EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Section 4.3: Contraindications

SmPC training presentation

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

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I. General objectives of section 4.3

This section should state situations where the medicine must not be given for safety reasons

Contraindications should be unambigiously, comprehensively and clearly outlined

II. Key principles

Situations where the product must not be given for safety reasons e.g. concomitant disease, demographic factor or predisposition, concomitant use with another medicine,... must be stated in section 4.3

Patient population excluded from clinical trial due to a contraindication on grounds of safety should be mentioned

Lack of data alone
should not lead to a contraindication

III. Examples of contraindications

A particular clinical diagnosis or concomitant disease

SmPC examples
1 clinical diagnosis
2 concomitant disease

Hypersensitivity — 3 hypersensitivity

Demographic factors — 4 demographic factors

Pregnancy and breastfeeding — 5 pregnancy; 6 breastfeeding

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8 medicines/classes of medicines

Medicines/classes of medicines which MUST NOT be used concomitantly or consecutively

Contraindication in a specific population should cross-refer to the section giving detailed information — 9 specific population

Patients excluded from clinical studies due to a contraindication on grounds of safety — 10 clinical trials

Example 1-clinical diagnosis

A particular clinical diagnosis

Active substance X 0.75 mg/ml, solution for infusion

Active substance X must not be used to treat patients with severe hypertension (systolic blood pressure > 200 mm Hg or diastolic blood pressure > 110mm Hg on antihypertensive therapy).

Example 2-concomitant disease

Concomitant disease

Active substance X 5 mg/1.5 ml powder and solvent for solution for injection

Cardiac failure or history of cardiac failure (NYHA stages I to IV).

Example 3-hypersensitivity

Hypersensitivity to active substance/excipients/residues

Active substance X powder and solvent for suspension for injection

Hypersensitivity to the active substance, to any of the excipients or trace residuals (e.g., neomycin) (see sections 4.4 and 6.1).

Example 4-demographic factors

Specific population contraindication, Lack of data alone should not lead to a contraindication. (contraindication should be listed without subheading in paediatric population)

Demographic factors (gender and age)

Active substance X 400mg film-coated tablets

Patients below 18 years of age.

Example 5-pregnancy

Pregnancy
(Further background information provided in 4.6 with a cross reference to 4.3)

Active substance XYZ 5 mg/160 mg/12.5 mg film-coated tablets

Section 4.3
Second and third trimesters of pregnancy (see sections 4.4 and 4.6).

Section 4.4
Pregnancy
Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Section 4.6
(…) Exposure to angiotensin II receptor antagonist therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3). Should exposure to angiotensin II receptor antagonists have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. (…)

Example breastfeeding

Breastfeeding
(Further background information provided in 4.6 with a cross reference to 4.3)

Active substance X 250 mg film-coated tablets

Section 4.3
X is contraindicated in women who are breastfeeding (see section 4.6).

Section 4.6
X has been shown to be excreted in the milk of lactating rats. It is not known whether this substance is excreted in human milk. Because of the potential for serious adverse reactions to active substance X in breast-fed infants, X is contraindicated in nursing mothers (see section 4.3).

Example 7-predispositions

Predispositions
e.g. metabolic or immunological factors

Active substance X 1.5 mg/ml powder and solvent for concentrate for solution for infusion

Section 4.3
G6PD deficiency and other cellular metabolic disorders known to cause haemolytic anaemia. Hydrogen peroxide is a by-product of the conversion of uric acid to allantoin. In order to prevent possible haemolytic anaemia induced by hydrogen peroxide, active substance X is contraindicated in patients with these disorders.

Example 8-medicines/classes of medicines

Medicines/classes of medicines which **must not** be used concomitantly or consecutively.
Cross reference to 4.5 if applicable

Active substance X 150 mg film-coated tablets

Section 4.3
The concomitant use of active substance X with ciclosporin, a highly potent P-gp inhibitor, and other potent P-gp inhibitors (quinidine, verapamil), is contraindicated (see section 4.5).

Section 4.5
<u>P-gp potent inhibitors</u>
A single dose drug interaction study in healthy subjects has shown that ciclosporin (200 and 600 mg) increases C_{max} of active substance X 75 mg 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).

Example 9-specific population

Specific population contraindication (cross reference to relevant section with details of safety issue)
Lack of data alone should not lead to a contraindication.
(contraindication should be listed without subheading in paediatric population)

Active substance X 75 mg/ml concentrate for solution for infusion

Section 4.3
Active substance X administration is contraindicated in patients unable to receive probenecid or other sulfa-containing medication (see section 4.4 Prevention of nephrotoxicity).

Section 4.4 Prevention of nephrotoxicity:
Therapy must be accompanied by administration of oral probenecid and adequate intravenous saline prehydration with each active substance X dose. (.../...) Active substance X administration is contraindicated in patients unable to receive probenecid because of a clinically significant hypersensitivity to the active substance or medicinal product or to other sulfa-containing medicines. Use of active substance X without concomitant probenecid has not been clinically investigated. (.../...)

Example 10-clinical trials

Patient excluded from clinical studies due to a contraindication or due to predicted safety issue
Cross reference to 4.4 if applicable

Active substance X 2.5 mg film-coated tablets

Agents for the treatment of erectile dysfunction must not be used in men with cardiac disease for whom sexual activity is inadvisable. Physicians should consider the potential cardiac risk of sexual activity in patients with pre-existing cardiovascular disease.
The following groups of patients with cardiovascular disease were not included in clinical trials and the use of active substance X is therefore contraindicated in:
•patients with myocardial infarction within the last 90 days
•patients with unstable angina or angina occurring during sexual intercourse
•patients with New York Heart Association Class 2 or greater heart failure in the last 6 months
•patients with uncontrolled arrhythmias, hypotension (< 90/50 mm Hg), or uncontrolled hypertension
•patients with a stroke within the last 6 months

IV. FAQs

1. Should patient excluded from clinical trials be listed in contraindications?
2. Should section 4.3 explain the background of the contraindications?
3. Should hypersensitivity to the active substance or other excipient/residue always be included?

1. Should patient excluded from clinical trials be listed in contraindications?

- If the patient population has been excluded from the studies due to a contraindication on grounds of safety, the patient population should be mentioned in section 4.3. Other patient population excluded from the clinical trial may be mentioned in section 4.4 because of lack of data or potential risk as appropriate

2. Should section 4.3 explain the background of the contraindications?

- Section 4.3 should state the situations where the product must not be given for safety reasons. Information on the grounds of contraindication is not expected. However, if the reason is not obvious, it will be acceptable for an explanation to be given in other relevant sections e.g. 4.4, 4.5 of the SmPC

3. Should hypersensitivity to the active substance or other excipient/residue always be included?

- Information on hypersensitivity should always be included in the SmPC of a medicinal product except for those exceptional circumstances where the expected benefit of the drug will be greater than the risk of hypersensitivity e.g. treatment of life-threatening condition with no alternative therapy

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