin in Test Formulation (Vildamac-M®)

Pharmacokinetic Parameters	Vildamac-M®						
	N	Mean	Median	S.D.	C.V.	Minimum	Maximum
C_{max} (ng/mL)	12	1630.97	1681.81	307.87	18.88	947.35	2006.20
AUC_{0-48} (ng*hrs/mL)	12	18248.30	17789.59	2477.59	13.58	15230.38	21629.18
T_{max} (hrs)	12	5.62	5.75	1.33	23.71	2.00	8.00

Table-1B: Comparative Mean Pharmacokinetic Data of Metformin in Reference Formulation (Eucreas®)

Pharmacokinetic Parameters	Eucreas®						
	N	Mean	Median	S.D.	C.V.	Minimum	Maximum
C_{max} (ng/mL)	12	1589.45	1593.96	260.12	16.37	1098.40	2048.73
AUC_{0-48} (ng*hrs/mL)	12	17316.10	18174.73	2592.88	14.97	13676.95	20853.08
T_{max} (hrs)	12	5.77	6.00	1.47	25.50	2.33	8.00

Table-2A: Confidence Intervals of Ln-Transformed Parameters of Metformin.

Pharmacokinetic Parameters	Geometric Mean		Ratio (T/R) (%)	Intra Subject C.V. (%)	Power (%)	90% Confidence Interval (%)	
	Reference(R)	Test (T)				Lower	Upper
C_{max}	1569.24	1600.47	101.99	8.95	99.85	95.46	108.96
AUC_{0-48}	17133.79	18094.72	105.61	4.53	100.00	102.13	109.21

T: Vildamac-M®; R: Eucreas®

Following tables are added in revised manuscript

Table-1C: Comparative Mean Pharmacokinetic Data of Vildagliptin in Test Formulation (Vildamac-M®)

Pharmacokinetic Parameters	Vildamac-M®						
	N	Mean	Median	S.D.	C.V.	Minimum	Maximum
C_{max} (ng/mL)	12	167.17	166.38	49.76	29.77	98.41	292.85
AUC_{0-48} (ng*hrs/mL)	12	1060.07	1035.84	179.41	16.93	767.56	1431.01
T_{max} (hrs)	12	4.33	4.00	1.21	28.09	2.67	6.00

Table-1D: Comparative Mean Pharmacokinetic Data of Vildagliptin in Reference Formulation (Eucreas®)

Pharmacokinetic Parameters	Eucreas®						
	N	Mean	Median	S.D.	C.V.	Minimum	Maximum
C_{max} (ng/mL)	12	169.36	161.48	37.84	22.34	121.04	230.37
AUC_{0-48} (ng*hrs/mL)	12	1054.14	981.21	215.64	20.46	783.27	1478.57
T_{max} (hrs)	12	3.97	3.84	1.22	30.74	2.67	6.00

Table-2B: Confidence Intervals of Ln-Transformed Parameters of Vildagliptin.

Pharmacokinetic Parameters	Geometric Mean		Ratio (T/R) (%)	Intra Subject C.V. (%)	Power (%)	90% Confidence Interval (%)	
	Reference(R)	Test (T)				Lower	Upper
C_{max}	165.61	161.08	97.27	15.85	87.87	86.57	109.29
AUC_{0-48}	1035.59	1046.50	101.05	8.36	99.92	95.00	107.49

T: Vildamac-M®; R: Eucreas®