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Short communication

Adjusted indirect comparison as a method for justifying absence of drifting in the bioavailability of FDC products

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Introduction

Development of generic fixed dose combination (FDC) products has increased industry interest due to its advantages in disease management, patient compliance, and market benefits. According to the EMA FDC guideline (European Medicines Agency, 2017), for a generic FDC submission, the innovator has already established the first bridge between the FDC and co-administration of the mono-components, and the generic sponsor only demonstrates the second bioequivalence (BE) bridge between generic and innovator FDCs. However, this approach can trigger regulatory authorities' concerns and require justification why "drifting" of bioavailability (BA) is not considered relevant. Adjusted indirect comparison (AIC) is a statistical approach which can be used to provide this evidence.

Justification for absence of drifting of bioequivalence

During the registration procedure of Alkaloid`s FDC product, which was compared with reference FDC only, a letter of deficiency was received to provide justification why "drifting" of BA is not considered relevant and hence why the original demonstration of efficacy and safety can be applied to the generic product. To provide the response we conducted a statistical analysis "adjusted indirect comparison" to investigate the magnitude of potential drifting. Although there is no consensus on the statistical approach to be used, according to our findings, AIC assuming homogeneous variances is the most effective approach for this matter (Gwaza et al., 2012; Pejčić et al., 2019). The following pharmacokinetics (PK) bridges were considered:

Pharmacokinetic bridge 1: The reference FDC product vs concomitant administration of mono-components treatment A and treatment B. For this bridge, data was used from the study conducted for the registration of the reference FDC. As this study was designed for the approval of the original FDC, the direction of comparison pairs included FDC vs mono-components; Hence, in order to perform the indirect comparison to evaluate the drifting bioavailability between the test FDC (our test) and the mono-components, the BE data from PK bridge 1 should be reversed: Concomitant administration of treatment A and treatment B vs reference FDC product.

Pharmacokinetic bridge 2: Comparative bioavailability between the test FDC (our test) vs the reference FDC. Data for this bridge has been taken from our BE study for Alkaloid`s application of the test FDC.

Adjusted indirect comparison

Reversed data from PK bridge 1- Concomitant administration vs. FDC (reference product) and PK bridge 2 - test FDC vs reference FDC has been used

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to perform the AIC to evaluate the extension of drifting bioavailability. As stated earlier, the homoscedastic approach (assuming homogenous variances) was employed to calculate the width of the confidence interval of the AICs.

Discussion

In summary, the AIC point estimates of Treatment A component were 113.88% and 108.44% for C_{max} and AUC_t, respectively, with the corresponding 90% CIs contained within the conventional acceptance range of 80%-125%, demonstrating comparative bioavailability between the test FDC and the concomitant administration of mono components. Regarding Treatment B, the AIC point estimates were 118.53% and 106.72% for C_{max} and AUC_t, respectively, however the corresponding 90% CI of C_{max} was outside the conventional 80-125% range, with the upper value of 131%. This slight deviation has been observed in other works by several authors using the same approach to evaluate the interchangeability of different authorized generic products (Gwaza et al.,2012; Herranz et al.,2013; Pejčić et al.,2019).

Due to the pooled estimation of variability, the confidence interval of the AIC point estimates calculated by the homoscedastic approach was generally wider, thus deemed the most conservative method in this matter (Pejčić et al.,2019). According to a meta-analysis, which assessed the statistical discrepancy between the direct and indirect comparisons, the standard error of the adjusted indirect estimate can be inflated to approximately 1.41 times larger than that of the direct estimate. Additionally, the indirect estimates may be underpowered as the original BE studies were designed to have just enough power (e.g., 80 or 90%) to show equivalence with the initial reference product, not to conduct AICs (Gwaza et al., 2015). From a pharmacokinetic point of view, C_{max} was observed to have greater variability than AUC_t - i.e., for Treatment B, the ISCV of C_{max} was reported to be about 25%, which is higher than ISCV of its AUC_t and ISCV of Treatment A (~ 10%) - and demonstrates a wider confidence interval across different AIC statistical methods (Gwaza, L. et al., 2012). Therefore, due to the reduced precision, limited statistical power, and variable nature of C_{max}, several authors have proposed to use a widened acceptance range for the 90% CI of C_{max} (Gwaza et al.,2012, 2015; Pejčić et al.,2019). For instance, it is recommended to apply the BE acceptance criterion employed in Canada for C_{max}, where only the point estimate of C_{max} needs to be contained within the 80–125% range, or use a wider confidence interval (e.g., ±25%, i.e., 75-133%) for AIC, especially with drugs for chronic use and a wide therapeutic range, where a slightly larger difference is still considered clinically equivalent (Gwaza et al., 2012, 2015). If the widening criterion recommended by the experts is taken into consideration, the AIC point estimate values for Treatment B- C_{max} and its corresponding 90% CI under fasting conditions are within the acceptance range, discarding the possibility for BA “drifting”.

Conclusion

In conclusion, after taking the aforementioned arguments and the results of AIC into account, it could be considered that a potential “drifting” of bioavailability between the generic FDC - subject of the application - and the concomitant administration of individual components is not expected

References

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