CBG MEB | MEDICINES EVALUATION BOARD

Wording of indication, labelling and assessment report

Hans Hillege (NL) , Kristina Dunder (SE), CHMP

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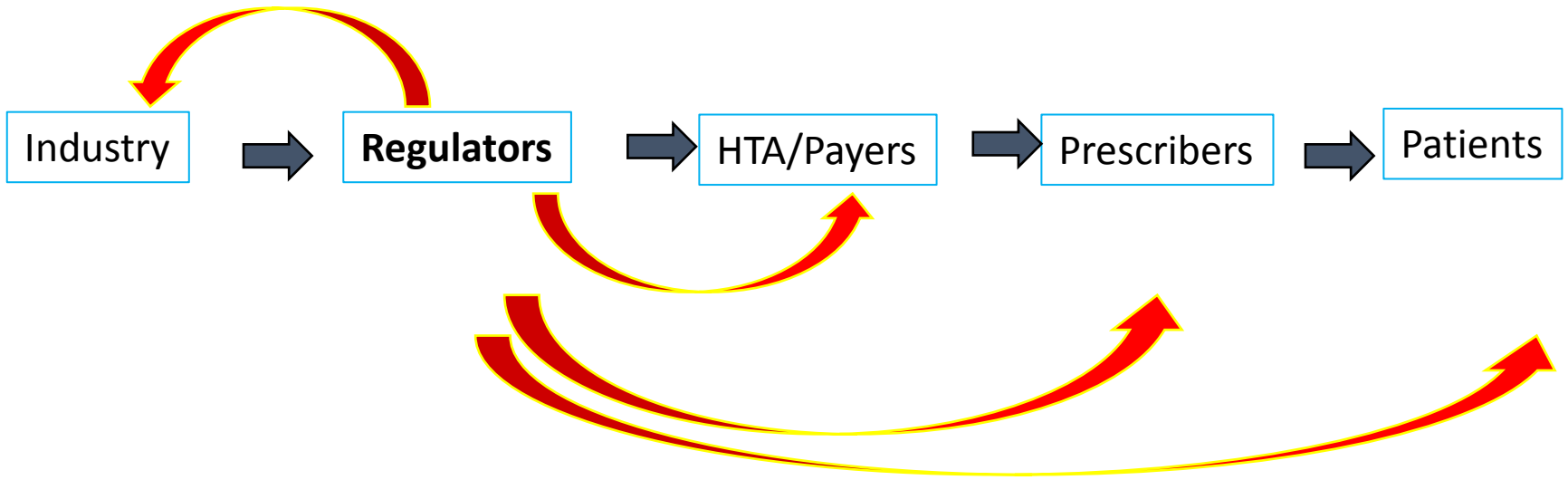
Zorginstituut Nederland (ZIN)

Outline

- General reflections; SmPC, section 4.1
- CHMP ”assessment process” for defining the therapeutic indication (reflection paper)
  - Target disease
  - Target population
  - Place in therapy
- Conclusions

Product labeling from development to patient



Key principles 4.1

- From a regulatory point of view, the therapeutic indication should be clearly and concisely stated in section 4.1 of the SmPC to reflect in which disease and target population the benefit risk balance is established to be positive
- Target disease or condition
  - Treatment ; *symptomatic, curative, modifying*
  - Prevention ; *primary, secondary*
  - Diagnostic
- Target population; *especially when restrictions to patient populations apply*
- Age groups, specifying age limits; *X is indicated in < adults > <adolescents> <children> <infants> <neonates> <aged x to y years, months>*

SmPC (4.1); Importance/understanding differs between stakeholders

Prescribers;

- Use treatment algorithms/clinical experience
- Hypothetical indication;
  - *X is indicated for the treatment of patients with type 2 diabetes (see section 5.1 for study results)*

- Maybe the most important information is in EPAR?
- Regulators should have standards for approval for each therapeutic area, prescribers choose how to use the product
- Importance of indication may differ between MS
  - Possibility to prescribe outside approved indication differs
  - Not in line with the SmPC guidance

SmPC (4.1); Importance/understanding differs between stakeholders

Payers

- generally it is the population the MAH seeks reimbursement for
- A trend is recognized towards a less precisely specified (“broad”) population (insufficient granularity)
- Unclear which patient populations are covered and which are not
- This leads to to challenges for reimbursement decisions and disputes about “ off-label use”
- Sometimes impossible to distinguish for which population the authorization is based on direct evidence and for which population the evidence was extrapolated
- (Cross) references further contribute to confusion
- Section 5.1 the extent of information differs substantially between SmPCs

4.1 Therapeutic indications

A GUIDELINE ON SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) September 2009

The indication(s) should be stated clearly and concisely and should define the target disease or condition distinguishing between treatment (symptomatic, curative or modifying the evolution or progression of the disease), prevention (primary or secondary) and diagnostic indication. When appropriate it should define the target population especially when restrictions to the patient populations apply.

Study endpoints should not normally be included, unless such mention is specified as being appropriate for the indication in CHMP Guidelines. The objective of a prevention indication may be mentioned in general terms only. This should also be done for the target population.

Where results from subsequent studies provide further definition or information on an authorized indication, such information, provided it does not itself constitute a new indication, may be considered for inclusion in section 5.1.

Mandatory conditions of product usage not covered more appropriately in other parts of the SmPC may also be included when relevant, e.g. concomitant dietary measures, lifestyle changes, or other therapy.

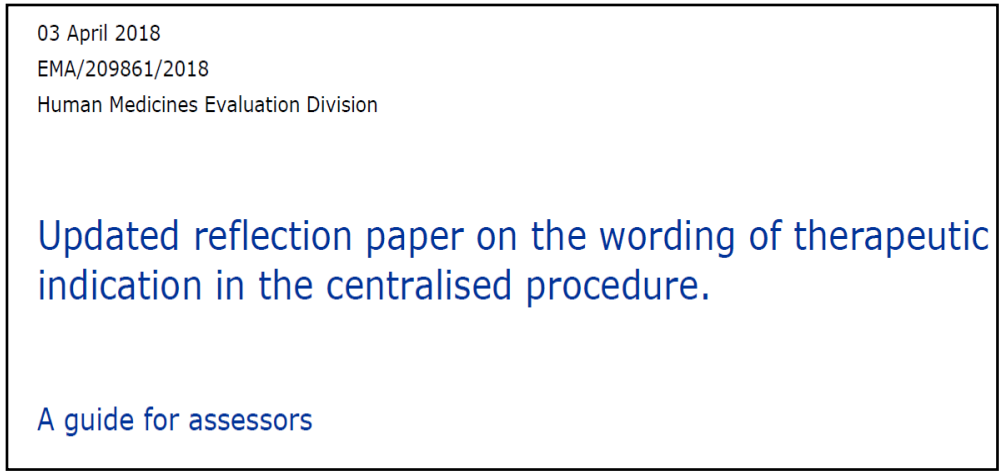
It should be stated in which age groups the product is indicated, specifying the age limits, e.g. 'X is indicated in <adults><neonates><infants><children> <adolescents> <aged x to y <years, months>>.

If the product's indication depends on a particular genotype or the expression of a gene or a particular phenotype, this should be stated in the indication.

The CHMP process for defining the wording of the indication

The objectives of this document are:

- To support a consistent approach in the process of defining the therapeutic indication;
- To clarify the regulatory framework surrounding the assessment of the therapeutic indication;
- To provide guidance on the wording of the therapeutic indication in section 4.1 that can be applied across therapeutic areas in order to limit discrepancies;
- To improve clarity of indications for stakeholders.


03 April 2018
EMA/209861/2018
Human Medicines Evaluation Division

Updated reflection paper on the wording of therapeutic indication in the centralised procedure.

A guide for assessors

This document should be considered together with other CHMP initiatives, such as benefit/risk, investigation of subgroups in confirmatory clinical trials, reflection paper on extrapolation and available core SmPCs for specific medicinal products.

The CHMP assessment process for defining the wording of the indication (I)

- Start with data submitted as part of the marketing authorisation application
  - population studied in clinical trials; results rather than inclusion/exclusion criteria
- Consider indication proposed by the Applicant
- Consider the therapeutic context, i.e. approved therapeutic alternatives, treatment algorithms
  - *If indication different compared to similar products or algorithms; justification crucial*
- Consider specific components of the indication in a structured manner

The CHMP process for defining the wording of the indication (II)

- Based on this decision making process, the final wording of the indication may be wider or more restricted compared to the therapeutic indication as initially proposed by the Applicant.
- The scientific basis for and the reasoning behind the final wording of the indication should be clearly documented in the benefit-risk section of the CHMP AR.
- In case an established positive benefit/risk balance in the studied population is extrapolated (broader) to subgroups for which data is scarce or absent this should be clearly justified. This is equally important if the target population identified by the indication is more restricted compared to the study population

Components of the therapeutic indication

- Target disease
- Target population
- Place in therapy (in relation to other treatments)
- Monotherapy/ combination use
- Mandatory conditions for use

- Cannot cover all aspects and eventualities!
- Gives a common ground, starting point

Target Disease

- Identify disease or condition and the effect of the product (treatment, prevention or diagnostic)?
- Treatment can be specified as symptomatic, curative or modifying the evolution or progression of the disease (section 4.1 if clinically relevant)
  - "Symptomatic" may be included to specify that that the treatment has no curative effect/ is not affecting the evolution of the disease.
  - "Disease modifying" is often difficult to define
- Information on duration of treatment (e.g. "long-term treatment") should in general be included in section 4.2, and should not be mentioned in section 4.1
- In principle study endpoints should not be included in section 4.1; however, in some cases, a product is not aimed for treatment of the disease as such but to alleviate a symptom; endpoint(s) may be included in section 4.1.

Target population

- The target population should be well defined and recognized within the clinical practice
- Even if a positive B/R balance has been established in the study population(s), in most cases, there will be subsets of the population (based on e.g. age, gender, certain severity stages of the disease, organ function impairment) in clinical practice which has not been studied or for which the available information is limited.
- In such subsets it is crucial to consider whether the B/R balance is positive or not and the evaluation should be reflected in the assessment report.

Target population, subgroups, benefit risk

Assessment of B/R in subpopulations	Wording in the SmPC
Benefit/risk positive based on efficacy and safety Efficacy/safety in subgroup consistent with study population and/or can be extrapolated	No need to restrict the indication with upper age limit, severity stage , gender etc **B/R is positive even if data is limited**
Benefit/risk negative based on lack of efficacy Effect is considered to be absent/very low in subgroup based on the available data and/or ”external knowledge” and results cannot be extrapolated from study population	Include restriction (e.g. age limit, disease severity) in 4.1
Benefit/risk negative based on safety issue based on available data	Include contraindication for the subgroup (e.g. severe renal impairment)
Efficacy consistent with/can be extrapolated from study population. Safety uncertain, but no confirmed issue that would result in a contraindication	Reflect safety uncertainties in the SmPC 4.2 and 4.4, but no restriction in 4.1 or 4.3

Target population, subgroups, available data

- Limited data available
  - Are results consistent or not with study population?
  - Important to consider biologic plausibility, credibility, consistency etc.
- No data available in a subgroup
  - Adequacy of extrapolating B/R from study population may be based on ”previous knowledge”, biologic plausibility? (age, gender)
  - Is subgroup excluded based on safety issue; contraindication?
  - Lack of data does not (by itself) translate into a contraindication
- Uncertainties will remain, B/R cannot be evaluated in some subgroups
  - Relevant to include information in 4.4 that data is limited in a certain population without excluding the subgroup from the target population in 4.1
  - B/R may be positive for an individual patient (prescribers choice)

Subgroups

A number of concepts in the assessment and decision making of the role and impact of subgroups are required to be discussed and communicated :

- Heterogeneity
- Consistency
- Credibility
- Biological plausibility
- Replication

Place in therapy

- Consider if there is a defined treatment pathway in the condition studied; are treatments defined as first and later line treatment? In which population/part of the pathway has the drug been studied?
- Can the data be extrapolated beyond the line of treatment which is studied such that the benefit risk is positive for a broader use (extrapolation)?
- If the data is not considered to support a first line indication, restrictions to second line treatment or to patients with contraindications or intolerance to standard of care could be considered if B/R is established to be positive in that population.
- Second/third line could also be considered if the benefit/risk balance is negative in first line treatment due to safety issues, but a relevant benefit is established in patients with a later stage of the disease who have fewer treatment alternatives.
  - *Note: if the data can be extrapolated to other lines of treatment or if the medicinal product has been studied in both first and later lines, it may not be necessary to specify "first line" or "second line" in 4.1.*

Communication; B/R section in EPAR

What should be communicated?

- All relevant parts of the indication;
- Disease, target population, use in montherapy etc.
- Why important subgroups were included/excluded from the indication,
- Differences compared to similar products
- In which section of the EPAR?
  - 5.7 Benefit-risk assessment and discussion (value judgements)
  - 5.7.1 Importance of favourable and unfavourable effects
  - 5.7.2 Balance of benefits and risk
  - 5.7.3 Additional considerations

Implementation/follow-up

Conclusions

- The therapeutic indication should reflect in which disease and target population the benefit/risk is positive
- B/R in subgroups should be reflected as far as possible in 4.1, but other sections of the SmPC must also be considered
- For some subgroups, there will be uncertainties (B/R can be positive for a specific patient)
- Not everything can be in 4.1
- Need to leave some flexibility for the prescriber, trust the specialist´s own judgement
- Not everything can be in the SmPC; often necessary to read EPAR
- Justify the final wording of the indication in the EPAR
  - Subgroups, extrapolations, restrictions, inconsistencies with other products in the same class/ treatment algorithms
- Survey ongoing, internal education, update of template etc

Thank you very much
for your attention !

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