



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

## Section 4.8: Undesirable effects

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





# Index

## I. [General objectives](#)

## II. Key principles

II.1 [Summary of safety profile](#)

II.2 [Tabulated list of adverse reactions](#)

II.3 [Description of selected adverse reactions](#)

II.4 [<Paediatric population>](#)

II.5 [<Other special population>](#)

## III. Additional information

III.1 [Guidance on the estimation of frequency of adverse reactions](#)

III.1 [Information not to be included](#)

## IV. [FAQs](#)\*



# I. General objectives of section 4.8

This section should include **all adverse reactions** from clinical trials, post-authorisation safety studies and spontaneous reporting for which, after **thorough assessment**, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual case reports

The content of this section should be justified in the clinical overview of the marketing authorisation application based upon a best-evidence assessment of all observed adverse events and all facts relevant to the assessment of causality, severity and frequency

Guidance regarding clinical overview may be found in the ICH Topic M 4 E

[Click here for section 2.5.5 of this guideline](#)

Whole section should be worded in CONCISE AND SPECIFIC LANGUAGE



## II.1 Summary of the safety profile

Provide information on the most serious and/or most frequently occurring adverse reactions. Frequencies to be stated as accurately as possible

HELPFUL to indicate timing when adverse reaction occurs e.g. information on reactions associated with long-term use, or adverse reactions that are frequent in the beginning of treatment but may disappear with continuation

SmPC examples

[1 safety profile](#)  
[2 safety profile](#)

Cross-reference to section 4.4 if relevant risk minimisation measures in that section

[3 safety profile -cross reference to 4.4](#)

Consistency with:

- Important identified risks in Safety Specification of Risk Management Plan
- Table of Adverse Reactions

[4 safety profile-risk management plan](#)

[5 safety profile consistent with table of adverse reactions](#)



# Example 1-safety profile

Most serious and/or frequently occurring adverse reaction. Frequencies stated as accurately as possible

## Active substance X 12.5mg capsules

### Summary of the safety profile

The most important serious adverse reactions associated with active substance X in patients with solid tumours were pulmonary embolism (1%), thrombocytopenia (1%), tumour haemorrhage (0.9%), febrile neutropenia (0.4%) and hypertension (0.4%).



## Example 2-safety profile

Most serious and/or frequently occurring adverse reaction. Frequencies stated as accurately as possible

HELPFUL to indicate timing when adverse reaction occurs

### Active substance X solution for injection in pre-filled syringe

#### Summary of the safety profile

The highest incidence of adverse reactions associated with active substance X therapy is related to flu-like syndrome. Flu-like symptoms tend to be most prominent at the initiation of therapy and decrease in frequency with continued treatment. Approximately 70% of patients treated with active substance X can expect to experience the typical interferon flu-like syndrome within the first six months after starting treatment.



## Example 3-safety profile

Most serious and/or frequently occurring adverse reaction. Frequencies stated as accurately as possible

Cross-reference to section 4.4 if relevant risk minimisation measures have been proposed in that section

### Active substance X 30 MIU/0.5 ml solution for injection or infusion

#### Summary of the safety profile

Rare pulmonary undesirable effects including interstitial pneumonia, pulmonary oedema and pulmonary infiltrates have been reported in some cases with an outcome of respiratory failure or adult respiratory distress syndrome (ARDS) which may be fatal (see section 4.4).

#### 4.4 Special warnings and precautions for use

Rare pulmonary undesirable effects, in particular interstitial pneumonia, have been reported after GCSF administration. Patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk. The onset of pulmonary signs such as cough, fever and dyspnoea in association with radiological signs of pulmonary infiltrates and deterioration in pulmonary function may be preliminary signs of Adult Respiratory Distress Syndrome (ARDS).

Active substance X should be discontinued and appropriate treatment given in these cases.



## Example 4-safety profile

Most serious and/or frequently occurring adverse reaction. Frequencies stated as accurately as possible

Consistency with important identified risks in Safety Specification of Risk Management Plan

Active substance X 30 MIU/0.5 ml solution for injection or infusion

Rare pulmonary undesirable effects including interstitial pneumonia, pulmonary oedema and pulmonary infiltrates have been reported in some cases with an outcome of respiratory failure or adult respiratory distress syndrome (ARDS) which may be fatal (see section 4.4).

*Table Summary of Risk Management Plan*

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimization activities
<b>Important identified risks</b>		
Adult respiratory distress syndrome (ARDS) (PT: acute respiratory distress syndrome) Interstitial pneumonia (PT: interstitial lung disease) Pulmonary oedema (PT) Pulmonary infiltrates (PT: lung infiltrates) Respiratory failure (PT)	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR	Routine risk minimisation (labelling) Pulmonary undesirable effects including interstitial pneumonia, pulmonary oedema and pulmonary infiltrates in some cases with an outcome of respiratory failure or adult respiratory distress syndrome (ARDS) which may be fatal are mentioned in section 4.8 of the SmPC . Mention in section 4.4 of the SmPC that patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk. The onset of pulmonary signs such as cough, fever and dyspnoea in association with radiological signs of pulmonary infiltrates and deterioration in pulmonary function may be preliminary signs of ARDS





## Example 5-safety profile

Most serious and/or frequently occurring adverse reaction. Frequencies stated as accurately as possible

Consistency with Table of Adverse Reaction

Active substance X 1.5 mg hard capsules or infusion

### *Summary of the safety profile*

The most commonly reported adverse reactions are gastrointestinal, including nausea (38%) and vomiting (23%), especially during titration.

### *Tabulated Summary of Adverse Reactions (Extract)*

#### *Gastrointestinal disorders*

Very common

Nausea

Very common

Vomiting



## II.2 Tabulated list of adverse reactions

Introduce table with short paragraph stating source of safety database

Single table (or structured listing) of all adverse reactions with respective frequency category

[See next slide for table structure →](#)

[6 Introduction to tabulated list](#)

Separate tables are acceptable in exceptional cases where adverse profiles markedly differ depending on the use of the product. *For example, it might be the case for a product used for different indications (e.g. an oncology and a non oncology indication) or at different posologies*



## II.2 Tabulated list of adverse reactions (Table structure)

Present according to MedDRA system organ classification

A pragmatic approach to the location of terms should be taken in order to make the identification of adverse reactions simpler and clinically appropriate for the reader

[Click here for access to the Annex MedDRA of SmPC guideline](#)

Within each

- SOC, adverse reactions should be ranked under headings of frequency, most frequent reactions first
- Frequency grouping, adverse reactions should be presented in order of decreasing seriousness

Where additional details about an adverse reaction are described after the tabulated list, the reaction concerned should be highlighted in the table, for example with an asterisk referring to the detailed description

*Frequency Grouping*

*Very common ( $\geq 1/10$ );*

*common ( $\geq 1/100$  to  $< 1/10$ );*

*uncommon ( $\geq 1/1,000$  to  $< 1/100$ );*

*rare ( $\geq 1/10,000$  to  $< 1/1,000$ );*

*very rare ( $< 1/10,000$ );*

*Frequency not known (cannot be estimated from the available data)*

In some cases for common or very common reactions, and when necessary for clarity of information, frequency figures may be presented



## Example 6-introduction to tabulated list

Introduce table with short paragraph stating source of safety database

*(e.g. from clinical trials, post-authorisation safety studies or spontaneous reporting)*

Active substance X 25 mg hard capsules

Tabulated list of adverse reactions

Adverse reactions associated with active substance X obtained from clinical studies and post-marketing surveillance are tabulated below.



## II.3 Description of selected adverse reactions

Information characterising individual serious and/or frequently occurring adverse reactions, or those where there have been reports of particularly severe cases

[7 description](#)

[8 description](#)

[9 description](#)

[10 description](#)

[11 description](#)

[12 description](#)

Description of specific adverse reactions which may be useful to prevent, assess or manage the occurrence in clinical practice

FREQUENCY should be described together with for example information on: reversibility, time of onset, severity, duration, mechanism of action (if of clinical relevance), dose relationship, risk factors, differences between different dosage forms

Combination products: a statement at the beginning of this section pointing out which particular adverse reactions are usually attributable to which active substance of the combination, where known



## Example 7-description

Information characterising individual serious and/or frequently occurring adverse reactions, or those where there have been reports of particularly severe cases

Describe for example:

reversibility, time of onset, severity, duration, mechanism of action, (if of clinical relevance), (Frequency should be described)

A cross reference to Section 4.4 should be made if measures to be taken to avoid specific adverse reactions or actions to be taken if specific reactions occur are mentioned in 4.4

### Active substance X 1 g oral powder

#### *Description of selected adverse reactions*

Uncommon cases of severe cerebral oedema and hypermethioninemia were reported within 2 weeks to 6 months of starting active substance X therapy, with complete recovery after treatment discontinuation. High increases in plasma methionine levels in a range from 1,000 to 3,000  $\mu\text{M}$  were noted in these patients. As cerebral oedema has also been reported in patients with hypermethioninemia, secondary hypermethioninemia due to active substance X therapy has been postulated as a possible mechanism of action. For specific recommendations, refer to section 4.4.



## Example 8-description

Information characterising individual serious and/or frequently occurring adverse reactions, or those where there have been reports of particularly severe cases

Describe for example:

**time of onset, severity, mechanism of action**, (if of clinical relevance), (FREQUENCY should be described)

A cross reference to Section 4.4 should be made if measures to be taken to avoid specific adverse reactions or actions to be taken if specific reactions occur are mentioned in 4.4

### Active substance X mg/ml solution for infusion

#### Infusion-related reactions

Mild or moderate infusion-related reactions are very common comprising symptoms such as fever, chills, dizziness, or dyspnoea that occur in a close temporal relationship mainly to the first infusion.

Severe infusion-related reactions may commonly occur, in rare cases with fatal outcome. They usually develop during or within 1 hour of the initial infusion, but may occur after several hours or with subsequent infusions. Although the underlying mechanism has not been identified, some of these reactions may be anaphylactoid/anaphylactic in nature and may include symptoms such as bronchospasm, urticaria, increase or decrease in blood pressure, loss of consciousness or shock. In rare cases, angina pectoris, myocardial infarction or cardiac arrest have been observed.

For clinical management of infusion-related reactions, see section 4.4.



## Example 9-description

Information characterising individual serious and/or frequently occurring adverse reactions, or those where there have been reports of particularly severe cases

Describe for example:  
Severity

A cross reference to Section 4.4 should be made if measures to be taken to avoid specific adverse reactions or actions to be taken if specific reactions occur are mentioned in 4.4

### Active substance X 1 mg/24 h transdermal patch

#### *Description of selected adverse reactions*

##### Sudden onset of sleep and somnolence

Active substance X has been associated with somnolence including excessive daytime somnolence and sudden sleep onset episodes. In isolated cases “sudden onset of sleep” occurred while driving and resulted in motor vehicle accidents. See also section 4.4 and 4.7





## Example 10-description

Information characterising individual serious and/or frequently occurring adverse reactions, or those where there have been reports of particularly severe cases

Describe for example:  
Severity

A cross reference to Section 4.2 Information on the occurrence of withdrawal reactions may be mentioned here with cross-reference to section 4.2 in case of need for tapering off or advice on discontinuation of the product

A cross reference to Section 4.4

### Active substance X 30 mg hard gastro-resistant

#### *Description of selected adverse reactions*

Discontinuation of active substance X (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), fatigue, agitation or anxiety, nausea and/or, headache, irritability, diarrhoea, hyperhidrosis and vertigo are the most commonly reported reactions. Generally, for SSRIs and SNRIs, these events are mild to moderate and self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when active substance X treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).



## Example 11-description

Adverse reactions with very low frequency or with delayed onset of symptoms which may not have been observed in relation to the product, but which are considered to be related to the same therapeutic, chemical or pharmacological class. The fact that this is a class attribution should be mentioned

Active substance X 50 mg powder for solution for infusion

### Tetracycline Class Effects:

Glycylcycline class antibiotics are structurally similar to tetracycline class antibiotics. Tetracycline class adverse reactions may include photosensitivity, pseudotumour cerebri, pancreatitis, and anti anabolic action which has led to increased BUN, azotaemia, acidosis, and hyperphosphataemia (see section 4.4).



## Example 12-description

A cross reference to section 4.4 should be made if measures to be taken to avoid specific adverse reactions or actions to be taken if specific reactions occur are mentioned in 4.4

Any adverse reactions specific to excipients or residues from the manufacturing process

Active substance X suspension for injection in pre-filled syringe

This medicinal product contains thiomersal (an organomercuric compound) as a preservative and therefore, it is possible that sensitisation reactions may occur (see section 4.4).



## II.4 <Paediatric population>

The subsection should always be included (unless irrelevant) and describe:

- The extent and age characteristics of the safety database (*e.g. from clinical trials or pharmacovigilance data*)
- Any clinically relevant differences (i.e. in nature, frequency, seriousness or reversibility of adverse reactions) between the safety profiles in adult and in paediatric populations or in any relevant age groups

[13 paediatric](#)

[14 paediatric](#)

[15 paediatric](#)

Uncertainties due to limited experience should be stated

If the observed safety profile is similar in children and adults this could be stated: e.g. "*Frequency, type and severity of adverse reactions in children are <expected> to be the same as in adults*".

Differences should be presented by age group. A separate table listing such adverse reactions by frequency can be added stratified by relevant age groups if appropriate.

If some paediatric adverse reactions are considered common ( $\geq 1\%$  and  $< 10\%$ ), or very common ( $\geq 10\%$ ) the frequency needs to be provided in parentheses.

If relevant, symptoms of neonatal withdrawal should be listed in a separate paragraph with cross-reference with 4.6

[16 paediatric](#)



## Example 13-paediatric

If the observed safety profile is similar in children and adults this could be stated

The extent and age characteristics of the safety database (e.g. from clinical trials or pharmacovigilance data)

Active substance X 75 mg film-coated tablets

### Paediatric population

The safety assessment in children and adolescents is based on the safety data from the Phase II trial DELPHI in which 80 ART experienced HIV-1 infected paediatric patients aged from 6 to 17 years and weighing at least 20 kg received active substance X with low dose ritonavir in combination with other antiretroviral agents (see section 5.1). Overall, the safety profile in these 80 children and adolescents was similar to that observed in the adult population.



## Example 14-paediatric

Major difference with safety profile in adults

Extent and age characteristics of safety database

Cross reference to 4.4

### Active substance X 1 million IU/ml powder and solvent for solution for injection

#### Children and adolescent population

##### *Chronic Hepatitis C - Combination therapy with Y*

In clinical trials of 118 children and adolescents (3 to 16 years of age), 6 % discontinued therapy due to adverse reactions. In general, the adverse reaction profile in the limited children and adolescent population studied was similar to that observed in adults, although there is a paediatric- specific concern regarding growth inhibition as decrease in height percentile (mean percentile decrease of 9 percentile) and weight percentile (mean percentile decrease of 13 percentile) were observed during treatment. Within the 5 years follow-up post-treatment period, the children had a mean height of 44th percentile, which was below the median of the normative population and less than their mean baseline height (48th percentile). Twenty (21 %) of 97 children had a > 15 percentile decrease in height percentile, of whom 10 of the 20 children had a > 30 percentile decrease in their height percentile from the start of treatment to the end of long-term follow-up (up to 5 years).

During combination therapy for up to 48 weeks with X and Y, growth inhibition is observed, the reversibility of which is uncertain. In particular, decrease in mean height percentile from baseline to the end of the long-term follow-up was most prominent in prepubertal age children (see section 4.4).

Furthermore, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4% vs 1%) during treatment and during the 6 month follow-up after treatment. As in adult patients, children and adolescents also experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence) (see section 4.4). In addition, injection site disorders, pyrexia, anorexia, vomiting, and emotional lability occurred more frequently in children and adolescents compared to adult patients. Dose modifications were required in 30 % of patients, most commonly for anaemia and neutropaenia.



# Example 15-paediatric

Any **clinically relevant differences** (i.e. in nature, frequency, seriousness or reversibility of adverse reactions) between the safety profiles in adult and in the paediatric population, or in any relevant age groups, presented by age group

The extent and age characteristics of the safety database (e.g. from clinical trials or pharmacovigilance data)

## Active substance X 250 mg film-coated tablets

### Paediatric population

The adverse event profile of active substance X is generally similar across age groups and across the approved epilepsy indications. Safety results in paediatric patients in placebo-controlled clinical studies were consistent with the safety profile of active substance X in adults except for behavioural and psychiatric adverse reactions which were more common in children than in adults. In children and adolescents aged 4 to 16 years, vomiting (very common, 11.2%), agitation (common, 3.4%), mood swings (common, 2.1%), affect lability (common, 1.7%), aggression (common, 8.2%), abnormal behaviour (common, 5.6%), and lethargy (common, 3.9%) were reported more frequently than in other age ranges or in the overall safety profile. In infants and children aged 1 month to less than 4 years, irritability (very common, 11.7%) and coordination abnormal (common, 3.3%) were reported more frequently than in other age groups or in the overall safety profile.



## Example 16-paediatric

If relevant, symptoms of neonatal withdrawal should be listed in a separate paragraph with cross reference to 4.6

### Active substance X 2 mg/0.5 mg sublingual tablets

A neonatal abstinence syndrome has been reported among newborns of women who have received active substance X during pregnancy. The syndrome may be milder and more protracted than that from short acting full  $\mu$ -opioid agonists. The nature of the syndrome may vary depending upon the mother's drug use history (see section 4.6).





## II.5 <Other special populations>

Any clinically relevant differences (i.e. in nature, frequency, seriousness or reversibility of adverse reactions, or need for monitoring) specifically observed in other special populations

Special populations such as:

Elderly patients

Patients with renal or hepatic impairment

Patients with other disease or specific genotypes

[17 elderly](#)

[18 renal](#)  
[19 hepatic](#)

[20 other disease](#)  
[21 bodyweight](#)

Cross-reference to other sections such as 4.3, 4.4 or 4.5 may be added as appropriate

Adverse reactions may also be related to genetically determined product metabolism. Subjects or patients deficient in the specific enzyme may experience a different rate or severity of adverse reactions. This should be mentioned and where relevant correlated with data from clinical trials



## Example 17-other special populations

Active substance X 5 mg film-coated tablets

### Older population

At the 20mg dose, elderly ( $\geq 65$  years old) patients had higher frequencies of headaches (16.2% versus 11.8%) and dizziness (3.7% versus 0.7%) than younger patients ( $< 65$  years old).



## Example 18-other special populations

Active substance X 375 mg prolonged-release tablets

### Renal impairment

In patients with mild or moderate renal impairment (creatinine clearance 30–80 ml/min) compared to those with normal renal function (creatinine clearance > 80 ml/min), the most commonly reported events and their placebo-corrected frequencies included: constipation (8% versus 4%), dizziness (7% versus 5%), and nausea (4% versus 2%).



## Example 19-other populations

Active substance X 0.44 mg/ml solution for injection

### Patients with hepatic impairment

Patients with ALT or AST  $> 3 \times$  ULN experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia. Although data are limited, patients with bilirubin  $> 1.5 \times$  ULN also have a higher incidence of Grade 4 neutropenia and febrile neutropenia (see also sections 4.2 and 5.2).



## Example 20-other populations

### Active substance X 150mg hard capsules

Patients co-infected with hepatitis B and/or hepatitis C virus

Among 1,151 patients receiving active substance X 400 mg once daily, 177 patients were co-infected with chronic hepatitis B or C, and among 655 patients receiving active substance X 300 mg once daily with active substance Y 100 mg once daily, 97 patients were co-infected with chronic hepatitis B or C. Co-infected patients were more likely to have baseline hepatic transaminase elevations than those without chronic viral hepatitis. No differences in frequency of bilirubin elevations were observed between these patients and those without viral hepatitis. The frequency of treatment emergent hepatitis or transaminase elevations in co-infected patients was comparable between active substance X and comparator regimens (see section 4.4).



## Example 21-other populations

Active substance X 375 mg prolonged-release tablets

### e. Other special populations

#### Low weight

In general, the type and frequency of adverse reactions reported in patients with low body weight (60 kg) were similar to those of patients with higher weight (> 60 kg); however, the placebo corrected frequencies of the following common adverse reactions were higher in low body weight than heavier patients: nausea (14% versus 2%), vomiting (6% versus 1%), and hypotension (4% versus 2%).



## III.1 Guidance on the estimation of frequency of adverse reactions

**[Click here for link to 'Further guidance on the estimation of frequency of adverse reactions' of the SmPC guideline](#)**

**[Points to consider on application with 1. Meta-analyses; 2. One pivotal study section II.4 provide some guidance on pooled analyses of safety endpoints](#)**



## III.2 Information not to be included in section 4.8



Adverse events, without at least a suspected causal relationship



Comparative frequency statements other than those described in the subsection entitled '*Further guidance on the estimation of frequency of adverse reactions*'



Statements of general good tolerability such as "well tolerated"



Claims regarding absence of specific adverse reactions





## IV. FAQs (1/2)\*

1. [Which information should be included in the summary of safety profile?](#)
2. [What is the difference between an adverse event and an adverse reaction? Which information should be included in the SmPC?](#)
3. [When is it acceptable to have two tables of adverse reactions?](#)
4. [Should adverse reactions from off-label use be included in section 4.8?](#)
5. [Can the tabulated list of adverse reactions be presented as comparative table of frequency between the product and the comparator?](#)
6. [Can adverse reactions not observed in clinical trials at the time of initial marketing authorisation be included in section 4.8 ?](#)
7. [Should adverse reactions derived from spontaneous reporting be included in the single tabulated list if adverse reactions?](#)
8. [How should SmPC section 4.8 be updated after the initial marketing authorisation?\\*](#)
9. [Is there exemption when applying the "rule of 3" to estimate the frequencies of spontaneously reported adverse reactions \(e.g. in the case of an orphan medicinal products with a limited clinical safety database\)? \\*](#)
10. [When and how should differences in the safety profile in a subset of the populations be stated in the SmPC? \\*](#)



## IV. FAQs (2/2)\*

11. Should new signals identified which are related to a disorder/symptom already listed in the SmPC be included?\*
12. Should adverse reactions related to a procedure necessary for the preparation or administration of a product (e.g. surgical procedures collecting or administering cells in cell therapy) be presented in section 4.8?\*



# 1. Which information should be included in the summary of safety profile?

- The summary of safety profile should provide information on the most serious and/or most frequent occurring adverse reactions. It should not be a summary of the safety database. Brief information on the source of the safety database can be provided to introduce the tabulated list of adverse reactions



## 2. What is the difference between an adverse event and an adverse reaction? Which information should be included in the SmPC?

- An adverse event is any untoward medical occurrence in a patient administered a drug and which does not necessarily have to have a causal relationship with the treatment. An adverse reaction is a response to a drug which is noxious and unintended and which occurs at doses normally used in man
- It is critical to include all adverse reactions and not adverse events in the SmPC and it is a matter of thorough assessment to classify an adverse event as an adverse reaction taking into account all relevant clinical trials' or post-marketing data. There is not a single simple mathematical tool to decide on the causal relationship between an adverse event and a product. For example, a low frequency is not a justification for deletion of an adverse reaction. Further information can be found in ["Section 2.5.5 Safety overview' in the ICH guideline M4 E"](#)
- In summary, inclusion or deletion of information in section 4.8 is based on a thorough assessment of whether or not a causal relationship between the product and each individual adverse event is at least a reasonable possibility



### 3. When is it acceptable to have two tables of adverse reactions?

- The purpose of a single table of adverse reactions with their respective frequency is to integrate comprehensive data from different sources to provide clear and informative data to healthcare professionals
- Only in exceptional cases can two tables of adverse reactions be acceptable: when the adverse reaction profiles markedly differ depending on the use of the product e.g. different indications (e.g. an oncology and a non-oncology indication) or at different posologies.



## 4. Should adverse reactions from off-label use be included in section 4.8?

- The SmPC is the basis of information for HCP on how to use the medicinal product safely and effectively in the approved indication. Information on non-approved use is not expected in the SmPC (with the exception of data in the paediatric population). However, if HCP need to be warned of specific adverse reactions due to an off label use of the medicinal product, this information should be included as a warning in section 4.4 “Special warnings and precautions for use” of the SmPC



## 5. Can the tabulated list of adverse reactions be presented as comparative table of frequency between the product and the comparator?

- The purpose of the single table is to be informative to healthcare professionals by integrating comprehensive data from different sources and listing all adverse reactions with their frequency category (from very common to very rare). Presenting the adverse reactions in a comparative table is useful for assessment purpose and is better presented in the EPAR. Specific frequency information on adverse reactions requiring particular attention can be presented in other parts of section 4.8, i.e. summary of safety profile (for the most serious or most frequent adverse reactions) or in the description of selected adverse reactions which could also describe other relevant information e.g. the severity of the reaction



## 6. Can adverse reactions not observed in clinical trials be included in section 4.8 at the time of initial marketing authorisation?

- Yes. The SmPC guideline states that subsection “Description of selected adverse reactions” should inform on adverse reactions with very low frequency or with delayed onset of symptoms which may not have been observed in relation to the product, but which are considered to be related to the same therapeutic, chemical or pharmacological class e.g. anaphylactoid reactions in vaccines. The fact that this is a class attribution should be mentioned





## 7. Should adverse reactions derived from spontaneous reporting be included in the single tabulated list of adverse reactions? (1/2)

- The SmPC guideline states that a single table should list all adverse reactions with their respective frequency category. The table should be introduced with a short paragraph stating the source of the safety database (e.g. clinical trials, post-authorisation safety studies, spontaneous reporting). The purpose is to be informative to healthcare professionals by integrating comprehensive data from different sources. Therefore, it is essential to adequately combine data (new and old) from different sources in a single table. The guideline provides some guidance to facilitate these recommendations.
- At the time of initial marketing authorisation, most of the safety data are combined and often come from pooled analysis across suitable studies, which is usually considered to provide the best estimate of frequency
- See next slide



## 7. Should adverse reactions derived from spontaneous reporting be included in the single tabulated list of adverse reactions? (2/2)

- After the initial authorisation, where new data become available, a distinction should be made between new adverse reactions and adverse reactions already included in the SmPC:
  - If an adverse reaction is already included, the SmPC guideline states “If the choice of the frequency category is based on different sources, the category representing the highest frequency should be chosen unless a more specific method has been applied”
  - If an adverse reaction is new, it should be included after estimation of its frequency. An option of estimation frequency provided by the guideline is the 3/X methodology; if the adverse reaction was not observed in clinical trials, then the upper limit of the 95% confidence interval is not higher than 3/X, with X representing the total sample size summed up across all relevant clinical trials and studies (e.g. those with a follow-up long enough to detect the adverse reaction)



## 8. How should SmPC section 4.8 be updated after the initial marketing authorisation?\*(1/2)

- Section 4.8 should integrate comprehensive safety data from different sources (clinical trials, post-authorisation safety studies, spontaneous reporting) and should be regularly reviewed and updated to ensure that appropriate information is continuously provided.
- Best evidence assessment of new and existing safety information, including assessment of causality, severity and frequency of new signal will drive the update of the SmPC.
- In case of a new signal is identified and a causal relationship is at least reasonably possible:
  - If the adverse effect is not yet covered by an already listed adverse reaction, it should be listed in the tabulated list of adverse reactions with its best-estimated frequency category. As any adverse reaction, it can then be further characterised, e.g. in term of severity if useful to prevent, assess or manage the adverse reaction in clinical practice;
  - If the adverse effect is already covered by a listed adverse reaction, information should be updated if current information is not explicit in terms of description, frequency or severity of the reaction. For example, the frequency category can be updated in the tabulated list, or, the adverse reaction can be further characterised (e.g. adding newly reported hypersensitivity reactions or a new type of infection of greater severity.).



## 8. How should SmPC section 4.8 be updated after the initial marketing authorisation?\*(1/2)

- In case of new safety data come from a different use of the medicinal product:
  - If adverse drug reaction profiles are considered similar (e.g. different indication but same posology), the new safety data should be merged in the existing (single) table, to ease readability by healthcare professionals:
  - If adverse drug reaction profiles clearly differ depending on the use of the product (e.g. new dosing schedule), the adverse reactions should be presented in a separate table:
  - In case safety profiles only differ regarding specific adverse reactions, this could be highlighted in the description of those selected adverse drug reactions. This could be also apply when data come from a different population, e.g. elderly or children.
- When adding information in section 4.8, it should also be ensured that the summary of safety profile is updated if necessary, e.g. in adding newly identified important serious adverse reaction, or, important difference in the safety profile in a newly approved use.



## 9. Is there an exemption when applying the “rule of 3” to estimate the frequencies of spontaneously reported adverse reactions (e.g. in the case of an orphan medicinal products with a limited clinical safety database)?\*

- In case of an orphan medicinal product, the authorisation may have been granted based on limited data because the disease is rare. Therefore, applying the 3/X rule may lead to categorise a new adverse reaction in this methodology but this should be justified appropriately i.e. in explaining why the frequency category resulting with the 3/X methodology does not lead to a reasonable estimation of the frequency category (e.g. pharmacovigilance data on the reporting rate of the specific adverse reaction and on patient exposure to the medicinal product supports that the frequency of the adverse reaction (or another justified methodology for assessing frequency) would be rarer than with the 3/X methodology).
- The frequency unknown i.e. cannot be estimated from the available data, should only be used as last resort, because it is uninformative and opened to interpretation.



## 10. When and how should differences in the safety profile in a subset of the population be stated in the SmPC?\*

- Information on any clinically relevant differences (.e. in nature, frequency, seriousness or reversibility of adverse reactions, or need for monitoring) observed in a subgroup (e.g. elderly, patients with renal impairment, patients with hepatic impairment, patients with other diseases or a specific genotype) should be described in the SmPC. If there are special patient groups at increased risk of an adverse drug reaction, this risk should be clearly described in section 4.4, together with any need for special precautions or monitoring.
- Main data illustrating the differences in the safety profile of a specific subgroup can be presented at the end of section 4.8, under a subheading identifying the subgroup. Major differences between safety profiles may also be communicated in the summary of safety profile at the beginning of section 4.8.
- Please note that for paediatric population there is existing guidance in the SmPC guideline.



## 11. Should new signals identified which are related to a disorder/symptom already listed in the SmPC be included?\*

- If new signal is identified and the causality assessment confirms that there is at least a reasonable causal relationship, it should be listed in section 4.8.
- If the identified signal is covered by an adverse reaction already listed in the SmPC, it should be considered if current information is sufficiently explicit in terms of description and of clinical relevance, in particular regarding severity and frequency, e.g. if frequency or severity of the identified signal are greater than the already listed adverse reaction, information should be updated.



## 12. Should adverse reactions related to a procedure necessary for the preparation or administration of a product (e.g. surgical procedures collecting or administering cell in cell therapy) be presented in section 4.8?\*

- Yes, specific aspects of the treatment related to the use of medicinal product or its effects should be mentioned and all adverse reactions listed in section 4.8.
- When procedures are intrinsic parts of the treatment, their adverse reaction should be communicated. Providing information on the root and timing of the different adverse reactions is however important not only to clearly describe the risks in the short-term and longer term but also to facilitate their prevention, monitoring and management. This could be achieved with a short statement distinguishing adverse reactions related to the medicinal product itself versus those related to the procedure in the summary of safety profile. All adverse drug reactions from the medicinal product and from the procedure can be listed in a single list of adverse reactions.
- The root and timing of the various adverse reaction may be specified through use of footnotes or when describing selected adverse reactions.





# 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