1. **NAME OF THE MEDICINAL PRODUCT**
   Bleo for inj. 5mg, 15 mg and 30 mg
   (Bleomycin Hydrochloride for Injection)

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**
   Bleo for inj. 5mg, 15 mg and 30 mg contain the following ingredient per vial.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Content (potency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>Bleomycin Hydrochloride</td>
</tr>
<tr>
<td></td>
<td>5mg</td>
</tr>
<tr>
<td></td>
<td>15mg</td>
</tr>
<tr>
<td></td>
<td>30mg</td>
</tr>
</tbody>
</table>

3. **PHARMACEUTICAL FORM**
   Bleo for inj. 5mg, 15 mg and 30 mg are white to yellowish white lyophilized product for injection.

4. **CLINICAL PARTICULARS**
   4.1 **Therapeutic indications**
   Skin cancer, head and neck cancer (maxillary cancer, tongue cancer, lip cancer, pharyngeal cancer, laryngeal cancer, oral cavity cancer, etc.), lung cancer (especially, primary or metastatic squamous cell carcinoma), esophageal cancer, malignant lymphoma, uterine cervical cancer, neuroglioma, thyroid cancer, germ cell tumor (testicular tumor, ovarian tumor, extra-gonadal tumor).
   (See the respective local package insert.)

   4.2 **Posology and method of administration**
   (1) **Intravenous Injection**
   Usually, for adults, dissolve 15–30 mg (potency) of Bleomycin hydrochloride in about 5–20 mL of a solvent suitable for intravenous injection such as physiological sodium chloride solution or dextrose solution, etc., and inject intravenously at a slow rate. In case of high fever, reduce the dose to 5 mg (potency) or less.

   (2) **Intramuscular and Subcutaneous Injection**
   Usually, for adults, dissolve 15–30 mg (potency) of Bleomycin hydrochloride in about 5 mL of a suitable solvent such as physiological sodium chloride solution, etc. and inject intramuscularly or subcutaneously.
   In the case of subcutaneous injection into the area adjacent to the lesion(s), the concentration of Bleomycin hydrochloride is 1 mg (potency)/mL or less.

   (3) **Intra-arterial Injection**
   Usually, for adults, dissolve 5–15 mg (potency) of Bleomycin hydrochloride in a solvent suitable for injection such as physiological isotonic sodium chloride solution or dextrose solution, etc., and administer by one-shot intra-arterial injection or by continuous intra-arterial infusion.

   (4) **Frequency of Injection**
   As a general rule, this drug is injected twice a week. This dose may be increased to once a day (every day) or decreased to once a week, depending on the patients’ condition.

   (5) **Total Dose**
   Administer Bleomycin hydrochloride to a total dose of 300 mg (potency) or less, with the disappearance of tumor as the goal.
   For germ cell tumor, however, a total dose of this drug should be not more than 360 mg (potency) in the established and standardized combination therapy with other anticancer drugs.
(6) Pediatric Use
For germ cell tumor and malignant lymphoma in pediartics, this drug should be administered in accordance with the following measure and dosage.
Administer intravenously 10-20 mg (potency)/m² (body surface area) of Bleomycin hydrochloride once every 1-4 weeks. The dosage per one infusion should not be over 30 mg (potency), which is the maximum dosage per one infusion in adults.

<Precautions>
(1) For germ cell tumor, the administration frequency of this drug in the established and standardized combination therapy with other anticancer drugs should in principle be once a week.
(2) There is significant individual variation in the appearance of adverse reactions, and since adverse reactions can appear even with relatively small doses, it is important to be fully cognizant of "PRECAUTIONS" concerning its use. It is necessary to begin with a low dosage, in relation to the condition of the patient and the disease.
(3) The total dosage should not be over 300 mg (potency). Furthermore, in case of multi-route administration, it is necessary to consider the resulting additive dosage. [Results at the time of reevaluation showed an increase of the incidence rate of pulmonary manifestation such as interstitial pneumonia and pulmonary fibrosis, etc. with an increase of a total dose, for example, the incidence rate was 6.5% at a total dose of 150 mg (potency) or less, 10.2% at a total dose of 151-300 mg (potency), and 18.8% at a total dose of over 301 mg (potency).]
(4) For germ cell tumor, in case that a total of more than 300 mg (potency) is unavoidably administered by applying the established and standardized combination therapy with other anticancer drugs, much attention should be paid to an increase of the incidence rate of pulmonary manifestation such as interstitial pneumonia and pulmonary fibrosis, etc.
(5) For germ cell tumor, in the established and standardized combination therapy with other anticancer drugs (BEP therapy (combination therapy with bleomycin hydrochloride, etoposide and cisplatin)), the package inserts for combined drugs should also be referred.
(6) In cases that have received peplomycin, as a general rule, the amount of that drug administered must be included in the computation of the overall dosage of Bleomycin.

4.3 Contraindications
(1) Patients with serious pulmonary function impairment or with chest X-ray findings suggesting diffuse fibrotic changes or any other remarkable changes. [Pulmonary function impairment or fibrotic lesions, etc. may deteriorate.]
(2) Patients with a history of hypersensitivity to this or a similar drug (peplomycin).
(3) Patients with serious renal function disorder. [Since excretion function is lowered, such serious pulmonary manifestation as interstitial pneumonia or pulmonary fibrosis, etc. may occur.]
(4) Patients with serious heart disease. [Since cardiovascular function is lowered, such serious pulmonary manifestation as interstitial pneumonia or pulmonary fibrosis, etc. may occur.]
(5) Patients treated with radiation on the chest and around the chest [See 4.5. Drug Interactions section.]

4.4 Special warnings and precautions for use
4.4.1. Posology and method of administration
(1) Such serious pulmonary manifestation as interstitial pneumonia and pulmonary fibrosis, etc. may develop as a result of the administration of this drug, with occasional fatal outcome. Therefore, this drug must be administered only in those cases that are thought appropriate to receive this drug and a physician should keep the patient under observation during the administration of this drug and for a period approximately 2 months) after the completion of administration. Particularly, administration of this drug to the elderly of age of 60 or over or patients with underlying diseases in the lung should only be performed after full consideration of “PRECAUTIONS”. Administration should be discontinued immediately on appearance of the initial symptoms of exertional dyspnea, fever, cough, crepitation (rales), abnormal chest X-ray findings and abnormalities of A-aDo₂, Pao₂ or DLco, etc., and appropriate measures should be taken.

(2) Cancer combination chemotherapy including this drug should be done only to patients who are considered suitable for the therapy by physicians having enough experiences in the chemotherapy for cancers at medical institutions where emergency cares can sufficiently be handled. Furthermore, much attention should be paid to select applicable patients by referring the package inserts for each combined drug.

4.4.2. Careful Administration (Bleo should be administered with care in the following patients. The dosage should be reduced or the intervals between administrations of the drug should be extend, based on clinical observation of the patient.)

(1) Patients with a history of, or accompanied by pulmonary dysfunction.
[Such serious pulmonary manifestation as interstitial pneumonia or pulmonary fibrosis, etc. may occur.]

(2) The elderly of age of 60 or over
[Such serious pulmonary manifestation as interstitial pneumonia or pulmonary fibrosis, etc. may occur.]

(3) Patients with renal dysfunction.
[Adverse reactions may occur strongly.]

(4) Patients with heart disease.
[Adverse reactions may occur strongly.]

(5) Patients receiving, or having received radiotherapy over the chest.
[Such serious pulmonary manifestation as interstitial pneumonia or pulmonary fibrosis, etc. may occur.]

(6) Patients with hepatic dysfunction.
[Adverse reactions may occur strongly.]

(7) Patients with varicella.
[Fatal systemic dysfunctions may occur.]

4.4.3. Important Precautions

(1) Interstitial pneumonia or pulmonary fibrosis
Such serious pulmonary manifestation as interstitial pneumonia or pulmonary fibrosis may occur. It is important to keep the patient under sufficient observation [see 2) below] and be aware that the crepitation (rales) can be an early sign of these conditions. If any abnormality is noted, administration should be immediately discontinued, adrenal cortex hormones should be administered for the treatment of idiopathic pulmonary fibrosis and a suitable antibiotic for the prevention of secondary infection should be also given.

1) In patients with underlying disease in the lung or in the elderly of age of 60 or over, interstitial pneumonia or pulmonary fibrosis appears with a high rate of frequency even with administration of low doses less than 150 mg (potency), thus great care is required.
2) Patients receiving this drug should be maintained under sufficient observation of clinical symptoms as fever, cough, and exertional dyspnea and should also be followed up to detect any abnormality on chest X-ray film or the crepitation (rales). Also, where such examination techniques are available, alveolar-arterial oxygen tension difference (A-aDo2), arterial oxygen tension (Pao2) and carbon monoxide diffusing capacity (DLco), etc. should be examined. These observations and examinations should periodically be taken not only during the administration of the drug, but also for a period of approximately 2 months after the completion of administration.

3) A-aDo2 and Pao2, etc. should be examined once a week if possible, and if there is an increase or decrease during 2 consecutive weeks, administration should be discontinued. Concretely, if there is a worsening of either of these parameters greater than 10 Torr, careful observation of other clinical symptoms is necessary and if it is judged that these are adverse reactions related to the drug, administration should be immediately discontinued and administration of steroid be commenced. Also, the same steps should be taken if there is a decrease of more than 15% in DLco.

In cases with poor pulmonary function in which administration is unavoidable, the treatment must be followed with great care and if any further decrease in pulmonary function is recognized, administration should be discontinued immediately.

(2) Shock (< 0.1%)
Because this drug treatment may give rise to shock, if any abnormalities appear, withdraw this drug immediately, and take appropriate measures. (Because shock is likely to develop in patients with malignant lymphomas at the 1st – 2nd administration, start this drug treatment with an initial and 2nd dose at 5 mg (potency) or less. After establishing that no acute reactions to the drug occur, increase the dose to the usual level).

(3) With long-term administration, adverse reactions may appear strongly and become prolonged, thus administration must be performed with care.

(4) In cases that have received peplomycin or other forms of bleomycin, toxicity is thought to be additive, therefore the necessary caution to observe the adverse reactions should be taken.

(5) Attention should be paid to the appearance or exacerbation of infection and any bleeding tendency.

(6) In children or patients at an age capable of reproduction, particular effects on the sexual glands should be considered.

4.4.4. Precautions concerning Use
(1) Intravenous administration: Vascular pain may occur, therefore, it is important to pay due attention to concentration of the injection and administration rate. Give intravenously as slowly as possible.

(2) Intramuscular administration: To avoid affecting tissue and nerves, etc., the following points must be considered.
1) Since intramuscular administration may cause induration at the injection site, avoid repeated injections at the same site. Take special care to neonates, low birth weight infants, infants and children.
2) Pay due attention to avoid injection at innervated sites.
3) If insertion of the injection needle provokes intense pain, or if blood flows back into the syringe, withdraw the needle immediately and inject at a different site.

4.4.5. Pediatric Use
Particular care is required concerning the appearance of adverse reactions when administering this drug to children.

**4.4.6. Use in the Elderly**
Because interstitial pneumonia or pulmonary fibrosis is likely to occur in the elderly of age of 60 or over, this drug should be administered with care.

[The frequency of such serious pulmonary manifestation as interstitial pneumonia or pulmonary fibrosis, etc. has been increased by age, 5.9% in the under 50’s, 8.1% in the 50’s, 10.9% in the 60’s and 15.5% in the patients aged 70 or more.]

**4.4.7. Other Precautions**
According to the foreign reports, the occurrences of cardiac infarction, cerebral infarction, etc. are reported when this drug was administered with other antineoplastic agents.

### 4.5 Interaction with other medicinal products and other forms of interaction

#### 4.5.1. Contraindications for coadministration (Bleo should not be coadministered with the following drugs.)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Signs, Symptoms, and Treatment</th>
<th>Mechanism and Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irradiation to the thorax and its peripheral</td>
<td>Signs and Symptoms: Such serious pulmonary manifestation as interstitial pneumonia or pulmonary fibrosis may occur. Treatment: See 4.4.2. Important Precautions in &quot;PRECAUTIONS&quot; section.</td>
<td>Both irradiation and this drug may induce serious interstitial pneumonia and pulmonary fibrosis.</td>
</tr>
</tbody>
</table>

#### 4.5.2. Precautions for coadministration (Bleo should be administered with care when coadministered with the following drugs.)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Signs, Symptoms, and Treatment</th>
<th>Mechanism and Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other antitumor agents</td>
<td>Signs and Symptoms: Such serious pulmonary manifestation as interstitial pneumonia or pulmonary fibrosis may occur. Treatment: See 4.4.2. Important Precautions in &quot;PRECAUTIONS&quot; section.</td>
<td>Both this drug and other antitumor agents may induce serious interstitial pneumonia and pulmonary fibrosis.</td>
</tr>
<tr>
<td>Irradiation for area of head and neck</td>
<td>Stomatitis and angular stomatitis may deteriorate. It may cause inflammation of pharyngolaryngeal mucosa infrequently, resulting in hoarseness.</td>
<td>Both irradiation and this drug may cause inflammation of pharyngolaryngeal mucosa.</td>
</tr>
</tbody>
</table>

### 4.6 Pregnancy and lactation

(1) The administration of this drug is not recommended to pregnant patients or women suspected of being pregnant. [This drug has been reported to cause fetal malformation in laboratory animals (mice and rats)]
(2) Administration to nursing mother should be avoided. If administration of this drug is absolutely necessary, instruct the patient to discontinue breast feeding. [The safety of this drug in nursing mothers has not been established.]

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

<table>
<thead>
<tr>
<th>Very common or Not know</th>
<th>Common</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Leukopenia</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea, vomiting and stomatitis</td>
<td>Angular stomatitis</td>
</tr>
<tr>
<td>General disorders and administrative site conditions:</td>
<td>Pyrexia* and malaise</td>
<td>Injection site induration</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td>Hepatocellular injury</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Scleroderma</td>
<td></td>
</tr>
<tr>
<td>Neoplasms, Benign and Malignant and Unspecified (Including Cysts And Polyps)</td>
<td></td>
<td>Pain at the tumor site</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td>Oligurea, Dysuria, pollakiuria, Urinary retention</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders:</td>
<td>Interstitial pneumonia and pulmonary fibrosis</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td>Alopecia, skin hypertrophy, pigmentation, nail disorder, nail discolouration and scratch dermatitis</td>
<td>Rash, urticaria and erythroderma</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hemorrhage</td>
<td>Shock, vein wall hypertrophy and venous stenosis</td>
</tr>
</tbody>
</table>

*: Fever may develop with a lag time of 45 hours or more after the administration of this drug. Because a dose- response relation exists between the fever and dose at a given time, if the fever is severe, appropriate measures should be taken such as administering a reduced dose at shorter intervals, or antihistaminic and antipyretic agents before and/or after administration of this drug.
Appendix B

Bleomycin
Company Core Data Sheet

4.9 Overdose
There are no reports.

5. PHARMACOLOGICAL PROPERTIES
Nonproprietary name: Bleomycin Hydrochloride (JAN)
Bleomycin (INN)
Abbreviation: BLM
Structural formula: The structure of its main component, Bleomycin A₂ (content ratio: 55–70%) is shown below.

Description: Bleomycin Hydrochloride occurs as a white to yellowish white powder. It is freely soluble in water and slightly soluble in ethanol (95%). It is hygroscopic.

5.1 Pharmacodynamic properties
ATC code: LO1D C01, other cytotoxic antibiotic

5.1.1. Antitumor activity
(1) In vitro: It has been demonstrated that bleomycin inhibits growth and DNA/protein synthesis in HeLaS3 cells, Ehrlich cancer cells and Yoshida sarcoma cells, etc.
(2) In vivo: Disappearance of spontaneous lympho-sarcoma in dogs is observed.

5.1.2. Mechanism of action
The main mechanism of action is the inhibition of DNA synthesis and the splitting of DNA strand.

5.2 Pharmacokinetic properties
PHARMACOKINETICS
< Pharmacokinetics and metabolism >
Pharmacokinetics of this drug is characteristic and bleomycin A₂, a main component of bleomycin, distributes highly in skin. When measured a biological activity of bleomycin distributed in each tissue, this drug remained as an active form in skin, lung, kidney and bladder but it was inactivated in other tissues such as liver and spleen, etc. From these
results, it was proved that this drug was especially effective against skin cancer and head and neck cancer without hematopoietic disorder. When 15 mg of this drug was intravenously administered to an adult, concentration in blood was 3 μg/mL just after administration and was < 0.5 μg/mL one hour later. The highest concentration in blood after intramuscular administration was approximately one-third of that after intravenous administration and it decreased slowly thereafter. Urinary excretion up to 24 hours was 38.3% after intravenous administration and 19.2% after intramuscular administration. When three patients with penile cancer were intravenously treated with 15 mg of this drug and were operated 30-37 minutes later, concentrations in blood and tumor were 0.69-0.94 μg/mL and 0.08-0.49 μg/mL, respectively. When one patient with testicular tumor was intravenously treated with a cumulative dose of 300 mg of this drug and was operated 7 days later, concentrations in skin and tumor were 430 μg/g and 4 μg/g, respectively. Urinary excretion as an intact form was 68%. Systemic clearance, distribution volume and a half-life in blood were 1.1 mL/min/kg, 0.27 L/kg and 3.1 hours, respectively.

< Blood concentration >

The figure below shows the serum concentrations of Bleomycin in groups of 4 cancer patients given 15 mg (potency) of bleomycin intravenously or intramuscularly by a crossover technique.

![Blood concentration graph]

5.3 Preclinical safety data
This drug has been reported to cause fibrosarcoma and renal carcinoma in a laboratory animal (rat) administered subcutaneously.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
None.

6.2 Incompatibilities
Not reported.

6.3 Shelf life
Expiration date: Two years

6.4 Special precautions for storage
Store at room temperature.
6.5 Nature and contents of container
Bleo for inj. 5 mg (potency): 1 vial
Bleo for inj. 15 mg (potency): 1 vial
Bleo for inj. 30 mg (potency): 1 vial

6.6 Special precautions for other handling
Technical measures: Avoid skin, mucous membrane, clothing and eye contact.
Precautions: After handling, wash hands and face thoroughly and gargle. Forbid entry of unauthorized persons to the handling area.
Precautions for safe handling: This material is a powerful drug designated by the Pharmaceutical Affairs Law (Japan). When handling, wear appropriate protective equipment and pay great attention.

7. MARKETING AUTHORISATION HOLDER
Nippon Kayaku Co., Ltd.
11-2, Fujimi 1-chome, Chiyoda-ku, Tokyo 102-8172, Japan.

8. MARKETING AUTHORISATION NUMBER(S)

<table>
<thead>
<tr>
<th>Approval No. (Japan)</th>
<th>5 mg potency</th>
<th>15 mg potency</th>
<th>30 mg potency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>21800AMX10209</td>
<td>21800AMX10210</td>
<td>21800AMX10211</td>
</tr>
</tbody>
</table>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
International birth date: December 16, 1968 (Japan)

10. DATE OF REVISION OF THE TEXT
February 2011