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EFFICACY WORKING PARTY (EWP)

Questions & Answers on the use of Cocktail studies for investigating *in vivo* drug interaction potential

Question

How can so called Cocktail studies be used for investigations of *in vivo* drug interaction potential?

Answer

Background

During the last decade, use of cocktail studies has become a more common tool for investigating a drug's interaction potential *in vivo*. A cocktail study is a study where a number of *in vivo* probe drugs for enzymes (and transporters) are administered together for simultaneous assessment of enzyme/transport activities before and during treatment with another drug. The approach is used for investigating the induction potential *in vivo*, as induction generally affects multiple enzymes and transporters, as well as for studying inhibition of enzymes or transport proteins. Concerns have been raised regarding the validity of cocktail studies, how cocktails should be composed and if the results can be extrapolated to other drugs. The intention of this document is to clarify the EWP view on these issues.

Composition of satisfactory drug cocktails for use in interaction studies

The cocktail should consist of safe, validated probe drugs for the specific enzymes intended to be studied. Preferably, only one enzyme, or one transporter, should be involved in the elimination of each of the included probe drugs. If a second enzyme is catalysing metabolism of the parent drug, its contribution to total clearance should be very small (<10%). The cocktail of probe drugs should have been validated. The validation could have been performed by the applicant or have been published in the scientific literature. The validation of the cocktail includes a validation of the included probe drugs *per se* by investigation of the effect of a selective potent enzyme (or transporter) inhibitor on the pharmacokinetics of the probe drug. In addition, it should also have been verified that the probe drugs used in the cocktail do not affect each others pharmacokinetics. The doses used should preferably be the doses used in the validation. Deviations from this should be justified.

Pharmacokinetic parameters

The use of a cocktail study and conclusions that can be drawn from such a study depends on the objectives of the study and the design and conduct of the study. As in all interaction studies, the dose and duration of the investigational drug should be sufficient for estimating the maximum induction and/or inhibition achieved at a clinically relevant dose. When the objective of the study is to quantify the effect on different enzymes or transporters, it is recommended to determine complete AUCs for the probe drugs in order to estimate effects on (oral) clearance. Simpler ratios such as metabolite to parent drug ratios in urine are usually not a satisfactory parameter as results may have more confounding factors and as the magnitude of

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an effect is difficult to translate into inhibition or induction potency and to treatment recommendations in the SPC. Additional conventional interaction studies with a probe drug measuring drug clearance may in that case be needed.

Extrapolating results from cocktail studies

If satisfactorily performed, the results of the cocktail studies could be extrapolated to other drugs and to treatment recommendations of the SPC. The extrapolation could then be performed in the same way as from *in vivo* studies using only one probe drug.