Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country.

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

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2. SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: Lendormin® D tablets				
Name of active ingredient: Brotizolam (WE 941)		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**	**to**	**Addendum No.:**
Report date: 28 November 2002	**Number:** U03-3267	**Study period (years):** 18 July 2000 to 19 August 2000		

Title of study:	The bioequivalence between WE 941 OD tablets (0.25mg as the basis) taken without water and brotizolam conventional tablets (Lendormin® tablets, 0.25mg as the basis) taken with water, as a single administration in healthy adult male subjects (open-labelled, 2-way cross-over study)	
Investigator:	[redacted]	
Study centre:	[redacted] Japan	
Publication (reference):	Not yet published	
Clinical phase:	I	
Objectives:	The bioequivalence of WE 941 OD tablets prepared in oral disintegrating tablet form taken without water and brotizolam conventional tablets (Lendormin® Tablets) taken with water, was evaluated in healthy adult male subjects	
Methodology:	Cross-over comparison of two treatment, open-labelled ,PK-measurement	
No. of subjects entered:		
total:	30 (15 subjects repeated the study and are counted twice)	
each treatment:	WE 941 OD tablet p.o. - 15; brotizolam conventional tablets p.o. - 15	
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age 20 - 35 years, body weight 50 - 80 kg, BMI: ± 20 %	
Test product:	WE 941 OD tablet	Brotizolam conventianal tablet(Lendormin® Tablets)
dose:	0.25 mg as the basis	0.25 mg as the basis
mode of admin.:	per os	per os
batch no.:	00048	00046
Duration of treatment:	Single dose	
Reference therapy:	None	
dose:	Not applicable	
mode of admin.:	Not applicable	
batch no.:	Not applicable	

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Name of company: Boehringer Ingelheim		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: Lendormin® D tablets		**SUPPLEMENTARY SHEET**		
Name of active ingredient: Brotizolam (WE 941)		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**	**to**	**Addendum No.:**
Report date: 28 November 2002	**Number:** U03-3267	**Study period (years):** 18 July 2000 to 19 August 2000		

Criteria for evaluation:

Efficacy:	Not applicable
Pharmacokinetics:	Bioequivarence
Safety:	Adverse events, vital signs, laboratory tests
Statistical methods:	Based on calculated values of $AUC_{0\text{-}24\,h}$ and C_{max}, the bioequivalence between WE 941 OD tablets and brotizolam conventional tablets (Lendormin® Tablets) was evaluated using 90% confidential intervals. Safety was analysed using descriptive statistics.

SUMMARY - CONCLUSIONS:

Efficacy results: Not applicable (In this pharmacokinetic study, there were no measures of efficacy.)

Pharmacokinetic results:
For brotizolam conventional tablets and WE 941 OD tablets, C_{max} was calculated to be 4.40 ± 1.02 ng/mL and 4.08 ± 1.30 ng/mL, respectively; $AUC_{0\text{-}24\,h}$ 34.03 ± 12.09 ng hr/mL and 36.23 ± 12.75 ng hr/mL, respectively; t_{max} 1.0 ± 0.8 hours and 1.5 ± 1.1 hours, respectively; and $MRT_{0\text{-}24\,h}$ 7.0 ± 0.9 hours and 7.3 ± 0.8 hours, respectively.
For C_{max}, the ratio of geometric mean for WE 941 OD tablets to that of brotizolam conventional tablets was 90.9%, and the 90% confidence interval for the difference of mean log-transformed values was 83.5 to 98.9%; for $AUC_{0\text{-}24\,h}$, the corresponding values were 107.5% and 102.1 to 113.3%, respectively.

Safety results:
In WE 941 OD tablets administration group, fatigability generalized in one subject was assessed as "related" to the trial drug. In the brotizolam conventional tablet administration group, hypobulia and malaise in each one were assessed as "related" to the trial drug. All AEs were assessed as mild. Furthermore, no AEs were assessed as "related" to the trial drug in laboratory test and vital signs. In the post-administration observations conducted following completion of administration period II, all AEs obserbed were assessed as "unrelated" to the trial drug.

Conclusions:
The 90% confidence intervals for the difference between the two drugs in respective log transformed values of C_{max} and $AUC_{0\text{-}24\,h}$ were within the range of 80 to 125%. The drugs were thus assessed as bioequivalent each other.