EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Section 4.5: Interaction with other medicinal products and other forms of interaction

SmPC training presentation

Note: for full information refer to the European Commission's Guideline on summary of product characteristics (SmPC)

SmPC Advisory Group

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I. General objectives of section 4.5

This section should provide information on the potential for clinically relevant interactions based on the pharmacodynamic properties and in vivo pharmacokinetic studies of the medicinal product

Information should highlight clinically relevant interactions, i.e. those resulting in recommendation on the use of this medicine or other medicines

II. Key principles

Recommendations might be:

- Contraindications of concomitant use
- Concomitant use not recommended
- Precautions including dose adjustment mentioning situations where these may be required e.g. duration of clinically important interaction considering discontinuation (e.g. enzyme inhibitor or reducer) or need for washout period

SmPC examples

1 contraindication

2 contraindication

3 concomitant use not recommended

4 precaution

5 precaution

- Any clinical manifestations and effects on plasma levels and AUC of parent compounds or active metabolites and/or on laboratory parameters should be given
- Mechanism of the interaction should be explained if known

Interactions affecting the use of the medicinal product should be given first, followed by those interactions resulting in clinically relevant changes on the use of others

Cross reference to section 4.2, 4.3, 4.4, and/or 5.2 as appropriate

III. Additional information

Information on other relevant interactions
(e.g. herbal medicinal products, food, alcohol, smoking)

6 food
7 food
8 smoking
9 herbal

If no interaction studies have been performed, this should be clearly stated

In vivo data demonstrating an absence of interaction should only be mentioned here if this is of major importance to the prescriber (e.g. in therapeutic area where potentially problematic interactions have been identified such as with anti-retroviral medicines)

In vitro data should be summarised in section 5.2 and not in section 4.5 unless the data results in a change in the use of the medicinal product

Use a separate subheading for

Other special populations

Paediatric population

Example 10 special population
Example 11 paediatric population

Example 1-contraindication

CONTRAINDICATIONS OF CONCOMITANT USE (cross-refer to section 4.3)

- Any clinical manifestations, effects on plasma levels + AUC of parent compounds, active metabolites +/- laboratory parameters
- Mechanism of the interaction

Active substance XY 150 mg/12.5 mg film-coated tablets

Section 4.5

P-gp potent inhibitors: A single dose drug interaction study in healthy subjects has shown that ciclosporin (200 and 600 mg) increases C_{max} of active substance X 75mg approximately 2.5-fold and AUC approximately 5 fold. The increase may be higher with higher active substance X doses. Therefore, concomitant use of active substance X and P gp potent inhibitors is contraindicated (see section 4.3).

Section 4.3

The concomitant use of active substance X with ciclosporin, a highly potent P-glycoprotein (P-gp) inhibitor, and other potent P-gp inhibitors (quinidine, verapamil), is contraindicated (see section 4.5).

Example 2-contraindication

CONTRAINDICATIONS OF CONCOMITANT USE (cross refer to section 4.3)

- Any clinical manifestations, effects on plasma levels + AUC of parent compounds, active metabolites +/- laboratory parameters
- Mechanism of the interaction

Active substance X 62.5 mg film-coated tablets

Section 4.5
Cyclosporine A: co-administration of active substance X and cyclosporine A (a calcineurin inhibitor) is contraindicated (see section 4.3). Indeed, when co-administered, initial trough concentrations of active substance X were approximately 30-fold higher than those measured after active substance X alone. At steady state, active substance X plasma concentrations were 3- to 4-fold higher than with active substance X alone. The mechanism of this interaction is most likely inhibition of transport protein-mediated uptake of active substance X into hepatocytes by cyclosporine. The blood concentrations of cyclosporine A (a CYP3A4 substrate) decreased by approximately 50%. This is most likely due to induction of CYP3A4 by active substance X.

Section 4.3
Concomitant use of cyclosporine A (see section 4.5)

Example 3-concomitant use not recommended

CONCOMITANT USE NOT RECOMMENDED
(cross-refer to section 4.4)

- Any clinical manifestations, effects on plasma levels + AUC of parent compounds, active metabolites +/- laboratory parameters
- Mechanism of the interaction

Active substance X 5 mg film-coated

Section 4.5
Concomitant use not recommended
Moderate CYP3A4 inhibitors: specific interaction studies in healthy volunteers and patients have shown that the combination of active substance X with the heart rate reducing agents diltiazem or verapamil resulted in an increase in active substance X exposure (2 to 3 fold increase in AUC) and an additional heart rate reduction of 5 bpm. The concomitant use of active substance X with these medicinal products is not recommended (see section 4.4).

Section 4.4
Combination with other antianginal therapies
Concomitant use of active substance X with heart rate reducing calcium channel blockers such as verapamil or diltiazem is not recommended (see section 4.5).

Example 4-precaution

PRECAUTIONS INCLUDING DOSE ADJUSTMENT (cross-refer to section 4.2 or 4.4, as appropriate), mentioning specific situations where these may be required

- Any clinical manifestations, effects on plasma levels + AUC of parent compounds, active metabolites +/- laboratory parameters
- Mechanism of the interaction

Active substance X 75 mg hard capsules

Transporter interactions:

Amiodarone, verapamil and clarithromycin are inhibitors of the efflux transporter P-glycoprotein and active substance X is a substrate of this transporter.

Amiodarone: When active substance X was coadministered with a single oral dose of 600 mg amiodarone, the extent and rate of absorption of amiodarone and its active metabolite DEA were essentially unchanged. The active substance X AUC and C_{max} were increased by about 60 % and 50 %, respectively. The mechanism of the interaction has not been completely clarified. In view of the long half-life of amiodarone the potential for drug interaction may exist for weeks after discontinuation of amiodarone.

Dosing should be reduced to 150 mg active substance X daily in patients who received concomitantly active substance X and amiodarone (see section 4.2).

Example 5-precaution

PRECAUTIONS INCLUDING DOSE ADJUSTMENT (cross-refer to section 4.2 or 4.4, as appropriate), mentioning specific situations where these may be required

- Any clinical manifestations, effects on plasma levels + AUC of parent compounds, active metabolites +/- laboratory parameters
- Mechanism of the interaction

Active substance XY 1 mg/500 mg film-coated tablets

Cationic medicinal products that are eliminated by renal tubular secretion (e.g. cimetidine) may interact with active substance X by competing for common renal tubular transport systems. A study conducted in seven normal healthy volunteers showed that cimetidine, administered as 400 mg twice daily, increased active substance X systemic exposure (AUC) by 50% and C_{max} by 81%. Therefore, close monitoring of glycaemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when cationic medicinal products that are eliminated by renal tubular secretion are co-administered (see section 4.4).

Example 6-food

Information on **other relevant interactions such as** with herbal medicinal products, **food,** alcohol, smoking, or pharmacologically active substances not used for medical purpose**,** should also be given. With regard to pharmacodynamic effects where there is a possibility of a clinically relevant potentiation or a harmful additive effect, this should be stated

Active substance X 2 g granules for oral suspension

Section 4.5

Food, milk and derivative products, and medicinal products containing calcium may reduce the bioavailability of active substance X by approximately 60-70%. Therefore, administration of active substance X and such products should be separated by at least two hours (see section 5.2).

Section 4.2

The absorption of active substance X is reduced by food, milk and derivative products and therefore, active substance X should be administered in-between meals. Given the slow absorption, active substance X should be taken at bedtime, preferably at least two hours after eating (see sections 4.5 and 5.2).

Example 7–food

Information on **other relevant interactions such as** with herbal medicinal products, **food,** alcohol, smoking, or pharmacologically active substances not used for medical purpose, should also be given. With regard to pharmacodynamic effects where there is a possibility of a clinically relevant potentiation or a harmful additive effect, this should be stated

Active substance X suspension and effervescent granules for oral suspension

Section 4.5

Active substance X is acid labile. Food and/or drink will increase acid production in the stomach and the effect of active substance X may be impaired. Consequently, food and drink should be avoided 1 hour before and 1 hour after administration.

Section 4.2

Method of administration: Food and drink should be avoided 1 hour before and 1 hour after administration (see section 4.5).

Example 8–smoking

Information on **other relevant interactions such as** with herbal medicinal products, food, alcohol, **smoking,** or pharmacologically active substances not used for medical purpose**,** should also be given. With regard to pharmacodynamic effects where there is a possibility of a clinically relevant potentiation or a harmful additive effect, this should be stated

Active substance X 25 mg film-coated tablets

Results of a pharmacokinetic interaction study indicated a significant 2.8-, 1.5- and 9-fold reduced AUC_{inf}, C_{max} and plasma concentration at 24 hours, respectively, after administration of active substance X in smokers as compared to non-smokers (see section 5.2). Therefore, patients who are still smoking should be encouraged to stop smoking as early as possible before initiation of treatment with active substance X , as plasma active substance X concentrations are reduced otherwise. The clinical effect of the decreased exposure has not been formally assessed but it is likely to be clinically significant.

Example 9–herbals

Information on **other relevant interactions such as with herbal medicinal products,** food, alcohol, smoking, or pharmacologically active substances not used for medical purpose, should also be given. With regard to **pharmacodynamic effects** where there is a possibility of a **clinically relevant potentiation** or a **harmful additive effect**, this should be stated

Active substance X 75 mg film-coated tablets

Section 4.5

St John's wort is expected to decrease the plasma concentrations and reduce clinical effects of active substance X. (CYP450 induction). Active substance X must not be used concomitantly with products containing St John's wort (Hypericum perforatum) (see section 4.3). If a patient is already taking St John's wort, stop St John's wort and if possible check viral levels. Active substance X exposure may increase on stopping St John's wort. The inducing effect may persist for at least 2 weeks after cessation of treatment with St John's wort.

Section 4.3

Herbal preparations containing St John's wort (Hypericum perforatum) must not be used while taking active substance X (see section 4.5).

Example 10-special population

PATIENT GROUPS in which the IMPACT OF AN INTERACTION IS MORE SEVERE, OR THE MAGNITUDE OF AN INTERACTION IS EXPECTED TO BE LARGER e.g., patients with decreased renal function (in case the parallel pathway is renal excretion), paediatric patients, elderly etc, this information should be given here

Active substance X 200 mg hard capsules

NSAIDs may reduce the effect of diuretics and antihypertensive medicinal products. As for NSAIDs, the risk of acute renal insufficiency, which is usually reversible, may be increased in some patients with compromised renal function (e.g. dehydrated patients or elderly patients) when ACE inhibitors or angiotensin II receptor antagonists are combined with NSAIDs, including active substance X.

Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Example 11–paediatric population

Any **identified treatment recommendations** should be given in relation to **concomitant use in paediatric subset(s)** (***e.g. dose adjustment, extra-monitoring of clinical effect marker/adverse reactions, therapeutic drug monitoring)***

Active substance X 50 mg powder for concentrate for solution for infusion

In paediatric patients, results from regression analyses of pharmacokinetic data suggest that co-administration of dexamethasone with active substance X may result in clinically meaningful reductions in active substance X trough concentrations. This finding may indicate that paediatric patients will have similar reductions with inducers as seen in adults. When active substance X is co administered to paediatric patients (12 months to 17 years of age) with inducers of drug clearance, such as rifampicin, efavirenz, nevirapine, phenytoin, dexamethasone, or carbamazepine, a active substance X dose of 70-mg/m2 daily (not to exceed an actual daily dose of 70mg) should be considered.

IV. FAQs

1. Where can we find additional information on investigation of drug interactions and guidance to ensure that the prescriber receives clear information on the interaction potential?

2. Are they specific recommendations for anti-retroviral agents with high propensity for pharmacokinetic interactions?

1. Where can we find additional information on investigation of drug interactions and guidance to ensure that the prescriber receives clear information on the interaction potential?

- Please consult the CHMP guideline on the investigation of drug interactions

2. Are they specific recommendations for anti-retroviral agents with high propensity for pharmacokinetic interactions?

- See annex A of the guideline on the clinical development of medicinal products for the treatment of HIV infection

Thank you for consulting this training presentation

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Please note the presentation includes examples that may have been modified to best illustrate the related principle