

## OVER-ENCAPSULATED IMITREX<sup>®</sup> 50 MG TABLETS ARE BIOEQUIVALENT TO MARKETED IMITREX<sup>®</sup> 50 MG TABLETS

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### BACKGROUND

A blinded, active control formulation of Imitrex<sup>®</sup> was required for a Phase III study in patients suffering from an acute migraine attack. Marketed Imitrex<sup>®</sup> 50mg Tablets were over-encapsulated using commonly available excipients. This bioequivalence study was conducted to confirm that over-encapsulation does not alter the bioavailability of the marketed product.

The Phase III migraine study compared the efficacy and safety of MT 100<sup>™</sup> tablets, a novel combination product of metoclopramide hydrochloride and naproxen sodium that releases metoclopramide hydrochloride followed by naproxen sodium in a coordinated and sequential manner with over-encapsulated Imitrex<sup>®</sup> Tablets.

### OBJECTIVES

To assess the bioequivalence of over-encapsulated Imitrex<sup>®</sup> 50 mg Tablets with marketed (non-encapsulated) Imitrex<sup>®</sup> 50 mg Tablets.

### METHODS

This was a single-center, Phase I, randomized, open-label, two-period crossover, pharmacokinetic study in 28 non-smoking healthy volunteers. All doses were administered under fasting conditions (10-hour fast predose and 4-hour fast postdose), and were separated by at least 5-day (120-hr) washout period. Blood samples were obtained from all subjects over the 12 hours following oral administration of study drug. Information regarding clinical adverse events and concurrent medication were collected throughout the study. Plasma samples were analyzed using a validated HPLC assay with a quantifiable range of 1 to 100 ng/mL.

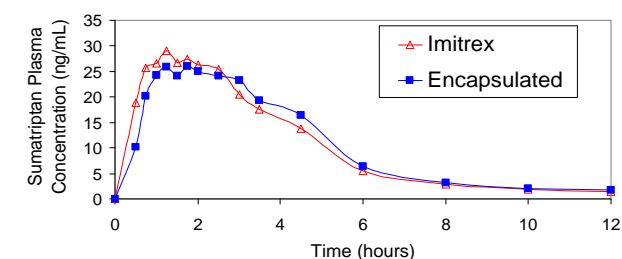
Pharmacokinetic parameters evaluated included: peak plasma concentration ( $C_{max}$ ) and corresponding peak time ( $t_{max}$ ); area under the curve (AUC). The peak plasma concentration ( $C_{max}$ ) and the corresponding peak time ( $t_{max}$ ) was determined directly from the concentration vs. time profile. The area under the curve from time zero to the last measurable concentration ( $AUC_{last}$ ) was calculated using the linear trapezoidal method. The area under the curve from time zero to time infinity ( $AUC_{inf}$ ) was calculated as the sum of  $AUC_{last}$  plus the ratio of the last measurable concentration to the elimination rate constant.

Bioequivalence testing between the over-encapsulated Imitrex<sup>®</sup> 50 mg tablet (test treatment) and the non-encapsulated 50 mg tablet (reference standard) was performed using the two one-sided test procedure. In addition, 90% confidence interval test for the ratios between test treatment and reference standard was calculated. Statistical analysis of  $t_{max}$  was based on the standard non-parametric method devised by Koch.<sup>1</sup>

### RESULTS

The mean sumatriptan plasma concentration time profile is presented in Figure 1. The  $C_{max}$  was 32.7 ng/mL for over-encapsulated Imitrex<sup>®</sup> compared to 33.6 ng/mL for marketed Imitrex<sup>®</sup>.

Figure 1: Mean Sumatriptan Plasma Concentration Time Profile



The ratios of least square means (LSM) and 90% confidence intervals for the ln transformed parameters  $AUC_{last}$ ,  $AUC_{inf}$  and  $C_{max}$  for sumatriptan in plasma were within the 80-125% FDA acceptance range as summarized in Table 1. The median (range)  $t_{max}$  values for the over-encapsulated tablet and Imitrex<sup>®</sup> tablet were 1.75 (0.75-4.5) hours and 1.25 (0.5-4.5) hours, respectively. The non-parametric differences of the median  $t_{max}$  and 90% confidence interval for the difference was 0.375 (-0.125, 0.875).

### RESULTS (cont'd)

Table 1: Summary of Pharmacokinetic Parameters

Parameter	Marketed Imitrex <sup>®</sup> Tablet (n=26)	Over-encapsulated Imitrex <sup>®</sup> Tablet (n=26)	Ratio (Capsule/Tablet) LSM	90% Confidence Interval
$AUC_{last}$ (ng•hr/mL)	111.5 (105.0-118.5%)	111.0 (104.5-118.0%)	99.6	92.7-106.9%
$AUC_{inf}$ (ng•hr/mL)	116.6 (110.0-123.6%)	116.5 (109.9-123.4%)	99.9	93.3-106.9%
$C_{max}$ (ng/mL)	33.6 (30.0-37.6%)	32.7 (29.2-36.7%)	97.5	85.3-111.4%

### CONCLUSIONS

The over-encapsulated Imitrex<sup>®</sup> 50 mg Tablets were shown to be bioequivalent to the marketed Imitrex<sup>®</sup> 50 mg Tablets.

### REFERENCES

- G.G. Koch, The use of nonparametric methods in the statistical analysis of the two period change-over design, Biometrics, 28, 577-588, 1972.