Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human

REVISION OF THE ~~P~~CORE~~ROPOSAL FOR A HARMONISED~~ SPC FOR TRIVALENT INFLUENZA VACCINES

October 2003
Revision ~~1~~2, ~~December~~June 200~~3~~6

Introduction

The ~~Pharmaceutical Committee has agreed with a proposal from the influenza vaccine manufacturers to use the Mutual Recognition Procedure, so that the~~ **annual** review of ~~the annual update of~~ **influenza vaccines** ~~these products can follow a new specific and fast track procedure~~ in order to **meet the EU recommendations for human influenza vaccine composition for the coming season follows a special variation procedure, the so called "fast track procedure".** ~~comply with 1998 regulatory requirements for pharmaceuticals (Directive 93/39).~~
~~The requirements for the Core dossier for the Mutual Recognition Procedure have been laid down in the decision of the Pharmaceutical Committee (Pharm 155).~~

~~The future RMSs – France, Germany, The Netherlands and United Kingdom – have prepared the following proposal for a harmonised SPC in order to facilitate the above mentioned Mutual Recognition Procedures.~~

Recommendations for SPCs for inactivated influenza vaccines prepared using influenza viruses grown in fertilised hens' eggs constitute the subject matter of this guideline.
~~This harmonised~~ SPC**s live** ~~is intended solel~~**influenza** ~~y for subunit and split virus~~ vaccines**, and for influenza vaccines produced using** ~~. Whole c~~**c**ell ~~vaccine o~~**cultures as virus propagation substrates, fall outside the scope of the document.** ~~r other types of influenza vaccines (including new developments) are not covered.~~
~~Please note that the text proposal should be considered as a minimum requirement. Additional claims should be substantiated with data.~~

In effect, this means that SPCs for vaccines complying with the following PhEur monographs are affected:

- **Influenza vaccine (split virion, inactivated).**
- **Influenza vaccine (surface antigen, inactivated).**
- **Influenza vaccine (surface antigen, inactivated, virosome).**
- **Influenza vaccine (whole virion, inactivated).**

Text proposals are highlighted in bold.
Sometimes no concrete text proposal has been formulated, but instead remarks with indications for the text are given.
On some places a justification (in italic) concerning a proposal has been included.

1. NAME OF THE MEDICINAL PRODUCT

~~(Trade) name of product/ pharmaceutical form~~

~~Common name1~~**The standard requirement is for the invented name of the medicinal product, the strength and the pharmaceutical form to appear.**

However, in the case of influenza vaccines, the strength (the haemagglutinin (HA) content for each strain present in the vaccine) should be omitted from the invented name in the SPC.

The common name should be that of the monograph in the *European Pharmacopoeia* with which the vaccine complies.

~~1 The common name should be inspired by the title of the Ph. Eur. Monograph for influenza vaccines~~

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

~~<~~Influenza virus surface antigens (haemagglutinin and neuraminidase)~~*~~ of ~~strains> or <split Influenza virus, inactivated containing antigens equivalent to>~~**the following strains***:

A/~~<~~Official strain~~>~~ (H_1N_1) like strain **(<actual strain>)….<n> micrograms HA**~~used (add: specific, actual strains used) ……X micrograms~~**

A/~~<~~Official strain~~>~~ (H_3N_2) like strain **(<actual strain>)** ~~used (add: specific, actual strains used) X micrograms~~ **<n> micrograms HA****

B/~~<~~Official strain~~>~~ like strain **(<actual strain>)** ~~used (add: specific, actual strains used) X micrograms~~**<n> micrograms HA****

……~~pe~~

per <n> ml dose

~~r X ml dose~~

* propagated in ~~{specific}~~**fertilised hens' eggs**

** haemagglutinin

NOTE: the core SPC is for non-adjuvanted influenza vaccines. For adjuvanted influenza vaccines different (clinical) criteria may apply.

"This vaccine complies with the WHO recommendation (northern hemisphere) and EU decision for the <year/year> season."

"For a full list of excipients see section 6.1."

3. PHARMACEUTICAL FORM

~~Product specific (Rules given by the Standard terms should be applied)~~
The full *European Pharmacopoeia* standard term should be used.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

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

The use of <invented name of vaccine> should be based on official recommendations.
Note: this is standard wording for vaccines.

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 ml 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."

Justification:
There have been differences in children dosage between Member States and no sound evidence is available to justify a specific dosage.

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

A text like "Immunodeficient patients are recommended to be immunised twice with an interval of at least 4 weeks" should not be included in the SPC.

For instructions for preparation, see section 6.6.

4.3 CONTRA-INDICATIONS

"Hypersensitivity to the active substances, to any of the excipients and to" {residues ~~(~~<product specific~~)~~**:** e.g. eggs, chicken proteins**>**~~.~~**.** **<Invented name of vaccine> does not contain more than <n> microgram ovalbumin per dose. The vaccine may contain residues of the following substances <product specific>,** antibiotics, thiomersal, etc.}

Wordings between {} mean that they have to appear when necessary.

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

4.4. SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

"As with all injectable vaccines, appropriate medical treatment and supervision should always be readily ava~~l~~ilable in case of a rare anaphylactic event following the administration of the vaccine.

<Invented name of the ~~The~~ vaccine> ~~(Tradename)~~ should under no circumstances be administered intravascularly.

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

If the vaccine contains residues of thiomersal the following should be mentioned:
"Thiomersal (an organomercuric compound) has been used in the manufacturing process of this medicinal product and residues of it are present in the final product. Therefore, sensitisation reactions may occur (see section 4.3)."

Justification:
There may be special warnings related to country specific patient populations (see section 4.1). These may be included in the text.

4.5. INTERACTIONS WITH OTHER MEDICINA~~MENTS~~L PRODUCTS AND OTHER FORMS OF INTERACTION

"<Invented name of ~~T~~the vaccine> ~~(Tradename)~~ may be given at the same time as other vaccines. Immunisation 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 l~~L~~imited 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.
<Invented name of ~~T~~the vaccine> ~~(Tradename)~~ 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 from clinical 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 60 years or older. Safety evaluation is performed during the first 3 days following vaccination.

The following ~~U~~undesirable effects have been ~~reported~~observed with the following frequencies ~~are listed according to the following frequency.~~:

~~Adverse events from clinical trials:~~very common (>1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000); very rare (<1/10000), including isolated reports, not known (cannot be estimated from the available data).

Blood and Lymphatic system disorders
Rare: transient thrombocytopenia

Immune system disorders
Allergic reactions, in rare cases leading to shock, have been reported.

Nervous system disorders
Common: headache
Rare: neuralgia, paraesthesia, convulsions,
Very rare: Neurological disorders, such as encephalomyelitis, neuritis and Guillain Barré syndrome.

Vascular disorders
Very rare: Vasculitis with transient renal involvement

Skin and subcutaneous tissue disorders
Common: sweating
Uncommon: Generalised skin reactions including pruritus, urticaria or non-specific rash

Musculoskeletal and connective tissue disorders
Common: myalgia, arthralgia.

General disorders and administration site conditions
Common ~~(>1/100, <1/10)~~:
Local reactions: redness, swelling, pain, ecchymo~~i~~sis, induration
Systemic reactions: Fever, malaise, shivering, fatigue~~, headache, sweating,~~. ~~myalgia, arthralgia.~~
These reactions usually disappear within 1-2 days without treatment.

~~From Post-marketing surveillance additionally, the following adverse events have been reported:~~

~~Uncommon (>1/1,000, <1/100):~~
~~Generalised skin reactions including pruritus, urticaria or non-specific rash~~

~~Rare (>1/10,000, <1/1,000):~~
~~neuralgia, paraesthesia, convulsions, transient, thrombocytopenia.~~
~~Allergic reactions, in rare cases leading to shock, have been reported.~~

~~Very rare (<1/10,000):~~
~~Vasculitis with transient renal involvement~~
~~Neurological disorders, such as encephalomyelitis, neuritis and Guillain Barré syndrome."~~

If the vaccine contains thiomersal as a preservative the following should be mentioned:
"This medicinal product contains thiomersal (an organomercuric compound) as a preservative and therefore, it is possible that sensitisation reactions may occur (see Section 4.3)."

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 homologuous 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
Product specific

~~According to the recommendation given by the Guideline on Summary of Product Characteristics (SPC) (December 1999) in 6.1., residues of production should not be stated in this section.~~

6.2. INCOMPATIBILITIES

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

<This medicinal product must not be mixed with other medicinal products except those mentioned in 6.6>

6.3. SHELF-LIFE

"~~X~~**<n>** months" **"<1 year>"**

The value of n should not normally be greater than eleven~~When the shelf-life corresponds to 12 months, the wording should be "1 year"~~.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Product specific.

6.5. NATURE AND CONTENTS OF THE CONTAINER

X ml <pharmaceutical form>* in <container>, <nature>, {additional characteristics (nature)}{other components (nature)}- pack of Y

Wordings between <> should be chosen;

Wordings between {} mean that they have to appear when necessary.

* only applicable when the SPC relates to more than one pharmaceutical form.

6.6. INSTRUCTIONS FOR USE/HANDLING

Unused vaccine and other waste material should be disposed of in compliance with local rules for the disposal of products of this nature.

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

Shake before use."

Where a single dose 0.5 ml syringe is to be used for administration of a 0.25 ml dose, specific instructions will be required. **See also section 4.2.**

Other SPC sections

See the ~~Note for Guidance~~**Guideline on** –Summary of Product Characteristics**/Notice to Applicants/Volume 2C** ~~(III/9163/90-EN)~~.