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Prograf® 5 mg vs. Tacrolimus medis in healthy volunteers: A bioequivalence

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For FDA approval, bioequivalence of a generic version of Tacrolimus must be demonstrated in a randomized two-treatments, two-periods, two-sequences, single-dose crossover study in healthy adult volunteers. Currently there are at least 3 differents generic equivalent for Tacrolimus that are approved by the EMA and the FDA with a USA market share of nearly 50%. However the market share of generic immunosuppressive drugs in the Middle East region is still very low due to the reluctance of the physician to accept Tacrolimus generics, considered to be a narrow therapeutic window drug that are approved using the standard bioequivalence criteria of 80-125%. We here present a bioequivalence study of a new Tacrolimus generic, Tacrolimus medis 5 mg developed by Medis Tunisia batch number 12G3003 compared to Prograf® 5 mg batch number 7202 manufactured by Astellas Toyama Co., Ltd., Japan and HIKMA Pharmaceuticals, Amman-Jordan in healthy adult volunteers using the 90-111% criteria recommended for drugs with narrow therapeutic window. The study was, balanced, randomized, two-treatments, two-periods, two-sequences, single dose, crossover, comparative oral bioavailability study in healthy adult human volunteers. The study was carried out in accordance with the basic principles defined in the U.S. 21 CFR Part 312.20, the principles enunciated in the declaration of Helsinki (World Medical Association Declaration of Helsinki). Thirty six (36) non-smoking healthy as determined by medical history, volunteers, between the ages of 18 years and above were included. Following randomization using a computer software (pharma solution). The volunteers were given a single oral dose of 5 milligrams following a 12 hour fast with a wash out period of 7 days. Pharmacokinetics profile with blood levels at: 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 and 24 hours were performed following each dose. Tacrolimus plasma level was determined using an HPLC validated method (Transmedical For Life S.A.R.L. Beirut Lebanon) for accuracy, suitability, reproducibility, precision, long term stability and robustness. Physical examinations, hematology, urine analysis and serum chemistry tests were performed at screening and before dosing in each period and at end of the study. Volunteers were monitored for safety and adverse events throughout the study. Both products were bioequivalent at the entire pharmacokinetic parameters tested (Graph). The LSM were 95.31-101.21% for AUC, 94.65-101.11% for AUC0-inf, 97.15-100.02% for Cmax and 91.54-103.75% for half-life. Respectively all of which are within the EU and FDA approval limits (90-111%) indicating that the 2 products are equivalent and switchable.

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Confidence assessment of absorption/disposition modeling within PBPK modeling paradigm

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The objective of this study was to assess the accuracy and precision of the Simcyp ADAM model to predict from a 'bottom-up' approach, the human absorption component within a physiologically-based pharmacokinetic profile. 21 literature compounds with respective *in vitro* Caco-2 permeability and aqueous solubility limits were inputted in ADAM along with clinical values for volume of distribution and clearance. In this fashion, we directly test the absorption component predicted by ADAM within the PBPK model. Simulated pharmacokinetic parameters (Tmax, Cmax and AUC0-τ) were compared to clinical parameters. With respect to Tmax predictions, 58% of the simulations had an error of less than 2-fold. For the compounds with error >2-fold, 75% were over-predicted. Predictions of Cmax showed that 48% of the simulations had an error of less than 2-fold. For the compounds with error >2-fold, the majority (90%) of the Cmax values were under-predicted. Similar to this, 43% of the AUC0-τ predictions had an error of less than 2-fold. For the compounds with error >2-fold, 83% were under-predicted. Taken together, caution must be exercised in the utilization of a 'bottom-up' PBPK model approach using limited *in vitro* permeability data and/or solubility limits to simulate the exposure in human.

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