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Introduction or discontinuation of additional risk minimisation measures of medicines during the life cycle of medicines in Europe

Declaration of interests

No conflicts of interest to declare

Background

Additional risk minimisation measures (aRMMs)

- Adequate patient selection
- Timely recognition of adverse drug reactions (ADRs)
- Appropriate management of ADRs
- Prevention of medication errors

Background

Types of aRMMs

- Educational materials
 - Healthcare providers
 - Patients caregivers
- Controlled access
- Controlled distribution
- Pregnancy prevention programme

When to permanently discontinue ipilimumab

Permanently discontinue ipilimumab in patients with the following irARs:

- Grade 3 or 4 diarrhoea or colitis
- Grade 3 or 4 elevation in AST, ALT or total bilirubin
- Grade 4 skin rash (including Stevens-Johnson syndrome or toxic epidermal necrolysis) or Grade 3 pruritus
- Grade 3 or 4 motor or sensory neuropathy
- Grade 3 or 4 immune-related reactions (except for Grade 3-4 endocrinopathies controlled with hormone replacement therapy or Grade 3 skin rash)
- \geq Grade 2 for immune-related eye disorders NOT responding to topical immunosuppressive therapy
- Severe infusion reactions

Management of these adverse reactions may also require systemic high-dose corticosteroid therapy if demonstrated or suspected to be immune-related (see SmPC).

When to withhold a dose of ipilimumab

Yervoy (ipilimumab)

This card has important information on advanced melanoma.

Always carry this alert card with you as an example, if your regular doctor is unavailable you keep this card for at least 6 months

Tell your Doctor right away if you have any of the following symptoms:

BOWEL AND STOMACH*

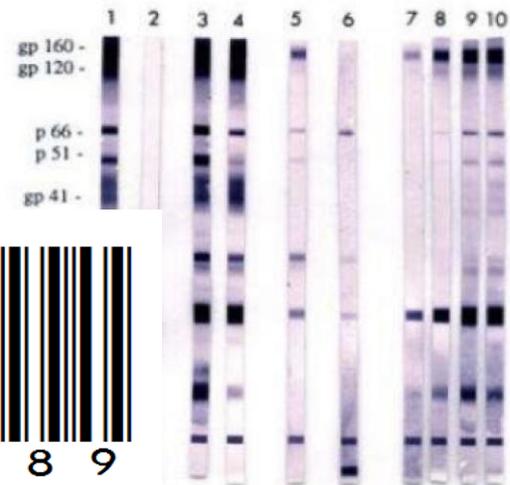
- diarrhoea (watery, loose or soft stools), bloody or darker-coloured stools
- more frequent bowel movements than usual
- pain or tenderness in the abdomen area, nausea

LIVER†

- eye or skin yellow
- pain on the right side of the abdomen
- dark urine

SKIN‡

- skin rash with or without blisters and/or peeling sores
- swelling of the face



Introduction

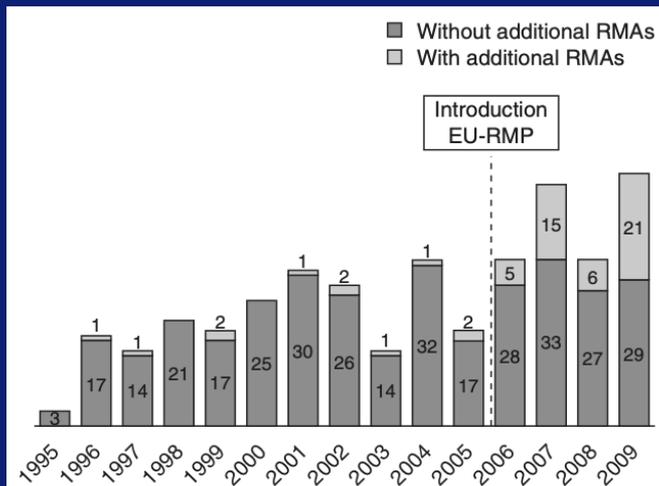
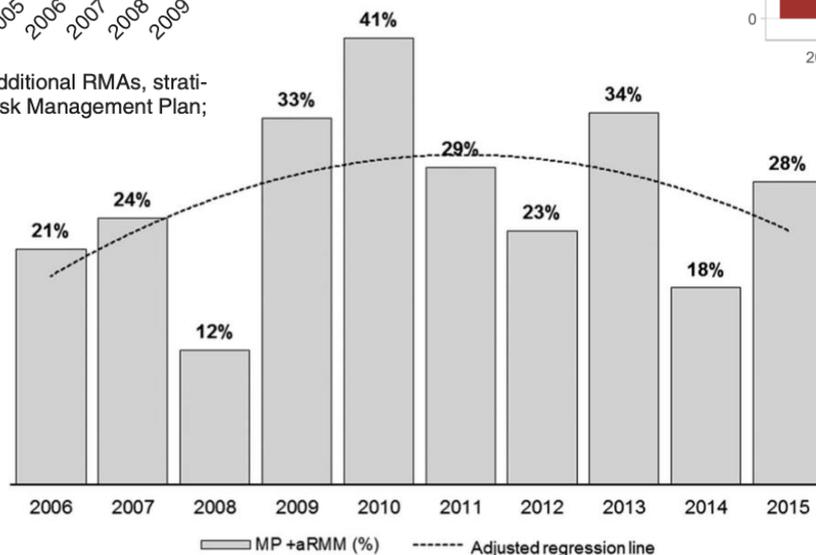
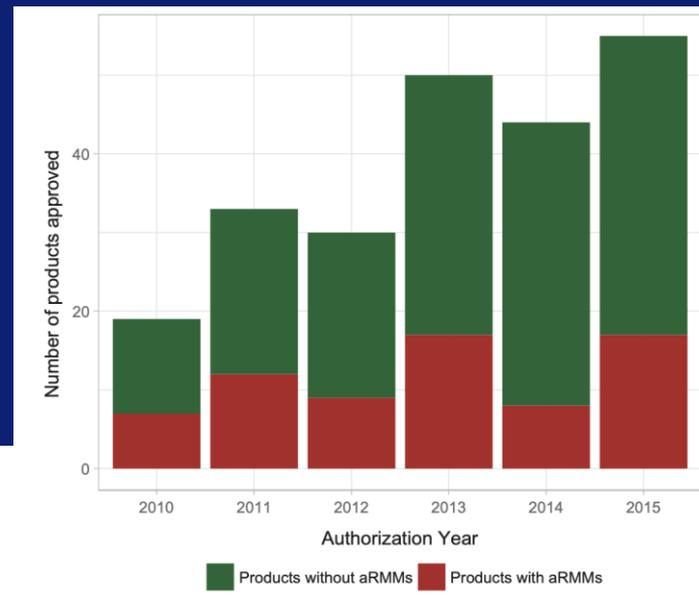


Fig. 1. Active substances with and without additional RMAs, stratified by year of authorization. **EU-RMP** = EU Risk Management Plan; **RMAs** = risk management activities.



From left to right:

1. Zomerdiijk IM, Sayed-Tabatabaei FA, Trifiro G, et al. Risk minimization activities of centrally authorized products in the EU: a descriptive study. *Drug Saf.* 2012 Apr 1;35(4):299–314.
2. Annalisa Rubino & Esther Artime (2017) A descriptive review of additional risk minimisation measures applied to EU centrally authorised medicines 2006-2015, *Expert Opinion on Drug Safety*, 16:8, 877-884
3. Reynold D. C. Francisca, Inge M. Zomerdiijk, Miriam C. J. M. Sturkenboom & Sabine M. J. M. Straus (2018) Measuring the impact of the 2012 European pharmacovigilance legislation on additional risk minimization measures, *Expert Opinion on Drug Safety*, 17:10, 975-982

Aims

To estimate

the probability of introduction of aRMMs during the life cycle for products without aRMMs at the time of authorisation

and

the probability of discontinuation of aRMMs during the life cycle for products with aRMMs at the time authorisation

Methods

Study design:	Cohort study
Drugs of interest:	New chemical entities authorised through EU central procedure between January 1st 2006 and December 31st 2017
Study period:	January 1st 2006 – July 1st 2018
Data source:	European Public Assessment Reports (EPAR) on www.ema.europa.eu



Methods

- Outcomes:
- 1) introduction of aRMMs post-authorisation in medicines without aRMM
 - 2) discontinuation of aRMMs post-authorisation in medicines with aRMM
- Covariates:
- Type of marketing authorisation (MA)
 - Orphan designation
 - Authorisation status at the end of follow-up
- Analysis:
- Survival analysis (Kaplan Meier)

Results

	Medicines without aRMMs at authorisation (N = 346)	Medicines with aRMMs at authorisation (N = 130)
Median follow-up time in months (range)	58 (8-150)	65 (8-150)
Type of MA (%)		
- Regular	320 (92%)	111 (85%)
- Conditional	12 (3%)	8 (6%)
- Exceptional	14 (4%)	11 (8%)
Orphan designation (%) *	54 (16%)	32 (25%)
Authorisation status at end follow-up (%)		
- Authorised	316 (91%)	117 (90%)
- Withdrawn	29 (8%)	13 (10%)
- Suspended	1 (0%)	0 (0%)

Results

Probability of *introduction* of aRMMs:

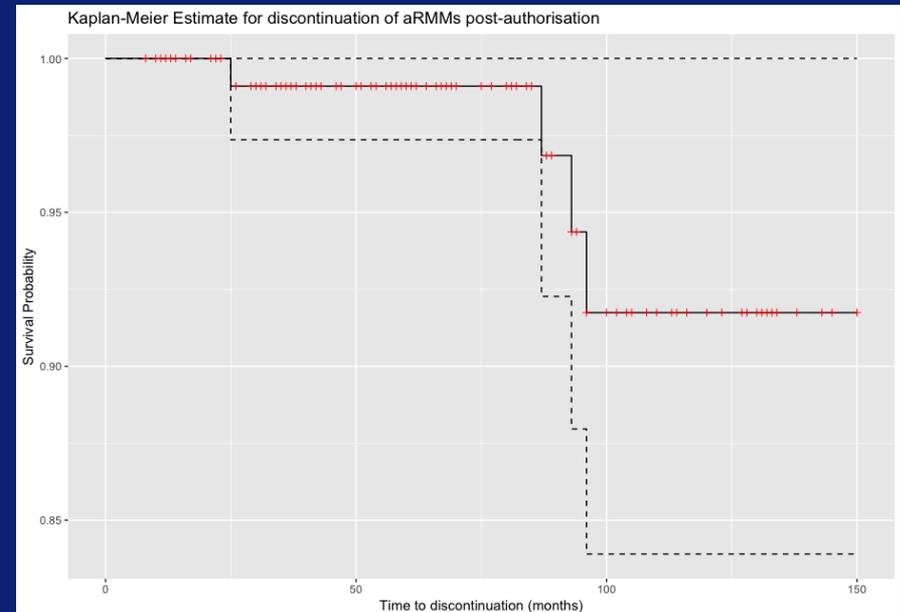
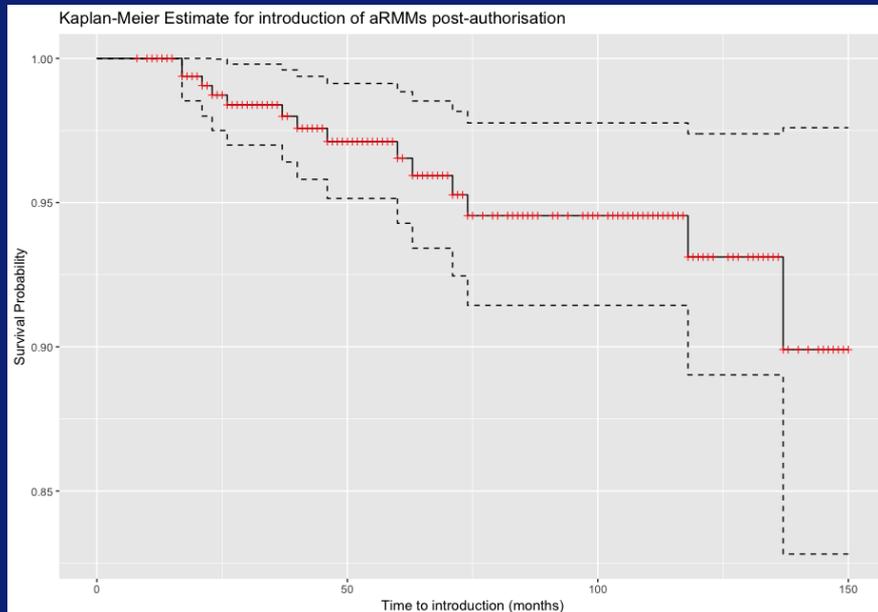
5y after MA: 3.5% (95%CI 1.2%-5.7%)

10y after MA: 6.9% (95%CI 2.6%-11%)

Probability of *discont'* of aRMMs:

5y after MA: 0.9% (95%CI 0%-2.6%)

10y after MA: 8.3% (95%CI 0%-16.1%)



Conclusion

- Low probability of introduction of aRMMs for medicines without aRMMs at authorisation
- Low probability of discontinuation of aRMMs for medicines with aRMMs at authorisation

Questions?

The End

Thank you for your attention!

