

FLUVIRIN

[Influenza Vaccine (Surface Antigen, Inactivated) Ph. Eur.]

PL 18532/0038

PL 18532/0039

UKPAR

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FLUVIRIN

[Influenza Vaccine (Surface Antigen, Inactivated) Ph. Eur.]

PL 18532/0038-39

LAY SUMMARY

The MHRA today granted Novartis Vaccines and Diagnostics Ltd a Marketing Authorisation (licence) for the medicinal product Fluvirin (PL 18532/0038-39), which is a vaccine. This vaccine is prescription only and may be administered to adults and children from the age of four years for active immunisation against influenza, especially in those who run an increased risk of influenza associated complications. Fluvirin is a trivalent vaccine, usually containing two influenza A subtypes and one influenza B subtype and consists of purified haemagglutinin and neuraminidase antigens prepared from those strains of influenza virus recommended by the WHO and national authorities each year.

Influenza is a contagious disease caused by the influenza virus. It affects the respiratory tract, often resulting in cough, sore throat, runny or stuffy nose, as well as fever, headache, extreme tiredness and muscle aches. It can also lead to complications such as bacterial pneumonia, dehydration and worsening of chronic medical conditions, such as congestive heart failure, asthma or diabetes. Children may get sinus problems and ear infections.

Adults and children from the age of four years are dosed with 0.5 ml of the vaccine. For children who have not previously been vaccinated, a second dose should be given after an interval of at least four weeks. Immunisation should be carried out by intramuscular or deep subcutaneous injection.

The original clinical data presented to the MHRA demonstrated that Fluvirin actively immunises adults and children against influenza and there were no unexpected safety concerns. It was therefore judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of data on quality, the UK granted a marketing authorisation for the medicinal product Fluvirin (PL 18532/0038-39) to Novartis Vaccines and Diagnostics Ltd on 7th June 2006. The product is prescription only and intended for adults and children.

This was a stand-alone, national application for Fluvirin, containing Influenza Virus (Surface Antigen, Inactivated), submitted under *Article 8.3 (i) of Directive 2001/83/EC*. The application is for a fundamental change to an existing marketing authorisation (PL 18532/0001 & 0002) and under article 10.1 (a)(i) is an informed consent application.

Fluvirin is indicated in the prophylaxis of influenza, especially in those who run an increased risk of associated complications

Fluvirin is for administration by intramuscular or deep subcutaneous injection only. The vaccine may be used to provide active immunisation when given to adults and children from four years. For children who have not previously been vaccinated, a second dose should be given after an interval of at least 4 weeks.

QUALITY ASSESSMENT

Background

This application is for a national license for a product that the applicant intends to license in other member states by a subsequent mutual recognition procedure (AT, BE, DE, FI, FR, DE, EI, IE, IT, L U, NL, NO, PT, ES, SE). The application is for a fundamental change to an existing marketing authorisation (PL 18532/0001 & 0002) and under Article 10.1 (a)(i) is an informed consent application. The product also has marketing authorisation for USA, Argentina, Australia, Israel, South Africa and Taiwan. A certificate of consent is not provided as Chiron Vaccines Ltd (now Novartis Vaccines and Diagnostics Limited) is the marketing authorisation holder for both the products.

In the period between Sept 04 and March 05, the company made changes to its manufacturing process. Several meetings with the company have been held to determine how best to reflect the changes in the process in the marketing authorisation.

The table below summarizes the changes made to the dossier in this submission:

CTD Section	Changes in new CTD Application
3.2.S Drug Substance	
3.2.S.1 General Information	Increased detail
3.2.S.2 Manufacture	Thorough review and increase in detail for virus seed and monovalent virus pool manufacture. Updated flow diagrams and manufacturing description in line with GMP process improvement changes highlighted in 3.2.s.2.6 (see attachment 1 of this document).
S.2.1 Manufacturer(s)	No change
S.2.2 Description of Manufacturing Process and Process Controls	Increased detail
S.2.3 Control of Materials	Increased detail
S.2.4 Controls of Critical Steps & Intermediates	Registration of additional in process controls
S.2.5 Process Validation and/or Evaluation	Review and increased detail
S.2.6 Manufacturing Process Development	Review and increased detail
3.2.S.3 Characterization	Increased detail
3.2.S.4 Control of Drug Substance	
S.4.1 Specifications	Additional specifications registered
S.4.2 Analytical Procedures	Updated summaries provided
S.4.3 Validation of Analytical Procedures	Updated summaries provided
S.4.4 Batch Analyses	Additional batch data provided
3.2.S.5 Reference Standards or Materials	Increased detail
3.2.S.6 Container Closure System	Addition of option to store monovalent virus pools in bags
3.2.S.7 Stability	Additional stability data provided including data on storage of monovalent virus pools in bags.

3.2.P Drug Product	
3.2.P.1 Description and Composition of the Drug Product	Increased detail
3.2.P.2 Pharmaceutical Development	
P.2.1 Components of the Drug Product	Increased detail
P.2.2 Drug Product	Increased detail
P.2.3 Manufacturing Process Development	Increased detail
P.2.4 Container Closure System	Increased detail
P.2.5 Microbiological Attributes	Increased detail
P.2.6 Compatibility	Increased detail
3.2.P.3 Manufacture	
P.3.1 Manufacturer(s)	No change
P.3.2 Batch Formula	Increased detail
P.3.3 Description of Manufacturing Process and Process Controls	Increased detail
P.3.4 Control of Critical Steps and Intermediates	Increased detail
P.3.5 Process Validation and/or Evaluation	Increased detail
3.2.P.4 Control of Excipients	Increased detail
3.2.P.5 Control of Drug Product	
P.5.1 Specifications	Registration of additional specifications
P.5.2 Analytical Procedures	Procedure Summaries Provided
P.5.3 Validation of analytical procedures	Increased detail
P.5.4 Batch Analysis	Additional batch data provided
P.5.5 Characterization of Impurities.	Increased detail
P.5.6 Justification of Specifications	Increased detail
3.2.P.6 Reference Standards or Materials	Increased detail
3.2.P.7 Container Closure System	Increased detail
3.2.P.8 Stability	Additional stability data/commitments provided
3.2.A. Appendices	
3.2.A.1 Facilities and Equipment	Additional information
3.2.A.2 Adventitious Agents Safety Evaluation	Review/additional data
3.2.A.3 Novel Excipients	N/A
3.2.R Regional Information	N/A
3.3 Literature References	N/A

FLUVIRIN REMEDIATION ACTIVITIES

The basic manufacturing process of Fluvirin has remained unchanged. However, a number of GMP related process control improvements have been identified and validated as outlined in Section 3.2.5. Improvements were made to the egg virus unit, zonal centrifuge area formulation as well as some general changes designed to improve the quality of the product.

The dossier originally submitted for this license application did not contain full validation data for the process and batch data were still being accumulated, but is now complete. The MHRA is also aware that further data (including some clinical data) will become available in time for the annual strain update. WHO and EMEA indicate that strains for the season 2006/2007 will be:

- an A/New Caledonia/20/99 (H1N1)-like strain;
- an A/Wisconsin/67/2005 (H3N2)-like strain;
- a B/Malaysia/2506/2004-like strain.

A variation to remove the paediatric indication in children under four years of age following comparative studies with competitor vaccines has been completed for the current Fluvirin licenses (PL 18532/0001), UK/H/0215/001/II/026.

Following the acquisition of Chiron Vaccines by Novartis, the Company name was changed during assessment of this application from Chiron Vaccines Limited to Novartis Vaccines and Diagnostics Limited. The legal entity remains the same.

REQUESTS FOR INSPECTION ACTION PRIOR TO AUTHORISATION

The site has been inspected several times in the last two years, following suspension of the manufacturing license on 5th October 2004. The suspension of the manufacturing license was lifted on 2nd March 2005. The applicant has provided a copy of the most recent manufacturing license dated 7th December 2005.

INTRODUCTION

Fluvirin is for active immunisation against influenza (suspension for injection in a pre-filled syringe), especially in those who run an increased risk of influenza associated complications. The vaccine is indicated for adults and children from four years. For children who have previously not been vaccinated, a second dose should be given after an interval of four weeks. The vaccine is administered by deep subcutaneous or intramuscular injection. Contraindications are hypersensitivity to the active substances, to any excipients and to eggs, chicken proteins, betapropiolactone, nonoxyl 9, neomycin, polymyxin, formaldehyde or thiomersal.

DRUG SUBSTANCE

This application does not have a closed/confidential part.

S.1 General Information

S.1.1 Nomenclature

Ph. Eur. Influenza Vaccine (Surface Antigen, Inactivated).

S.1.2 Structure

The structure was adequately described.

S.1.3 General Properties

Fluvirin or Influenza Vaccine (Surface Antigen, Inactivated) Ph. Eur consist of haemagglutinin proteins of three strains of influenza virus and the neuraminidase protein of those strains.

Influenza viruses are divided into three groups of serologically distinct type, A, B and C. The three types differ in antigens, epidemiology and to some extent disease severity. The subtypes of these groups are characterised by antigenic variation of the haemagglutinin and neuraminidase antigens. Influenza A viruses are known to undergo periodic antigenic shift (thought to be by recombination of virus RNA segments) which have been associated with pandemics, but both A & B viruses undergo minor antigenic variation as a result of point mutation and selection which may mean that subtype specific immunity is not effective.

Influenza virus strains are named by antigen specificity (A, B, C)/location of isolation/isolate number/year of isolation.

S.2 Manufacture

S.2.1 Manufacturer

Details have been provided.

The acceptance criteria were met.

S.2.3 Starting Materials

S.2.3.1 Virus Seeds

Seed virus for the production of the vaccine is manufactured using the seed virus system recommended by WHO and EU, obtained by NIBSC or an equivalent institute recognised by WHO.

S.2.3.3 Production Eggs

In accordance with the Ph.Eur. the eggs for manufacture of Monovalent Virus Pool are taken from healthy flocks of chickens.

Since the initial submission of the MAA, Novartis Vaccines and Diagnostics Limited have acquired the site where primary incubation of eggs is performed. The egg supplier has not changed. **The applicant commits to inform the MHRA inspectorate if the supplier of eggs changes.**

S.2.3.3 Substances and Solutions Used During Production

The substances and solutions used during the production of the Monovalent Virus Pool do not have any component of biological origin and they comply with Ph. Eur. or with in-house specifications.

Full specifications of tests performed on substances and solutions have been provided.

S.2.4 In-Process Controls and Criteria for Acceptance

The WHO recommends the virus strains to be used on an annual basis.

The virus seed histories and strains used for each batch are reported in the Batch Protocol.

Egg cleaning machinery: The validation reports have been provided.

All eggs are sanitised using the machine immediately before incubation and the process occurs in three stages; wash, rinse and sanitise.

Validation for the egg cleaning machinery is complete.

As discussed with MHRA inspectorate, any changes to the egg sanitisation process will be notified to the inspectorate and reviewed as GMP issues, rather than generate a formal product licence variation. The MAH has committed to provide details of bioburden levels for the 2006/7 season in the annual update for 2007/8, and tighten the bioburden specifications where possible.

Bioburden Tests and Specification

Testing is carried out according to the Ph. Eur monograph.

The MAH has committed to provide details of bioburden levels for the 2006/7 season in the annual update for 2007/8, and tighten the bioburden specifications where possible.

According to the Standard Operating Procedure for Investigation, Corrective Action and Follow-Up of Laboratory Results Indicating Non-Conformance, if an alert limit is exceeded at any stage of the process, it is recorded as an atypical out of trend result (OOT) and investigated.

The registered specifications for bioburden were newly introduced limits for the 2005 campaign.

The applicant has committed to provide details of bioburden levels for the 2006/7 season in the annual update for 2007/8, and tighten the bioburden specifications where possible.

Sampling for bioburden testing has been introduced at a number of additional post-inactivation process steps to increase monitoring of potential organisms in the product.

S.2.5 Process Validation and/or Evaluation to 2004/5

Fluvirin is manufactured in compliance with Good Manufacturing Practices; according to specifications detailed in monographs of the European Pharmacopoeia, the Compendium of Licensing Requirements for the Manufacture of Certain Biological Medicinal Products and the requirements of the World Health Organisation. Fluvirin has been produced at the Liverpool site since 1976, with a proven safety and efficacy record during that time. Recent expansion of capacity involved extensive revalidation of specific areas. A summary of validation for certain processes have been provided.

Electron microscopy studies of the monovalent virus pools from the 2005/2006 season confirmed the purity was high. New EM photographs have been taken using product manufactured during the 2005/2006 campaign.

In 2005, the manufacturing site underwent a large **GMP review** and identified a number of key remediation activities. A full process validation, including the process and facility improvements identified by the remediation activities, is complete.

The process validation data is provided for 5 lots, as missing data, lost samples and invalid or incomplete testing of the first 3 lots compromised the validation. A large number of non-conformance events occurred during this process validation, a summary of the non-conformance issues, the investigation and the recommendations for remedial action are also supplied with each report.

The process validation, in the areas where non-conformance issues were reported, is to be repeated and will be available prior to entry of the Fluvirin dossier into the Mutual Recognition Procedure.

A report on the implementation of the recommendations that arise from process validation study, in particular highlighting progress made to date and when the remaining actions are likely to be complete has been provided. The report shows that action has been taken to prevent non-conformance issues arising again, SOPs have been revised and equipment checks introduced.

S.2.5.1 Validation of Critical Manufacturing Steps for Individual Strains

In line with the EU Notice to Applicants Regulatory Guideline – Fast Track Procedure for Human Influenza Vaccines (1999), the capability of the process to perform viral inactivation and viral splitting is assessed as each new influenza strain is introduced into the formulation.

The BPL inactivation step is validated according to the Ph. Eur monograph for a minimum of three consecutive production egg harvests for each one of the strains of the current influenza season.

In addition, efficacy of viral splitting and purification (i.e. removal of the viral core material) is also confirmed by analysis of the Polyacrylamide Gel Electrophoresis results (PAGE) routinely obtained for each monovalent virus pool.

Validation data has been provided for strains used in the 2004/2005 season and is acceptable.

Data is supplied to demonstrate satisfactory inactivation of several batches of A/New Caledonia, as demonstrated by the egg safety test. Data has been provided for several batches of the A/New Caledonia and B/Jiangsu strains and for several batches of A/New York to show consistency of the modified process.

S.2.6 Manufacturing Process Development

Over the years, the basic manufacturing process of Monovalent Virus Pool for Fluvirin has remained unchanged.

Starting from 2005, a number of GMP related process control improvements have been identified but the basic manufacturing process of Fluvirin has remained unchanged.

S.3 Characterisation (monovalent pools)

S.3.1 Elucidation of Structure and Other Characteristics

Monovalent Virus Pools of Fluvirin are tested in compliance with Ph. Eur. monograph for Influenza Vaccine, Surface Antigen, Inactivated.

The potency of the vaccine is expressed as the concentration of the haemagglutinin protein.

S.3.2 Impurities

Tests are performed to determine the levels of potential impurities/residuals, which may arise in the Monovalent Virus Pools. These are acceptable.

S.4 Control of Drug Substance (Monovalent Pools)

S.4.1 Specifications and Justification

Monovalent Virus Pool of surface antigens from each of the three influenza virus strains recommended annually by WHO/EU.

Each Monovalent Virus Pool complies with the Ph.Eur monograph on Influenza Vaccine (Surface Antigen, Inactivated) and reflects the requirements of the monograph.

The monovalent bulk testing regime and specification is in line with Ph. Eur. monograph.

S.4.2 Analytical Procedures

Analytical procedures have been adequately described.

S.4.3 Validation of Analytical Procedures

Analytical procedures have been adequately validated. All acceptance criteria have been met.

S.4.4 Batch Analysis

S.4.4.1 Working Seed

Batch analysis data for working seeds show the analytical results for the Working Seed batches produced in 2004/2005 influenza season and for Monovalent Virus Pools manufactured for the 2003/2004 and 2005/6 influenza seasons. Certificates of identity, virus seed release, QC testing are provided for each of the 2004/5 strains (some working seeds date from 2003).

S.4.4.2 Monovalent Virus Pool

The monovalent batch protocol is provided for previous seasons including 2003/4. The consistency of the process has been demonstrated by testing of MVPs manufactured for 05/06 season.

Bioburden data is to be collected from a larger number of process steps in 2005/6 season. Historical data are available for a limited number of steps and provide information on the process only prior to the remediation.

In addition to data from 2003/2004 campaign, batch analysis of each of the 2005/2006 strains is provided. Data are provided for the first three batches of each strain manufactured in the 2005 campaign and also for the monovalent batches that were subsequently used to manufacture the EU formulation vaccine. The data provided show that all batches met the specifications. Batch analysis of monovalent virus pools show that the revisions to the process have not affected the ability of MVPs to be produced consistently and to current specifications.

S.4.5 Justification of Specification

The specifications for the virus seed and the monovalent bulk vaccine reflect Ph. Eur. requirements.

S.4.6 Reference Standards or Materials, (CTD Module 3.2.S.5)

Official WHO recommended sources produce the reference antigen and antisera needed for in-process and final product testing. Examples of NIBSC instructions for antisera use have been provided.

S.6 Container Closure System

This is adequately described.

S.7 Stability

S.7.1 Stability Summary and Conclusion

The proposed shelf life for the monovalent virus pools is acceptable.

The storage conditions for the materials are those recommended for the final vaccine lots, as stated on the outer carton and syringe label.

All stability reports referenced show that the potency of the stored Monovalent Virus pools is maintained for the duration of the studies. For the 2005/2006 season, the applicant has initiated a comprehensive stability study for the monovalent virus pools.

While studies on the 2005/2006 season product are ongoing, stability data generated on the previous studies support the proposed shelf life.

S.7.2 Post-Approval Stability Protocol

The applicant notes the post-approval commitment that data should be provided at regular time points. For the 2005/2006 season, the available monovalent virus pool stability data are provided. All test results were within specification. **The applicant has committed to provide further data with the annual strain update.**

S.7.3 Stability Data Results

Stability data show that all several strains remained within specification after storage.

Drug Product

Description and Composition of the Drug Product

P.1 Description and Composition of the Drug Product

Fluvirin is an influenza vaccine (surface antigen, inactivated). The antigens are suspended in a sterile, buffered aqueous solution. The potency of the vaccine is expressed as the concentration of HA protein. It is a sterile suspension for injection in a pre-filled syringe. The final product is a slightly opalescent liquid, free from extraneous particles.

Each single dose pre-filled syringe of Fluvirin contains 0.5 ml of influenza vaccine.

P.2 Pharmaceutical Development

The product was first licensed in UK under the trade name Fluvirin® in 1984. In 1998, the thiomersal reduced formulation was approved, through a MRP, in 15 EU countries.

P.2.1 Components of the Drug Product

Drug Substance

The active ingredients in Fluvirin are purified surface antigens prepared from three strains of influenza virus supplied by the NIBSC or other recognised WHO influenza reference centre under the recommendations of the WHO/EU. The recommended strains of virus, and therefore the antigens, normally change with each influenza season. The selection of strains is in compliance with CHMP guidelines. Monovalent Virus Pools comply with the relevant Ph.Eur. monograph for influenza vaccines, surface antigen, inactivated.

Excipients

Excipients used to formulate Fluvirin comply with the pharmacopoeia and are used industry wide as a pH buffering diluent for injectables. The pH and the buffering capacity of this medium are compatible with both the antigenic protein structure and function and patient acceptability.

P.2.2 Drug Product

Formulation development

The final formulation was developed to provide a stable, isotonic, injectable, vaccine.

Apart from the monovalent virus pools, the only other ingredient in the final product is the buffer. The strain of the antigens normally changes with every influenza season; therefore, clinical studies are conducted with antigens from different strains of influenza depending on the year in which the study was conducted.

An overage for each type of HA antigen may be included to allow for variability in the assay and to ensure the requirements of the CPMP guidelines and Ph. Eur. for the finished product are met.

P.2.4 Container Closure System

The product is presented as a single dose for multination pre-filled into a syringe, selected as being compatible with the final product. Stability studies on the final product have established the compatibility of the components of the container with the final product.

The integrity and sterility of the pre-filled syringe system remain secure and maintain the sterility, integrity and quality of the product when processed under typical routine manufacturing conditions. Media fills have also been carried out to confirm that filling complies with GMP requirements.

P.3 Manufacture

P.3.1 Information on the Manufacturer

Manufacture, filling, testing and release of drug product are performed by Novartis Vaccines and Diagnostics Limited, Gaskill Road, Speke, Liverpool L24 9GR in the United Kingdom.

P.3.2 Batch Formula

The batch size of monovalent virus pools is subject to inherent variability from the size of the eggs received and the corresponding growth of the virus within the egg.

P.3.3 Brief Description of the Manufacturing Process

Final Bulk Process

Depending on the number of doses to be filled and the antigen concentration of each monovalent virus pool, appropriate volumes of each of monovalent virus pool from the three different strains are aseptically transferred to a trivalent bulk blend tank and appropriate amounts of buffer are sterile filtered and added to form the trivalent bulk.

The trivalent bulk is mixed to form a homogeneous solution. It is then sampled and tested. The trivalent bulk is transferred into sterile receiving vessels and tested for sterility. The trivalent vessels are stored at 2-8°C until they are transferred to the filling area.

Data from the 2003 campaign was originally presented to show the stability of MVP stored at 2-8°C for 12 months. The company has already committed to further stability studies on MVPs produced during the 2005/6 and 2006/7 seasons. The MAH has already committed to place three batches of final filled product from the 2005/6 season in a stability study. The Company proposes to put any MVPs that are carried over from one year to the next in a stability study. Also, any trivalent material and filled product that contains MVP that has been carried over would be placed in a stability study to further assess the impact of the storage times on the filled product stability. In-process controls are performed during the packaging process. Samples of finished, packed product are taken for QC testing and the packed syringes are stored at 2-8°C until released.

P.4 Control of Excipients

All the ingredients used for the manufacture of Fluvirin comply with Ph. Eur.

Excipients are fully tested and the supplier, to the appropriate pharmacopoeial specification.

P.5 Control of Drug Product

P.5.1 Specifications and their justification

The specifications for trivalent bulk vaccine and final filled vaccine reflect the requirements of the European Pharmacopoeia monograph for Influenza Vaccine (Surface Antigen, Inactivated). The drug product is composed of the monovalent virus pools (drug substance), for three influenza strains, suspended in a phosphate buffered saline.

P.5.2 Analytical procedures and validation

All methods have been validated for the trivalent vaccine.

P.5.3 Validation of analytical procedures

Validation data is presented for each test method. All other methods are either compendial or have been validated already for monovalent pools. This is acceptable.

P.5.4 Batch Analysis

A summary of the analytical results for trivalent bulk vaccine and filled vaccine batches from the 2002/2003 and 2005/6 influenza seasons has been provided.

P.5.5 Characterisation of Impurities

As for drug substance.

P.6 Reference Standards or Materials

For the Haemagglutinin Content (SRD), NIBSC reagents of the relevant strains are used (or an equivalent recognised by WHO).

P.7 Container Closure System

Fluvirin is supplied to the market in single dose 0.5 ml, pre-filled syringes. A certificate of analysis from the supplier accompanies each batch of Components. Examples of the certificates of analysis are provided

P.8. Stability

P.8.1 Stability Summary and Conclusions

Influenza Vaccine is a seasonal product in which usually at least one of the strains changes each year. Syringes approved for marketing are stored inverted in the secondary packaging used for marketing.

Testing is performed according to the stability protocol and is acceptable.

P.8.2 Post-approval Stability Protocol

Several batches of filled product from 2005/6 will be used in a stability program.

P.8.3 Stability Results

Both routine and accelerated test results for batches of Fluvirin manufactured in 2002 have been presented and are acceptable.

APPENDICES

A.1 Facilities and Equipment

A manufacturer's license has been provided and is acceptable.

A.3 Novel Excipients

Not applicable.

REGIONAL INFORMATION

Process validation scheme for the drug product

Medical Device issues

TSE Issues

ASSESSOR'S COMMENTS ON THE SPC, LABELS AND PACKAGE LEAFLET

Following the acquisition of Chiron Vaccines by Novartis, the Company name was changed during assessment of this application from Chiron Vaccines Limited to Novartis Vaccines and Diagnostics Limited. The legal entity remains the same. This change is reflected in the SPC.

ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY

All issues have been satisfactorily resolved. The quality provided support the conclusion that the product can be consistently manufactured to acceptable specifications.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT

No new clinical data have been supplied with this application and none are required for an application of this type.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Fluvirin are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

CLINICAL

The application is for a fundamental change to an existing marketing authorisation (PL 18532/0001 & 0002). No new clinical data were submitted for this application and no new or unexpected safety concerns arose from this application. Further clinical data will be provided at the time of annual strain updates.

The SPC, PIL and labelling are satisfactory.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The risk-benefit assessment is therefore considered to be favourable.

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STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 28 th May 2005.
2	The MHRA's assessment of the submitted data was completed on 8 th June 2005.
3	Following assessment, a request for supplementary information was sent to the applicant on the 8 th June 2005.
4	The applicant submitted its responses to supplementary information request in a letter dated 8 th March 2006.
5	Following assessment of the RSI, a further RSI was sent to the applicant on the 24 th March 2006.
6	The applicant submitted its responses to supplementary information request in a letter dated 30 th April 2006.
7	The MHRA completed its assessment of the application on 6 th June 2006.
8	The application was determined on 7 th June 2006.

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STEPS TAKEN AFTER AUTHORISATION – SUMMARY

Date submitted	Application type	Scope	Outcome
30.03.07	Type II National Variation	To introduce the use of 0.1M sodium hydroxide to sanitise the zonal centrifuges used in the manufacturing process for health and safety reasons and to bring the zonal centrifugation sanitisation process in line with other sanitisation processes on site.	Granted 14.05.07
30.03.07	Type II National Variation	To update the Summary of Product Characteristics (SPC) in line with all influenza vaccines, in accordance with recommendations made by the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh).	Granted 04.06.07
24.03.12	Type IB National Variation	To update sections 2, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8 and 6.6 of the SPC in line with the Core SPC for Trivalent Influenza Vaccines. In addition, to update section 4.8 following a review of post marketing surveillance data. These changes have been grouped.	Granted 20.06.12
24.07.12	Type II National Variation	To update the influenza vaccine strain as recommended by World Health Organisation and European decision for 2012/2013 season. As a consequence section 2 of the SPC, labels and leaflets have been updated.	Granted 06.09.12

Summary of Product Characteristics

FLUVIRIN

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In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Patient Information Leaflet

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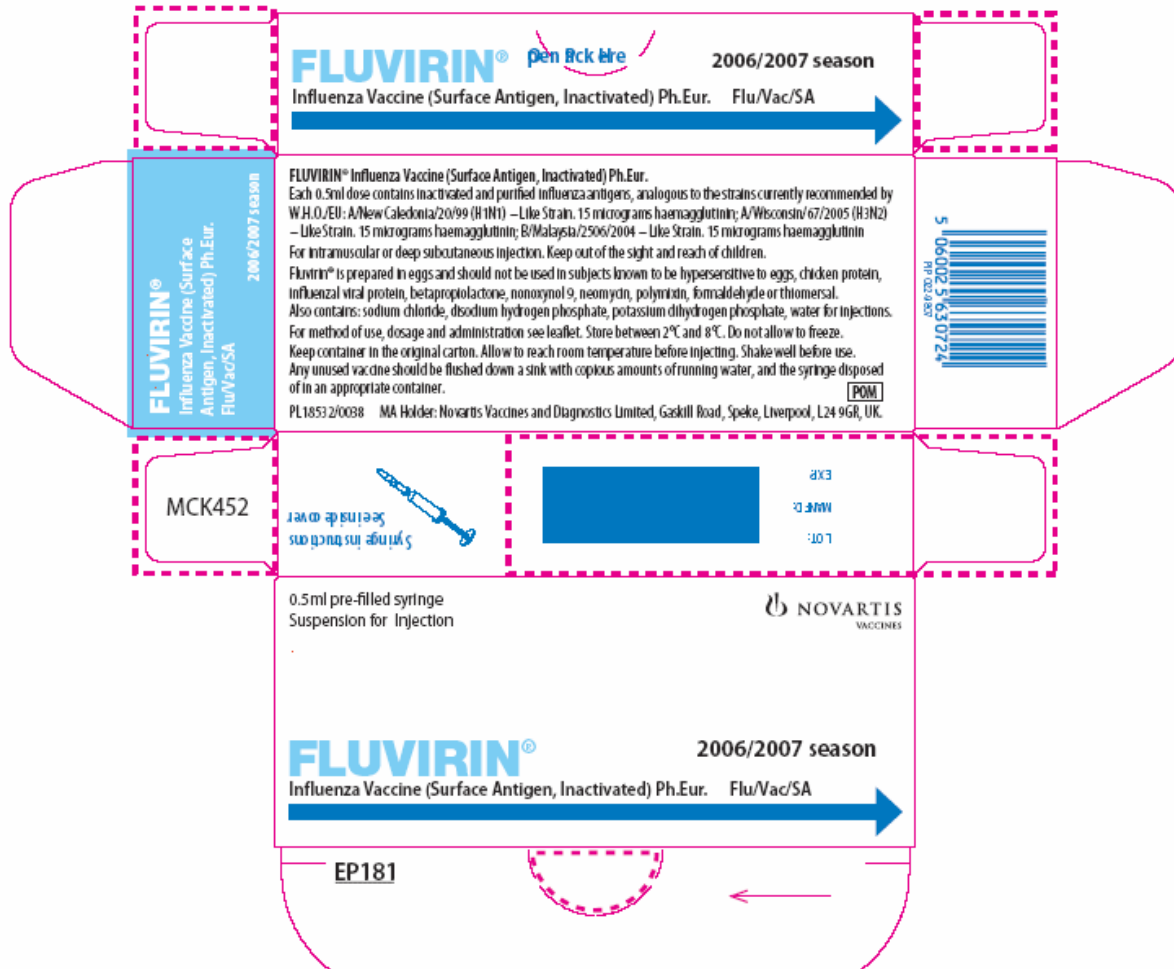
Labelling

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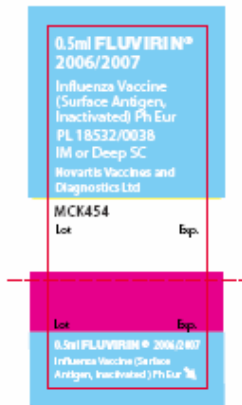
Carton






magenta does not print

VARNISH FREE AREA

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	Profile/Spec. No.	EP181
	Scale	100%
	Draft no./Date	5 26.02.07
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FLUVIRIN® Open Pack Here 2006/2007 season
 Influenza Vaccine (Surface Antigen, Inactivated) Ph.Eur. Flu/Vac/SA

FLUVIRIN®
 Influenza Vaccine (Surface Antigen, Inactivated) Ph.Eur.
 Flu/Vac/SA

2006/2007 season

FLUVIRIN® Influenza Vaccine (Surface Antigen, Inactivated) Ph.Eur.

Each 0.5ml dose contains inactivated and purified influenza antigens, analogous to the strains currently recommended by W.H.O./EU

- A/New Caledonia/20/99 (H1N1) – Like Strain. 15 micrograms haemagglutinin
- A/Wisconsin/67/2005 (H3N2) – Like Strain. 15 micrograms haemagglutinin
- B/Malaysia/2506/2004 – Like Strain. 15 micrograms haemagglutinin

For intramuscular or deep subcutaneous injection.

Keep out of the sight and reach of children.

Fluvirin® is prepared in eggs and should not be used in subjects known to be hypersensitive to eggs, chicken protein, influenza viral protein, betapropiolactone, nonoxynol 9, neomycin, polymixin, formaldehyde or thiomersal.

Also contains: sodium chloride, disodium hydrogen phosphate, potassium dihydrogen phosphate, water for injections.

For method of use, dosage and administration see leaflet.
 Store between 2°C and 8°C. Do not allow to freeze. Keep container in the original carton. Allow to reach room temperature before injecting. Shake well before use.

Any unused vaccine should be flushed down a sink with copious amounts of running water, and the syringe disposed of in an appropriate container.

PL18532/0038
 MA Holder: Novartis Vaccines and Diagnostics Limited, Gaskell Road, Speke, Liverpool, L24 9GR, UK.

PIP 048-0715



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MCK455



Syringe Instructions
 See inside cover

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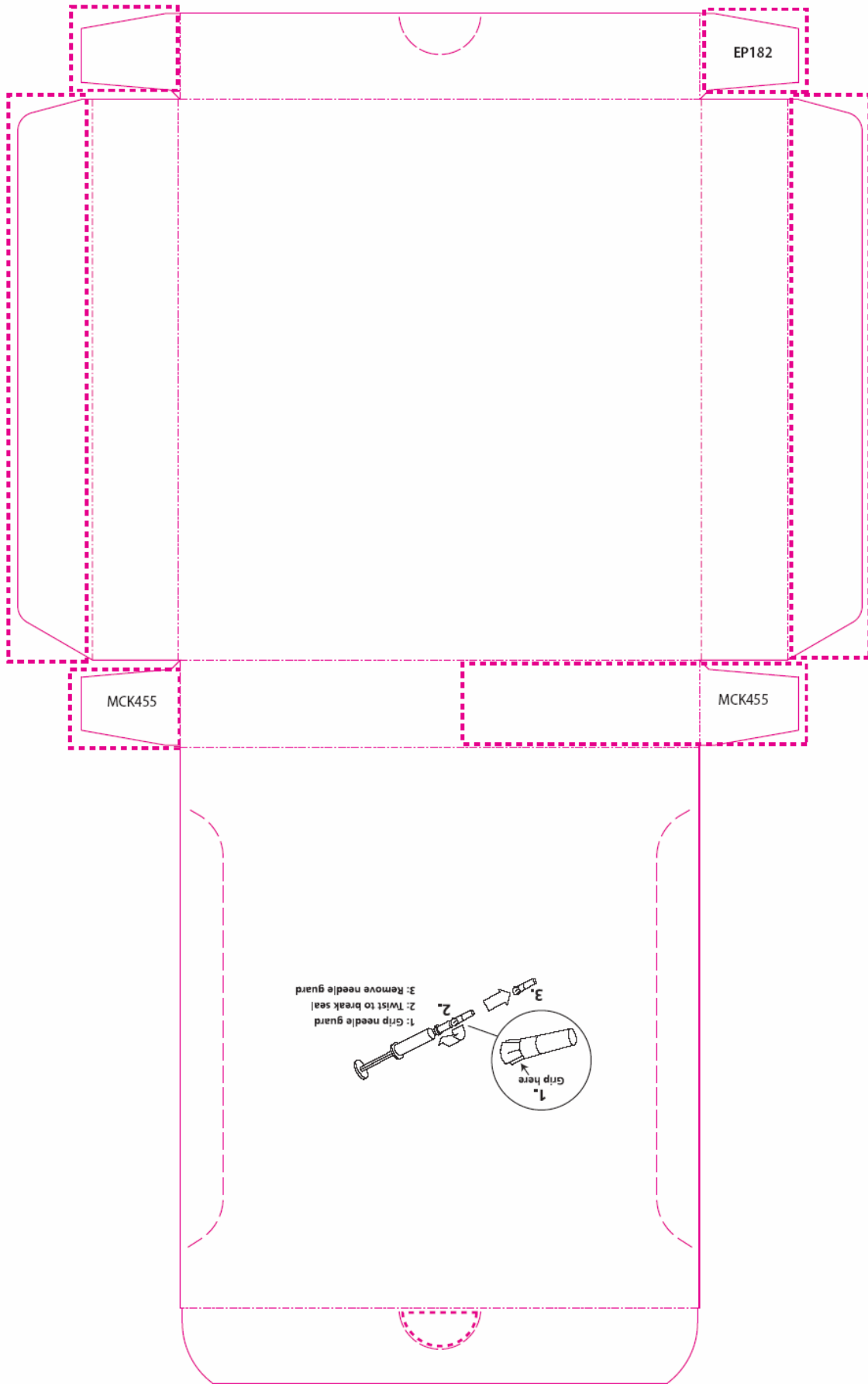
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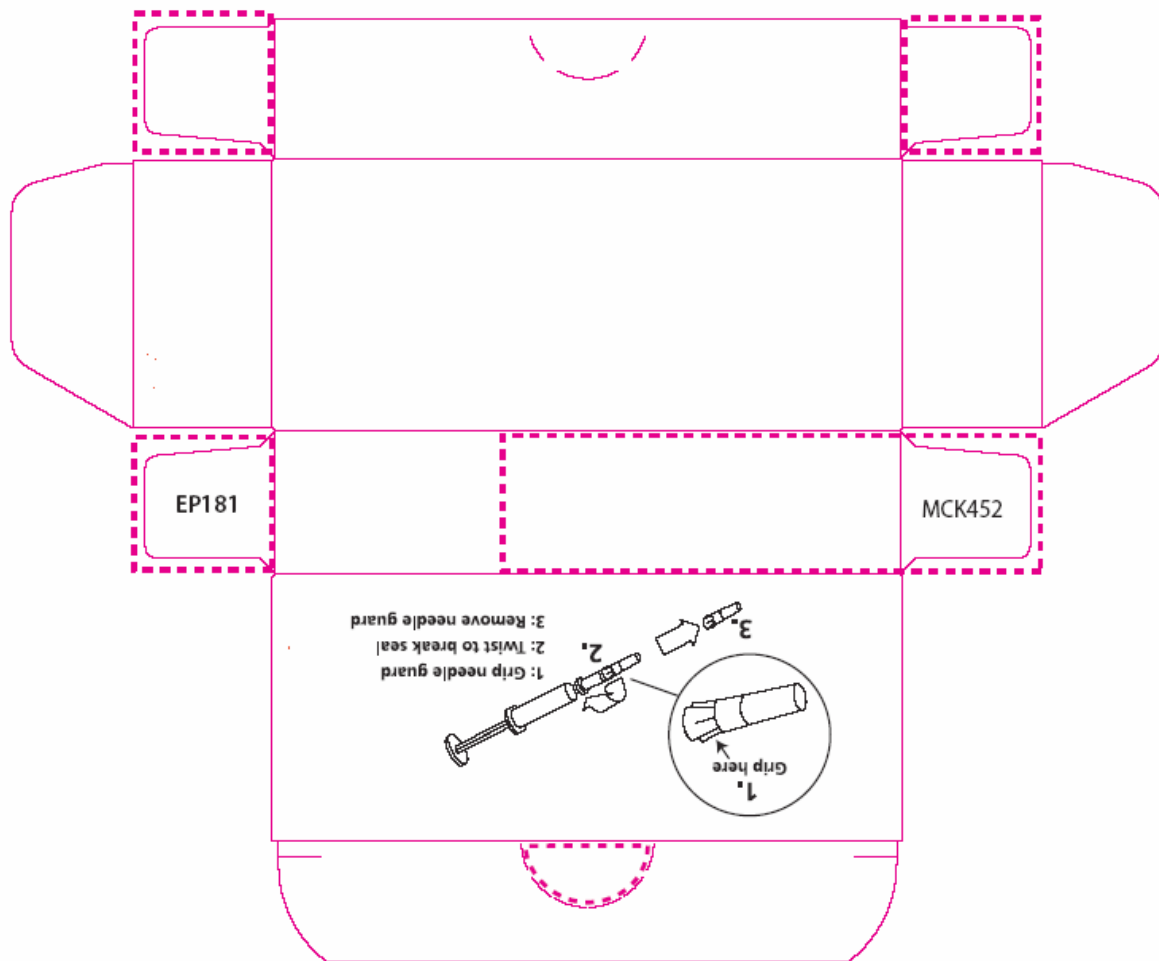
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10 x 0.5ml pre-filled syringes
 Suspension for Injection

FLUVIRIN® 2006/2007 season
 Influenza Vaccine (Surface Antigen, Inactivated) Ph.Eur. Flu/Vac/SA

EP182





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--- VARNISH FREE AREA

Annex 1 - Quality

Our Reference:	PL 18532/0038–0038
Product:	PL 18532/0038–0038 FLUVIRIN suspension for injection in pre-filled syringe
Marketing Authorisation Holder:	NOVARTIS VACCINES AND DIAGNOSTICS LIMITED
Active Ingredient(s):	VIRUS INFLUENZA A/CALIFORNIA/7/2009 (H1N1) DERIVED STRAIN USED NYMC X-181, A/VICTORIA/361/2011 (H3N2) - DERIVED STRAIN USED IVR-165, B/WISCONSIN/1/2010 - LIKE STRAIN USED NYMC BX-39 DERIVED FROM B/HUBEI-WUJIAGANG/158/2009.

Reason:

To update the influenza vaccine strain as recommended by World Health Organisation and European decision for 2012/2013 season. As a consequence section 2 of the SPC, labels and leaflets have been updated.

Linked / Related Variation(s) or Case(s):

NA

Supporting Evidence

See case folder.

Evaluation

For the 2012/2013 influenza season, Novartis Vaccines changes all seeds:

Novartis will use

- A/California/7/2009 (H1N1) pdm09 - like strain used (NIB-74) derived from A/Christchurch/16/20 10
- A/Victoria/361120 11 (H3N2) - derived strain used (IVR-165)
- B/Wisconsin/112010 - like strain used (NYMC BX- 39) derived from B/Hubei-Wujiagang/158/2009.

See report below for assessment.

Drug Substance

Master and Working Seeds (3.2.S)

The official documents showing that identity testing for seeds from reference antigens is acceptable are provided.

Process Validation (3.2.S)

The H1N1 inactivation data have been provided and show acceptable inactivation (infectivity titre). The data are acceptable.

Analytical methods (3.2.S)

Some changes are made to the preparation of samples/standards for the neuraminidase ID test – these are accepted.

Validation of Analytical methods (3.2.S)

Sufficient data have been supplied to demonstrate that the analytical methods have been adequately validated.

Batch Analysis (3.2.S)

Batch analytical data for the monobulks are presented and are satisfactory.

Stability (3.2.S)

Stability data from a number of studies is presented covering long-term and accelerated conditions and also the previous and current egg scales and inactivation scales. Additionally, stability data from last years strains are presented for a number of lots of each strain (9 to 12 months stability data). The data is satisfactory.

Post-Approval Stability Protocol (3.2.S)

This protocol is as in previous seasons – and is accepted.

Drug Product

Description, Pharmaceutical Development and Batch Formula (3.2.P)

The above sections have been updated accordingly.

Validation of Analytical methods (3.2.P)

The MAH have provided the requalification reports for quantification of HA at the level of the final bulks/final containers. These are acceptable.

Batch Analysis (3.2.P)

Batch data for the bulk blend and filled final containers are satisfactory.

Stability (3.2.P)

Long-term interim stability data are provided for several batches of Fluvirin final containers produced for the 2011/12 season. Short-term accelerated data is also provided for several batches.

The batches show satisfactory stability over the timepoints for which data are available.

Stability Supporting the Introduction of changes to the Fluvirin Manufacturing Process

3.2.P.8.2.2.1 Stability Supporting the Introduction of Site 4 for Monovalent Production

Several conformance lots of monovalent virus pool were produced; formulated into lots of thimerosal-reduced trivalent bulk; and filled into syringes. The complete real-time data is available for the trivalent bulk lots, and complete real-time and accelerated data are available for the filled vaccine lots. Any data not meeting specification was promptly investigated.

3.2.P.8.2.2.2 Stability Supporting the Introduction of Trivalent Bulk Manufactured at Novartis Vaccines Rosia.

Several conformance lots of trivalent bulk material were produced and the resulting material was placed on stability. The complete real-time data is available for the trivalent bulk lots.

Post-Approval Stability Protocol (3.2.P)

This protocol is as in previous seasons – and is accepted.

SPC, PIL, Labels

Track change documents are provided – these are satisfactory.

Conclusion

The changes proposed by the MAH are accepted.

Decision - Approve

Annex 1 - Clinical

Our Reference:	PL 18532/0038–0038
Product:	PL 18532/0038–0038 FLUVIRIN suspension for injection in pre-filled syringe
Marketing Authorisation Holder:	NOVARTIS VACCINES AND DIAGNOSTICS LIMITED
Active Ingredient(s):	VIRUS INFLUENZA A/CALIFORNIA/7/2009 (H1N1) DERIVED STRAIN USED NYMC X-181, A/VICTORIA/361/2011 (H3N2) - DERIVED STRAIN USED IVR-165, B/WISCONSIN/1/2010 - LIKE STRAIN USED NYMC BX-39 DERIVED FROM B/HUBEI-WUJIAGANG/158/2009.

Reason:

To update the influenza vaccine strain as recommended by World Health Organisation and European decision for 2012/2013 season. As a consequence section 2 of the SPC, labels and leaflets have been updated.

Linked / Related Variation(s) or Case(s):

NA

Supporting Evidence

Annual strain change for the 2012/2013 formulation of Novartis vaccines and diagnostics influenza vaccine (Fluvirin).

Immunogenicity

The applicant has conducted V78_10S open label single-treatment arm study, 126 subjects were planned to be enrolled into two groups (63 subjects in each age group) to ensure evaluable data on at least 50 subjects ≥ 18 years to ≤ 60 years and at least 50 subjects ≥ 61 years. The study was carried out at University of Rostock, Department of Tropical Medicine and Infectious Diseases, Ernst-Heydemann-Straße 6, D-18057 Rostock, Germany. GCP was assured and minimal number of deviations and protocol violations were reported.

The World Health Organization (WHO) recommended the use of the following strains in influenza vaccines for the 2012/2013 season in the Northern Hemisphere: A/California/7/2009 (H1N1) pdm09 - like strain used (NIB-74) derived from A/Christchurch/16/2010, A/Victoria/361/2011 (H3N2) - derived strain used (IVR-165), B/Wisconsin/1/2010 - like strain used (NYMC BX-39) derived from B/Hubei-Wujiagang/158/2009. The Committee for Human Medicinal Products (CHMP) Biologics Working Party (BWP, Ad hoc Influenza Working Group) confirmed that the WHO recommendation was accepted for vaccine use in the European Member States. This Marketing Authorization Variation (MAV) contains the supporting data as listed in the Notice to Applicants Guideline for a fast track procedure for human influenza vaccines (May 1999). The immunogenicity objective for the 2012/2013 formulation was determined according to the CHMP guideline Committee for

Proprietary Medicinal Products (CPMP)/BWP/214/96, i.e. at least one of the following serological assessments for each antigen (assessed with hemagglutination inhibition [HI] or single radial hemolysis [SRH] assay) has to be achieved:

In subjects ≥ 18 years to ≤ 60 years

- proportion of subjects achieving an HI titer ≥ 40 or SRH area ≥ 25 mm² should be $> 70\%$;
- proportion of subjects with seroconversion or with a significant increase in HI titer or SRH area $> 40\%$;
- mean geometric increase > 2.5 .

In subjects ≥ 61

- proportion of subjects achieving an HI titer ≥ 40 or SRH area ≥ 25 mm² should be $> 60\%$;
- proportion of subjects with seroconversion or significant increase in HI titer or SRH area $> 30\%$;
- mean geometric increase > 2.0 .

Fluvirin fulfilled CHMP requirement that at least one of the criteria for subjects ≥ 18 years to ≤ 60 years and at least one of the criteria for subjects ≥ 61 years was met for each strain with SRH assay ([Table 11.4.7-1](#) and [Table 11.4.7-2](#)).

HI assay results:

≥ 18 years to ≤ 60 years

For the A/H1N1 strain and A/H3N2 strain 3 out of 3 CHMP criteria were met. For the B strain 2 out of 3 CHMP criteria were met (CHMP criterion HI titer ≥ 40 was not met).

≥ 61 years

For the A/H1N1 strain and A/H3N2 strain 3 out of 3 CHMP criteria were met. For the B strain 0 out of 3 CHMP criteria was met.

SRH assay results:

≥ 18 years to ≤ 60 years

For all 3 strains 3 out of 3 CHMP criteria were met.

≥ 61 years

For all 3 strains 3 out of 3 CHMP criteria were met.

Publications have shown that unlike influenza A, even influenza B infection often results in poor antibody responses when tested by HI assay (1,2). A general difference between HI and SRH assay performance was also noted in this study (V78_10S) against the B/Wisconsin/1/2010 - like strain used (NYMC BX-39) derived from B/Hubei-Wujiagang/158/2009.

Table 11.4.7-1 CHMP Criteria met (+) by HI Assay (Subjects ≥ 18 Years to ≤ 60 Years and Subjects ≥ 61 Years) at 21 Days after Vaccination (Day 22) – Per Protocol Set

		A/H1N1	A/H3N2	B
≥18–60 Y ^a	Geometric mean increase	+	+	+
	HI titer ≥ 40 ^c	+	+	-
	Seroconversion or significant increase ^d	+	+	+
≥61 Y ^b	Geometric mean increase	+	+	-
	HI titer ≥ 40 ^c	+	+	-
	Seroconversion or significant increase ^d	+	+	-

Source: [Module 5 CSR V78_10S](#); ^a ≥ 18 years to ≤ 60 years; ^b ≥ 61 years; ^c proportion of subjects with a protective titer (HI titer ≥ 40). ^d Seroconversion or significant increase: proportion of subjects with either seroconversion or significant increase. Seroconversion: proportion of subjects with antibody increase from < 10 prevaccination to ≥ 40 postvaccination. Significant increase: proportion of subjects with an antibody titer of ≥ 10 prevaccination and ≥ 4-fold antibody increase postvaccination; HI – hemagglutination assay; "+" CHMP criteria met; "-" CHMP criteria not met.

Table 11.4.7-2 CHMP Criteria met (+) by SRH Assay (Subjects ≥ 18 Years to ≤ 60 Years and Subjects ≥ 61 Years) at 21 Days after Vaccination (Day 22) – Per Protocol Set

		A/H1N1	A/H3N2	B
18–60 Y ^a	Geometric mean increase	+	+	+
	SRH area ^c ≥ 25 mm ²	+	+	+
	Seroconversion or significant increase ^d	+	+	+
≥61 Y ^b	Geometric mean increase	+	+	+
	SRH area ^c ≥ 25 mm ²	+	+	+
	Seroconversion or significant increase ^d	+	+	+

Source: [Module 5 CSR V78_10S](#); ^a ≥ 18 years to ≤ 60 years; ^b ≥ 61 years; ^c proportion of subjects with a pre- or postvaccination area ≥ 25 mm²; ^d Seroconversion or significant increase: proportion of subjects with either seroconversion or significant increase; Seroconversion: proportion of subjects with increase from SRH area ≤ 4mm² prevaccination to SRH area ≥ 25 mm² postvaccination; Significant increase: proportion of subjects with at least a 50% increase in area from positive prevaccination serum; SRH – single radial hemolysis; "+" CHMP criteria met; "-" CHMP criteria not met.

Safety results

Solicited local and systemic reactions:

In subjects ≥ 18 years to ≤ 60 years incidences of any solicited local and systemic reactions were higher than in the previous seasonal study (V78_08S, submitted with the seasonal strain variation 2 years ago) with this vaccine (V78_10S: any solicited local reactions in 59% of subjects, any solicited systemic reactions in 51% of subjects; V78_08S, previous seasonal study: any solicited local reactions in 51% of subjects, any solicited systemic reactions in 46% of subjects). The difference in solicited local reactions was mainly due to higher incidences of injection site pain in study V78_10S

(V78_10S: 56%; V78_08S: 49%). The difference in solicited systemic reactions was mainly due to higher incidences of malaise, myalgia and sweating in study V78_10S (V78_10S: malaise 16%, myalgia 29% and sweating 17%; V78_08S: malaise 5%, myalgia 16% and sweating 5%). In subjects ≥ 61 years the incidences of any solicited local and systemic reactions in study V78_10S were higher than in the previous seasonal study (V78_08S) with this vaccine (V78_10S: any solicited local reactions in 29% of subjects, any solicited systemic reactions in 33% of subjects; V78_08S, previous seasonal study: any solicited local reactions in 16% of subjects, any solicited systemic reactions in 24% of subjects). The difference in solicited local reactions was mainly due to higher incidences of injection site pain and erythema in study V78_10S (V78_10S: injection site pain 19%, erythema 11%; V78_08S: injection site pain 13%, erythema 4%). The difference in solicited systemic reactions was mainly due to higher incidences of myalgia and sweating in study V78_10S (V78_10S: myalgia 16%, sweating 14%; V78_08S: myalgia 9%, sweating 3%). In study V78_10S the most commonly reported solicited local reaction in subjects ≥ 18 years to ≤ 60 years was injection site pain (56%) followed by induration (10%). The most commonly reported solicited systemic reaction in this age group was myalgia (29%), followed by fatigue (24%), headache (22%), sweating (17%) and malaise (16%). In subjects ≥ 61 the most commonly reported solicited local reaction years was injection site pain (19%) followed by erythema (11%). The most commonly reported solicited systemic reaction in this age group was myalgia (16%), followed by fatigue (14%), sweating (14%) and headache (10%).

In study V78_10S in both age groups all solicited reactions (except 1 erythema of > 50 mm in each age group, respectively) were mild and moderate. One erythema of 70 mm was resolved on day 4 and 1 erythema of 60 mm was resolved on day 3. Most solicited local reactions and all solicited systemic reactions were resolved up to and including day 4. All solicited reactions were resolved by the end of the study. This is mostly similar to study V78_08S. In this study most solicited local and systemic reactions were mild and moderate, most of them were resolved up to and including day 4 and all were resolved by study termination.

Other adverse events (AEs, i.e., unsolicited AEs or local and systemic reactions persisting after day 4): In study V78_10S incidences of other AEs were higher than in study V78_08S, but incidences of AEs that were judged by investigator as possibly or probably related were lower than in the previous seasonal study (V78_10S: any other AEs in 11% of subjects ≥ 18 years to ≤ 60 years and in 13% of subjects ≥ 61 years, possibly/probably related AEs in both age groups 3% of subjects; V78_08S: any other AEs in both age groups 9% of subjects, possibly/probably related AEs in 8% of subjects ≥ 18 years to ≤ 60 years and in 9% of subjects ≥ 61 years). In study V78_10S AEs which were judged by investigator as possibly or probably related to study vaccine were unsolicited AEs in subjects ≥ 18 years to ≤ 60 years and solicited local reactions persisting after day 4 in subjects ≥ 61 years. All (except 1 moderate nasopharyngitis) possibly/probably related AEs were mild. All possibly/probably related AEs were resolved before study termination (approximately 21 days after vaccination). This was similar to the previous seasonal study in which most possibly/probably related AEs were solicited local and systemic reactions persisting after day 4, all possibly/probably related AEs were mild or moderate and were resolved before study termination.

Similar in both studies (V78_10S and V78_08S) no subject died. No subject reported SAEs and no AE led to premature withdrawal. The PSURs for Fluvirin during the period 01 May 2011 - 30 April 2012 (two reports: one for reporting period of 01 May 2011 to 31 August 2011 and one for reporting period from 01 September 2011 to 30 April 2012) confirm that the safety data remain in accord with the previous cumulative experience and the safety information presented in the currently valid SPCs except for the event “injection site cellulitis-like reaction” which is being included in the Fluvirin SPC.

For subjects in the age groups ≥ 18 years to ≤ 60 years and ≥ 61 years, Fluvirin, surface antigen, inactivated, influenza vaccine, formulation 2012-2013, is well tolerated and complies with the CHMP immunogenicity criteria for the approval of influenza vaccines.

References:

1. Chakraverty P. Comparison of Haemagglutination-Inhibition and Single-Radial-Haemolysis techniques for detection of antibodies to Influenza B virus. Arch of Virology 1980; 63:285-289.
2. Monto AS, Maassab HF. Ether treatment of type B influenza virus antigen for the hemagglutination inhibition test. J.Clin. Microbiol. 1981;13: 54-57

Assessor’s Evaluation

The immunogenicity evaluation using HA assay fulfilled at least one assessment criteria for all strains in 18-60 year age group and for two strains except B strain in subjects >60 years of age. Notwithstanding, SRH assessment criteria were for each criterion for each strain in both age strata. Therefore, Fluvirin has met CHMP criteria for annual seasonal influenza vaccine updates from clinical perspective. The discordance in the performance of HI and SRH assays has been detected with other seasonal vaccine during this season and the trend with performance of assays in relation to B strain should be monitored in the future.

From safety perspective, the reactogenicity profile and the pattern of SAEs with Fluvirin remain broadly in line with those reported previously with this product. No unexpected safety findings were reported with current cycle of PSURs. Section 4.8 was updated in line with reporting of thrombocytopenia and cellulitis during postmarketing period and relevant information was added into an appropriate section in 4.8. Sentinel and rare SAEs known with influenza vaccines remain extremely rare and no new unexpected SAEs were reported.

Therefore, an overall benefit-risk balance is favourable.

Decision - Approved

Summary of Product Characteristics

FLUVIRIN

[Influenza Vaccine (Surface Antigen, Inactivated) Ph. Eur.]

PL 18532/0038-39

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Patient Information Leaflet

FLUVIRIN

[Influenza Vaccine (Surface Antigen, Inactivated) Ph. Eur.]

PL 18532/0038-39

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Labelling

FLUVIRIN

[Influenza Vaccine (Surface Antigen, Inactivated) Ph. Eur.]

PL 18532/0038-39

Carton

