抗腫瘤抗生素

BLEOCIN 撲類黴注射劑

BLEOCIN for Injection 5mg：衛署藥統字第019191號
BLEOCIN for Injection 15mg：衛署藥統字第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導與處方使用

| 儲存 | 1. 儲存於室溫（25℃以下）
2. 置於兒童無法拿取處 |
|------|----------------------------------|

| 有效期限 | 2年（有效期間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 |

警告

患有間質性肺炎（interstitial pneumonia）與肺纖維化（pulmonary fibrosis）等嚴重肺部病變的患者使用BLEOCIN有時可能造成患者死亡，因此必須確定有這些病變的患者適合使用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受到疾病的患者時，更須在完全考慮「注意事項」中所列要求後才施行治療。

若患者出現用力性呼吸困難（exertional dyspnea）、發燒、咳嗽、呼吸急促（水泡音）（crepitation，rare）及X光片出現異常影像，或是A-aDO2、DLco或PaO2數值異常時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光攝影顯示有表現性纖維化（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（peptomycin）有過敏反應史的患者

(3) 腎功能出現嚴重病變的患者，[因本藥本會降低排泄作用，可能導致間質性肺炎或肺纖維化等嚴重肺部病狀]。

(4) 患有嚴重腫瘤性疾病者，[因本藥本會降低心肌功能，可能導致腫瘤性肺炎或肺纖維化等嚴重肺部病狀]。

(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。

<table>
<thead>
<tr>
<th>成分</th>
<th>活性成分</th>
<th>每玻璃瓶含量</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bleomycin hydrochloride</td>
<td>5 mg（效價）</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 mg（效價）</td>
</tr>
</tbody>
</table>

2. 產品描述（Product Description）

BLEOCIN為白色到淡黃色的注射用冷凍乾燥品。

<table>
<thead>
<tr>
<th>成分/每玻璃瓶含量</th>
<th>pH</th>
<th>渗透壓比值</th>
</tr>
</thead>
<tbody>
<tr>
<td>5mg（效價）</td>
<td>4.5 - 6.5</td>
<td>約為1</td>
</tr>
<tr>
<td>15mg（效價）</td>
<td>4.5 - 6.5</td>
<td>約為1</td>
</tr>
</tbody>
</table>

pH值：將不同效價玻璃瓶的內容物物用蒸餾水泡製成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液於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、頭與顱部癌症（上頜癌、舌癌、脣癌、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兩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。

皮下注射需使用溶量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. 注射频率
按一般守则，一个期内注射次数BLEOCIN，可视患者情况增加为一天一次（每日）或减少到一星期一次。

5. 總劑量
給予BLEOCIN hydrochloride的總劑量視腫瘤消失的狀況而定，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
有顯著差異，故於相當然量的劑量內，可能引起不良反應，因此充分瞭解關於本藥品使用之「注意事項」相當重要。
(2) 總劑量不應超過300mg（效價）；此外，在多節點
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peptomycin治療時，必須按一般守則將
tomycin的投藥量納入 BLEOCIN總劑量計算。

嚴重注意事項（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狀況決定投藥量）
(1) 有肺功能不良史的患者。
(2) 60歲以上之老年人。
(3) 肺功能不良的患者。
(4) 患有心臟疾病者。
(5) 正在接受或曾經接受胸部放射線治療的患者。
(6) 肺功能不良的患者。
(7) 水痘患者。

2. 重要注意事項
(1) 腫門性肺癌或肺纖維化
可能發生腫門性肺癌或肺纖維化等嚴重肺部症狀，因此充分觀
察患者狀況[見下方之 2)]是重要的，並要觀察呼吸困難（水泡音）
及其它腫瘤相關症狀，若發現任何異常應立即停止投藥，並且施
打胸腔穿刺素原發性肺纖維化及給予適當的抗生素預防感染性性。
(1) 使投藥的劑量不應高於150mg（效價）。肺部有潛在疾病或
60歲以上的患者發生腫門性肺癌或肺纖維化的頻率仍然
很高，因此需要極為細心的照護。
(2) 以本品治療肺癌患者時必須持續審慎觀察Currency、咳嗽、呼
吸困難等症狀，此乃肺部有腫瘤的早期徵候。若發現任何異常應立即
停止投藥。施打胸腔穿刺素原發性肺纖維化及給予適當的抗生素預防感染性性。
(3) 若出現病情惡化之情形
應立即停止投藥，若發生惡化至超過10 Torr時，則必須施打胸腔穿刺素原發性肺纖維化及給予適當的抗生素預防感染性性。

＜注意事項＞
(1) 不良反應（adverse reactions）的症狀表現在不同個體上
有顯著差異，故於相當然量的劑量內，可能引起不良反應，因此充分瞭解關於本藥品使用之「注意事項」相當重要。
(2) 總劑量不應超過300mg（效價）；此外，在多節點
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peptomycin治療時，必須按一般守則將
tomycin的投藥量納入 BLEOCIN總劑量計算。

3. 潤腸交作用
1) 協同用藥（coadministration）之禁忌症（BLEOCIN不
應與下列藥物等治療同時使用）：

<table>
<thead>
<tr>
<th>藥物或治療</th>
<th>傾斜、症狀與治療</th>
<th>機轉與危險因子</th>
</tr>
</thead>
<tbody>
<tr>
<td>胸腔或其周邊之放射線治療</td>
<td>傾斜與症狀：可能發生腫門性肺癌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。</td>
<td>放射線與本藥皆可能引起腫門性肺癌或肺纖維化。</td>
</tr>
<tr>
<td>其它抗腫瘤藥物放射線治療</td>
<td>傾斜與症狀：可能發生腫門性肺癌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。</td>
<td>本藥與其它抗腫瘤治療皆可能引起腫門性肺癌或肺纖維化。</td>
</tr>
</tbody>
</table>

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）：

<table>
<thead>
<tr>
<th>藥物或治療</th>
<th>傾斜、症狀與治療</th>
<th>機轉與危險因子</th>
</tr>
</thead>
<tbody>
<tr>
<td>頭頸部放射線治療</td>
<td>口腔炎 ( stomatitis)</td>
<td>放射線與本藥皆可能造成咽喉黏膜發炎。</td>
</tr>
<tr>
<td>與口腔炎相關 (angular stomatitis)</td>
<td>可能惡化，口腔炎 ( stomatitis)</td>
<td>可能惡化，口腔炎 ( stomatitis)</td>
</tr>
<tr>
<td>與會喉痛 (angina stomatitis)</td>
<td>可能惡化，口腔炎 ( stomatitis)</td>
<td>可能惡化，口腔炎 ( stomatitis)</td>
</tr>
</tbody>
</table>

4. 不良反應
＜摘要＞1)
在1,163名以本品治療的患者中（374人接受研究，1,239
人在上市之查接受調查），最常見的不良反應是腫門性肺癌
或肺纖維化此類的嚴重肺部症狀（10.2%）。皮膚硬化
性滲進（40.6%）、乾燥裂開（39.8%）、皮膚
癞癬病（29.9%）、飲食退化及體重減輕（28.7%）、身體不適
（16.0%）, 植入假體（14.6%）, 口腔炎（13.3%）
及指甲產生變化（11.2%）。

(1) 資料的臨床意義的不良反應
1) 腫門性肺癌、肺纖維化（10%）：因為可能發生嚴重
的腫門性肺癌或肺纖維化症狀，因此必須細心監測患
者的情況，若 A-do2、Dlo2、Dloco 或光片等檢查
結果發現任何異常（見（1）3）「重要注意事項」。若
測試發現咳嗽、呼吸困難、呼吸聲嘶裂（水
泡音）等肺部病症，则应立即停止投药，并且改以肾
上腺皮质素与適當的抗生素治療患者。
2) 休克（<0.1%）：因用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。（恶性淋巴瘤患者可能在
第一次或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

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

*1) 適用這種情形停止用藥
*2) 出現這種情形時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溶液間會呈現情況，反應關係
（dose-response relation）。若發燒情況嚴重，則應做適當
的處置，以減少注射物質與注射時間間隔，或是在注射
本藥之前/及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都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）不建議懷孕或懷疑懷孕之婦女注射本藥。
（2）懷孕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。

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。

8. 使用注意事項
（1）靜脈注射：可能出現血管痛的情形，因此必須注意注
射的濃度以及點滴速度，速度盡可能改慢。
（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
童與兒童應採取特別照護。
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，必須立即拔除針頭換別的部
位注射。

9. 其它注意事項
根據國外報告，本藥與其它抗腫瘤療法治合使用時，患者可
能出現心肌梗塞或栓塞性腦中風（cerebral infarction）

藥物動力學（Pharmacokinetics）

<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

<table>
<thead>
<tr>
<th>疾病</th>
<th>反應比率</th>
</tr>
</thead>
<tbody>
<tr>
<td>皮膚癌</td>
<td>57.4% (58/101)</td>
</tr>
<tr>
<td>頭顱部癌症</td>
<td>55.6% (69/124)</td>
</tr>
<tr>
<td>網狀細胞肺癌</td>
<td>50.0% (11/22)</td>
</tr>
<tr>
<td>食道癌</td>
<td>70.6% (36/51)</td>
</tr>
<tr>
<td>恶性淋巴瘤</td>
<td>73.8% (31/42)</td>
</tr>
<tr>
<td>子宮頸癌</td>
<td>57.1% (52/91)</td>
</tr>
<tr>
<td>神經膠質瘤</td>
<td>41.0% (16/39)</td>
</tr>
<tr>
<td>甲狀腺癌</td>
<td>71.1% (32/45)</td>
</tr>
</tbody>
</table>

藥理學（Pharmacology）

1. 抗腫瘤活性
（1）體外試驗（in vitro）：研究顯示bleomycin能夠抑制
HeLaS细胞、Ehrlich癌细胞與Yoshida肉瘤细胞等的生长與DNA/蛋白质合成。

(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）断裂。

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_{66}H_{84}ClN_{17}O_{21}S_{3}·HCl (BLM·A2)

分子量（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為白色淡黃色粉末狀，易溶於水中，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)

製造廠：
Nippon Kayaku Co., Ltd.
239, Iwahana-machi, 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
ANTINEOPLASTIC ANTIMICROBIAL AGENT
BLEOCIN
Beclomycin Hydrochloride for Injection. JMRAP®
Abbreviation: BLM

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

[COMPOSITION]
BLEOCIN is available in ampoules, each containing 5 mg (potency) of beclomycin hydrochloride, which needs to be administered 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 bronchial metastatic squamous cell carcinoma), esophageal carcinoma, cancer of the uterine cervix, malignant lymphomas (e.g., nodular lymphoma, lymphosarcoma, Hodgkin's disease, etc.), glioma, thyroid carcinoma.

[DOSAGE AND ADMINISTRATION]

1. Intravenous injection
   Discontinue 5 - 15 mg (potency) of BLEOCIN in about 5 - 20 ml of a suitable solvent for intravenous injection such as isotonic sodium chloride solution or phosphate buffered saline. Administer slowly over several minutes. Do not inject intravenously at a rate faster than 1 mg/min. If the rate is too high, the patient may experience chills or fever.

2. Phlebotomy
   Discontinue 5 - 15 mg (potency) of BLEOCIN in about 5 ml of a suitable solvent such as isotonic sodium chloride solution and inject intramuscularly or subcutaneously. In case of subcutaneous injection, inject a solution at a concentration of 1 mg (potency)/ml or less.

3. Intramuscular injection
   Discontinue 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 intramuscular or subcutaneous injection.

4. 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.

5. Total dose
   Total dose of BLEOCIN should not be more than 300 mg-P, with the appearance of toxic side effects such as nausea, vomiting, etc.

[PREPARATION OF SOLUTION]
An appropriate volume (with reference to the DOSAGE AND ADMINISTRATION) of a suitable solvent 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.

[WARRANT]
Serious conditions such as interstitial pneumonia and pulmonary fibrosis etc. can develop as a result of the administration of the 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 and after the administration of the drug. If the symptoms of the drug appear within a period of 2 - 3 days after the completion of administration, administration of BLEOCIN should be stopped immediately.

[NOTICE]
Serious adverse reactions such as interstitial pneumonia or other fibroses can develop. It is important to keep the patient under sufficient observation (see 2 below) and be aware that the appearance of these conditions is an early sign of the patient's condition and that if amniblastoma is recognized, administration should be immediately halted, adrenal cortical hormones should be administered for the treatment of interstitial pneumonia or pulmonary fibrosis. A suitable antibiotic for the prevention of secondary infection should also be given.

1) 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-P, thus good care is required.

2) Patients receiving this drug should be maintained under observation for the development of cough, fever, dyspnea and other clinical symptoms and should also be followed up to detect any abnormality in chest X-ray film, the appearance of the drug, also, where such examination techniques are available, alveolar-arterial oxygen tension difference (AaDO2), pulmonary arterial oxygen (Pao2) and carbon monoxide diffusion capacity (Dco) should be examined. Carry out laboratory tests during the administration of the drug, but also for a period of approximately 2 months after the completion of administration.

3) A-aDO2 and Adverse reaction examination once per week if possible and if there is a decline during 2 consecutive weeks, administration should be halted. It is important to observe the vital signs (greater than 10 Torr) carefully, 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 it is a decrease of more than 15% in Dco. In cases with poor pulmonary function in which administration is unavoidable, the treatment must be followed with utmost caution. Further detailed information on further care of the patient after administration is function is recognized, administration should be halted immediately.

4) With long-term administration, strong adverse reactions can appear and once these have become prolonged, feedback with treatment is necessary.

5) In cases that have received pleomycin or other forms of bleomycin, this drug should be administered at an initial dose, therefore the necessary caution to observe for side adverse reactions should be taken.

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

7) Particular care should be taken concerning the appearance of adverse reactions when administering the drug to children.

8) In children or patients with renal insufficiency, particular attention should be paid to the sexual glands should be considered.

2. Do not administer the drug to the following patients:

1) Patients with severe pulmonary dysfunction or chest X-ray findings suggesting diffuse fibrotic changes or any other remarkable changes.

2) Patients with a high degree of sensitivity to this or a similar drug (pleomycin).

3) Cases with severe renal disorder.

4) Cases with severe cardiac disorder.

3. In the following types of cases great caution should be exerted and the dosage should be adjusted to be kept between administrations of the drug should be increased.

4. Cases accompanied by, or with a history of, pulmonary dysfunction.

5. Elderly patients who are 60 years old or more. (serious complications can be caused).

6. Patients with renal dysfunction.

7. Patients with cardiac ailments.

8. Patients receiving, or having received, radiation therapy.

9. Patients with hepatic dysfunction.

10. Patients with varicose (fatal systemic dysfunctions can occur).

4. ADVERSE REACTION

1) Lung: Since severe interstitial pneumonia or pulmonary fibrosis can be caused, it is necessary to make close careful observations and if any change in A-aDO2 or Dco or any abnormality of the chest roentgenogram is recognized (see 2 above), use of O2 is recommended. Adverse reactions of clinical symptoms such as cough, dyspnea or the appearance of cyanosis, steatorrhea in the appearance of cyanosis, steatorrhea in the appearance of cyanosis, steatorrhea in the appearance of cyanosis, steatorrhea in the appearance of steatorrhea in the appearance of steatorrhea in the appearance of steatorrhea, nausea, vomiting, etc. are sometimes recognized. If established that no acute reactions, of the drug occur, increase the dose to the usual level.

3) Hypersensitivity: In the use of BLEOCIN is in some cases be accompanied by manifestations of hypersensitivity e.g., rashes, urticaria, fever etc. In such cases, administration of corticosteroid and adrenaline should be used immediately.

4) 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 of the drug. After establishing that no acute reactions to the drug occur, increase the dose to the usual level.

5) Hypersensitivity: In the use of BLEOCIN is in some cases be accompanied by manifestations of hypersensitivity e.g., rashes, urticaria, fever etc. In such cases, administration of corticosteroid and adrenaline should be used immediately.

6) Skin and mucosa: Scleroderma-like changes in the skin such as hyperrophy of the skin, pigmentation, deformation and discoloration of the nail, scratch dermatitis, also, 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.

7) Gastrointestinal: BLEOCIN treatment may be accompanied by nausea, vomiting, anorexia, and diarrhea. If established that no acute reactions to the drug occur, increase the dose to the usual level.

8) Hepatic: Hepatic disorder may occur on rare occasion with BLEOCIN treatment.

9) Renal: Renal disorder such as oliguria may accompany BLEOCIN treatment in some cases.

10) Urinary: BLEOCIN treatment may sometimes give rise to manifestations of urinary disorder such as micturition pain, pollakiuria and feeling of residual urine.

11) Hematologic: Leukopenia may occur with BLEOCIN treatment.

12) Neuropsycosomatic: Systemic malaise, or occasionally headache and dizziness may occur under BLEOCIN treatment.

13) Site of administration:

1) Repetitive intramuscular injection may give rise to hypertrophy of the vein wall and narrowing of the venous lumen around the administration site. In such cases, change the administration site or switch to intramuscular injection.

2) Intramuscular or Intravenous injection of BLEOCIN may cause hardening (induration) of the administration site.

14) Others: Pain may appear at the tumor site under BLEOCIN treatment.

5. USE THE ELDERLY

Administer BLEOCIN carefully in the Elderly. See (WARNING) and (PRECAUTIONS) for details.

6. USE DURING PREGNANCY OR LACTATION

1) It has been reported in animal experiments (mice and rats following administration of BLEOCIN to pregnant animals) that BLEOCIN is teratogenic. Therefore, it is advisable not to administer the drug to pregnant women.

2) 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 discontinue breast-feeding.

7. DRUG INTERACTIONS

Adverse reactions of pulmonary symptoms can be exacerbated by the combined administration with other antineoplastic agents. In cases of severe reactions, the drug must be administered by the combined administration of radiotherapy. It is particularly important to avoid irradiation of the thorax and surrounding structures. The combined administration of radiotherapy 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

(1) 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.

(2) Intramuscular administration: To avoid affecting tissue and nerves, the following points must be considered:

1) Intramuscular administration can cause induration.
2) Avoid repeated injections at the same site. Especial care must be exercised in cases of neonates, premature, infants and children.
3) Avoid sites with a large distribution of nervous tissue.
4) In cases complaining of extreme pain or in which there is reflux of blood immediately withdraw the needle and select another site.

(3) Caution in cutting the ampoule: To prevent glass fragments entering the liquid, wipe with ethanol-imregnated 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) 113

1. Antitumor activity

(1) In vivo: It has been demonstrated that bleomycin inhibits growth and DNA/protein synthesis in HeLa S3 cells, Ehrlich carcinosarcoma cells and Yoshida sarcoma cells.

(2) In vitro: 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) 41

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 evaluated in the each disease is 57.4% (58/101) in skin cancer, 55.6% (69/124) in the tumor of head and neck, 50.6% (11/22) in the squamous cell lung cancer in the experiment of the effectiveness especially in the patients aged 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) 33

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%), scoliosis of the fingers and palms, pigmentation (46.6%), change of nail (11.2%) and stomatitis (14.6%), gastrointestinal disturbances, anorexia (38.7%) 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 50s, 8.1% in the 50s, 10.9% in the 60s 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

1) 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.

2) 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 bilateral lower lobe infiltrates in many cases), withdraw the treatment.

3) Pulmonary function test(VC, DLco 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)

<table>
<thead>
<tr>
<th>Species</th>
<th>Intravenous</th>
<th>Intraperitoneal</th>
<th>Subcutaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>mouse</td>
<td>315</td>
<td>465</td>
<td>300</td>
</tr>
<tr>
<td>rat</td>
<td>281</td>
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<tr>
<td></td>
<td>215</td>
<td>339</td>
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</table>

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 – 24.3 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 exerted thickening of foot, bleeding of nail and omination of blood immediately withdraw the needle and select another site.

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.

<table>
<thead>
<tr>
<th>pH and osmotic pressure ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
</tr>
<tr>
<td>5mg(potency)/A</td>
</tr>
<tr>
<td>4.5 ~ 6.5</td>
</tr>
<tr>
<td>Osmotic pressure ratio</td>
</tr>
<tr>
<td>approx. 1</td>
</tr>
<tr>
<td>pH: The pH value of a solution prepared by reconstituting the respective amide contents with distilled water for injection into a 5 mg (potency)/ml solution</td>
</tr>
</tbody>
</table>

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

(Physicochemical properties of the active ingredient)

Proprietary name: Bleomycine hydrochloride

Molecular formula: C₂₉₆H₃₅Cl₁₂N₄O₂₂S₄·H₂Cl·H₂O

Molecular weight: 1487.49 (BLM-A₅)

Structural formula: The structure of its main component, bleomycin A₅ (content ratio: 55 ~ 70%) is shown below.

![](bleomycin.png)

Description: Bleomycine 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)


4) Jiro, S.: Japan J. Chemother., 11, 7546(1967)

5) YAKUHIN FUKUSAYO JOHO (Information on Adverse Reactions to Drugs) No. 17 (1976)

(Requests for References)

Nippon Kayaku Co., Ltd.

International Div., Pharmaceuticals group.

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(TEL) 813-2327-5072

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