AGENZIA ITALIANA DEL FARMACO

Tutela Ricerca e Sviluppo per la Salute

IMPROVING PATIENT SAFETY

ANTI-CANCER DRUGS

Alessandra Ranuncoli

Parma, 18 May 2018

Public Declaration of transparency/interests*

The view and opinions expressed are those of the individual presenter and should not be attributed to AIFA

Interests in pharmaceutical industry	NO	Current	From 0 to 3 previous years	Over 3 preavious years
DIRECT INTERESTS:				
1.1 Employment with a company: pharmaceutical company in an executive role	X	☐	☐	☐ mandatory
1.2 Employment with a company: in a lead role in the development of a medicinal product	X	☐	☐	☐ mandatory
1.3 Employment with a company: other activities	X	☐	☐	☐ optional
2. Consultancy for a company	X	☐	☐	☐ optional
3. Strategic advisory role for a company	X	☐	☐	☐ optional
4. Financial interests	X	☐	☐	☐ optional
5. Ownership of a patent	X	☐	☐	☐ optional
INDIRECT INTERESTS:				
6. Principal investigator	X	☐	☐	☐ optional
7. Investigator	X	☐	☐	☐ optional
8. Grant or other funding	X	☐	☐	☐ optional
9. Family members interests	X	☐	☐	☐ optional

*Alessandra Ranuncoli, in accordance with the Conflict of Interest Regulations approved by AIFA Board of Directors (25.03.2015) and published on the Official Journal of 15.05.2015 according to EMA policy /626261/2014 on the handling of the conflicts of interest for scientific committee members and experts.

N.B. I am not receiving any compensation

Outlines

- All the new anti-cancer drugs are innovative and EMA centralized.
- EU regulatory environment supporting the development of Risk Minimization Measures (RMMs).
- Examples of RMMs in the anti-cancer drugs
  - Nivolumab: Health Professional Care Booklet and Patient Alert Card
  - Lenalidomide: Pregnancy prevention programmes (PPP)
  - Blinatumomab: Direct Healthcare Professional Communication (DHPC)

EU regulatory environment supporting the development of Risk Minimization Measures (RMMs)

L 348/74 EN Official Journal of the European Union 31.12.2010

DIRECTIVES

DIRECTIVE 2010/84/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

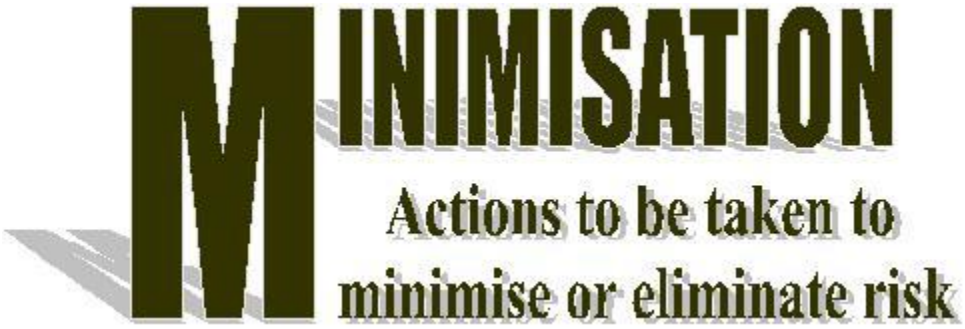
of 15 December 2010

amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use

(Text with EEA relevance)

(2) Pharmacovigilance rules are necessary for the protection of public health in order to prevent, detect and assess adverse reactions to medicinal products placed on the Union market, as the full safety profile of medicinal products can only be known after they have been placed on the market.

Risk Minimisation Measures (RMMs)



Risk Minimisation Measures (RMMs)

- RMM are interventions intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicine, or to reduce their severity or impact on the patient should adverse reactions occur.

- Planning and implementing RMM and assessing their effectiveness are key elements of risk management (RM).

- The anti-cancer drugs have often severe and frequent adverse reactions and the regulatory should protect the patient.

Anti-cancer drugs. Early approval.

Approval Decision

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Critical Juncture

manage emerging knowledge about B/R uncertainty

maintaining a positive B/R balance as evidence is gathered in clinical use reducing uncertainties which exist at time of MA

Anti-cancer drugs. Early approval

OPINION

Balancing early market access to new drugs with the need for benefit/ risk data: a mounting dilemma

Hans-Georg Eichler, Francesco Pignatti, Bruno Flamion, Hubert Leufkens and Alasdair Breckenridge

Nat Rev Drug Discov. 2008

The life-cycle approach of the risk management

1. Risk identification and characterisation
2. Planning of PhV activities
3. Planning of RMMs and assessment of their effectiveness

GVPs of specific relevance:

GVP V Risk Management Plan

GVP VIII Post authorisation safety studies

GVP XV Safety communication

GVP XVI Risk minimisation measures: selection of tools and effectiveness indicators

Additional Risk Minimisation Measures (aRMM)

Measures beyond those routinely required:

- Educational tools for HCPs or patients.

- Controlled access programme:
  - requirements needs to be fulfilled before the product is prescribed and/or dispensed

- Other risk minimisation measures:
  - Pregnancy prevention programmes (PPP)
  - Controlled distribution system
  - Direct healthcare professional communication(DHPC)

Need for aRMMs

- Not all drugs need for aRMM

- Depends on the safety concern and on the frequency and severity of the ADR:
  - Might be a condition with very serious consequences
  - Might be very frequent event
  - New complicated method of administration
  - Potential for misuse/overdose

- For these reasons in the anti-cancer drugs the aRMM are often mandatory

i.e. Nivolumab

- Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2.

- Nivolumab is indicated for various cancer in monotherapy or in association: Melanoma, Non Small Cell Lung Cancer (NSCLC), Renal Cell Carcinoma RCC), classical Hodgkin Linfoma (cHL), Squamous Cell Cancer of the Head and Neck (SCCHN) and Urothelial Carcinoma.

i.e. Nivolumab - Educational tools

- Aimed at different target groups:
  - for prescribers, pharmacists or other HCPs
  - patients, caregivers
- Format
  - Brochure, checklist, website
- Tools to communicate and remind
  - knowledge on risks
  - recommended actions (what to do, what not to do)
- The principal risk: Immune related adverse reactions (pneumonitis, colitis, hepatitis, skin)

i.e. NIVOLUMAB - EDUCATIONAL TOOL for HCP

Immune related adverse reaction	Severity	Recommended treatment (nivolumab or nivolumab + ipilimumab) modification
Pneumonitis (radiographic changes like focal ground glass opacities or patchy filtrates, dyspnoea, hypoxia)	Grade 2 pneumonitis	Withhold treatment. Initiate corticosteroids at a dose of 1 mg/kg/day methylprednisolone equivalents. Upon improvement, treatment may be resumed after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 2 to 4 mg/kg/day methylprednisolone equivalents and treatment must be permanently discontinued.
	Grade 3 or 4 pneumonitis	Permanently discontinue treatment. Initiate corticosteroids at a dose of 2 to 4 mg/kg/day methylprednisolone equivalents.

i.e. NIVOLUMAB - EDUCATIONAL TOOL for HCP

Pneumonitis

Grade definition according to NCI CTCAE v. 4				
Grade1	Grade2	Grade3	Grade4	Grade 5
Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental Activity Daily Living (ADL)	Severe symptoms; limiting self-care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death

i.e. Nivolumab - Patient Alert Card (PAC)

- To ensure that special information regarding the patient's current therapy and its important risks (e.g. potential developing of severe pneumonits, colitis et. from Grade 1 to Grade 5 - Death) are highlighted
- Patient always should carry this card with him and reaches the relevant healthcare professional as appropriate
- Ability to carry this easily (e.g. can be fitted in a wallet) should be a key feature of this tool

i.e. Nivolumab - Patient Alert Card (PAC)

This card contains important information.

Always carry this card with you and show it if you need to consult another doctor (for example, if you are travelling).

Tell your doctor right away if you have any of these symptoms or any other symptoms

LUNGS[1]
breathing difficulties, cough.

i.e. Nivolumab - Patient Alert Card (PAC)

My Doctor's contact information
Name of Doctor
Office Phone
After-hours Phone

My contact information
My Name and Phone Number
Emergency Contact (in case of emergency)

IMPORTANT Information for Healthcare Providers

- This patient is treated with nivolumab or nivolumab in combination with ipilimumab.
- Immune-related adverse reactions (irARs), may appear at any time during the treatment or months after its discontinuation.
- Early diagnosis and appropriate management are essential to minimise life-threatening complications. Nivolumab specific management guidelines for irARs are available.
- If you are a doctor who is not a specialist in oncology, please contact an oncologist

i.e. Lenalidomide

- The lenalidomide has anti-neoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory properties.

- Lenalidomide is indicated in monotherapy or in combination for Multiple myeloma, Myelodysplastic syndromes and Mantle cell lymphoma.

i.e. Lenalidomide

Other-RMM: Pregnancy prevention programmes (PPP)

- Pregnancy Prevention Programme - education, therapy management, distribution control
  - Patient and healthcare professional education
  - Therapeutic management advice to avoid foetal exposure
    - Women of non-childbearing potential
    - Women of childbearing potential
    - Men
  - Prescribing Revlimid
  - A distribution control system

- Pregnancy Reporting Form

i.e. Blinatumomab

- Blinatumomab is a bispecific T-cell engager antibody construct that binds specifically to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T-cells.

- Blinatumomab is indicated for the treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL).

i.e. Blinatumomab

Other-aRMM:Direct Healthcare Professional Communication (DHPC) Risk of Pancreatitis

Dear Health Care Professional,

<The Company> in agreement with the European Medicines Agency (EMA) and *<insert NCA>* would like to inform you of the following:

Summary

- Cases of pancreatitis, some life-threatening or fatal, have occurred in patients treated with Blinatumomab in clinical trials and in the post-marketing setting. High-dose corticosteroid therapy may have contributed, in some cases, to the pancreatitis.
- Patients should be closely monitored for signs and symptoms of pancreatitis, including physical examination, laboratory evaluation for serum amylase and serum lipase and abdominal imaging.

i.e. Blinatumomab

Other-aRMM:Direct Healthcare Professional Communication (DHPC) Risk of Pancreatitis

- Blinatumomab should be withheld if pancreatitis grade 3 occurs, then restarted at 9 micrograms/day after improvement to grade 1 and escalate to 28 micrograms/day after 7 days if pancreatitis does not recur.
- In the event of pancreatitis grade 4, permanent discontinuation of Blinatumomab should be considered.
- Patients should be advised to recognize features of pancreatitis such as upper abdominal tenderness and pain (made worse by eating), nausea and vomiting. They should be instructed to get medical advice if symptoms occur.

Conclusions

- Regulators should protect the patient implementing tools to be used by HCPs during the visit (HCP booklet), and materials for the patient (PAC and Patient booklet).
- Materials for the patients should be transmitted properly from the HCP.
- The oncologists should carefully inform the patients about all the possible adverse reactions and how to manage them.
- The oncologists should carefully balance precise information and reassurance.