Indications and labelling; general aspects

EMA-Payer Community meeting

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Scope; Smpc

Try to reflect current regulatory thinking on indications and labelling…

to reach a common understanding

Will not discuss level of evidence for a positive benefit/risk balance…

but say something about the B/R template

EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

Revision 2

NOTICE TO APPLICANTS

A GUIDELINE ON

SUMMARY OF PRODUCT CHARACTERISTICS

(SmPC)

September 2009

This guideline will be included in The Rules Governing Medicinal Products in the European Union Volume 2C Notice to Applicants

Key considerations

- **The SmPC reflect the disease and the population in which B/R balance is positive**
  - Not a treatment guideline
  - The whole SmPC is ”on label”

> The SmPC is the basis of information for healthcare professionals on how to use the medicinal product safely and effectively. The Package Leaflet (PL) shall be drawn up in accordance with the SmPC. The

- **Other documents must be consulted to get the full picture**

> - Public Assessment Reports provide detailed information on medicinal products and are available on the website of the European Medicines Agency, of Heads of medicines Agencies or other National Competent Authorities. A link to the relevant website should be included in SmPCs when a public assessment report is available.

- **Regulators need to communicate reasons and considerations supporting SmPC/EPAR**

4.1 Therapeutic indications

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 authorised 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.

SmPC 4.1; Importance/understanding differs between stakeholders

- **HTA/Payers ;**
  - Inconsistency/lack of clarity concerning level of details in section 4.1
  - "What patients are and are not covered by the approved indication?"
  - Preference for detailed indications to differentiate between products/ to decide on reimbursement ?
  - Preference for relative benefit/risk assessments?

- **Prescribers;**
  - Use treatment algorithms/clinical experience
  - Maybe the most important information is in EPAR?
  - Importance may differ between MS
    - » Possibility to prescribe outside approved indication differs

- **Patients**
  - How is the indication understood; product COULD or SHOULD be used in the target population?
  - Regulators; most often absolute B/R assessments = COULD be used

The CHMP process of defining the wording of the indication

- **Multidimensional analysis based on several aspects**
  - 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; justification crucial
  - Consider specific components of the indication in a structured manner

- **Extrapolation/ restrictions**
  - 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 and compared to the studied population. (BUT, we cannot force the Applicant to accept a wider indication)

Components of the therapeutic indication

Target disease

Target population

Place in therapy (in relation to other treatments)

Combination use

Mandatory conditions for use

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** and it should be considered **<u>if</u>** specifying this in 4.1 is of clinical relevance or not.
    - "Symptomatic" may be included to specify that that the treatment has no curative effect/ is not affecting the evolution of the disease
- **Information on <u>duration of treatment</u> (e.g. "long-term treatment", "maintenance treatment") should in general be included in section 4.2, and should not be mentioned in 4.1**
- **<u>Study endpoints</u> should not be included in 4.1**
  - Remicade: treatment of RA ; "*a reduction in the rate of the progression of joint damage, as measured by X-ray, has been demonstrated*"

Target population

- **Studied population never representative of full target population**
  - Always subgroups with no or limited data
  - Age, gender, severity/stage/phenotypes of the disease, previous treatment

- **Should 4.1 only include studied population?**
  - Data may support that benefit/risk balance is positive also in not studied groups
    - Extrapolation
  - Not feasable to perform studies in all subgroups
    - If you can extrapolate; waste of resources?

Target population; how do we extrapolate?

- **Qualitative assessment**
  - Previous knowledge about disease (how it behaves in differenet subgroups),
  - Knowledge about drug class (mechanism of action)

- **Quantitative assessment**
  - PK/PD modelling
  - Pop-PK

- **Any available data to support extrapolation**

1 1 April 2016
2 EMA/199678/2016

3 Reflection paper on extrapolation of efficacy and safety in
4 paediatric medicine development
5 Draft

Target population; possible outcomes of extrapolation exercise

- **Benefits and risk in subgroup are expected to be similar to the study population**
  - No need to specify upper age limit, severity stage in 4.1
  - Explanation needed in EPAR

- **Effect is expected to be absent in subgroup**
  - Include an age limit in 4.1

4.1 Therapeutic indications

Circadin is indicated as monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over.

- **Benefits are expected to be larger in a subgroup**
  - Eg in the severe stage of disease with no other options
  - May outride safety issue in the full target population; restricted indication

Target population; possible outcomes of extrapolation exercise

- **Specific safety issue in a subgroup**
  - Contraindication in that group (eg severe renal impairment)

- **Very limited/no data but no signal of absent effect or specific safety issue in a subgroup**
  - Limitations reflected in other parts of the SmPC
  - Request additional studies?
    - Feasability

Place in therapy

- **First line / later line (non responders, intolerant to etc)**
- **Depends on study population**
- **Approval of not studied "line" (eg approve first line even if studies as second line) depends on the severity/ progression of the disease and available therapies**

  - Considerations could include if the target disease is **slowly or rapidly progressing**. If the disease has rapid progression, a first line indication may not be acceptable without a comparison to standard of care since this could result in patients getting an inferior treatment. On the other hand, in less severe, slowly progressive diseases, such a comparison may not be crucial.

Combination therapy (both products contribute to the effect, not concomitant therapy)

- **Is there a need to specify in 4.1 that the product should be used in monotherapy and/or in combination therapy to ensure that patients are not getting an inferior treatment regimen not tested in clinical trials?**

- **Does lack of data with specific combination(s) lead to a risk that should be communicated in a warning in 4.4/4.5?**

- **If there is a need to specify the combinations;**

  - Could a general statement "in combination with other products for the treatment of X" be adequate instead of listing all studied combinations (beyond those described in section 4.5 +/- 4.3 or 4.4)?

Mandatory condition of product usage

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

- **(*"Mysimba is indicated, as an adjunct to a reduced-calorie diet and increased physical activity, for the management of body weight"*)**

Documentation of data and evaluation; B/R section in EPAR

5.1Therapeutic context

- 5.1.1 Disease or condition
- 5.1.2 Available therapies and unmet medical need
- 5.1.3 Main clinical studies

5.2 Favourable effects (quantify, no value judgements)

5.3 Uncertainties/limitations of favourable effects

5.4 Unfavourable effects (quantify, no value judgements)

5.5 Uncertainties/limitations of unfavourable effects

5.6 Effects Table

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

Conclusion

The SmPC is the basis of information for healthcare professionals on how to use the medicinal product safely and effectively. The Package Leaflet (PL) shall be drawn up in accordance with the SmPC. The

- Everything cannot be in the SmPC
- SmPC written for different health care providers
- All subgroups cannot be studied
  - Extrapolation sometimes acceptable/adequate

- **Regulators can improve the communication of our assessment of benefits/risks/wording in 4.1**
  - In particular when principles/standards change; different wordings within the same therapeutic area

Examples

Plaque psoriasis; Cosentyx	Plaque psoriasis; Enbrel	MS; Aubagio	MS; Gilenya	T2DM; Forxiga	T2DM; Galvus
Treatment of **moderate to severe** plaque psoriasis in adults who are candidates for systemic therapy.	Treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy, including ciclosporin, methotrexate or psoralen and ultraviolet-A light (PUVA)	Treatment of adult patients with relapsing remitting multiple sclerosis (please refer to section 5.1 for important information on the population for which efficacy has been established).	Gilenya is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following adult patient groups: - Patients with high disease activity despite treatment with at least one disease modifying therapy (for exceptions and information about washout periods see sections 4.4 and 5.1). These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of at least one disease modifying therapy. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gadolinium-enhancing lesion. A “non-responder” could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year. or - Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.	Forxiga is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as: Monotherapy When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance. **Add-on combination therapy** **In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control** (see sections 4.4, 4.5 and 5.1 for available data on different combinations).	Vildagliptin is indicated in the treatment of type 2 diabetes mellitus in adults: As monotherapy - in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance. As dual oral therapy in combination with - metformin, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin, - a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of a sulphonylurea and for whom metformin is inappropriate due to contraindications or intolerance, - a thiazolidinedione, in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate. As triple oral therapy in combination with - a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control. Vildagliptin is also indicated for use in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control.