EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

SmPC of fixed combination medicinal products

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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Introduction

- The combination of active substances within a single pharmaceutical form of administration is a so-called ‘fixed combination’ medicinal product.
- CHMP Guideline on clinical development of fixed combination medicinal products (CHMP/EWP/240/95 Rev. 1, Feb. 2009):

It is necessary to assess the potential advantages (e.g. product rapidly effective, higher efficacy or equal efficacy and better safety) in the clinical situation against possible disadvantages (e.g. cumulative toxicity), for each fixed combination product and for each dose of the fixed combination product.

General principles for presenting information in SmPC of fixed dose combination products

- The principles of the SmPC guideline apply.
- The SmPC of a fixed combination should inform on the characteristics of the fixed combination.
  - "The product information should be an integrated evaluation of the FDC, and not a summation of the product information for each of the actives." *(WHO Technical Report Series, No. 929, 2005; Annex 5: Guidelines for registration of fixed-dose combination medicinal products)*
  - Information should be primarily based on data collected with the use of the components in combination, complemented as appropriate with data collected with the components in monotherapy.
  - In the rare cases where a component is not authorised in monotherapy, its characteristics should be detailed.

Section 1: Name of the medicinal product

- The (invented) name should be followed by both the strength and the pharmaceutical form.
- The strength should be the relevant quantity for identification and use of the product and should be consistent with the quantity stated in the qualitative composition and in the posology.
- The strength should inform on the quantity of each active substance presented in the order of the WHO classification.

Section 4.1 Therapeutic indications

- The indications claimed for a fixed combination medicinal product should be such that the presence of each active substance makes a contribution to the claimed effect or improves the overall benefit risk ratio by mitigating side effects.
- It should be clear whether the indication is a first line, second line or substitution indication. The clinical development should be performed accordingly.

Examples

Examples of indications

X is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years and over who are antiretroviral treatment-naïve or are infected with HIV-1 without known mutations associated with resistance to any of the three antiretroviral agents in X.

Treatment of essential hypertension. This fixed dose combination is indicated in patients whose blood pressure is not adequately controlled by X alone or Y alone.

Treatment of essential hypertension as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of amlodipine, valsartan and hydrochlorothiazide (HCT), taken either as three single-component formulations or as a dual-component and a single-component formulation.

Section 4.2 Posology and method of administration

- The product should be formulated so that the dose and proportion of each substance present is appropriate for the intended use.
- If the strength(s) is (are) not suitable to adjust the posology to a special population subgroup (e.g. patient with renal impairment), it should be stated in section 4.2.

Examples

Example of 4.2 statement on suitability of strength

X is not recommended for patients with moderate or severe renal impairment (creatinine clearance < 50 ml/min). Patients with moderate or severe renal impairment require a dose interval adjustment of A and B that cannot be achieved with the combination tablet.

A/B tablets should not be used for children weighing less than 14 kg, since doses can not be appropriately adjusted for the weight of the child. In these patients, A and B should be taken as separate formulations according to the prescribed dosing recommendations for these products. For these patients and for patients who are unable to swallow tablets, oral solutions of A and B are available.

For situations where discontinuation of therapy with one of the active substances of A/B, or dose reduction is necessary, separate preparations of A and B are available in tablets/capsules and oral solution.

Contraindications, Warnings and precautions for use

- Contraindications, warnings and precautions for use of individual components will be relevant for the fixed dose combination, and should therefore be listed in section 4.3 and 4.4 respectively. Any deviation should be justified.
- Warning and precautions for use should inform on additive (or counteractive) effect of the different components. Such effect should be presented prominently.

Example – additive effect

- Warning and precautions for use should inform on the component(s) leading to the warning or precaution when known and specific to one of the components.
- The order of warnings and precautions should in principle be determined by the importance of the safety information provided. Presentation of information should facilitate its consultation and has to be considered on a case by case basis, however, in general;
  - All contraindications can be listed together,

Example - contraindications

  - Warning and precautions should be integrated and presented with sub-headings naming the effect or the sub-population at risk to facilitate usability

Example – warnings and precautions

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Example - Contraindications

4.3 Contraindications

- Hypersensitivity to the active substances, to other sulphonamide derivatives, to dihydropyridine derivatives, or to any of the excipients.
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- Hepatic impairment, biliary cirrhosis or cholestasis.
- Severe renal impairment (GFR <30 ml/min/1.73 m2), anuria and patients undergoing dialysis.
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia, and symptomatic hyperuricaemia.
- Severe hypotension.
- Shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g. hypertrophic obstructive cardiomyopathy and high grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction.

4.4 Special warnings and precautions for use (extracts)

Serum electrolyte changes

In the controlled trial of Amlodipine/valsartan/hydrochlorothiazide, the counteracting effects of valsartan 320 mg and hydrochlorothiazide 25 mg on serum potassium approximately balanced each other in many patients. In other patients, one or the other effect may be dominant. Periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Primary hyperaldosteronism

Patients with primary hyperaldosteronism should not be treated with the angiotensin II antagonist valsartan as their renin-angiotensin system is not activated. Therefore, Copalia HCT is not recommended in this population.

Systemic lupus erythematosus

Thiazide diuretics, including hydrochlorothiazide, have been reported to exacerbate or activate systemic lupus erythematosus.

Warning on additive effect

Musculoskeletal and connective tissue disorders

As with other lipid lowering substances, pravastatin or fenofibrate have been associated with the onset of myalgia, myopathy and very rarely rhabdomyolysis with or without secondary renal insufficiency.

The risk of muscle toxicity is increased when a fibrate and a 3-hydroxy-3-methyl-glutaryl-Coenzyme A (HMG-CoA) reductase inhibitor are administered together. Myopathy must be considered in any patient presenting with unexplained muscle symptoms such as pain or tenderness, muscle weakness, or muscle cramps. In such cases CK levels should be measured. Consequently, the potential benefit/risk ratio of X should be closely assessed before treatment initiation and patients should be monitored for any signs of muscle toxicity. Certain predisposing factors such as age > 70, renal impairment, hepatic impairment, hypothyroidism, personal history of muscular toxicity with a statin or fibrate, personal or familial history of hereditary muscular disorders or alcohol abuse may increase the risk of muscular toxicity and therefore CK measurement is indicated before starting the combination therapy in these patients.

Section 4.5: Interactions with other medicinal products

- A brief introductory summary of the mechanistic basis for the interaction potential of each component is recommended.

Example – general statement

Example – basis for interactions

- All clinically relevant interactions between the FDC and other drugs should be described, together with the resulting contraindications and precautions.

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Section 4.5: Interactions with other medicinal products

No drug interaction studies have been performed using X. As X contains efavirenz, emtricitabine and tenofovir disoproxil fumarate, any interactions that have been identified with these agents individually may occur with X.

Section 4.5: brief introductory summary of the mechanistic basis for the interaction

Y contains lamivudine and zidovudine, therefore any interactions identified for these individually are relevant to Y. Clinical studies have shown that there are no clinically significant interactions between lamivudine and zidovudine.

Zidovudine is primarily metabolised by UGT enzymes; co-administration of inducers or inhibitors of UGT enzymes could alter zidovudine exposure. Lamivudine is cleared renally. Active renal secretion of lamivudine in the urine is mediated through organic cation transporters (OCTs); co-administration of lamivudine with OCT inhibitors or nephrotoxic drugs may increase lamivudine exposure.

4.6 Fertility, pregnancy and lactation

- Section 4.6 should be reviewed with due consideration to the CHMP guideline: Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling as for other products
- Clinical data (if available) and relevant conclusions from non-clinical toxicity studies for the fixed combination (if available) and each individual component should be summarised before concluding on the recommendations for use or not.
- Information and recommendations should be based on an integrated evaluation of the FDC

Example

Example – Pregnancy and lactation

Pregnancy

There are no adequate data from the use of sitagliptin in pregnant women. Studies in animals have shown reproductive toxicity at high doses of sitagliptin (see section 5.3).

A limited amount of data suggest the use of metformin in pregnant women is not associated with an increased risk of congenital malformations. Animal studies with metformin do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition or postnatal development (see also section 5.3).

X should not be used during pregnancy. If a patient wishes to become pregnant or if a pregnancy occurs, treatment with X should be discontinued and switched to insulin treatment as soon as possible.

Breast-feeding

No studies in lactating animals have been conducted with the combined active substances of X. In studies performed with the individual active substances, both sitagliptin and metformin are excreted in the milk of lactating rats. Metformin is excreted in human milk in small amounts. It is not known whether sitagliptin is excreted in human milk. X must therefore not be used in women who are breast-feeding (see section 4.3).

Section 4.8: Undesirable effects

- All safety data from the fixed dose combination and the individual components should be considered
- The summary of safety profile should provide information about the most serious and most frequent adverse reactions of the fixed combination, based on the integrated evaluation of all relevant safety data

Example – summary of safety profile

- All adverse reactions should be listed in a single tabulated listing with its respective frequency category for the fixed combination. If the choice of the frequency category is based on different sources, the category representing the highest frequency should be chosen unless another one is of clearly higher validity

Example

- Where known, information should point out which particular adverse reaction is usually attributable to which active substance e.g. in subsection c, description of selected adverse reactions. Such description can also inform on clinically relevant difference in the safety profile of the combination compared to that of the individual components if any.

Example

Presenting the adverse reactions of each active substance in a sequential way is not acceptable because it does not provide the integrated evaluation and information expected for a fixed combination.

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Example summary of safety profile

The most frequently reported adverse reactions with X are dyskinesias occurring in approximately 19% of patients; gastrointestinal symptoms including nausea and diarrhoea occurring in approximately 15% and 12% of patients, respectively; muscle, musculoskeletal and connective tissue pain occurring in approximately 12% of patients; and harmless reddish-brown discolouration of urine (chromaturia) occurring in approximately 10% of patients. Serious events of gastrointestinal haemorrhage (uncommon) and angioedema (rare) have been identified from the clinical trials with X or entacapone combined with levodopa/DDC inhibitor. Serious hepatitis with mainly cholestatic features, rhabdomyolysis and neuroleptic malignant syndrome may occur with X although no cases have been identified from the clinical trial data.

Example of tabulated listing of adverse reactions (extract)

Vascular disorders	
Common	Orthostatic hypotension[h]
Uncommon	Hypotension[c, a]
Respiratory, thoracic and mediastinal disorders	
Uncommon	Cough[a]
Very rare	Respiratory distress (including pneumonitis and pulmonary oedema) [h]
Gastrointestinal disorders	
Common	Diarrhoea[c, a, h], decreased appetite[h], mild nausea and vomiting[h]
Rare	Abdominal discomfort[h], constipation[h]
Very rare	Pancreatitis[h]

[c] – *Adverse reaction observed with X (aliskiren + hydrochlorothiazide)*

[a] – *Adverse reaction observed with monotherapy with aliskiren*

[h] – *Adverse reaction observed with monotherapy with hydrochlorothiazide*

Example of description of selected adverse reactions pointing out individual components' effects

c. Description of selected adverse reactions

Adverse reactions that are mainly attributable to entacapone or are more frequent with entacapone than levodopa/DDC inhibitor alone are indicated with an asterisk in the tabulated listing of adverse reactions (see section 4.8b). Some of these adverse reactions relate to the increased dopaminergic activity (e.g. dyskinesia, nausea and vomiting) and occur most commonly at the beginning of the treatment. Reduction of levodopa dose decreases the severity and frequency of these dopaminergic reactions. Few adverse reactions are known to be directly attributable to the active substance entacapone including diarrhoea and reddish-brown discolouration of urine. Entacapone may in some cases cause also discolouration of e.g. skin, nail, hair and sweat. Other adverse reactions with an asterisk in the tabulated listing are marked based on either their more frequent occurring (by the frequency difference of at least 1%) in the clinical trial data with entacapone than levodopa/DDCI alone or the individual case safety reports received after the introduction of entacapone into the market.

Section 5.1: Pharmacodynamic properties

- The mechanism of action of each component should be presented.
- Unless limited to the simplification of the administration, the rationale of the fixed combination should be explained. (e.g. potentiation or counteracting effect)

Examples

- Results of clinical trials supporting the indication(s) and recommended posology for the use of the products in combination may be presented. It is usually not necessary to present the results of clinical trials performed with the individual components only.

Example

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Example - Mechanism of action

Buprenorphine is an opioid partial agonist/antagonist which binds to the μ and κ (kappa) opioid receptors of the brain. Its activity in opioid maintenance treatment is attributed to its slowly reversible properties with the μ-opioid receptors which, over a prolonged period, might minimise the need of addicted patients for drugs.

Naloxone is an antagonist at μ-opioid receptors. When administered orally or sublingually in usual doses to patients experiencing opioid withdrawal, naloxone exhibits little or no pharmacological effect because of its almost complete first pass metabolism. However, when administered intravenously to opioid-dependent persons, the presence of naloxone in X produces marked opioid antagonist effects and opioid withdrawal, thereby deterring intravenous abuse.

X is an oral fluoropyrimidine anti-cancer medicinal product. It is a fixed dose combination of three active substances, tegafur, which after absorption is converted into the anti-cancer substance 5-FU; gimeracil, a dihydropyrimidine dehydrogenase (DPD) inhibitor to prevent degradation of 5-FU by the body; and, oteracil, an orotate phosphoribosyltransferase (OPRT) inhibitor that decreases the activity of 5-FU in normal gastrointestinal mucosa. The combination of tegafur, gimeracil, and oteracil was set at 1:0.4:1 molar ratio as optimum in order to maintain 5-FU exposure and thus sustain anti-tumour activity while reducing toxicity associated with 5-FU alone.

Example - section 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiglaucoma preparation and miotics, ATC code: S01ED51

Mechanism of action

X contains two active substances: brinzolamide and timolol maleate. These two components decrease elevated IOP primarily by reducing aqueous humour secretion, but do so by different mechanisms of action. The combined effect of these two active substances results in additional IOP reduction compared to either compound alone.

Brinzolamide is a potent inhibitor of human carbonic anhydrase II (CA-II), the predominant iso-enzyme in the eye. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humour secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport.

Timolol is a non-selective adrenergic-blocking agent that has no intrinsic sympathomimetic, direct myocardial depressant or membrane-stabilising activity. Tonography and fluorophotometry studies in man suggest that its predominant action is related to reduced aqueous humour formation and a slight increase in outflow facility.

Clinical effects

In a twelve-month, controlled clinical trial in patients with open-angle glaucoma or ocular hypertension who, in the investigator's opinion could benefit from a combination therapy, and who had baseline mean IOP of 25 to 27 mmHg, the mean IOP-lowering effect of X dosed twice daily was 7 to 9 mmHg. The non-inferiority of AZARGA as compared to dorzolamide 20 mg/ml + timolol 5 mg/ml in the mean IOP reduction was demonstrated across all time-points at all visits.

In a six-month, controlled clinical study in patients with open-angle glaucoma or ocular hypertension and baseline mean IOP of 25 to 27 mmHg, the mean IOP-lowering effect of X dosed twice daily was 7 to 9 mmHg, and was up to 3 mmHg greater than that of brinzolamide 10 mg/ml dosed twice daily and up to 2 mmHg greater than that of timolol 5 mg/ml dosed twice daily. A statistically superior reduction in mean IOP was observed compared to both brinzolamide and timolol at all time-points and visits throughout the study.

Section 5.2: Pharmacokinetic properties

- Pharmacokinetic information on the fixed dose combination, e.g. rate and extent of absorption of the different component compared with absorption when administered as individual dosage forms, should be presented first.

Examples

- The pharmacokinetic properties of each component should be then described

Example of information on pharmacokinetics of a fixed combination in - section 5.2

Lopinavir is essentially completely metabolised by CYP3A. Ritonavir inhibits the metabolism of lopinavir, thereby increasing the plasma levels of lopinavir. Across studies, administration of lopinavir/ritonavir 400/100 mg twice daily yields mean steady-state lopinavir plasma concentrations 15 to 20-fold higher than those of ritonavir in HIV-infected patients. The plasma levels of ritonavir are less than 7% of those obtained after the ritonavir dose of 600 mg twice daily. The in vitro antiviral EC50 of lopinavir is approximately 10-fold lower than that of ritonavir. Therefore, the antiviral activity of lopinavir/ritonavir is due to lopinavir.

Following single and repeated combination doses of X 23 mg / 9 mg, subjects had an approximately 20-fold increase in dextromethorphan exposure compared to subjects given dextromethorphan without quinidine.

Thank you for consulting this training presentation

SmPC Advisory Group

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