QUANTITATIVE DETERMINATION OF PERINDOPRIL AND ITS ACTIVE METABOLITE PERINDOPRILAT IN HUMAN PLASMA BY HIGH PERFORMANCE LIQUID CHROMATOGRAPHY COUPLED TO TANDEM MASS SPECTROMETRY (LC/MS-MS)

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Perindopril is an angiotensin-converting enzyme inhibitor used in the treatment of hypertension and heart failure. It is a prodrug which is hydrolyzed in vivo to its active metabolite perindoprilat following oral administration.

In the study, LC/MS-MS system was used for the quantitative determination of perindopril and perindoprilat by means of method which was developed in human plasma and validated originally in Novagenix Bioanalytical Drug R&D Center. Perindopril and perindoprilat was extracted from human plasma by solid phase method and calibration curve was obtained with 0.1-200 ng/mL (for perindopril); 0.5-20 ng/mL (for perindoprilat) concentration interval. LC/MS-MS system with Thermo Hypersil Hypurity C18 (150.0 x 3.0 mm ID, 5 um), analytical column and Alltech Repl. Filter for Rheodyne (5 mm) column filter were used to perform experimental procedures.

Retention times of perindopril, perindoprilat and lisinopril (used as internal standard) were obtained as 0.95, 0.95 and 0.99 minute, respectively. During analysis any interferences were not observed. Absolute and relative recovery results were 53.08-51.9% and 89.2-75.81% for perindopril and perindoprilat, respectively. Correlation constants were calculated as 0.99931-0.99486 for perindopril and 0.99763-0.97293 for perindoprilat after 5 day validation study. Quality control samples used in validation study have batch to batch and within batch mean accuracy ranges are 114.580-90.467% and 123.539-77.697% for perindopril; 99.565-91.768% and 119.176-83.114% for perindoprilat. Precision values (CV%) of those parameters for perindopril and perindoprilat were 19.994-9.107%, 19.069-0.998%; 19.701-8.128%, 27.991-2.791% respectively. Batch to batch statistics for mean accuracy ranges of calibration standard samples were 118.271-85.37% (for perindopril) and 110.226-93.096% (for perindoprilat); precision values are (CV%) 13.883-3.135% (for perindopril) and 14.161-3.202% (for perindoprilat). Determined results were in the range of validation parameters pointed out in FDA Guidance 2001.

Clinical study was carried out with 24 healthy volunteers to determine the pharmacokinetics profile of two different brand named drug which are available actually in national drug market. Originally developed and validated method was simple, sensitive, rapid and suitable for the analysis of perindopril and perindoprilat in blood samples taken during clinical studies. As a result, our method is appropriate and useful for the determination of perindopril and perindoprilat in human plasma in terms of bioequivalence studies.

REFERENCES