September 9, 2002

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Announcement of the Suspension of Overseas Clinical Study with Elaspol® 100 for Injection

Ono Pharmaceutical Co., Ltd. has announced that Eli Lilly and Company, the licensee of Elaspol® 100 for injection, has suspended its overseas clinical study for this drug. Elaspol was launched in Japan in June 2002 for treatment of acute lung injury (ALI) associated with systemic inflammatory response syndrome (SIRS).

As this suspension was decided based on data not yet validated, Eli Lilly is now collecting the study data for complete analysis. To further promote appropriate use of this drug, Ono Pharmaceutical has decided to inform medical institutions of the presently available information on the suspension.

Information dissemination on this matter began on September 9 (Mon.), 2002.

* Refer to the attached materials for the information disseminated to medical institutions

Early Post-marketing Phase Vigilance
June 2002 - December 2002

- The information described in this notice is essential for the proper use of Elaspol® 100 for Injection. Please read this before use. -

Elaspol® 100 for Injection

Notice: Suspension of the overseas clinical study

September 2002

ONO PHARMACEUTICAL CO.,LTD.

Announcement on the Suspension of Overseas Clinical Study with Elaspol® 100 for Injection

We announce that Eli Lilly and Company, the licensee of Elaspol® 100 for injection, has suspended its overseas clinical study for this drug, which was launched in Japan in June 2002. As this suspension was made based on data not yet validated, the data of the overseas clinical study are being collected to undergo analysis. Therefore, this includes only presently available information on the suspension. We will inform you of the analysis results as soon as obtained. We would appreciate it if you could reconfirm the indications, dosage and administration, and precautions specified upon approval of Elaspol in Japan.

The process by which the overseas clinical study has been suspended

Eli Lilly was performing a double-blind, placebo-controlled Phase II clinical study in patients with acute lung injury (ALI) in six Western countries. As you well know, ALI is a life-threatening disease, which leads to death in 30 – 50% patients. Effective drugs for this disease have long been awaited.

The placebo-controlled clinical study was being performed with drug administration for up to 14 days, with ventilator-free days (VFD) and mortality during the 28-day evaluation period as primary endpoints. As scheduled, an interim analysis was performed by the Data and Safety Monitoring Board (DSMB)[1)], an external organization, when the enrollment had reached approximately half the target patient number (620). This analysis revealed no difference in mortality and safety between Elaspol and placebo groups during the 28-day evaluation period. However, the 180-day mortality (approx. 170 days after completion of drug administration) in the Elaspol group was slightly higher than that of the placebo group, based on data not yet validated[2)]. Following the suggestion of the DSMB, Eli Lilly has decided to suspend the clinical study and to collect data maintaining the blinding to determine the future of this study after thorough data analysis.

Results of clinical studies in Japan

In the double-blind, placebo-controlled Phase III clinical study conducted earlier in Japan, the mortality of the Elaspol group (approved dose group) was not higher than that of the control group (low dose group) both at 30 days and 90 days after the administration commencement. The 180-day follow-up investigation showed similar results.

All deaths occurring within 180 days from the initiation of study drug infusion in PIII double-blind study (Number of deaths)

Group	Patients Enrolled	Day 0 – 30	Day 30 - 60	Day 60 - 90	Day 90 - 180	Total
Low dose group*	108	30 (27.8%)	11 (38.0%)	0 (38.0%)	6 (52.8%)	47

Approved dose group**	113	25 (22.1%)	4 (25.7%)	7 (31.9%)	3 (46.4%)	39

The above table shows the death number as of September 2, 2002. Cumulative mortality is provided in percent figures in parentheses. However, the investigations have not been performed for 19 patients in the low dose group and 29 in the approved dose group yet.

*: 0.004 mg/kg/hr

**: 0.2 mg/kg/hr

Phase III clinical study in Japan also revealed that Elaspol improves lung function, enabling early removal from mechanical ventilation and early discharge from the ICU. With no major problems in safety, the clinical study of Elaspol provided no concerns about long-term patient prognosis. The efficacy and safety of Elaspol were also confirmed in a further clinical study in Japan performed in compliance with the guidelines of ARDS Network. Through these studies, we obtained the manufacturing approval for Elaspol this April.

Future actions

Since data are still blinded, we have not obtained detailed information about the concerns over the long-term prognosis seen in the overseas clinical study. We consider that the reasons for the interim analysis results will be clarified when the data of the overseas clinical study are validated. We will inform you of the results of the data analysis as soon as obtained.

We will also conduct the post-marketing clinical study, a condition of the approval, to clarify the effect on mortality, and to confirm the appropriateness of the administration period and indication.

1): External organization that advocate the study sponsor to continue, change, or suspend/discontinue the clinical study by evaluating the protocol of the study, safety data, and important efficacy

2): The presently available data have not been assessed through checking with medical records, and include those of patients who have not completed the 180-day evaluation period. Therefore, the data have not been validated.

- Neutrophil elastase inhibitor -

Designated drug
Prescription-only drug

ELASPOL® 100 for Injection

CONTRAINDICATIONS (Elaspol® 100 for Injection is contraindicated in the following patients.)
Patients with a history of hypersensitivity to any of the ingredients of this product.

BRAND NAME	ELASPOL® 100 for Injection	Standard Commodity Classification No. of Japan	87399
NONPROPRIETARY NAME:	Sivelestat sodium hydrate (JAN)	Approval No.	21400AMZ00462
		Date of listing in the NHI reimbursement price	June 2002
		Date of initial marketing in Japan	June 2002
		International birth date	April 2002

DESCRIPTION

Brand name	ELASPOL® 100 for Injection
Ingredient/content (per vial)	Sivelestat sodium hydrate 100 mg
Additives (per vial)	D-mannitol (excipient) 200 mg, pH adjuster
Dosage form	Injection (vial)
pH	7.5 - 8.5 (when dissolving one vial of this product in 10 mL of water for injection)
Osmotic pressure ratio	Approx. 0.6 (when dissolving one vial of this product in 10 mL of water for injection)
Color	White lump or powder, freeze-dried product

INDICATIONS

Improvement of acute lung injury associated with systemic inflammatory response syndrome (SIRS)

<Precautions relating to indications>

This product should be administered to patients who satisfy both criteria 1 and 2 shown below.

1. For SIRS, satisfy 2 or more of the following items:
   ① Body temperature of >38°C or <36°C, ② Heart rate of >90 beats/min, ③ Respiratory rate of >20/min or $PaCO_2$ of <32 mmHg, ④ WBC of >12,000/μL or <4,000/μL or band cells of >10%
2. For acute lung injury, satisfy all of the following items:
   ① Decreased pulmonary function (PaO_2/F_IO_2 ≤300 mmHg under the control of mechanical ventilation), ② Chest X-ray showing bilateral infiltrative shadow, ③ Pulmonary arterial wedge pressure of ≤18 mmHg when it is measured, or no clinical finding of increased left atrial pressure when it is not measured.

DOSAGE AND ADMINISTRATION

Usually, dissolve this product in physiological saline, dilute a daily dose (4.8 mg/kg of sivelestat sodium hydrate) of the solution in 250 - 500 mL of transfusion, and continuously administer intravenously for 24 hours (0.2 mg/kg/hour). The duration of administration should be limited within 14 days.

<Precautions relating to dosage and administration>

- It is recommended that the administration of this product be started within 72 hours after onset of lung injury. (See "Item 3 of CLINICAL STUDIES.")
- It should be considered that the administration be completed in a short-term period depending on the symptom. When the improvement rate is lower 5 days after the start of administration of this product, it is shown that the subsequent improvement rate (14 days after the start of administration) is lower. (See "Item 4 of CLINICAL STUDIES.")
- Preparation: The mixed infusion of this product with amino acid transfusion should be avoided. Caution should be exercised because a precipitation may occur when a transfusion containing calcium is employed and the concentration of this product becomes ≥2 mg/mL or when the pH of the mixed solution becomes ≤5 by diluting with a transfusion (See Section of "Precautions concerning Use.")

PRECAUTIONS

1. Important Precautions

(1) The administration of this product is not substituted for general treatment of acute lung injury such as respiratory control, correction of circulatory blood volume and antibiotics. Therefore, appropriate treatment should be given to the underlying disease.

(2) The efficacy of this product in the patients complicated with multiple organ failures (4 or more organ failures) has not been established. Therefore, this product should be administered while observing the patient's condition, only if the expected therapeutic benefit is judged to be prioritized. (See "Item 5 of CLINICAL STUDIES.")

(3) The efficacy of this product has not been established in patients complicated with acute lung injury resulting from burns or trauma or those complicated with severe chronic respiratory disease. Therefore, this product should be administered while observing the patient's condition only if the expected therapeutic benefit is judged to be prioritized. (The clinical experience is limited.)

2. Adverse Reactions

Adverse reactions to this product were observed in 93 (16.0%) of the 580 patients evaluated for analysis of adverse reactions. The major adverse reactions were hepatic function abnormalities in 49 cases (8.4%), such as increased AST (GOT), ALT (GPT) and increased Al-P in 36 cases (6.2%), increased bilirubin in 11 cases (1.9%), leukopenia in 9 cases (1.6%) and eosinophilia in 7 cases (1.2%). (At the time of approval)

(1) Clinically significant adverse reactions

1) Dyspnea
Dyspnea (0.3%) may occur. In the event of such symptom, administration should be discontinued and appropriate measures be taken.

2) Leukopenia
Leukopenia (0.5%) may occur. In the event of such symptom, administration should be discontinued and appropriate measures be taken.

(2) Other adverse reactions

	10%> ≥1%	< 1%
Hypersensitivity		Rash, etc
Hepatic	Increased bilirubin, AST (GOT), ALT (GPT), γ-GTP and Al-P	Positive urobilinogen, increased LDH
Hematologic	Eosinophilia	Thrombocytopenia, thrombocytosis, anemia, bleeding tendency
Renal		Increased BUN, pollakiuria, increased urine protein
Others		Decreased total protein

3. Use during Pregnancy, Delivery or Lactation

(1) This product should be used in pregnant women or in women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment. [The safety of this product in pregnant women has not been established.]

(2) Breast feeding should be avoided during administration of this product. [Animal studies have shown that this product is excreted in breast milk.]

4. Pediatric Use

The safety of this product in low birth weight infants, neonates, nursing infants, infants, or children has not been established. (No clinical experience)

5. Precautions concerning Use

Preparation: When a transfusion containing calcium is employed, this product should be used at the concentration of 1 mg/mL or less (Precipitation may occur when the concentration of this product exceeds 2 mg/mL or more). Attention should be paid because precipitation may occur when the pH becomes ≤5 by diluting this product with a transfusion. The mixed infusion of this product with amino acid transfusion should be avoided because degradation may occur with the use of amino acid transfusion. As a result of compatibility test with this product, the following transfusions were incompatible: Moriamin® S, Amizet® B, Amiparen®, Aminolevan® and Moripron® F. The following transfusions were compatible: physiological saline, 5% Glucose injection, and Solita®-T No. 3.

CONDITIONS FOR APPROVAL

1. The post marketing clinical trial should be conducted to clearly demonstrate an effect on survival rate and verify an adequacy of the administration duration and target diseases.
2. As soon as the results of clinical trials being conducted in accordance with ARDS Network will be made available, they should be promptly reported and submitted as one of application document for the re-examination.

PRECAUTIONS RELATING TO HANDLING

1. Caution: Designated drug - Use only pursuant to the prescription or directions of a physician, etc. This product is a prescription-only drug.
2. Storage: Store in a light-proof container at room temperature.
3. Expiration date: The expiration date is indicated on the package (3 years)

PACKAGING

ELASPOL®100 for injection: 10 and 30 vials

• Please see Package Insert for others and detail. **• Please pay much attention to Contraindications and Precautions when revised.** May 2002

Manufactured and Distributed by

Ono Pharmaceutical Co., Ltd.
1-5 Doshomachi 2-chome, Chuo-ku, Osaka 541-8526

An important notice for use of Elaspol® 100 for Injection

Ono Pharmaceutical Co., Ltd.

1. Please carefully confirm if the patients meet the following criteria for acute lung injury (ALI) associated with systemic inflammatory response syndrome (SIRS), the indication of "Elaspol® 100 for Injection," BEFORE you administer it to them.

1. For SIRS, satisfy 2 or more of the following items:
   - (1) Body temperature of >38°C or <36°C,
   - (2) Heart rate of >90 beats/min,
   - (3) Respiratory rate of >20/min or $PaCO_2$ of <32 mmHg,
   - (4) WBC of >12,000/μL or <4,000/μL or band cells of >10%

2. For acute lung injury, satisfy all of the following items:
   - (1) Decreased pulmonary function (PaO_2/F_IO_2 ≤300 mmHg under the control of mechanical ventilation),
   - (2) Chest X-ray showing bilateral infiltrative shadow,
   - (3) Pulmonary arterial wedge pressure of ≤18 mmHg when it is measured, or no clinical finding of increased left atrial pressure[1)] when it is not measured.

[1)]: "Clinical finding of increased left atrial pressure" means "left-sided heart failure."

Please carefully confirm, before use of this drug, that patients do NOT have any evidence of "left-sided heart failure" in echocardiogram or in electrocardiogram, when they have with well-defined coronary artery disease (myocardial infarction and stenocardia) either at present or in the past, or they are definitely diagnosed as having aortic valve disease, mitral regurgitation, cardiac myopathy, or hypertensive heart disease.

2. Please pay careful attention to the following precautions when you administer Elaspol® 100 for Injection to patients.

Precautions

1. It is recommended that the administration of this product be started within 72 hours after onset of lung injury.

The improvement rate on pulmonary function was 72.5% (66/91 patients) for "Moderately improved" or more in the patients in whom this drug was administered within 72 hours after onset of lung injury, and 54.5% (12/22 patients) in those exceeding 72 hours after onset of lung injury in the double-blind comparative study.

2. The efficacy of this product in the patients complicated with multiple organ failures (4 or more organ failures) has not been established. Therefore, this product should be administered while observing the patient's condition, only if the expected therapeutic benefit is judged to be prioritized.

In the late Phase II clinical study, the global improvement rate was 63.2% (24/38 patients) for "Moderately improved" or more in the patients with 3 or less organ failures including lung failure before administration and 33.3% (5/15 patients) in those with 4 or more organ failures. (In this clinical study, no diagnostic criteria on organ failures except lung failure was defined.)
In addition, in the case of patients with 4 or more multiple organ failures, the efficacy of the drug has not been established because organ failures other than lung injury are considered to badly affect the patient clinical condition.

3. The efficacy of this product has not been established in patients complicated with acute lung injury resulting from burns or trauma or those complicated with severe chronic respiratory disease. Therefore, this product should be administered while observing the patient's condition only if the expected therapeutic benefit is judged to be prioritized (Insufficient clinical data).

In patients with burns and trauma, their prognosis will be greatly affected by their severity or presence of direct damage to the lungs. In addition, patients complicated with severe chronic respiratory diseases usually have their lungs damaged prior to onset of acute lung injury, and their lung function is lowered. Therefore, the efficacy of this product has not been established in those patients yet.

3. Please pay careful attention to the following precautions during administration of Elaspol® 100 for Injection.

Precautions

1. The administration of this product is not substituted for general treatment of acute lung injury such as respiratory control, correction of circulatory blood volume and antibiotics. Therefore, appropriate treatment should be given to the underlying disease.

As this product is not for treatment of underlying diseases, appropriate treatments should be provided for the underlying diseases.

2. It should be considered that the administration be completed in a short-term period depending on the symptom. When the improvement rate is lower 5 days after the start of administration of this product, it is shown that the subsequent improvement rate (14 days after the start of administration) is lower.

The following table indicates the improvement rate on pulmonary function judged to be "Moderately improved" or more 10 and 14 days after the start of administration is shown below in comparison with that observed 5 days after the start of administration in clinical studies including the double-blind study where this drug was administered for 14 days. .

Change in improvement rate on pulmonary function in comparison with that 5 days after the start of administration

5 days after start of administration	10 days after start of administration ("Moderately improved" or more)	14 days after start of administration ("Moderately improved" or more)
Markedly improved	100.0% (56/56 patients)	100.0% (56/56 patients)
Moderately improved	90.0% (36/40)	90.0% (36/40)
Slightly improved	64.5% (20/31)	80.6% (25/31)
Unchanged	27.8% (10/36)	34.3% (12/35)
Aggravated	0.0% (0/12)	0.0% (0/12)
Total	69.7% (122/175)	74.1% (129/174)

In one patient judged to be "Unchanged" 5 days after the start of administration, the administration was discontinued because of an adverse reaction and thereby the data on the patient 14 days after the start of administration is not assessed.

Please make a decision on whether the administration of the drug will be continued or not, taking into consideration the fact that the lung function, which was judged to be "Aggravated" 5 days after administration commencement, would not be improved.