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Ministério da Saúde

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Editor's Notes

In line with the start of the immunisation campaign for pandemic (H1N1v) influenza, the Info Note issued by INFARMED on 22nd October is published in this Number.

A new ADR report card comes into effect, which reflects the evolution of the National Pharmacovigilance System and the profile of the reporting professionals. An important goal was also to provide a clearer layout to prompt crucial data to be fed into the system. This can further motivate and facilitate ADR reporting, and better elicit data which are essential for the analysis of suspected adverse reactions.

Although the new card should start to be used as it becomes available to the professionals, all reports sent in by means of the former layout will go on being accepted. Active participation by every professional irrespective of which means they choose to use for reporting is one of the vital tennets that ensure the effectiveness of the National Pharmacovigilance System.

Immunization against Pandemic (H1N1v) Influenza A

Following a recommendation from EMEA, the European Commission has recently authorized through centralized procedure three vaccines for the influenza A (H1N1v) pandemic: Focetria® (Novartis), Pandemrix® (GlaxoSmithKline), and Celvapan® (Baxter). Focetria and Pandemrix were authorized on 29 Sep 2009 and contain fragmented and inactivated surface viral antigen corresponding to the A/California/7/2009 (H1N1)v (X-179A) strain. Celvapan® was authorized on 6th Oct 2009 and contains inactivated flu virus corresponding to the same strain.

After the current pandemic started, and once the new A (H1N1)v viral strain was definitively identified by the World Health Organization, the manufacturers were able to obtain these final pandemic vaccines by substituting the mock-up H5N1 strain with H1N1v.

In what concerns the safety of theses vaccines, decades of experience with seasonal flu vaccines suggest that the inclusion of a strain or its replacement by another does not significantly alter the vaccine's safety profile. On the other hand, authorization for vaccines against the H1N1v strain was given following a CHMP evaluation based on a set of quality, safety and immunogenicity data. These indicate a **favourable risk-benefit ratio within the defined indications**.

Focetria® and Pandemrix® contain **adjuvants**. The latter have been vastly used in the production of vaccines, and present a favourable safety profile: the adjuvant of Focetria® (MF59C.1) has been used since 1997 in a seasonal influenza vaccine in an estimated total of about 45 million doses. The adjuvant of Pandemrix® (AS03) has been tested in clinical trials that included several thousands of subjects. Celvapan® is an adjuvant-free vaccine. EMEA has required that the vaccine manufacturers roll out their **risk management plans** in order to actively research and monitor the safety of the vaccines as they are being used throughout the EU. Measures will thus be able to be taken early on in case a safety problem arises. The manufacturers have indeed committed themselves to conducting post-marketing studies which will include about 9000 subjects for each vaccine.

The **ADR profile** of the pandemic flu vaccine does not seem to differ greatly from what could be expected from a **seasonal flu vaccine**. A detailed account can be found in the **Summary of the Product's Characteristics** of the authorized vaccines. Nevertheless, just like for any other medicinal product, adverse effects may occur which, especially when rare, may only be detected at a time when vaccines will already have been in wide use.

The National Pharmacovigilance System monitors the safety of medicinal products in general and specifically of the pandemic flu vaccines. As these vaccines start to be used in large numbers in the community, the **cooperation of health professionals** who prescribe, dispense or administer them, or who diagnose and treat ADRs, is crucial. Regarding vaccine administration it is also essential that the routines of **recording batch and site of administration** be strictly followed as usual, so that the vaccines and their eventual adverse effects may be easily traced.

Health professionals are reminded of the importance of reporting suspected adverse reactions, of which the following, according to the CHMP, are of special interest:

- **serious and unexpected** reactions;
- very serious reactions that are **life-threatening or fatal**;
- adverse events of special interest: **neuritis, seizures, anaphylaxis, encephalitis, vasculitis, Guillain-Barré syndrome, facial palsy, demyelinizing conditions**;
- and also **vaccine failure**.

As usual, reports can be sent in by one of the fast track procedures indicated in "How can I report an adverse drug reaction?" above.

INFARMED I.P., in consonance with the CHMP's continuing evaluation and monitoring, will issue any necessary updates, so that a favourable risk-benefit balance can be ensured taking into account the seriousness and severity of the pandemic.

Additional reading recommended:
Pandemrix®, Focetria® Celvapan® SPCs in Portuguese at the INFARMED Infomed page:
www.infarmed.pt/infomed/inicio.php

or in English and other EU languages at the EMEA site:
http://www.emea.europa.eu/htms/human/epar/eparintro.htm

Infarmed Information Circulars (in Portuguese):
179/CD/2009
www.infarmed.pt/portal/page/portal/INFARMED/MAIS_ALERTAS/DETALHE_ALERTA?itemid=2188361

184/CD/2009
www.infarmed.pt/portal/page/portal/INFARMED/MAIS_ALERTAS/DETALHE_ALERTA?itemid=2196271

Main points of the safety profile of the seasonal influenza vaccine in the previous issue of the Boletim, in English at:
http://www.infarmed.pt/pt/vigilancia/medicamentos/pdf/en/2009/farmac_3trim_09_ing_site.pdf

What do they stand for?!

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

How can I report an adverse reaction?

Postage Paid Card

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

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SISTEMA NACIONAL DE FARMACOVIGILÂNCIA
Notificação de Reacções Adversas a Medicamentos

Ministério da Saúde

infarmed
Autoridade Nacional do Medicamento e Produtos de Saúde I.P.

Notifique sempre que suspeitar de uma reacção adversa

Confidencial

A. Reacção adversa a medicamento (RAM)

Descrição	Data início[1]	Data fim	Duração RAM se < 1 dia
	__/__/____	__/__/____	__h__min
	__/__/____	__/__/____	__h__min
	__/__/____	__/__/____	__h__min
	__/__/____	__/__/____	__h__min

Considera a reacção adversa (ou o caso, se mais do que uma reacção)[2] grave? Sim ☐ Não ☐

Se sim, porque considera grave?

- ☐ Resultou em morte __/__/____
- ☐ Colocou a vida em risco
- ☐ Motivou ou prolongou internamento
- ☐ Resultou em incapacidade significativa (especifique em F.)
- ☐ Causou anomalias congénitas
- ☐ Outra[3] (especifique em F.)

Tratamento da reacção adversa:

B. Medicamento(s) suspeito(s)

Nome de marca	Lote	Dose diária	Via adm.	Indicação terapêutica	Data início	Data fim
#1						
#2						

O medicamento foi suspenso devido à reacção ☐ A reacção melhorou após suspensão ☐ Ou manteve-se ☐

Houve redução da posologia (especifique em F.) ☐ Suspeita de interacção[4] entre medicamentos (especif. em F.) ☐

O mesmo fármaco foi reintroduzido ☐ Ocorreu reacção adversa idêntica quando da reintrodução ☐

São conhecidas reacções anteriores ao mesmo fármaco ☐ São conhecidas reacções anteriores a outros fármacos ☐

Considera a relação causal: ☐ Definitiva (certa) ☐ Provável ☐ Possível ☐ Improvável

C. Medicamentos concomitantes, incluindo auto-medicação (e outro tipo de produtos)

Nome de marca	Dose diária	Via adm.	Indicação terapêutica	Data início	Data fim
#3					
#4					
#5					
#6					
#7					

D. Doente

Iniciais do nome _____ ☐ Feminino ☐ Masculino Peso _____ Kg Altura _____ cm

Data de nascimento __/__/____ Ou idade à data da ocorrência da(s) RAM(s) _____

Como evoluiu o doente em relação à(s) RAM(s)?

- ☐ Cura
- ☐ Em recuperação
- ☐ Persiste sem recuperação
- ☐ Morte sem relação com a reacção
- ☐ Cura com sequelas
- ☐ Desconhecida
- ☐ Morte com possível relação com a reacção

E. Profissional de saúde

Nome

Profissão Especialidade

Local de trabalho

Contactos[5]: ☐ Telefone/Telemóvel ☐ *e-mail*

Data __/__/____ Assinatura

F. Comentários (Dados relevantes de história clínica e farmacológica, alergias, gravidez, exames auxiliares de diagnóstico ou outros)

Obrigado pela sua colaboração

[1] Se for inferior a 1 dia o intervalo de tempo entre a 1.ª administração do medicamento e a RAM, especifique em F.
[2] Se ocorreu mais do que uma RAM, considere a gravidade do caso i.e. o conjunto das reacções adversas.
[3] No conceito de gravidade, o item "Outra" é utilizado quando a RAM não colocar imediatamente a vida em risco ou resultar em morte, ou em internamento, mas requeira intervenção do profissional de saúde para prevenir que a reacção evolua para qualquer um dos outros critérios de gravidade.
[4] Se existir suspeita de interacção, considere os respectivos medicamentos como suspeitos.
[5] Mencione os melhores meios de contacto para ser possível a partilha de informação durante o processamento da notificação. Os dados do profissional de saúde notificador são confidenciais.

Para ser considerada válida, uma notificação de reacção adversa deverá ter, no mínimo: a informação do profissional de saúde com o meio de contacto; a identificação do doente por iniciais, data de nascimento, idade, grupo etário ou sexo; pelo menos um fármaco/medicamento suspeito e pelo menos uma reacção adversa suspeita.

Devem ser notificadas todas as suspeitas de reacções adversas graves, mesmo as já descritas; todas as suspeitas de reacções adversas não descritas (desconhecidas até à data) mesmo que não sejam graves e todas as suspeitas de aumento da frequência de RAM (graves e não graves).

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Unidade de Farmacovigilância de Lisboa e Vale do Tejo	217 802 120/7	217 802 129	uflvt@sapo.pt	uflvt.fm.ul.pt
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New ADR Reporting Form for Health Professionals

In order to further promote ADR reporting a new card (form) is now presented (see previous pages). Its layout is more functional and improvements result from a broad consensus and an in-depth analysis of glitches and difficulties that were found to be recurrent with the previous format. This new tool still is for health professional use only, but now has a single but versatile layout that makes it easy to be used by any professional group.

At first glance, the form has a different overall structure and more space for writing, thus making for easier and clearer filling out. On the other hand, more and more paper documents are being made virtual, and online reporting directly on a dedicated automated electronic platform at the INFARMED site is the probable next step in the horizon.

Contrarily to the former layout, filling in now starts with the description of the adverse reaction, followed by suspected and concomitant medicines, the patient's data and, last but not least, the reporting professional's own identification data, which are required for validation of the report. The **National Pharmacovigilance System protects the patient's and the professional's confidentiality**.

The main functional changes in this layout are the following:

- **Item A.**
  - This item concerns the **ADR** proper. Both dates of start and end of the reaction can be filled in, and specifics are clearly requested for ADRs lasting less than one day. Should the ADR **have begun only minutes or a few hours after administration of the suspected drug**, this can also be clearly detailed in the **comments section** at the back (item F).
  - **Duration of ADR** should be filled in with the time lapse from the start to total cure of the adverse reaction.
  - In case of **more than one ARD**, **seriousness** should be considered globally for the whole of the effects.
  - The **"Other"** field can be ticked off whenever the ADR, though not life threatening nor resulting in death or hospital admittance, requires specific medical intervention to prevent it from progressing to an actual serious outcome.
- **Item B.**
  - **Suspected Medicine(s)**. In most cases, there is only one suspected product, less often two. For more than two medicines, the comments section at the back can be used.
  - The data requested regarding the suspected medicine and the reaction is of relevance for case analysis and causality assessment, which in turn allow for safety problems to be detected.
- **Item C.**
  - This concerns any **Concomitant Medications or other products** that the patient may have been taking. Any possibility of interaction is analyzed from these data. Should the professional suspect an **interaction** from the outset, every medicine taken should be recorded. Since some drugs have a prolonged effect, it is sometimes necessary to know which had been taken before the suspected medicine (interaction) was started or before onset of the reaction itself. This can be recorded in the pharmacological history included in the comments section (item F).
- **Item D.**
  - The **Patient's** demographic data are recorded here.
  - Clinical **evolution** is also recorded here.
- **Item E.**
  - This is the **Health Professional** identification field, including his or her signature.
  - It is important that the professional give their contact details so they can be easily reached during report processing to clear any doubts or discuss any interpretation issues that may arise. These contacts presuppose total confidentiality within the System.
- **Item F.**
  - This is the **Comments** field on the back page for diverse additional data. **Instructions** on how to fill in the form and useful **information** on what to report can also be found here.

To be entered as **valid**, an ADR report must include at the very least: an identified health professional who can be reached if necessary; the patient's identification by means of initials, date of birth, age or age group, gender; one or more suspected medicines; and one or more suspected adverse reactions.

It is particularly relevant to report **suspected serious adverse reactions**, even those that have been described before. It is also of major interest to receive reports of adverse reactions **not previously described** (unknown at the time of reporting) even if not serious, as well as any suspected **increase in the frequency** of a given ADR (either serious or non-serious).

Although underreporting is a fact and the national reporting rate (2008) is of *circa* 175 reports per one million inhabitants per year (desired objective: 250 reports/million inhab./yr), health professionals in this country have become more aware of the need to report ADRs supervening in their daily practice. Such a responsible attitude contributes towards monitoring the safety profile of medicines and protecting public health.

For any doubts or comments you may wish to make on this matter do not hesitate to contact us at: farmacovigilancia@infarmed.pt

Fátima Pereira de Bragança

ADRs in the literature...

Anti-influenza vaccination in children allergic to egg

Main points

- Egg-free, mammalian culture based flu vaccines should be given preferentially to individuals allergic to egg
- If an egg-free vaccine is not available, only vaccines with a stated maximum egg content <1.2 µg/ml (0.6 µg per dose) should be used in individuals allergic to egg
- If egg based vaccine is administered to individuals with egg allergy, this should be done in a centre experienced in the management of anaphylaxis
- A single dose protocol is recommended for those with less severe egg allergy
- A two dose, split protocol can be used in those with anaphylaxis to egg or those with moderate or uncontrolled asthma

Common false contraindications to influenza immunisation

The following are not contraindications to immunisation with flu vaccine:

- A history of egg allergy but now able to eat eggs without reaction.
- A family history of egg allergy in a sibling or other family member.
- A family history of reaction to flu or any other vaccine.

Immunisation with an egg containing vaccine

This table considers the approach if an egg-free vaccine is not available. Mild gastrointestinal and dermatological reactions include urticaria, angio-oedema, and vomiting. Anaphylaxis is characterised by symptoms involving the airway and respiratory tract, such as pharyngeal oedema, stridor, respiratory distress, and wheeze. Cardiovascular complications include circulatory shock, hypotension, severe abdominal pain, or collapse. Positive diagnostics are skin prick and specific IgE tests to egg protein.

Risk	Worst previous reaction to egg	Vaccine protocol
lower	Previous mild gastrointestinal or dermatological reaction to egg and positive diagnostics; or positive diagnostics but never knowingly exposed to egg.	Single dose schedule 0.5 ml intramuscular dose of a virosomal vaccine or a vaccine with low egg content (<1.2 µg/ml) if virosomal not available.
higher	Previous respiratory or cardiovascular reaction to egg, and positive diagnostics; or "lower risk" individual with uncontrolled asthma treated at BTS/SIGN step 3 or higher.	Two dose, split protocol of 0.05 ml intramuscularly, followed 30 minutes later by 0.45 ml of a virosomal vaccine or a vaccine with low egg content (<1.2 µg/ml) if virosomal not available.

In : *Erlewyn-Lajeunesse M et al. Recommendations for the administration of influenza vaccine in children allergic to egg.* ***BMJ 2009;339:b3680***