
C B G
M E B

Regulatory tools for risk minimisation and their effectiveness

Monitoring health outcomes and patient compliance

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Medicines Evaluation Board
The Netherlands

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M E B

Increase in US medica

David P Phillips, Nicholas Christenfeld,

Between 1983 and 1993 the numbe
the USA increased by 75%, while t
days fell by 21%.[1] This shift to outpa
that more medications are taken
medical personnel, exercising qualitv

World Health Or
Medical Errors
Patients

Posted by Staff Writer
May 02, 2007 7:30 PM

0 Comments Print Artic

According to the World Health
healthcare errors affect one o
patients worldwide. Based on t
Organization prepared patient
providers avoid simple medica
Solutions," the organization ho
reductions. The the nine safety

1. Look-alike, sound-alike
2. patient identification;

TO ERR IS HUM
BUILDING A SAFER H

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RESEARCH LETTER

Pharmaceutical Overdose Deaths, United States, 2010

To the Editor: Data recently released by the National Center for Health Statistics show drug overdose deaths increased for the 11th consecutive year in 2010.[1] Pharmaceuticals, especially opioid analgesics, have driven this increase.[2] Other pharmaceuticals are involved in opioid overdose deaths, but their involvement is less well characterized. Using 2010 mortality data, we describe the specific drugs involved in pharmaceutical and opioid-related overdose deaths.

Methods. Data are from the National Vital Statistics System multiple cause-of-death file, which is based on death certificates submitted by medical examiners or coroners.[1] Drug overdose deaths were those assigned an underlying cause of death using the *International Classification of Diseases, Tenth Revision (ICD-10)* codes X40-X44 (unintentional), X60-X64 (suicide), X85 (homicide), and Y10-Y14 (undetermined intent). Pharmaceutical-related overdose deaths were those assigned specific *ICD-10* codes T36-T39, T40.2-T40.4, T41-T43.5, and T43.8-T50.8; psychotherapeutic and central nervous system pharmaceuticals were defined as T40.2-T40.4, T42, T43.0-T43.5, T43.8, T43.9; and opioid analgesics were those assigned codes T40.2-T40.4. Pharmaceutical deaths by this definition are predominately due to prescription drugs; a small minority involve over-the-counter or illicit drugs combined with prescription drugs in the same *ICD-10* T codes. Institu-

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504
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ıo killers:

4 80
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'act doesn`t hold true for every 300th patient admitted to
or blame human error for it, but the World Health
hospital admissions leads to an adverse event and one in

he patient having to spend an extra day in hospital or
Nikhil Datar, a gynaecologist and health activist.
threat to patient safety.

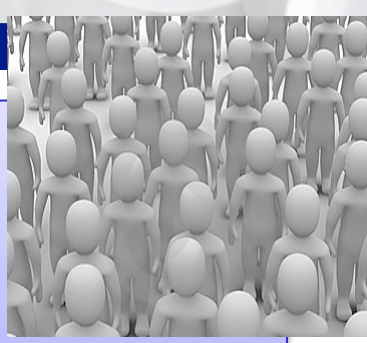
To Err Is Human:
BUILDING A SAFER HEALTH SYSTEM

TYPE OF ERRORs	
DIAGNOSTIC	Error of delay in diagnosis
	Failure to employ indicated tests
	Failure to act on results of monitoring
TREATMENT	Error in performance
	Error in administration
	Error om dose or method of use
	Avoidable delay
	Inappropriate care
PREVENTIVE	Failure to provide prophylactic treatment
	Inadequate monitoring or FU treatment
OTHER	Failure of communication
	Equipment failure
	Other system failure

Avoiding risk is impossible, but managing it is critical to sustained success

Individual

Recklessness
Intended actions (violations, mistakes)
Unintended actions (lapses, slips)

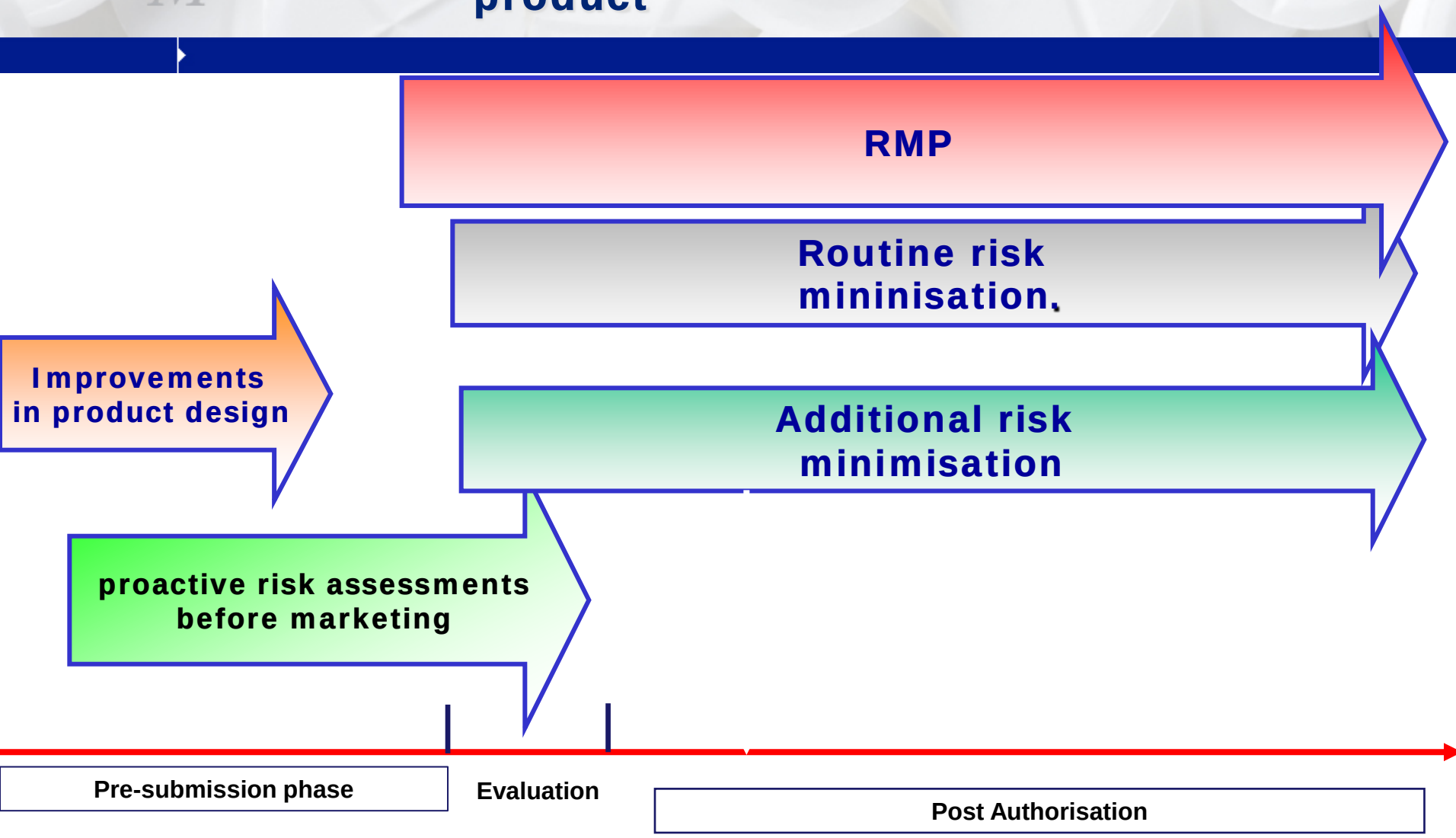


System

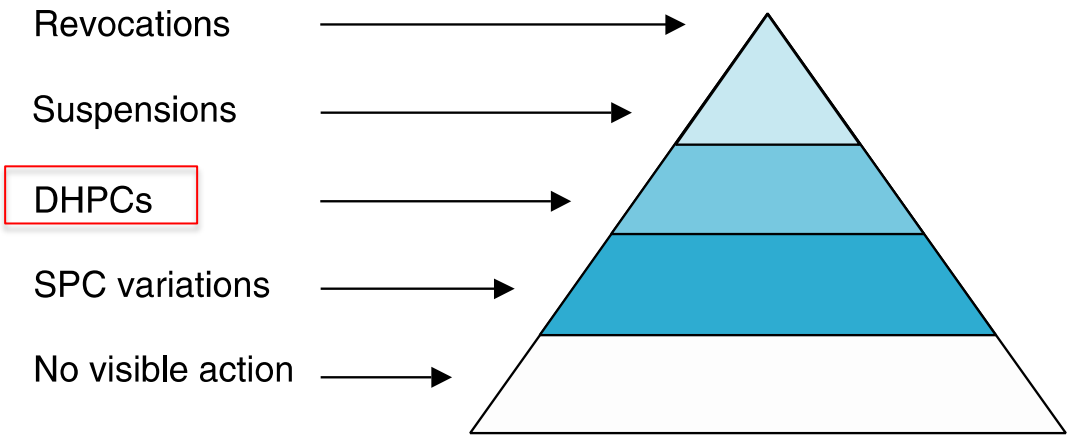
Faulty systems
Processes
Conditions

One of the report's main conclusions is that the majority of medical errors do not result from individual recklessness or the actions of a particular group--this is not a "bad apple" problem. More commonly, errors are caused by faulty systems, processes, and conditions that lead people to make mistakes or fail to prevent them. For example, stocking patient-care units in hospitals with certain full-strength drugs, even though they are toxic unless diluted, has resulted in deadly mistakes.

Preventing errors
A state of mind during the lifecycle of a product



Regulatory tools/actions



A Cohort Study Exploring Determinants of Safety-Related Regulatory Actions for Biopharmaceuticals

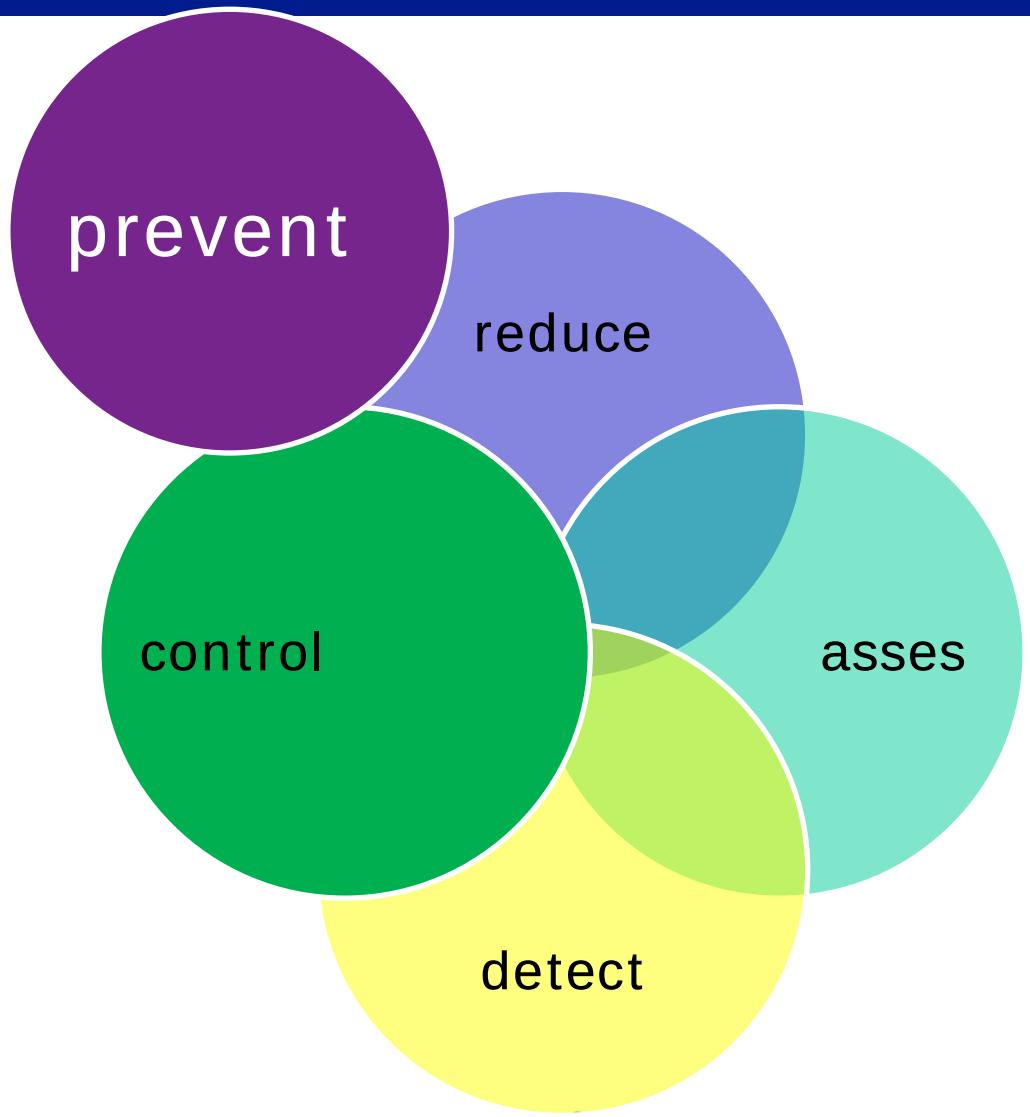
Hans C. Ebbers,[1] Aukje K. Mantel-Teeuwisse,[1] Ellen H.M. Moors,[2] Fakhredin A. Sayed Tabatabaei,[3] Huub Schellekens[2,4] and Hubert G.M. Leufkens[1,3]

Drug Saf 2012; 35 (5)

CBG MEB

FLAVOUR OF DHPCs for medication errors

reteplase	24-12-99	Incorrect route of drug administration
thiopental	11-01-01	Incorrect route of drug administration
moroctocog alfa	27-05-03	Circumstance or information capable of leading to medication error
lopinavir /ritonavir	01-09-06	Circumstance or information capable of leading to medication error
somatropin	18-06-07	Circumstance or information capable of leading to medication error
lopinavir /ritonavir	06-08-07	Incorrect dose administered
bivalirudin	29-10-07	Incorrect dose administered
levetiracetam	13-11-07	Incorrect dose administered
tacrolimus	05-12-08	Drug prescribing error
protein C agalsidase beta	04-02-09	Drug dispensing error
rivastigmine hydrogen tartrate	04-05-10	Circumstance or information capable of leading to medication error
nafareline	23-09-10	Device breakage
memantine	26-10-10	Circumstance or information capable of leading to medication error
memantine	11-02-11	Circumstance or information capable of leading to medication error
lacosamide	29-07-11	Circumstance or information capable of leading to medication error
bortezomib	17-01-12	Circumstance or information capable of leading to medication error
eribulin	29-02-12	Incorrect dose administered [10064355]
paracetamol i.v.	27-04-12	Accidental overdose
pegaptanib sodium	12-09-12	Intraocular pressure increased


prevent
reduce
control
asses
detect

HMA Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 June 2012
EMA/838713/2011

Guideline on good pharmacovigilance practices (GVP)

Module V – Risk management systems

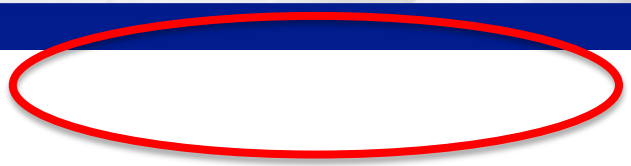
V.B.9.1. RMP part III section "Routine pharmacovigilance activities"

Routine pharmacovigilance is the set of activities required to fulfil the legal requirements for pharmacovigilance contained within Directive 2001/83/EC and Regulation (EC) No 726/2004. The Pharmacovigilance System Master File contains details of the system and processes each marketing authorisation applicant/holder has in place to achieve this. These details are not required to be submitted in the RMP.

V.B.9.2. RMP part III section "Additional pharmacovigilance activities"

Additional Pharmacovigilance activities may be non-clinical studies, clinical trials or non- interventional studies. A safety concern may have no, or a number of, additional pharmacovigilance activities associated with it depending upon its nature, the degree to which it has already been characterised, and the feasibility of studying it. Applicants/marketing authorisation holders should consider the situations when additional pharmacovigilance activities are needed. For example, a medicinal product intended for chronic use may only have relatively short term follow up data at the time of authorisation. Long term follow-up of patients from the clinical trial population or a cohort study may provide additional reassurance on the long term effects of the medicinal product. A medicinal product,

GVP V Risk Management Plan



In 2012 review of new MAA and their RMPs:

11 products have as a safety issue ‘medication error’, categorized as follows:

Identified risk	Potential risk	Missing information
1 product	9 products	1 product

•these risks were rarely addressed by additional pharmacovigilance or additional risk minimization activities.

•<u>Only 1 product has additional activities:</u>

•2 additional pharmacovigilance activities (1 PASS and 1 Registry) and

•2 additional risk minimization activities (educational material for HCP and patient)

Regarding Risk Minimization Activities, they were all versions or combinations of the following:

- Different size of containers
- Visible labelling with different colours
- Product information with ‘how to use?’
- PI with pictures
- Statement in 4.4
- Special warning imprinted on packaging
- Warning to users: ‘only administered by qualified physicians…’

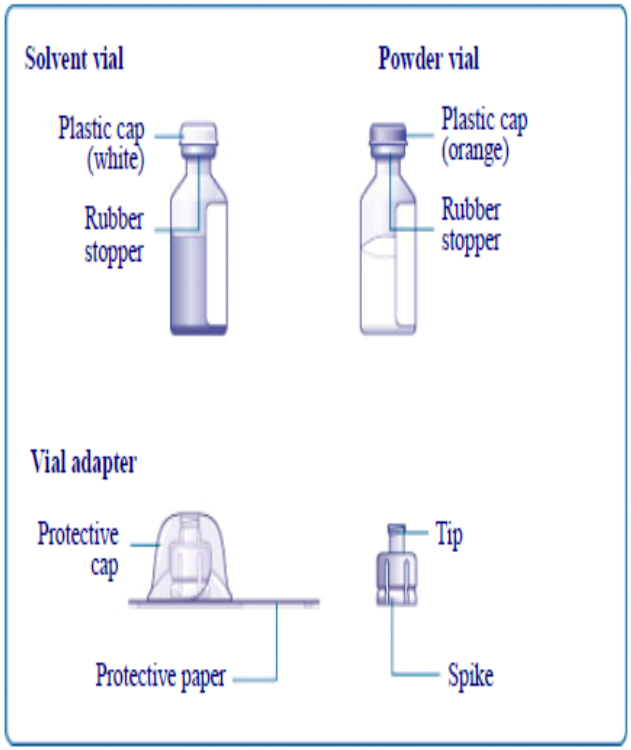
3. How to use Eklira Genuair

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

- The recommended dose is one inhalation twice a day in the morning and evening.
- The effects of Eklira Genuair last for 12 hours; therefore, you should try to use your Eklira Genuair inhaler at the same time every morning and evening. This ensures that there is always enough medicine in your body to help you breathe more easily throughout the day and night. It will also help you to remember to use it.

NovoThirteen user instructions

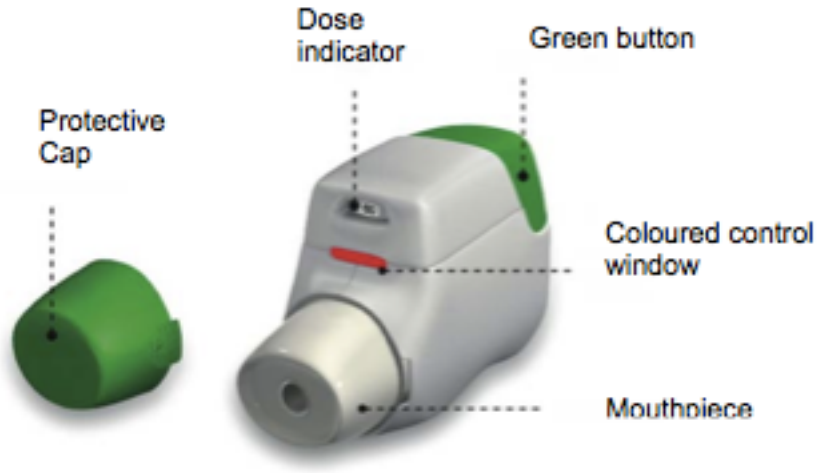
To reconstitute and administer this product the following tools ar
syringe of a convenient size according to injection volume, alcoh
and an infusion set (tubing, butterfly needle).



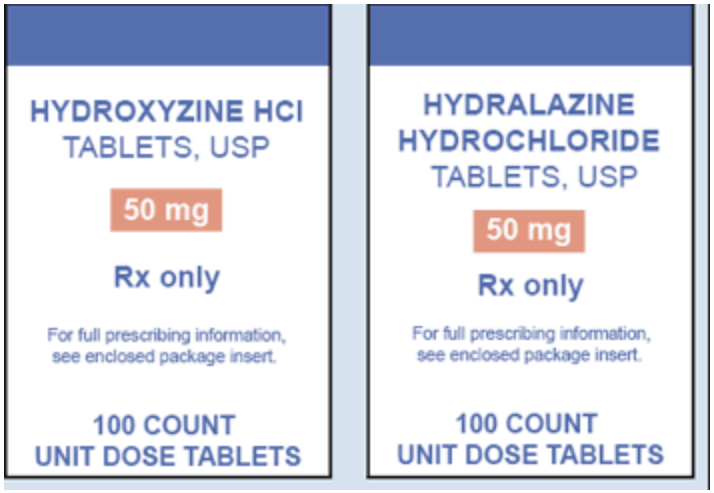
Method of administration
For inhalation use.

Instructions for use:

Becoming familiar with Eklira Genuair:



Remove the Genuair inhaler from the pouch and become familiar with its components.


HYDROXYZINE HCl
TABLETS, USP
50 mg
Rx only
For full prescribing information,
see enclosed package insert.
100 COUNT
UNIT DOSE TABLETS
HYDRALAZINE
HYDROCHLORIDE
TABLETS, USP
50 mg
Rx only
For full prescribing information,
see enclosed package insert.
100 COUNT
UNIT DOSE TABLETS

Additional risk minimisation measures

For some risks, additional risk minimisation measures will be necessary to manage risk and/or improve the benefit-risk balance of a medicinal product:

- ✓ **Educational programme**
  - targeted at HCP
  - targeted at patients
- ✓ **Controlled access programme**
- ✓ **Other:**
  - PPP
  - DHPC

- CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTI

The MAH shall ag
National Compete
This educational p
- recommend
- instructions
- warnings ar
  - to mo
  - to pr
    admi
  - in pa

Name	Language	First published	Last updated
NovoThirteen : EPAR - Conditions imposed on member states for safe and effective use	EN = English GO	05/12/2012	

The Marketing Authorisation Holder (MAH) shall ensure that, at launch, a letter is sent to all expected and actual prescribers of NovoThirteen with an Educational Pack containing the following:

1. Physician brochure
2. Patient brochure

Both documents are to be used as part of an educational plan aiming to minimise risks of medication errors, risk of thromboembolic events due to increased levels of non-proteolytically activated rFXIII in connection with incorrect storage, and risk of off-label use for treatment of breakthrough bleeding. The MAH should ensure harmonisation between terminology used in the brochures and the product information.

Pharmacovigilance
2010 pharmacovigilance legislation
Electronic submission of information
Good pharmacovigilance practices
European Risk Management Strategy
EudraVigilance
Framework

The remaining modules below are under development and are scheduled for release for an eight-week public consultation as indicated below:

Module number	Module title	Date of release for public consultation
XI	Public participation in pharmacovigilance	Second quarter 2013
XII	Continuous pharmacovigilance, ongoing benefit-risk evaluation, regulatory action and planning of public communication	First quarter 2013
XIV	International cooperation	Second quarter 2013
XVI	Risk-minimisation measures: selection of tools and effectiveness indicators	First quarter 2013

9.7.3 Outcomes of regulatory action

The strengths and weaknesses of the European PhV System regarding the outcomes of regulatory action can be summarised as follows:

Strengths of the PhV System	Weaknesses of the PhV System
•	• The outcomes of regulatory action are only assessed in exceptional cases. • There is very little information about what prescribers do with label information and label changes. Moreover, when information is there, the results are not very encouraging. • The missing information on outcomes is partially attributed to far too few inspections of MAHs with a pharmacovigilance focus.

Generally, the outcomes of regulatory action cannot easily be evaluated, because even the agencies do normally not have such information. Actions are not evaluated pro-actively, and even if changes in the morbidity and mortality caused by ADRs were detected they could not causally be related to single regulatory acts.

RMM effectiveness:

what to measure?

- Process indicators

evidence that the implementing steps of risk minimisation measures have been successful

- Outcome indicators

provide an overall measure of the level of risk control that has been achieved with a risk minimisation measure

- ✓ performance of the overall program
- ✓ individual tool performance

RMM effectiveness

- Process indicators
  - Implementation logistics/coverage/distribution
    - Distribution plan, target group, quality of the content
  - Awareness and clinical knowledge
    - % of HCP or patients with sufficient knowledge regarding the risk and ways to minimise it
  - Behavorial change/clinical action
    - Impact on daily practice, adherence to guidance, impact on patients

- Outcome indicators
  - Measure directly the health outcome goal
  - Surrogate endpoints if necessary

Complex
Many stakeholders
Potential for failure is
packaging lab
medical use
human failure
system failure
behaviour (ski

COMMENTARY

Mindfulness and Patient Safety

Erica M. S. Sibinga, MD, MHS
Albert W. Wu, MD, MPH

PATIENT SAFETY HAS BEEN A TOPIC OF CONSIDERABLE

Roots of Diagnostic Errors

Cognitive dispositions to respond that influence the diagnostic process are characterized by a lack of awareness and responsiveness by the individual to his or her own cognitive and affective processes.[2,3] For example, confirmation bias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