

The refocussed PSUR and a new approach to assessment



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Outline of this presentation

- ▶ Background
- ▶ new approach to assessment
- ▶ Q & A document for assessors
- ▶ General principles
- ▶ Specific assessment aspects
- ▶ Joint effort
- ▶ Summary

Background

- ▶ The PSUR single assessment (PSUSA) procedure has posed a certain number of challenges that are specific to the EU single assessment of PSURs of medicinal products approved nationally.
- ▶ A Joint PRAC/CMDh Recommendation paper has been agreed to ensure common understanding on EU PSUR single assessment
- ▶ The key issues relate to 3 topics:
 - role of the PSUR (single assessment) in the lifecycle of a medicinal product and how to take into account the stage at which a medicine is in its lifecycle
 - the evidentiary standard needed (both in a PSUR submission and/or as basis for recommendations)
 - the need for critical appraisal as a basis for PRAC recommendations (i.e. setting information provided cumulatively and/or iteratively in a PSUR into the context of the use of the medicine).

Background

- ▶ The Joint PRAC/CMDh Recommendation paper served as a basis for a guidance document for industry and a document for assessors
- ▶ The guidance document for assessors document is written in a questions and answers format
- ▶ It aims at providing further guidance to assessors, based on the experience gained since the start of the PSUSA procedure for NAPs in January 2015.
- ▶ In some instances, the issues addressed may also apply to the assessment of PSURs of CAPs.
- ▶ The Q & A document should be read in conjunction with the GVP VII.

New approach to assessment

► General principles:

- Refocus on aim of the PSUSA
- Data driving the assessment
- Strength of evidence in the context of the stage in the product lifecycle
- Scope and link to outcomes of other regulatory procedures

► Practical assessment aspects

- Dealing with inconsistencies in national PIs or in safety specification/RMP
- Harmonisation vs consistency
- Signals, close monitoring
- Benefit data and (no new) indications
- Exceptional follow-up after PSUSA

General principles

- ▶ Aim and data to be reviewed
 - Purpose laid down in legislation - new risks, whether risks or B/R have changed
 - Critical appraisal – taking into account maturity and utilisation data and the place in therapeutics
 - Assessment should focus on real improvements for patients
 - No detailed line listings – high quality PSUR is prerequisite

- ▶ Data to be reviewed
 - Focus is primarily on the data provided by the MAH - critical that information provided by the MAH is of sufficiently good quality
 - Preparation for assessment is key – assessors to familiarise themselves with therapeutic role and be aware of current scientific issues of importance or major questions under debate
 - LMS not to compensate for deficiencies encountered in PSURs – RSI at D60 – significant concerns may be reason for a Pharmacovigilance Inspection
 - But LMS may search EudraVigilance or literature which data might be incorporated into the assessment

General principles

- ▶ Strength and nature of the evidence that is needed to support regulatory action
 - Case by case basis in the context of the stage in the product lifecycle.
 - Assessment not limited to suspected adverse reaction reports - broader view and includes all information available from CTs, epidemiological studies and meta-analysis etc.
 - Mechanistic plausibility, extent of patient exposure and how long the product has been on the market, as well as the clinical context and relevance for patients will be taken into account

- ▶ Link with outcomes of other regulatory procedures
 - Assessment focuses on PSUR data
 - However, important information relevant for the B/R or PI will not be ignored
 - Inconsistency or non-compliance with previous regulatory procedure outcomes (e.g. post-referral) will be flagged to CMDh – new 'other considerations' section in Assessment Report

General principles

- ▶ Scope of conclusions – impact on products outside the PSUSA
 - If new drug-drug interaction or contraindication for concomitant use is added, due consideration will be given to the other impacted product(s) (i.e. the interacting substance(s)) outside the scope of the PSUSA
 - Also, it will be considered from a scientific point of view whether a conclusion on a mono product or on a combination can also be extrapolated to the other combinations/mono products
 - Will be flagged to CMDh – new ‘other considerations’ section in Assessment Report

Specific assessment aspects

- ▶ Inconsistencies in product information
 - PSUSA procedure is not the appropriate tool for harmonisation of the existing product information across products
 - It is acknowledged that it would be appreciated to have consistent EU product information
 - Recommendations to update PI are PSUR data driven, applicable to all respective national versions of the product information
 - PI proposal is not differentiated per product or MAH, but indication and/or formulation differences of medicines are taken into account if applicable
 - Important lack of consistency across PIs will be included in the new “other consideration” section
 - In exceptional situations, triggering an Article 30 or 31 referral can be considered in case of important differences in safety aspects

Specific assessment aspects

- ▶ Inconsistencies in safety specification / RMP
 - PSUSA procedure is not the appropriate tool for harmonisation of the safety specification per se
 - If PSUR assessment identifies a new important risk, all MAHs to include that particular risk in the safety specification
 - No amendment or harmonisation of entire safety specification
 - Independent of a safety issue being included in the safety specification, MAHs are (in line with the legislation) obliged to review and discuss all issues identified during the interval period

Specific assessment aspects

► Signals and issues under close monitoring

- A refuted signal - provided the LMS and ultimately PRAC agrees - should not lead to additional follow up for precautionary reasons ('keep under close monitoring')
- Routine pharmacovigilance will apply from this time on
- Issues under close monitoring to be presented in section 15 or 16.2

► Dealing with new data/studies on efficacy

- new positive benefit information + no significant change in the risk profile → no full re-evaluation of the baseline efficacy data – focus on changes
- assessment of the PSUR will not conclude on evidence of efficacy in new indications - application to be submitted by the MAH via an appropriate procedure
- Lack of efficacy or studies challenging the established efficacy profile → detailed benefit/risk balance analysis

Specific assessment aspects

- ▶ Achieving a common position on the B/R balance when different indications are authorised in different MS
 - Principle is that at the beginning of the PSUR period the benefit/risk balance profile of the medicinal product is positive
 - LMS should not question the benefit/risk balance only because an indication is not authorised in their member state
 - Conclusion of “benefit risk balance remains unchanged” should not be understood as an endorsement by the PRAC of all existing indications
 - PSURs cannot be used as a basis for extensions of indications
 - Any claim for a new indication needs to be submitted via the appropriate regulatory procedure (variation) including a comprehensive data package.

Specific assessment aspects

- ▶ Requests for further/supplementary information within or at next PSUR
 - Requests to be risk based and in spirit and format of PSUR
 - Consideration given as to whether the request will provide meaningful information
 - Preferably in RSI or next PSUR
- ▶ Dealing with issues that cannot be finalized within the PSUSA
 - No LEG (as for CAPs)
 - Follow-up request exceptional and scientifically justified
 - LMS/PRAC will consider on a case by case basis which tool is the preferred option for the submission of the requested data
 - Optimal procedure to be developed by CMDh's Working Party on Pharmacovigilance Procedures Work Sharing
 - Existing tools: WS variation, signal procedure, bringing next DLP forward, referral

Refocussed PSUR and a new approach to assessment

- ▶ Joint effort
- ▶ High quality PSUR allows high quality assessment
- ▶ Importance to provide full response to PAR: exceptional follow-up after PSUSA
- ▶ Refocus on aim of the PSUSA and data driving the assessment
- ▶ Strength of evidence considered in the context of the stage in the product lifecycle
- ▶ Harmonisation vs consistency for national PIs or in safety specification/ RMP

Ask

