Risk Management

Pia Caduff-Janosa MD

Annual Course 2013

Outline

- Why risk management?
- ICH Guideline E2E
  - Safety specification
  - Pharmacovigilance Plan
  - Risk Evaluation and Mitigation Strategies (REMS)
  - Pharmacovigilance methods

Why risk management?

- Significant gaps in the safety profile of newly approved medicines in the early postmarketing period
- Marketing authorisation granted on limited data from clinical trials
- Historically: approval followed by pharmacovigilance activities based on spontaneous and periodic reporting

ICH E2E

- Recommended for adoption November 2004
- Focus on documents to be submitted when applying for a marketing authorization
  - Safety Specification
  - Pharmacovigilance Plan
- For new chemical entities or products with major changes
  - Populations, indications, dosage, formulation, manufacturing etc

Safety Specification

- Identified risks
  - Preclinical findings not adressed/resoved in clinical phase
- Potential risks
  - General pharmacology
  - Interactions
  - Toxicity
- Important missing information
  - Populations not studied

Safety Specification

- Development to start very early in the pre-marketing phase
- Stand alone document
- Dynamic document

Key elements

- Non clinical findings not adressed/resolved during clinical development
  - Teratogenicity
  - Nephrotoxicity
  - Hepatotoxicity
  - Carcinogenicity
  - Drug-drug and drug-food interactions
  - Repeat-dose toxicity
  - ...

Key elements

- Clinical
  - Worldwide exposure/regulatory action
  - Populations not studied
    - Children/elderly/pregnant
    - Patients with comorbities
    - Patients with disease severity excluded during development
    - Genetic polymorphism
    - Different ethnic backgrounds

Key elements

- Clinical
  - Identified and/or potential risks that need further investigation
    - Characterisation of ADRs
    - Potential mechanisms
    - Incidence under normal conditions of use
    - Identification of risk factors
  - Pharmacological class effects
  - Epidemiology of indications
  - Background rates of AE/ADRs

Pharmacovigilance Plan

- Based on Safety Specification
- Ongoing safety issues
  - From clinical development and/or postauthorization
- Routine PV
  - Spontaneous reporting
  - PBRER
- Action plan for safety issues incl. milestones
  - Objective/rationale/monitoring
  - Milestones for evaluation and reporting

Routine PV Practices

- System and processes in place to ensure that incoming safety information is collected, collated and evaluated in a systematic manner
- Adaequate reporting to Regulatory Authorities
  - Expedited reporting
  - Periodic reporting
  - Ad hoc reporting

Action Plan

- Safety issue identified
- Proposed action and rationale of it
- Monitoring of safety issue
- Milestones for data evaluation and reporting

PV Methods

- Method chosen must be the most appropriate for the issue under investigation
  - Enhanced/targeted spontaneous reporting
  - Pharmacoepidemiological studies
- Annex to ICH Guideline E2E describes different methods/studies

REMS

- Risk Evaluation and Mitigation Strategies
- Not routine – FDA can request REMS based on:
  - Size of exposed population
  - Seriousness of treated disease
  - Expected benefit
  - Expected duration of treatment
  - Safety profile
  - New molecular entity

REMS - elements

- Medication guides for patients
- Plan for communications to HCP and professional societies
- Elements to Assure Safe Use
  - Training for HCPs
  - Restriction of use/dispensing
  - Patient selection
  - Monitoring/registries
- Timetable for assessment
  - 18 months, 3 years and 7 years (can be amended)

Take home messages

- Proactive, targeted pharmacovigilance and risk management measures are necessary due to the limited safety data at approval
- RMP are only useful if
  - Appropriate to address the issues concerned
  - Monitored
  - Evaluated

Questions?

the UPPSALA MONITORING CENTRE

Uppsala Monitoring Centre
Box 1051
SE-751 40 Uppsala, Sweden
Visiting address: Bredgränd 7, Uppsala

tel +46 18 65 60 60
fax +46 18 65 60 88
website www.who-umc.org