



EUROPEAN MEDICINES AGENCY
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Committee for Medicinal Products for Human Use (CHMP)

Appendix 3 to the Guideline on the clinical evaluation of anticancer medicinal products

The Summary of Product Characteristics for an Anticancer medicinal product – mock-up of 4.8

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Appendix 3: to the Guideline on the clinical evaluation of anticancer medicinal products

The Summary of Product Characteristics for an Anticancer medicinal product:

- mock-up of SmPC section 4.8: Undesirable effects

This mock-up is proposed as a tool to facilitate the review of the presentation and update of section 4.8 of anticancer products, in accordance with the recommendations of the SmPC guideline, the QRD template and the Anticancer guideline, which should be read for full guidance (See References).

Information presented in 4.8 should reflect the expected safety profile when used in the approved indication(s). Estimation of frequency will therefore often be based on data from a pooled population of patients within the approved indication(s) from different phases of development, exposed to the recommended posology (doses and duration). Exceptions may include situations where the safety population in the approved indication and/or with the recommended posology is small, and a broader population therefore is considered to provide a better estimate of the safety profile. In addition, other data should be considered and reflected in the SmPC, if relevant to describe the safety profile in the approved indication, e.g. rare effects that are not dose-dependent or identified at the recommended dose in a different population. When pooling safety data, the possibility of any bias due to differential study factors, including patient population and disease under study, should be considered. Particular consideration should be given to a potential dilution of negative effects due to the inclusion of studies of inadequately short duration.

4.8 Undesirable effects¹

Summary of the safety profile

The text in this subsection should capture the essence and key elements of the safety profile; use template text below as appropriate, alternative wording may be used if appropriate.

The most common adverse reactions are; *list the most common adverse reactions with their respective frequency, in the order of decreasing frequency.*

<The most common severe adverse reactions (NCI CTAE² Grade ≥ 3) are; *list the most common severe adverse reactions with their respective frequency, in the order of decreasing frequency.*>

<The most common serious adverse reactions are; *list the most common serious adverse reactions with their respective frequency, in the order of decreasing frequency.*>

¹ In case the adverse reaction profiles of a product markedly differ from one indication, posology and/or combination to another, information could be presented separately for each indication in each subsection where appropriate. In other situations, common information should be presented first followed with a statement informing on any clinically relevant safety difference if any.

² National Cancer Institute Common Terminology Criteria for Adverse Events. When referring to this classification, the definition of the grade should be presented as follows; < *The severity of adverse drug reactions was assessed based on the CTCAE, defining grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4=life threatening, and 5=death.*>

<The frequency of treatment discontinuation due to adverse reactions is *<add frequency>*. The most common adverse reactions leading to treatment discontinuation are: *list the adverse reactions leading to treatment discontinuation with their respective frequency, in the order of decreasing frequency.*>

<The frequency of dose modification or interruption due to adverse reactions is *<add frequency>*. The most common adverse reactions leading to dose modification or interruption are: *list the adverse reactions leading to dose modification or interruption with their respective frequency, in the order of decreasing frequency.*>

The fact that major differences in the safety profile exist for different indications, posologies or combination treatments may be briefly highlighted here, if relevant. See footnote 1.

If known, it may be helpful to indicate the timing when adverse reactions occur or whether an adverse reaction is associated with long-term use, e.g. cumulative toxicity.

If known, it may be helpful to indicate an identified clinically relevant difference in a subpopulation.

Tabulated list of adverse reactions

Adverse reactions reported in clinical trials <and in post-marketing> are listed by system organ class and by frequency.

When considered necessary for contextualising how frequencies of adverse reactions have been estimated, the safety data source may be shortly further described as illustrated below;

Example of wordings

Unless otherwise stated, the frequencies of adverse reactions are based on all-cause adverse event frequencies identified in *<add total number>* patients exposed to *<add INN>* during a median duration of *<add time>* in clinical trial(s). <See section 5.1 for information on <the main characteristics of participants in> the main clinical trial(s).>

The frequencies of adverse reactions is based on <pooled data from> *<add number>* clinical <phase 1/2/3> trials with *<add number>* patients. Patients were exposed to X during a median of *<add time>* months. <Additional adverse reactions were reported post-marketing.> <The adverse reaction frequencies from clinical trials are based on all-cause adverse event frequencies, where a proportion of the events for an adverse reaction may have other causes than the drug, such as the disease, other medication or unrelated causes.>

Frequencies are defined as: 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 available data)".

System organ class	Frequency category	Adverse reaction(s) ^{3, 4, 5, 6}
See list in the Appendix II of QRD product information template .	very common	
	common	
	uncommon	
	rare	
	very rare	

³ In case adverse reactions are grouped together as a single adverse reaction (e.g. rash) a description of the most frequent or important ADRs that each single term represents should be included as a footnote, unless obvious.

⁴ Where additional details about an adverse reaction are described in section c), the reaction concerned should be highlighted, for example with an asterisk, and, "see section Description of selected adverse reactions " should be included as a footnote.

⁵ When it improves the clarity of the information, frequency figures may be presented in the table. When an adverse reaction is then added from another source than the initial data set, this may be communicated with a footnote to the table, e.g., "From spontaneous reporting", "From post-marketing data" etc.

⁶ When it improves the clarity of the information, e.g. when there are many adverse reactions where the incidence of grade 3 or more adverse reactions is common or very common, the grade 3 or more incidences could be presented in an additional column to avoid lengthy description of selected adverse reactions without additional information in the next subsection. In such case, the incidences of the adverse reactions for all grades should be presented in one column followed with the incidences for grade 3 or more in the other column.

System organ class	Frequency category	Adverse reaction(s) ^{3, 4, 5, 6}
	frequency not known (cannot be estimated from available data)	

Description of selected adverse reactions

This subsection should not repeat information or recommendations already presented earlier in the SmPC e.g. in section 4.2 or 4.4, but present factual data, which support them and could be useful in clinical practice, as illustrated with the proposed standard statement:

Adverse reaction "A":

In clinical trials *<cross-refer to 5.1 or specify if needed>*, "A" occurred in *<add figure>*% of patients⁷. Incidences of Grade 3/4 "A" were *<add figure(s)>*. *<"A" was fatal in <add figure> % of patients>*. Median time to *<first>* onset was *<add time (range)>*. Median duration of "A" was *<add time (range)>*.

<"A" was managed with <...> (see sections 4.2 and 4.4).>

<"A" led to dose reduction/temporary interruption in <add figure> %.> *< Treatment was permanently discontinued in <add figure>%.>*

<A dose relationship was <not> shown to be associated with the occurrence of "A".>

Comparative data, i.e. information from the control arm in randomised studies, may be presented for selected reactions of interest for contextualisation. See footnote 7.

Presentation of time-adjusted adverse reaction frequencies may sometimes be warranted.

Information on dose-relationship, the mechanism of the adverse reactions (if specific) or a class attribution may be communicated if relevant.

<Special populations>⁸

X has been studied in N patients <age range or other characteristic>. No relevant difference in safety profile was observed, except <...>.

References:

- [SmPC guideline](#),
- [SmPC Advisory Group training presentation on section 4.8](#),
- [QRD Product Information templates](#),
- [CHMP guideline on Evaluation of anticancer medicinal products in man](#),
- [CHMP Points to consider on application with 1. Meta-analyses; 2. One pivotal study](#)

⁷ Incidence in comparator group may be considered if helping in the contextualisation of the risk. (e.g. When a common, very common or serious adverse reaction (e.g. suicide) also occurs in the placebo group with a relevant frequency, both incidence rates can be stated to put the risk into perspective)

⁸ This could consist e.g. in patients receiving the product in combination with another anticancer product, when the product is indicated both in monotherapy or in combination with other product(s), elderly, paediatric population (See *SmPC guideline*), or any relevant subset(s)...