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Editor's Notes

When an ADR report sent by a health professional or the pharmaceutical industry reaches the INFARMED Adverse Drug Reactions Monitoring Sector, a series of administrative and technical (medical and pharmaceutical) procedures is set in motion, which will ensure that each ADR will be recorded and analysed. This issue's opening article draws a schematic picture of the pathways followed by ADR reports from the point where they are fed into the system to the final feedback given to reporting professional(s), and possible measures triggered.

Also in this issue: the safety profile of the pentavalent vaccines that have recently been added to the Portuguese National Immunisation Plan, EMEA's conclusions from the benefit-risk review of non-selective, non-steroidal anti-inflammatory agents, and the usual section on medicinal herbs. An article on the two co-existing formulations of the antiretroviral lopinavir/ritonavir aims to contribute to preventing ADRs arising from mistaking one formulation for the other.

What happens to ADR reports once they reach INFARMED?

Adverse drug reaction reports are processed at INFARMED by means of a sequential system of reception, validation, collection of additional data, checking for duplications, coding, database recording, technical and scientific analysis including causality assessment, and problem detection and eventual generation of safety signals. These procedures are schematically depicted in the simplified flowchart overleaf.

Feedback to health professionals who report ADRs to the National Pharmacovigilance System is given using the WHO Probability Scale as follows.

Sandra Queiroz

What do they stand for?!

ADR	Adverse Drug Reaction
CHMP	Committee for Medicinal Products for Human Use
EMEA	European Medicines Agency
IL	Information Leaflet
MA	Marketing Authorisation
SPC	Summary of the Product's Characteristics

How can I report an adverse reaction?

Postage Paid Card
yellow *(physicians)*, **purple** *(pharmacists)* **or white** *(nurses)*

Also online at:
www.infarmed.pt/pt/vigilancia/medicamentos/reacções_adversas/fichas_notificação/index.html

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Southern Regional Pharmacovigilance Unit
Tel: 217 971 340 - Fax: 217 971 339
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World Health Organization Probability Scale (WHO) adapted

1. Definitive (Certain)

A clinical event or laboratory alteration that occurs within a plausible time frame, and cannot be explained by concomitant diseases or other drugs. Response to withdrawal of the medicine should be clinically plausible. The event should be convincing from the pharmacological and phenomenological standpoints using, if necessary, re-exposure data.

2. Probable

A clinical event or laboratory alteration that occurs within an acceptable time frame, for which a causal nexus with concomitant diseases or other drugs is unlikely, and evolution after withdrawal of the medicine is acceptable from a clinical standpoint. To establish this degree of probability, re-exposure data are not necessary.

3. Possible

A clinical event or laboratory alteration that occurs within an acceptable time frame, but which may alternatively be explained

(cont'd overleaf)

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by concomitant diseases or other medicines. Data on evolution after medicine withdrawal may not be available or be inconclusive.

4. Improbable

A clinical event or laboratory alteration that occurs within a time frame that renders improbable a causal nexus with the medicine, and for which an association with other medicines or concomitant diseases is a plausible explanation.

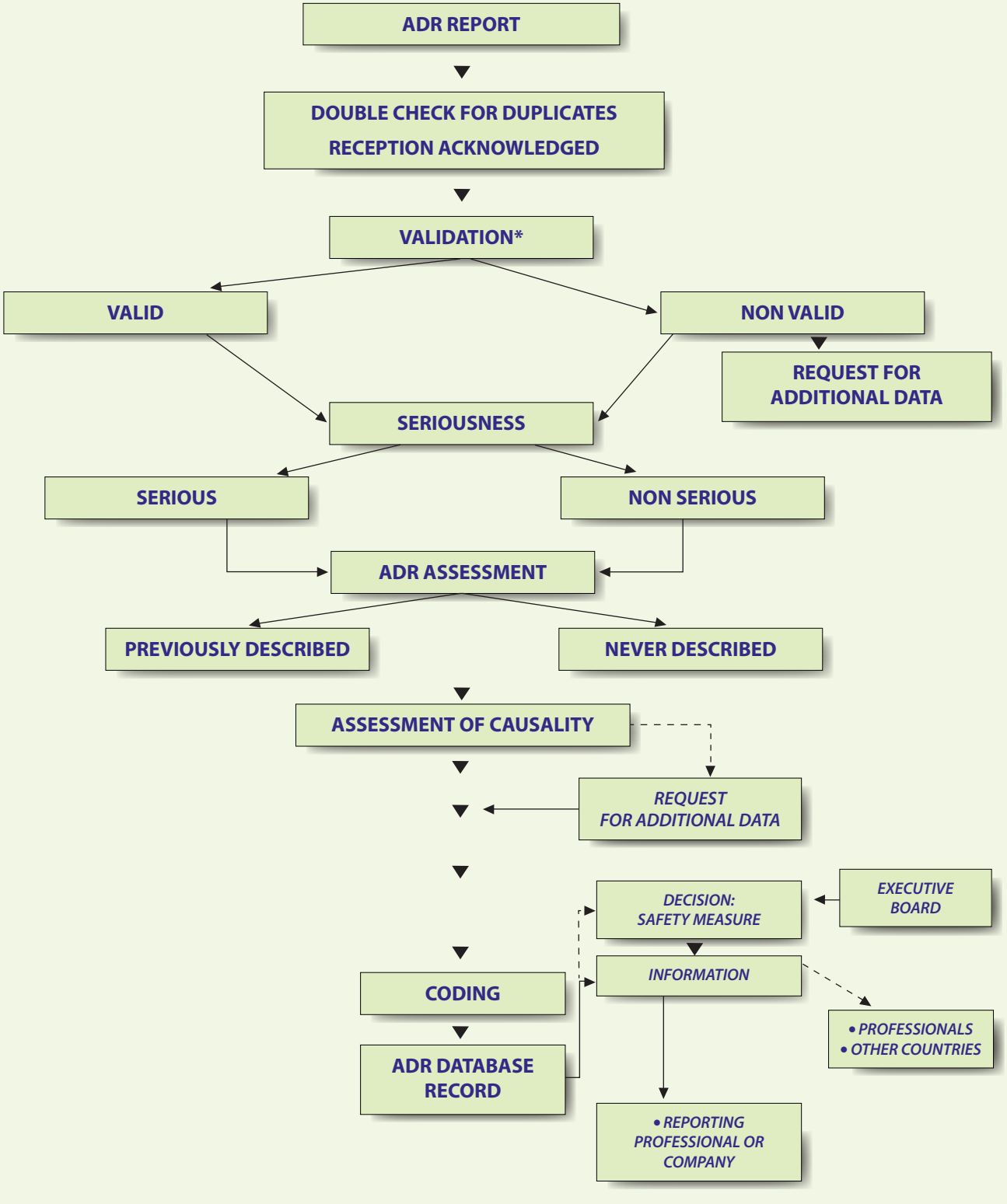
5. Conditional / Not classified

A clinical event or laboratory alteration that has been reported as an adverse reaction, but on which additional data are required for adequate causality assessment, or for which an assessment process is still ongoing.

6. Non Classifiable

A report suggesting an adverse reaction, but for which a causality assessment cannot be made, in that data are insufficient or contradictory, and cannot be complemented or confirmed.

Processing of ADR reports - an overview



***** Minimum criteria: a reporting person, a patient, an ADR, and a medicine.

Pentavalent vaccines in the National Immunisation Plan – safety profile highlights

A one-jab, pentavalent vaccine has recently been introduced in the National Immunisation Plan, which provides active immunisation against: diphtheria, pertussis, polio, and type b Haemophilus influenzae invasive disease.

Contraindications

- **Hypersensitivity** to any of the vaccine components, or hypersensitivity after previous administration of vaccines against diphtheria, pertussis, polio, and type b Haemophilus influenzae invasive disease, in monovalent form or varying combinations.
- Child with an **encephalopathy** of unknown aetiology which has occurred within 7 days of receiving a vaccine containing the pertussis component (acellular pertussis or whole-cell pertussis).
- Acute febrile disease or infection (vaccination should be **postponed**).

Warnings and special precautions

- As for any other injection vaccine, medical supervision and treatment should be immediately available in the rare event of **anaphylaxis**.
- Should any of the effects described below occur with a time relation with administration of any **vaccine containing DiTeP**, serious consideration should be given to the decision to administer further doses of any vaccine containing a pertussis component:
  - Rectal temperature ≥ 40.0ºC within 48 hours, which cannot be ascribed to another identifiable cause.
  - Collapse or shock-like state (hyporeactivity and hypotonia) within 48 hours after vaccination.
  - Persistent, uncontrollable crying lasting for ≥ 3 hours, within 48 hours after vaccination.
  - Seizures, with or without fever, occurring within 3 days after vaccination.
- The vaccine's immunogenicity may be impaired by **immunosuppressants and immunodeficiency**. In these cases, vaccination should be postponed. However, in patients with chronic immunosuppression (e.g., HIV), vaccination is recommended even when the immunological response is limited.
- The **Hib component** of the vaccine does not protect against other types of Haemophilus influenzae, nor against meningitides caused by other agents.

Drug interactions

- Except for the cases of immunosuppressant therapy, no clinically significant interaction has been reported with other treatments or biological medications.
- When administered simultaneously with other vaccines, this pentavalent vaccine should always be given at a different injection site.

Undesirable effects

- **At the injection site:** pain, redness, swelling/mass at injection site, or diffuse swelling of the corresponding limb, sometimes affecting the adjacent joint.
- **General:** fever, fatigue, allergic reactions (including anaphylactoid reactions).
- **Nervous system:** sleepiness, collapse or shock-like state (episodes of hyporeactivity and hypotonia), seizures.
- **GI system:** loss of appetite, diarrhoea, vomiting, constipation, flatulence.
- **Psychiatric:** agitation, sleep disorders, unusual crying (prolonged, inconsolable crying).
- **Skin:** rash, urticaria, pruritus.

Madalena Arriegas

Conclusion of the risk-benefit review by EMEA of non-selective, non-steroidal anti-inflammatory agents

The European Medicines Agency (EMEA) has concluded that the risk-benefit ratio for non-selective, non-steroidal anti-inflammatory medicines (NSAIDs) remains favourable. This conclusion follows on a review that had been announced in September 2006 of new safety data on cardiovascular, thrombotic risk.

Since the initial recommendations were issued in October 2005, EMEA has been actively monitoring the safety of non-selective NSAIDs. The latest review is based on new data that have recently been made available, and on an analysis of cardiovascular safety, both from clinical and epidemiological studies, which pointed to a potential increase in thromboembolic risk (namely myocardial infarction or stroke) with non-selective NSAIDs, especially when given in high doses for long periods of time. Former safety reviews on non-selective NSAIDs and cox-2 inhibitors were also taken into account.

Thus, based on currently available data, EMEA has concluded that:

- Non-selective NSAIDs are an important therapy for **arthritis** and other **painful conditions**.
- It is not possible to exclude the fact that non-selective NSAIDs might be associated with a **small** increased absolute **risk** of **thromboembolic events,** especially when given in high doses for long periods of time.
- In general, the **risk-benefit** ratio of non-selective NSAIDs remains **favourable** whenever given according to the SPC of the medicine, that is, taking into account its specific safety profile and the patient's own individual risk factors (e.g., gastrointestinal, cardiovascular, and renal).

Once again physicians and patients are advised to continue using the lowest effective dose for the shortest period of time necessary to control the symptoms.

What should one report?

Every suspected **serious** adverse reaction, even if already previously described. Seriousness criteria include:

- causing death
- life threatening
- prompting hospital admission
- prolonging hospital stay
- resulting in persistent or significant incapacity
- suspected congenital anomaly or malformation
- does not meet any of the above criteria but health professional considers it to be a serious ADR

Every suspected adverse reaction which has thus far **not been described** (unknown thus far), even if not serious or severe.

Every suspected **increase in the frequency** of ADRs (both serious and non-serious)

Two different formulations of Lopinavir/Ritonavir that risk to be mixed up

Recently, a new formulation of Kaletra® (lopinavir/ritonavir) in **melt-extrusion tablets (200/50 mg)** has been introduced which, since October 2006, has been gradually replacing the former soft gel capsules (133.3/33.3 mg).

During the transition period, while Kaletra® in soft gel capsules and Kaletra® tablets are simultaneously in the market, mix-ups may occur with the number of tablets to be taken. These may result in accidental overdose.

The table below sums up the important differences between the two formulations of Kaletra®.

	Former Kaletra® soft gel capsules	New Kaletra® Tablets
Indication	Treatment of HIV-1 infection in adults and children.	
Dose	133.3/33.3 mg capsules: 3 capsules, twice daily.	200/50mg tablets: 2 tablets, twice daily.
Effect of food	Should be taken with food.	Can be taken with or without food.
Co-administration with efavirenz, nevirapine, amprenavir, or nelfinavir	4 capsules, twice daily	Co-administration is not recommended. Should it be clinically indicated, an increase in the dose of Kaletra® 200/50-mg tablets may be considered, from 2 to 3 tablets, twice daily, with careful monitoring.
Storing	Should be kept at room temperature (up to 25°C) if used within 42 days. Refrigerated capsules or oral solution remain stable until the end of the expiry date printed on the label.	Keep at room temperature. Does not require refrigeration before or after dispensing.
Colour and logo	Orange Abbott PK logo	Yellow Abbott KA logo

Madalena Arriegas

Medicinal Plants from A to Z described adverse reactions

- **Blessed Thistle** *(Cnicus benedictus)*
  - chemical burn of oropharyngeal and oesophageal mucosa (in high doses)
  - vomiting, diarrhoea

N.º of Medline citations: 1
Main uses described: appetite stimulant, ulcer and wound healing, diuretic.

- **Cascara sagrada / Californian Buckthorn** *(Rhamnus purshiana)*
  - habituation (prolonged use in chronic constipation)
  - GI colic
  - nausea, vomiting, diarrhoea
  - cholestasis

N.º of Medline citations: 4
Main uses described: cathartic laxative

- **Horse chestnut** *(Aesculus hippocastanum)*
  - serious neurotoxicity (herb considered "unsafe" by FDA)
  - allergy, contact dermatitis
  - liver toxicity
  - carcinogenic potential (topical skin use)
  - potentiation of anticoagulant effect

N.º of Medline citations: 16
Main uses described: anti-inflammatory; haemorrhoids, varicose veins

- **Onion** *(Allium cepa)*
  - dyspepsia?
  - contact dermatitis

N.º of Medline citations: 13
Main uses described: respiratory conditions, urinary infection (anti-inflammatory, sedative)

- **Brazilian Aristolochia species akin to Snakeroot / Cipó-mil-homens** *(Aristolochia cymbiphera)*
  - central nervous system disorder clinically similar to alcohol intoxication (in high doses)
  - abortive (in high doses)
  - renal toxicity, dyspepsia, mutagenesis: all herbs containing aristolochic acid

N.º of Medline citations: 16
Main uses described: dyspepsia, pre-menstrual tension, asthma, sedative

- **Citronella** *(Cymbopogon nardus)*
  - ?

N.º of Medline citations: 4
Main uses described: flying insect repellent

- **Cumin** *(Cuminum cyminum)*
  - contact dermatitis
  - potentiation of anticoagulant effect

N.º of Medline citations: 1
Main uses described: dyspepsia, flatulence, abdominal colic

NB 1:
The main uses are those most frequently described in the literature irrespective of evidence of effectiveness.

NB 2:
The number of Medline citations is merely intended to give an idea of the magnitude of publications on adverse reactions associated with the product. Key-words used: "human side effects", "toxicity in humans", "adverse reactions".