

# **SPCC(TDM): Catalogue for the content analysis of summary of product characteristics (SPCs) with reference to therapeutic drug monitoring (TDM)**

## **Introduction**

Summary of product characteristics (SPCs) may contain information on therapeutic drug monitoring (TDM). TDM is the control of plasma levels during drug treatment and the scientific discipline dealing with it. TDM is a practical-therapeutic application of pharmacokinetics.

The SPC-content(TDM) (SPCC(TDM)) as an instrument for content analysis provides a quantitative and qualitative summary score of the content of TDM in SPCs.

## **Abstract**

The catalogue SPCC(TDM) consists of 10 Items. The content of single paragraphs of the SPC is analysed in the Items SPCC(TDM)-1 to SPCC(TDM)-6. SPCC(TDM)-7 to SPCC(TDM)-9 count the declaration of special ranges of plasma levels. SPCC(TDM)-10 codes the declaration of a recommendation of TDM. SPCC(TDM)-7 to SPCC(TDM)-10 apply to the entire SPC irrespective of paragraphs.

The SPCC(TDM) deliberately avoids a too complicated approach, e.g. no comprehensive check list of key words is used. Only examples of key words and key word groups are provided as well as counter-examples. Expert knowledge in TDM, pharmacokinetics and pharmacology is needed. Only this way, the SPCC(TDM) is regarded as manageable and was possible to develop. Due to the lack of a comprehensive list of key words some imprecision in the coding of implicit and explicit content (see below) may arise. The reliability of SPCC(TDM) was estimated as  $W = 0,847$  (Kendall's coefficient of concordance).

In the content analysis, each Item is coded with a positive integer value. The summary score of all 10 Items is the SPCC(TDM) and provides a rough estimate of the content of TDM in an SPC according to a prognostic approach, i.e. in its effect to the reader. A rigid quantitative approach is avoided (e.g. TDM-content in per cent of lines), because this is not the intention of this instrument and because this is also regarded as too complicated. A qualitative valuation *pro* TDM can be derived from Item SPCC(TDM)-10. According to experience in TDM, a qualitative valuation *pro* TDM can also be derived from SPCC(TDM)-8 and SPCC(TDM)-9.

Important: The SPCC(TDM) does not measure the content of pharmacokinetics. TDM is only a part of pharmacokinetics.

## **SPCC(TDM)-1 to SPCC(TDM)-6**

Content of SPCC(TDM)-1 to SPCC(TDM)-6 is coded strictly within the paragraphs according to the structure of the SPC. That is, even in case a TDM-content actually describes a drug interaction but occurs in the paragraph dose, for example, this is coded in the Item of paragraph dose. A drug interaction occurring in the paragraph dose is not coded in the Item of paragraph drug interactions! Subheadings in a

paragraph, e.g. "Treatment" in the paragraph "Overdose", are included in this paragraph and coded together in the corresponding Item.

**Explicit TDM-content** (score 2 per paragraph):

- occurrence of words/ word groups such as "TDM", therapeutic drug monitoring", "control of plasma levels", "assay of plasma levels", also "toxicological analysis of blood" or similar (alternative terms such as "investigation", "serum" or "concentration" or similar are used)
- i.e. not only a steady-state plasma level is included as a content but also the activity of measuring it by some method
- providing therapeutic and/or toxic plasma levels or limits of clinically relevant plasma levels
- counter-example: the term "therapeutic range" alone, without a relationship to plasma levels, is insufficient because this is also used in the context of dose (in the sense of a "therapeutic dose range")
- statements on the relationship between plasma levels and therapeutic effect, adverse effects, risk of malformation, severity of intoxications
- statements on the relationship between dose and steady-state trough plasma levels (not C<sub>max</sub> - except in the case of C<sub>max</sub> is relevant for the TDM of the special drug coded, and not after a single dose – except plasma levels after a single dose are relevant for the TDM of the drug coded)
- coding is independent whether or not positive or negative statements are found (*pro* and *con* TDM)

**Implicit TDM-content** (score 1 per paragraph, not assigned if explicit content has already been coded):

- not explicit content (see above)
- contains the way of thinking and the knowledge of TDM in the description and evaluation of too low, normal or too high plasma levels (mainly steady-state), however, the activity of the assay of plasma levels is not included. The reader could be provoked to measure plasma levels. The distance of the statement to the thinking of TDM is short.
- examples: increased plasma levels in the elderly and therefore lower doses to apply, increased/ decreased plasma levels because of drug interactions, a statement on induction/ inhibition of drug-metabolizing enzymes, adverse effects at increased plasma levels, lower doses for liver and renal function disorders
- counter-example 1: giving charcoal in intoxication is regarded as not sufficient for an implicit TDM-content, because mainly pharmacokinetics after single dose is taken into account and the relationship with the activity of a control of plasma levels is not close enough
- counter-example 2: transfer of active substance into milk is not a sufficient implicit information for TDM, because the relationship with the activity of control of plasma levels is too far (control of plasma levels in infants is not established)
- counter-example 3: higher sensitivity of the elderly to adverse effects not taking into account pharmacokinetics is no implicit TDM-content because also a sole pharmacodynamic mechanism is possible
- counter-example 4: implicit and explicit content on the TDM of other drugs in the SPC of the molecule under investigation is not coded (this applies for instance to drug interactions: only drug interactions are coded which change plasma

concentrations of the molecule under investigation, i.e. the direction of drug interaction must be considered)

- counter-example 5: content concerning pharmacokinetics after single dose (t<sub>max</sub>, C<sub>max</sub>, t<sub>1/2</sub>, clearance, bioavailability, first-pass-effect, metabolites, metabolism etc.) as such is no implicit TDM-content. It is coded as implicit TDM-content only if a relationship with a therapeutic situation is also given (e.g. in old patients, in interactions, for adverse effects).
- coding is independent whether or not positive or negative statements are found (*pro* and *con* TDM)

**Paragraphs of the SPCs:** The structure of an SPC may be different according to the year of publication. There is a paragraph “Other information” for example in old German SPCs within which a subheading “Pregnancy/ breast feeding” is included. This subheading corresponds to the paragraph “Pregnancy/ breast feeding” of new SPCs. However, most SPCs available in Europe have a conform structure now according to recent guidance.

SPCC(TDM)-1 (Dose): Evaluation of the paragraph “Posology and method of administration” of the SPC

SPCC(TDM)-2 (Adverse effects): Evaluation of the paragraph “Undesirable effects/ Adverse effects” of the SPC

SPCC(TDM)-3 (Drug interactions): Evaluation of the paragraph “Interactions with other medicinal products” of the SPC

SPCC(TDM)-4 (Overdose): Evaluation of the paragraph “Overdose” of the SPC

SPCC(TDM)-5 (Pregnancy/ Breast feeding): Evaluation of the paragraph “Pregnancy and lactation” of the SPC

SPCC(TDM)-6 (Pharmacokinetics): Evaluation of the paragraph “Pharmacokinetic properties” of the SPC

In summary, Items SPCC(TDM)-1 to SPCC(TDM)-6 can be coded with a score of 0 to 12.

If the minimal content for coding is found more than once in a paragraph, nevertheless, only the maximal score per paragraph (implicit: score 1, explicit: score 2) can be coded. This may occur in SPCC(TDM)-3 (Drug interactions) for example, i.e. more than one pharmacokinetic drug interaction may be found. On the other hand, equal content can be coded more than once if it is repeated in different paragraphs. For example, a pharmacokinetic drug interaction may occur in the paragraph “Drug interactions” and in the paragraph “Pharmacokinetics”. It will be coded in both Items. This approach was introduced to facilitate the coding.

The paragraphs of the SPC “Therapeutic indications”, “Contraindications”, “Special warnings and precautions for use” etc. are not coded in extra Items. For instance in “Contraindications” and “Special warnings and precautions for use” mainly redundant information is provided.

### **SPCC(TDM)-7**

Evaluation of the entire SPC.

Dose-related plasma levels (score 3):

A range of steady-state plasma trough levels ( $C_{min}^{ss}$ ) for a certain dose or dose range is provided at least once (numerical values). Maximum plasma levels  $C_{max}$  are usually not coded except  $C_{max}$  is relevant for TDM of the molecule under investigation. Plasma levels after a single dose are also usually not coded except TDM after single dose is established for the molecule under investigation. A correlation between dose and plasma levels using numerical values is also coded in this Item. Giving the information in numerical values, however, not using the exact scientific terms is also coded. A negative statement is not coded, e.g. "relationship between dose and plasma levels does not exist".

### **SPCC(TDM)-8**

Evaluation of the entire SPC.

Toxic range of plasma levels (score 3):

A toxic range or a toxic limit of plasma levels is provided at least once ( $C_{min}$ ,  $C_{max}$ , steady-state or after single dose) or a relationship of plasma levels with toxicity is provided using numerical values. Giving the information in numerical values, however, not using the exact scientific terms is also coded. A negative statement is not coded, e.g. "toxic range of plasma levels does not exist".

### **SPCC(TDM)-9**

Evaluation of the entire SPC.

Therapeutic range of plasma levels (score 4):

A therapeutic range of plasma levels is provided at least once ( $C_{min}$ ,  $C_{max}$ , AUC, steady-state or after single dose) or a relationship between plasma levels and response/ therapeutic effect is provided using numerical values. Giving the information in numerical values, however, not using the exact scientific terms is also coded. A negative statement is not coded, e.g. "therapeutic range of plasma levels does not exist".

### **SPCC(TDM)-10**

Evaluation of the entire SPC.

General recommendation of TDM/ control of plasma levels (score 5):

A general recommendation of TDM/ control of plasma levels is expected. This applies for

- 1) A general statement for at least one big group of patients (e.g. children, old patients, however, patients with hepatic insufficiency is not sufficient), i.e. without limitation to a special clinical situation. This is most often found in the paragraphs "Posology and method of administration" or "Pharmacokinetics", sometimes in the paragraph "Special warnings and precautions for use".
- 2) Recommendation of TDM in special clinical situations (e.g. renal insufficiency, hepatic insufficiency, drug interactions) in at least two paragraphs (dose, adverse effects, interactions, pregnancy/breast feeding, overdose) of the SPC (drug interactions is counted only if at least two particular drug interactions are connected with the recommendation for TDM).
- 3) The score 5 is also coded if two TDM-recommendations are given for different therapeutic situations in one paragraph (e.g. one recommendation of TDM

according to adverse effects and one recommendation of TDM according to a drug interaction in the paragraph “Posology and method of administration”).

A score of 3 is coded in Item 10 if recommendations of TDM do not achieve this general level, however, if a recommendation of TDM is given in a special clinical situation anyway (in one paragraph or in different paragraphs according to the same clinical situation).

A statement “no correlation between plasma level and therapeutic effect” or similar does not exclude the coding of a score 3 or 5 in Item 10 if the above conditions apply.

There is no conservative approach in SPCC(TDM) concerning the scientific terms used in the SPC, e.g. the term “clinical-toxicological investigation of blood” is also considered as a TDM-term.

The SPCC(TDM) can reach a maximum summary score of 27.

### **Recommendations for an effective proceeding**

The catalogue should be thoroughly read before coding is started. Then, the paragraphs according to SPCC(TDM)-1 to SPCC(TDM)-6 are coded first one after another, and in doing so it is already paid attention to contents of SPCC(TDM)-7 to SPCC(TDM)-10. Thereafter, the remaining paragraphs of the SPC are analysed for a final evaluation of SPCC(TDM)-7 to SPCC(TDM)-10 (for instance “Special warnings and precautions for use” and “Other information”). After completion of an SPC the catalogue should be read again for instance by untrained coders. Corrections should be performed if needed.