1 What should be done about the declaration of excipients containing sodium if the sodium content is less than 1 mmol (23 mg)?

A statement must be included in the medicinal product information texts even where sodium content <1mmol (23 mg) (see the corresponding entry in Annex 3a TPLRO). Therefore, since any content of sodium necessitates the inclusion of a warning, sodium is always considered to be an excipient of particular interest during oral or parenteral administration, regardless of the quantity, i.e. the threshold for sodium is effectively zero.

Hence the need for the quantitative declaration in the Information for healthcare professionals and the qualitative declaration on the packaging materials.

2 How should the quantitative declaration appear in the Information for healthcare professionals if the precise sodium content is not known or is variable, e.g. if sodium hydroxide is used for pH adjustment? Revised November 2020

In such cases either the maximum content should be declared, or the sodium content stated as a range.

Example of declaration as maximum content:
According to Ph.Eur., croscarmellose sodium has a substitution grade of up to 0.85 (i.e. on average it contains a maximum of 0.85 O-carboxymethyl groups per glucose unit). If all O-carboxymethyl groups of the polymer are present as sodium salt, then – based on the resulting molecular formula, e.g. $C_{770}H_{1085}O_{670}Na_{85}$ calculated for 100 monomer units, of which 85 are simply substituted [$C_8H_{11}O_7Na$] and 15 are unsubstituted [$C_6H_{10}O_5$]), – a maximum sodium content of approximately 9% results.

Example of declaration as a range:
According to Ph.Eur., carboxymethyl starch sodium (type A) contains 2.8-4.2% sodium.

Alternatively, if sodium hydroxide is used only in very small quantities to adjust the pH value of liquid pharmaceutical forms, the quantitative information on sodium content may be omitted and the additional information “(for pH adjustment)” included instead.

3 How must excipients containing sodium be declared on the folding carton?

The exact sodium-containing excipients should preferably be stated individually. If several excipients containing sodium are included in the medicinal product, a blanket statement is possible (e.g. "contains sodium compounds").

4 If an active substance is formulated as a sodium salt and already declared accordingly, and if no other sodium-containing excipient is included in the medicinal product, does "sodium" still have to be declared additionally on the folding carton as an excipient?

No, the full active substance declaration, e.g. "xy as xy sodium" is sufficient in this case.

5 A particular product includes a fragrance containing allergens, which must be listed as excipients of particular interest according to Annex 3a TPLRO. Is it correct, therefore, that the fragrance followed by the allergens in brackets must be stated on the packaging materials "Fragrance (allergen 1, allergen 2, etc.)"?

In this case, there are several correct options for the declaration on the folding cartons:

One variant would be similar to the suggested option, "Fragrance (contains allergen 1, allergen 2 and allergen 3)". Alternatively, only the allergens contained in the product can simply be listed under the composition, or a sentence can be added at the end of the composition, e.g. "contains a fragrance with allergen 1, allergen 2 and allergen 3.".

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6 If substances listed in Annex 3a TPLRO – for example sodium, potassium, glucose and soya bean oil – are present as active substances, does the requirement according to Annex 3a TPLRO need to be implemented even if contraindications and warnings that are specific to these active substances, or to the therapeutic class of the medicinal product, are already included in the Information for healthcare professionals?

The warnings in Annex 3 a TPLRO apply to the use of the corresponding substances as excipients. If sodium, potassium, glucose or soya bean oil are included as active substances and if corresponding entries are already included in the Information for healthcare professionals, then this is usually sufficient.

7 May the quantity of excipients of particular interest also be specified in the Patient information?

Yes, this is possible.

8 Do the statements concerning the excipients of particular interest, described under "Information in the package leaflet" in Annex 3a of the TPLRO, need to appear on the packaging if no Information for healthcare professionals or Patient information is required? Or can this "Information in the package leaflet" be omitted in this case?

In these cases the statements should be included on the packaging, in accordance with sections 1.1 and 1.4 of Annex 3 of the TPLRO.

9 For co-marketing medicinal products, the text in the product information and on the packaging elements must be identical to that for the basic medicinal product. In this scenario, what is the procedure for the full declaration, the content of which is, after all, dependent on – and must be taken over from – the basic medicinal product (for the basic medicinal product the full declaration is implemented on the basis of its own renewal cycle)?

Co-marketing medicinal products are a special case here, i.e. the modifications under the revised TPLRO are not linked to renewal. As soon as the modifications under the revised TPLRO have been implemented for the basic product, the corresponding changes must be implemented by means of a type IA / IB variation (the application type A.101 should be used for this purpose).

10 Can the full declaration be included in ongoing applications under the terms of the old legislation?

Inclusion in ongoing procedures according to the old legislation is not possible as a rule. An exception may be made only for new applications, in which case the following should be observed:

- The integration of the new requirements according to the revised TPLRO can lead to an additional loop if corrections are required or questions arise (i.e. risk of a delayed official decision on first authorisation).
- For the additional work required for integrating the new requirements according to the revised TPLRO, a fee is charged when the new medicinal product is authorised.
- The applicant is solely responsible for submitting the application. Swissmedic does not refer to this option either in the "List of Questions" or in the Preliminary decision of approval.

11 Are collective applications permitted for variation A.109?

No.

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12 Do the constituents of printing inks on the back of transdermal plasters have to be declared? New from September 2020

No, a general declaration as “printing ink” is sufficient, as there is no direct contact with the skin, and usually no relevant penetration through the plaster material.

13 Do the constituents of inhaler capsule shells have to be declared?
New from September 2020

No, as in this case the capsule shell forms part of the packaging material and is not administered.

14 On 1 July 2020 the entry into force of the revised Annex 3a of the TPLRO was published announced on the Swissmedic website. The revision took effect on 1 July 2020. Are there any transitional periods for implementation? What is the procedure for implementation?
New as of October 2020

Since 1 July 2020, the revised Annex 3a of the Therapeutic Products Licensing Requirements Ordinance (TPLRO, SR 812.212.22) has applied. This means that, as of this date, the requirements for pharmaceutical excipients of particular interest must be complied with and any applications for variations (also in connection with the full declaration) must be submitted to Swissmedic in accordance with Arts. 21-24 of the Therapeutic Products Ordinance (TPO; SR 812.212.21) in conjunction with TPLRO Art. 22a ff.
In the case of authorised medicinal products for which adjustments in line with the TPLRO revision as of 1.1.2019 have not yet fallen due, therefore, the revised Annex 3a TPLRO must be taken into account for the future submission of variation A.109. In the case of medicinal products for which variation A.109 has already been completed, an A.100 variation must be submitted where necessary so that the requirements of the Annex revision of 1.7.2020 are implemented. In these cases, there is no transitional period. The procedure outlined here also applies to subsequent revisions of Annex 3a TPLRO.

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