Well-established use
–
case studies

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ŠÚKL
ŠTÁTNY ÚSTAV PRE KONTROLU LIEČIV

Directive 2001/83/EC

Article 10a

By way of derogation from Article 8(3)(i), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of pre-clinical tests or clinical trials if he can demonstrate that the active substances of the medicinal product have been in well-established medicinal use within the Community for at least ten years, with recognised efficacy and an acceptable level of safety in terms of the conditions set out in Annex I. In that event, the test and trial results shall be replaced by appropriate scientific literature.

Commission proposal for the Pharmaceutical Directive

Article 13

In cases where no reference medicinal product is or has been authorised for the active substance of the medicinal product concerned, the applicant shall, by way of derogation from Article 6(2), not be required to provide the results of non-clinical tests or clinical studies if the applicant can demonstrate that the active substances of the medicinal product have been in well-established medicinal use within the Union for the same therapeutic use and route of administration and for at least ten years, with recognised efficacy and an acceptable level of safety in terms of the conditions set out in Annex II. In that event, the test and trial results shall be replaced by appropriate bibliographic data in the form of scientific literature.

Directive 2001/83/EC, Annex 1:

Factors taken into account in order to establish a well-established medicinal use of constituents of medicinal products:

- the time over which a substance has been used,
- quantitative aspects of the use of the substance,
- the degree of scientific interest in the use of the substance (reflected in the published scientific literature)
- the coherence of scientific assessments

Name	Active Substance	Indication
Elmiron	pentosan polysulfate sodium	bladder pain syndrome
Granupas (o)	para-aminosalicylic acid	multi-drug resistant tuberculosis
Lutetium (177Lu) chloride Billev	lutetium (177Lu) chloride	radiolabelling of carrier molecules
Ketoconazole HRA (o)	ketoconazole	endogenous Cushing's syndrome
Lumark	lutetium (177 Lu) chloride	radiolabelling of carrier molecules
LysaKare	arginine / lysine	reduction of renal radiation exposure during peptide-receptor radionuclide therapy (PRRT) with lutetium (177Lu) oxodotreotide
Orphacol (o)	cholic acid	the treatment of inborn errors in primary bile acid synthesis
Peyona	caffeine	primary apnoea of premature newborns
Sialanar	glycopyrronium	treatment of severe sialorrhoea
SomaKit TOC (o)	edotreotide	PET imaging of somatostatin receptor overexpression in gastroenteropancreatic neuroendocrine tumours
Tepadina	thiotepa	conditioning treatment before hematopoietic stem cell transplantation

The time over which a substance has been used (minimum 10 years)

- Use in clinical studies
- Guidelines for treatment of the disease
- Statement of patients´ associations
- Use in hospital settings (time frame included)
- Published literature over prolonged period of time
- Use in clinical practise based on survey

Quantitative aspects of the use of the substance

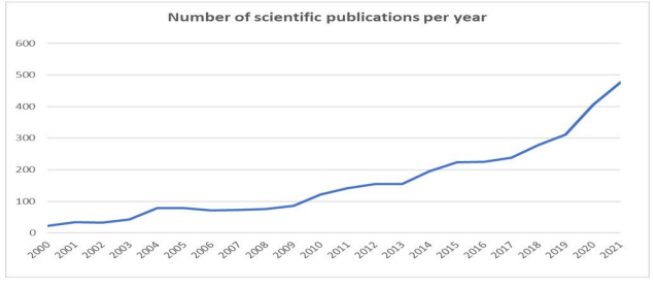
- Use in several EU countries
- Records from patients survey
- Information from medicines agency
- Consumption data (on active substance)
- Compassionate scheme
- Published data on patients/ number of patients in the studies
- Patients´ registry data
- Survey on usage
- Guideline recommendation

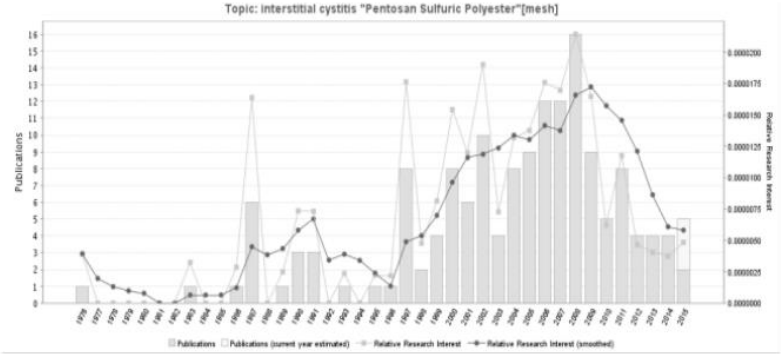
Depends on prevalence of the disease

The degree of scientific interest in the use of the substance (reflected in the published scientific literature)

- Analysis of published literature over the time
- Inclusion in guidelines, scientific literature
- Number of scientific publication per year

Figure 1. Number of scientific publications per year





EPAR Lutetium (177Lu) chloride Billev and Elmiron: https://www.ema.europa.eu/en/documents/assessment-report/illuzyce-epar-public-assessment-report_en.pdf
https://www.ema.europa.eu/en/documents/assessment-report/elmiron-epar-public-assessment-report_en.pdf

The coherence of scientific assessments

- Use in clinical setting, treatment guidelines
- Published clinical studies with consistent results
- Scientific societies recommendation

The similarity of the claimed formulation to the formulations examined in the literature

- Comparison of composition to the product used in the literature, dissolution data
- PK study to bridge the product to the literature data
- Comparability of formulation

Bridging of submitted literature data and proposed product

- Two uncertainties: What data to use?
  What reference to choose?
- What data to use?
  - Depends on the product (pharmaceutical form, type of active substance, excipients used)
  - Comparison of composition
  - In vitro data (BCS-based biowaiver, dissolution profiles)
  - BEQ study
  - PK study
- What product to choose as a reference?
  - Difficulties to indentify product from the published literature
  - In case of multiple studies, multiple products used
  - Use of product from the study – preferred solution
  - In case of need – alternatives (EU reference product, market leader?)

Assessment of WEU application – frequent issues:

- Missing (efficacy) data for „older“ active substances
- Submitted published studies do not meet criteria of today
- Submitted data do not concern proposed indication, strength, population
- Line extensions to medicinal products registered many years ago
- Missing justification
- WEU application should be generic one
- Dificulty to identify response of the applicant („clinical overview was updated“)

To conclude:

- It is not easy to prepare high-quality well established use dossier

Thank you for your attention!

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