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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Example of mock-up of the SmPC section 4.8 for anticancer products

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.

4.8 Undesirable effects[1]

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 <serious> <severe> adverse reactions are; *list the most common serious adverse reactions and/or the most common severe NCI CTAE[2] Grade ≥3 adverse reactions in identifying them as such (e.g. "severe anaemia of grade 3 or more"), with their respective frequency, in the order of decreasing frequency*.

<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 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.

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 at *<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

[1] In case the adverse reaction profiles of a product markedly differ from one indication 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

Example of wordings

than the drug, such as the disease, other medication or unrelated causes.>

< 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.>

Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to <1/1,000); very rare (< 1/10,000); "frequency not known (cannot be estimated from available data)". Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

System organ class	Frequency category	Adverse reaction(s)[3], [4], [5], [6]
• Infections and infestations • Neoplasms benign, malignant and unspecified (including cysts and polyps) • Blood and lymphatic system disorders • Immune system disorders • Endocrine disorders • Metabolism and nutrition disorders • Psychiatric disorders • Nervous system disorders • Eye disorders • Ear and labyrinth disorders • Cardiac disorders • Vascular disorders • Respiratory, thoracic and mediastinal disorders • Gastrointestinal disorders • Hepatobiliary disorders • Skin and subcutaneous tissue disorders • Musculoskeletal and connective tissue disorders • Renal and urinary disorders • Pregnancy, puerperium and perinatal conditions • Reproductive system and breast disorders • Congenital, familial and genetic disorders • General disorders and administration site conditions • Investigations • Injury, poisoning and procedural complications • Surgical and medical procedures • Social circumstances	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 ADRs that each single term represents should be included as a footnote.

[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 c)" should be included as a footnote.

[5] In some cases, for common or very common reactions, and when it improves the clarity of the information, frequency figures may be presented in the table.

[6] In some cases, e.g. when the incidence of grade 3 or more adverse reactions is high for many adverse reactions, these incidences could be presented in an additional column to avoid lengthy description of selected adverse reactions without additional information in the next subsection.

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 patients[7].
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/interruption in *<add figure>* %. Treatment was 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 <…>.

[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 patient receiving the product in combination with another anticancer product, when the product is indicated both in monotherapy or in combination with other product(s).