How do we tell them?

Navigating safety issues – for healthcare professionals and the public

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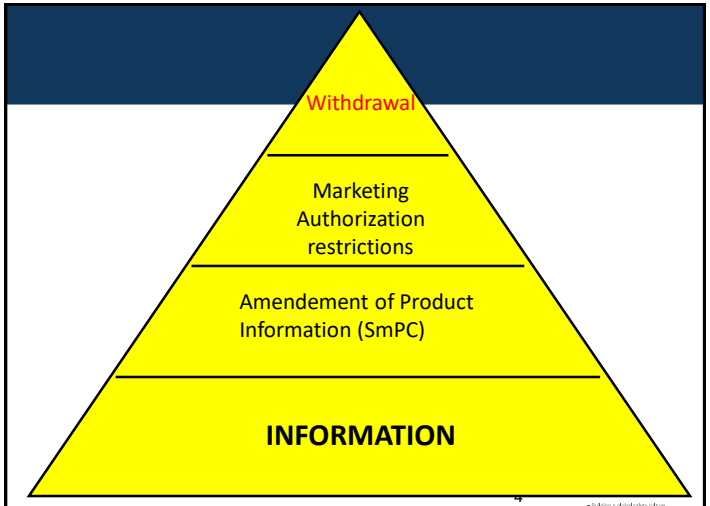
MURIA 2019

And now

A few basic concepts

Risk minimization

Action taken by Drug Regulatory Authorities and/or Marketing Authorization Holder (MAH) on a product with the aim of keeping a positive benefit risk balance



Signal

A safety signal is information on a new or known adverse event that may be caused by a medicine and requires further investigation.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000587.jsp&mid=WC0b01ac0580727d1b

Notice of an early concern or hypothesis about a possible medicines safety problem, with evidence and arguments to support it.

https://www.who-umc.org/global-pharmacovigilance/global-pharmacovigilance/glossary/

Safety issue

Whatever can constitute a risk to a patient taking a medicine

- Quality problem
- Adverse Drug Reactions (ADR)
- Inappropriate use (from prescription to administration) resulting in (potential) harm

Emerging safety issues - characteristics

Information is

- **New**
- **Incomplete**
- **(Apparently) urgent**

→ **Risk assessment difficult**

Example

November 1st 2012

One European country raises a concern over the quality of some batches of an influenza vaccine through the Rapid Alert System – visible particles suspended in the solution

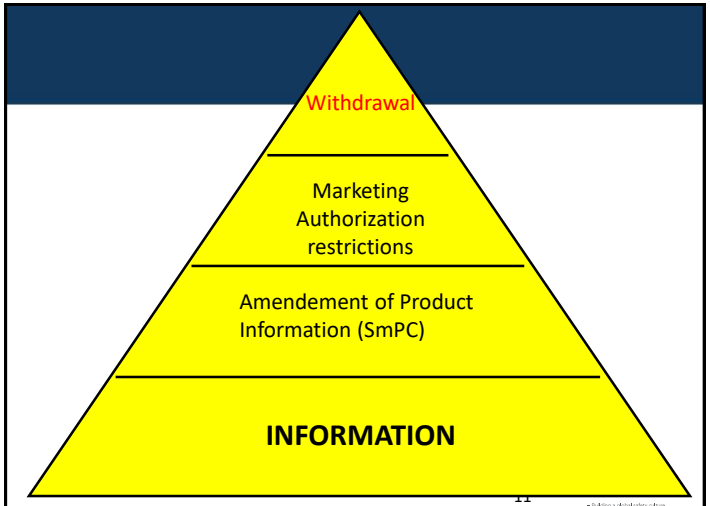
Recall the vaccine?

- Is this a problem? Safety or efficacy or both?
- What is the cause?
- All or only selected batches affected?
- Where have the affected batches been distributed?

- MAH could not track the affected batches
- All batches in quarantine
- HCP informed to store but not use the vaccine until further notice
- Hotline opened for questions
- Vaccine released for use 1 week later

Potential risk – points to consider

- Exposed population (size, sensitive populations)?
- Essential medicinal product?
- Seriousness and severity of ADR?
- Preventable ADR?
- Rapid increase of number of reports?
- Public impact and perception?



A 'good' safety communication

- Contributes to risk minimization
- Helps HCP and patients to make wise decisions in their choice of therapeutics
- Fosters trust in competent authorities/MAH

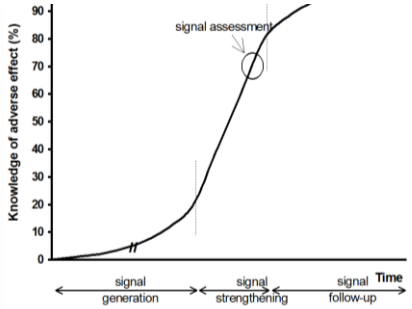
A 'bad' safety communication

- Is useless
- Causes confusion and anxiety
- Can lead to more damage than the potential risk being communicated
- Undermines trust in HCP, authorities and MAH

"Good" safety messages

- Are timely
- Target the right audience
- Use appropriate channels
- Provide essential and useful information
- Use appropriate language
- Are truthful

Meyboom RH et al, Drug Safety 1997: 17(6): 374-89



If the risk is assessed as very high, risk minimizing actions might be justified even in the very early stages of signal evaluation

Who needs to know about a drug safety issue?

- The prescriber?
- The dispenser?
- The HCP likely to see the patient having a problem?
- The patient/carer?
- The National PV centre/regulator?
- The Minister of Health?
- The MAH?
- All of the above?

Case studies

DRA website

A Drug Regulatory Authority communicates on its website

***"..**that severe cases of liver disease have been reported in patients under treatment with drug X. As a causal relationship has not been established so far, more investigations are needed…"*

- **Who is being addressed?**
- **What is the message?**
- **What are the consequences of such a message?**

Safety information in a SmPC

Adverse reactions reported in controlled clinical trials (less than 1% more on benazepril than on placebo), and rarer events seen in post-marketing experience, include the following (in some, a causal relationship to drug use is uncertain):

.....

Got it?

What do we need to communicate?

- What is happening/has been observed and why we are worried about it
- What we know
  - Who is concerned
  - What evidence we have evaluated and how
  - The results of our evaluation
- What we don't know
- Next steps planned/When can we expect to know more
- What is the addressee requested to do
- Point of contact

Examples

US FDA: Elevated levels of Belladonna in homeopathic teething products

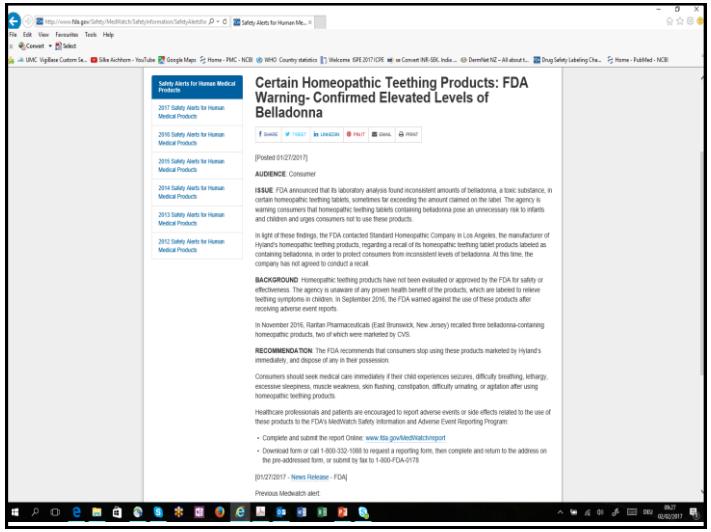
http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm538687.htm

MHRA: Trametinib and risk of GI perforation and colitis

https://www.gov.uk/drug-safety-update/trametinib-mekinist-risk-of-gastrointestinal-perforation-and-colitis[07/04/2016 15:28:51]

US FDA: Bi yan pian – risk of stroke

U.S. Food & Drug Administration (FDA) Daily Digest Bulletin Feb 9th 2017



Safety Alerts for Human Medical Products

2017 Safety Alerts for Human Medical Products

2016 Safety Alerts for Human Medical Products

2015 Safety Alerts for Human Medical Products

2014 Safety Alerts for Human Medical Products

2013 Safety Alerts for Human Medical Products

2012 Safety Alerts for Human Medical Products

Certain Homeopathic Teething Products: FDA Warning- Confirmed Elevated Levels of Belladonna

[Posted 01/27/2017]

AUDIENCE: Consumer

ISSUE: FDA announced that its laboratory analysis found inconsistent amounts of belladonna, a toxic substance, in certain homeopathic teething tablets, sometimes far exceeding the amount claimed on the label. The agency is warning consumers that homeopathic teething tablets containing belladonna pose an unnecessary risk to infants and children and urges consumers not to use these products.

In light of these findings, the FDA contacted Standard Homeopathic Company in Los Angeles, the manufacturer of Hyland's homeopathic teething products, regarding a recall of its homeopathic teething tablet products labeled as containing belladonna, in order to protect consumers from inconsistent levels of belladonna. At this time, the company has not agreed to conduct a recall.

BACKGROUND: Homeopathic teething products have not been evaluated or approved by the FDA for safety or effectiveness. The agency is unaware of any proven health benefit of the products, which are labeled to relieve teething symptoms in children. In September 2016, the FDA warned against the use of these products after receiving adverse event reports.

In November 2016, Raritan Pharmaceuticals (East Brunswick, New Jersey) recalled three belladonna-containing homeopathic products, two of which were marketed by CVS.

RECOMMENDATION: The FDA recommends that consumers stop using these products marketed by Hyland's immediately, and dispose of any in their possession.

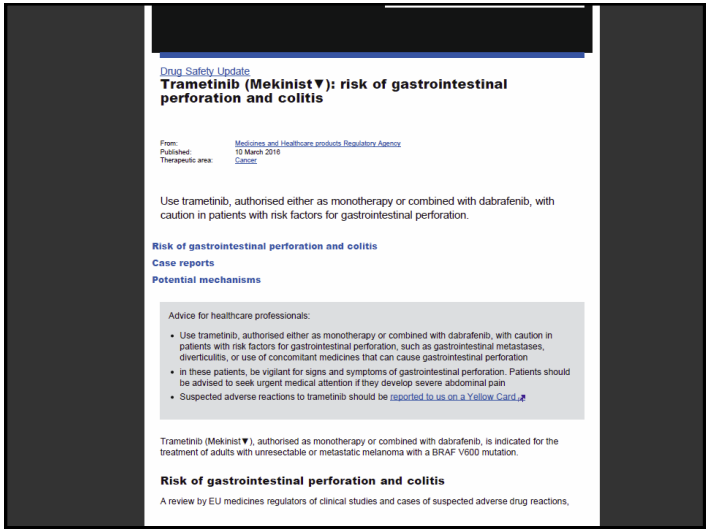
Consumers should seek medical care immediately if their child experiences seizures, difficulty breathing, lethargy, excessive sleepiness, muscle weakness, skin flushing, constipation, difficulty urinating, or agitation after using homeopathic teething products.

Healthcare professionals and patients are encouraged to report adverse events or side effects related to the use of these products to the FDA's MedWatch Safety Information and Adverse Event Reporting Program:

- Complete and submit the report Online: www.fda.gov/MedWatch/report
- Download form or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178

[01/27/2017 - News Release - FDA]

Previous Medwatch alert:



Drug Safety Update

Trametinib (Mekinist▼): risk of gastrointestinal perforation and colitis

From: Medicines and Healthcare products Regulatory Agency
Published: 10 March 2016
Therapeutic area: Cancer

Use trametinib, authorised either as monotherapy or combined with dabrafenib, with caution in patients with risk factors for gastrointestinal perforation.

Risk of gastrointestinal perforation and colitis

Case reports

Potential mechanisms

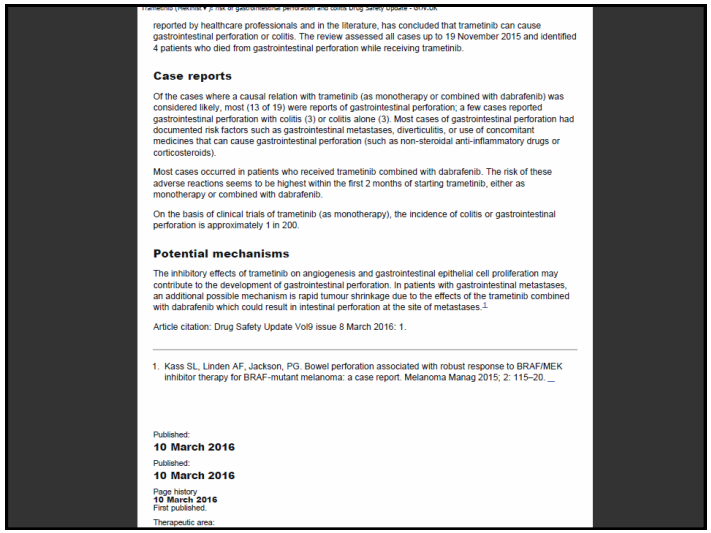
Advice for healthcare professionals:

- Use trametinib, authorised either as monotherapy or combined with dabrafenib, with caution in patients with risk factors for gastrointestinal perforation, such as gastrointestinal metastases, diverticulitis, or use of concomitant medicines that can cause gastrointestinal perforation
- in these patients, be vigilant for signs and symptoms of gastrointestinal perforation. Patients should be advised to seek urgent medical attention if they develop severe abdominal pain
- Suspected adverse reactions to trametinib should be reported to us on a Yellow Card

Trametinib (Mekinist▼), authorised as monotherapy or combined with dabrafenib, is indicated for the treatment of adults with unresectable or metastatic melanoma with a BRAF V600 mutation.

Risk of gastrointestinal perforation and colitis

A review by EU medicines regulators of clinical studies and cases of suspected adverse drug reactions,



reported by healthcare professionals and in the literature, has concluded that trametinib can cause gastrointestinal perforation or colitis. The review assessed all cases up to 19 November 2015 and identified 4 patients who died from gastrointestinal perforation while receiving trametinib.

Case reports

Of the cases where a causal relation with trametinib (as monotherapy or combined with dabrafenib) was considered likely, most (13 of 19) were reports of gastrointestinal perforation; a few cases reported gastrointestinal perforation with colitis (3) or colitis alone (3). Most cases of gastrointestinal perforation had documented risk factors such as gastrointestinal metastases, diverticulitis, or use of concomitant medicines that can cause gastrointestinal perforation (such as non-steroidal anti-inflammatory drugs or corticosteroids).

Most cases occurred in patients who received trametinib combined with dabrafenib. The risk of these adverse reactions seems to be highest within the first 2 months of starting trametinib, either as monotherapy or combined with dabrafenib.

On the basis of clinical trials of trametinib (as monotherapy), the incidence of colitis or gastrointestinal perforation is approximately 1 in 200.

Potential mechanisms

The inhibitory effects of trametinib on angiogenesis and gastrointestinal epithelial cell proliferation may contribute to the development of gastrointestinal perforation. In patients with gastrointestinal metastases, an additional possible mechanism is rapid tumour shrinkage due to the effects of the trametinib combined with dabrafenib which could result in intestinal perforation at the site of metastases.[1]

Article citation: Drug Safety Update Vol9 issue 8 March 2016: 1.

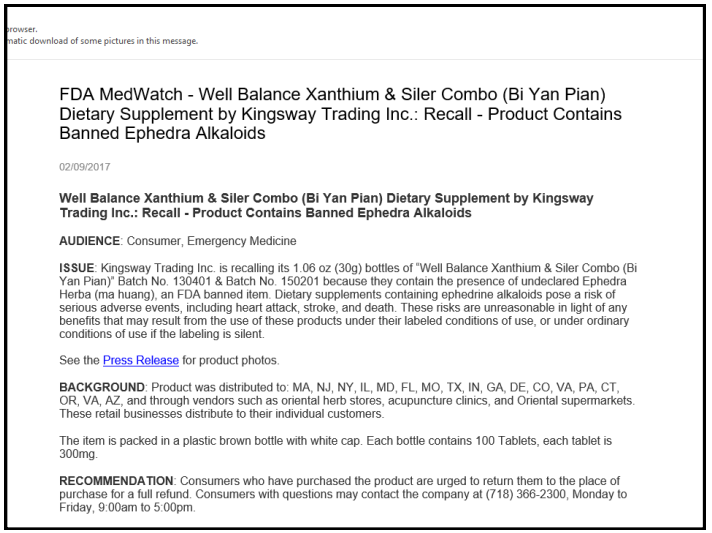
1. Kass SL, Linden AF, Jackson, PG. Bowel perforation associated with robust response to BRAF/MEK inhibitor therapy for BRAF-mutant melanoma: a case report. Melanoma Manag 2015; 2: 115–20. _

Published:
10 March 2016

Published:
10 March 2016

Page history
10 March 2016
First published.

Therapeutic area:



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matic download of some pictures in this message.

FDA MedWatch - Well Balance Xanthium & Siler Combo (Bi Yan Pian) Dietary Supplement by Kingsway Trading Inc.: Recall - Product Contains Banned Ephedra Alkaloids

02/09/2017

Well Balance Xanthium & Siler Combo (Bi Yan Pian) Dietary Supplement by Kingsway Trading Inc.: Recall - Product Contains Banned Ephedra Alkaloids

AUDIENCE: Consumer, Emergency Medicine

ISSUE: Kingsway Trading Inc. is recalling its 1.06 oz (30g) bottles of "Well Balance Xanthium & Siler Combo (Bi Yan Pian)" Batch No. 130401 & Batch No. 150201 because they contain the presence of undeclared Ephedra Herba (ma huang), an FDA banned item. Dietary supplements containing ephedrine alkaloids pose a risk of serious adverse events, including heart attack, stroke, and death. These risks are unreasonable in light of any benefits that may result from the use of these products under their labeled conditions of use, or under ordinary conditions of use if the labeling is silent.

See the Press Release for product photos.

BACKGROUND: Product was distributed to: MA, NJ, NY, IL, MD, FL, MO, TX, IN, GA, DE, CO, VA, PA, CT, OR, VA, AZ, and through vendors such as oriental herb stores, acupuncture clinics, and Oriental supermarkets. These retail businesses distribute to their individual customers.

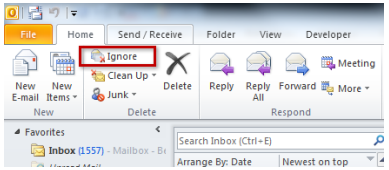
The item is packed in a plastic brown bottle with white cap. Each bottle contains 100 Tablets, each tablet is 300mg.

RECOMMENDATION: Consumers who have purchased the product are urged to return them to the place of purchase for a full refund. Consumers with questions may contact the company at (718) 366-2300, Monday to Friday, 9:00am to 5:00pm.

Information channels

- Scientific publications/conferences
- SmPC and PIL (Product information leaflet)
- DRA website/Newsletter
- Dear Health Care Professional Letter
- Media

Information floods lead to



Think ahead

- What effect will our communication have?
- What questions will it raise?
- Are we ready to answer them?

Take home messages

Communication of emerging safety issues needs particular care due to their characteristics

- Evolving nature
- Missing information
- Urgency real or perceived

We need to define our audience and choose the appropriate channel

Key points to be communicated

- Description of the issue
- What we know/don't know
- What is the addressee requested to do
- Next steps planned/When can we expect to know more
- Point of contact

Uppsala Monitoring Centre

– Building a global safety culture

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