EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Information Management

Coding of indications in the eXtended EudraVigilance Medicinal Product Dictionary (XEVMPD)

Best practice for coding of indications based on section 4.1 of the Summary of Product Characteristics (SmPC) using MedDRA terminology

Background

In accordance with Article 57(2) of Regulation 726/2004, marketing authorisation holders (MAHs) are obliged to electronically submit information on all medicinal products authorised for human use in the European Union (EU) and the European Economic Area (EEA).

The International Organization for Standardization (ISO) standard 11615: 2012 on "Data elements and structures for the unique identification and exchange of regulated medicinal product information" was published in 2012.

As part of the electronic submission of information for authorised medicinal products, the authorised therapeutic indications should be provided using the MedDRA dictionary for coding. For each indication, the following information should be provided: the MedDRA version selected for coding (AP.IND.1), the MedDRA level selected for coding (AP.IND.2), and the selected MedDRA code (AP.IND.3).

In the future, the use of ISO standard will allow the coding of further structured details related to indication, such as populations specifics (e.g.: age, age range, gender, race) and other therapy specifics (e.g. second line treatment, co-treatment) related to the approved therapeutic indication. To check the latest developments of the EU implementation of ISO IDMP please refer to the 'Implementation of the ISO IDMP standards' webpage.

This document details how the coding is currently performed with the view of facilitating future migration of data in ISO format. Any references to future coding practices are made for illustrative purposes only.

This document should be read in conjunction with Chapter 3.II of the XEVPRM User Guidance, section 1.2.19.3 on selection of MedDRA Code (AP.IND.3).

Scope of this document

The aim of this document is to clarify the current selection of MedDRA codes for authorised indications using the data structure in the XEVMPD in relation to the new data structure of the ISO IDMP standard

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to achieve a consistent way of coding that will simplify the subsequent migration of Article 57 data into the new ISO structure. A further aim is to reinforce the existing guidance for selecting MedDRA codes for the coding of authorised indications.

The core principle of indication coding (in the context of Art. 57 product submission) is the purpose of capturing of the most detailed and complete MedDRA LLT (low level term) code, based on the indication text in section 4.1 of the SmPC, following the principles described below.

Coding principles

A set of guiding principles to be followed are listed below:

- The basis for the coding of therapeutic indications is **the SmPC as authorised by the Member State**, which means that a difference in authorised therapeutic indications across Member States is to be reflected also by the data submitted. Marketing-authorisation holders (MAHs) should not use a single core data sheet for all authorised products unless all SmPCs are completely aligned to the core data sheet.

  Any information not listed in the section 4.1 of the SmPC should not be captured in the structured indication field; however, information in other sections of the SmPC, such as section 5.1, may be helpful to create a better understanding of the indication text.

- The MedDRA codification of an indication should be provided in the form of the **most suitable low level term (LLTs)**. Note that the purpose is not to capture *all* of the applicable LLTs for a particular concept – these are often designed as linguistic variances with the same meaning. Similarly, all medical concepts that could be covered by the indication should also not be captured. Instead, one LLT that provides the most accurate, comprehensive and detailed level of information matching to the verbatim of the indication text should be sought. If necessary, more than one LLT may be selected.

  Using internal coding based on the preferred term (PT) translated in the XEVMPD in exports of all the applicable LLT as found in the MedDRA hierarchy is not a correct approach and should be discouraged.

- The basis for the selection of a MedDRA term for the indication corresponds conceptually to the **'Disease/symptoms/procedure'** described in the ISO standard; i.e. the (underlying) disease, symptom or a procedure that is the indication for treatment, including the disease or symptom part of the intended effect where stated in the indication text.

  Coded indication in current system **should not capture the 'Comorbidity/concurrent conditions'** aspect of the indication. This refers to further conditions (concurrent conditions or co-infections) that define the patient population apart from the 'Disease/symptoms/procedure' aspect of the indication. It should be noted that 'Comorbidity/concurrent conditions' is used in a broader sense than its common medical interpretation.

  Coding indication in the current system should also capture the **disease or symptom part of the 'Intended effect'**, where stated in the indication text.

- The chosen MedDRA term should be **as specific as possible**, targeting to capture the most detailed level of information presented in the indication section. If a term can be identified, additional information should be captured; e.g.:

  – both the disease and its cause as provided in the SmPC, (e.g. 'Osteoporosis steroid-induced');

- aspects of 'Disease status specification' (e.g. 'Pancreatic adenocarcinoma metastatic');
- details related to the target population (e.g.: 'Osteoporosis postmenopausal');
- timing/duration (e.g.: 'Hepatitis chronic persistent').

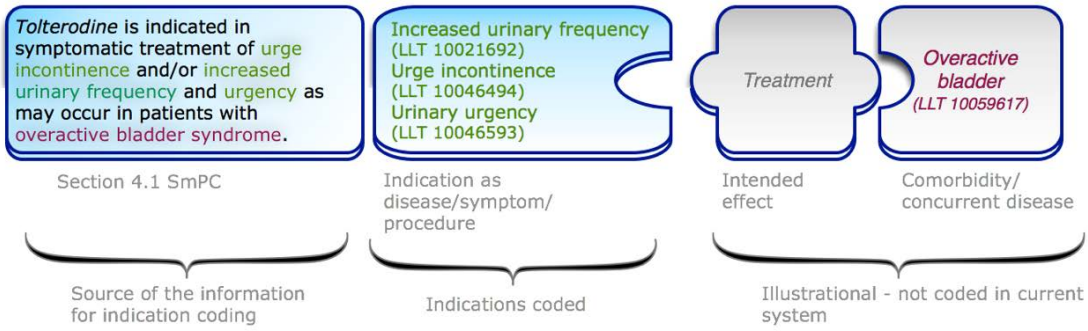
- When the indication is for prophylaxis or prevention, and no relevant combined term (e.g. 'Constipation prophylaxis') can be identified, a term for 'Prophylaxis' or 'Prevention' needs to be added separately. While the two terms are indeed captured individually with no apparent relation between them (e.g.: 'Cardiovascular events' and 'Prophylaxis') this manner of coding is accepted as a convention until further development will be put in place. It needs to be considered whether a drug indicated for prophylaxis or prevention is also indicated for treatment. In that case, the treated symptom or disease should also be coded.

Examples

Please note that the examples are for illustrational purposes only and are not presented in any particular order. The purpose is not to indicate how to code parts of the indication that are not currently coded. It is very important to note that the information that is within the scope of the current guidance is illustrated below in green (i.e.: indication as disease/symptom/procedure) whereas the rest of information is not currently captured in the system; the manner in which this will be structured in the future remains to be established.

The examples are using terminology available in MedDRA 18.1.

Example (1): showing coding of indication as symptom for a product, where an underlying disease is mentioned as a possible cause of the symptoms treated, indicated here as comorbidity.



To further exemplify the separation between the therapeutic indication and the comorbidity, where the indication text states: 'Treatment of pancreatic insufficiency in patients with cystic fibrosis', then 'pancreatic insufficiency' needs to be included as indication, whereas 'cystic fibrosis' represents the 'Comorbidity/concurrent conditions' aspect of the indication and it should not be included at this stage in the indication field. This is because the treatment specifically targets the pancreatic insufficiency, and although pancreatic insufficiency is common in cystic fibrosis, many patients with cystic fibrosis do not have pancreatic insufficiency.

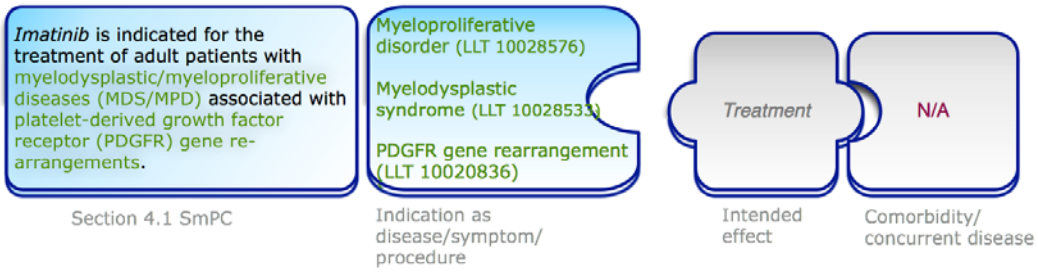
Careful consideration of the disease in relation to the stated therapeutic indication as well as of the drug's mechanism of action and impact on the disease itself is required when assessing whether the diseases mentioned in the indication text should be considered a 'comorbidity' (and left out at this stage) or whether they constitute in fact the therapeutic indication (and need to be included). To be considered as indication, the signs or symptoms treated should not only be typical for the

disease, i.e. shared by all or almost all patients with the disease, they should also represent the most important signs or symptoms for patients with the disease.

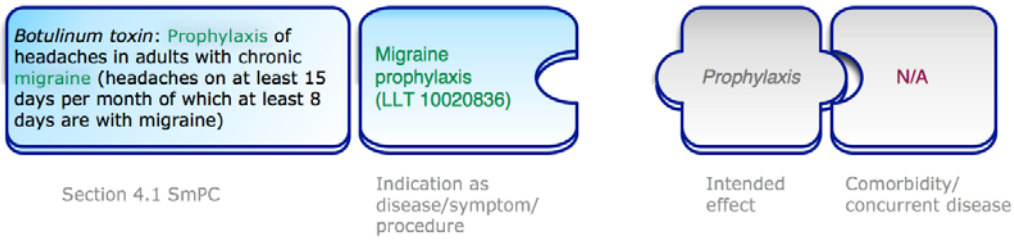
Looking at an example where indication states: 'For the treatment of hyperglycaemia in type II diabetes', then it needs to be considered that treatment of hyperglycaemia (i.e. achieving normoglycaemia), is the goal of all antidiabetic treatment, and type II diabetes should therefore be considered as an indication for treatment and not a concurrent disease.

Other examples further illustrating the points presented in this document are described below.

Example (2): a case where both indications captured in SmPC are to be coded because no single code covers the entire indication:

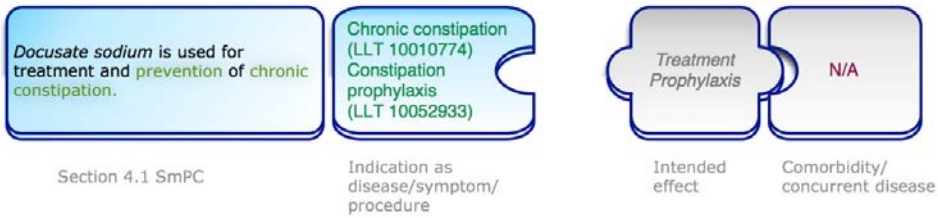


Example (3): a case where the indication needs to be carefully considered in its context (migraine is not a concurrent condition in this case - migraine is being prevented in patients with chronic migraine). In this case the term captures both the information on prophylaxis and on the targeted event:

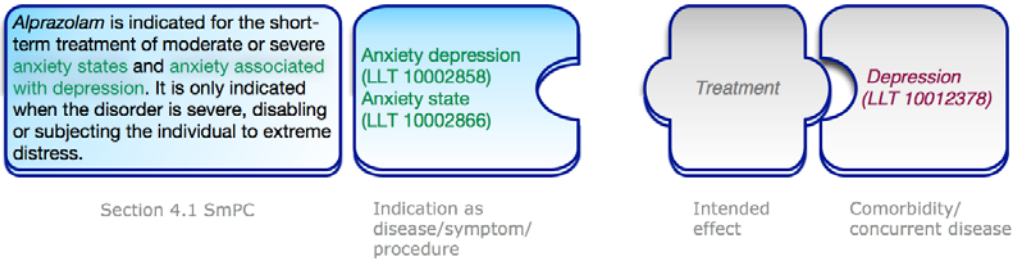


Example (4): a case where the most detailed level of information is used to capture the indication, as available in MedDRA terminology:

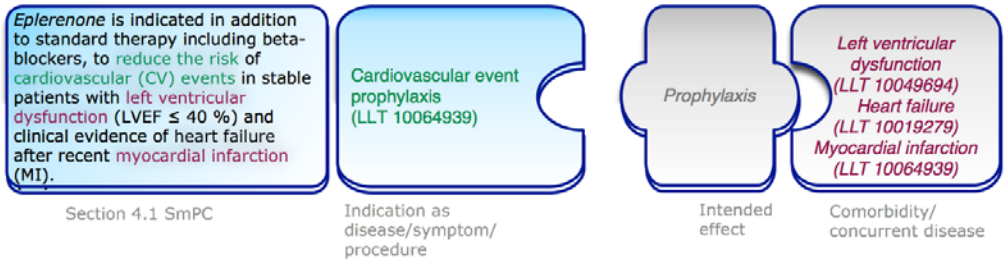
Example (5): a case where both treatment and prophylaxis are to be coded in indication section, as the medicinal product is used for both purposes:



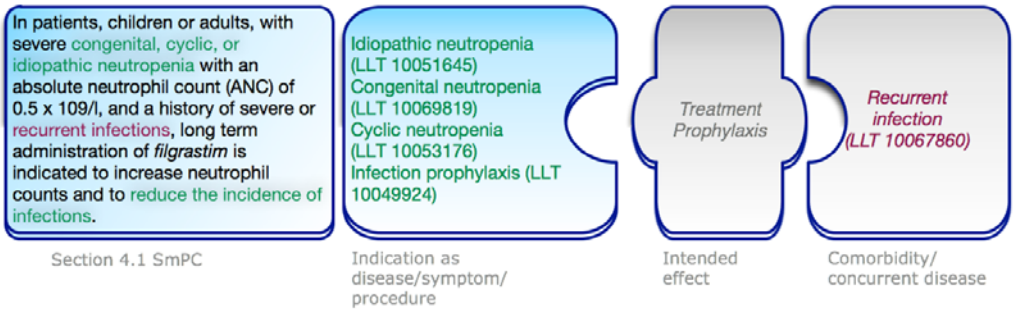
Example (6) a case where most detailed information about the treated conditions is captured, showing that the indication is for anxiety both with and without depression. The code for depression might also be captured (in future system enhancements) in the comorbidity/concurrent disease part of the indication, but it does not constitute the indication of this medicine (i.e.: alprazolam is not used to treat “depression”, but “anxiety” (associated or not with depression).



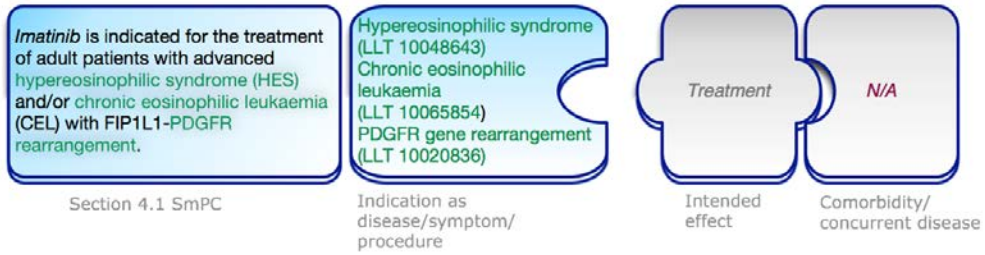
Example (7): a case of a prophylaxis indication ('to reduce the risk) where an appropriate LLT is available in MedDRA (composed term that captures both the information on prophylaxis and on the targeted event):



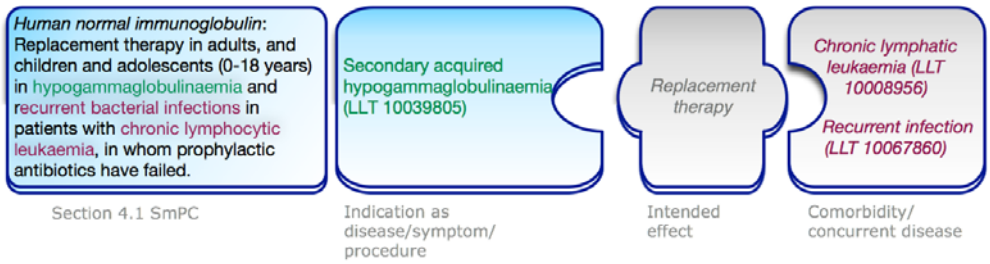
Example (8): a case where the drug is indicated for congenital, cyclic or idiopathic neutropenia for which appropriate MedDRA LLTs are available. Additional requirements are a specified absolute neutrophil count level, and a history of severe or recurrent infections. In addition, the indication text states a prophylaxis indication ('to reduce the incidence'), where an appropriate LLT is available in MedDRA (composed term that captures both the information on prophylaxis and on the targeted event):



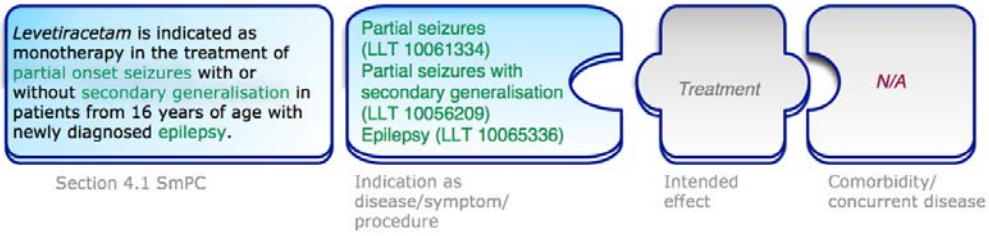
Example (9): a case of coding a treatment indication:



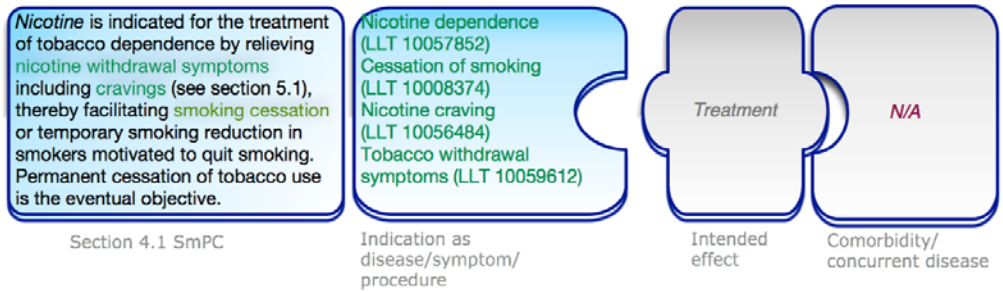
Example (10): a case where the capturing of indication of a replacement therapy is presented. The drug is a gamma globulin replacement in hypogammaglobinaemia. The patients have chronic lymphocytic leukaemia, which is not treated by the drug, and similarly, recurrent bacterial infections are encountered but not directly treated:



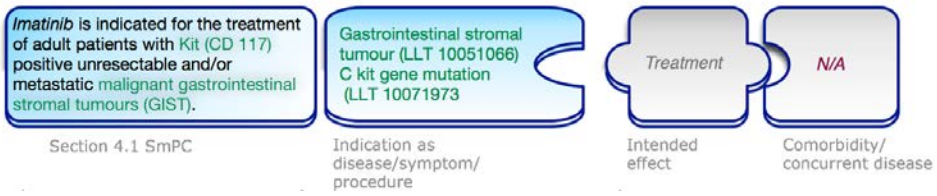
Example (11): a case where an antiepileptic drug is indicated for treatment of partial onset seizure type epilepsy. The most detailed information is captured. Epilepsy is also captured to reflect the disease part of the intended effect:



Example (12): a case where treatment is for tobacco dependence. In addition, terms representing the intended treatment effects as described in the indication text have been selected:

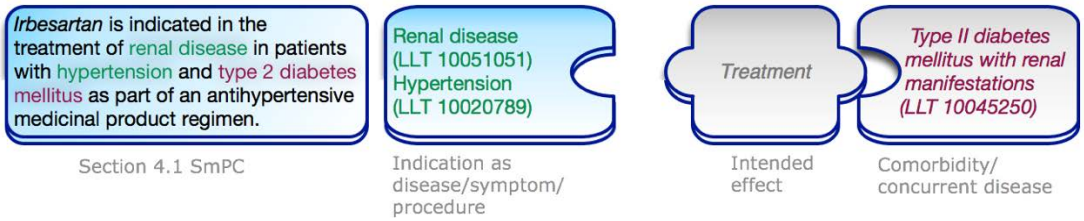


Example (13): a case of coding a treatment indication, where there is no term available to describe also the disease status:

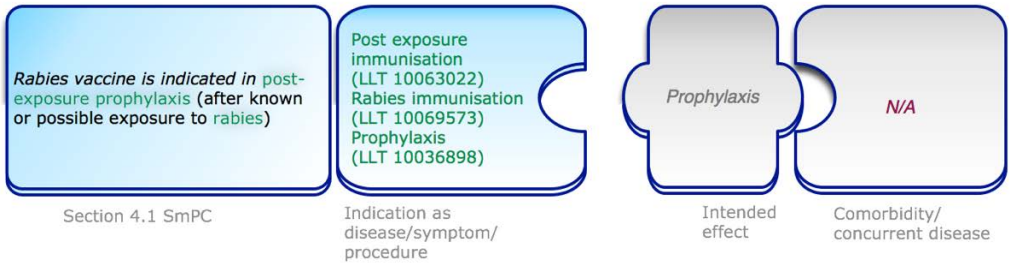


Example (14): a case where both the treated symptom and its cause can be coded with the same term:

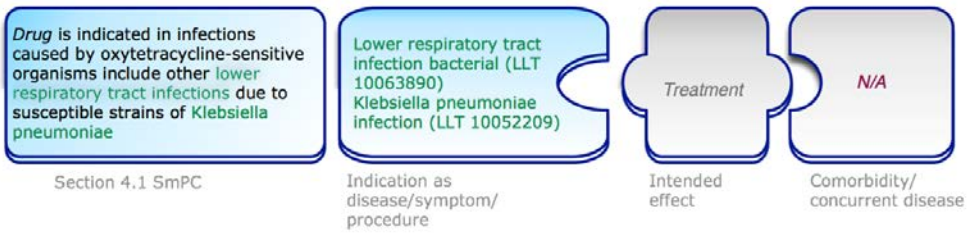
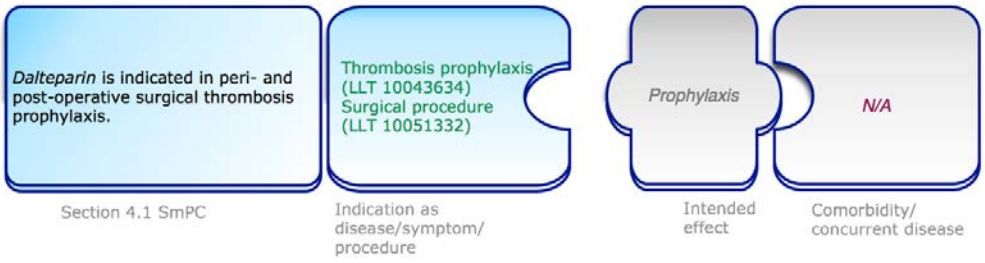
Example (15): a case where the target and effect of the medication needs to be considered to discriminate between the indication as disease/symptom/procedure and the comorbidity to be included at a later stage of data submission. Hypertension is captured to reflect the disease part of the intended effect:



Example (16): a case of a vaccine where a separate code is added to specify that the immunisation is carried out post exposure for rabies immunization:



Example (17): a case where two codes are needed to specify both the microorganism and the location of the infection to be treated:



Example (18): Product indicated for prevention of complications/events in a patient undergoing or scheduled for medical procedure; both complications prevention and medical procedure are coded: