PUBLIC ASSESSMENT REPORT
FOR
Begrivac®

Common Name: Influenza Vaccine, Split Virion, Inactivated

Application No. 2C 90009/52 (NB)

Assessment Report as adopted by the TFDA with all information of a commercially confidential nature deleted
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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Biogenetech Co., Ltd. submitted on October 20, 2009 an application for Marketing Authorization to the Thailand Food and Drug Administration (TFDA). At the time of submission and validation, Begrivac® was designated as medicinal product in the following indication: For prophylaxis of influenza, especially in those who run an increased risk of associated complications.

The legal basis for this application refers to: Drug Act 2510 B.E.

The application submitted was a complete dossier: composed of administrative information, complete quality data, non-clinical and clinical data based on applicants’ own tests and studies and bibliographic literature substituting/supporting certain tests or studies.

Licensing status:

The product was licensed in European countries like Austria, Belgium, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Norway, Poland, Sweden and United Kingdom including the countries in the other continents like Argentina, Chile, Colombina, Czech Republic, Iran, Mexico, New Zealand, Peru, Russian Federation, Slovakia, Slovenia and Trinidad and Tobago at the time of submission of the application.

TFDA Product Team Leader: (PTL)
Ms. Prapassorn Thanaphollert

1.2 Steps taken for the assessment of the product

- The application was received by the TFDA on October 20, 2009
- The procedure started on October 20, 2009
- A List of questions, the overall conclusion and review of the scientific data were prepared by the TFDA’s PTL and sent to the applicant on November 2009
- The applicant submitted of the responses, including revised SPC, labeling and package leaflet texts in English and/ or Thai (where required by Drug Act) on December 9, 2009
- TFDA prepared preliminary Assessment Report based on responses from the applicant and dispatched the assessment report to external experts for their consideration and comments on December 15, 2009.
2. SCIENTIFIC DISCUSSION

2.1 Introduction

Influenza is a highly contagious acute respiratory illness, and a major cause of morbidity and mortality worldwide. The disease typically presents with an abrupt onset of a broad range of symptoms like various respiratory syndromes, fever, chills, malaise, fatigue and myalgia. Lower respiratory tract complications like primary viral pneumonia or secondary bacterial pneumonia, cardiac complications and the exacerbation of chronic bronchitis and asthma are responsible for a substantial increase in hospitalization and deaths.

According to the WHO, in annual influenza epidemics 5-15% of the population are affected with upper respiratory tract infections. Hospitalization and deaths mainly occur in high-risk groups, i.e. for example in the elderly and chronically ill. Although it is difficult to assess, these annual epidemics are thought to result in between three and five million cases of severe illness and between 250,000 and 500,000 deaths every year around the world. Most deaths currently associated with influenza in industrialized countries occur among the elderly over 65 years of age.

In Thailand, there are 2 types of influenza vaccine registered and used in the market.

1. Split influenza vaccine (Combination of surface antigen and internal antigen)
2. Subunit influenza vaccine (Purified surface antigen, no internal antigen). Some subunit vaccine has also been developed by adding the adjuvant in order to use in the elderly or produced by virosome technology.

2.2 Quality aspects

Introduction

**Begrivac®**, the influenza vaccine, is a trivalent inactivated viral vaccine, which belongs to the pharmacotherapeutic group of J07BB02 vaccines (ATC CODE).

Begrivac® is a sterile, aqueous suspension for injection of influenza virus, type A and B, grown individually in fertilized hen’s eggs, inactivated and treated so that the integrity of the virus particles has been disrupted without diminishing the antigenic properties of the haemagglutinin and neuraminidase antigens.

Active Substance

Each dose (0.5 ml) contains:

- Final draft of English SPC, labeling and package leaflet was sent by applicant to the TFDA PTL on June 1, 2010.
- TFDA adopted the decision on marketing authorization on June 11, 2010.
A/Brisbane/59/2007 (H1N1) like strain used
(A/Brisbane/59/2007, Reass. IVR-148) 15 micrograms HA*
A/Brisbane/10/2007 (H3N2) like strain used
(A/Uruguay/716/2007, Reass. NYMC X-175C) 15 micrograms HA*
B/Brisbane/60/2008 like strain used
(B/Brisbane/60/2008) 15 micrograms HA*

*haemagglutinin

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<td>Emil-von-Behring Str. 76</td>
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<td>D-35041 Marburg Germany</td>
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<tr>
<td>Loc. Belleria 53018 Rosia Italy</td>
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<tr>
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<tr>
<td>87000 Limoges France</td>
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<td>Catalent UK Packaging Limited</td>
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<tr>
<td>Sedge Close, Headway, Great Oakley, Corby, Northamptonshire, NN18 8HS, United Kingdom</td>
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<td>Packaging</td>
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I. DRUG SUBSTANCE(S)

1. General Information, Starting Materials and Raw Materials
Begrivac® is an influenza vaccine, split virion, inactivated. It is a sterile, aqueous suspension for injection of influenza virus, type A and B, grown individually in fertilized hen’s eggs, inactivated and treated so that the integrity of the virus particles has been disrupted without diminishing the antigenic properties of the haemagglutinin and neuraminidase antigens.

2. Manufacturing Process of the Drug Substance(s)
2.1 Seed Virus Process
Primary Seed Virus
Seed virus for the production of the vaccine is manufactured using the seed virus system recommended by World Health Organization (WHO) and European Union (EU), obtained by NIBSC or an equivalent institute recognized by WHO. Seed virus is inoculated in the SPF eggs under specified temperature and humidity. The strain is subjected to further passaging on SPF eggs for further adaptation to the production system.
Working Seed
The working seed is then prepared from SPF eggs with the optimal propagation parameters and filled into ampoules. Determining the suitable working dilution in order to achieve the maximum virus titre. Finally, pass the working seed lot for quality control.

2.2 Monovalent Bulk Process
The seed virus passes to the inoculation, incubation, harvest, filtration, concentration, ultrafiltration, purification and disruption. The treated concentrate is diluted and filtrated. Inactivate the monovalent bulk and transport the qualified bulk to the blending unit.

3. Characterization of the Drug Substance(s)
Characterization of Haemagglutinin and Neuraminidase at the Seed Virus level is performed at an external competent institute certified by WHO. Impurity tests are performed to determine manufacturing process related impurities or residuals of manufacturing.

4. Quality Control of the Drug Substance(s)
Several tests are included in drug substance specification. Appropriate validation data have been submitted in support of the test procedures.
5. **Reference Standards or Materials**
All antisera reagents as well as antigen reagents for all three influenza virus strains use for haemagglutinin antigen content test were supplied by the National Institute for Biological Standards and Control (NIBSC), UK.

6. **Packaging and Container Closure System of the Drug Substance(s)**
Monovalent bulks are stored in the bottles.

7. **Stability of the Drug Substance(s)**
The stability test of Monovalent Bulks of Begrivac are performed according to ICH Q1A, “Stability Testing of new Drug Substances and Products” and ICH Q5C “Stability Testing of Biotechnological/Biological Products”.
3 Lots of each monovalent bulk are tested at the temperature of +2 to +8 °C.

II. **DRUG PRODUCT**

1. **Description and composition of the Drug Product**
Begrivac® is an influenza vaccine, split virion, inactivated without preservative. It is a suspension for injection in pre-filled syringe. Each dose (0.5 mL) of Begrivac contains: Purified antigens from 3 influenza virus strains (A/H1N1, A/H3N2 and B), Sucrose, Buffer Solution (Sodium Chloride, Potassium Chloride, Magnesium Chloride Hexahydrate, Disodium Phosphate Dihydrate, Potassium Dihydrogen Phosphate) and Water for Injection

2. **Pharmaceutical Development**
Monovalent Bulks of the strains annually recommended by WHO or European Union are used to formulate Begrivac®. Excipients used to formulate Begrivac are sucrose, buffer solution (sodium chloride, potassium chloride, magnesium chloride hexahydrate, disodium phosphate dihydrate, potassium dihydrogen phosphate and water for injection)
The manufacturing process is properly designed and carried out in accordance with GMP.

3. **Manufacturing Process of the Drug Product**
Calculated the amount of monovalent bulks. Blending of three monovalent bulks with phosphate buffer solution to produce final bulk and filling into the final container.
4 Control of the Adjuvant(s), Preservative(s), Stabilizer(s), and Excipients(s)

All excipients are controlled by the specification according to the requirements in the European Pharmacopoeia. Only excipients tested and released by the Quality Control Department/Production Department are used for the production of Begrivac®.

5 Quality Control of the Drug Product

Several tests are included in drug product specification. Appropriate validation data have been submitted in support of the test procedures.

6 Reference Standards and Materials

All antisera reagents as well as antigen reagents for all three influenza virus strains used for hemagglutinin antigen content test were supplied by the National Institute for Biological Standards and Control (NIBSC), UK.

7 Packaging and Container Closure System of the Drug Product

Begrivac is filled in glass syringe with or without needle and with or without paediatric dose mark (PDM).

8 Stability of the Drug Product

The stability test of Begrivac® are performed according to ICH Q1A, “Stability Testing of new Drug Substances and Products” and ICH Q5C “Stability Testing of Biotechnological/Biological Products”. According to the stability results, the shelf life for Begrivac is 12 months at the temperature of +2 to +8 °C.

III. APPENDICES

The following information may be needed on a case by case basis.

1 Equipment and Facilities

2 Evaluation of the Safety of Adventitious Agents
The TFDA recommended on The Quality Dossiers as The followings:

**Drug substance**

1. SOP of some test methods of drug substance shall be additionally submitted.
2. Information about the source and quality control of fertilized eggs for the production of the influenza vaccine including the certificate from the health authority to perform the control information of such chicken flocks shall be additionally submitted.
3. Qualification of contract poultry farm shall also be submitted.
4. Test report of the completeness of inactivation and analytical method validation of SRD assay of some virus strains shall be substituted with the report of the current strain of virus.
5. The specification, control, test report and COA of the container closure system for drug substance shall also be submitted.
6. The stability data of the drug substance shall be updated and completed up to 9 months.
7. The data to confirm the absence of adventitious agents of vaccine shall also be submitted.
**Drug product**

1. The free sale certificate for Thailand, COA of sucrose, English translation of the certificate of lot release issued by German health authority shall also be submitted.
2. SOP of some test methods of drug product shall be additionally submitted.
3. The analytical results of some test methods shall be additionally submitted.
4. The system suitability of the HPLC test methods shall be additionally submitted.
5. The analytical report of the primary packaging of drug product shall also be submitted to confirm the amount of ethylene oxide residue.
6. Updated stability data up to 12 months shall also be submitted. In case it is not yet available, the accelerated stability data for 6 months can be submitted together with the commitment letter to confirm that 12 months long term stability data will be submitted as soon as it is available. Moreover, as much as stability data of the current strain shall also be submitted.
7. Freezing point of vaccine needed to be defined.
8. Critical process validations e.g. purification, inactivation, splitting efficiency should be submitted.
9. The shipment validation from production to filling site and also stability study of final bulk should be performed.
10. The shipment validation study was submitted but in worst case conditions, the study under continuous outside ambient temperature of +43°C and -5°C for at least 48 hours should also be considered.
11. Request for the clarification why the samples used for the stability study shall be prior kept at 25°C for 5 days.
12. Request for the clarification about the HA content specification.
The company responded to the above recommendations as the followings:

**Drug substance**

1. SOP of some test methods of drug substance is being translated. The company committed to submit it as soon as the translation is finished.
2. Information about the source and quality control of fertilized eggs for the production of the influenza vaccine including the certificate from the health authority to perform the control information of such chicken flocks were submitted.
3. Qualification of contract poultry farm was submitted.
4. Test report of the completeness of inactivation and analytical method validation of SRD assay of some virus strains was updated.
5. The specification, control, test report and COA of the container closure system for drug substance were submitted.
6. The 9 months stability data of the drug substance was submitted.
7. The data to confirm the absence of adventitious agents of vaccine was submitted.
Drug product
1. The free sale certificate for Thailand, COA of sucrose, English translation of the certificate of lot release issued by German health authority were submitted.
2. SOP of some test methods of drug product is being translated. The company committed to submit it as soon as the translation is finished.
3. The analytical results of some test methods were submitted.
4. The system suitability of the HPLC test methods was submitted.
5. The analytical report of the primary packaging of drug product to confirm the amount of ethylene oxide residue was submitted.
6. Updated stability data up to 12 months of the previous strain was submitted. By the way, the manufacturer committed to submit the completed stability data of the current strain to Thai FDA as soon as it is available.
7. Critical process validations e.g. purification, inactivation, splitting efficiency were submitted.
8. The shipment validation from production to filling site was submitted.
9. The shipment validation of the packaging for international transport will be provided as soon as it is available.
10. Clarification why the samples used for the stability study shall be prior kept at 25°C for 5 days was provided.
11. Clarification about the HA content specification was provided.

TFDA PTL AND EXTERNAL EXPERT’S OVERALL CONCLUSIONS ON QUALITY ASPECTS

All documents are completed and the dossier can be accepted with the following conditions.

1. The missing analytical test methods in details, packaging validation for international transport shall be additionally submitted after their preparation is finished.
2. The LCL (p=0.95) of the HA content shall be reported on the COA or summary of production and quality control.
3. The 12 months long term stability data can be additionally submitted later after it is available. During this period, 12 months shelf life can be temporarily applied with the product.

BASED ON THE RESULTS THESE QUALITY ASPECT COULD BE ACCEPTED

2.3 Non Clinical aspects

Introduction
I. PHARMACOLOGY
   1. Pharmacodynamic studies (immunogenicity of the vaccine)
      Not applicable.
   2. Pharmacodynamic studies of adjuvant(s) (if applicable)
      Not applicable.

II. PHARMACOKINETICS
    Not applicable.

III. TOXICOLOGY
    1. General toxicology
       Nonclinical toxicology testing was conducted in mice, rats, rabbits by using 3 different
       formulations or 3 different lots of vaccine which had the trivalent antigens concentration. The
       vaccine was subcutaneously injected by single time. After 14 days, considered the effect found
       from the animals. In the rabbits, the manufacturer also checked with the skin thickness.

       After testing finished, there were no treatment-related effects to any in-life parameters. None of
       animal died or has the adverse effects. Body weight again of all animal was normal. None of
       pathological findings was found. No change of skin thickness in the rabbits receiving 0.5 ml of each
       vaccine formulation. This can conclude that all animals well tolerated with 3 formulations/lots of
       Begrivac®.

       With the safety record from 30 years of clinical experience of Begrivac®, none of other nonclinical
       testing studies have been requested.

    2. Special toxicology for vaccines (when applicable)
       Not applicable.

    2.1 Special immunological investigations
       - Toxicity studies in special population
         Not applicable.
       - Genotoxicity and carcinogenicity studies, when applicable
         Not applicable.
       - Reproductive toxicity studies for vaccines to be administered to pregnant
         women or individuals of fertile age.
         Not applicable. From the post marketing surveillance, no report of adverse fetal and maternal
         outcomes was found.
3. SPECIAL CONSIDERATIONS (if applicable)

3.1 Live attenuated vaccines.
Not applicable as Begrivac is inactivated vaccine

3.2 New substances incorporated into the formulation
None of new substances are used in vaccine formulation.

4. TFDA PTL AND EXTERNAL EXPERT’S COMMENTS ON THE SPC, LABELS AND PACKAGE LEAFLET
The labels are acceptable.
Only the SPC is available. The English contents of SPC are acceptable. Only some of Thai translation should be additionally revised.

5. TFDA PTL AND EXTERNAL EXPERT’S OVERALL CONCLUSIONS ON NON-CLINICAL ASPECTS
Based on the acute toxicity study in the animal and the data from the post marketing surveillance report, this vaccine is safety and efficacy and the registration dossier can be accepted. By the way, there shall also be the additional revision or feedback for the following points.
1. The HI titer performed in the summary of clinical studies shall be corrected.
2. Request of the documents to confirm if there is the release testing for Begrivac® 2009/2010.
3. Request the importer to do the post marketing surveillance and send the report to Thai FDA every 6 months.

BASED ON THE STUDIES DESIGN AND RESULTS THESE NON-CLINICAL ASPECT COULD BE ACCEPTED

2.4 Clinical aspects

Introduction

1. REPORTS OF CLINICAL STUDIES
1 Phase I Studies
Acute toxicity study in mice, rats and rabbits was conducted for both male and female animals. 3 Different lots of vaccines which had the trivalent antigens concentration were used in the study. The vaccine was subcutaneously injected by single time. After 14 days, considered the effect found from the animals. In the rabbits, the manufacturer also checked with the skin thickness.
2 Phase II Studies
Not available.

3 Phase III Studies

4 Special Considerations
From the multiple immunization, the interaction between the antigen and the antibody in the circulation does not have an effect to the vaccine protection. By the way, the high antibody titre may interfere the antibody production effect of the vaccine antigen.

5 Adjuvant(s)
None of adjuvant was used.

6 Phase IV Studies and/or Pharmacovigilance plan (if applicable)
Million doses of Begrivac® was distributed in 2008-2009. The post marketing surveillance conducting by 2 phases (May-August 2008 and September 2008-April 2009) confirm the safety of vaccine.

7 Non-inferiority Studies (for combined vaccines, or approved vaccines prepared by new manufacturers)
Not applicable.

8 Co-administration Studies with other Vaccines
From the PSUR during May-August 2008 of Begrivac 2007/2008, it can only be concluded that Begrivac 2007/2008 can be given at the same time as other vaccines but it shall be given to the different injection site.

2. TFDA PTL AND EXTERNAL EXPERT’S COMMENTS ON THE SPC, LABELS AND PACKAGE LEAFLET
The labels are acceptable.
Only the SPC is available. The English contents of SPC are acceptable. Only some of Thai translation should be additionally revised.

3. TFDA PTL AND EXTERNAL EXPERT’S OVERALL CONCLUSION ON CLINICAL ASPECTS
This vaccine has been manufactured according to the international standard and has been registered in many countries. The vaccine composition conforms with WHO recommendations. Therefore, it can be acceptable to register and market in Thailand.

BASED ON THE STUDIES DESIGN AND RESULTS THESE NON-CLINICAL ASPECT COULD BE ACCEPTED

2.5 Pharmacovigilance (If applicable)

2.6 Overall Conclusion on Risk/benefit Assessment and Recommendation

Recommendations

The TFDA and external experts have reviewed the clinical studies and found them evidently supportive; therefore positive opinion was given towards the approval of marketing authorization of Begrivac® with 1, 2 or 3 conditions requesting the applicant to additionally submit and conduct:

1. The missing analytical test methods in details, packaging validation for international transport shall be additionally submitted after their preparation is finished.
2. The LCL (p=0.95) of the HA content shall be reported on the COA or summary of production and quality control.
3. The 12 months long term stability data can be additionally submitted later after it is available.
4. The applicant shall conduct a clinical phase IV study as under Safety Monitoring Program (SMP) for a period of two years.