EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines Division

Severe cutaneous adverse reactions (SCARs)

Standard template wording for product information

1. Background

The following templates contain standard wordings for sections 4.4 and 4.8 of the SmPC (Summary of Product Characteristics) and for sections 2 and 4 of the Patient Leaflet and are intended to be used in any regulatory procedures when SCARs are to be reflected in the product information.

2. Standard statements for the SmPC

Section 4.4

	Template *(Text in Italic only for information and not to be included in the SmPC)*
1	Severe cutaneous adverse reactions (SCARs) [*SPECIFY AS APPROPRIATE*: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), generalised bullous fixed drug eruption (GBFDE)], which can be life-threatening or fatal, have been reported in association with <medicine> treatment (see section 4.8).
2	*{For prescription only and over-the-counter medicinal products:}* Patients should be advised of the signs and symptoms of the severe cutaneous adverse reactions and should seek medical advice from their physician immediately when observing any indicative signs or symptoms. If signs and symptoms suggestive of these reactions appear, <medicine> should be withdrawn immediately and an alternative treatment considered (as appropriate).
3	{*If known and helpful to manage the risk*:}

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	These reactions are estimated to affect [xx] per [xx,000] patients <in countries with mainly Caucasian populations, but the risk is [*SPECIFY HOW MUCH*] higher in patients of [*SPECIFY*] ancestry>. The HLA-B*XX:XX allele(s) has been identified as a genetic risk factor for <medicine> associated SJS/TEN (and possibly other serious hypersensitivity reactions) in patients of Han Chinese, Thai, Korean, Japanese and European descent. *{Can be expanded further:}* Up to xx% of people of [Han Chinese, African and Indian] ancestry whereas only xx% of [European and Japanese] patients carry the HLA-B*XX:XX allele. Screening for HLA-B*XX:XX should be considered before starting treatment with <medicine> in these patients. If these individuals test positive, <medicine> should not be started unless there are no other reasonable therapeutic options and the expected benefits of use outweigh the potential risks. *Patients who are found to be negative for HLA-B*XX:XX are still at risk of developing SJS/TEN.* *{Risk factors can be added based on known data, such as:}* Additionally, the overall risk appears to be higher in patients with: - high initial doses of <medicine> or exceeding the recommended dose escalation of <medicine> therapy (see section 4.2) - concomitant use of <medicine 2> (see section 4.2). - a history of sulphonamide allergy. *This might qualify for additional risk minimisation.*
4	If the patient has developed a severe cutaneous adverse reaction such as [*SPECIFY AS APPROPRIATE* SJS, TEN, DRESS, AGEP or GBFDE] with the use of <medicine>, treatment with <medicine> must not be restarted in this patient at any time. *{A specific text for the paediatric population can be considered as appropriate:}* In children, the initial presentation of a rash can be mistaken for an infection. Physicians should consider the possibility of a reaction to <medicine> in children that develop symptoms of rash and fever during therapy with <medicine>.
5	Cross-reactivity can occur between <medicine> and <medicine2> and [xx %] patients who experienced a serious skin reaction with <medicine>[1] may be at risk of serious skin reactions with <medicine2>.

If in the SmPC section 4.4 there is already a statement of some types of SCARs, e.g. as a class effect following the previous EU regulatory procedure, the statement regarding the newly identified risk of the definite type of the SCAR related to the use of the particular active substance can be aligned to the already existing wording:

Section 4.4 Special warnings and precautions for use

<u>Severe cutaneous adverse reactions</u>

[1] Consider whether such cross-reactivity should be included as a contraindication for use in SmPC section 4.3. If reliable data exist and a contraindication is introduced, add reference to 4.3 here accordingly.

<Type of the SCAR> has been reported in relation to <active substance> containing products.

Section 4.8

Tabulated list of adverse reactions

Skin and subcutaneous tissue disorders SOC: Frequency: [*AS APPROPRIATE*]

[*SPECIFY AS APPROPRIATE* Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), generalised bullous fixed drug eruption (GBFDE)].

3. Standard statements for the Patient leaflet

If there is a warning in section 4.4 in the SmPC or a contraindication in section 4.3 for patients who previously have experienced SCARs, that information would be relevant to list in section 2, with a cross-reference to section 4 where information regarding symptoms that the patient should be aware of are listed. If there is additional available information, for example that the skin reaction is more common in certain groups, this could be equally stated in section 2 with a cross reference to section 4.

Section 2 - What you need to know before you use <medicine>

DO NOT TAKE <medicine> - OR - TELL YOUR DOCTOR BEFORE TAKING <medicine>:

- If you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking <medicine> or other <related medicines>.

Warnings and precautions - Take special care with <medicine>:

This medicine can cause serious skin reactions. Stop using <medicine> and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.

{Specify if known to mirror the information in the SmPC section 4.4: These serious skin reactions can be more common in people from some Asian countries. The risk of these reactions in patients of Han Chinese or Thai origin may be predicted by testing a blood sample of these patients. Your doctor should be able to advise if a blood test is necessary before taking <medicine>.*}*

Section 4 – Possible side effects

According to annotated QRD regarding section 4 of the PL, the section should generally be divided into two sections bearing in mind that there should be sufficient patient-friendly description of the overt clinical signs and symptoms to enable the patient to recognise all side effects which may occur as set out in section 4.8 of the SmPC:

1) the most serious side effects need to be listed prominently first with clear instructions to the patients on what action to take (e.g. to stop taking the medicine and/or seek urgent medical advice).

2) then a list of all other side effects, listed by frequency and starting with the most frequent (without repeating the most serious included above).

Therefore, severe cutaneous adverse reactions should be listed first in section 4, under the below heading:

Stop using <medicine> and seek medical attention immediately if you notice any of the following symptoms of serious skin reactions: (use either of them as appropriate):

- reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms [SPECIFY Stevens-Johnson syndrome (SJS)/ toxic epidermal necrolysis (TEN) or generalised bullous fixed drug eruption (GBFDE)].
- [*If only GBFD is mentioned in the PL*:] distinct, reddish or purplish, round or oval patches with blisters and peeling of the skin [generalised bullous fixed drug eruption (GBFDE)]
- Widespread rash, high body temperature and enlarged lymph nodes (DRESS syndrome or drug hypersensitivity syndrome).
- A red, scaly widespread rash with bumps under the skin and blisters accompanied by fever. The symptoms usually appear at the initiation of treatment [acute generalised exanthematous pustulosis (AGEP)].

The frequency for occurrence of the reaction should be specified, as appropriate.

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