

Date: 13th October 2011

Your Account Number:

Increased risk of fever in children immunised against seasonal flu with Viroflu[®] (and other trade name in the UK Inflexal[®]V)

Dear,

Crucell UK in agreement with the Medicines and Healthcare products Regulatory Agency (MHRA) wishes to inform you about important information on the clinical safety of Viroflu[®]/Inflexal[®]V indicated for active immunisation against influenza:

Summary:

- ✓ A clinical trial has shown a higher number of children experiencing fever and particularly fever 39-40° C compared what has been reported in earlier studies of Viroflu[®]/Inflexal[®]V
- ✓ Due to the risk of high fever, consideration should be given to use of alternative seasonal influenza vaccines in children under the age of 5 years.
- ✓ If Viroflu[®]/Inflexal[®]V is used in children, parents should be advised to monitor for fever for 2 -3 days following vaccination.

Further information on the safety concern

Viroflu[®] is a polyvalent, inactivated virosome formulated subunit vaccine for active immunisation against influenza supplied in the UK this year. It is also marketed as Inflexal[®]V in United Kingdom.

Results from one clinical trial of Viroflu[®]/Inflexal[®]V in children conducted, during the period May 2010-Apr 2011, showed a percentage of fever up to 18.2%, with a percentage of children who experienced fever 39-40°C of 5.1% . Fever is often seen after flu vaccination, but these findings on fever are considered more frequent than those reported previously with other Viroflu[®]/Inflexal[®]V studies.

The reasons of these findings on fever are still unknown.

As a possible increased risk of febrile convulsions cannot be ruled out at present, healthcare professionals are recommended to consider other alternatives to Viroflu[®]/Inflexal[®]V in children under 5 years of age as a precautionary measure.

The product information of Viroflu[®]/Inflexal[®]V has been updated to reflect the above listed recommendation and safety information.

Call for reporting:

Please report any suspected adverse reactions to the Medicines and Healthcare products Regulatory Agency through the Yellow Card Scheme online at www.yellowcard.gov.uk.

Alternatively, prepaid Yellow Cards for reporting are available:

- upon request by mail: "FREEPOST YELLOW CARD"
- at the back of the British National Formulary (BNF)
- by telephoning the Commission of Human Medicines (CHM) free phone line: 0800-731-6789
- or by electronic download through the MHRA website (<http://yellowcard.mhra.gov.uk/downloads/>)

Communication information

Should you have any questions or require additional information regarding the use of Viroflu[®]/Inflexal[®]V please contact Crucell UK medical information on **0844 800 3908**.

Yours sincerely,



Graeme Whitehouse
UK Sales & Marketing Director

Crucell UK Ltd

Annexes

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VIROFLU

Suspension for injection

Influenza vaccine (surface antigen, inactivated, virosome)

Season 2011/2012

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Influenza virus surface antigens (haemagglutinin and neuraminidase), virosome, of the following strains*:

A/California/7/2009 (H1N1) derived strain used (NYMC X-181)

15 micrograms HA**

A/Perth/16/2009 (H3N2)-like strain used (NYMC X-187 derived from A/Victoria/210/2009)

15 micrograms HA**

B/Brisbane/60/2008

15 micrograms HA**

per 0.5 ml dose

* propagated in fertilised hen's eggs from healthy chicken flocks

** haemagglutinin

Viroflu is an inactivated influenza vaccine formulated with virosomes as carrier/adjuvant system, composed of highly purified surface antigens of strain A and B of the influenza virus propagated in fertilized hen's eggs. This vaccine complies with the WHO recommendation (Northern hemisphere) and EU decision for the 2011/2012 season.

For a full list of excipients see section 6.1

3. PHARMACEUTICAL FORM

Suspension for injection.

Slightly opalescent liquid.

Supplied in a pre-filled syringe.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prophylaxis of influenza, especially in those who run an increased risk of associated complications.

The use of Viroflu should be based on official recommendations.

4.2 Posology and Method of Administration

Adults and children from 36 months: 0.5 ml.

Children from 6 months to 35 months: Clinical data are limited. Dosages of 0.25 or 0.5 ml have been used.

For children, who have not previously been vaccinated, a second dose should be given after an interval of at least 4 weeks.

Immunisation should be carried out by intramuscular or deep subcutaneous injection.

For instructions for preparation, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances, to any of the excipients and to residues e.g. eggs, chicken proteins, such as ovalbumin.

The vaccine may contain residues of the following substances, e.g. polymyxin B and neomycin.

Immunisation shall be postponed in patients with febrile illness or acute infection.

4.4 Special warnings and special precautions for use

[Due to the risk of high fever, consideration should be given to the use of alternative seasonal influenza vaccines in children under the age of 5 years.](#)

[In case it is used in children, parents should be advised to monitor for fever for 2 -3 days following vaccination.](#)

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine.

Viroflu should under no circumstances be administered intravascularly.

Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient.

4.5 Interactions with other medicinal products and other forms of interaction

Viroflu may be given at the same time as other vaccines. Immunisations should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified.

The immunological response may be diminished if the patient is undergoing immunosuppressant treatment.

Following influenza vaccination, false-positive results in serology tests using the ELISA method to detect antibodies against HIV1, Hepatitis C and especially HTLV1 have been observed. The Western Blot technique disproves the false-positive ELISA test results. The transient false positive reactions could be due to the IgM response by the vaccine.

4.6 Pregnancy and lactation

The limited data from vaccinations in pregnant women do not indicate that adverse fetal and maternal outcomes were attributable to the vaccine. The use of this vaccine may be considered from the second trimester of pregnancy. For pregnant women with medical conditions that increase their risk of complications from influenza, administration of the vaccine is recommended, irrespective of their stage of pregnancy.

Viroflu may be used during lactation.

4.7 Effects on ability to drive and use machines

The vaccine is unlikely to produce an effect on the ability to drive and use machines.

4.8 Undesirable effects

ADVERSE REACTIONS OBSERVED FROM CLINICAL TRIALS:

Results from one clinical trial conducted with Viroflu in children, during the period May 2010-Apr 2011, showed a percentage of fever up to 18.2%, with a percentage of children who experienced fever 39-40°C of 5.1%. Fever is an already known adverse event that can occur after flu vaccination, but the findings on fever coming from the study are considered higher than those reported previously with other Viroflu studies/trials.

The safety of trivalent inactivated influenza vaccines is assessed in open label, uncontrolled clinical trials performed as annual update requirement, including at least 50 adults aged 18 – 60 years of age and at least 50 elderly aged 61 years or older. Safety evaluation is performed during the first 3 days following vaccination.

The following undesirable effects have been observed during clinical trials with the following frequencies: very common (>1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports.

Organ class	Very common >1/10	Common >1/100, <1/10	Uncommon >1/1,000, <1/100	Rare > 1/10,000, <1/1,000	Very rare <1/10,000
Nervous system disorders		Headache*			
Skin and subcutaneous tissue disorders		Sweating*			
Musculoskeletal and connective tissue disorders		Myalgia, arthralgia*			
General disorders and administration site conditions		fever, malaise, shivering, fatigue. Local reactions: redness, swelling, pain, ecchymosis, induration*			

* These reactions usually disappear within 1-2 days without treatment

ADVERSE REACTIONS REPORTED FROM POST-MARKETING SURVEILLANCE

Adverse reactions reported from post marketing surveillance are, next to the reactions which have also been observed during the clinical trials, the following:

Blood and lymphatic system disorders:

Transient thrombocytopenia, transient lymphadenopathy

Immune system disorders:

Allergic reactions, in rare cases leading to shock, angioedema

Nervous system disorders:

Neuralgia, paraesthesia, febrile convulsions, neurological disorders, such as encephalomyelitis, neuritis and Guillain Barré syndrome

Vascular disorders:

Vasculitis associated in very rare cases with transient renal involvement

Skin and subcutaneous tissue disorders:

Generalised skin reactions including pruritus, urticaria or non-specific rash

4.9 Overdose

Overdosage is unlikely to have any untoward effect.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccine, ATC code: J07BB02

Seroprotection is generally obtained within 2 to 3 weeks. The duration of postvaccinal immunity to homologous strains or to strains closely related to the vaccine strains varies but is usually 6-12 months.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, disodium phosphate dihydrate, potassium dihydrogen phosphate, lecithin, water for injections.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf-life

1 year.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C)

Do not freeze: the vaccine must not be used if it is inadvertently frozen.

Protect from the light.

6.5 Nature and contents of the container

0.5 ml suspension in pre-filled syringe (type I glass) with plunger stopper (chlorobutyl rubber) with needle in pack sizes of 1 or 10.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The vaccine should be allowed to reach room temperature before use. Shake before use.

When a dose of 0.25 ml is indicated, the pre-filled syringe should be held in upright position and half of the volume should be eliminated up to the 0.25 ml mark. The remaining volume should be injected.

See also section 4.2.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Crucell Italy S.r.l.
Via Zambelletti 25
20021 Baranzate (MI)
Italy

8. MARKETING AUTHORISATION NUMBER(S)

PL 15747/0005

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF AUTHORIZATION

28. October 2005/20 December 2006

10. DATE OF REVISION OF THE TEXT

October 2011