Identification, Synthesis and Characterization of Process Related Impurities of Benidipine Hydrochloride

Esen Bellur Aticia,*, Bekir Karlığaa

aDeva Holding A.Ş., Čerkezköy-2 Production Plant, Karaağaç Mh. Fatih Blv. No: 26 Address No: 2278035833 Kapaklı, Tekirdağ, TURKEY

*Corresponding author e-mail addresses: ebellur@deva.com.tr, esenbellur@yahoo.com

Benidipine hydrochloride, (±)-(4R*)-3-(R*)-1-benzylpiperidin-3-yl 5-methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate hydrochloride, is a racemic mixture of two isomers RR-(−) and SS-(+) and called α-benidipine hydrochloride. It is used as an antihypertensive agent and long-acting calcium antagonist, and synthesized for commercial use as a drug substance in highly pure form. During the synthetic process development studies of benidipine, process related impurities were detected. As per the general guidelines recommended by International Conference on Harmonisation (ICH)1-2 to qualify the drug substance, the amount of acceptable level for a known and unknown related compound (impurity) should be less than 0.15% and 0.10%, respectively. In order to meet the stringent regulatory requirements, impurities should be identified and their amounts should be controlled carefully. The impurities observed on HPLC analyses during the process development studies of benidipine were identified by LC-MS, synthesized, characterized (1H, 13C, DEPT NMRs, MS, IR, and DSC) and mechanisms of their formation have been discussed in detail. After all standardization procedures, they were used as reference standards for analytical studies. In addition, a separate HPLC method was developed and validated for detection of residual 1-benzylpiperidin-3-ol (Ben-2), which is used during benidipine synthesis and controlled as a potential process related impurity. As complementary of this work, stress-testing studies of benidipine was carried out under specified conditions and a stability indicating UPLC assay method was developed, validated and used during stability studies of benidipine.3

References: