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Guideline on the investigation of interactions in the gastrointestinal tract

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Guideline on the investigation of interactions in the gastrointestinal tract

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Executive summary

This guideline provides recommendations with regards to situations where the absorption of a drug from a medicinal product is altered by extrinsic factors in the gastrointestinal tract. Recommendations are provided on design, conduct and interpretation of in vitro and clinical absorption-related interaction studies. Treatment recommendations based on the clinical relevance of the interactions and the possibility to make dose adjustments or treatment monitoring are addressed.

1. Introduction (background)

Patients are often prescribed more than one medicinal product and interactions between the medicines (drug-drug interactions (DDI)), sometimes lead to adverse events or alternatively can partially or completely negate treatment efficacy. The ageing European population, in which polypharmacy is more frequent, increases the likelihood of such interactions. The aim of interaction studies performed on new medicinal products is to gain knowledge of how the new medicinal product affects the safety and efficacy of other medicinal products and vice versa.

Interactions in the upper gastrointestinal tract can result from extrinsic factors affecting the absorption of orally administered medicinal products. In addition to gastric pH changes, food intake, product formulation and formation of complexes or chelates can affect the intestinal absorption of a drug and this may have consequences for efficacy or safety.

On 30 November 2024, ICH M12 Guideline on drug interaction studies (EMA/CHMP/ICH/652460/2022) formally superseded EMA Guideline on the investigation of drug interactions Revision 1 (CPMP/EWP/560/95/Rev. 1 Corr. 2**) which had been in effect since 1 January 2013. ICH M12 focuses on pharmacokinetic drug interactions mediated by metabolic enzymes and drug transporters and as such, does not address drug interactions mediated in the upper gastrointestinal part to the same extent that the EMA guideline did. However, the latter interactions are an important component of evaluating a new drug’s interaction potential.

This document, therefore, describes the investigation of absorption related interactions affecting the investigational drug through extrinsic factors in the gastrointestinal tract. This includes advice on study design, presentation of study results and translation of these results to treatment recommendations in the labelling of the medicinal product.

2. Scope

The scope of this guideline is to provide advice and recommendations on how to evaluate the absorption interaction potential of a new medicinal product in the gastrointestinal tract e.g. due to gastric pH change, formation of complexes or chelates and investigation of food effect. The recommendations may also be applicable to changes in product formulations or method of administration.

- The guideline mostly describes interactions with the new medicinal product as an object, however, for some aspects (e.g. effect on gastric emptying, effect of excipients) the potential influence of the new medicinal product on the exposure of another medicinal product is also addressed.
- The guideline primarily applies to systemically acting active substances that need to be absorbed to exert their pharmacological effect. Many of the recommendations can also be considered for medicinal products that are locally applied and locally acting in the

gastrointestinal tract, as many of the interactions described are also likely to affect the concentration of the active substance in the gastrointestinal tract.

- The guideline covers mainly orally administered medicinal products, but some aspects (e.g. effect of gastric emptying and motility) may be applicable also to other routes of administration.
- Drug interactions mediated by metabolic enzymes and drug transporters in the intestinal cells are not included in this guideline as these are covered in ICH M12.

3. Legal basis and relevant guidelines

This guideline should be read in conjunction with the introduction and general principles (4) of the Annex I to Directive 2001/83/EC as amended, as well as European and ICH guidelines for conducting clinical trials, including

- ICH M12 Guideline on drug interaction studies (EMA/CHMP/ICH/652460/2022)
- EC SmPC Guideline (London, 20 November 2008)
- Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (EMA/CHMP/QWP/545525/2017 Rev. 2)
- Guideline on quality of oral modified release products (EMA/CHMP/QWP/428693/2013)
- Guideline on the clinical evaluation of modified release dosage forms (EMA/CHMP/EWP/280/96 Rev1)
- Guideline on pharmaceutical development of medicines for paediatric use EMA/CHMP/QWP/805880/2012 Rev. 2
- Reflection paper on the pharmaceutical development of medicines for use in the older population EMA/CHMP/QWP/292439/2017

4. Investigation of interactions in the gastrointestinal tract

The investigation of absorption interactions serves to identify situations where the solubility, dissolution or absorption of a drug is altered by extrinsic factors leading to a change in the rate and/or extent of drug absorption to an extent which may affect the efficacy or safety of the drug. Studies of the effect of food, increased gastrointestinal pH, complex binding, gastrointestinal motility, and modified intestinal active transport should be considered.

General principles regarding DDI study design and evaluation as well as reporting and interpretation of clinical DDI results presented in ICH M12 are generally applicable also for the evaluation of interactions in the gastrointestinal tract.

4.1. Effects of food intake on the pharmacokinetics of the investigational drug

Food changes temporarily the physiological conditions in the human gastrointestinal tract by increasing the gastric pH, slowing the gastric emptying, increasing luminal bile salts and enzymes and increasing intestinal and hepatic perfusion. In this way, food may affect the rate and extent of absorption of a drug, e.g. by slower release from the stomach, by changes in solubility, in contact with enterocytes and in first pass-effect.

The effect of food intake on the rate and extent of absorption of the active substance of an orally administered medicinal product should be investigated as early as possible during drug development to optimise dose finding and to ensure appropriate food recommendations in phase 3 clinical studies. In

general, intake of a medicinal product in relation to meal times should aim at minimising variability of exposure and obtaining safe and efficacious exposure, without causing unnecessary restrictions for the patient. Another common reason for recommending intake with food is gastrointestinal tolerability issues.

Although it is recommended to evaluate the food effect early in clinical development, the food effect of the commercial formulation also needs to be addressed if formulation changes have been made. The food effect of the commercial formulation should be investigated in a food effect study or it needs to be adequately justified that a similar food effect is expected e.g. based on the nature of the formulation changes performed, the evaluated food effect of earlier clinical development formulations and the solubility of the drug and bioavailability of the active substance.

In general, the bioavailability of the active substance of a new medicinal product should be compared under the most extreme situations i.e., in fasted state and with a high-fat meal. When a clinically significant effect of a high-fat meal is found, further food interaction studies may be needed (see section on *Study design*). On the other hand, if there is no clinically relevant effect of a high-fat meal on the absorption of the active substance compared to fasted conditions, it can generally be assumed that other types of meals will not affect the absorption of the active substance.

Study design

In a standard cross-over food effect study, a single dose of the investigational medicinal product is administered with 150-250 ml of water after a 10-hour fasting period either without food, or 30 minutes after intake of a meal has started. Thereafter, the subjects should refrain from food for at least 4 hours after drug administration and all food intakes should be standardised for at least 12 hours post-dose. The recommended composition of a high fat meal and a moderate fat/calorie meal are described below. In case a single dose study cannot be performed in healthy subjects or patients, a multiple dose, steady-state study with administration of doses of the medicinal product under fasting and fed conditions, respectively, may be satisfactory.

When a clinically significant food effect is found (section 5), further food interaction studies may be warranted to support recommendations regarding type of food and the timing of drug administration in relation to food intake.

Dose

Usually, a therapeutic dose is evaluated in the food effect study. Any dose in the therapeutic dose range can be selected for the food effect study when the pharmacokinetics is dose proportional. The results obtained with one dose can be extrapolated to the other doses. If the pharmacokinetics is non-linear with less than dose-proportional increases in the AUC or Cmax when increasing the dose, it is recommended to investigate the effect of food on both the highest and lowest doses of the therapeutic range. If the pharmacokinetics is non-linear with larger than dose-proportional increases, studying the food effect with the highest dose is generally sufficient.

Strengths

For the food effect study the clinical dose range rather than the strengths are considered. In rare cases that the various strengths deviate markedly in composition, food effect of more than one strength may need to be investigated. In such case, excipients, availability of pharmacokinetic data with various strengths and whether a food effect has been observed on other strength(s), solubility of the drug and linearity of the pharmacokinetics should be considered. The strengths that deviate most in composition should be selected if an additional food effect study is deemed necessary.

Standardised meals

The high fat meal should contain 800-1000 kcal with 500-600 kcal from fat and 250 kcal from carbohydrates. A standard test high fat meal can be composed of: two eggs fried in butter, two strips of bacon, two slices of toast with butter, 120 ml of hash brown potatoes and 240 ml of whole milk. Substitutions in this test meal can be made as long as the meal provides similar amounts of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity.

A moderate fat/calorie meal can contain approximately 400-500 kcal with fat contributing to ca. 150 kcal.

Other considerations

When the effect of food cannot be studied in healthy subjects but has to be studied in patients, the type of meal recommended for the target patient population or a moderate-fat meal can be considered.

If physicochemical properties of the drug and in vitro data indicate that complex binding with bivalent cations might become an issue in vivo, the need for a food interaction study with a dairy food product (calcium-rich) should be considered. This should be addressed especially when the medicinal product is intended for newborns and infants whose diet is different than adults (e.g. 100% milk-based in newborns). See also section 4.5.

Some foods or beverages (e.g. grapefruit juice, coffee) have the potential to inhibit or induce intestinal enzymes or transporters and thus can affect the oral bioavailability of an investigational drug. When the mechanism of such interaction is known, interactions with this type of food are usually not investigated in a clinical drug interaction study, but avoidance of this type of food might be recommended in the product information. Consumption of these products prior to and during a food effect or drug drug interaction study is usually excluded or limited.

For modified release formulations, advice regarding the investigation of the effect of food or alcohol on drug release are given in guidelines specific for these formulations (see EMA Guideline on pharmacokinetic and clinical evaluation of modified-release dosage forms (EMA/CHMP/EWP/280/96 Rev1)).

In many cases, it is desirable to be able to administer an oral formulation in alternative ways to patients with difficulties to swallow. For example, a drug product could be opened, crushed, disintegrated in liquid or sprinkled on soft food or administered via a feeding tube. In order to include information on these alternative ways of handling the medicinal product in the Summary of Product Characteristics, supporting data is usually needed. Generally, an in vivo relative bioavailability study is expected unless justified. A justification may include a discussion on Biopharmaceutics Classification System-class, dissolution rate of drug product or available bioequivalence data on other oral formulations and the therapeutic window. The bioavailability study should reflect the intended administration conditions for both the crushed/opened and intact formulation. In addition, quality data should be provided, e.g. to demonstrate a lack of physicochemical interactions between soft food or liquid and the drug product (Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials, EMA/CHMP/QWP/545525/2017 Rev. 2; Guideline on pharmaceutical development of medicines for paediatric use, EMA/CHMP/QWP/805880/2012 Rev. 2; Reflection paper on the pharmaceutical development of medicines for use in the older population, EMA/CHMP/QWP/292439/2017).

4.2. Gastric pH: drug-drug interaction with acid reducing agent

Drugs with in vitro solubility that is markedly pH dependent within the physiological pH range (between 1.2 and 6.8), may have their absorption affected by concomitant administration of drugs which change the gastrointestinal pH. If in vitro data indicate that pH-dependent solubility may impact the absorption

of the investigational drug, an in vivo DDI study should generally be performed with an appropriate acid reducing agent (ARA). The potential for a pH-dependent DDI should preferably be evaluated early in clinical development to ensure subsequent efficacy and safety for patients.

Drugs at the highest risk for a clinically relevant interaction with ARAs are weak-bases with low aqueous intrinsic solubility, where increased gastric pH (i.e. pH>4) can decrease solubility and absorption, potentially leading to loss of efficacy.

Absorption of weak-acidic drugs with low solubility at low pH (~1.2) and increased solubility at higher pH may also theoretically be affected by co-administration with an ARA. However, there are currently limited data and the observed effects are generally minor and not considered clinically significant under most circumstances. Therefore, for weak acids the need for a clinical DDI study should be evaluated based on the drug safety profile.

In general, if the drug has pH dependent solubility but exhibits high solubility across the physiological pH range, a DDI study with an ARA is not required. If the tested drug is a modified release formulation with a pH-sensitive release mechanism, gastrointestinal pH modification may affect the drug release and consequently the drug absorption. Further recommendations on in vitro and in vivo investigations to conduct are provided in EMA Guideline on quality of oral modified release products (EMA/CHMP/QWP/428693/2013) and EMA Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CHMP/EWP/280/96 Rev1), respectively.

Considerations for study design

An in vivo DDI study quantitatively determines the DDI potential of the investigated drug with an ARA. The aim of the study could be either to evaluate the worst-case scenario, or to support alternative dosing regimens to avoid clinical drug-drug interactions. If the purpose of the study is to evaluate the worst-case magnitude of a DDI, the investigated drug and the ARA should be administered when the ARA effects are most pronounced. On the other hand, if the purpose is to support an alternative dosing regimen to avoid clinical DDI, then staggered administration should be applied.

Generally, the ARA should be administered at the highest recommended dose under therapeutic conditions with a sufficiently long duration to reach the maximal pharmacodynamic effect. Usually, single dose administration of the investigational drug is adequate unless the absorption is modified following repeated administrations, or if the study is conducted in patients in whom a single administration is not adequate.

The interaction study of the investigational drug with an ARA should be conducted under the prandial conditions consistent with the intended clinical use. For investigational drugs intended to be administered in a fasted state, drug interaction studies should thus be conducted under fasted conditions. Conversely, if the investigational drug is intended for administration with food, studies should be conducted under fed conditions using a moderate fat/calorie meal to align with clinical practice.

If the investigational drug is to be administered regardless of food intake, studies should still be conducted under fasted conditions, as this represents the worst-case scenario for absorption. For several drugs the impact of ARAs on the absorption is considerably less under fed conditions compared to fasted conditions. When there is a clinically relevant effect of an ARA on the absorption of an investigational drug under fasted conditions and the drug can be administered with and without a meal, applicants are encouraged to evaluate the effect of ARAs also under fed conditions.

Selection of the ARAs to be used in the in vivo study should consider the aim of the study, the ARA's properties, including its onset and duration of action, the extent of acid secretion inhibition, and the

enzymes involved in its metabolism. Specific considerations for the common pharmacological classes are provided below.

- Proton pump inhibitors

Proton pump inhibitors (PPIs) are the most commonly prescribed ARAs. PPIs irreversibly bind to H^+-K^+-ATPase thereby reducing gastric acid production. PPI's effect on gastric pH is dose-dependent and is more pronounced and lasts longer than the effect of H2 antagonists. The baseline gastric acid secretory capacity may not be restored for up to 24–48 h after discontinuing PPI therapy.

In the DDI study, the PPI should be administered for at least 4 days to reach pharmacodynamic steady state. The magnitude of increase of gastric pH and its duration over 24 hours is dependent on the selected PPI and the dose applied. Choice of PPI, dose and timing of dosing between PPI and the medicinal product should be justified.

Additionally, if the investigational drug is a CYP2C19 substrate, it should be considered that many proton pump inhibitors (e.g. omeprazole) are CYP2C19 inhibitors.

- H2 antagonists

H2 antagonists compete with histamine for the H2 receptor. In a DDI study, H2 antagonists should be administered at the therapeutic dosing regimen. Given the rapid onset of action, usually gastric pH is increased 2h post-dosing, and the effect lasts up to approximately 12h, multiple administration is not required to obtain a maximal increase in gastric pH. Hence, a single dose, cross-over study of the new medicinal product with and without H2 antagonist with justified timing between administration of the medicinal product and the H2 antagonist is adequate.

It should be noted that some H2 antagonists are weak inhibitors of some CYPs isoforms, and/or transporters.

- Antacids

Antacids are cationic bases that increase intragastric pH by neutralisation of local acidity. Their onset of action is fast but also short-lived. The timing of the antacid and the investigational drug administrations should be carefully considered.

Given the salt nature of antacids, possible complex binding with the investigational drug might occur depending on the physicochemical properties of the investigational product.

Study results interpretation

DDI study results obtained with an ARA may only be extrapolated within the same pharmacological class. However, if an adequate DDI study conducted with a PPI demonstrates the absence of a clinically significant interaction, extrapolation of this finding to the other ARA classes is considered acceptable. Given the pronounced and prolonged effect of PPIs on gastric pH elevation, well-performed PPI studies are regarded as a worst-case scenario for assessing potential interactions with ARAs.

In cases where a study with a PPI indicates a clinically significant alteration in the exposure of the investigated drug, DDI mitigation strategies are encouraged. Further investigation with H2 antagonists or antacids is recommended to support alternative dosing regimens to potentially avoid clinical drug-drug interactions.

Modelling and Simulation approach

In some cases, the population pharmacokinetic modelling analyses of data from the pivotal clinical trials can be used to gain some information on a potential ARA-interaction, provided that a sufficient number of subjects have received ARAs in the clinical trials. Information on duration of ARA

administration should be documented and preferably also information on dose, time of administration as well as prandial state. Whereas time of administration of a PPI might be less critical due to its prolonged effect, inclusion of antacids and H2 antagonists as covariates in the population pharmacokinetic analysis is only possible when timing of administration of the drug in relation to intake of ARAs is well documented. The analysis should preferably be pre-specified, and a stratified covariate analysis, based on the pharmacological class of ARA, on the effect of the ARA on the pharmacokinetics of the drug is performed. Pharmacokinetics of subjects without co-medication with any ARA should be compared to the individual ARA pharmacological classes. ARAs of the different pharmacological classes should not be pooled.

Physiologically based pharmacokinetic modelling or semi-mechanistic absorption models may also be used in some cases, provided that the model has been adequately qualified for the appropriate context of use (see ICH M15 Guideline on general principles for model-informed drug development (EMA/CHMP/ICH/496426/2024); Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation (EMA/CHMP/458101/2016)).

4.3. Gastric emptying or intestinal motility

Certain drugs (e.g. opioids, GLP-1 receptor agonists) and excipients (e.g. polyols) are known to affect gastric emptying or intestinal motility and may thus affect the rate and extent of absorption of concomitantly administered drugs. This is particularly relevant for drugs with a narrow therapeutic window or for medicinal products for whose early onset of action is of clinical relevance. It may also be relevant for modified release formulations or drugs with a limited physiological absorption window, marked permeability limited absorption or significant C_{max} related effects.

If the investigational drug affects the gastrointestinal motility or gastric emptying, the interaction potential should be considered and, if indicated, the effect should be studied on relevant drugs (e.g. paracetamol as probe substrate in case of effects on gastric emptying). It should be noted that effects on the gastrointestinal motility are often due to a systemic effect and may be caused also by parenterally administered medicinal products e.g. GLP-1 receptor agonists.

4.4. Excipients

Excipients, such as diluents, fillers, binders, lubricants, coatings, solvents, flavouring and dyes, are often inert substances used to manufacture a reproducible, stable drug product. However, some excipients can significantly influence the absorption characteristics of drugs through mechanisms such as an impact on solubility, dissolution or stability, a change in intestinal permeability (including transporters), modulation of the gastrointestinal motility, or site-specific delivery of a drug.

Effect of an excipient on concomitantly used medicinal products

Widely used excipients such as macrogols, polysorbates, cyclodextrins, sodium laurilsulfate, macrogolglycerol ricinoleate and tocofersolan, are used to improve the solubility and dissolution of a drug and thus improve absorption of the drug. Whilst improving the absorption of the drug of interest, the excipient may inadvertently impact the drug absorption of concomitantly administered medicinal products. Also sugar-alcohols such as mannitol and sorbitol, which are frequently used as sweeteners to mask poor taste of the active substance, are known to affect the absorption of drugs (see section 4.3). The risk that a given excipient will influence the absorption of another co-administered drug should be assessed mechanistically by considering:

- the amount of excipient used,
- the mechanism by which the excipient may affect absorption,

• absorption properties (rate, extent and mechanism of absorption of the concomitantly administered drug).

For most commonly used excipients, literature data describing the potential impact on the absorption of drugs is expected to be sufficient to provide relevant information in the Summary of Product Characteristics, when needed. However, if the risk of a clinically relevant effect of the excipient on the absorption of concomitantly used drugs cannot be estimated using other data, an in vivo interaction study is recommended.

Distinct function of excipient to increase absorption of the investigational drug

Sometimes an excipient is claimed to have a more distinct function on the absorption of a drug resulting in a specific formulation characteristic, e.g. salcaprozate sodium as absorption enhancer for peptides or tartaric acid to create a micro-acid environment in the stomach while the gastric pH is increased by ARAs. The mechanism by which such an excipient is expected to enhance the bioavailability of the investigational drug should be discussed and a comparative pharmacokinetic study with and without the excipient is recommended to demonstrate the impact of the excipient on the bioavailability of the drug. The design of the study with regard to the use of fasting and/or fed conditions depends on the dosing instructions in the Summary of Product Characteristics.

4.5. Complex formation

Other mechanisms of interference with drug absorption, such as complex binding should also be considered. For example, simultaneous administration of multivalent cation-containing drugs and mineral supplements (e.g. calcium, magnesium, aluminium, iron) or polymeric phosphate binders (e.g. sevelamer or lanthanum carbonate), reduces the absorption of many orally administered drugs including some antibiotics.

If physicochemical properties of the drug and in vitro data indicate that complex binding might become an issue in vivo, an in vivo interaction study should be considered. Also, a time interval between administration of the two medicinal products so that the interaction is minimal or not present should be proposed based on in vivo data or other justification.

4.6. Enterohepatic recirculation

Bioavailability of drugs that undergo enterohepatic recirculation may be reduced in situations when the enterohepatic recirculation is affected. For example, bile acid sequestrants can decrease the absorption of drugs that undergo hepatic recirculation by mechanisms such as complex formation or decreased solubility. Additionally, several oral antibiotics may interfere with the enterohepatic recirculation of drugs excreted in the bile as glucuronide-metabolites. These metabolites are further deglucuronidated by β-glucuronidase enzymes present in intestinal bacteria allowing the parent drug to be reabsorbed into the circulation. Antibiotics, which kill those bacteria, prevent the glucuronide-metabolite to be converted back to the parent drug, and in this way lower the bioavailability of the parent drug.

For drugs for which significant enterohepatic recirculation is suspected (e.g. substantial secondary peaks in the pharmacokinetic curve, bile excretion in animals...etc), clinical DDI interaction studies should be conducted on a case-by-case basis, considering contribution of enterohepatic recirculation to the oral bioavailability, the therapeutic window as well as the likelihood of co-administration of the medicine with bile acid sequestrants or/and oral antibiotics.

5. Reporting and interpretation

For the food or drug interaction studies, the following exposure measures should be determined for each subject: AUC0-t, Cmax, and time to Cmax (tmax). These parameters for metabolites, when measured, should also be presented. Pharmacokinetic results of the interaction studies should be reported as the geometric mean ratio of the observed pharmacokinetic exposure measures with and without food / the precipitant drug and the associated 90 percent confidence interval. Measures of the observed variability of the interaction, such as the range of AUC or Cmax ratios for individuals in a cross-over study, should be reported.

Results from pharmacodynamic endpoints, whenever available, should be reported and summarised.

The results of the interaction study should be discussed considering the therapeutic window (no-effect boundaries) of the medicinal product (ICH M12 guideline on drug interaction studies, section 5.3.1).

If there is no clinically relevant food effect but the medicinal product is to be administered under certain fasted or fed conditions for tolerability or pharmacodynamic reasons, the reason for the food restriction should be explicitly indicated in the Summary of Product Characteristics section 4.2 'Method of administration'.

6. Risk assessment and management

DDI management strategies such as interaction prevention and risk minimisation strategies, should be based on the assessment of interaction risk from altered drug absorption, with relevant principles from ICH M12 applying.

Since the interactions described in this guideline involve absorption mediated interactions, these interactions are limited by the time span in the gastrointestinal tract. Many interactions could be mitigated by staggering the administration between the two medicinal products. However, for an interaction with the long acting proton pump inhibitors as precipitant, this is usually not an option.

The risk of adverse events and reduced efficacy should be discussed in the registration dossier for a patient erroneously taking the medicinal product occasionally under the not-recommended food conditions when there is a clinical relevant food effect and the medicinal product should be administered either under fasted or fed conditions. If there is considered a risk, risk minimisation and communication of risks should be applied.

In general, DDI management strategies should ensure that drug concentrations of the investigational drug fall within the no-effect boundaries. The risk assessment and development of risk minimization strategies should consider the following factors:

- The exposure-response relationships for safety and efficacy;
- The variability of the observed DDI data, if available;
- The expected duration of concomitant medicinal product use (e.g., acute, short-term, or chronic use of one or both medicinal products);
- The anticipated timing of the introduction of the concomitant medication;
- The mechanism of the DDI;
- The availability of monitoring parameters (e.g., therapeutic drug monitoring, laboratory tests);

- The ability to interrupt the investigational medicinal product or concomitant interacting medication and the availability of other therapeutic options for either drug;
- The clinical importance of the relevant adverse outcome relative to the clinical benefit of the medicinal products;

After considering the items above, DDI management strategies can include the following:

- Contraindication or avoiding concomitant use;
- Temporarily discontinuing one of the interacting medicinal products;
- Modifying the dosing regimen of one of the medicinal products;
- Staggering drug administration (e.g., administer the investigational medicinal product at a different time than a concomitant medicinal product);
- Replacing one of the interacting drugs with a drug not expected to interact;
- Implementing specific monitoring strategies (e.g., therapeutic drug monitoring, laboratory testing).

Any proposed risk minimisation measures or alternative strategies for mitigating potential gastrointestinal interactions should be documented in the Summary of Product Characteristics (SmPC) in accordance with the EC SmPC guideline (2009).