K-SG2206-4

** Revised: October 2023

Human Placental Extract

Rx **LAENNEC®**

112 mg/2 mL

Solution for Injection (IM/SC)

Hepatoprotectants

Liver function improving drug / hepatic reserve activator

Specific Biological Products / Prescription drug note)

Storage: Store at temperatures not exceeding 30ºC. Do not refrigerate or freeze.

Expiry date: Indicated on the container and package

Note): Use under prescription from a licensed physician

This product contains the human placenta-derived component as its active ingredient, and when collecting placenta which became raw material, we conduct interview, diagnosis related to infectious diseases.

In addition, measures to prevent transmission of infectious diseases such as heat treatment in manufacturing process, but since it is not possible to completely eliminate the risk of transmission of infectious diseases using human placenta as a raw material, when using this product, keep it to the minimum with the necessity of treatment of the disease in mind (See the section on "Precautions").

1 NAME OF THE MEDICINAL PRODUCT

LAENNEC

1.1 Product Name

Human Placental Extract

1.2 Strength

112 mg/2 mL

1.3 Pharmaceutical Dosage Form

Solution for Injection (IM/SC)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 Qualitative Declaration:

Each ampoule contains:

Water soluble human placenta hydrolysate ..... 112 mg

2.2 Quantitative Declaration

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection (IM/SC)

This product is a light to yellowish brown transparent liquid with a distinctive odor in a brown borosilicate glass ampule. The pH level ranges from 5.5 to 6.5 and the osmotic pressure ratio (to physiological saline) is approximately one.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Human Placental Extract “Laennec” is indicated for improvement of hepatic function in chronic liver diseases.

4.2 Posology and method of administration

For intramuscular or subcutaneous administration only.

A normal adult dose of 2 mL is administered by intramuscular injection, or subcutaneous injection once daily. The dose can be increased to two or three times daily depending on symptoms.

4.3 Contraindications

Patients with a history of hypersensitivity to this product.

4.4 Special warnings and precautions for use Special warnings and precautions for use

PRECAUTIONS

1. Careful Administration (LAENNEC should be administered with care in the following patients.)

Patients predisposed to allergies.

*2. Important Precautions

[Explanation to patients]

The necessity of this product for disease treatment, as well as the fact that despite the employment of safety measures to prevent the spread of infectious agents at the time of manufacture of this product, the risk of transmission of infectious agents from raw materials derived from human placenta cannot be eliminated, should be explained to the patient and every effort made to obtain their understanding.

(1) This product is manufactured from the extract of human placenta delivered full term in Japan. Each placenta donor has received a medical interview about medical history, travel history, etc.
Furthermore, after screening for viral and bacterial infections by serological examination etc., nucleic acid amplification test (NAT) is performed on HBVDNA, HCV-RNA and HIV-1-RNA.
In addition, it has been confirmed that high-pressure steam sterilization treatment at 121ºC. for 20 minutes in the production process of this drug has an inactivating effect on various viruses. This product has passed HBV - DNA, HCV - RNA, HIV - 1 - RNA, HTLV - I - DNA, parvovirus B19 - DNA nucleic acid amplification test (NAT) in product testing. However, there is a possibility that the virus below the limit is contaminated. Since the possibility of infection by this drug administration cannot be denied, observe the course after

(2) There have been no reports of transmission of infections, such as variant Creutzfeldt-Jakob disease (vCJD), through the administration of this product in Japan or abroad to date. Nevertheless, it is theoretically impossible to eliminate the risk of transmission of such agents as vCJD completely when administering this product, therefore, an enough explanation should be made to the patient, and the product administered only after thorough examination of the necessity of treatment.

(3) Attention must be paid to the indication of this product, which is for the improvement of liver function in chronic liver diseases, and off-label use should be avoided.

4.5 Interaction with other medicinal products and other forms of interaction
The potential of drug or food interactions have not been evaluated.

4.6 Use in the Elderly
Since elderly patients often have reduced physiological function, it should be administered with care.

4.7 Pediatric Use
The safety of this product in premature infants, newborns, infants, toddlers or children has not been established (No clinical data available).

4.8 Fertility, pregnancy, and lactation
No information on safety for use during pregnancy or breast-feeding is available.

4.9 Effects on ability to drive and use machines
No information for effects on ability to drive and use machines is available.

4.10 Undesirable effects
A total of 10 cases (3.7 %) of adverse reactions or suspected adverse reactions to this product were reported among the 273 patients eligible for safety evaluation in a clinical study performed during implementation of a re-evaluation of drug efficacy (re-examination). The most frequently observed adverse reaction was injection site pain reported in 7 patients (2.6 %), and hypersensitivity (such as rash, fever, and itching), injection site indurations, and gynaecomastia, each in 1 patient (0.4 %). The causal relationship between gynaecomastia and this product is uncertain.
No abnormal changes in laboratory values were observed.

Tabulated list of adverse reactions
The adverse reactions listed in this section fall into the following frequency categories: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Clinically significant adverse reactions
Shock (Incidence unknown):
Since this product contains proteins, amino acids and others derived from human tissue, it may cause shock. The patient should be carefully monitored, and if any signs of abnormalities are observed, administration should be discontinued immediately, and appropriate measures taken.

Other adverse reactions

Injection site pain	2.56 %
Hypersensitivity (rash, fever, itching etc.)	0.37 %
Injection site indurations	0.37 %
Gynaecomastia	0.37 %
Impaired liver function (increased AST, ALT etc.) Note	Incidence Unknown
Headaches	Incidence Unknown

Note: Administration should be discontinued if impaired liver function is suspected.

4.11 Overdose
Overdosage of this product and the resulting efficacy or safety has not been established (No clinical data available).

4.12 Precautions concerning Use
Injection site:
In order to avoid any effect on tissue or nerves, this product should be injected subcutaneously or intramuscularly taking the following precautions:

a) Care should be taken when administering to avoid nerve pathways at the injection site.
b) In the case of repeated injections, avoid injecting into the same site by alternating left and right sides etc.
c) On insertion of the needle, if the patient complains of intense pain or if blood backflow is observed, the needle should be removed immediately, and injected into a different site.

Opening the ampoule:
It is desirable to wipe the part of the ampoule to be cut with an ethanol swab before opening.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacology
*1. Promotional effect on liver regeneration *(Liu K. et al.: Yakuri to Rinsho, vol.5, 2187, 1995* and *Sakamoto K. et al.: Journal of Tokyo Medical University, vol.33, 271, 1975)*
Laennec was administered at higher than the clinical dose to healthy rats after 70 % partial hepatectomy and a comparison of liver weight was made over time with control groups. The results revealed a significant promotional effect on liver regeneration in the Laennec groups.

*2. Stimulatory effect on cellular DNA synthesis (*Liu K. et al.: Yakuri to Rinsho, vol.5, 2187, 1995)*
In in vitro study using primary culture rat hepatocytes, a significant DNA-synthesis promoting activity was observed in Laennec group, compared with control groups. In in vivo study, the proportion of hepatocyte nuclei in the DNA synthesis phase in stained liver tissue of ANIT-induced acute hepatitis rat was evaluated. Laennec group, at higher than the clinical dose, showed significant DNA synthesis promotion compared to the control groups.

*3. Inhibitory effect on experimental liver injury *(Liu K. et al.: Yakuri to Rinsho, vol.5, 2187, 1995 and Nakayama S. et al.: Folia Pharmacologica Japonica, vol.94, 137, 1989)*
In in vivo study using ANIT-induced acute hepatitis rat, the serum levels of liver cytosolic enzymes (GPT, ALP, LAP and γ- GTP) and bilirubin significantly decreased in Laennec group at a dose higher than the clinical dose, compared with the control groups.
In addition, in in vivo study using CCl4-induced acute hepatitis and chronic hepatitis rats, Laennec group at a dose higher than the clinical dose, showed a significant decrease in liver cytosolic enzymes in serum (GPT, GOT) and histopathological improvements in liver injury, compared to control groups.

*4. Anti-fatty liver effect *(Sakamoto K. et al.: Journal of Tokyo Medical University, vol.31, 829, 1973)*
In vivo study using CCl4-induced acute hepatitis rat, pre-administered Laennec at a dose higher than the clinical dose showed a significant reduction in total liver lipids and total liver cholesterol, compared with the control groups.

*5. Inhibitory effect on liver fibroplasia *(Sakamoto K. et al.: Journal of Tokyo Medical University, vol.32, 351, 1974)*
Laennec at a dose higher than the clinical dose exhibited an inhibitory effect on fibroplasia in rat livers which was induced by repeated administrations of CCl4 over 12 weeks. Also, histological finding suggested that even already proliferated interstitial connective tissue had also been absorbed.

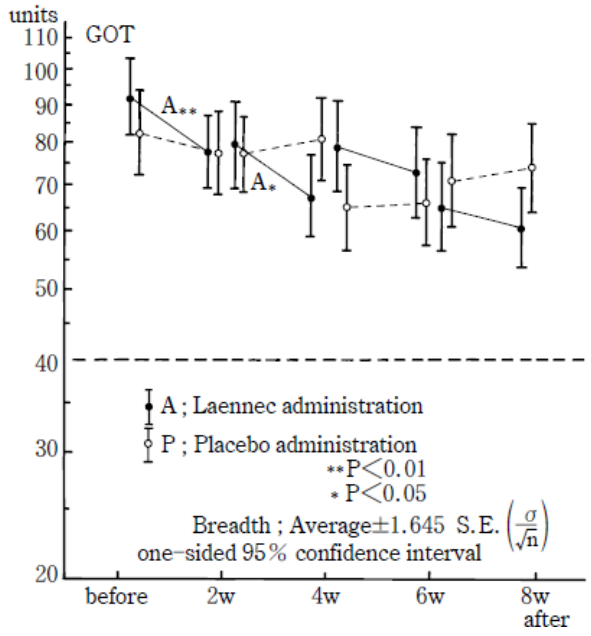
5.2 Pharmacokinetic properties
The bioactive ingredients of LAENNEC are extracted from human placenta, and the primary pharmacological action of this product cannot be attributed to any single substance or group of substances. Therefore, pharmacokinetic evaluation (absorption, distribution, metabolism, and excretion) of this product has not been established.

5.3 Preclinical safety data
With regard to toxicity, large safety margin was confirmed in single dose and repeated dose studies and the mutagenicity test was also negative. Further, with regard to reproductive and developmental toxicity, no differences were observed compared with the control.

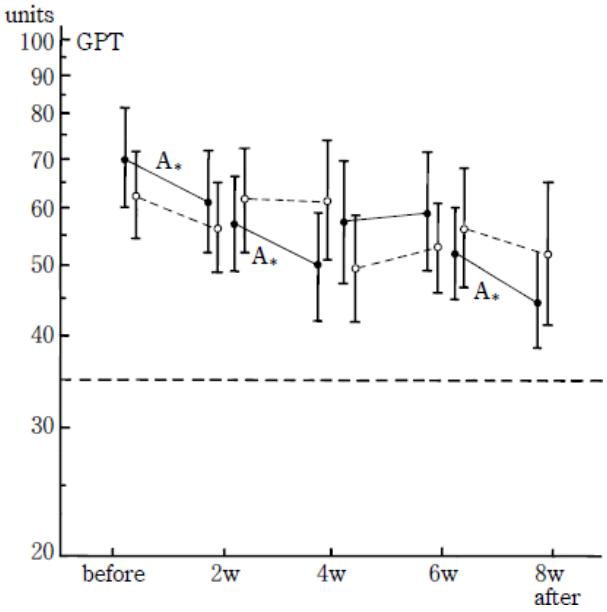
*CLINICAL STUDIES
Double blind comparative study for chronic hepatitis and liver cirrhosis *(Ueda H. et al.: Kanzo, vol.15, 162, 1974)*

Double-blind crossover study evaluating the effect of Laennec in 124 chronic hepatitis or liver cirrhosis patients in Japan revealed that serum transaminase (GOT, GPT) levels improved significantly by Laennec (see figures below).

Efficacy to GOT



Efficacy to GPT



	Subject	Transitional subjects				
Gr. I	58		A	P	A	P
			58	57	50	48
Gr. II	66		66	62	56	52
			P	A	P	A

Summary of drug-efficacy [(A)Items having a tendency to decrease or increase significantly by Laennec]

Examination-items	Before～2w	2w～4w	4w～6w	6w～8w
○ GOT	＊＊	＊		
○ GPT	＊	＊		＊
● Al-P	＊			
○ TTT				＊＊
○ ZTT	＊			
● LDH				(cf.)＊
○ T-chol				(cf.)＊(I)

＊＊ Significant under 1% level,
＊ Significant under 5% level,
(I) to increase significantly, Nothing is to decrease,
(cf.) to have a tendency inside of normal range,
○ Calculated logarithmically
● Calculated by original-value
Method : t-Test(II) of the related samples

(Data on pharmacological reevaluation)

Summary of drug-efficacy [(B)Items having a tendency to decrease or increase significantly by Placebo]

Examination-items	Before～2w	2w～4w	4w～6w	6w～8w
○ Al-P		＊		
● LDH	(cf.)＊			
○ A/G	＊			
○ Albumin		＊(I)		
○ γ-globulin				＊＊(I)

＊＊ Significant under 1% level,
＊ Significant under 5% level,
(I) to increase significantly, Nothing is to decrease,
(cf.) to have a tendency inside of normal range,
○ Calculated logarithmically
● Calculated by original-value
Method : t-Test(II) of the related samples

(Data on pharmacological reevaluation)

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients

Sodium hydroxide*
Hydrochloric acid*

*q.s. quantity is used for pH adjustment (pH: 5.5 to 6.5)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
Ampoule (unopened) 36 months

6.4 Special precautions for storage
Store at temperatures not exceeding 30ºC. Do not refrigerate or freeze.

6.5 Nature and contents of container
In 2 mL brown Borosilicate glass ampoule (Box of 10's and 100's)

6.6 Special precautions for disposal of a used medicinal product or waste materials derived
Any unused medical product or waste material should be disposed of in accordance with local requirements.

7. CAUTION

FOODS, DRUGS, DEVICES and COSMETICS ACT prohibits dispensing without prescription.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

For suspected adverse drug reaction, Seek medical attention immediately and **report to the FDA: www.fda.gov.ph** and RAPharma at (+632) 8363 3513 loc. 112 or JBP at pharmacovigilance@placenta-jbp.co.jp. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

8. MANUFACTURED BY
JAPAN BIO PRODUCTS CO., LTD. (L'ATELIER FUJIMITSU)

735-14, Aza Edamitsu, Fujimitsu-machi, Kurume-shi,
Fukuoka-ken, Japan

9. MARKETING AUTHORISATION HOLDER
RAQUEL-ABBAS PHARMACEUTICALS & GENERAL MERCHANDISE

No. 17 Madre Isabella di Rocis St., Multinational Village,
Moonwalk, Parañaque City, Manila

10. MARKETING AUTHORISATION NUMBER

BR-1449

11. DATE OF FIRST AUTHORIZATION

October 2023

12. DATE OF REVISION OF THE TEXT

October 2023