SYNOPSIS

NAME OF SPONSOR/COMPANY: Xian-Janssen Pharmaceutical Ltd NAME OF FINISHED PRODUCT: Galantamine Oral Solution NAME OF ACTIVE INGREDIENT(S): Galantamine		
Protocol Number: GALALZ301 (CR002848) **Title of Study:** A Bioequivalent Study to Compare HBr Galantamine Oral Solution with Immediate Release Tablet in Male Healthy Volunteers After Single Oral Administration		
Principle Investigator: Dr. Shu Liang, Dr. Si Tianmei, Beijing University Institute of Mental Health (No. 51 HuayuanBei Road, Haidian District, Beijing 100083)		
Publication (Reference): none		
Study Initiation/Completion Dates: 14 September 2004 / 28 September 2004 Sample Analysis Initiation/Completion Dates: October 2004 / March 2005		**Phase of Development: I**
Objective: The objective of the study is to investigate the pharmacokinetics and tolerance of galantamine oral solution (4mg) vs. galantamine tablet (4mg), and to evaluate the bioequivalence of galatamine oral solution and tablet. The clinical data will be used to support the licensing of galantamine oral solution in China.		
Methodology: This is an open-label, two-treatment, two-period, cross-over, single center, phase I study. The duration of study is 9 days. 24 subjects were randomized into 2 treatment periods to receive either 4mg glantamine oral solution (12 subjects) or 4mg glantamine tablet (12 subjects). The subjects were crossed over to receive the other treatment after 7-day washout period. Each treatment period has 2 days. The plasma were collected during each treatment period at immediately before dosing and . Safety evaluation were performed 32 hours after second treatment (Day 9). **Pharmacokinetic Evaluation:** The plasma were collected immediately before and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 and 32 hours after single oral administration. A HPLC method was developed to determine galantamine concentration. The concentration-time curves were drawn and main pharmacokinetic parameters were calculated. The main parameters include C_{max}, t_{max}, $AUC_{0-\infty}$, AUC_{0-t} and $t_{1/2}$, etc. The AUC and Cmax were analyzed to evaluate the bioequivalence. All clinically significant changes were listed and summeriez.		
Number of Subjects: 24 subjects		
Diagnosis and Main Criteria for Inclusion: 24 male healthy volunteers, Chinese, 18-45 years with body index between 18 and 28kg/m^2. All subjects are deemed healthy at screening based on medical history, physical examination, electrocardiogram and laboratory tests. All subjects must sign informed consent prior to any trial-specific procedures were performed.		
Test Product, Dose and Mode of Administration, Batch No.: Galantamine oral solution (Drug A), 4mg/ml, single oral administration of 4mg galantamine oral solution. Batch No. is 04071966, expire date is June 2006.		
Reference Therapy, Dose and Mode of Administration, Batch No.: Galantamine tablet (Drug B), 4mg/tablet, single oral administration of 4mg galantamine tablet. Batch No. is 04072769, expire date is January 2006.		
Duration of Treatment: Each treatment period has 2 day. Subjects cross over to receive the other treatment after 7-day washout.		

SYNOPSIS (CON'T)

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Xian-Janssen Pharmaceutical Ltd

NAME OF FINISHED PRODUCT:
Galantamine Oral Solution

NAME OF ACTIVE INGREDIENT(S):
Galantamine

Evaluation Criteria:

Pharmacokinetc Parameters: plasma concentrations were measured immediately before doing and at specific time-points after dosing. The concentration-time curve was drawn and pharmacokinetic parameters are calculated. The main parameters include C_{max}, T_{max}, $AUC_{0-\infty}$ and AUC_{0-t}、 $t_{1/2}$.

Safety Parameters: changes in vital signs, physical examination, ECG and laboratory test before study and at the end of study. All adverse evens occurred during the study were recorded.

Statistical Methods:

Pharmacokinetics: A pharmacokinetic software 3P97 is used for main pharmacokinetic parameters and bioequivalent analysis.

Safety: Clinically significant safety assessment is listed by type and frequency.

SUMMARY - CONCLUSIONS

PHARMACOKINETICS:

The pharmacokinetic parameters after single oral administration of galantamine oral solution or galantamine tablet are as follows:

PK parameters	Galantamine tablet (Reference) N=24	Galantamine OS (Test product) N=24
C_{max} (μg/L)	33.44±5.72	31.53±5.59
T_{max}(hr)	1.51±0.72	1.66±0.79
AUC_{0-t}(μg/hr/L)	306.52±65.33	319.23±65.60
$t_{1/2}$(hr)	6.64±2.30	7.06±2.16
$AUC_{0-\infty}$(μg/hr/L)	325.5±77.7	340.6±77.2

SAFETY RESULTS: 5 subjects reported adverse events. 2 subjects reported adverse events during test drug treatment period, 3 subjects reported adverse events during reference drug treatment period. One subject was detected slow heart rate 30 minutes after dosing and recovered shortly after 6 hours. One subject was detected increased blood pressure 1 hour after dosing and recovered to normal 4 hours later. No discomforts were reported by subjects. All these adverse events are mild and transient.

CONCLUSION: HBr Galantamine oral solution is a safe inhibitor of acetylcholinesterase. It is estimated that the plasma maximal concentration of galantamine (C_{max}=31.53μg·L^{-1}) after single oral administration can be reached in Chinese young volunteers at the peak time of 1.66 hours. The half life is 7.06 hours, so it is appropriate to administer galantamine oral solution or tablet twice daily. Glantamine is safe and well tolerated with minor side effects. The relative bioavailability of galantamine oral solution is 105.6%. Galantamine oral solution and galantamine tablet are bioequivalent.

Date of the report: 29 April 2005

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