EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

PSUR procedure and concept of Benefit-Risk evaluation

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Benefit- Risk Balance

During the marketing authorisation process, pharmaceutical companies need to establish and demonstrate the benefits and the risks of the medicinal product.

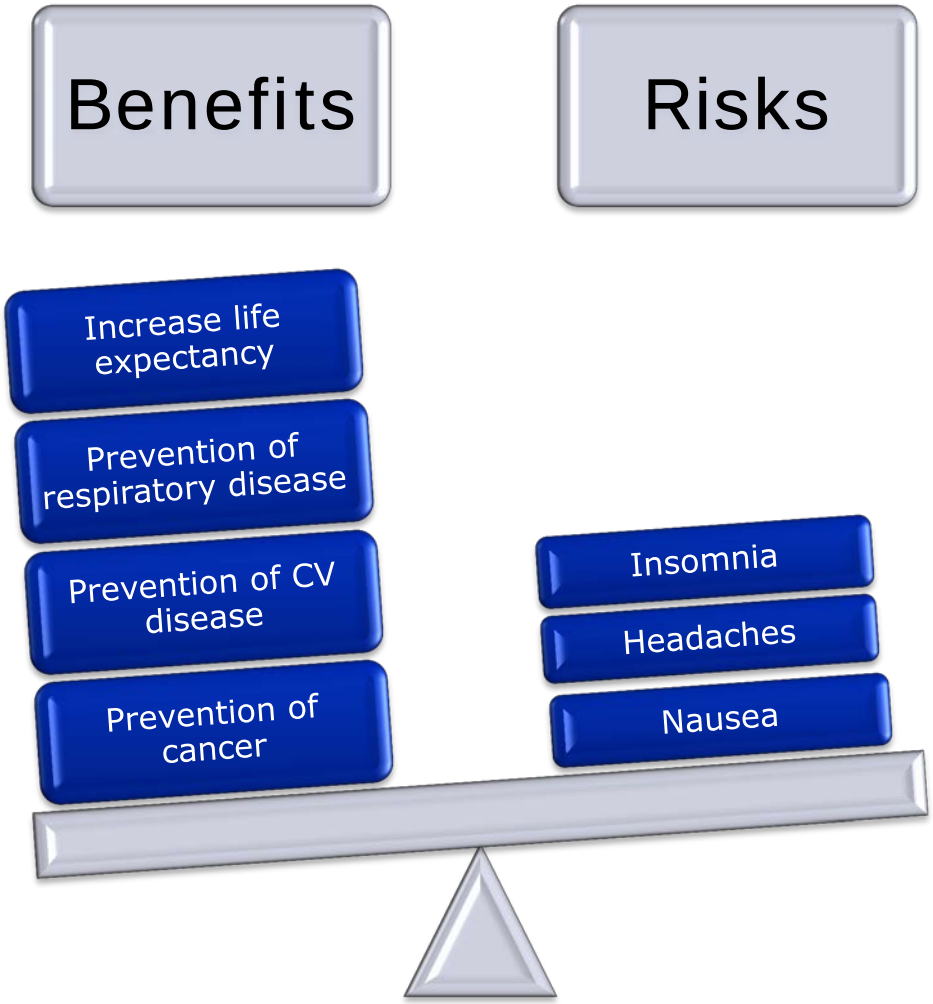
Regulators need to assess those benefits and risks.

When a new product is authorised for marketing, that decision is based on a benefit-risk balance

With the information available at that specific moment, products are authorised if it is considered that the benefits are greater than the risks

“Positive benefit-risk balance”

Example of Benefit- Risk balance for a medicinal product authorised for smoking cessation



Changes in the Benefit-Risk balance

- The Benefit-Risk balance is valid at a given point in time, but may change later on.
- New information on the benefits and risks may emerge once the drug is on the market and it is used in clinical practice.
  - Greater number of patients compared to clinical trials.
  - Rare adverse reactions may not have been discovered during clinical trials.
  - Used of the medication in “real world” in patients with other co-existing diseases and taking other medications.
  - Post-marketing studies may be ongoing to demonstrate benefits in other indications or to measure risks.

Periodic Safety Update Reports (PSURs)

To enhance patient safety and protect public health:

- This new information should be assessed promptly (e.g. signal detection).
- Periodic re-examination of the benefit-risk balance is needed to ensure that the balance remains positive.

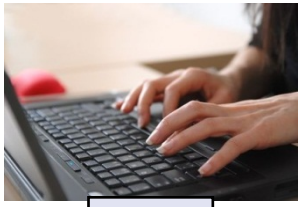
– This periodic re-examination is performed in a document called Periodic Safety Update Report (PSUR).

– PSURs: *"Pharmacovigilance documents intended to provide an evaluation of the benefit-risk balance of a medicinal product for submission by pharmaceutical companies to the regulators at define time points during the post-authorisation phase".*

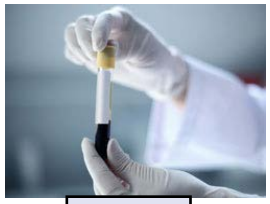
– The frequency for the submission of PSURs depends on the risks and may change with the time and the knowledge of the product.

Benefit-Risk balance reassessment - PSURs

HCP



Patients



Studies

Literature

Pre-marketing

Initial Marketing Authorisation

e.g. 6 months

PSUR 1

e.g. 6 months

PSUR 2

All available cumulative information

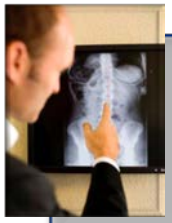
PSURs and the new Pharmacovigilance legislation

- PSURs are not new documents introduced with the new legislation, but the content, the scope and the outcome have changed.
  - New format should include information about Benefits and not only Risks.
  - Should integrate the new information in the context of what is already. known about the product - cumulative information.
  - Should incorporate a critical analysis of the benefit-risk balance.
  - The outcome of the PSUR assessment is legally binding

Main content of the PSUR

Actions taken for safety reasons

- e.g. clinical trial suspension, communications to healthcare professionals



Significant findings

- Clinical trials, spontaneous adverse reactions reports, patient support programs, literature…

Risks

- New risks identified and new information about already known risks

Benefit- Risk analysis

- Reassessment of the benefit-risk balance

Patient exposure

- Volume of prescriptions
- Actual use including use outside the authorised conditions

Signals

- New signals analysed

Benefits

- New benefits identified and new information about already known benefits

Conclusions and actions

- e.g. update of the product information with the new identified risk and risk communication as appropriate

PSUR Assessment

- PSURs are going to be assessed by regulators and this assessment will result in a legally binding outcome:

Maintenance

Variation

withdrawal

European Union Context and Transparency

- In the EU context the PSURs are going to be assessed by EMA Scientific Committees and a European Commission decision will be issued in cases or variations and withdrawals.
- Documents related to PSURs will be published: Conclusions, recommendations, opinions and decisions.
- The EMA has published a list of substances indicating the frequency for the submission of PSURs. The list has been created in collaboration with the national competent authorities in the Member States.

➢ "European Union Reference Dates List" – Legally binding list

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Patient Health Protection

List of Union reference dates and frequency of submission of periodic safety update reports

Active substances and combinations of active substances	European Union reference date (EURD) Not Available* = EURD not provided during the consultation phases	PSUR Submission Frequency	DLP	Are PSURs required for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended? Yes/No	Publication Date	Notes
loratadine	01/10/1991	5 years	02/02/2017	No	01/10/2012	
loratadine, pseudoephedrine	01/10/1991	5 years	02/02/2017	No	01/10/2012	
lorazepam	31/12/1963	5 years	31/12/2015	No	01/10/2012	
lormetazepam	07/12/1980	3 years	07/12/2014	No	01/10/2012	
lornoxicam	Not Available*	13 years	01/01/2025	No	01/10/2012	
losartan	02/09/1994	5 years	01/09/2017	No	01/10/2012	
loteprednol	31/03/2003	13 years	31/03/2025	No	01/10/2012	
lovastatin	21/07/1987	3 years	20/07/2013	No	01/10/2012	
lovastatin, nicotinic acid	Not Available*	13 years	01/01/2025	No	01/10/2012	
loxapine	20/12/1961	13 years	20/12/2025	No	01/10/2012	
lumiracoxib	Not Available*	13 years	01/01/2025	No	01/10/2012	
lutropin alpha	29/11/2000	3 years	28/11/2013	No	01/10/2012	
lymecycline	31/01/1961	13 years	31/01/2025	No	01/10/2012	
lynestrenol	20/03/1973	13 years	20/03/2025	No	01/10/2012	
lysine acetylsalicylate	25/09/1989	5 years	25/09/2017	No	01/10/2012	
lysine acetylsalicylic acid, metoclopramide	08/12/1993	13 years	08/12/2025	No	01/10/2012	
lysine amidotrizoate, sodium amidotrizoate	Not Available*	13 years	01/01/2025	No	01/10/2012	
mabuprofen	Not Available*	13 years	01/01/2025	No	01/10/2012	
macrogol 3350	15/04/1991	3 years	31/05/2013	No	01/10/2012	

Take home messages

- ✓ Benefit-Risk balance of a medicinal product can change and there is a need for re-assessment.
- ✓ PSURs permit the periodic re-assessment of the benefit risk balance.
- ✓ Legal actions can be taken from the PSUR assessment.
- ✓ Minimising risks and optimising benefits throughout the lifecycle of a medicinal product will promote and protect public health and enhance patient safety by avoiding unnecessary risks to patients.

Thank you for your attention