



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Section 4.4: Special warnings and precautions for use

Rev. 1

SmPC training presentation

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

SmPC Advisory Group

An agency of the European Union





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I. Objective of section 4.4

The objective of section 4.4 is to provide information on a specific risk when healthcare professionals have to be warned of this risk or the risk leads to a precaution for use to avoid harm

The exact content will be different for each product and for the therapeutic conditions it is intended to treat

Safety warnings should be **clear, compelling** and **effective**



II.1 Situations leading to a warning or precaution (1/2)

Conditions to fulfill before use, e.g. measure required by Risk Management Plan, should be described

[e.g.1](#)

Serious adverse reactions for alerting healthcare professionals

[e.g. 2](#)

Measures to identify patients at risk or to prevent noxious conditions

[e.g.3](#)
[e.g. 4](#)

Risks associated with starting or stopping the product

[e.g. 5](#)
[e.g. 6](#)

Special population at increased risk

[e.g.7](#)
[e.g.8](#)

Specific clinical or laboratory monitoring

[e.g.9](#)

In general, patient population not studied in the clinical trial should be mentioned in section 4.4 and not in section 4.3 unless a safety issue can be predicted



II.2 Situations leading to a warning or precaution (2/2)

Warnings and precautions for use that are specific to the paediatric population or any subset of the paediatric population (to be identified under a subheading)

[e.g.10](#)
[e.g.11](#)
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Warnings necessary for excipients or residues

[e.g.13](#)
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Ethanol content in herbal medicinal products

[e.g.17](#)

Warnings necessary with respect to transmissible agents

[e.g.18](#)

Risks associated with incorrect route of administration

[e.g.19](#)

Specific interference with laboratory tests

[e.g.20](#)



III.1 Structure and readability of section 4.4

Order of warnings and precautions should be determined by the importance of safety information provided

Subheadings are encouraged to facilitate readability

Warnings and precautions regarding pregnancy and breast-feeding, ability to drive and use machines and interactions should be dealt with in their respective sections, unless they are of major clinical importance and specific precautionary measures should be described in section 4.4

In exceptional cases, especially important safety information may be included in **bold type within a box**



III.2 Information not to be included

- ✘ Detailed information of adverse reactions with no recommendation



Example 1-special condition

Conditions in which use of product could be acceptable provided special conditions are fulfilled. To ensure safe and effective use describe specific risk minimisation measures as part of a risk minimisation plan

Active substance X mg film-coated tablets

Section 4.4

LVEF* should be evaluated in all patients prior to initiation of treatment with active substance X to ensure that the patient has a baseline LVEF that is within the institutions normal limits. LVEF should continue to be evaluated during treatment with active substance X to ensure that LVEF does not decline to an unacceptable level (see section 4.2).

Risk Management Plan Summary

Warning in section 4.4 of the SmPC (LVEF should be evaluated in all patients prior to initiation of treatment with active substance X to ensure that the patient has a baseline LVEF that is within the institutions normal limits. LVEF should continue to be evaluated during treatment with active substance X to ensure that LVEF does not decline to an unacceptable level) and information in dose/administration section

*LVEF – left ventricular ejection fraction



Example 2-serious adverse reaction

Serious adverse reactions to which health care professionals need to be alerted.
The situations in which these may occur and the action that may be required

Active substance X 100 mg powder for concentrate for solution for infusion

Infections

Patients must be monitored closely for infections including tuberculosis before, during and after treatment with active substance X. Because the elimination of active substance X may take up to six months, monitoring should be continued throughout this period. Further treatment with active substance X must not be given if a patient develops a serious infection or sepsis.



Example 3-detect onset of noxious condition

Detect early onset of noxious condition

Active substance X 1.5 mg hard capsules

In case of severe vomiting associated with active substance X treatment, appropriate dose adjustments as recommended in section 4.2 must be made. Some cases of severe vomiting were associated with oesophageal rupture (see section 4.8).

Such events appeared to occur particularly after dose increments or high doses of active substance X.



Example 4-statement of early symptoms of serious adverse reaction

Measures taken to identify patients at risk of noxious conditions/prevent their occurrence and for early detection of onset or worsening of noxious conditions. If there is a need for awareness of signs or symptoms representing early warning of a serious adverse reaction, a statement should be included

**In exceptional cases:
bold type within a box**

Active substance X 5 mg/ml solution for infusion

NEUROLOGICAL ADVERSE EVENTS

Severe neurological events have been reported with the use of active substance X. These events have included altered mental states including severe somnolence, central nervous system effects including convulsions, and peripheral neuropathy ranging from numbness and paresthesias to motor weakness and paralysis. There have also been reports of events associated with demyelination, and ascending peripheral neuropathies similar in appearance to Guillain-Barré Syndrome. Full recovery from these events has not always occurred with cessation of active substance X. Therefore, close monitoring for neurological events is strongly recommended, and active substance X must be discontinued at the first sign of neurological events of NCI CTCAE Grade 2 or greater.



Example 5-start treatment

Particular risks associated with starting
(*e.g. first dose effects*) the medicinal product and action required for prevention

Active substance X 100 mg (10 mg/ml) concentrate for solution for infusion

Severe cytokine release syndrome is characterised by severe dyspnea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with some features of tumour lysis syndrome such as hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphatemia, acute renal failure, elevated lactate dehydrogenase (LDH) and may be associated with acute respiratory failure and death. The acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest x-ray. The syndrome frequently manifests itself within one or two hours of initiating the first infusion. Patients with a history of pulmonary insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome and should be treated with increased caution.

Patients who develop severe cytokine release syndrome should have their infusion interrupted immediately (see section 4.2) and should receive aggressive symptomatic treatment.



Example 6-stop treatment

Particular risks associated with stopping
(*e.g. rebound, withdrawal effects*) the medicinal product and action required for prevention

Active substance X 0.5 mg film-coated tablets

At the end of treatment, discontinuation of active substance X was associated with an increase in irritability, urge to smoke, depression, and/or insomnia in up to 3% of patients. The prescriber should inform the patient accordingly and discuss or consider the need for dose tapering.



Example 7-special patient group

Special patient groups at increased risk or only group at risk of experiencing product or product class-related adverse reactions (usually serious or common)

Active substance X 500 micromol/ml solution for injection in a pre-filled syringe

Renal impairment and liver transplant patients

There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of some gadolinium-containing contrast agents in patients with severe renal impairment (GFR $<30\text{ml/min/1.73m}^2$) and those who have had or are undergoing liver transplantation. Therefore active substance X should not be used in these populations (see section 4.3).

Cases of NSF have also been reported in patients with moderate renal impairment (GFR $<60\text{ml/min/1.73m}^2$) with use of gadolinium-containing contrast agents. Active substance X should be used in these patients with caution.

Active substance X is dialysable. Haemodialysis shortly after active substance X administration in patients currently receiving haemodialysis may be useful at removing active substance X from the body. There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.



Example 8-special patient group

Special patient groups at increased risk or only group at risk of experiencing product or product class-related adverse reactions (usually serious or common)

Active substance X 1.5 mg/0.3 ml solution for injection, pre-filled syringe

Elderly patients

The elderly population is at increased risk of bleeding. As renal function is generally decreasing with age, elderly patients may show reduced elimination and increased exposure of active substance X (see section 5.2). Active substance X should be used with caution in elderly patients (see section 4.2).



Example 9-clinical/lab monitoring

Any need for specific clinical or laboratory monitoring should be stated. Recommendation for monitoring should address why, when and how the monitoring should be conducted in clinical practice. A cross-reference to section 4.2 should be included if a dose reduction or other posology is recommended in such circumstances or conditions

Active substance X 4 mg powder and solvent for solution for infusion

Patients should have their serum creatinine levels assessed prior to each dose of active substance X. Upon initiation of treatment in patients with bone metastases with mild to moderate renal impairment, lower doses of active substance X are recommended. In patients who show evidence of renal deterioration during treatment, active substance X should be withheld. Active substance X should only be resumed when serum creatinine returns to within 10% of baseline (see section 4.2).



Example 10-paediatric population

Any necessary warning or precaution in relation to **long-term safety** (e.g. On growth, neuro-behavioural development or sexual maturation) or **specific monitoring** (e.g. Growth). When long-term safety data are necessary but not yet available, it should be stated in this section

Active substance X powder and solvent for solution for injection

Children and adolescent population: Growth and development (chronic hepatitis C)

During the course of interferon X/Y combination therapy lasting up to 48 weeks in patients ages 3 through 17 years, weight loss and growth inhibition were common (see sections 4.8 and 5.1). The longer term data available in children treated with the combination therapy with standard X/Y are also indicative of substantial growth retardation (> 15 percentile decrease in height percentile as compared to baseline) in 21 % of children despite being off treatment for more than 5 years.

Case by case benefit/risk assessment in children

The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials (see sections 4.8 and 5.1).

- It is important to consider that the combination therapy induced a growth inhibition, the reversibility of which is uncertain.
- This risk should be weighed against the disease characteristics of the child, such as evidence of disease progression (notably fibrosis), co-morbidities that may negatively influence the disease progression (such as HIV co-infection), as well as prognostic factors of response, (HCV genotype and viral load).

Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition. There are no data on long term effects on sexual maturation.



Example 11-paediatric population

Any necessary warning or precaution in relation to **long-term safety** (e.g. On growth, neuro-behavioural development or sexual maturation) or **specific monitoring** (e.g. Growth). When long-term safety data are necessary but not yet available, it should be stated in this section

Active substance X powder and solvent for solution for injection

Thyroid supplemental monitoring specific for children and adolescents

Approximately 12 % of children treated with X and Y combination therapy developed increase in thyroid stimulating hormone (TSH). Another 4 % had a transient decrease below the lower limit of normal. Prior to initiation of X therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. X therapy may be initiated if TSH levels can be maintained in the normal range by medication. Thyroid dysfunction during treatment with X and Y has been observed. If thyroid abnormalities are detected, the patient's thyroid status should be evaluated and treated as clinically appropriate. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).



Example 12-paediatric population

Any necessary warning or precaution in relation to **long-term safety** (e.g. On growth, neuro-behavioural development or sexual maturation) or **specific monitoring** (e.g. Growth). When long-term safety data are necessary but not yet available, it should be stated in this section

Active substance X 250 mg film-coated tablets

Available data in children did not suggest impact on growth and puberty. However, long term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children remain unknown.



Example 13-excipient

Any warnings necessary for excipients

Active substance X 50 mg/g oral powder

Active substance X oral powder also contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase isomaltase insufficiency should not take this medicine.



Example 14-excipient

Any warnings necessary for excipients

Active substance X 5 mg tablets

Lactose: patients with rare hereditary problems of galactose intolerance, the lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.



Example 15-excipient

Any warnings necessary for excipients

Active substance X 1 mg/ml solution for injection

This product contains 48 vol % ethanol (alcohol), i.e. up to 4.2 g per dose, equivalent to 84 ml of beer, 35 ml wine per dose. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease or epilepsy.



Example 16-residue

Any warnings necessary for residues from the manufacturing process

Active substance X suspension and effervescent granules for oral suspension

Formaldehyde is used during the manufacturing process and trace amounts may be present in the final product. Caution should be taken in subjects with known hypersensitivity to formaldehyde.



Example 17-Ethanol-Herbal medicinal products

Any warnings necessary for excipients

SmPC Guideline

For herbal preparations containing alcohol, information about the ethanol content in the medicinal product should be included in accordance with the [Guideline on excipients in the label and package leaflet of medicinal products for human use](#)



Example 18-transmissible agents

Any warnings necessary with respect to transmissible agents (e.g. *Warning of Transmissible Agents in SmPCs and Package Leaflets for Plasma-Derived Medicinal Products*)

Active substance X 100 mg/ml solution for infusion

Information on safety with respect to transmissible agents

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV, and HCV, and for the non-enveloped viruses HAV and B19V.

There is reassuring clinical experience regarding the lack of hepatitis A or B19V transmission with immunoglobulins and it is also assumed that the antibody content makes an important contribution to the viral safety.

It is strongly recommended that every time active substance X is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.



Example 19-route of administration

Risk associated with an incorrect route of administration (e.g. necrosis with extravasation of intravenous formulation, or neurological consequences of intravenous use instead of intramuscular use), should be presented, with advice on management if possible

Active substance X medicated sponge

For local use only.

Do not use intravascularly. Life threatening thromboembolic complications may occur if the preparation is unintentionally applied intravascularly.



Example 20-interference with laboratory tests

Specific interference with laboratory tests should be mentioned when appropriate e.g. Coombs test and Beta-lactams. They should be clearly identified with a **subheading** e.g. "*Interference with serological testing*"

CHMP guideline on core SmPC for human fibrinogen products

<Interference with clotting tests

When performing clotting tests which are sensitive to heparin in patients receiving high doses of human fibrinogen, the heparin as a constituent of the administered product must be taken into account. >



Example of presentation of information on a specific risk throughout the SmPC

Specific risk: respiratory depression and fentanyl

SmPC	SmPC Guideline	Fentanyl SmPC
4.4	Serious adverse reactions to which healthcare professionals need to be alerted, the situations in which these may occur and the action that may be required, e.g. emergency resuscitation	<i>Respiratory depression</i> As with all potent opioids clinical significant respiratory depression may occur with fentanyl, and patients must be observed for these effects. Patients with pain who receives chronic opioid therapy develop tolerance to respiratory depression and hence the risk of respiratory depression in these patients is reduced. The use of concomitant central nervous system depressants may increase the risk of respiratory depression (see section 4.5)
4.2	Advice on preventive measures to avoid certain adverse drug reactions	Patients should be individually titrated to the dose that provides adequate analgesia with tolerable adverse drug reactions
4.3	Situations where the medicinal product must not be given for safety reasons	Severe respiratory depression or severe obstructive lung conditions
4.5	With regard to pharmacodynamic effects where there is a possibility of a clinically relevant potentiation or a harmful additive effect, this should be stated	The concomitant use of other central nervous system depressants, including other opioids, sedatives or hypnotics, general anaesthetics, phenothiazines, tranquillisers, skeletal muscle relaxants, sedating antihistamines and alcohol may produce additive depressant effects
4.8	The summary of the safety profile should provide information about the most serious and/or most frequently occurring adverse reactions	The most serious adverse reactions are respiratory depression (potentially leading to apnoea or respiratory arrest), circulatory depression, hypotension and shock and all patients should be closely monitored for these
5.1	Sections 5.1 – 5.3 should normally mention information, which is relevant to the prescriber and to other health-care professionals, taking into account the approved therapeutic indication(s) and the potential adverse drug reactions	Fentanyl is an opioid analgesic interacting primarily with the opioid μ -receptor as a pure agonist with low affinity for the δ - and κ -opioid receptors. The primary therapeutic action is analgesia. The secondary pharmacological effects are respiratory depression, bradycardia, hypothermia, constipation, miosis, physical dependence and euphoria



III. FAQs

1. [Which information regarding starting and stopping treatment should be included in section 4.4 versus 4.2?](#)
2. [Can section 4.4 include information related to off-label use of a medicinal product?](#)
3. [Should the SmPC inform on the educational material requested as part of a marketing authorisation?*](#)
4. [When and where to present a risk with no established casual association?*](#)



1. Which information regarding starting and stopping treatment should be included in section 4.4 versus 4.2?

- Section 4.2 should provide posology recommendations regarding starting and stopping treatment while section 4.4 should state the particular risks associated with starting or stopping the treatment
- E.g. section 4.2 states that the treatment should be started gradually in specifying the dose while the related information in 4.4 states the risk that may be cause if the treatment is started at a high dose.



2. Can section 4.4 include information related to off-label use of a medicinal product?

- The SmPC is expected to provide information on how to use the product safely and effectively in the approved indication(s). However, if an important safety issue has been identified with off-label use, a warning may be included in section 4.4 if it is relevant to warn healthcare professionals on this risk. (The SmPC guideline asks for a description of serious adverse reactions to which healthcare professionals need to be alerted, together with the situations in which these may occur in section 4.4).



3. Should the SmPC inform on the educational material requested as part of a marketing authorisation? *

- Additional risk minimisation measures requested are described in ANNEX II D of the marketing authorisation. The Marketing Authorisation Holder shall agree the content and format of the updated educational materials with the national competent authority. A detailed description of the education material is not expected in the SmPC.
- However, section 4.4 should describe specific risk minimisation measures requested as part of the Risk Management Plan to ensure safe and effective use of the medicinal product (before prescribing, during dispensing or during medicinal product use), including the need of educational material whether addressed to healthcare professional or patients.
- The purpose and scope of the educational material should be clearly but succinctly explained (E.g. "*Prescribers should be familiar with the educational material prepared for the management of <e.g. hepatotoxicity>, <and, inform the patient about the Patient Card explaining the monitoring of liver function>*"). Other sections may refer to the educational materials, if necessary.



4. When and where to present a risk with no established casual association?*

- Section 4.4 aims to inform Healthcare professionals on specific risks only, i.e. those which lead to a precaution for use or those to which healthcare professional have to be warned of. It should not be overloaded with other information to avoid diluting the important precautions and warnings.
- Section 4.8 should only include adverse reactions if a causal relationship is at least reasonable. Adverse events, without at least a suspected casual relationship, should not be listed in the SmPC.
- An exception for communicating a risk in section 4.4 but not listing it in section 4.8 could consist in an important potential risk (i.e. which could have an impact on the benefit/risk balance of the product or have implications for public health) for which the causality assessment is inconclusive.



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