TOWARDS A MANAGED OFF-LABEL USE OF DRUGS

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Unauthorised use vs use of unauthorised pharmaceuticals

Unauthorised use of authorised medicines

OFF LABEL use = deviant from leaflet/SPC
- In early market access: medical need programme
- In routine medical practice

Unauthorised use
- Magisterial formulas
- Same medicine, different pharmaceutical form

Use of unauthorised medicines
- In early market access: compassionate use programme
- Magistral formulas
- Clinical trials
- Import on prescription for individual patients
Concerns parties involved

- **Authorities**: safety? efficacy?
- **Payers**: hesitate to reimburse
- **Patients**: informed?
- **Prescriber**: responsible?
- **Pharmacist**: responsible?
What did we do and how?

### Research questions

- Possibilities of national authorities under EU law to manage off-label use
- Can off-label use be brought in-label through a new marketing authorisation or a variation to the existing marketing authorisation(s)?
- How can relevant evidence be gathered on off-label use of medicines?

### Method

- Identification of existing regulation and jurisprudence on EU level
- Identification situation in other countries
- Step-plan for Belgium
EU legal framework

- **MA standard, limited exceptions:**
  - Medical need (CU, MN, emergency cases, special need)
  - Clinical trials
  - Magistral formula

- **Off-label use not, as such, defined**

- **EU pharmaceutical law does not preclude** the off-label prescription at the discretion of the doctor and at his own responsibility (**therapeutic freedom**)

- Increasing EU attention to off-label use, in particular in pharmacovigilance rules:
  - E.g.: Adverse reaction reporting now also includes off-label use

- **Commercial promotion off-label use is prohibited** for firms

- Initiatives to **stimulate extensions of indications**, but not always successful
SAFETY/PROTECTION

Marketing authorisation
Supports R&D for safe, qualitative and effective drugs

(PUBLIC) HEALTH

Health policy
“access to safe, qualitative, effective drugs”

SAFETY/PROTECTION

Off-label
What can MS allow?

- No alternative available
  - Allowed in case of medical need, Clinical trials, Magistral formula

- Alternative available
  - No ECJ-judgement yet
  - Promoting solely for cost considerations not valid
  - Nevertheless:
    - Stakeholders are free to perform research
    - Member States are free to provide neutral scientific information regarding off-label used products
    - Member States can foresee specific reimbursement schemes enabling the public funding of off-label therapies in individual patients
    - Prescribers have therapeutic freedom (due diligence)

See 8-Step plan
Liability

- **Product liability:**
  - Warning of possible side effects
  - Foresee ability off-label use ➔ pharmacovigilance rules
  - Unlikely for wrong decision physician

- **Practitioner’s liability:**
  - No prohibition of off-label prescription, sometimes sole option
  - Solid scientific basis
  - Informed consent

- **Pharmacist + Medical Pharmaceutical Committee:**
  - Advising patient ➔ able to be aware of off-label?
  - Carefull preparation

- **Public health authorities’ liability:**
  - Unlawful or careless policy: Promoting off-label use for budgetary reasons
STEP 1: Identification of off-label use with a focus on: 1) widespread or increased off-label use; 2) off-label use with (potential) evidence of safety and efficacy.

STEP 2: Is an (authorised) alternative available? Comment: this may also be a non-pharmaceutical intervention.

no

yes

Step 3: is the producer willing/able to avail of the medical need, compassionate use or unmet medical need programme for reimbursement purposes?

yes: application of the current modalities, incl. the collection of research data.

no

STEP 4: is there enough evidence of the safety and efficacy (and cost-effectiveness) of the off-label use?

• Start: use of off-label
  ➔ Priority is public health

• Evaluation of (quality), safety, efficacy (and cost-effectiveness)
There is not enough evidence yet but there is sufficient potential for further research.

Yes, there is reliable evidence to hand of the safety and efficacy (and the cost-effectiveness).

STEP 5: is the company prepared to conduct further research within a reasonable period of time?

No. Possibility to consider a publically funded trial (→ See KCE Report 246 (Publicly funded practice-oriented clinical trials)).

Yes. Arrangements can be made with regard to e.g. study design, comparator and endpoints.

STEP 6: is the company prepared to file an MA application within a reasonable period of time?

No. The company does not accept the offer or does not reduce the price sufficiently.

Yes. The company agrees to enter into negotiations and reduces the price sufficiently.

Once an MA has been obtained, a national application for reimbursement can be submitted.

Yes. Arrangements can be made with regard to e.g. study design, comparator and endpoints.

STEP 7: Is there room for price negotiations with the manufacturer of an authorised (more expensive) alternative?

No. There is no more expensive authorised alternative.

Yes. The company agrees to enter into negotiations and reduces the price sufficiently.

STEP 8: the authorities can work out a financial arrangement (e.g. by opting for a fixed reimbursement) with regard to off-label use that has been proven to be safe, effective and cost-effective.

Measures can be taken to support the authorised alternative.

• Discussion with MAHs
• Financing
Recommendations

- Inform prescriber that off-label prescribing is possible
  - Informed consent + diligence + note in patient file
- The roadmap should help to manage the off-label use of drugs
  - Competent authorities to evaluate quality, safety and efficacy (to be discussed at STAMP)
Recommendations

- Reevaluate policy for price reduction in case of extension of indication
- Manufacturers to include all information about off-label use in the application file for an MA.
- Research agenda: how to make relevant non-clinical data available for non-commercial trials
Bedankt, Merci, Thank you!
Colophon

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