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PAKAWADEE SERMSAPPASUK: PHARMACEUTICAL EQUIVALENCE AND BIOEQUIVALENCE STUDIES OF 100 MG SUSTAINED-RELEASE DICLOFENAC SODIUM TABLETS. THESIS ADVISORS: SUVATNA CHULAVATNATOL, Ph.D., AMPOL MITREVEJ, Ph.D., WINAI WANANUKUL, M.D., BOARD OF INTERNAL MEDICINE. 125 p. ISBN 974-664-998-1.

The objectives of this study were to determine pharmaceutical equivalence and bioequivalence of 100 mg sustained-release diclofenac sodium tablets (Voltaren SR 100, Abitren 100 and Remethan 100 R) presently available in Thailand and to evaluate in-vitro/in-vivo correlation between the rate of dissolution and bioavailability of these tablets.

The pharmaceutical equivalence study was assessed by comparison of dissolution rate and content uniformity between generic products (Abitren 100 and Remethan 100 R) and an innovator's product (Voltaren SR 100). The dissolution test was carried out firstly 2 hrs in 0.1 N HCl and 22 hrs thereafter in phosphate buffer, pH 6.8. The amount of the drug in a tablet was determined by content uniformity testing. It was found that generic products were not pharmaceutical equivalent to the innovator's product in terms of dissolution rate and content uniformity. Additionally, basic properties of tablets such as disintegration time, hardness, thickness and diameter were investigated for those brands. In disintegration testing, Remethan 100 R was disintegrated in gastric fluid TS at 0.86 ± 0.10 hr whereas Voltaren SR 100 and Abitren 100 were disintegrated in intestinal fluid TS at 2.50 ± 0.15 and 1.33 ± 0.13 hrs, respectively. The mean ± SD of hardness of Voltaren SR 100, Abitren 100 and Remethan 100 R were 12.8 ± 0.7, 12.6 ± 0.5 and 10.6 ± 1.2 Kp, respectively. For thickness, the mean ± SD were 4.48 ± 0.02, 4.46 ± 0.02 and 4.07 ± 0.04 mm, respectively, and for diameter were 9.23 ± 0.05, 9.20 ± 0.01 and 9.23 ± 0.05 mm, respectively.

Bioequivalence study was performed in 15 healthy Thai male volunteers. The study design was a single-dose, randomized, crossover study. Blood samples were collected prior to and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12 and 24 hrs after dosing. Diclofenac concentrations were determined by HPLC method. Mean ± SEM of pharmacokinetic parameters of Voltaren SR 100, Abitren 100 and Remethan 100 R were as follows: maximum plasma concentration ($C_{max}$) were 0.761 ± 0.098, 2.103 ± 0.149 and 3.793 ± 0.323 μg/mL, respectively, time to reach maximum concentration ($T_{max}$) were 6.25 ± 1.56, 3.07 ± 0.38 and 1.37 ± 0.16 hrs, respectively, and the area under the plasma concentration-time curve at 0-12 hrs ($AUC_{0-12}$) were 3.450 ± 0.305, 5.477 ± 0.367, 5.217 ± 0.249 μg·hr/mL, respectively. The pharmacokinetic parameters were tested for statistical difference by two-way ANOVA and Tukey's multiple range test. The results indicated that $C_{max}$ and $AUC_{0-12}$ of these generic products were significantly different from those of the innovator's product ($p < 0.05$). Bioinequivalence of the generic products to the innovator's product was demonstrated, 90% confidence interval of ratio of mean of $AUC_{0-12}$ and that of $C_{max}$ were not within 80-125%. Thus, the generic products should not be used interchangeably with the innovator's product.

Finally, comparative analyses of the pharmacokinetic parameters and the in-vitro release profiles were performed to assess in-vitro/in-vivo correlation. Only level C correlation between $C_{max}$ and time for 50% drug to be released ($T_{50\%}$) showed good correlation ($r^2 = 0.9970$). Therefore, the dissolution test was validated by the weakest level of in-vitro/in-vivo correlation.