FLUVIRIN

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

PL 18532/0038
PL 18532/0039

UKPAR

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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 sub-types and one influenza B sub-type 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.

FLUVIRIN

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

PL 18532/0038-39

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, LU, 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.S.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

Samples were taken from various stages of the influenza vaccine manufacture and analysed by transmission electron microscopy and negative staining.

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 period 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

The monovalent virus pool is manufactured by:
Novartis Vaccines and Diagnostics Limited,
Gaskill Road,
Speke,
Liverpool.
L24 9GR, UK.

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:

Inactivation

(i) Validation for the inactivation of A/New Caledonia/20/99 IVR-116 strain. Three batches were inactivated. All three batches were negative for haemagglutination at passage 1. This indicated that there was no proliferating, viable virus in the treated inoculum for the new strain. The assay was suitably controlled.

(ii) Validation for the inactivation of A/Wyoming/3/2003 X-147. Three batches were harvested and inactivated. All three batches were negative for haemagglutination at passage 1. This indicated that there was no proliferating, viable virus in the treated inoculum for the new strain. The assay was suitably controlled.

(iii) Validation for the inactivation of B/Jiangsu/10/03 were harvested and inactivated. All three batches were negative for haemagglutination at passage 1. This indicated that there was no proliferating, viable virus in the treated sample for the new strain. The assay was suitably controlled.

Splitting

(iv) Splitting efficiency, A/NewCaledonia/20/99 IVR-116 strain. Graphical comparison of intact and split virus was provided showing effective splitting efficacy.

(v) Splitting efficiency, A/Wyoming/3/2003 X-147. Graphical comparison of intact and split virus was provided and demonstrated effective splitting.

(vi) Splitting efficiency, of B/Jiangsu/10/03. Graphical comparison of intact and split virus demonstrated effective splitting.

Data is supplied to demonstrate satisfactory inactivation of 3 batches of A/New Caledonia, as demonstrated by the egg safety test Data has been provided for 5 batches of the A/New Caledonia and B/Jiangsu strains and for 4 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).

Experiments have been carried out to determine the levels of antibiotics in the finished product. No antibiotic is detectable in the final vaccine using current microbial assay techniques.

A study of estimates of antibiotic levels in stages of Fluvirin production, by microbiological assay is provided.

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

Test for Viral Inactivation (Egg Safety Test), Sterility, Endotoxins and Appearance are performed using Ph. Eur. analytical methods. These methods have been qualified for monovalent virus pools.

Purity is determined using the Polyacrylamide Gel Electrophoresis (PAGE) to assess the purity of monovalent virus pool samples before they are formulated together to form the final blended vaccine.

Methods used to control the potential impurities/residual solvents from production have been validated. Validation studies have demonstrated that the relevant methods, performed adequately within the tested parameters and are suitable for use in testing the monovalent virus pools.

The determination of the **formaldehyde** content in the monovalent virus pools is performed using UV / Visible spectroscopy. The method used does not fully comply with the Ph. Eur as a range of standard solutions are used to form the calibration graph. This is acceptable.

The determination of **nonoxyl 9** content in the monovalent virus pools is performed using UV / Visible spectroscopy.

Sucrose is quantified using ion chromatography.

The **thiomersa**l content of the monovalent virus pools is determined by using Atomic Absorption Spectrophotometry. The **total nitrogen** content of the monovalent virus pool is measured using an automated nitrogen analyser.

The **phosphate** content in the monovalent virus pool is quantified using ion exchange chromatography.

S.4.3 Validation of Analytical Procedures

SDS-PAGE validation has been performed to demonstrate the suitability of the PAGE assay for routine use.

The **sterility test** method (filtration) has been validated according to Ph Eur monograph 2.6.1.for the 4 manufacturing stages routinely tested. The acceptance requirements were met. The **neuraminidase** assay method has been validated and shown to be suitable for the identification of neuraminidase and is a Ph. Eur. method. The assay is repeatable and reliable, and is suitable for its intended use.

The haemagglutinin assay method has been validated. The acceptance criteria were met.

The technical reports for the optimisation and re-qualification of the haemagglutinin assay for the three 2005/2006 strains have been provided. The assay was successfully validated for all 3 strains for the 2005-6 season vaccine.

The **pH** method has been validated. All parameters met the relevant acceptance criteria.

The **nonoxyl 9** method has been validated. All parameters met the relevant acceptance criteria. P**arameters studied** for **monovalent pools include accuracy, repeatability, intermediate precision, reproducibility, drift of retention times, specificity, linearity, range, sensitivity, robustness, limit of detection and limit of quantitation.**

The total **nitrogen** content method has been validated for the trivalent vaccine. All parameters met the relevant acceptance criteria.

The **phosphate** content method has been validated. All parameters met the relevant acceptance criteria.

Viral inactivation (egg safety test)
The qualification of the viral inactivation test (egg safety test) has been performed, and is provided. The assays met all the acceptance criteria and showed the ability of this assay to distinguish live and inactivated flu virus.

Endotoxin
Method based on Ph. Eur. limulus amoebocyte lysate assay has been studied to determine interfering factors and assurance of a standard curve.

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 testingExamples of NIBSC instructions for antisera use have been provided.

S.6 Container Closure System
The monovalent pools are stored at 2-8^{o}C in vessels or bags.

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 3 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 formulation 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^{o}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. Where an excipient is classified as ‘approved’, a reduced testing schedule is employed. The excipients, present in the Fluvirin formulation, all have ‘approved’ status and are therefore subject to a reduced testing regime. One batch in five is fully tested to the current Ph. Eur. specification and the remainder of batches undergo the

reduced testing schedule, which typically involves a review of the suppliers' results and testing for appearance and identification.

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.

The **ovalbumin validation** method has been validated. The study has demonstrated that the method performed adequately within the tested parameters and is suitable for use.

The **betaproiolactone** test method has been validated.

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.
The empty Readyject syringe barrels are manufactured by Bunderglas GmbH

A certificate of analysis from the supplier accompanies each batch of Components. Examples of the certificates of analysis are provided

The applicant does not routinely test the components as the filling line is revalidated periodically.

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.

The key stability-indicating parameter of product is the potency.

Batches produced for the seasons from 2000-2001 to 2002-2003 have been placed on stability, and the results of these stability studies support the shelf life assigned to the product of 12 months.

Historically the finished product has been shown to maintain adequate stability over the course of its shelf life.

Three batches from the 2005/6 season will be used in a stability study. This includes the clinical trial batch.

P.8.2 Post-approval Stability Protocol
Three 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.

The applicant notes the requirement to provide data from the 2005/6 vaccine stability studies as it becomes available**.** For the 2005/2006 season, the available trivalent and filled product stability data have been provided. **Updates on these stability studies will be provided with the next strain update variation.** All test results show that this trivalent bulk remained within specification.

In accordance with the relevant guideline for influenza vaccines, the Company will report stability data of new vaccine if outside specification.

APPENDICES

A.1 Facilities and Equipment

The Novartis Vaccines and Diagnostics Limited site is situated in an industrial zone at Speke, on the outskirts of Liverpool, UK. The site is approximately 30,000 square metres. There are several buildings on site, which are dedicated to pharmaceutical and biopharmaceutical operations. The EVU Seed Laboratories produce Influenza Master and Working Virus seed under sterile conditions.

A manufacturer's license, dated 7/12/05 has been provided. A copy of the letter confirming that the suspension to the license was lifted as of 2/3/05, has also been provided.

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.

FLUVIRIN

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

PL 18532/0038-39

STEPS TAKEN FOR ASSESSMENT

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

FLUVIRIN

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

PL 18532/0038

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

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

FLUVIRIN®, suspension for injection in pre-filled syringe. [Influenza Vaccine (Surface Antigen, Inactivated) Ph.Eur.]

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

A/New Caledonia/20/99 (H1N1) - Like strain (A/New Caledonia/20/99 IVR-116)	15 micrograms HA**
A/Fujian/411/2002 (H3N2) - Like strain (A/Wyoming/3/2003 X–147)	15 micrograms HA**
B/Shanghai/361/2002 - Like strain (B/Jiangsu/10/2003)	15 micrograms HA**

per 0.5 ml dose.
* propagated in fertilised hens' eggs from healthy chicken flocks
** haemagglutinin

This vaccine complies with the WHO recommendation (northern hemisphere) and EU decision for the 2004/2005 season.

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Suspension for injection in 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 Fluvirin® should be based on official recommendations.

4.2 Posology and method of administration

Adults and children from 4 years: 0.5 ml.

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 eggs, chicken proteins. FLUVIRIN® does not contain more than 1 microgram ovalbumin per dose. The vaccine may contain residues of the following substances, betapropiolactone, nonoxynol 9, neomycin, polymixin, formaldehyde or thiomersal.

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

4.4 Special warnings and precautions for use

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

FLUVIRIN® should under no circumstances be administered intravascularly.

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

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). The maximum thiomersal content in FLUVIRIN® is 0.002mg (0.0004% w/v).

4.5 Interaction with other medicinal products and other forms of interaction

FLUVIRIN® 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 limited data from vaccinations in pregnant women do not indicate that adverse foetal 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.

FLUVIRIN® 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 61years 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 (>1/1000, <1/100); rare (>1/10000, <1/1000); very rare (<1/10000), including isolated reports.

Organ class	**Very common >1/10**	**Common >1/100, <1/10**	**Uncommon >1/1000, <1/100**	**Rare >1/10000, <1/1000**	**Very rare <1/10000**
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, febril 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

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 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

Buffer solution:
- Potassium dihydrogenphosphate
- Disodium hydrogenphosphate
- Sodium chloride
- Water for injection.

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 at +2°C to +8°C (in a refrigerator). Do not freeze. Keep container in the original carton.

6.5 Nature and contents of container

0.5 ml in pre-filled syringe (glass, type I) with stopper (rubber), fitted with a stainless steel needle, pack sizes of 1 and 10 syringes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Unused vaccines 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.

7 MARKETING AUTHORISATION HOLDER

Novartis Vaccines and Diagnostics Limited
Gaskill Road
Speke
Liverpool
L24 9GR
UK.

8 MARKETING AUTHORISATION NUMBER

PL 18532/0038.

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7 June 2006

10 DATE OF REVISION OF THE TEXT

24/05/2007

Patient Information Leaflet

FLUVIRIN

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

PL 18532/0038-39

FLUVIRIN®

Influenza Vaccine (Surface Antigen, Inactivated) Ph.Eur.
Suspension for Injection

NOVARTIS VACCINES

PACKAGE LEAFLET: INFORMATION FOR THE USER

For persons receiving (or parents or guardians of children receiving) vaccination with Fluvirin®.

READ ALL OF THIS LEAFLET CAREFULLY before you (or your child) are vaccinated.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- If any of the side effects get serious or you notice any side effects not listed in the leaflet, please tell your doctor, nurse or pharmacist.

In this leaflet:

1. WHAT IS FLUVIRIN® AND WHAT IT IS USED FOR

The full name of this vaccine is Fluvirin®, or Influenza Vaccine (Surface Antigen, Inactivated) Ph.Eur.

Fluvirin® is a vaccine that contains three types of killed influenza viruses. The types that are used to make the vaccine each year are chosen according to the most common types that are known to be circulating in the world.

The vaccine is used to protect against influenza in people aged 4 years and over, who may be at risk of severe infections with complications.

After injection, the killed viruses stimulate the production of antibodies against influenza virus. This takes about 2-3 weeks. These antibodies help to protect against the infection with the types of virus in the vaccine and may also be able to provide some protection against similar types. However, as with other vaccines against influenza, Fluvirin® cannot completely protect all persons vaccinated against influenza.

It is thought that protection may last for 6-12 months. However, because of changes in the types of virus circulating it is necessary to be vaccinated every year.

2. BEFORE YOU ARE GIVEN FLUVIRIN®

Fluvirin® is not suitable for everyone.

If the answer to any of the following questions is "YES" for the person who is to be vaccinated, Fluvirin® should not be given. If you are not sure about anything, ask your doctor or nurse before Fluvirin® is given.

- Have you ever had an allergic reaction following a previous vaccination with any influenza vaccine?
- Are you allergic to egg or chicken protein? The virus in Fluvirin® is grown in eggs and there may be traces left in the vaccine.
- Are you allergic to polymyxin or neomycin (antibiotics), thiomersal (a mercury containing compound), nonoxynol 9, formaldehyde or betapropiolactone? Very tiny amounts of these substances may be present in the vaccine as a result of the production process.

If the answer to any of the following questions is "YES", tell your doctor or nurse as vaccination may need to be delayed

- Do you feel feverish?
- Do you have any illness or infection?

If the answer to any of the following questions is "YES", tell your doctor or nurse as vaccination may not be recommended. Your doctor or nurse may still advise you to be vaccinated but the protection against influenza may not be as good as in other people

- Are you receiving any treatment that lowers your resistance to infections? For example, are you taking high dose steroids by mouth or injections, having radiotherapy, or having drugs used for treating cancer?
- Do you have a medical condition that lowers your resistance to infection?

Using other medicines

Please tell your doctor or nurse if you are taking or have recently taken any other medicines, including those that have not been prescribed. Unless they tell you otherwise, you should continue to take your usual medicines before and after having Fluvirin®

The results of tests for HIV, hepatitis C or a virus called HTLV1 may be affected for a short while if the test is carried out soon after vaccination. Other tests can be performed to get the right answer.

Other vaccines may be given at the same time as influenza vaccine provided that separate needle and syringes are used and that the injections are made into separate body sites.

Pregnancy

The vaccine may be given from about month 4 onwards of pregnancy and may be given in the first three months if your doctor or nurse thinks you might be at particular risk of problems if you caught influenza.

Breast-Feeding

Fluvirin® may be given during breast-feeding.

Driving and using machines.

Fluvirin® is unlikely to produce an effect on your ability to drive or operate machinery. However if you feel unwell following vaccination, it is advisable not to drive or operate any tools or machines until you feel well again.

3. HOW IS FLUVIRIN® GIVEN

Your doctor or nurse will inject Fluvirin®

Adults and children over 4 years of age are given a single injection of half a millilitre of the vaccine deep under the skin or into a muscle (usually in the arm).

For children who have not previously been vaccinated, a second injection should be given at least 4 weeks after the first to improve protection.

If you receive more FLUVIRIN® than you should:

Because Fluvirin® will be given by a doctor or nurse who has been trained to give vaccines, it is very unlikely that you will be given too much vaccine or that you will receive more then one dose. If you think that you may have been given too much or had an extra dose that was not needed, talk to your doctor or nurse about this.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Fluvirin® can cause side effects, although not everybody gets them.

The most common side effects with Fluvirin® are local reactions at the injection site and/or influenza-like symptoms.

As with all vaccines, severe allergic reactions can occur rarely or very rarely following vaccination. These can involve difficulty breathing, low blood pressure and loss of consciousness in the most severe cases.

These symptoms usually occur very soon after vaccination and your doctor or nurse should be trained and equipped to deal with these side effects. If you have any of these symptoms after leaving the place of vaccination you should get medical help immediately.

Common side effects (reported by less than 1 in 10 but more than 1 in 100 people) include:
- Local effects at the site of injection such as redness, swelling, pain, bruising or hardness
- High temperature, shivering, tiredness, headache, sweating, muscle pain, joint pain and generally feeling unwell.

These side effects usually disappear within one or two days.

Uncommon side effects (reported by less than 1 in 100 but more than 1 in 1,000 people) include:
- Widespread skin reactions such as itching and red or lumpy rashes

Rare side effects (reported by less than 1 in 1,000 but more than 1 in 10,000 people) include:
- Pins and needles
- Sharp pain in or along a nerve
- Fits
- A low platelet count in the blood which can result in bleeding or bruising for a short period.

Very rare side-effects (reported by less than 1 in 10,000 people) include:
- Inflammation of the blood vessels which can cause skin rashes, joint pain and kidney problems
- Problems with the brain and nerves such as inflammation and a loss of movement.

If you notice any of these side effects, or other changes in your health after receiving the vaccine, TELL YOUR DOCTOR, NURSE OR PHARMACIST IMMEDIATELY.

5. HOW TO STORE FLUVIRIN®

Keep out of the reach and sight of children.

Store in a refrigerator (2°C to 8°C). Store in the original package to protect from light.

Do not freeze.

Do not use Fluvirin® after the expiry date which is stated on the carton and the syringe label. The expiry date refers to the last day of the month.

6. FURTHER INFORMATION

What Fluvirin® contains:

This vaccine does not contain any live viruses. The active ingredients of the vaccine are purified proteins (termed haemagglutinin and neuraminidase) from the three types of viruses in the vaccine.

The three types of virus in the vaccine for the 2006/2007 winter season have been recommended by the World Health Organisation (northern hemisphere), and comply with the European Union decision. They are:

- A/New Caledonia/20/99 (H1N1) - Like strain (A/New Caledonia/20/99 IVR-116) 15 micrograms haemagglutinin
- A/Wisconsin/67/2005 (H3N2) - Like strain (A/Wisconsin/67/2005 NYMCX-161-B) 15 micrograms haemagglutinin
- B/Malaysia/2506/2004 - Like strain (B/Malaysia/2506/2004) 15 micrograms haemagglutinin

The other ingredients in the vaccine are disodium hydrogen phosphate, potassium dihydrogen phosphate, sodium chloride and water for injection.

One dose (half a millilitre or 0.5 ml) of the vaccine contains at least 15 micrograms (a very small amount) of protein of each type of virus.

What Fluvirin® looks like and contents of pack:

Fluvirin® is a suspension for injection which is supplied in a single dose 0.5ml syringe.

Marketing Authorisation Holder and Manufacturer is:

Novartis Vaccines and Diagnostics Limited,
Gaskill Road, Speke,
Liverpool L24 9GR,
United Kingdom.
Tel: 0151 705 5000
Fax: 0151 705 5018
E-mail: serviceuk@chiron.com

This leaflet was last approved in: June 2006

This leaflet does not contain the complete information about your vaccine. If you have any questions or are unsure of anything, ask your doctor who has access to additional information.

This leaflet only applies to the product Fluvirin® for which it has been prepared.

Fluvirin® is a registered trademark of Novartis Vaccines and Diagnostics Limited.

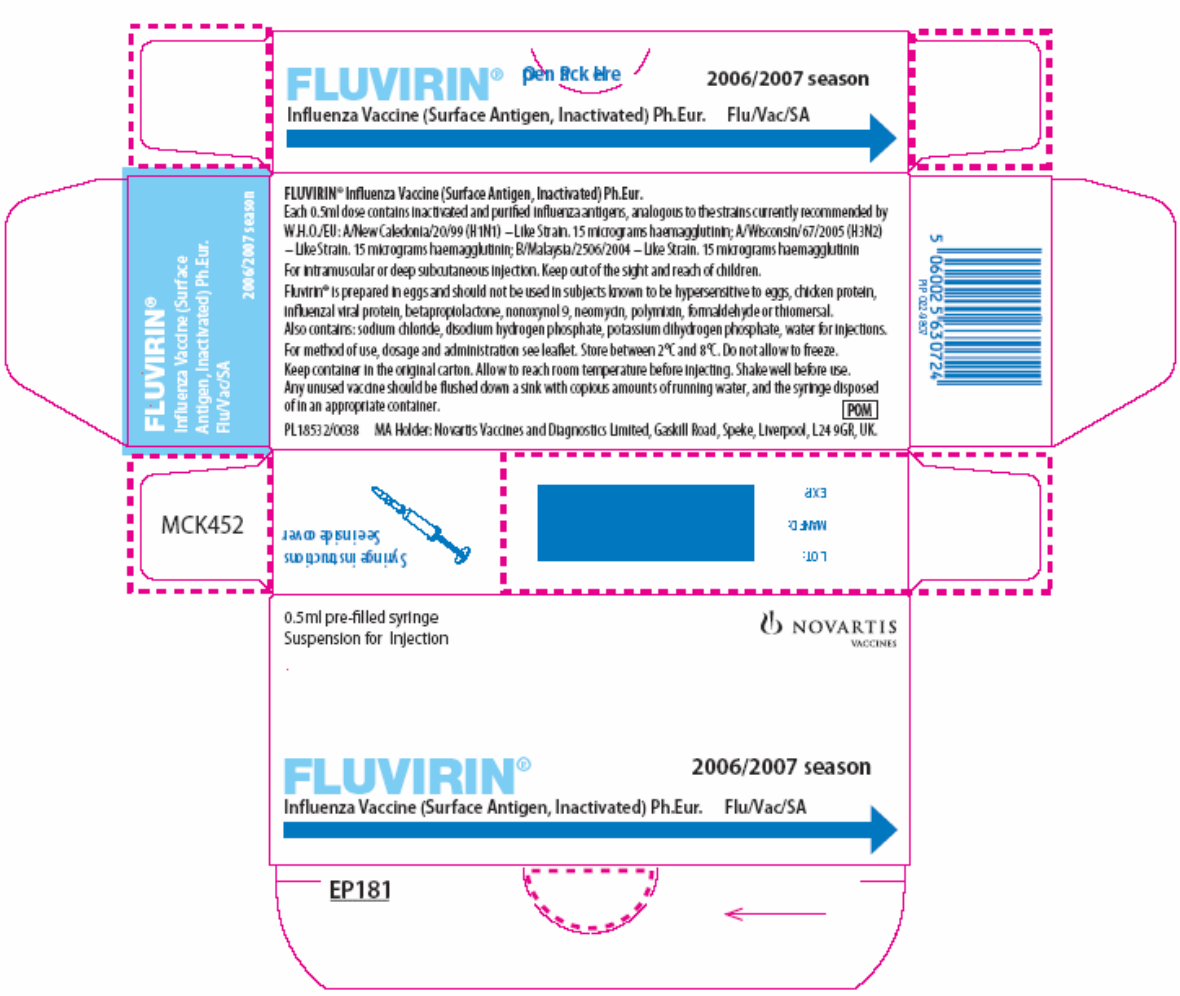
Labelling

FLUVIRIN

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

PL 18532/0038-39

Carton



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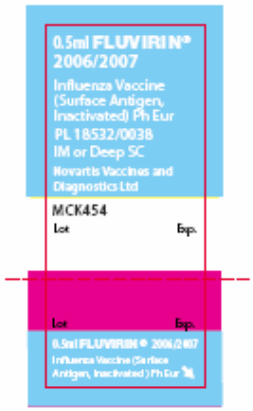

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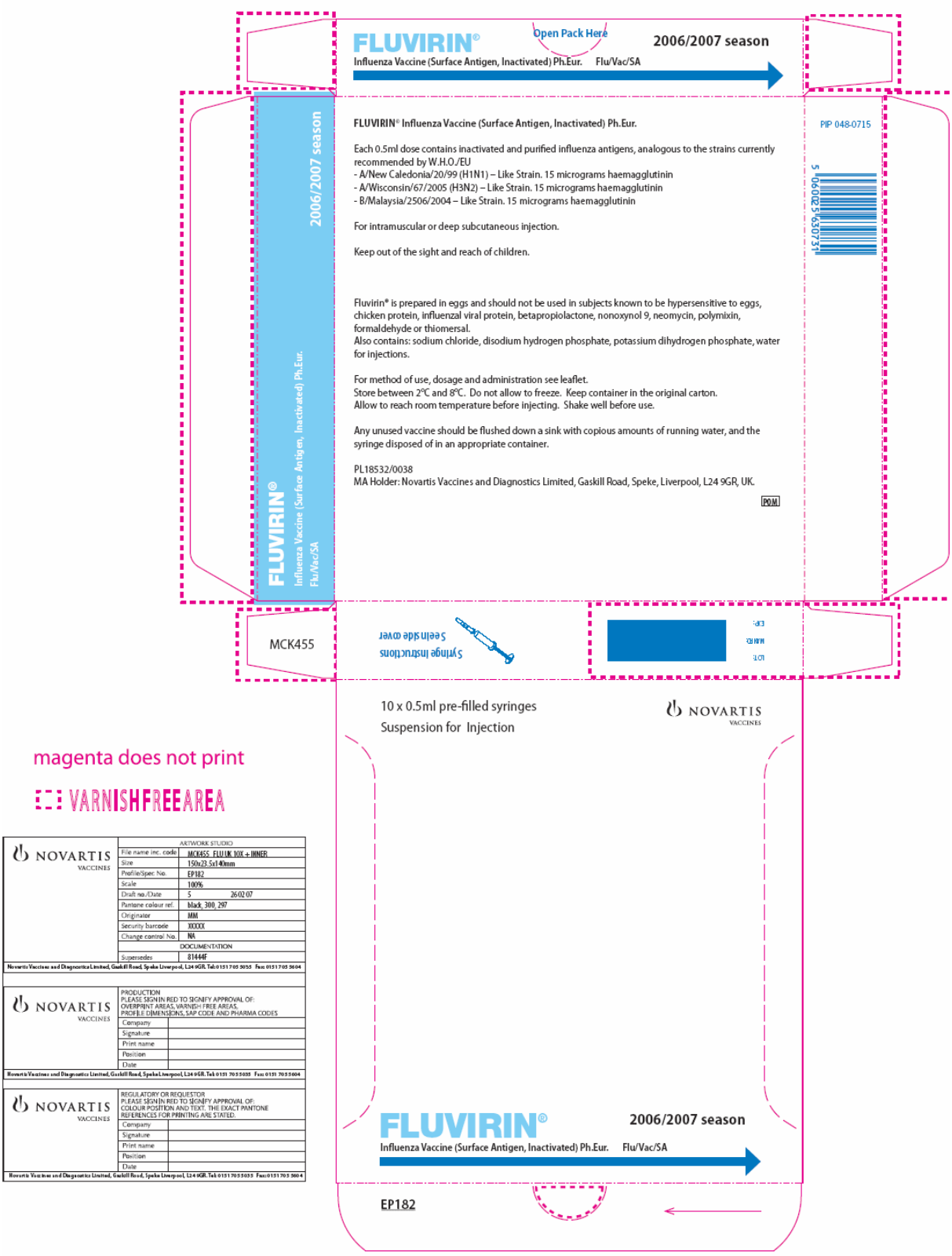

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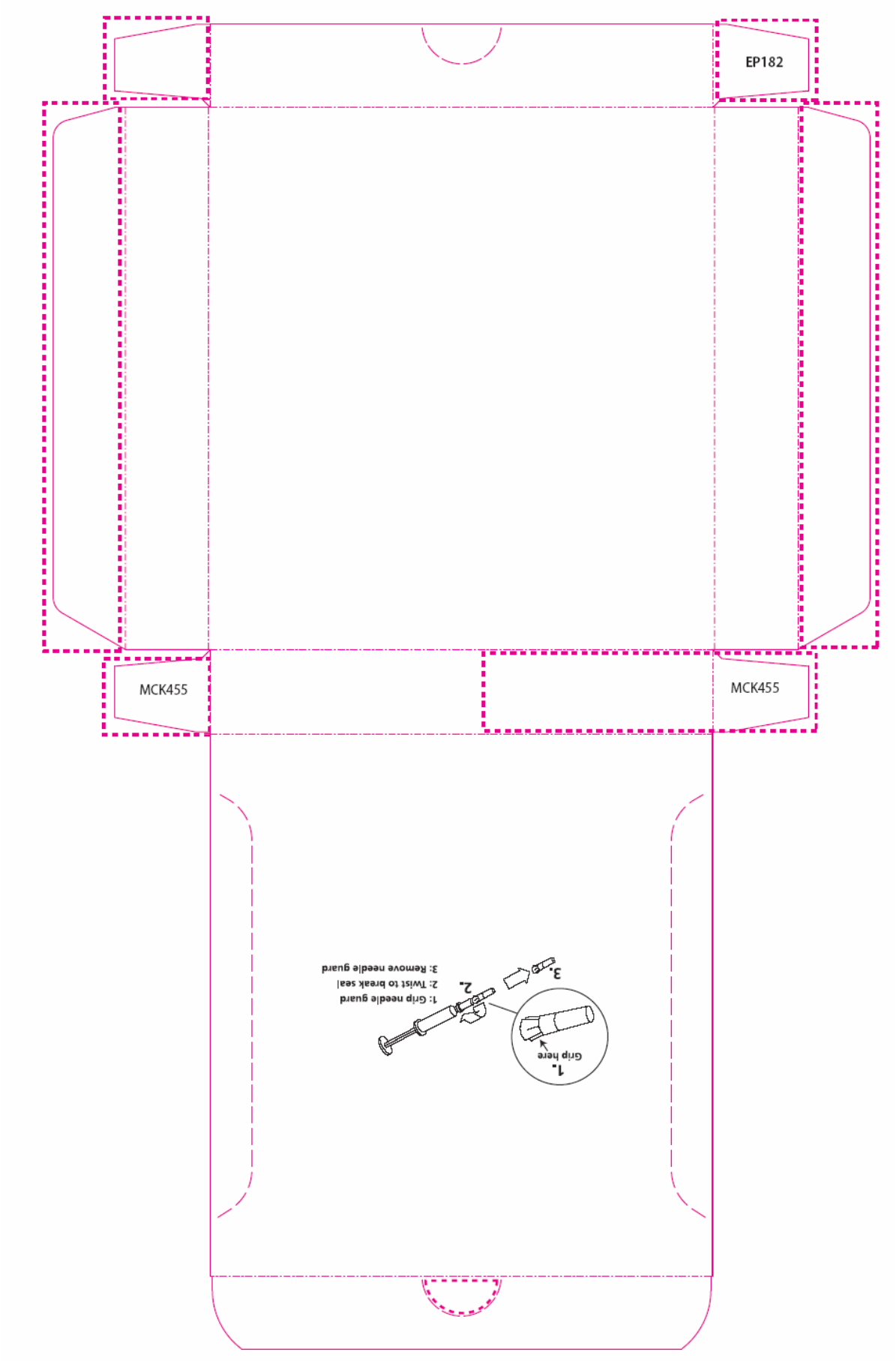
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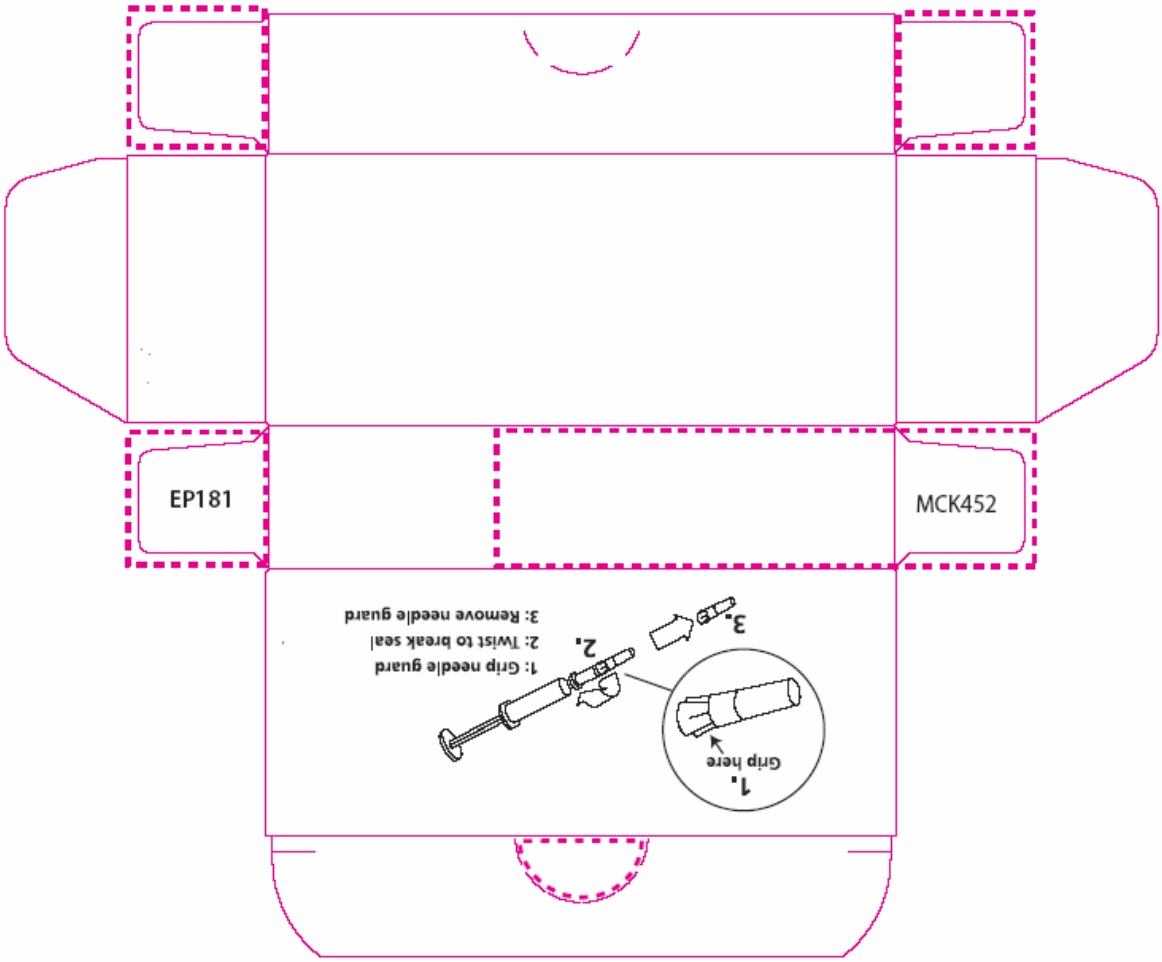

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