Title: Post-Marketing Surveillance Study on NesinaAct Tablet®

NCT Number: NCT04980014

Protocol Approve Date: 31-JAN-2018

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

PROTOCOL

NesinaAct Tablet ®

(NesinaAct Tablet)

Post Marketing Surveillance Protocol

Sponsor: Takeda Pharmaceuticals Korea Co,. Ltd.
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Compound: Nesina Act Tab.(Alogliptin Benzoate+ Pioglitazone HCl)

Date: 31-JAN-2018

Amendment History: Amendment 3.2

TABLEOF CONTENTS

1. Summary of product under re-examination

1.1 Product Name

- NesinaAct Tablet 12.5/30mg, 12.5/15mg, 25/30mg, 25/15mg

1.2 Re-examination period

- 24 Oct 2014~ 30 May 2019

1.3 Approval Number

- NesinaAct Tablet 12.5/30mg : 96
- NesinaAct Tablet 12.5/15mg : 97
- NesinaAct Tablet 25/30mg : 95
- NesinaAct Tablet 25/15mg : 94

1.4 Date of approval

- 24 October 2014

2. Safety Information

2.1 Information under development

Overall, 1783 subjects have been enrolled in phase 1 clinical trials (clinically completed trials for which a study report has been submitted to a regulatory authority) and 17,547 subjects have been enrolled in phase 2/3 clinical trials with alogliptin monoproduct, alogliptin FDC with pioglitazone or alogliptin FDC with metformin based upon actual exposure data from completed studies and enrollment at time of data lock point (DLP) for ongoing clinical trials.

2.2 Information on similar agents

Alogliptin is a potent, highly selective orally-available, quinazolinone-based, inhibitor of serine protease dipeptidyl peptidase-4 (DPP-4) developed to treat patients with type 2 diabetes mellitus (T2DM). The alogliptin monoproduct is available in oral tablet form in dosages of 6.25 mg, 12.5 mg and 25 mg. Not all strengths may be approved in all markets.
Pioglitazone hydrochloride, [(±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-] thiazolidinedione monohydrochloride, is an insulin sensitivity enhancer. Alogliptin fixed-dose combination (FDC) product with pioglitazone is available as an agent to treat patients with T2DM as oral tablets containing either 12.5 mg or 25 mg of alogliptin with either 15 mg, 30 mg or 45 mg of pioglitazone. Not all strengths may be approved in all markets.
Metformin, 1,1-dimethylbiguanide hydrochloride, improves glucose tolerance in patients with T2DM, lowering both basal and postprandial plasma glucose. Alogliptin FDC with metformin is available as an agent to treat patients with T2DM as an oral tablet containing 12.5 mg of alogliptin with 500 mg, 850 mg or 1000 mg of metformin. Not all strengths may be approved in all markets.

2.3 Information on experiences of the use in each country

In this PSUR (covering period 16 October 2013 to 15 October 2015), all data obtained during the reporting period as well as cumulative adverse drug reaction data have been reviewed. The review of cumulative data revealed no new safety concerns. No changes in characteristics of listed or unlisted adverse drug reactions or increase in reporting frequency associated with alogliptin monoproduct, alogliptin FDC with pioglitazone or alogliptin FDC with metformin were identified. No new significant information on drug interactions, experience with overdose, drug abuse or misuse, experiences during pregnancy or lactation, experience in special patient groups or effects of long term treatment, consumer reports or prescription errors was brought to the attention of Takeda during the reporting period.

2.4 Overseas approval and sales status

- See Appendix.

3. PMS OBJECTIVES

This surveillance is to evaluate the safety and effectiveness of NesinaAct therapy in real-world setting for its approved indications.

3.1 Primary Objective

The primary objective of this surveillance is to estimate the proportion of all adverse events (AEs) including serious adverse events (SAEs) and serious adverse drug reactions (SADRs) in patients who are treated for type 2 diabetes mellitus under NesinaAct therapy with a dose of 12.5/30mg, 12.5/15mg, 25/30mg, 25/15mg (alogliptin/pioglitazone) once daily by physicians in the real-world clinical practice setting over a period of 26 weeks.

① Serious AEs(SAEs) and Serious ADRs(SADRs)
② Unexpected AEs and ADRs that are not mentioned in precautions.
③ ADRs that are already known.
④ Non-serious Adverse Drug Reaction (ADR)
⑤ Other safety-related information (influence upon laboratory values, etc.)

3.2 Secondary Objective

The secondary objectives of this surveillance are to monitor in this cohort of patients from baseline to endpoint (at 26 weeks):

- HbA1c
- Fasting serum glucose
- Lipid profile
- Body weight
- Blood Pressure

4. SUBJECT POPULATIONS

4.1 Inclusion Criteria

This product will be given to Type 2 Diabetes Mellitus subjects aged 19 years old or older who sign and date a written, informed consent form and who are eligible for the combination of Alogliptin and Pioglitazone as an adjunct to diet and exercise to improve glycemic control and with one of the following criteria:

① For subjects inadequately controlled on diet and exercise

② For subjects inadequately controlled on metformin alone

③ For subject inadequately controlled on pioglitazone alone

④ For subject inadequately controlled on metformin and pioglitazone combination therapy

⑤ For subject switching from alogliptin co-administered with pioglitazone

4.2 Exclusion Criteria

① Patients treated with study drug outside of the locally approved label in Korea

② Patients with contraindication for the use of study drug (as described in the Korean product label)

5. THE NUMBER OF SUBJECTS

In accordance with the guidelines provided by the MFDS(Ministry of Food and Drug Safety), at least 600 subjects will be enrolled. The objective of the re-examination system in Korea is to reconfirm the clinical safety and effectiveness of NesinaAct through collecting, reviewing, identifying, and verifying the safety and effectiveness information about NesinaAct in general practice for 600 subjects during re-examination period following Korean regulations.

Subjects will be enrolled by a continuous registration method. Subjects who agree to participate in this study will sign the Informed Consent Form. Treatment with NesinaAct may be stopped at anytime and for any reasons according to subject's or investigator's intention, and the reason for discontinuation of NesinaAct (if applicable), shall be entered in CRF.

In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the next planned visit as per protocol schedule.

6. EXPECTED SURVIELLANCE PERIOD

This drug has been approved for marketing by Ministry of Food and Drug on 24 October 2014 and has been designated to conduct the PMS to 30 May 2019, according to the examination period of Nesina™ Tab, a single agent.
As required for any new medicine approved by MFDS, safety and effectiveness should be evaluated in the setting of routine practice during the re-examination period of from the approval date.

① Re-examination period: 24 Oct 2014 ~ 30 May 2019
② Re-examination application period: 31 May 2019 –30 August 2019

7. EXPECTED SURVEILLANCE INSTITUTIONS

Takeda will select more than 10 medical institutions(Department of internal medicine, Family medicine, etc.) which include the staff who have expertise in the treatment of type 2 diabetic subjects who can sufficiently fulfill the objectives of the surveillance and request for surveillance after signing a written contract. The investigators will be qualified representative physicians who provide care to patients with type 2 diabetes mellitus.

8. SURVEILLANCE ITEMS AND METHOD

8.1 Surveillance items

8.1.1 Site Information

① Name of Site
② Name of Department
③ Name of Investigator

8.1.2 Subject's basic information

① Subject Information : Subject Number, Signed Date of Informed Consent Form
② Demographic Information: Gender, Age, Pregnant and Breastfeeding (only for women), Height, Weight, Type of Treatment(Outpatient/Hospitalization),
③ Inclusion/Exclusion Criteria

8.1.3 Medical history of subjects

① First diagnosed date of T2DM
② Concurrent disease : Renal Impairment (Including Severity), Diabetes complications, Lifestyle related diseases, Liver disease (Including Severity), Kidney disease (Including Severity), Gastrointestinal disease, Cardio Cerebro-vascular disease, Allergic diseases (Including allergen), Malignant tumor and Others
③ Drinking and Smoking

8.1.4 Study drug administration status

Administration of study drug

① Start Date/Ongoing/Stop Date
② Daily dose
③ Daily frequency
④ Reason for Dose change/Stop of administration

Pre-treatment/Concomitant Medication

① Pre-treatments for T2DM for 12 weeks prior to study drug treatment
② Concomitant Medications prescribed during study drug treatment

- Presence/Absence of Concomitant Medication

- Product Name /Generic Name
- Daily Dose and Frequency
- Route of Administration
- Duration of Administration: Start Date/Stop date(or Ongoing)
- Purpose of Administration(such as Treatment(for T2DM and Concurrent disease), AE and Prevention)

8.1.5 Abnormal change in Laboratory data

Laboratory tests are not mandatory because of the non-interventional nature of this study. Check "Not done" on the eCRF if testing is not performed or there is not a tested item whose value is significantly changed to abnormal value after initiating Nesina Act. If laboratory result collected, record the following in detail:

- Presence/Absence of significant data in laboratory result
- Date of test before Nesina Act Tab administration
- Date of test after Nesina Act Tab administration
- Result of the laboratory test
- Unit of tested item Normal range of tested item
- Investigator's remarks

If abnormal change in clinical laboratory is related to an adverse event of the subject, the related details are recorded in Safety Surveillance Section Page on eCRF.

8.1.6 Safety assessment

① Body weight at baseline, 13 and 26 weeks after initiating Study drug

② Blood Pressure at baseline,13 and 26 weeks after initiating study drug

③ All AEs that occurred on the surveillance drug treatment or within 30 days after the end of the treatment, whether or not related to the drug, will be recorded. The safety assessment should include all undesirable changes of medical findings (including a clinical test finding) noted during medical visits as needed according to local practice guidelines and all AEs associated with the surveillance drug administration.
The following information should be included in the AE investigation:

- Occurrence of AE
- Name of AE
- Onset and stop date of AE
- Severity of AE
- AE of special interest
- Seriousness of AE
- Outcome of AE
- Causal relationship to the surveillance drug
- Causal relationship except the surveillance drug
- Actions taken to the surveillance drug due to AE
- Treatment of AE/details

- Investigator's remark

The time windows allowed for the scheduled visits will be ± 2 weeks. Follow up visits for safety assessment of subjects will be conducted via mail, phone or email.

8.1.7 Effectiveness assessment

① HbA1c at baseline, 13 and 26 weeks after initiating Study drug
② Fasting Plasma Glucose at baseline, 13 and 26 weeks after initiating study drug
③ Lipid profile at baseline, 13 and 26 weeks after initiating study drug

The time windows allowed for the scheduled visits will be ± 2 weeks.

8.1.8 Special population

Elderly(65 years or older), pregnant women, patients with renal impairment, and patients with hepatic impairment shall be categorized into specific subjects, and once data of such subjects are collected, their safety and effectiveness shall be analyzed additionally.

8.1.9 Long-term use subjects(for more than 26 weeks)

In this PMS, all patients taking the drug for more than 26 weeks shall be categorized into long-term use subjects, and their safety and effectiveness shall be analyzed. Among subjects of safety evaluation, at least 50% of long-term use subjects shall be secured.

8.1.10 Other subjects

If patients excluded from safety analysis are collected such as off label case, an AE occurred during the PMS period shall be additionally checked or separately analyzed as the case may be.

8.2 PMS Procedure

8.2.1 Surveillance request and agreement

To obtain the information of PMS data, the sponsor will execute the PMS agreement with applicable hospitals (related department or investigator). To reach the number of contracted cases, each investigator will sequentially enroll the first subject who meets the inclusion and exclusion criteria who receives this drug for the first time under the approval label by MFDS after the effective agreement date. The subjects will receive the treatment from the investigator in the routine medical setting.
The treatment with the study drug and PMS population should comply with the recommendations written in the local product information at the timing of enrollment (as the local product information may change).

8.2.2 Data collection

Each subject will be followed for a 26 week treatment period. Data will be collected at 13 weeks and 26 weeks after enrollment during standard of care office visits or email. All subjects will be evaluated for safety during the study drug use and for 30 days after their last dose to confirm the safety profile of the study drug under routine, daily practice or to learn of previously unsuspected adverse reactions. The decision about the duration and closure of treatment is solely at the discretion of the treating physician with agreement of the subject.

8.2.3 CRF collection and surveillance re-inquiry

Investigators will use an eCRF(electronic Case Report Form). Therefore, the investigator will record the enrolled subject's data on the eCRF during the surveillance. The assigned Data Management vendor will be responsible for checking entries for accuracy and will requery, if necessary.

8.2.4 Data retention

The investigator shall comply with local laws and regulations in relation to storage of records. The data on this PMS shall be retained for three years from the completion date of re-examination in compliance with Standard Operating Procedures of Takeda Pharmaceuticals Korea Co., Ltd.

All information on this PMS and patient's personal medical information arising out of this study shall be deemed confidential and the disclosure to the third party shall be prohibited unless permitted by the regulatory authorities and laws. This PMS data will be used for the submission to MFDS according to Standard for Re-examination of New Drugs, etc..

9. SAFETY REPORTING

9.1 Adverse Event Definitions

Adverse Event(AE) means any and all undesirable or unintended signs(including abnormal clinical laboratory values), symptoms, or diseases that are incurred when the drug is administered, and is not related to causal relationship with the drug.

Adverse Drug Reaction(ADR) means a harmful and unintended reaction resulting from usual administration and use of the drug, whose causal relationship with the drug cannot be excluded, and if causal relationship with the drug is unknown among AEs reported spontaneously, it is regarded as ADR.

Unexpected ADR means an ADR with difference in the nature or severity, specificity, or the outcome, compared to the product licensure/notification of the drug.

9.2 AE Assessment

9.2.1 Causality of Study drug

① Certain: it has reasonable temporal relationship with the drug, and it cannot be explained

with either drugs or chemical agents. Clinically acceptable response is shown at the drug discontinuation as well as it shows decisive response pharmaceutically or phenomenological when the drug resumes as necessary.

② Probable/likely: it has reasonable temporal relationship with the drug, and it is not likely caused by other drugs or chemical agents or concomitant diseases. Also clinically acceptable response is show when the drug discontinuation (no information about resumption)

③ Possible: it has reasonable temporal relationship with the drug, but it can be explained with other drugs or chemical agents or accompanied diseases. It has insufficient or unclear information about drug discontinuation.

④ Unlikely: it is a temporary case which does not seem to have causal relationship with the administration or use of the drug, and it can be reasonably explained with other drugs or chemical agents or underlying diseases.

⑤ Conditional/unclassified: there is a need to get more data for proper evaluation of causality of event. The investigators reviewing the additional data of event.

⑥ Unassessable /unclassifiable: there is not enough or conflicting information so the investigator cannot make evaluation or confirmation.

⑦ Not applicable

9.2.2 The severity of AE

① Mild: there are self-aware or objective symptoms, but they do not interrupt daily life. The treatment can be continued without dose adjustment.

② Moderate: interruption in daily life is recognized. Dose adjustment or additional treatment is required due to the adverse event.

③ Severe: daily life cannot be managed with the symptom. The administration of the drug should be discontinued due to significant adverse event.

9.2.3 The outcome of AE

① Recovered

② Recovering

③ Not recovered

④ Recovered with sequelae

⑤ Unknown

⑥ Fatal injury

⑦ Death potentially related to AE

⑧ Death not related to AE

9.2.4 The SAE

The SAE will be determined according to the following seriousness criteria.

① Causing death or life-threatening
② Requiring hospitalization or extension of hospitalization
③ Causing continuous or significant disability or dysfunction
④ Is a congenital malformation or abnormality
⑤ Other medically significant event *

*「Takeda Medically Significant AE List」is included in this clause. (for example, bronchospasm requiring short-term intensive treatment at emergency room.)

Takeda Medically significant AE List

General Malignancy Endotoxic shock Sepsis Transmission of an infectious agent by a medicinal product Necrosis including Gangrene	**Hepatobiliary System** Acute hepatic failure Fulminant hepatitis **Immune system** Anaphylaxis Progressive multifocal leukoencephalopathy (PML) Transplant rejection
Blood and lymphatic System Bone marrow failure Disseminated Intravascular Coagulation Haemolytic anaemia Thrombotic Thrombocytopenic Purpura Hematocytolysis	**Musculoskeletal System** Rhabdomyolysis **Nervous System** Cerebrovascular accident Coma Convulsive seizures Hyperthermia malignant Macular oedema Psychosis Meningoencephalitis Neuroleptic malignant syndrome Suicidal behaviour

Cardiovascular System Cardiac arrest Cardiac failure Cardiomyopathy acute Malignant hypertension Ventricular arrhythmias Cerebral embolism and infarction Desquamation and burst of important blood vessel	**Reproductive System** Abortion Uterine perforation
Endocrine System Adrenal crisis	**Respiratory System** Acute respiratory failure Pulmonary hypertension
Gastrointestinal System Acute pancreatitis GI haemorrhage GI perforation GI obstruction Necrotising colitis Peritonitis	**Skin and subcutaneous tissue** Toxic epidermal necrolysis Stevens-Johnson syndrome **Urinary System** Acute renal failure

Special Interest AEs

A Special Interest Adverse Event (serious or non-serious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them and would be described in protocols and instructions provided for investigators as to how and when they should be reported to Takeda.

- **Bladder Cancer**
  This is an adverse event of special interest for pioglitazone.
  Patients will be advised to promptly notify the investigator if macroscopic hematuria or other symptoms such as dysuria or urinary urgency develop during treatment with study drug.

  Study drug will be discontinued while additional investigations to establish a diagnosis are made. The investigator must complete the AE/SAE (e)CRF page if the event meets serious criteria.

  If a diagnosis of bladder cancer is confirmed, study drug will be permanently discontinued and a Bladder Cancer Adverse Event of Special Interest Form will be completed and report it to Takeda within 24 hours of first onset or notification of the event.

- **Pancreatitis**
  This is an adverse event of special interest for alogliptin.
  Study drug should be interrupted immediately if any of the following circumstances occur at any time during treatment:
    - If pancreatitis is suspected
    - Serum amylase ≥2 x ULN
    - Serum lipase ≥2 x ULN.

  If any of the circumstances described above occur during the study, the investigator must complete the AE/SAE Case Report Form [(e)CRF] page, a Pancreatitis Adverse Event of Special Interest Form and report it to Takeda within 24 hours of first onset or notification of the event. The investigator will determine if the subject has a diagnosis of pancreatitis. If yes, full details of the event should be obtained and recorded.

- **Hypersensitivity reactions**
  This is an adverse event of special interest for alogliptin.
  If any of the subject experiences a hypersensitivity reaction during the study, the investigator must complete the AE/SAE Case Report Form [(e)CRF] page, a Hypersensitivity reactions Adverse Event of Special Interest Form and report it to Takeda within 24 hours of first onset or notification of the event. The investigator will determine if the subject has a diagnosis of hypersensitivity reaction. If yes, full details of the event should be obtained and recorded.

- **Liver Function Test Abnormalities**
  This is an adverse event of special interest for alogliptin.

If the subject is experiencing symptoms or if the liver test is abnormal (as defined below), the abnormality should be documented as an adverse event, and a Liver Function Test Abnormality (LFTA) Form completed. If the event meets serious criteria, the SAE (e)CRF page must be completed within 24 hours of first onset or notification of the event;

- ALT or AST ≥3 times ULN in conjunction with a bilirubin >2 times ULN
- ALT or AST >5 times ULN for more than 2 weeks
- ALT or AST ≥3 times ULN with the appearance of fatigue, nausea, vomiting, upper right-quadrant tenderness, fever, rash or eosinophilia.

In each of these instances, the patient should be followed to a satisfactory conclusion (ie, until the adverse event resolves, the laboratory value returns to baseline, or the condition becomes stable).

NOTE: All SAEs which start during the study and are not resolved by the end of the observational period should be followed until resolved if possible.

10. EFFECTIVENESS ASSESSMENT

Effectiveness will be determined through improvement in Fasting blood glucose or HbA1c, Lipid profile and Blood pressure. Final assessment will be evaluated for investigator's clinical judgment

at 26 weeks(or stop date of treatment) after the start of therapy.
The final effectiveness assessment will be characterized according to the classification criteria below:

① Improved: signs and symptoms are significantly improved
② Unchanged: improvement in signs and symptoms is not significant or there is no change in signs and symptoms
③ Worsened: signs and symptoms are worsened
④ Assessment impossible: assessment is impossible because the surveillance drug was discontinued before 13 weeks

Among these, “Improved” is classified as ‘effectiveness’, and “unchanged” and “worsened” are classified as ‘ineffectiveness’.

11. STATISTICAL ANALYSIS

11.1 Composition of subjects

Lists of planned number of patients, completed number of patients, number of patients for safety analysis set, and number of patients for effectiveness analysis set will be presented like following;

- Planned (Agreed) subjects includes subjects agreed for surveillance by written contract with investigator
- Completed subjects includes subjects whose CRFs are retrieved after completion of surveillance
- Safety analysis set includes subjects who were treated with the surveillance drug at least once and completed the follow-up for safety
- Effectiveness analysis set includes subjects who have completed the surveillance drug treatment for more than 13 weeks and have performed overall assessment according to the investigator’s clinical discretion.

11.2 Subject demographic data analysis

All background data such as patient demographics, diagnosis, pre-treatment for T2DM, concurrent disease and concomitant medications, administration period and dosage of NesinaAct tablet will be expressed in descriptive statistics. For continuous data, mean, standard deviation, minimum value, maximum value, and median will be calculated, and for categorical data, frequency and percentage will be summarized.

11.3 Safety Analysis

In the safety set, serious adverse events/adverse drug reactions, unexpected adverse events/adverse drug reactions, adverse events/ adverse drug reactions will be classified by system organ class (SOC) and preferred term (PT) of WHO ART. These events will be tabulated for status of incidences by type and status of collected incidence cases then analyzed by severity

and outcome of adverse event, causal relationship to the study drug, and causal relationship to factors other than the study drug.

To identify factors considered to affect safety, incidence rates of adverse events will be estimated according to the demographic data of subjects and in special populations (e.g., the elderly, pregnant women, patients with hepatic or renal impairment). The significant difference in incidence rates will be tested by statistical analysis tests such as the Chi-square test or the Fisher's Exact test. Items to be analyzed will be adjusted according to the content of the study data, circumstances of the study, and significance status. If necessary, multivariate analysis for the impact of demographic data on incidence rates of adverse events may be carried out using logistic regression analysis.

In the final report, incidence rates of all adverse events identified during the post-marketing surveillance will be analyzed and their 95% confidence intervals will be presented.

11.4 Effectiveness Analysis

In the effectiveness set, effectiveness rates and their 95% confidence intervals will be presented based on the final effectiveness assessment. Chi-square test or Fisher's Exact test will be used for statistical analysis. Continuous effectiveness endpoints (change in HbA1c, change in fasting blood glucose) will be presented as descriptive statistics. For categorical effectiveness endpoints (number of patients with HbA1c <7% and overall effectiveness), frequency and percentage will be calculated. In addition, effectiveness rates by each demographic characteristic will be compared using the Chi-square test and the Fisher's Exact test. Items to be analyzed will be adjusted according to the content of the study data, circumstances of the study, and significance status. If necessary, multivariate analysis for the impact of the effectiveness may be carried out using logistic regression analysis.

12. OTHER REQUIREMENT

12.1 Amendment of Plan

The need for amendment of the plan shall be examined based on new knowledge obtained from the course of this PMS, and if necessary, the plan shall be amended. Also, if a partial change in the administration and dosage or indications is approved during this PMS, the need for amendment of this plan shall be examined, and if necessary, it shall be amended. In case of an amendment of the plan, except for a minor change, an amendment plan shall be submitted to the Ministry of Food and Drug Safety in advance.

12.2 Measures when problem or doubt is identified

If an unexpected ADR or SAE is observed or the frequency of an AE is sharply increased, or a safety and effectiveness problem is found compared to before marketing, execution of a special investigation shall be examined to verify the significance.

12.3 Serious Adverse Event Collection and Reporting

Following the patient's written consent to participate in the study, all SAEs, whether or not related to NesinaAct Tab under study, must be collected. SAEs must be individually recorded on the SAE Report Form presented by MFDS and reported to Takeda Pharmaceuticals Korea Co., Ltd within 24 hours to comply with regulatory requirements. A form should be completed for any event where doubt exists regarding its status of seriousness.
All SAEs must be reported by confirmed facsimile (fax) transmission or reported via electronic mail to

Notification of Serious Adverse Events to Takeda Pharmaceuticals Korea Co., Ltd.

24 /7 SAE Hotline	
Phone Number	PPD
Fax Number	
For <u>SAE Reporting</u>, **please E-MAIL the completed SAE Report Form to Takeda within 24 HOURS of first awareness**	

Even if the investigator is aware of additional information or FU information on SAE, he/she should report to the sponsor within 24 hours.

12.4 Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin at initiation of the study. Non-serious adverse events must be recorded in the safety section of the Case Report Form, regardless of the causality with this drug. Non-serious adverse events should be followed until resolution or stabilization or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of this drug under study and for those present at the end of the study, as appropriate.

12.5 Pregnancy reporting

If the patient becomes pregnant during drug treatment or within 30 days after the end of treatment, the administration of the drug under study should be immediately discontinued and the subject should be terminated early from the study. Once the investigator confirms that the subject becomes pregnant during drug treatment or within 30 days after the end of treatment, pregnancy related information will be collected after obtaining the ICF for the use of pregnancy information from the subject. Takeda Pregnancy Notification Form should be completed and should be reported to Safety Staff of Takeda Pharmaceuticals Korea Co., Ltd within 24 hours of his/her awareness. In addition, if the partner (spouse) of the male subject is also reported to have a pregnancy during drug treatment or within 30 days after the end of treatment, pregnancy related

information will be collected after obtaining the ICF for the use of pregnancy information from the partner (spouse) of the subject. Takeda Pregnancy Notification Form should be completed and should be reported to Safety Staff of Takeda Pharmaceuticals Korea Co., Ltd within 24 hours of his/her awareness. The investigator should provide follow up information to Takeda Pharmaceuticals Korea Co., Ltd during the pregnancy and until delivery or the end of the pregnancy.

13. APPENDICES

APPENDIX 1. PMS Case Report Form Template
APPENDIX 2. Effectiveness/Efficacy and Regimen/Dose of Nesina Act Tablet
APPENDIX 3. Cautions in Use of Nesina Act Tablet
APPENDIX 4. Copy of Product License Certificate

[ATTACHMENT] LISTING OF OVERSEAS APPROVAL AND SALES STATUS

	Country	Regulatory Approval	Launch	Local trade name	Comment
1	AUSTRALIA	2013-09-19	2014-04	INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	-
2	BELGIUM	2013-09-19		INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	-
3	BULGARIA	2013-09-19	-	INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	-
4	CANADA	2014-01-16	-	OSENI 12.5/15mg-F OSENI 12.5/30mg-F OSENI 12.5/45mg-F OSENI 25/15mg-F OSENI 25/30mg-F OSENI 25/45mg-F	-
5	CROATIA	2013-09-19	-	INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	-
6	CYPRUS	2013-09-19	-	INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	-
7	CZECH REPUBLIC	2013-09-19		INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	-
8	DENMARK	2013-09-19	2013-11	INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	-
9	ECUADOR	2014-04-15	-	NESINA PIO 12.5/15mg-F	-
10	ESTONIA	2013-09-19	-	INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	-
11	FINLAND	2013-09-19		INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	-

	Country	Regulatory Approval	Launch	Local trade name	Comment
12	FRANCE	2013-09-19	--	INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	- - -
13	GERMANY	2013-09-19	-	INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	-
14	GREECE	2013-09-19	-	INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	-
15	HUNGARY	2013-09-19	-	INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	-
16	ICELAND	2013-10-14	-	INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	-
17	IRELAND	2013-09-19	2013-12	INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	-
18	ITALY	2013-09-19	-	INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	-
19	JAPAN	2011-07-01	2011-11	LIOVEL HD 25/30mg-F LIOVEL LD 25/15mg-F	-
20	LATVIA	2013-09-19		INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	-
21	LIECHTENSTEIN	2013-09-19	-	INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	-
22	LITHUANIA	2013-09-19		INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	-
23	LUXEMBOURG	2013-09-19		INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	-

	Country	Regulatory Approval	Launch	Local trade name	Comment
24	MALTA	2013-09-19	-	INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	-
25	MEXICO	2013-05-23	-	INVRESINA P 25/15mg-F INVRESINA P 25/30mg-F INVRESINA P 25/45mg-F	-
26	NETHERLANDS	2013-09-19	-	INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	-
27	NORWAY	2013-10-10	2013-12	INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	-
28	POLAND	2013-09-19	-	INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	-
29	PORTUGAL	2013-09-19	-	INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	-
30	ROMANIA	2013-09-19	-	INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	-
31	SLOVAKIA	2013-09-19	-	INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	-
32	SLOVENIA	2013-09-19	-	INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	-
33	SPAIN	2013-09-19	-	INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	-
34	SWEDEN	2013-09-19	-	INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	-
35	UNITED KINGDOM	2013-09-19	2013-12	INCRESYNC 12.5/30mg-F INCRESYNC 12.5/45mg-F INCRESYNC 25/30mg-F INCRESYNC 25/45mg-F	-

	Country	Regulatory Approval	Launch	Local trade name	Comment
36	UNITED STATES	2013-01-25	2013-06	OSENI 12.5/15mg-F OSENI 12.5/30mg-F OSENI 12.5/45mg-F OSENI 25/15mg-F OSENI 25/30mg-F OSENI 25/45mg-F	-