

· 抗腫瘤抗生素 ·

BLEOCIN 撲類惡注射劑

BLEOCIN for Injection 5mg：衛署藥輸字第019191號

BLEOCIN for Injection 15mg：衛署藥輸字第019124號

<注射用 Bleomycin Hydrochloride>

— 縮寫：BLM —

特效藥、指示用藥及處方藥

*警告：只可依照醫師等專業人員之指示與處方使用

儲存
1. 儲存於室溫（25°C以下）
2. 置於兒童無法拿取處

有效期限
2年（有效期限應標示於玻璃瓶身或包裝上）

使用注意事項
1. 在泡製後要盡快使用完畢
2. 避免接觸皮膚

	5mg（效價） 15mg（效價）
國際上市日期	1968年12月（日本）

警告

患有間質性肺炎（interstitial pneumonia）與肺纖維化（pulmonary fibrosis）等嚴重肺部症狀的患者使用BLEOCIN有時可能造成患者死亡，因此必須確定有這些症狀的患者適合使用BLEOCIN才可給予BLEOCIN。使用BLEOCIN治療期間應有醫師在旁觀察指導，並且在治療完成後追蹤情況（約2個月）；尤其是使用BLEOCIN治療60歲以上的老人或肺部有潛在疾病的患者時，更須在完全考慮「注意事項」中所列要點後才可施行治療。

若患者出現用力性呼吸困難（exertional dyspnea）、發燒、咳嗽、呼吸聲碎裂（水泡音）（crepitation, rale）、X光片出現異常影像，或者是A-aDO₂、DLco或PaO₂數值異常等情況時應立即停止治療，並且施行適當的處置。

禁忌症（BLEOCIN禁用於下列患者）：

- （1）肺功能嚴重受損的患者或胸部X光攝影顯示有瀰漫性纖維化（diffuse fibrotic）病變或其它顯著肺部病變的患者[肺功能受損或纖維化病灶等病變有可能惡化]
- （2）對本藥品或類似藥物（peplomycin）有過敏病史的患者。
- （3）腎功能出現嚴重病變的患者。[因為本藥會降低排泄作用，可能導致間質性肺炎或肺纖維化等嚴重肺部症狀。]
- （4）患有嚴重心臟疾病者。[因為本藥會降低心血管功能，可能導致間質性肺炎或肺纖維化等嚴重肺部症狀。]
- （5）胸部或胸部周圍曾接受放射線治療的患者。[見3.「注意事項」一節中的對於藥物交互作用的說明]

產品介紹（Description）

1. 成分組成（Composition）

BLEOCIN每玻璃瓶含有下列成分。

成分	活性成分	每玻璃瓶含量
	Bleomycin hydrochloride	5 mg（效價） 15 mg（效價）

2. 產品描述（Product Description）

BLEOCIN為白到淡黃色的注射用冷凍乾燥品。

成分/每玻璃瓶含量	pH	滲透壓比值
5mg（效價）	4.5 - 6.5	約為 1
15mg（效價）	4.5 - 6.5	約為 1

pH：將不同效價玻璃瓶的內容物用蒸餾水泡製成5mg（效價）/mL注射液時之pH值。

滲透壓比值：不同效價玻璃瓶的內容物溶解於5mL生理食鹽水中泡製成之溶液與生理食鹽水溶液兩者間滲透壓之比值。

適應症（Indications）

皮膚癌、頭頸部癌症（上頷癌、舌癌、唇癌、咽癌、喉癌、口腔癌等）、肺癌（尤其是原發性或轉移性的鱗狀上皮細胞癌）、食道癌、惡性淋巴瘤（網狀細胞肉瘤、淋巴肉瘤、Hodgkin's病等）。

用量與用法（Dosage and Administration）

1. 靜脈注射

用生理食鹽水或葡萄糖溶液這類適合靜脈注射的溶劑溶解15-30mg（效價）的Bleomycin hydrochloride，以慢速注入靜脈，為了避免發燒的情況發生，可將劑量減少到5mg（效價）以下。

2. 肌肉與皮下注射

以5mL生理食鹽水等合適的溶劑溶解15-30mg（效價）的Bleomycin hydrochloride，再以肌肉或皮下注射的方式注入患者體內。

皮下注射需使用劑量1mg（效價）/mL以下的Bleomycin hydrochloride注入病灶的鄰近部位。

3. 動脈注射

以5mL生理食鹽水或葡萄糖溶液等合適的溶劑溶解5-15mg（效價）的Bleomycin hydrochloride，接著將泡製好的溶液一次打入動脈中或是以持續性動脈灌注法（continuous intra-arterial infusion）投藥。

4. 注射頻率

按一般守則，一個星期注射兩次 BLEOCIN，可視患者情況增加為一天一次（每日）或減少到一星期一次。

5. 總劑量

給予 Bleomycin hydrochloride 的總劑量視腫瘤消失的情況而定，但最多不應超過 300mg（效價）。

<注意事項>

- (1) 不良反應 (adverse reactions) 的症狀表現在不同個體上會有顯著差異，由於相當小的劑量即有可能引起不良反應，因此充分瞭解關於本藥品使用的「注意事項」相當重要。
- (2) 總劑量不應超過 300mg（效價）；除此之外，在多路徑投藥 (multi-route administration) 的情況下必須考慮最後所有投藥路徑加總的劑量。
- (3) 當患者同時接受 peplomycin 治療時，必須按一般守則將 peplomycin 的投藥量納入 Bleomycin 總劑量計算。

注意事項 (Precautions)

1. 謹慎投藥（給予下列患者 BLEOCIN 時應小心，應當減少劑量或延長投藥時間間隔，按臨床觀察到的患者病況決定投藥量）

- (1) 有肺功能不良病史的患者。
[可能發生間質性肺炎或肺纖維化等嚴重肺部症狀。]
- (2) 60 歲以上的老年人。
[可能發生間質性肺炎或肺纖維化等嚴重肺部症狀。]
- (3) 腎功能不良的患者。
[可能出現強烈不良反應。]
- (4) 患有心臟疾病者
[可能出現強烈不良反應。]
- (5) 正在接受或曾接受胸部放射線治療的患者。
[可能發生間質性肺炎或肺纖維化等嚴重肺部症狀。]
- (6) 肝功能不良的患者。
[可能出現強烈不良反應。]
- (7) 水痘患者。
[可能引發致命的全身性功能失調]

2. 重要注意事項

(1) 間質性肺炎或肺纖維化

可能發生間質性肺炎或肺纖維化等嚴重肺部症狀，因此充分觀察患者情況 [見下方之 (2)] 是很重要的，並要瞭解呼吸聲碎裂（水泡音）可能是這些病症的早期徵候。若發現任何異常應立即停止投藥，並且施打腎上腺皮質素治療原發性肺纖維化以及給予適當的抗生素預防繼發性感染。

- 1) 即使投藥的劑量低於 150mg（效價），肺部有潛在疾病或 60 歲以上的患者發生間質性肺炎或肺纖維化的頻率仍然很高，因此需要極為細心的照護。
- 2) 以本藥品治療患者時必須持續審慎觀察發燒、咳嗽、呼吸困難等症狀，並且應追蹤監測 X 光片上的任何異常影像或呼吸聲碎裂（水泡音）症狀；同時，若備有肺泡-動脈氧氣壓力差 (Alveolar-arterial oxygen tension difference) A-aDO₂、肺動脈含氧量 (pulmonary arterial oxygen) Pao₂、一氧化碳擴散能力 DLco 等技術，也應對患者進行這些檢查。這些觀察與檢驗不止在投藥期間需定期施行，在投藥治療完成後仍須持續追蹤約 2 個月。
- 3) 若情況允許應每星期進行一次 A-aDO₂ 及 Pao₂ 等檢查，若連續兩週出現 A-aDO₂ 而上升而 Pao₂ 下降的情況，應立即停止投藥。若兩種檢查數值的其中一種惡化至超過 10 Torr 時，則必須仔細監測其它臨床症狀，若判斷患

者出現之症狀為本藥引起的不良反應，應立即停止投藥並開始給予患者類固醇類藥物。同樣地，若 DLco 下降超過 15% 亦應採取相同步驟處理。

在一定要使用本藥治療肺功能低下患者的情況下，治療後必須給予患者周全的照護，若發現任何肺功能更加惡化的跡象，應立即停止投藥。

- (2) 在長期投藥治療的療程中可能出現強烈不良反應，且症狀持續時間也較長，因此投藥治療時必須謹慎處理。
- (3) 若患者同時使用 peplomycin 或其它型式的 Bleomycin 治療，則毒性會有加成作用，因此比需審慎監測患者的不良反應。
- (4) 應當注意是否有出現感染或感染惡化以及出血的情形發生。
- (5) 用本藥治療兒童或已屆生育年齡的患者時，應當考慮本藥對性腺的異常影響。

3. 藥物交互作用

1) 協同用藥 (coadministration) 之禁忌症 (BLEOCIN 不應與下列藥物等治療共同使用)：

藥物或治療	徵候、症狀與治療	機轉與危險因子
胸腔或其周邊之放射線治療	徵候與症狀： 可能發生間質性肺炎或肺纖維化等嚴重肺部症狀。 治療： 見「注意事項」一節中的 2. 重要注意事項	放射線與本藥皆可能引起間質性肺炎或肺纖維化

2) 協同用藥之注意事項 (BLEOCIN 在與下列藥物或治療同時進行時應謹慎)：

藥物或治療	徵候、症狀與治療	機轉與危險因子
其它抗腫瘤藥物 放射線治療	徵候與症狀： 可能發生間質性肺炎或肺纖維化等嚴重肺部症狀。 治療： 見「注意事項」一節中的 2. 重要注意事項	本藥與其它抗腫瘤治療皆可能引起間質性肺炎或肺纖維化
頭頸部放射線治療	口腔炎 (stomatitis) 與口角炎 (angular stomatitis) 可能惡化。有時引起咽喉黏膜發炎，造成聲音沙啞。	放射線與本藥皆可能造成咽喉黏膜發炎。

4. 不良反應

<摘要> ¹⁾

在 1,613 名以本藥治療的患者中 (374 人接受研究，1,239 人在上市之初接受調查)，最常見的不良反應是間質性肺炎或肺纖維化這類的嚴重肺部症狀 (10.2%)、皮膚硬化、色素沈澱 (40.6%)、發燒與寒顫 (rigors) (39.8%)、禿頭 (29.5%)、食慾減退與體重減輕 (28.7%)、身體不適 (16.0%)、噁心與嘔吐 (14.6%)、口腔炎 (13.3%) 以及指甲產生變化 (11.2%)。

(1) 具臨床意義的不良反應

- 1) 間質性肺炎、肺纖維化 (10%)：因為可能發生嚴重的間質性肺炎或肺纖維化症狀，因此必需細心監測患者的情況，若 A-aDO₂、Pao₂、DLco 或 X 光片等檢查結果發現任何異常 [見 (1) - (3)「重要注意事項」]，或者是出現咳嗽、用力性呼吸困難、呼吸聲碎裂 (水

泡音)等肺部症狀,則應立即停止投藥,並且改以腎上腺皮質素與適當的抗生素治療患者。

2) 休克 (<0.1%): 因為BLEOCIN治療會升高休克發生的機率,若患者出現任何異常情況時應立即停用BLEOCIN並採取適當處置。(惡性淋巴瘤患者可能在第一-第二次投藥治療時出現休克的情形,所以在一開始與第二次治療時,BLEOCIN的劑量應少於5mg(效價),確定患者不會對本藥出現急性反應後才將劑量提高到一般使用的效價。)

3) 出血 (2%): 小心防範一些患者會由於本藥治療讓腫瘤病灶迅速壞死而出現出血的情況。

(2) 其它不良反應

	≥10%	10% >, ≥1%	<1%
過敏反應*1)		隨著發燒出現紅疹(rash)、蕁麻疹(urticaria)與紅皮症(erythroderma)	
皮膚症狀	禿投與皮膚增生、色素沈澱、指甲變形與褪色		
胃腸道症狀	食慾減退、噁心與嘔吐以及口腔炎	口角炎	腹瀉
肝臟症狀			肝功能失調
泌尿道症狀			少尿、排尿疼痛、頻尿且有尿液殘留感
血液學症狀			白血球減少
神經心理症狀		頭痛	暈眩
注射部位			
靜脈注射*2)			靜脈管壁增生與靜脈管徑縮小
肌肉或局部注射			出現硬結(induration)
其它	發燒*3) 與寒顫		腫瘤部位疼痛

*1) 此類情況停止用藥

*2) 出現這類情形時換改成注射部位或肌肉注射。

*3) 發燒可能會在注射後出現,持續4~5小時以上,因為在注射後一段期間內發燒與劑量間會呈現劑量-反應關係(dose-response relation),若發燒情況嚴重,則應做適當的處置,像是減少注射劑量與注射時間間隔,或是在注射本藥之前或/和之後給予患者抗組織胺或退燒藥物。

5. 使用於老年患者時

因為60歲以上的老年人可能出現間質性肺炎與肺纖維化症狀,因此注射時須謹慎處理。

[間質性肺炎與肺纖維化等嚴重肺部症狀發生頻率會隨著年齡上升,50歲以下發生率為5.9%,51-60歲為8.1%,61-70歲為10.9%,而70歲以上為15.5%。]

6. 使用於懷孕中、即將分娩或哺乳期的患者時

(1) 不建議孕婦或疑似懷孕之婦女注射本藥。

[研究指出本藥會造成實驗用動物胎兒畸形兒致死(大

老鼠與小白鼠)。]

(2) 哺乳中的母親應避免注射本藥,若必須施打本藥則需請患者停止哺乳。

[本藥對於哺乳中母親的安全性尚未確定。]

7. 使用於兒童時

必須採取特別照護以防注射在兒童身上時出現不良反應。

[本藥對於兒童的安全性尚未確定。]

8. 使用注意事項

(1) 靜脈注射: 可能出現血管疼痛的情形,因此必須注意注射的濃度以及點滴流速,速度盡可能放慢。

(2) 肌肉注射: 為避免影響到周圍組織與神經等,必須注意下列事項。

1) 因為肌肉注射可造成注射部位出現硬結,因此須避免在相同部位重複注射。對於新生兒、早產兒、幼童與兒童需採取特別照護。

2) 應當注意避免在神經聚集處注射。

3) 若發生注射針頭插入造成劇烈疼痛或是血液回流至注射針筒內之情形時,必須立即拔出針頭換別的部位注射。

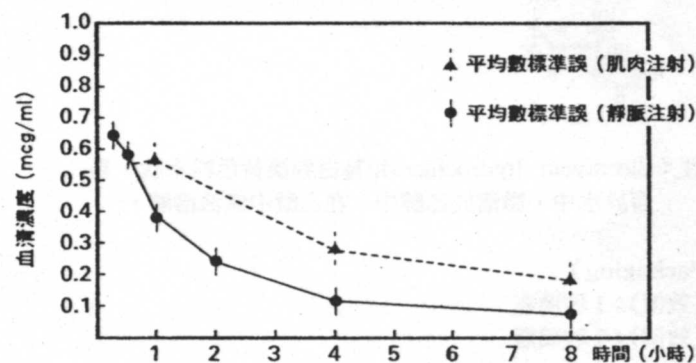
9. 其它注意事項

根據國外報告,本藥与其它抗腫瘤治療合併使用時,患者可能出現心肌梗塞或栓性腦中風(cerebral infarction)。

藥物動力學(Pharmacokinetics) 2)

<血液中濃度>

下圖中顯示4名癌症患者在交叉試驗(crossover design)中分組,以靜脈注射及肌肉注射投予15mg(效價)bleomycin後血清中Bleomycin的濃度變化。



臨床研究(Clinical Studies)

每種疾病的反應比率整理於下表中:

疾病	反應比率
皮膚癌	57.4% (58/101)
頭頸部癌症	55.6% (69/124)
鱗狀細胞肺癌	50.0% (11/22)
食道癌	70.6% (36/51)
惡性淋巴瘤	73.8% (31/42)
子宮頸癌	57.1% (52/91)
神經膠質瘤	41.0% (16/39)
甲狀腺癌	71.1% (32/45)

藥理學(Pharmacology) 3)-5)

1. 抗腫瘤活性

(1) 體外試驗(in vitro): 研究顯示bleomycin能夠抑制

HeLaS5細胞、Ehrlich癌細胞與Yoshida肉瘤細胞等的生長與DNA/蛋白質合成。

(2) 體內試驗 (*in vivo*): 研究顯示狗身上自然發生的肉瘤消失了。

2. 作用機轉

主要作用機轉為抑制DNA合成以及使DNA股 (strand) 斷裂。

物理化學 (Physicochemistry)

非專屬名稱 (Nonproprietary Name):

Bleomycin hydrochloride (JAN)

Bleomycin (INN)

縮寫 (Abbreviation): BLM

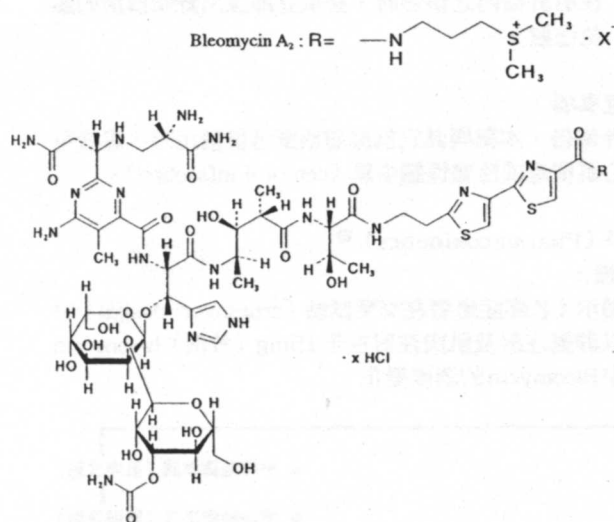
分子式 (Molecular formula):

$C_{55}H_{84}ClN_{17}O_{21}S_3 \cdot HCl$ (BLM-A₂)

分子重 (Molecular weight): 1487.49 (BLM-A₂)

結構式 (Structure formula): 下方為主要結構成分，

Bleomycin A₂ (含量比: 55-70 %)。



物理特性: Bleomycin hydrochloride 為白到淡黃色粉末狀，易容於水中，微溶於乙醇中，在乙醚中無法溶解。

包裝 (Packaging)

5mg (效價): 1玻璃瓶

15mg (效價): 1玻璃瓶

參考文獻 (References)

- 1) IYAKUHIN FUKUSAYO JOHO (Information on Adverse Reactions to Drugs), 17: (February, 1967)
- 2) Ikeda, S., et al.: GAN TO KAGAKU RYOHO (Jpn. J. Cancer Chemother), 7: 756 (1980)
- 3) Umezawa, H., et al.: J. Antibiotics, 20: 277 (1967)
- 4) Umezawa, H., et al.: J. Antibiotics, 21: 379 (1968)
- 5) Umezawa, H., et al.: J. Antibiotics, 20: 15 (1967)

製造廠:

Nippon Kayaku Co., Ltd.

239, Iwahanamachi, Takasaki-shi, GUNMA 370-1208
JAPAN

藥商:

台灣日化股份有限公司

台北市忠孝東路2段88號7樓702室

Powerful drug
 Designated drug
 Prescription-only drug

BLEOCIN

Bleomycin Hydrochloride for Injection, JMRAP®
 Abbreviation: BLM

BLEOMYCIN, an antineoplastic antibiotic agent discovered by Dr. Hamao Umezawa et al. in 1962, was shown by Dr. Tokuji Ichikawa et al., to be effective in treating skin cancers, cancers of the head and neck, lung cancer, esophageal carcinoma, malignant lymphomas, etc.

[COMPOSITION]

BLEOCIN is available in ampoules, each containing 15 mg (potency) of bleomycin hydrochloride, which needs to administer in dissolved state.

[INDICATION]

Skin cancers, cancers of the head and neck (maxillary carcinoma, tongue cancer, cancer of the lip, pharyngeal carcinoma, laryngeal carcinoma, cancer of the oral cavity, etc.), lung cancer (especially, primary and metastatic squamous cell carcinoma), esophageal carcinoma, cancer of the uterine cervix, malignant lymphomas (e.g., reticulosarcoma, lymphosarcoma, Hodgkin's disease, etc.), glioma, thyroid carcinoma.

* [DOSAGE AND ADMINISTRATION]

- Intravenous injection**
Dissolve 15 - 30 mg (potency) of BLEOCIN in about 5 - 20 ml of a solvent suitable for intravenous injection such as isotonic sodium chloride solution or a dextrose solution, and inject intravenously at a slow rate. If the treatment is accompanied by high fever, reduce the dose to 5 mg (potency) or less.
- Intramuscular and subcutaneous injection**
Dissolve 15 - 30 mg (potency) of BLEOCIN in about 5 ml of a suitable solvent such as isotonic sodium chloride solution and inject intramuscularly or subcutaneously. In cases of subcutaneous injection, inject a solution at a concentration of 1 mg (potency)/mg or less.
- Intra-arterial injection**
Dissolve 5 - 15 mg (potency) of BLEOCIN in a solvent suitable for injection such as isotonic sodium chloride solution or a dextrose solution, and administer by one-shot or continuous infusion.
- Frequency of injection**
Generally, BLEOCIN 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.
- Total dose**
Total dose of BLEOCIN should be not more than 300 mg·P, with the disappearance of tumor as the goal.

[PREPARATION OF SOLUTION]

Draw an appropriate volume (with reference to the [DOSAGE AND ADMINISTRATION]) of a suitable solution for injection such as isotonic sodium chloride solution or a dextrose solution into a syringe, and inject into an ampoule of BLEOCIN. Dissolve the contents and draw the solution again into the syringe before use.

* [WARNING]

Serious conditions such as interstitial pneumonia and pulmonary fibrosis etc. can 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 BLEOCIN and the patient should be kept under observation by a physician during the administration of the drug and for a certain period (approximately 2 months) after the completion of administration. Administration of BLEOCIN to elderly (more than 60 years old) or in cases with underlying pulmonary diseases should only be performed after full consideration of the warnings concerning its use. Administration should be halted immediately on appearance of the initial symptoms of exertional dyspnea, fever, cough, the presence of rales, abnormal chest X-ray findings and abnormalities of A-Do₂, Pao₂ or D_{Leo}, and appropriate measures should be taken.

[PRECAUTIONS]

1. General precautions

(1) Dosage

1) There is significant individual variation in the appearance of adverse reactions, and since adverse reaction can appear even with relatively small doses it is important to be fully attend to all warnings concerning use of BLEOCIN. It is necessary to begin with a low dosage, in relation to the condition of the patient and its symptom.

*2) Especially do not administer more than 300mg (potency) as a total dose in case of multi-route administration, it is necessary to consider the resulting additive dosage.

3) In cases that have received Peplomycin, the amount of that drug administered must be included in the computation of the overall dosage of Bleomycin.

* (2) Interstitial pneumonia or pulmonary fibrosis.

Serious adverse reactions such as interstitial pneumonia or fibrosis can develop. It is important to keep the patient under sufficient observation (see 2) below) and be aware that the appearance of rales can be an early sign of these conditions. If any abnormality is recognized, administration should be immediately halted, adrenal cortical hormones should be administered for the treatment of idiopathic pulmonary fibrosis and a suitable antibiotic for the prevention of secondary infection should also be given.

*1) In cases with underlying pulmonary diseases or in elderly cases (more than 60 years old), pulmonary symptoms appear with a high rate of frequency even with administration of low doses of not more than 150 mg, thus great care is required.

2) Patients receiving this drug should be maintained under observation for the development of fever, cough, exertional dyspnea and other clinical symptoms and should also be followed up to detect any abnormality on chest X-ray film, the appearance of rales. Also, where such examination techniques are available, alveolar-arterial oxygen tension difference (A-aDo₂), pulmonary arterial oxygen (Pao₂) and carbon monoxide diffusing capacity (D_{Leo}) should be examined. Carry out these observations 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 should be examined once per week if possible and if there is a decline during 2 consecutive weeks, administration should be halted. 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 decided that these are adverse reactions of the drug, administration should be immediately halted and administration of steroids commenced.

The same steps should be taken if there is a decrease of more than

15% in D_{Leo}. 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 halted immediately.

- With long-term administration, strong adverse reactions can appear and become prolonged, thus administration must be performed with care.
- In cases that have received peplomycin or other forms of bleomycin, this drug should be administered carefully because toxicity is thought to be additive, therefore the necessary caution to observe for side adverse reactions should be taken.
- Attention should be paid to the appearance or exacerbation of any bleeding tendency or infection.
- Particular care is required concerning the appearance of adverse reactions when administering the drug to children.
- In children or patients at an age capable of reproduction particular effects on the sexual glands should be considered.
- Do not administer the drug to the following patients
 - Patients with severe pulmonary dysfunction or with chest X-ray findings suggesting diffuse fibrotic changes or any other remarkable changes.
 - Patients with a history of hypersensitivity to this or a similar drug (peplomycin).
 - Cases with severe renal disorder.
 - Cases with severe cardiac disorder.
- In the following types of cases great caution should be exerted and the dosage should be reduced or the intervals between administrations of the drug should be increased.
 - Cases accompanied by, or with a history of, pulmonary dysfunction.
 - Elderly patients who is 60 years old or more. (serious complications can be caused).
 - Patients with renal dysfunction.
 - Patients with cardiac ailments.
 - Patients receiving, or having received, radiotherapy.
 - Patients with hepatic dysfunction.
 - Patients with varicella (fatal systemic dysfunctions can occur).

4. ADVERSE REACTION

- Lung:** Since severe interstitial pneumonia or pulmonary fibrosis can be caused it is necessary to make careful observations and if any change in A-Do₂, Pao₂ or D_{Leo} or any abnormality of the chest roentgenogram is recognized (see section 3) of (2) Pulmonary adverse reactions), or if clinical symptoms such as cough, exertional dyspnea or the appearance of rales develop, administration should be immediately halted and administration of adrenal cortical hormones and treatment with a suitable antibiotic commenced.
- Shock:** Because BLEOCIN treatment may on rare occasion give rise to shock, if any of signs or symptoms appear, withdraw BLEOCIN immediately, and take appropriate measures. (Because shock is likely to develop in patients with malignant lymphomas at the 1st-2nd administration, start BLEOCIN 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.
- Hypersensitivity:** Because BLEOCIN treatment may in some cases be accompanied by manifestations of hypersensitivity e. g., rashes, urticaria and erythroderma, associated with fever, withdraw BLEOCIN from such cases.
- Fever:** Fever may develop with a lag time of 4 - 5 hours or more after the administration of BLEOCIN. Because a dose-response relation exists between the fever and dose, if the fever is severe, administer a reduced dose at shorter intervals, or administer antihistaminic and antipyretic agents before and/or after administration of BLEOCIN.
- Hemorrhage:** Exercise care in hemorrhage which may in some cases result from a rapid necrosis of the cancer lesion due to BLEOCIN treatment.
- Skin and mucosa:** Scleroderma-like changes in the skin such as hypertrophy of the skin, pigmentation, deformation and discoloration of the nail, scratch dermatitis, alopecia and angular stomatitis may appear with BLEOCIN treatment. Exercise care especially at or above a cumulative dose of about 150 mg (potency) when these changes are likely to appear.
- Gastrointestinal:** BLEOCIN treatment may be accompanied by anorexia nausea and vomiting, and occasionally by diarrhea.
- Hepatic:** Hepatic disorder may on rare occasion occur with BLEOCIN treatment.
- Renal:** Renal disorder such as oligouria may accompany BLEOCIN treatment in some cases.
- Urinary:** BLEOCIN treatment may sometimes give rise to manifestations of urinary disorder such as micturition pain, pollakiuria and feeling of residual urine.
- Hematologic:** Leukopenia may occur with BLEOCIN treatment.
- Neuropsychic system:** Malaise, or occasionally headache and dizziness may occur under BLEOCIN treatment.
- Site of administration:**
 - Repeated intravenous injection may give rise to hypertrophy of the venous wall and narrowing of the venous lumen around the administration site. In such cases, change the administration site or switch to intramuscular injection.
 - Intramuscular or local injection of BLEOCIN may cause hardening (induration) of the administration site.
- Others:** Pain may appear at the tumor site under BLEOCIN treatment.

** 5. USE IN THE ELDERLY

Administer BLEOCIN carefully in the Elderly. (See [WARNING] and 1. General precautions)

** 6. USE DURING PREGNANCY OR LACTATION

- It has been reported in animal experiments (mice and rats following intraperitoneal administration) that BLEOCIN is teratogenic. Therefore, it is advisable not to administer the drug to pregnant women or women suspected of pregnancy.
- It has been established whether it is safe to administer BLEOCIN during lactation. Therefore, if it is necessary to administer the drug to a nursing woman, instruct the woman to stop nursing.

** 7. DRUG INTERACTIONS

- Adverse reactions such as pulmonary symptoms can be exacerbated by the combined administration with other antineoplastic agents.
- Adverse reactions, including pulmonary symptoms, can be exacerbated by the combined administration of radiotherapy. It is particularly important to avoid irradiation of the thorax and surrounding structures.
- The combined administration of radiotherapy for tumors of the head and neck can exacerbate stomatitis and angular stomatitis. On occasion it can cause inflammation of pharyngeal mucosa, resulting in hoarseness.

8. CAUTIONS IN USE

- Intravenous administration:** Phlebitis can occur, therefore, it is important to give ample consideration to concentration and speed of delivery. Intravenous administration should be done as slowly as possible.
- Intramuscular administration:** To avoid affecting tissue and nerves the following points must be considered.
 - Intramuscular administration can cause induration. Avoid repeated injections at the same site. Especial care must be exercised in cases of neonates, prematures, infants and children.
 - Avoid sites with a large distribution of nervous tissue.
 - In cases complaining of extreme pain or in which there is reflux of blood, immediately withdraw the needle and select another site.
- Caution in cutting the ampoule:** To prevent glass fragments entering the liquid, wipe with ethanol-impregnated cotton after cutting with the file.

9. OTHERS

According to foreign report, Myocardial Infarction and Cerebral Infarction were occurred when administered BLEOCIN with other antineoplastic agents.

(PHARMACOLOGY) ¹⁻³⁾

1. Antitumor activity

- In vitro:** It has been demonstrated that bleomycin inhibits growth and DNA/protein synthesis in HeLa S₃ cells, Ehrlich carcinoma cells and Yoshida sarcoma cells.
- In vivo:** Bleomycin exerts an antitumor effect on dog spontaneous lymphosarcoma.

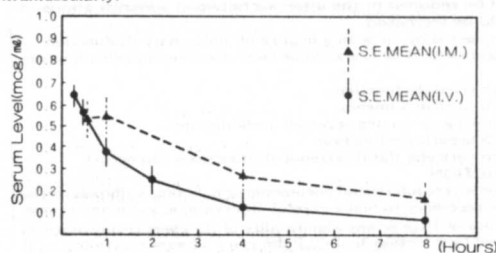
2. Mode of action

The main mode of action is the inhibition of DNA synthesis and the splitting of DNA strand.

(PHARMACOKINETICS) ⁴⁾

Blood concentration

The figure below shows the blood concentrations of BLEOCIN in groups of 4 cancer patients given 15 mg (potency) of BLEOCIN intravenously or intramuscularly.



(CLINICAL STUDIES)

Clinical efficacy

The response rate of patients evaluable in the each disease is 57.4% (58/101) in skin cancer, 55.6% (69/124) in the tumor of head and neck, 50.0% (11/22) in the squamous cell lung cancer, 70.6% (36/51) in the cancer of the esophagus, 57.1% (52/91) in the cancer of the uterine cervix, 73.8% (31/42) in the malignant lymphomas, 41.0% (16/39) in the glioma and 71.1% (32/45) in the cancer of the thyroid.

Adverse reactions ⁵⁾

The result of investigating 1,613 patients show the following high incident symptoms; the pulmonary manifestation, the most serious adverse reaction to this product, have been shown at 10.2% of the patients and also, changes of skin, nail and mucosa; alopecia (29.5%), sclerosis of the fingers and palms, pigmentation (40.6%), change of nail (11.2%) and stomatitis (14.6%), gastrointestinal disturbances; anorexia (28.7%) and nausea and vomiting (14.6%), others; fever and chill (39.8%) and general malaise (14.8%).

Pulmonary manifestations

(1) Age and pulmonary manifestations

The frequency of pulmonary manifestation by age has been 5.9% in the under the 50's, 8.1% in the 50's, 10.9% in the 60's and 15.5% in the patients aged 70 or more. In other words, care must be exercised in administering BLEOCIN to aged patients.

(2) Underlying pulmonary diseases and pulmonary manifestations

In the patient with an underlying disease of the lung, the incidence of pulmonary manifestation with BLEOCIN is high even at a cumulative dose of not more than 150mg (potency). Exercise particular care in administering the injection to such a patient.

(3) Methods for early prediction of pulmonary manifestation

- Clinical manifestations:** Exercise care when the patient does not feel well for unknown reasons, associated with nonproductive cough, sputum, anorexia, and especially persistent fever (37.5 – 38°C or higher), or when the patient gasps on moving the body, or the outpatient gasps after walking, or when crepitation is audible in the lung base on auscultation.
- Chest X-ray film:** Take chest X-ray film before, and once every 2 weeks (at each cumulative dose of 40 – 60mg (potency) during the treatment). When any abnormal shadow has appeared on the film (beginning with bibasilar lower lobe infiltrates in many cases), withdraw the treatment.
- Pulmonary function tests (VC, DL_{CO}, etc.) and arterial blood gas analysis (PaO₂):** Make the tests and analysis as frequently as possible, and withdraw the treatment when any parameter has dropped by 10% or more, compared with the pretreatment value.

(NON-CLINICAL STUDIES)

1. Acute toxicity: LD₅₀(mg(potency)/kg)

Animals	Route of admn	intravenous			intraperitoneal	subcutaneous
		♂	♀			
mouse	♂	315			465	300
	♀	281			285	282
rat	♂				252	252
	♀				215	339

2. Subacute toxicity and chronic toxicity

The i.p. application of 0.3 – 24.3 mg/kg of the drug was given to rats for the subacute toxicity test for 30 consecutive days, and the i.p. application of 0.15 – 2.4 mg/kg of the drug was administered to rats for the chronic toxicity test for 6 consecutive months. The results indicated that both of the subacute toxicity and the chronic toxicity are related to the doses of BLEOCIN it revealed general emaciation and incontinence of urine. The death cases were seen at the subacute toxicity test of the i.p. application of more than 8.1 mg/kg of the drug, and at the chronic toxicity test of the i.p. application of more than 0.3mg/kg of the drug. The subacute toxicity test of the i.p. application of more than 2.7mg/kg, and the chronic toxicity test of the i.p. application of more than 1.2mg/kg exert thickening of foot, bleeding of nail and omission of nail.

Autopsy demonstrated the congestions of lung, etc. relatively to the dosages.

3. Reproductivity

At the period of rats organogenesis, BLEOCIN of 0.3 – 1.0 mg/kg was administered into abdominal cavity. The results indicated that the large dose of BLEOCIN showed teratogenic, growth-inhibition, increase of skeletal abnormalities and retardation of ossification on fetus of rats.

4. Antigenicity

Antigenicity is not found at the test on guinea pig and rabbit.

(DESCRIPTION)

Product description

BLEOCIN is white to yellowish white powder and a lyophilized finish product for injection.

pH and osmotic pressure ratio

	5 mg(potency)/A	15 mg(potency)/A	30 mg(potency)/A
pH	4.5 ~ 6.5	4.5 ~ 6.5	4.5 ~ 6.5
Osmotic pressure ratio	approx. 1	approx. 1	approx. 1

pH: The pH value of a solution prepared by reconstituting the respective ampoule contents with distilled water for injection into a 5 mg (potency)/ml solution.

Osmotic pressure ratio: Ratio of the osmolality between a solution of the respective ampoule contents in 5 ml of 0.9% physiological saline and that of 0.9% physiological saline solution.

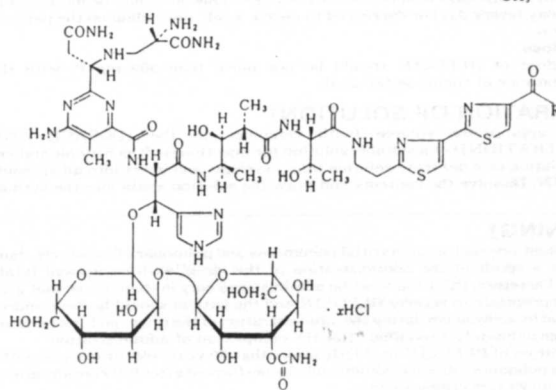
Physicochemical properties of the active ingredient

Non-proprietary name: Bleomycin hydrochloride

Molecular formula: C₅₅H₈₄ClN₁₇O₂₃S₃·HCl(BLM-A₂)

Molecular weight: 1487.49 (BLM-A₂)

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, slightly soluble in ethanol, and practically insoluble in ether.

(STORAGE AND HANDLING)

(1) Caution: Use only pursuant to the prescription or direction of a physician, etc.

(2) BLEOCIN is a Powerful, Designated and Prescription-only drug.

(3) After reconstitutions, use as promptly as possible.

Storage:

Store at room temperature.

Expiration date:

2 years (Indicated on the outer package.)

(PACKAGING)

5 mg (potency): 1 ampoule
15 mg (potency): 1 ampoule
30 mg (potency): 1 ampoule

(REFERENCES AND REQUESTS FOR REFERENCES)

References

- Umezawa, H; et al: J. Antibiotics, 20, 277(1967)
- Umezawa, H; et al: J. Antibiotics, 21, 379(1968)
- Umezawa, H; et al: J. Antibiotics, 20, 15(1967)
- Ikedo, S; et al: GAN TO KAGAKU RYOHO (Jpn. J. Cancer Chemother.), 7, 756 (1980)
- IYAKUJIN FUKUSAYO JOHO (Information on Adverse Reactions to Drugs) No. 17 (1976)

Requests for References

Nippon Kayaku Co., Ltd.
International Div., Pharmaceuticals group.
(Address) 11-2, Fujimi 1-chome, Chiyoda-ku, Tokyo 102-8172, Japan.
(TEL) 813-3237-5072