Pembroxim
Pembrolizumab INN

COMPOSITION
***Pembroxim Injection*:** Each 4 mL contains Pembrolizumab INN 100 mg.

Therapeutic Class: Anti cancer

CLINICAL PHARMACOLOGY
Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response.

Mechanism of Action
Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

Pharmacodynamics
Based on dose/exposure efficacy and safety relationships, there are no clinically significant differences in efficacy and safety between Pembrolizumab doses of 200 mg or 2 mg/kg every 3 weeks in patients with NSCLC.

Pharmacokinetics
The pharmacokinetics (PK) of Pembrolizumab was characterized using a population PK analysis with concentration data collected from 2841 patients with various cancers who received Pembrolizumab doses of 1 to 10 mg/kg every 2 weeks or 2 to 10 mg/kg every 3 weeks. Pembrolizumab clearance (CV%) is approximately 20% lower [geometric mean, 212 mL/day (46%)] at steady state than that after the first dose [267 mL/day (43.1%)]; this decrease in clearance with time is not considered clinically important. The geometric mean value (CV%) for volume of distribution at steady state is 6.1 L (21%) and for terminal half-life (t1/2) is 23 days (30%).
Steady-state concentrations of Pembrolizumab were reached by 19 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.2-fold. The peak concentration (C_{max}), trough concentration (C_{min}), and area under the plasma concentration versus time curve at steady state (AUCss) of Pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg every 3 weeks.

INDICATION
Pembrolizumab is a programmed death receptor-1 (PD-1)-blocking antibody indicated:

Melanoma
- For the treatment of patients with unresectable or metastatic melanoma.
- For the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection.

Non-Small Cell Lung Cancer (NSCLC)
- In combination with Pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations.
- In combination with Carboplatin and either Paclitaxel or Paclitaxel protein-bound, as first-line treatment of patients with Metastatic Squamous NSCLC.
- As a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is:
  o stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
  o metastatic.
- As a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Pembrolizumab.

Small Cell Lung Cancer (SCLC)
- For the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.

Head and Neck Squamous Cell Cancer (HNSCC)
- In combination with platinum and FU for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC.
- As a single agent for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test.
- As a single agent for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinumcontaining chemotherapy.

Classical Hodgkin Lymphoma (cHL)
- For the treatment of adult patients with relapsed or refractory cHL.
- For the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy.

Primary Mediastinal Large B-Cell Lymphoma (PMBCL)
- For the treatment of adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy.
- Limitations of Use: Pembrolizumab is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

Urothelial Carcinoma
- For the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.
- For the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
- For the treatment of patients with Bacillus Calmette-Guerin (BCG)- unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.

Microsatellite Instability-High or Mismatch Repair Deficient Cancer
- For the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)
  o Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options,
  or
  o Colorectal cancer that has progressed following treatment with a Fluoropyrimidine, Oxaliplatin, and Irinotecan.
- *Limitations of Use:* The safety and effectiveness of Pembrolizumab in pediatric patients with MSI-H central nervous system cancers have not been established.

Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer (CRC)
- For the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC).

Gastric Cancer
- For the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS)≥1] as determined by an FDA-approved test, with disease progression on or after 2 or more prior lines of therapy including Fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.

Esophageal Cancer
- For the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 10] as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy.

Cervical Cancer
- For the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test.

Hepatocellular Carcinoma (HCC)
- For the treatment of patients with HCC who have been previously treated with Sorafenib.

Merkel Cell Carcinoma (MCC)
- For the treatment of adult and pediatric patients with recurrent locally advanced or metastatic merkel cell carcinoma.

Renal Cell Carcinoma (RCC)
- In combination with Axitinib, for the first-line treatment of patients with advanced RCC.

Endometrial Carcinoma
- In combination with Lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.

Tumor Mutational Burden-High (TMB-H) Cancer
- For the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.
- Limitations of Use: The safety and effectiveness of Pembrolizumab in pediatric patients with TMB-H central nervous system cancers have not been established.

Cutaneous Squamous Cell Carcinoma (cSCC)
- For the treatment of patients with recurrent or metastatic cutaneous squamous cell carcinoma that is not curable by surgery or radiation.

Triple-Negative Breast Cancer (TNBC)
- In combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA approved test.

DOSAGE AND ADMINISTRATION
- *Melanoma:* 200 mg every 3 weeks or 400 mg every 6 weeks.
- *NSCLC:* 200 mg every 3 weeks or 400 mg every 6 weeks.
- *SCLC:* 200 mg every 3 weeks or 400 mg every 6 weeks.
- *HNSCC:* 200 mg every 3 weeks or 400 mg every 6 weeks.
- *cHL or PMBCL:* 200 mg every 3 weeks or 400 mg every 6 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics.
- *Urothelial Carcinoma:* 200 mg every 3 weeks or 400 mg every 6 weeks.
- *MSI-H or dMMR Cancer:* 200 mg every 3 weeks or 400 mg every 6 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics.
- *MSI-H or dMMR CRC:* 200 mg every 3 weeks or 400 mg every 6 weeks.
- *Gastric Cancer:* 200 mg every 3 weeks or 400 mg every 6 weeks.
- *Esophageal Cancer:* 200 mg every 3 weeks or 400 mg every 6 weeks.
- *Cervical Cancer:* 200 mg every 3 weeks or 400 mg every 6 weeks.
- *HCC:* 200 mg every 3 weeks or 400 mg every 6 weeks.
- *MCC:* 200 mg every 3 weeks or 400 mg every 6 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics.
- *RCC:* 200 mg every 3 weeks or 400 mg every 6 weeks with Axitinib 5 mg orally twice daily.
- *Endometrial Carcinoma:* 200 mg every 3 weeks or 400 mg every 6 weeks with Lenvatinib 20 mg orally once daily for tumors that are not MSI-H or dMMR.
- *TMB-H Cancer:* 200 mg every 3 weeks or 400 mg every 6 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics.
- *cSCC:* 200 mg every 3 weeks or 400 mg every 6 weeks.
- *TNBC:* 200 mg every 3 weeks or 400 mg every 6 weeks.

Preparation for Intravenous Infusion
- Visually inspect the solution for particulate matter and discoloration prior to administration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.
- Dilute Pembrolizumab injection (solution) prior to intravenous administration.
- Withdraw the required volume from the vial(s) of Pembrolizumab and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL.
- Discard any unused portion left in the vial.

Administer as an intravenous infusion over 30 minutes

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Immune-mediated Pneumonitis: Withhold for moderate, and permanently discontinue for severe, life-threatening or recurrent moderate pneumonitis.
- *Immune-mediated Colitis:* Withhold for moderate or severe, and permanently discontinue for life-threatening colitis.
- *Immune-mediated Hepatitis:* Monitor for changes in hepatic function. Based on severity of liver enzyme elevations, withhold or discontinue.
- Immune-mediated Endocrinopathies .
  o Hypophysitis: Withhold for moderate and withhold or permanently discontinue for severe or life-threatening hypophysitis.
  o Thyroid disorders: Monitor for changes in thyroid function. Withhold or permanently discontinue for severe or life-threatening hyperthyroidism.
  o Type 1 diabetes mellitus: Monitor for hyperglycemia. Withhold Pembrolizumab in cases of severe hyperglycemia.
- *Immune-mediated nephritis:* Monitor for changes in renal function. Withhold for moderate, and permanently discontinue for severe or life-threatening nephritis.
- *Infusion-related reactions:* Stop infusion and permanently discontinue Pembrolizumab for severe or life-threatening infusion reactions.
- *Embryofetal toxicity:* Pembrolizumab can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus.

ADVERSE REACTIONS
Most common adverse reactions (reported in ≥20% of patients) were fatigue, pruritus, diarrhea, decreased appetite, rash, dyspnea, constipation, and nausea (6.1).

USE IN SPECIFIC POPULATIONS
Pregnancy
Based on its mechanism of action, Pembrolizumab can cause fetal harm when administered to a pregnant woman. In animal models, the PD-1/PD-L1 signaling pathway is important in the maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. Human IgG4 (immunoglobulins) are known to cross the placenta; therefore, Pembrolizumab has the potential to be transmitted from the mother to the developing fetus. There are no available human data informing the risk of embryo-fetal toxicity. Apprise pregnant women of the potential risk to a fetus.
Lactation
It is not known whether Pembrolizumab is excreted in human milk. No studies have been conducted to assess the impact of Pembrolizumab on milk production or its presence in breast milk. Because many drugs are excreted in human milk, instruct women to discontinue nursing during treatment with Pembrolizumab and for 4 months after the final dose.
Females and Males of Reproductive Potential
Based on its mechanism of action, Pembrolizumab can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with Pembrolizumab and for at least 4 months following the final dose.
Pediatric Use
Safety and effectiveness of Pembrolizumab have not been established in pediatric patients.
Geriatric Use
In clinical trial no overall differences in safety or effectiveness were observed between elderly patients and younger patients.

DRUG INTERACTIONS
No formal pharmacokinetic drug interaction studies have been conducted with Pembrolizumab. Since Pembrolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.

OVERDOSAGE
There is no information on overdosage with Pembrolizumab.

PHARMACEUTICALS INFORMATION
Storage condition
Store the vial in original carton at 2°C to 8°C. Protect from light. Do not freeze or shake. Discard unused portion. Keep out of the reach of children.

Presentation & Packing
Pembroxim Injection: Each commercial box contains 1 vial of 4 mL solution.

Only for Export

LF26502

Manufactured By
Beacon Pharmaceuticals Limited
Bhaluka, Mymensingh, Bangladesh

Marketed By
BEACON®
Medicare Limited
Dhaka, Bangladesh

Length	460 mm	Width	120 mm