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BRILIQUE /TICAGRELOR/ SAFETY PROFILE RELATED TO THRESHOLD OF TOXICOLOGICAL CONCERN /TTC/ FOR IMPURITIES UL127, UL133,UL134 AND UL 111

MAJOR OBJECTIONS OF EVALUATION DOCUMENTATION FOR GRANTING MA PROCEDURE BY MEDICINES AND MEDICAL DEVICES AGENCY OF SERBIA-ALIMS

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Evaluation of risk for identification genotoxic potential in ticagrelor, genotoxic potential of impurities that appear in proces of synthesis raw material,intermediers or as degradation product, respectively, is important safety parametar for evaluation suspected and unsuspected adverse reactions/events that can be detected after putting drug on the Market.On December 2010., EMA approved Brilique®,AZ, 90mg film-coated tablets co-administered with acetylsalicylic acid, for the prevention of thrombotic events (CVS death, MI and stroke) in patients with ACS (unstable angina, non ST elevation M I or ST elevation MI including patients managed medically, and those who are managed with percutaneous coronary intervention or coronary artery by-pass grafting. for the prevention of atherothrombotic events in adults with ACS.Ticagrelor, cyclopentyltriazolopyrimidine is a selective and reversible binding adenosine diphosphate receptor antagonist acting on the P2Y12 ADP-receptor that can prevent ADP-mediated platelet activation and aggregation.The benefits with Brilique are its ability to rapidly and reversibly inhibit platelet aggregation and through this to prevent thrombotic events in patients with acute coronary syndromes. The most common side effects are dyspnoea, contusion and epistaxis.The Applicant did not perform immunotoxicity studies.Impurities UL127, UL133 and UL134 were above the qualification level of 0.15% but non-genotoxic. Applicant did not perform the animal qualification study, but it was showed by extensive comparison of studies with different amounts of these impurities that it is highly unlikely that especially UL127 but also UL133 at the proposed limits in the product pose a significant risk for toxicity in humans. Several of impurities have been tested for genotoxicity.The impurities AZ13232761 and C3RO were found positive but kept below the threshold of toxicological concern. In Module 3 CTD, ALIMS'assessor detected gentotoxic potential of impurity U 111 for which there was no explanation.Max daily dose of ticagrelor is 180 mg/day.Calculated, TTC of acceptable risk of daily intake of gentoxic impurity for this dose is: 1.5µg/day .Using this limit, gentoxic limit for this ticagrelor dose would be 8µg/day. According to EU Guidelines: CPMP/SWP/5199/02,CHMP/QWP/251344/2006 and ICH Q3A, Applicant was requested to submit additional PT report.The reason was the fact that this part of intermedier product of ticagrelor, *in vitro,* caused dose-dependent increase of chromosomal aberation frequency in human lymphocites . **CONCLUSION**: *In vivo and in vitro* results evaluation of additional PT related to genotoxic impurity U 111 (received on 19/01/2012), pointed out that maximal tolerated dose of 1000mg/kg of U 111 demonstrated important toxicological potential in rats during performing micronucleus test (study 1886QR).U111 is a part of intermedier development product and as it was found that in later proces of batch development for getting active substance-ticagrelor, U 111 could not be detected, nor in final intermedier, nor in active substance,Applicant exclaimed that there was no need to investigate further presence and potential toxicity of U 111 impurity in the final product.ALIMS assessor concluded that the this PT could be accepted, and that further proces for getting MAA can be continued, with suggestion for establishing close monitoring of performing RMP PhV after putting drug on the Serbian market.