EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES (RMAS)

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RISK MINIMIZATION MEASURES

An intervention intended to prevent or reduce the probability of the occurrence of an adverse reaction associated with the exposure to a drug product or to reduce its severity should it occur, including the evaluation of the effectiveness of these activities (the 'risk minimization plan')

RISK MINIMIZATION MEASURES

Rationale: Why is a RMM required?

Objectives: How and which safety concern is addressed with the proposed additional risk minimization measure(s)?

Description: What will be the additional risk minimization measures and what tools will be used?

Implementation: How will additional risk minimization measures be implemented

Evaluation: How will the effectiveness of additional risk minimization measures be evaluated (process and overall health outcome measures).

FACTORS TO CONSIDER IN THE SELECTION OF RMM

- Seriousness of the potential adverse reaction(s)
- Severity (impact on patient)
- Preventability
- Clinical actions required to mitigate the risk
- Indication
- Route of administration
- Target population
- Healthcare setting for the use of the product

ISPE/Edinborough 8/21/03

RISK MINIMIZATION MEASURES

What "tools" would be used to manage risk?	Who will be responsible for managing the risks? Defining roles and responsibilities of:
• What is known about the effectiveness of currently applied RM tools? • How do they relate to each other?	• Manufacturers • Healthcare providers/systems • Consumers • Regulators

RISK MINIMIZATION MEASURES. ROUTINE & ADDITIONAL RMM

- **Routine risk minimization measures include:**
  - the label, e. g. summary of product characteristics (SmPC), USPI
  - the package leaflet
  - the pack size and design
  - the legal (prescription) status of the product
- **Additional RMM**
  - educational programs
  - controlled access programs
  - other risk minimization measures

RISK MINIMIZATION MEASURES

<u>Routine RMM</u> – generally applies to every drug product

Package insert/leaflet/labeling

Examples:

- performing a test before the start of treatment;
- monitoring of laboratory parameters during treatment;
- monitoring for specific signs and symptoms;
- adjusting the dose or stopping the treatment when adverse events are observed or laboratory parameters change;
- performing a wash-out procedure after treatment interruption;
- providing contraception recommendations;
- prohibiting the use of other medicines while taking the product;
- treating or preventing the risk factors that may lead to an adverse event of the product;
- recommending long-term clinical follow-up to identify in early stages delayed adverse events

RISK MINIMIZATION MEASURES

- **<u>Additional RMM</u> – suggested when essential for the safe and effective use of the drug product**
  - Education program
  - Controlled access program
  - Patient alert cards
  - Healthcare professional communication

ATTRIBUTES OF ADDITIONAL PV ACTIVITIES

	Type of activity	In annex II of MA (CAPs only)	Study category (PhV plan)	Status	Supervised under	
					Article 107m	Article 107 n-q
Imposed PASS	"Interventional"*	Yes, in annex IID	1	Mandatory and subject to penalties	No	No
	Non-interventional	Yes, in annex IID			Yes	Yes
Specific obligation	"Interventional"*	Yes, in annex IIE	2	Mandatory and subject to penalties	No	No
	Non-interventional	Yes, in annex IIE			Yes	Yes
Required	"Interventional"*	No	3	Legally enforceable	No	No
	Non-interventional	No			Yes	No

RISK MINIMIZATION MEASURES

1. Educational Program

- For HCP: e.g. Prescribing Guide/checklist; Safety Guide
- For Patients/Caregivers: e.g. Alert Card; Reminder Card

2. Controlled Access Program

- Access subject to compliance with specific RMMs applied at the level of prescribing, dispensing, or use of a medicinal product. E.g.:
- Specific testing and/or examination of the patient to ensure compliance with strictly defined clinical criteria
- Patient enrolment in a registry

3. Pregnancy prevention program:

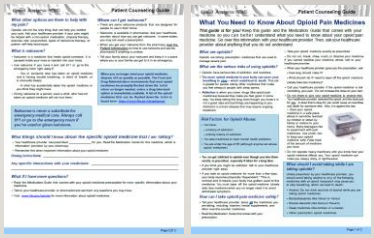
- A set of interventions to prevent pregnancy during treatment with a product with potential/known teratogenicity
- Male fertility: Interventions may involve the father

EDUCATIONAL MATERIALS

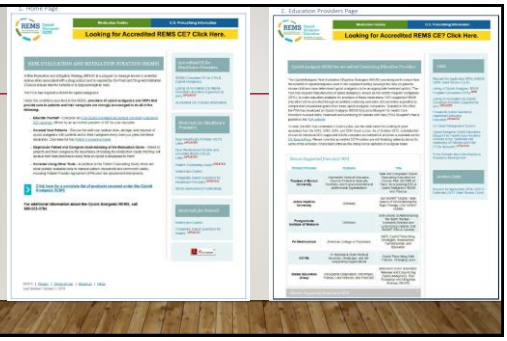
- Focus: Risk(s) related to the product and the management of those risk(s)
- Guidance on:
  - Prescribing, including patient selection, testing and monitoring;
  - Management of risks (to healthcare professionals and patients or caregivers);
  - Guidance on how and where to report adverse reaction of special interest.
- Example: FDA's Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain

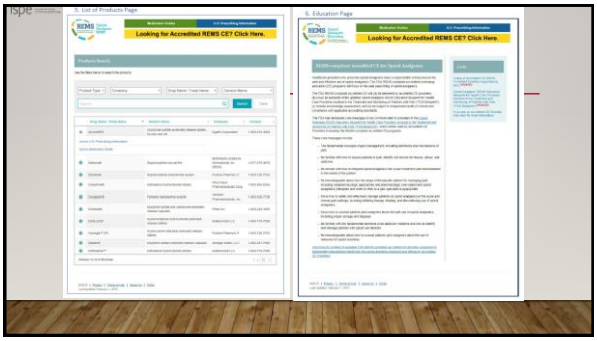
https://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM620249.pdf

EDUCATIONAL MATERIAL FOR PATIENTS



REMS





EDUCATIONAL TOOLS TARGETING HCPS

- Selection of patients
- Treatment management such as dosage, testing and monitoring
- Special administration procedures, or the dispensing of a medicinal product
- Details of information which needs to be given to patients

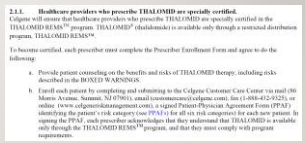
EDUCATIONAL TOOLS TARGETING PATIENTS/CAREGIVERS

Patient alert card

- Aim: To ensure that special information regarding the patient's current therapy and its important risks (e.g. potential life-threatening interactions with other therapies) is held by the patient at all times and reaches the relevant healthcare professional when needed.

CONTROLLED ACCESS PROGRAM

- Interventions seeking to control access to a medicinal product beyond the level of control ensured by routine risk minimization measures, i.e. the legal status.
- Guided by a clear therapeutic need for the product based on its demonstrated benefit (e.g. it treats a serious disease without alternative therapies; it treats patients who have failed on existing therapies), the nature of the associated risk (e.g. risk is life-threatening), and the likelihood that the risk will be managed by the program



2.1.1. **Healthcare providers who prescribe THALOMID are specially certified.**
Celgene will ensure that healthcare providers who prescribe THALOMID are specially certified in the THALOMID REMS[TM] program. THALOMID® (thalidomide) is available only through a restricted distribution program, THALOMID REMS[TM].

To become certified, each prescriber must complete the Prescriber Enrollment Form and agree to do the following:

a. Provide patient counseling on the benefits and risks of THALOMID therapy, including risks described in the BOXED WARNINGS.

b. Enroll each patient by completing and submitting to the Celgene Customer Care Center via mail (86 Morris Avenue, Summit, NJ 07901), email (customercare@celgene.com), fax (1-888-452-9325), or online (www.celgenerisk4management.com), a signed Patient-Physician Agreement Form (PPAF) identifying the patient's risk category (see PPAF) for all six risk categories) for each new patient. In signing the PPAF, each prescriber acknowledges that they understand that THALOMID is available only through the THALOMID REMS[TM] program, and that they must comply with program requirements.

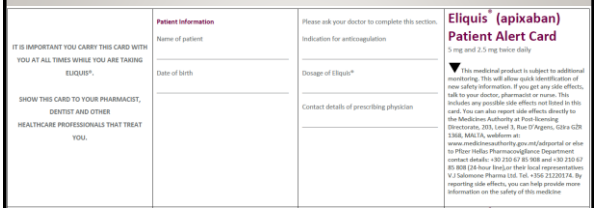
CONTROLLED DISTRIBUTION SYSTEMS

- Set of measures implemented to ensure that the stages of the distribution chain of a medicinal product are tracked up to the prescription and/or pharmacy dispensing the product.

PREGNANCY PREVENTION PROGRAM

- Set of interventions to minimize pregnancy exposure during treatment with a medicinal product with known or potential teratogenic

EXAMPLE



IT IS IMPORTANT YOU CARRY THIS CARD WITH YOU AT ALL TIMES WHILE YOU ARE TAKING ELIQUIS®.

SHOW THIS CARD TO YOUR PHARMACIST, DENTIST AND OTHER HEALTHCARE PROFESSIONALS THAT TREAT YOU.

Patient Information

Name of patient

Date of birth

Please ask your doctor to complete this section.

Indication for anticoagulation

Dosage of Eliquis®

Contact details of prescribing physician

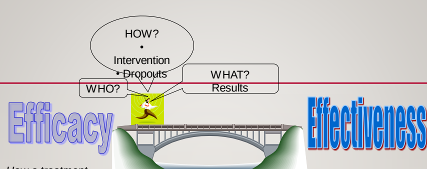
Eliquis® (apixaban)
Patient Alert Card
5 mg and 2.5 mg twice daily

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this card. You can also report side effects directly to the Medicines Authority at Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GZR 1368, MALTA, webform at: www.medicinesauthority.gov.mt/adrportal or else to Pfizer Hellas Pharmacovigilance Department contact details: +30 210 67 85 908 and +30 210 67 85 808 (24-hour line),or their local representatives V.J Salomone Pharma Ltd. Tel. +356 21220174. By reporting side effects, you can help provide more information on the safety of this medicine

DIRECT HEALTH CARE PROFESSIONAL COMMUNICATION (DHPC) OR DEAR DOCTOR LETTER

- Communication intervention by which important information is delivered directly to individual healthcare professionals by a marketing authorization holder or by a competent authority, to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product

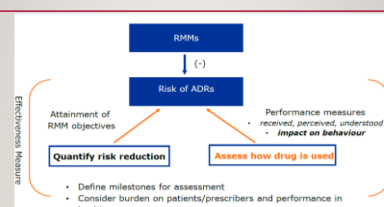
IS THE RMA EFFECTIVE?



How a treatment works in ideal circumstances, when delivered to selected patients by providers most skilled at providing it.

How a treatment works under ordinary conditions by the average practitioner for the typical patient.

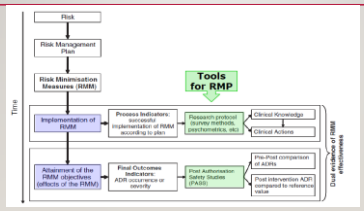
HOW TO ASSESS EFFECTIVENESS?



RMA. CRITERIA USED TO ASSESS EFFECTIVENESS OF THE PROGRAM

- Metrics
  - Baseline
  - Target
  - Process/outcome
- How to judge success/failure?
- When should it be modified or close?
- Is it forever?

ASSESSING EFFECTIVENESS



ARE RISK MINIMIZATION MEASURES FOR APPROVED DRUGS IN EUROPE EFFECTIVE? A SYSTEMATIC REVIEW

Objectives: The effectiveness of risk minimization measures (RMMs) requires evaluation. This study aims to evaluate the results of cross-sectional surveys assessing the effectiveness of RMMs in Europe (EU RM Surveys) and review the regulatory consequences.
Methods: The authors searched for study reports and manuscripts of completed EU RM surveys in the EU PAS Register, MEDLINE, and Google between 01/2011 and 01/2018. Regulatory responses were extracted from Assessment Reports. Random effects models to combine proportions were used.
Results: Twenty-four EU RM surveys were identified. Twenty-three studies targeted health-care professionals (HCPs). The pre-specified sample size was reached in 52% of studies. HCP participation was 5% defined as completers/invited and 89% for completers/eligible. Receipt of materials was recalled by 60% of HCPs and 77% of items scored knowledge >60%. Eight studies targeted patients/caregivers. The pre-specified sample size was reached in only two. Participation was 93%, defined as completers/eligible. Materials were received by 50–80% of patients and read by over 90%. Patients only scored knowledge >60% in 38% of items. Further action was requested by regulators in 59% of studies.
Conclusion: Surveys are necessary to evaluate many RMMs. Challenges remain in the design, conduct, and reporting of these studies which may benefit from the use of standard definitions and further guidance on reporting.

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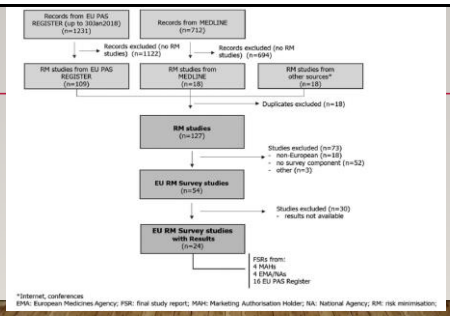
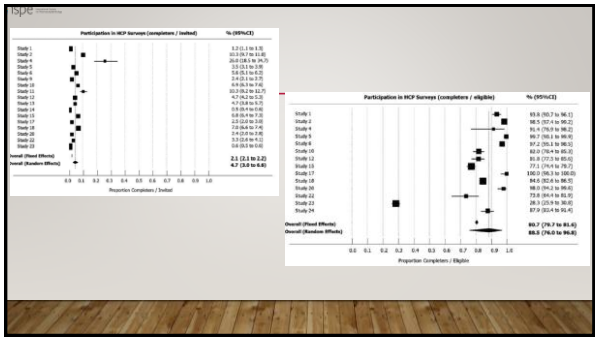
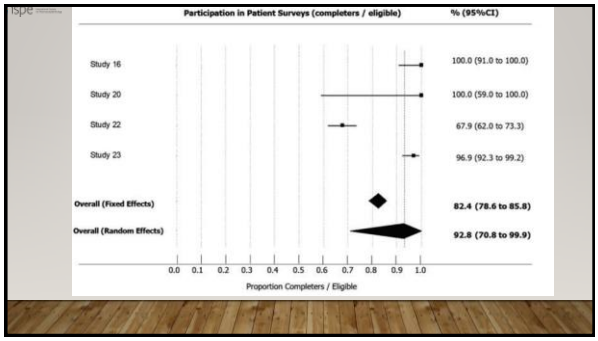
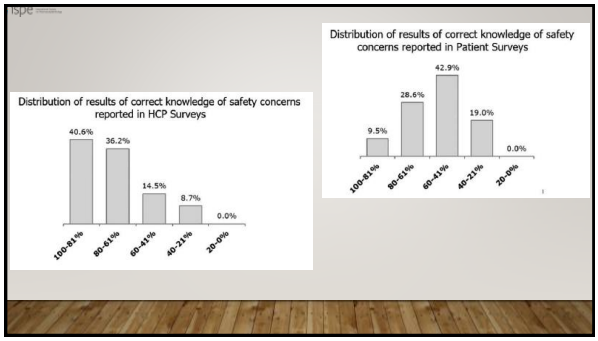


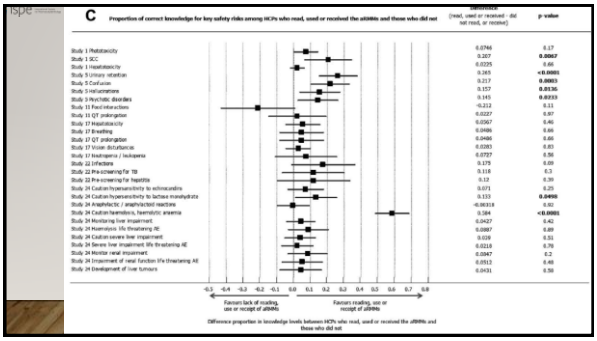
Characteristics	Included Studies [N=24] n (%)	Excluded Studies [N=30] n (%)	P value
Type of RMM			
Routine	2 (8.3)	1 (3.3)	*0.84*
Additional (i.e. aRMM)	22 (91.7)	29 (96.7)	
Patient cards	7 (29.2)	13 (44.8)	
DHPC	8 (36.4)	5 (17.2)	
HCP Brochure/Leaflet/Guide	15 (68.2)	20 (69.0)	
Patient Brochure/Leaflet/Guide	4 (16.7)	20 (69.0)	
Timing of aRMM	**N = 22**	**N = 29**	
At launch	10 (45.5)	17 (58.6)	*0.35*
After launch	1 (4.5)	2 (6.9)	
At extension of indication / new formulation	4 (18.2)	1 (3.4)	
After label changes / signal / restriction of indication	7 (31.8)	9 (31.0)	
Drug Approval Procedure			
Central Approval	17 (70.8)	27 (90.0)	*0.15*
National Approval	7 (29.2)	3 (10.0)	
Study Requested by Regulator			
Yes	18 (75.0)	24 (80.0)	*0.91*
No / Unspecified	6 (25.0)	6 (20.0)	
Study Category			
Cat 1 or Cat 2 (imposed by regulator)	3 (21.4)	3 (10.7)	*0.99*
Cat 3 (required in Risk Management Plan)	11 (78.6)	25 (89.3)	
Missing	10	2	
Study Design			
One-wave survey	21 (87.5)	25 (83.3)	*0.64*
Multi-wave survey	3 (12.5)	3 (10.0)	
Pre/Post survey	0 -	1 (3.3)	
Other	0 -	1 (3.3)	

Characteristics	Included Studies [N=24] n (%)	Excluded Studies [N=30] n (%)	P value
Study Population			
Clinical Specialists	22 (91.7)	17 (56.7)	***<0.01***
Primary care physicians	14 (58.3)	2 (6.7)	
Nurses	5 (20.8)	4 (13.3)	
Pharmacists	6 (25.0)	3 (10.0)	
Patients/Caregivers	8 (33.3)	9 (30.0)	
Physicians unspecified	0 -	7 (23.3)	
No. Target Participating Countries			
1 – 5	9 (37.5)	19 (63.3)	*0.17*
6 – 10	12 (50.0)	9 (30.0)	
>10	3 (12.5)	2 (6.7)	
Mean (SD)	7.1 (3.2)	5.5 (2.7)	
Number of Safety Concerns			
1 – 5	19 (79.2)	19 (67.9)	*0.31*
6 – 10	3 (12.5)	8 (28.6)	
>10	2 (8.3)	1 (3.6)	
Missing	0	2	
Median (Q1-Q3)	2.5 (1.0 – 5.0)	3.0 (1.0 – 7.5)	
Pre-specified criteria for success			
Yes	7 (29.2)		
Knowledge and/or behavior - Majority	3 (42.9)		
Knowledge and/or behavior - ≥80%	3 (42.9)		
Knowledge - 70%	1 (14.3)		
Receipt - 50%	1 (14.3)		
Use - 35%	1 (14.3)		
Unspecified	17 (70.8)		



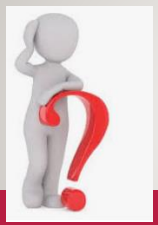






Regulatory actions according to Assessment Reports

		n (%) [N = 24]
Studies with Assessment Reports	22	(91.7)
Studies without Assessment Reports	2	(8.3)
Ongoing Procedure	1	
Reason unspecified by national regulator	1	
Main regulatory concerns		
Low response rates	7	(31.8)
Selection bias and generalizability of results	6	(27.3)
Limited receipt of materials	7	(31.8)
Regulatory Consequences		
No further action	9	(40.9)
Further action required	13	(59.1)
Improve distribution of aRMM or re-distribute	7	(31.8)
Changes to contents/format of existing aRMMs	4	(18.2)
Pending further discussion/data	4	(18.2)
Follow-up assessment requested	3	(13.6)
Removal of aRMMs	2	(9.1)
Changes to SmPC	1	(4.5)
aRMMs implemented	1	(4.5)
Re-analysis by reading/non-reading	1	(4.5)



QUESTIONS?