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Original Research Article

A comparative bioequivalence study to evaluate the pharmacokinetic profile and safety of single-dose of dydrogesterone 10 mg tablets in healthy adult female volunteers

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ABSTRACT

Background: Dydrogesterone is a progesterone derivative. It is indicated in variety of disorders requiring progesterone administration. The basic aim of this bioequivalence (BE) study was to compare the pharmacokinetic profile of generic dydrogesterone 10 mg tablets (test product- Dydrosure) versus the innovator brand.
Methods: This was a randomized, open-label, balanced, two-treatment, two-period, two-sequence, two-way crossover, single oral dose BE study conducted in healthy adult females under fasting conditions. A total of 28 subjects participated and 27 subjects completed both the study periods with 14 days washout in between. A total of 23 serial blood samples were collected starting from pre-dose to 72-hour post-dose. The primary pharmacokinetic parameters included peak plasma concentration (C_{max}), area under the curve from zero to time t (AUC_{0-t}) and zero to infinity (AUC_{0-inf}); and 90% confidence intervals (CIs) of geometric least square mean (LSM) ratio of test product versus reference product were computed to evaluate the BE. The safety evaluation was based on reported adverse events (AEs) and laboratory parameters.
Results: The 90% CIs of geometric LSM ratio of all primary pharmacokinetic parameters were within the range of 80 to 125%. The sequence, period and treatment did not have significant effect on the primary pharmacokinetic parameters. A single AE of dizziness was reported with the test product which was mild in intensity and transient in nature.
Conclusions: Based on the statistical analysis of dydrogesterone, it is concluded that the test product (T): Dydrosure (dydrogesterone tablets IP 10 mg) manufactured by Alkem Laboratories Ltd., India is bioequivalent to the innovator's brand, in terms of rate and extent of absorption under fasting conditions. The test product can be used interchangeably with the innovator's brand.

Keywords: Bioequivalence, Dydrogesterone, Pharmacokinetic

INTRODUCTION

Dydrogesterone is a synthetic stereoisomer of progesterone (a retroprogesterone), with an additional double bond between carbons 6 and 7. Differences in the structure of dydrogesterone and progesterone influence the potency and potential side effect profile of these progestogens. Dydrogesterone has been used globally since the 1960s for several conditions related to progesterone insufficiency. It facilitates changes in the secretary phase of endometrium in uterus primed by estrogen.[1]

Dydrogesterone is indicated in various disorders associated with progesterone deficiencies i.e., dysmenorrhea, endometriosis, secondary amenorrhea, irregular cycles, dysfunctional uterine bleeding, pre-menstrual syndrome, threatened miscarriage, habitual

miscarriage and infertility due to luteal insufficiency; to provide luteal support as a part of assisted reproductive technology (ART) treatment and in hormone replacement therapy (HRT) in women with natural or surgical induced menopause with an intact uterus to counteract the effects of unopposed estrogen. The usual recommended daily dose is 10 to 30 mg depending upon the clinical condition; the dosages, treatment schedule and duration of treatment may be adapted to the severity of the dysfunction and the clinical response.[2-4] Further, it gives protection against the increased risk of endometrial hyperplasia and/or endometrial carcinoma that is induced by estrogens. Dydrogesterone has no estrogenic, androgenic, anabolic and corticoid properties. It also does not suppress ovulation.[3,4]

Following oral administration, dydrogesterone is rapidly absorbed with a maximum temperature (T_{max}) between 0.5 and 2.5 hours. The absolute bioavailability of dydrogesterone (oral 20 mg dose versus 7.8 mg intravenous infusion) is 28%. Following oral administration, dydrogesterone is rapidly metabolized to 20α-dihydrodydrogesterone (DHD). The levels of the main active metabolite DHD peak about 1.5 hours post-dose. The plasma levels of DHD are substantially higher as compared to the parent drug. The AUC and C_{max} ratios of DHD to dydrogesterone are in the order of 40 and 25, respectively. Mean terminal half-lives of dydrogesterone and DHD vary between 5 to 7 and 14 to 17 hours, respectively. After oral administration of labelled dydrogesterone, on average 63% of the dose is excreted into the urine and excretion is complete within 72 hours. Comparison of the single and multiple dose kinetics have shown that the pharmacokinetics of dydrogesterone and DHD are not changed as a result of repeated dosing. Steady state is reached after 3 days of treatment.[2,3]

Dydrogesterone 10 mg tablets are being marketed globally by the innovator and various other generic manufacturers. M/s. Alkem Laboratories Ltd., India has developed a generic version of dydrogesterone 10 mg tablets. The current bioequivalence (BE) study has been conducted with a primary aim to evaluate and compare the pharmacokinetic profile including rate and extent of absorption of this generic formulation (test) with the Innovator formulation (reference).

METHODS

Study interventions

Dydrosure (dydrogesterone tablets IP 10 mg) manufactured by M/s. Alkem Laboratories Ltd. (Batch no. 21620001) was the test product and the innovator's brand were the reference product used in this BE study.

Study population

Since dydrogesterone is indicated for females, this study was conducted in female subjects only. Healthy adult females aged 18-45 years with body mass index (BMI) between 18.5 to 30.0 kg/m^2 who were non-smokers and non-alcoholic; having clinically acceptable medical history and physical examination including vitals, clinically acceptable screening laboratory values, negative UPT during screening and negative serum beta human chorionic gonadotropin (β-hCG) test at the time of check-in; willing to follow the protocol requirements and abstain from consuming any xanthine/caffeine containing food or beverages, grapefruit juice, alcoholic products, cigarettes and tobacco products for 48 hours prior to dosing until end of the study were considered for participation in the study.

Subjects who had hypersensitivity or intolerance to dydrogesterone or related class of drugs, ongoing clinically significant medical disorder, history of major illness or hospitalization, blood donation or participation in another clinical study within past 90 days, history of consumption of any medication within past 21 days and depot injections or implants within past 6 months were excluded. Pregnant and lactating women or those using hormonal contraceptives (oral/implants) were also excluded.

Ethical considerations

The study protocol including the informed consent document of the study was approved by the CLA and an independent ethics committee registered by CLA before initiation of the study. All the study subjects provided their voluntary written informed consent before participation in the study. This study was conducted in compliance to declaration of Helsinki and good clinical practice (GCP) guidelines and prevailing national and international regulations.[5-7]

Study design

This was a randomized, open-label, balanced, two-treatment, two-period, two-sequence, two-way crossover, single oral dose BE study conducted under fasting conditions. This BE study was conducted from December 2021 to February 2022 at clinical research unit of Bio Scientific Research Laboratories (I) Pvt. Ltd. Thane, Mumbai, an independent BE centre approved by Central Licensing Authority (i.e. Office of the Drugs Controller General of India). The subjects were administered a single tablet of either test or reference product with 240 ml of drinking water at ambient temperature in sitting position in each study period according to the SAS generated randomization schedule. Mouth check was done immediately after dosing to assess compliance of the procedure. Subjects were confined within the clinical facility from 11 hours pre-dose until 24 hours post-dose during each study period. All subjects were on an overnight fast for at least 10 hours pre-dose and remained fasted for 4 hours post-dose. Drinking water was not allowed for 1 hour before and after dosing (except which administered during dosing); at all other times water was provided *ad libitum*. A standardized meal was provided to

all the subjects at 4-, 9- and 13-hours post-dose. Respective meal contents were identical for both study periods. The subjects were advised to remain in sitting position for first 2 hours post-dose. Subjects were refrained from performing any strenuous activity during the confinement period at the clinical facility. The washout period between two study periods was 14 days.

Physical examination including recording of vital signs was performed during screening, at the time of check-in and check-out. Vitals signs were additionally recorded within 3 hours pre-dose and 1-, 3-, 6- and 12-hours post-dose and before ambulatory sample collection in each period. Routine laboratory investigations such as hematological, biochemical and serological investigations, urinalysis and urine pregnancy test (UPT) were performed and ECG was recorded during screening. Urine screening for drug of abuse, UPT and serum β-hCG test were performed at the time of check-in in each period. Urine alcohol test was also done at the time of check-in and before ambulatory sample collection in each period.

Since dydrogesterone is a light sensitive drug, all activities where the drug may be exposed to light were carried out under yellow monochromatic light. The study design was in line with US Food and Drug Administration (FDA) and CDSCO guidance for conduct of bioequivalence studies.

Blood sample collection

A total of 23 blood samples (5 ml each) were collected from the subjects in each study period. Blood samples were collected in pre-labelled vacutainers with K_3EDTA as an anticoagulant within 0.5-hour pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 48 and 72-hours post-dose. Blood samples were collected via an intravenous indwelling cannula from pre-dose up to 24 hours post-dose.

Samples collected at 48- and 72-hours post-dose were ambulatory samples. The plasma was separated from the collected blood samples and plasma samples were stored at -20°C till analysis.

Bioanalytical methods

Dydrogesterone concentration in the plasma samples was analyzed by a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method at the same contract research organization i.e., Bio Scientific Research Laboratories (I) Pvt. Ltd. Thane. The lower limit of quantitation was 50.6 pg/ml and the calibration range was 50.6 pg/ml to 8016.2 pg/ml.

This calibration range was considered enough to quantify the expected concentration range of drug from subject's plasma with the proposed dose of dydrogesterone. Concentration values below the limit of quantitation were considered zero for statistical calculation.

Pharmacokinetic analysis

The primary pharmacokinetic parameters included peak plasma concentration (C_{max}), area under the plasma concentration-time curve from 0 hour to the last measurable concentration (AUC_{0-t}) and area under plasma concentration-time curve up to infinity (AUC_{0-inf}) while secondary pharmacokinetic parameters included time to reach peak plasma concentration (T_{max}), elimination rate constant (K_{el}), elimination half-life ($t_{1/2}$) and percentage of AUC_{0-inf} due to extrapolation from last time point to infinity calculated ($AUC_{Extrapolated\%}$).

Statistical analysis

Sample size for the study was calculated considering the acceptance limits for bioequivalence of 80.00-125.00%, expected T/R ratio of 95-105%, power 80% and intra-subject variability of 20%. Based on these, a total of 28 healthy female subjects were required to be enrolled in the study to compensate for 10% dropouts.

All the statistical analysis were performed using SAS software. Analysis of variance (ANOVA) was performed on untransformed and log transformed pharmacokinetic parameters; C_{max}, AUC_{0-t} and AUC_{0-inf} at alpha level of 0.05. ANOVA model included sequences, subject nested within sequences, period and treatment as factors. The significance of the sequence effect was tested using the subject nested within sequences as the error term. All other main effects were tested against the residual error (mean square error) from the ANOVA model as the error term. Each ANOVA also included calculation of least-square means, adjusted differences between formulation means and the standard error associated with these differences. The 90% confidence intervals (CIs) were constructed for the difference (test versus reference) of least square mean (LSM) of the log-transformed C_{max}, AUC_{0-t} and AUC_{0-inf} for dydrogesterone. BE was concluded if CIs fell within the acceptable range of 80-125% for log transformed C_{max}, AUC_{0-t} and AUC_{0-inf} for dydrogesterone.[7-10]

Safety analysis

Subjects were monitored throughout the study for occurrence of any adverse events (AEs). The hematological and biochemical laboratory parameters were repeated at end of the study. Any clinically significant abnormality observed in physical examination including in vital signs was also to be considered as an AE.

RESULTS

A total of 28 healthy adult females participated in this study. The demographic details of the participants are shown in Table 1. Out of 28 enrolled subjects, 27 subjects completed the study while one subject was withdrawn from the study due to increased levels of β-hCG reported at the time of check-in for second study period. Therefore,

the data of 27 subjects was considered for pharmacokinetic and statistical analysis.

The mean values of primary and secondary pharmacokinetic parameters are presented in Table 2. The mean and log mean plasma dydrogesterone concentration versus time profile for both the study products is presented in Figures 1 and 2 respectively. The geometric LSM ratio (test versus reference) for C_{max}, AUC_{0-t} and AUC_{0-inf} reported was 98.6%, 98.1% and 97.2% respectively and the 90% CIs for all primary pharmacokinetic parameters were within the range of 80 to 125% which confirms the BE of the test product with the reference product under the fasting conditions (Table 3).

A single AE was reported with the test product in second study period. The subjects had dizziness which was of mild in severity and probably associated with the study product. The AE was reported after dosing and resolved completely within 2 hours of its occurrence without any medication. No severe or serious AE was reported in any subject. There was also no abnormality reported in physical examination including vital signs and safety laboratory parameters. Overall, both the study products were well tolerated in this study.

Table 1: Demographic data of the subjects completed the study (n=27).

Statistics	Age (years)	Weight (kgs)	Height (mts)	BMI (kg/m^2)
Mean	34.56	60.13	1.53	25.80
Maximum	43	71.9	1.58	29.3
Minimum	26	43.1	1.40	19.7
Standard deviation	5.35	7.56	0.04	2.57

Table 2: Pharmacokinetic parameters (untransformed) of dydrogesterone under fasting conditions.

Parameter	Test product (n=27)	Reference product (n=27)
C_{max} (pg/ml)	3064.2 (1428.6), (46.6%)	3131.4 (1469.2), (46.9%)
AUC_{0-t} (pg.hr/ml)	11742.0 (4673.6), (39.8%)	12273.3 (6085.4), (49.6%)
AUC_{0-inf} (pg.hr/ml)	12769.6 (4655.2), (36.5%)	13408.4 (6016.6), (44.9%)
T_{max} (hr)*	1.5 (0.5), (31.1%)	1.5 (0.6), (39.6%)
K_{el} (hr^{-1})#	0.1 (0.0)	0.1 (0.0)
$t_{1/2}$ (hr)#	8.0 (2.9)	8.5 (2.6)
AUC_{Ratio}#	91.1 (4.9)	90.2 (4.6)
$AUC_{Extrapolated\%}$#	8.9 (4.9)	9.8 (4.6)

Values presented as mean (SD) (CV%) unless specified, *values presented as median (SD) (CV%), #CV% not presented

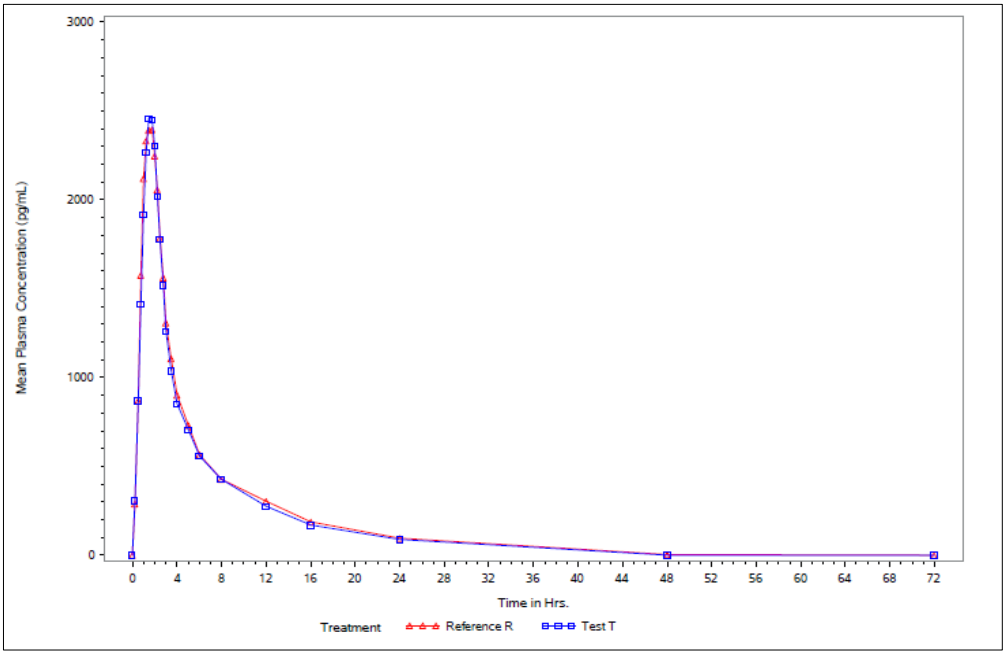

Figure 1: Mean plasma concentration vs time curve for test (T) and reference (R) products for dydrogesterone (n=27).

Table 3: Statistical comparison of log-transformed primary pharmacokinetic parameters between the test and reference products.

Parameter	Test product* (n=27)	Reference product* (n=27)	Geometric LSM ratio (90% CI)	Power	Intra subject CV (%)	ANOVA (p value)		
						Sequence	Period	Treatment
C_{max} (pg/ml)	2764.1	2802.9	98.6 (90.9, 106.9)	99.7	17.6	0.95	0.34	0.77
AUC_{0-t} (pg.hr/ml)	10987.1	11203.0	98.1 (89.4, 107.6)	98.8	20.2	0.48	0.87	0.72
AUC_{0-inf} (pg.hr/ml)	12082.3	12431.5	97.2 (89.2, 105.9)	99.5	18.5	0.45	0.94	0.57

* Data presented as geometric least square mean

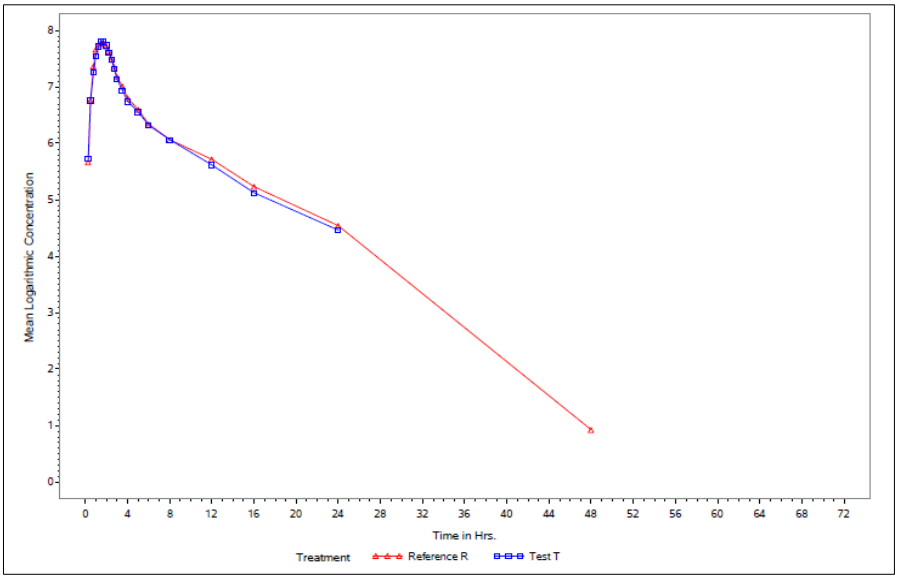

Figure 2: Log mean plasma concentration vs time curve for test (T) and reference (R) products for dydrogesterone (n=27).

DISCUSSION

The basic aim of this BE study was to evaluate whether the pharmacokinetic profile of the test product resembles with the reference product when administered to healthy adults under the fasting conditions. The pharmacokinetic results of this study indicate that 90% CI of geometric LSM ratio of the primary pharmacokinetic parameters i.e., C_{max}, AUC_{0-t} and AUC_{0-inf} falls within the acceptance range of 80 to 125% as recommended by the regulatory guidelines thus confirming the BE of the test product with the reference product.[8-11]

The study could demonstrate the BE of the test product with the reference product with the power of more than 95%. From the ANOVA analysis, it was also evident that there was insignificant effect of sequence, period and treatment on any of the primary pharmacokinetic parameters. The drug concentration was undetected in pre-dose samples of second study period which confirms that the washout period of 14 days was appropriate. Further, the mean $AUC_{Extrapolated\%}$ was in the range of 8.9 to 9.8% which again indicates that the timepoints for blood sampling were properly designed and it ensured that plasma AUCs were reliably estimated. The T_{max} reported for the both the study products in this study was 1.5 hour which was in line with the published literature.[1-3] The $t_{1/2}$ reported in the study was in the range of 8 to 8.5 hour while the same has been reported as 5 to 7 hour in the published literature.[1-3]

This minor difference in the $t_{1/2}$ reported in this study could be attributed to demographic differences in the population studies and this minor difference is not likely to be of much clinical relevance. Untransformed descriptive data of all the parameters studied i.e. C_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and T_{max} of the test product showed a lower intrasubject coefficient of variation (CV%) as compared to that of the reference product thereby indicating that the test product has more consistent pharmacokinetic performance when used across patient populations. A more consistent pharmacokinetic profile would lead to better pharmacodynamics outcomes on long term use.

The safety results of this study, although evaluated in a limited sample size, indicates that both the study products were well tolerated. A single AE of dizziness reported with the test product was of mild intensity and was transient in nature. This is a known AE of dydrogesterone as per the published literature. None of the subjects discontinued the study due to any AEs.[2-4]

Overall, the results of this study confirm that rate and extent of absorption of the test product did not differ significantly from the reference product in healthy adults under fasting conditions and thus, the test product can be considered bioequivalent with the reference product. The study was conducted in the adult females which is the ultimate target population for dydrogesterone. The reference product is indicated in multiple disorders associated with progesterone deficiency; ART and HRT. Based on the results of this BE study, it is reasonable to expect that the test product can be interchangeably used in these disorders with similar therapeutic effects.

CONCLUSION

Based on the statistical analysis of dydrogesterone, it is concluded that the test product (T): Dydrosure (dydrogesterone tablets IP 10 mg) manufactured by Alkem Laboratories Ltd., India is bioequivalent to the innovator's brand, in terms of rate and extent of absorption under fasting conditions. The test product can be used interchangeably with the innovator's brand.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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