Risk Management Plans

Review of Experience

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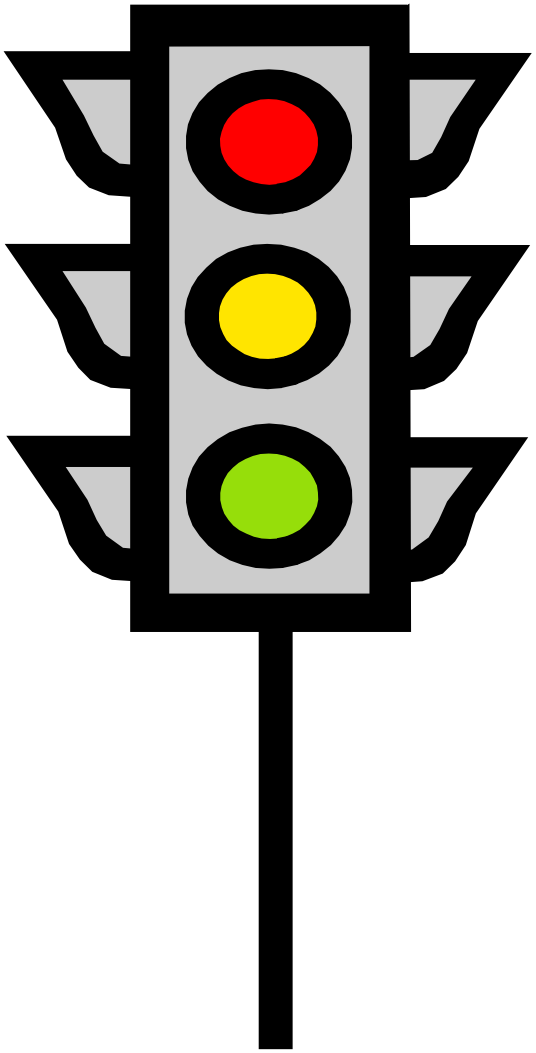
Risk Management Plans
November 05 till September 06

	Positive CHMP Opinions	RMP
MAA	31	29
Extensions of Indication	27	13
Line Extensions	3	1

Safety Specifications



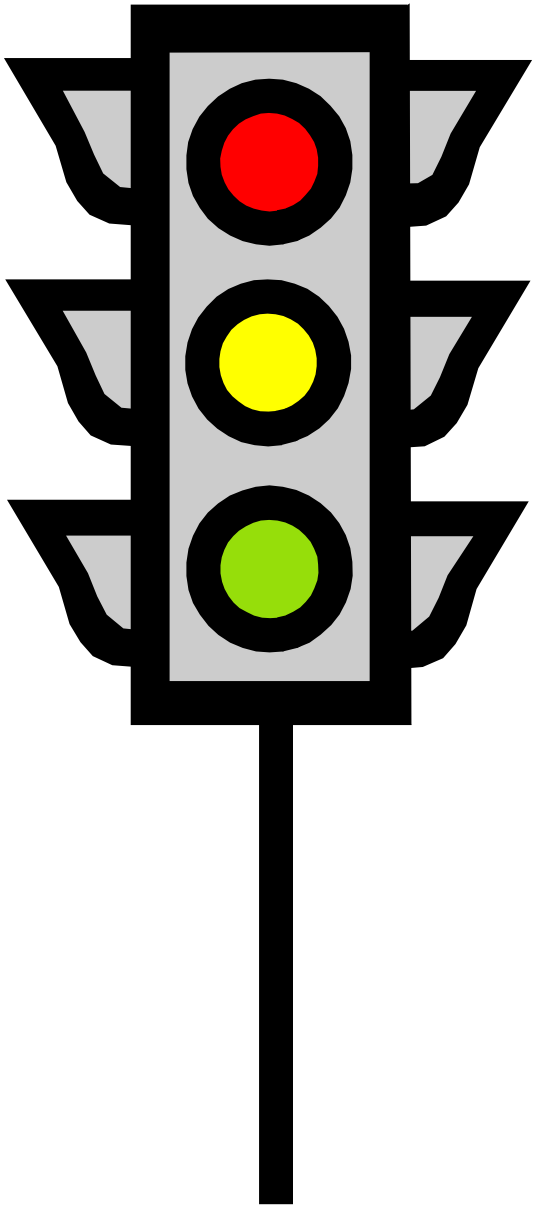
Safety Specification

Non Clinical

Clinical

- **Limitation of human safety database**
  - **Clinical trial population**
  - **Post-marketing exposure (if any)**
- **Populations not studied**
- **Post-marketing experience (actual use vs SPC)**
- **Adverse reactions**
  - **Risks (identified or potential)**
- **Identified and potential interactions**
- **Epidemiology**
- **Pharmacological class effects**

EU Specific



“ this EU Risk Management plan fulfils the requirements of article 8(3)(ia) of Directive 2001/83/EC and conforms to the EMEA Guideline on Risk Management Systems for Medicinal Products for Use (EMEA/CHMP/96268/2005) ”

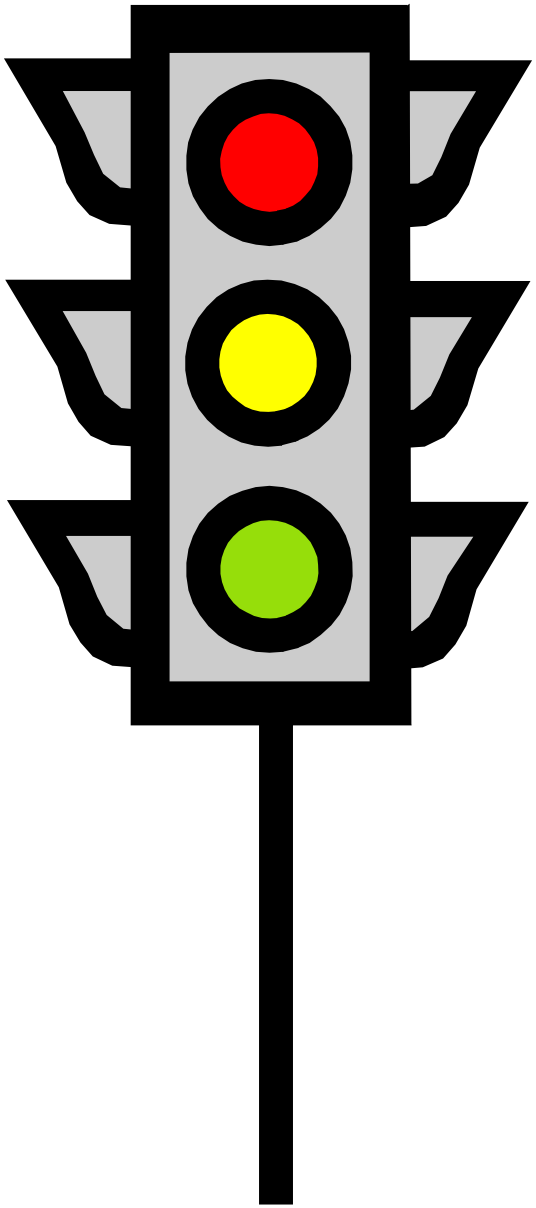
“ Overall, [redacted] offers significant advantage in overall survival and is an alternative to [redacted] for patients with [redacted] that prolongs survival and has a positive benefit- risk profile ”

Epidemiology

“Due to the limited population examined in pre-marketing studies, there is not sufficient data to provide conclusive assessments regarding incidence, prevalence, mortality, demographic and geographic variations”

Summary of the safety specification

“ There are no safety concerns with [redacted], therefore there is no need for a pharmacovigilance plan or risk minimisation activities ”



Limitations of the safety database

" Safety evaluations of [redacted] were based on an extensive safety database of 5409 patients who participated in phase II or III trials of ≥ 12 weeks. A total of 2006 and 1228 patients were exposed to [redacted] as monotherapy and as add on combination therapy. The total aggregate exposure to [redacted] was 995 patient years as monotherapy and 528 patient years as an add on therapy."

Clinical trial population aged 18 - 80

"All clinical trials in the development programme for [redacted] required women to use adequate contraception and to undergo a pregnancy test at screening and periodically during the study. There are limited data on the safety of [redacted] during pregnancy (see SCS-section 9.1 M2, 2.7.4 p162)"

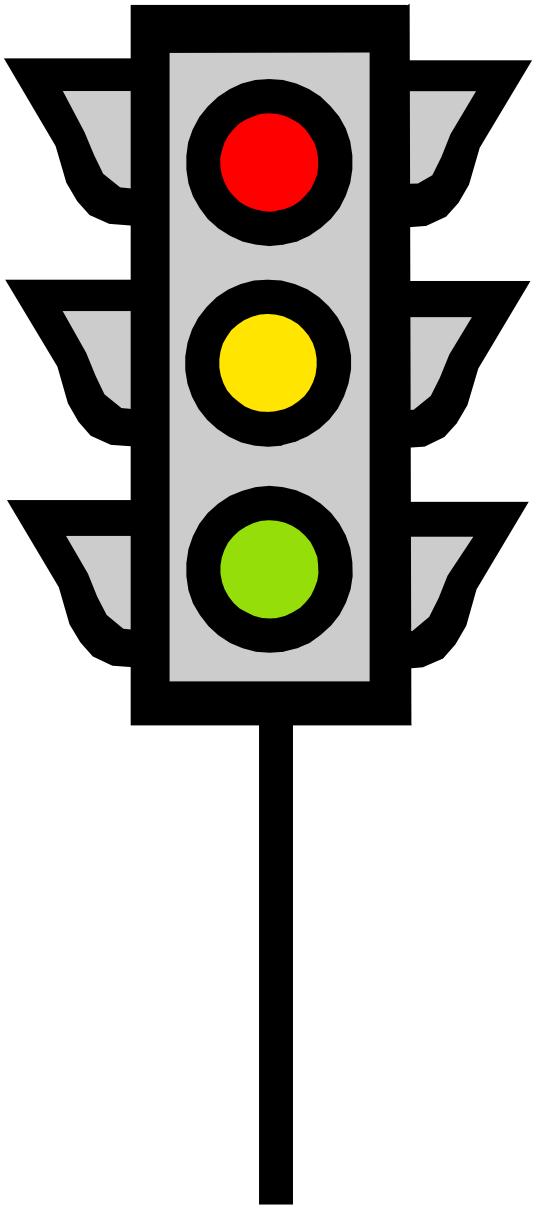
How many women became pregnant?

What went wrong?

What were the outcomes?

Adverse reactions

My favourite RMP recipe
547 serious adrs,
3059 adrs
That should keep the regulators nice and quiet!



Limitations of human safety database

Table x: Exposure by baseline disease

	No of patients Total (male/female)
Diabetic nephropathy	65 (39/26)
Hypertensive nephropathy	71 (47/24)
Glomerulonephritis	207 (143/64)
Other	246 (140/106)

Table y: Special population exposure

Population	Number of patients
Children (<12 years)	None
Elderly (>75 years)	14
Pregnant or lactating women	None
Relevant co-morbidities •Hepatic impairment •Cardiac disease •etc	 57 243 ….
Genetic polymorphism	Not applicable
Ethnic origin •Caucasian •other	 584 5

Adverse Events : epistaxis

Incidence	Placebo	Drug X	Odds ratio: 95%CI
Adult short term studies	32/775 (4%)	45/ 766 (6%)	1.44: 0.91 - 2.29
Adult long term studies	17/202 (8%)	124/ 608 (20%)	2.76: 1.61 - 4.73
Severity	All events in either placebo or active were mild or moderate in nature except for 1 subject who experienced 2 severe episodes. No serious event of epistaxis reported during clinical trials.		
Discontinuations	15 subjects on active and 3 on placebo discontinued during long term studies		
Time to onset	The majority of first events in long term studies occurred within the first 24 weeks of Rx.		

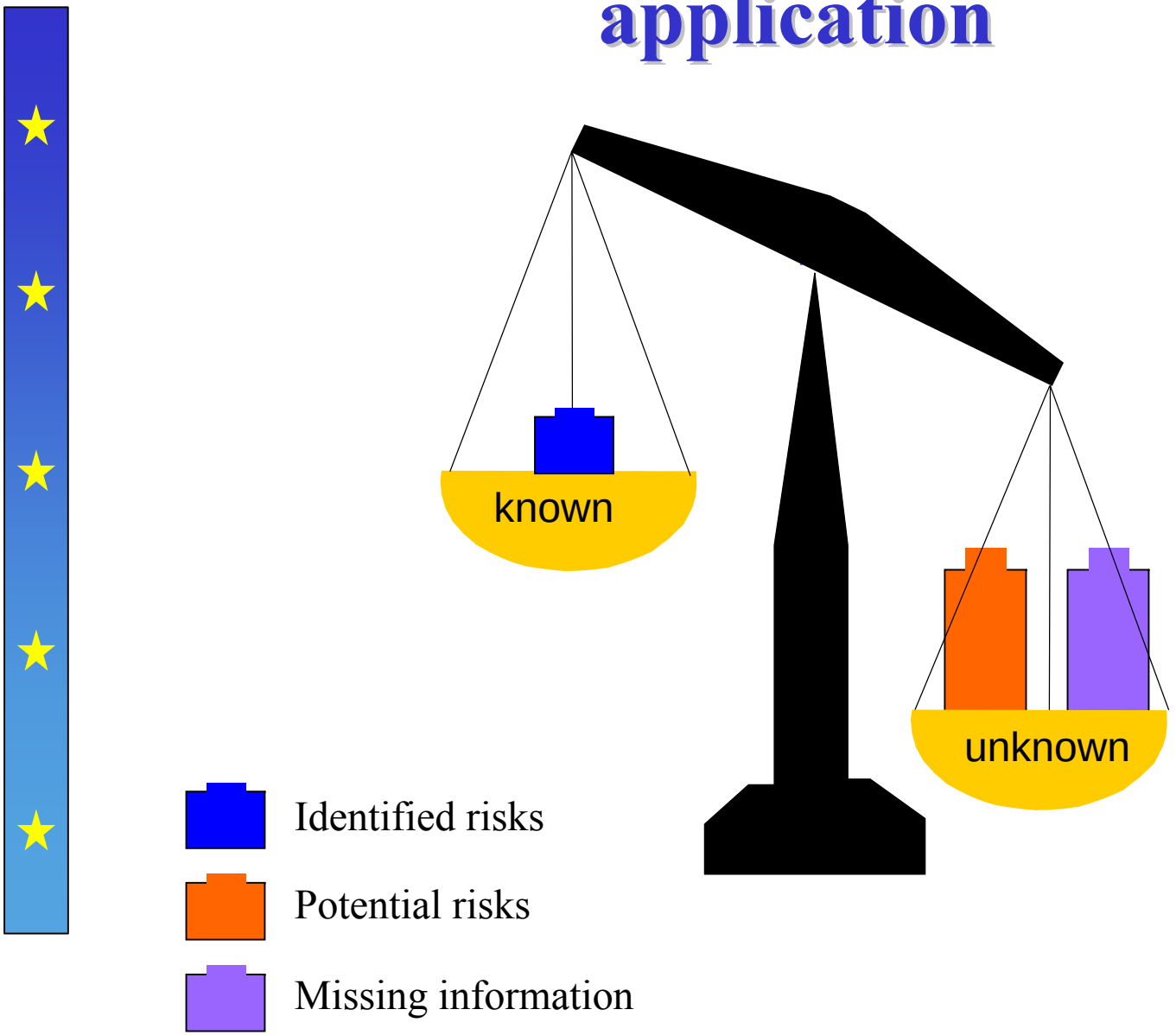
Cumulative incidence	≤ 2w	≤ 6 w	≤ 12 w	≤ 24 w	1-52 w
Placebo N=202	1 (<1%)	6 (3%)	8 (4%)	15 (7.5 %)	17 (8%)
Active N=608	11 (2%)	40 (7%)	72 (12%)	111 (18%)	125 (20%)

Epidemiology data

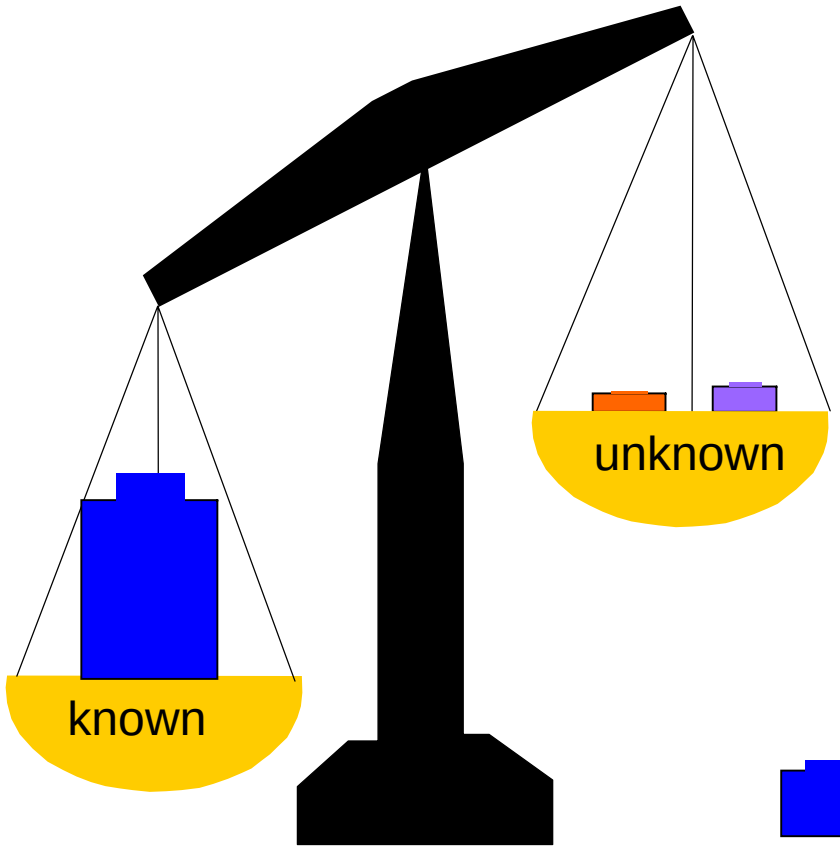
There are currently no population –based estimates of epistaxis prevalence among [redacted] sufferers. Data from the published literature has shown that among patients with [redacted] in clinical trials, epistaxis had a reported incidence of 17-23% vs a placebo incidence of 10-15% { Fisher 2004}. The placebo incidence of epistaxis in this programme was 4% for short term and 8% for long term studies

Pharmacovigilance Plans

At time of the marketing application



Mature Product



Identified risks

Potential risks

Missing information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Key things to think about with PhV Plans

What are the important potential risks?

What is the important missing information?

Are there obvious questions?

- Paediatric medicines
- Long term use?

What is the most appropriate way to investigate?

Numbers of exposed patients needed to detect adrs

Expected incidence of adr	Required number of adrs to detect signal		
	1	2	3
1 in 100	300	480	650
1 in 200	600	900	1,300
1 in 1,000	3,000	4,800	6,500
1 in 2,000	6,000	9,600	13,000
1 in 10,000	30,000	48,000	65,000

No background incidence of disease

Numbers of exposed patients needed to detect adrs

Incidence of adr to be detected	Spontaneous background incidence	*Minimum* number of patients
1 in 100	1 in 10,000 1 in 1,000 1 in 100	520 730 2,000
1 in 500	1 in 10,000 1 in 1,000 1 in 100	3,200 6,700 35,900
1 in 1,000	1 in 10,000 1 in 1,000 1 in 100	7,300 20,300 136,400
1 in 5,000	1 in 10,000 1 in 1,000 1 in 100	67,400 363,000 3,255,000

Evaluation of the need for risk minimisation activities

Evaluation of the need for risk minimisation activities

“ none of the safety concerns were serious and they can be managed by the means of the proposals in the pharmacovigilance plan. Therefore there is no need for a risk management plan.”

Safety concern

Abnormal LFTs

Routine risk min? YES

4.4

Monitor LFTs every month for the first 4 months. If levels rise >ULN monitor weekly. Levels >2 but <5 ULN decrease dose by 50% and monitor weekly. If levels continue to rise consider further dose reduction or discontinuation. ULN >5 discontinue immediately

4.8

very common abnormal LFTs

17 % of the clinical trial population had a rise in LFTs during the 24 week study. For 97% this started between 4 and 10 weeks after starting X. For the majority of patients, this was a transient rise which had spontaneously resolved by the next blood test. 2% went on to develop grade 3 or 4 abnormalities. This safety concern can be managed by a warning in section 4.4 advising doctors to monitor LFTs and a mention in 4.8.

Potential for medication errors

"There were medication errors identified in clinical trials presumably due to misunderstanding of, or non-compliance with, drug administration instructions."

Dose	**10 mg**	**20 mg**	**40 mg**
Shape	Round	Round	Round
Size mm	6.2 x 2.8	7.9 x 3.3	9.8 x 4.3
Colour	Pink	Light beige	Beige

Key messages

The EU-RMP is NOT a bureaucratic box to be ticked

Your audience are PhV people

Science not marketing!

Important to present relevant facts clearly and concisely but with sufficient detail for evaluation

The Safety Specification is the key to the EU-RMP

Base the PhV Plan and evaluation of the need for risk minimisation activities on the safety specification and think about how the medicine will be used and in whom

Think about your risk management plan from the start of your product development