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Wolters Kluwer

Bleomycin: Drug information

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(For additional information see "Bleomycin: Patient drug information" and see "Bleomycin: Pediatric drug information")

For abbreviations and symbols that may be used in Lexicomp (show table)

ALERT: US Boxed Warning

Experienced physician:

It is recommended that bleomycin be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

Pulmonary toxicity:

Pulmonary fibrosis is the most severe toxicity associated with bleomycin. The most frequent presentation is pneumonitis occasionally progressing to pulmonary fibrosis. Its occurrence is higher in elderly patients and in those receiving more than 400 units total dose, but pulmonary toxicity has been observed in young patients and those treated with low doses.

Idiosyncratic reaction:

A severe idiosyncratic reaction consisting of hypotension, mental confusion, fever, chills, and wheezing has been reported in approximately 1% of lymphoma patients treated with bleomycin.

Brand Names: Canada

Blenoxane; Bleomycin Injection, USP

Pharmacologic Category

Antineoplastic Agent, Antibiotic

Dosing: Adult

Note: The risk for pulmonary toxicity increases with age >70 years and cumulative lifetime dose of >400 units. **International considerations:** Dosages below expressed as USP units; 1 USP unit = 1 mg (by potency) = 1,000 international units (Stefanou 2001). During shortages within the US, temporary importation of international products may be allowed by the FDA. The imported bleomycin vial and product labeling may express strength and dosing as international units instead of USP units.

Hodgkin lymphoma (off-label dosing): IV:

ABVD regimen: 10 units/m^2 days 1 and 15 of a 28-day treatment cycle (in combination with doxorubicin, vinblastine, and dacarbazine) (Straus 2004)

BEACOPP regimen: 10 units/m^2 day 8 of a 21-day treatment cycle (in combination with etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) (Dann 2007, Diehl 2003)

Stanford V regimen: 5 units/m^2/dose in weeks 2, 4, 6, 8, 10 and 12 (in combination with mechlorethamine, vinblastine, vincristine, doxorubicin, etoposide, and prednisone) (Horning 2002; Horning 2000)

Test dose for lymphoma patients: IM, IV, SubQ: Due to the possibility of an anaphylactoid reaction, the manufacturer recommends administering 1 to 2 units of bleomycin before the first 1 to 2 doses; monitor vital signs every 15 minutes; wait a minimum of 1 hour before administering remainder of dose; if no acute reaction occurs, then the regular dosage schedule may be followed. **Note:** Test doses may not be predictive of a reaction (Lam 2005) and/or may produce false-negative results.

Testicular cancer (off-label dosing): IV: BEP regimen: 30 units/dose days 1, 8, and 15 of a 21-day treatment cycle for 4 cycles (in combination with etoposide and cisplatin) (Culine 2008, Nichols 1998)

Malignant pleural effusion: Intrapleural: 60 units as a single instillation; mix in 50 to 100 mL of NS

Ovarian germ cell cancer (off-label use): BEP regimen: IV: 30 units/dose days 1, 8, and 15 of a 21-day treatment cycle for 3 cycles (in combination with etoposide and cisplatin) (Williams 1994) **or** 15 units/m^2 day 1 of a 21-day treatment cycle for 4 cycles (in combination with etoposide and cisplatin) (Cushing 2004)

Dosing: Pediatric

(For additional information see "Bleomycin: Pediatric drug information")

Note: The risk for pulmonary toxicity increases with cumulative lifetime dose of >400 units. **International considerations:** Dosages below expressed as USP units; 1 USP unit = 1 mg (by potency) = 1,000 international units (Stefanou 2001). During shortages within the US, temporary importation of international products may be allowed by the FDA. The imported bleomycin vial and product labeling may express strength and dosing as international units instead of USP units.

Hodgkin lymphoma (off-label use): IV: ABVD regimen: 10 units/m^2 days 1 and 15 of a 28-day treatment cycle (in combination with doxorubicin, vinblastine, and dacarbazine) (Hutchinson 1998)

Test dose for lymphoma patients: IM, IV, SubQ: Due to the possibility of an anaphylactoid reaction, the manufacturer recommends administering 1 to 2 units of bleomycin before the first 1 to 2 doses; monitor vital signs every 15 minutes; wait a minimum of 1 hour before administering remainder of dose; if no acute reaction occurs, then the regular dosage schedule may be followed. **Note:** Test doses may not be predictive of a reaction (Lam 2005) and/or may produce false-negative results.

Germ cell tumors, malignant (off-label use): Children ≥1 year and Adolescents: IV: BEP regimen: 15 units/m^2 on day 1 of a 21-day treatment cycle (in combination with etoposide and cisplatin) for 4 cycles (Cushing 2004)

Dosing: Geriatric

Refer to adult dosing. The incidence of pulmonary toxicity is higher in patients >70 years of age.

Dosing: Renal Impairment

Manufacturer's labeling (creatinine clearance should be estimated using the Cockcroft-Gault formula):

CrCl ≥50 mL/minute: No dosage adjustment necessary.

CrCl 40 to 50 mL/minute: Reduce dose to 70% of normal dose

CrCl 30 to 40 mL/minute: Reduce dose to 60% of normal dose

CrCl 20 to 30 mL/minute: Reduce dose to 55% of normal dose

CrCl 10 to 20 mL/minute: Reduce dose to 45% of normal dose

CrCl 5 to 10 mL/minute: Reduce dose to 40% of normal dose

The following adjustments have also been recommended:

Aronoff 2007: Adults: Continuous renal replacement therapy (CRRT): Reduce dose to 75% of normal dose

Kintzel, 1995: Adults:

CrCl 46 to 60 mL/minute: Reduce dose to 70% of normal dose

CrCl 31 to 45 mL/minute: Reduce dose to 60% of normal dose

CrCl <30 mL/minute: Consider use of alternative drug

Dosing: Hepatic Impairment There are no dosage adjustments provided in the manufacturer's labeling (has not been studied); however, adjustment for hepatic impairment is not necessary (King, 2001).

Dosing: Obesity *ASCO Guidelines for appropriate chemotherapy dosing in obese adults with cancer:* Fixed doses (dosing which is independent of body weight or BSA), are used in some protocols (eg, testicular cancer); due to toxicity concerns, the same fixed dose should also be considered for obese patients (Griggs, 2012).

Dosing: Adjustment for Toxicity

Pulmonary changes: Discontinue until determined not to be drug-related.

Pulmonary diffusion capacity for carbon monoxide (DL_{CO}) <30% to 35% of baseline: Discontinue treatment.

Pulmonary diffusing capacity for carbon monoxide corrected for hemoglobin content [DLCOc] decrease of more than 25% during therapy (compared with baseline): Consider discontinuing bleomycin to avoid further pulmonary toxicity (Lauritsen 2016).

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution Reconstituted, Injection:

Generic: 15 units (1 ea); 30 units (1 ea)

Solution Reconstituted, Injection [preservative free]:

Generic: 15 units (1 ea); 30 units (1 ea)

Generic Equivalent Available (US) Yes

Dosage Forms Considerations During shortages within the US, temporary importation of international products may be allowed by the FDA. The imported bleomycin vial and product labeling may express strength and dosing as international units instead of USP units (1,000 international units = 1 USP unit).

Administration

IV doses should be administered slowly over 10 minutes (according to the manufacturer's labeling).

IM or SubQ: May cause pain at injection site

Intrapleural: 60 units in 50 to 100 mL NS; use of topical anesthetics or opioid analgesia is usually not necessary

Hazardous Drugs Handling Considerations

Hazardous agent (NIOSH 2016 [group 1]).

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage.

NIOSH recommends double gloving, a protective gown, ventilated engineering controls (a class II biological safety cabinet or a compounding aseptic containment isolator), and closed system transfer devices (CSTDs) for preparation. Double gloving, a gown, and (if dosage form allows) CSTDs are required during administration (NIOSH 2016).

Use

Head and neck cancers: Treatment of squamous cell carcinomas of the head and neck

Hodgkin lymphoma: Treatment of Hodgkin lymphoma

Malignant pleural effusion: Sclerosing agent for malignant pleural effusion

Testicular cancer: Treatment of testicular cancer

Use: Off-Label

Germ cell tumors, malignant

Medication Safety Issues

Sound-alike/look-alike issues:

Bleomycin may be confused with Cleocin

High alert medication:

This medication is in a class the Institute for Safe Medication Practices (ISMP) includes among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

International issues:

Some products available internationally may have vial strength and dosing expressed as international units or milligrams (instead of units or USP units). Refer to prescribing information for specific strength and dosing information.

Other safety concerns:

During shortages within the US, temporary importation of international products may be allowed by the FDA. The imported bleomycin vial and product labeling may express strength and dosing as international units instead of USP units (1,000 international units = 1 USP unit).

Adverse Reactions

Frequency not always defined. The pathogenesis of respiratory adverse effects is not certain, but may be due to damage of pulmonary, vascular, or connective tissue. Response to steroid therapy is variable and somewhat controversial.

>10%:

Cardiovascular: Phlebitis

Central nervous system: Tumor pain

Dermatologic: Hyperpigmentation (50%), atrophic striae (≤50%), erythema (≤50%), exfoliation of the skin (≤50%; particularly on the palmar and plantar surfaces of the hands and feet), hyperkeratosis (≤50%), localized vesiculation (≤50%), skin rash (≤50%), skin sclerosis (≤50%), alopecia (may be dose-related and reversible with discontinuation), nailbed changes (may be dose-related and reversible with discontinuation)

Endocrine & metabolic: Weight loss

Gastrointestinal: Stomatitis (≤30%), mucositis (≤30%), anorexia

Miscellaneous: Febrile reaction (25% to 50%; acute)

1% to 10%:

Dermatologic: Onycholysis, pruritus, thickening of skin

Hypersensitivity: Anaphylactoid reaction (including chills, confusion, fever, hypotension, wheezing; onset may be immediate or delayed for several hours; includes idiosyncratic reaction in 1% of lymphoma patients)

Neuromuscular & skeletal: Scleroderma (diffuse)

Respiratory: Tachypnea (≤5% to 10%), rales (≤5% to 10%), interstitial pneumonitis (acute or

chronic: ≤5% to 10%), pulmonary fibrosis (≤5% to 10%), hypoxia (1%)

<1%, postmarketing, and/or case reports: Angioedema, bone marrow depression (rare), cerebrovascular accident, cerebral arteritis, chest pain, coronary artery disease, hepatotoxicity, hyperpigmentation (flagellate), ischemic heart disease, malaise, myocardial infarction, nausea, nephrotoxicity, pericarditis, Raynaud's phenomenon, scleroderma (scleroderma-like skin changes), Stevens-Johnson syndrome, thrombotic thrombocytopenic purpura, toxic epidermal necrolysis, vomiting

Contraindications

Hypersensitivity to bleomycin or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

• Hepatotoxicity: May cause hepatic toxicity.

• Idiosyncratic reaction: **[US Boxed Warning]: A severe idiosyncratic reaction consisting of hypotension, mental confusion, fever, chills, and wheezing (similar to anaphylaxis) has been reported in 1% of lymphoma patients treated with bleomycin.** Since these reactions usually occur after the first or second dose, careful monitoring is essential after these doses.

• Pulmonary toxicity: **[US Boxed Warning]: Occurrence of pulmonary fibrosis (commonly presenting as pneumonitis; occasionally progressing to pulmonary fibrosis) is the most severe toxicity. Risk is higher in elderly patients or patients receiving >400 units total lifetime dose;** other possible risk factors include smoking and patients with prior radiation therapy or receiving concurrent oxygen (especially high inspired oxygen doses). A review of patients receiving bleomycin for the treatment of germ cell tumors suggests risk for pulmonary toxicity is increased in patients >40 years of age, with glomerular filtration rate <80 mL/minute, advanced disease, and cumulative doses >300 units (O'Sullivan 2003). Pulmonary toxicity may include bronchiolitis obliterans and organizing pneumonia (BOOP), eosinophilic hypersensitivity, and interstitial pneumonitis, progressing to pulmonary fibrosis (Sleijfer 2001); pulmonary toxicity may be due to a lack of the enzyme which inactivates bleomycin (bleomycin hydrolase) in the lungs (Morgan 2011; Sleijfer 2001), If pulmonary changes occur, withhold treatment and investigate if drug-related. In a study of patients with testicular cancer receiving bleomycin as part of the BEP regimen, pulmonary function testing (including forced vital capacity [FVC], forced expiratory volume in 1 second [FEV_1], and diffusing capacity of the lungs for carbon monoxide [DLCO]) was performed prior to treatment, before each chemotherapy cycle, and then repeated at 1 year, 3 years, and 5 years during follow up; if the carbon monoxide diffusing capacity corrected for hemoglobin content [DLCOc] decreased more than 25% during therapy (compared with baseline), bleomycin was discontinued to avoid further pulmonary toxicity (Lauritsen 2016).

• Renal toxicity: May cause renal toxicity.

Disease-related concerns:

• Hodgkin lymphoma: Positron emission tomography/computed tomography (PET/CT) may have a role in determining early response to therapy in patients with Hodgkin lymphoma; a negative interim PET/CT result after 2 cycles may indicate that bleomycin can be safely omitted from the ABVD treatment regimen (Johnson 2016). Longer follow-up is necessary to determine the effect of bleomycin omission on long-term morbidity and mortality in these patients.

• Renal impairment: Use with caution in patients with renal impairment (CrCl <50 mL/minute), may require dose adjustment.

Concurrent drug therapy issues:

• Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.

Special populations:

• Pediatric: In children, a younger age at treatment, cumulative dose ≥400 units/m^2 (combined with chest irradiation), and renal impairment are associated with a higher incidence of pulmonary toxicity (Huang, 2011).

Other warnings/precautions:

• Experienced physician: **[US Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

• International issues: Some products available internationally may have vial strength and dosing expressed as international units or milligrams (instead of units or USP units). During shortages within the US, temporary importation of international products may be allowed by the FDA. The imported bleomycin vial and product labeling may express strength and dosing as international units instead of USP units. One USP unit of bleomycin = 1 mg (by potency) = 1,000 international units (Stefanou 2001). Refer to prescribing information for specific dosing information.

• O_2 during surgery: Use caution when administering O_2 during surgery to patients who have received bleomycin; the risk of bleomycin-related pulmonary toxicity is increased.

Metabolism/Transport Effects

None known.

Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

BCG (Intravesical): Immunosuppressants may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

Brentuximab Vedotin: May enhance the adverse/toxic effect of Bleomycin. Specifically, the risk for pulmonary toxicity may be increased. *Risk X: Avoid combination*

Coccidioides immitis Skin Test: Immunosuppressants may diminish the diagnostic effect of Coccidioides immitis Skin Test. *Risk C: Monitor therapy*

Denosumab: May enhance the adverse/toxic effect of Immunosuppressants. Specifically, the risk for serious infections may be increased. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Filgrastim: May enhance the adverse/toxic effect of Bleomycin. Specifically, the risk for pulmonary toxicity may be increased. *Risk C: Monitor therapy*

Fingolimod: Immunosuppressants may enhance the immunosuppressive effect of Fingolimod. Management: Avoid the concomitant use of fingolimod and other immunosuppressants when possible. If combined, monitor patients closely for additive immunosuppressant effects (eg, infections). *Risk D: Consider therapy modification*

Gemcitabine: May enhance the adverse/toxic effect of Bleomycin. The risk of pulmonary toxicity may be increased. *Risk D: Consider therapy modification*

Leflunomide: Immunosuppressants may enhance the adverse/toxic effect of Leflunomide. Specifically, the risk for hematologic toxicity such as pancytopenia, agranulocytosis, and/or thrombocytopenia may be increased. Management: Consider not using a leflunomide loading dose in patients receiving other immunosuppressants. Patients receiving both leflunomide and another immunosuppressant should be monitored for bone marrow suppression at least monthly. *Risk D: Consider therapy modification*

Lenograstim: May enhance the adverse/toxic effect of Bleomycin. Specifically, the risk for pulmonary toxicity may be increased. Bleomycin may diminish the therapeutic effect of Lenograstim. Management: Avoid the use of lenograstim 24 hours before until 24 hours after the completion of bleomycin infusion. Additionally, monitor patients more closely for signs/symptoms of bleomycin pulmonary toxicity when used with lenograstim (G-CSF). *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Nivolumab: Immunosuppressants may diminish the therapeutic effect of Nivolumab. *Risk D: Consider therapy modification*

Ocrelizumab: May enhance the immunosuppressive effect of Immunosuppressants. *Risk C: Monitor therapy*

Palifermin: May enhance the adverse/toxic effect of Antineoplastic Agents. Specifically, the duration and severity of oral mucositis may be increased. Management: Do not administer palifermin within 24 hours before, during infusion of, or within 24 hours after administration of myelotoxic chemotherapy. *Risk D: Consider therapy modification*

Phenytoin: Bleomycin may decrease the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Pimecrolimus: May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Roflumilast: May enhance the immunosuppressive effect of Immunosuppressants. *Risk D: Consider therapy modification*

Sargramostim: May enhance the adverse/toxic effect of Bleomycin. Specifically, the risk for pulmonary toxicity may be increased. *Risk C: Monitor therapy*

Sipuleucel-T: Immunosuppressants may diminish the therapeutic effect of Sipuleucel-T. *Risk C: Monitor therapy*

Tacrolimus (Topical): May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Tertomotide: Immunosuppressants may diminish the therapeutic effect of Tertomotide. *Risk C: Monitor therapy*

Tofacitinib: Immunosuppressants may enhance the immunosuppressive effect of Tofacitinib.

Management: Concurrent use with antirheumatic doses of methotrexate or nonbiologic disease modifying antirheumatic drugs (DMARDs) is permitted, and this warning seems particularly focused on more potent immunosuppressants. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). Management: Vaccine efficacy may be reduced. Complete all age-appropriate vaccinations at least 2 weeks prior to starting an immunosuppressant. If vaccinated during immunosuppressant therapy, revaccinate at least 3 months after immunosuppressant discontinuation. *Risk D: Consider therapy modification*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines with immunosuppressants; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants. *Risk X: Avoid combination*

Pregnancy Risk Factor

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Pregnancy Implications

Adverse effects were observed in animal reproduction studies. According to the manufacturer, women of childbearing potential should avoid becoming pregnant during bleomycin treatment. The European Society for Medical Oncology has published guidelines for diagnosis, treatment, and follow-up of cancer during pregnancy; the guidelines recommend referral to a facility with expertise in cancer during pregnancy and encourage a multidisciplinary team (obstetrician, neonatologist, oncology team). In general, if chemotherapy is indicated, it should be avoided in the first trimester and there should be a 3-week time period between the last chemotherapy dose and anticipated delivery, and chemotherapy should not be administered beyond week 33 of gestation (Peccatori 2013). When multiagent therapy is needed to treat Hodgkin lymphoma during pregnancy, bleomycin (as a component of the ABVD [doxorubicin, bleomycin, vinblastine, and dacarbazine] regimen) may be used, starting with the second trimester (Follows 2014; Peccatori 2013).

Breast-Feeding Considerations

It is not known if bleomycin is excreted in breast milk. Due to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended by the manufacturer.

Monitoring Parameters

Pulmonary function tests, including total lung volume, forced vital capacity, diffusion capacity for carbon monoxide; vital capacity, total lung capacity and pulmonary capillary blood volume may be better indicators of changes induced by bleomycin (Sleijfer 2001); forced vital capacity [FVC], forced expiratory volume in 1 second [FEV_1], and diffusing capacity of the lungs for carbon monoxide [DLCO]) were performed prior to treatment, before each chemotherapy cycle, and then repeated at 1 year, 3 years, and 5 years during follow up for testicular cancer patients receiving bleomycin (Lauritsen 2016); chest x-ray, renal function, liver function, signs/symptoms of hypersensitivity; temperature initially; check body weight at regular intervals

Mechanism of Action

Inhibits synthesis of DNA; binds to DNA leading to single- and double-strand breaks; also inhibits (to a lesser degree) RNA and protein synthesis

Pharmacodynamics/Kinetics

Absorption: IM, SubQ, and intrapleural administration: 100%, 70%, and 45%, respectively, of IV serum concentrations

Distribution: V_d: IV: 17.5 L/m^2

Protein binding: 1%

Metabolism: Enzymatic inactivation by bleomycin hydrolase, a cytosolic cysteine proteinase enzyme; bleomycin hydrolase is widely distributed in normal tissues (except for the skin and lungs)

Half-life elimination: Terminal: IV: 2 hours

Time to peak, serum: IM, SubQ, Intrapleural: 30 to 60 minutes

Excretion: Urine (~65% [IV], 40% [Intrapleural])

Pricing: US

Solution (reconstituted) (Bleomycin Sulfate Injection)

15 unit (1): $59.65

30 unit (1): $110.68

Disclaimer: The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

International Brand Names

Bemocin (ZW); Bileco (AR); Blenamax (AU, RU, SG, TW); Blenoxane (BR, EC, EG, ZA); Bleo (HK); Bleocin (AE, BG, CZ, EE, EG, GR, HK, HN, HU, ID, IN, JO, JP, KR, KW, LB, LK, LT, MY, PE, PL, PT, QA, SA, SG, TH, TR, TW, VN); Bleocin-S (MY); Bleocina (UY); Bleocip (ET, LB, ZW); Bleocris (PY); Bleolem (CO, MX, TH); Bleomax (MX); Bleomedac (SK); Bleomicina (ES, IT); Bleomycin (AT, CH, DK, FI, GB, NO, SE); Bleomycin PFI (IL); Bleomycine (BE, FR, LU, NL); Bleomycinum (DE); Bleonko (UA); Blexit (CL); Bloicin-S (PH); Kupbloicin (VN); Lyoble (LK); Naprobleo (ET); Naproplat (ET)

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REFERENCES

1. *Aronoff GR, Bennett WM, Berns JS, et al, Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children, 5th ed. Philadelphia, PA: American College of Physicians; 2007, p 97.*
2. *Azambuja E, Fleck JF, Batista RG, et al, "Bleomycin Lung Toxicity: Who are the Patients With Increased Risk?" Pulm Pharmacol Ther, 2005, 18(5):363-66. [PubMed 15939315]*
3. *Blenoxane (bleomycin) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; April, 2010.*
4. *Bleomycin [prescribing information]. Lake Zurich, IL: Fresenius Kabi USA, LLC; February 2014.*
5. *Bleomycin [prescribing information]. North Wales, PA: Teva Pharmaceuticals; February 2016.*
6. *Bleomycin [product monograph]. Richmond Hill, ON: Fresenius Kabi Canada Ltd.; February 2016.*
7. *Carver JR, Shapiro CL, Ng A, et al, "American Society of Clinical Oncology Clinical Evidence Review on the Ongoing Care of Adult Cancer Survivors: Cardiac and Pulmonary Late Effects," J Clin Oncol, 2007, 25(25):3991-4008. [PubMed 17577017]*
8. *Culine S, Kramar A, Théodore C, et al, "Randomized Trial Comparing Bleomycin/Etoposide/Cisplatin With Alternating Cisplatin/Cyclophosphamide/Doxorubicin and Vinblastine/Bleomycin Regimens of Chemotherapy for Patients With*

Intermediate- and Poor-Risk Metastatic Nonseminomatous Germ Cell Tumors: Genito-Urinary Group of the French Federation of Cancer Centers Trial T93MP," J Clin Oncol, 2008, 26(3):421-7. [PubMed 18202419]

9. *Cushing B, Giller R, Cullen JW, et al, "Randomized Comparison of Combination Chemotherapy With Etoposide, Bleomycin, and Either High-Dose or Standard-Dose Cisplatin in Children and Adolescents With High-Risk Malignant Germ Cell Tumors: A Pediatric Intergroup Study -- Pediatric Oncology Group 9049 and Children's Cancer Group 8882," J Clin Oncol, 2004, 22(13):2691-700. [PubMed 15226336]*
10. *Dann EJ, Bar-Shalom R, Tamir A, et al, "Risk-Adapted BEACOPP Regimen Can Reduce the Cumulative Dose of Chemotherapy for Standard and High-Risk Hodgkin Lymphoma With No Impairment of Outcome," Blood, 2007, 109(3):905-9. [PubMed 17018856]*
11. *de Wit R, Skoneczna I, Daugaard G, et al. "Randomized phase III study comparing paclitaxel-bleomycin, etoposide, and cisplatin (BEP) to standard BEP in intermediate-prognosis germ-cell cancer: intergroup study EORTC 30983," J Clin Oncol. 2012;30(8):792-9. [PubMed 22271474]*
12. *Diehl V, Franklin J, Pfreundschuh M, et al, "Standard and Increased-Dose BEACOPP Chemotherapy Compared With COPP-ABVD for Advanced Hodgkin's Disease," N Engl J Med, 2003, 348(24):2386-95. [PubMed 12802024]*
13. *Engert A, Franklin J, Eich HT, et al, "Two Cycles of Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine Plus Extended-Field Radiotherapy is Superior to Radiotherapy Alone in Early Favorable Hodgkin's Lymphoma: Final Results of the GHSG HD7 Trial," J Clin Oncol, 2007, 25(23):3495-502. [PubMed 17606976]*
14. *Floyd JD, Nguyen DT, Lobins RL, et al, "Cardiotoxicity of Cancer Therapy," J Clin Oncol, 2005, 23(30):7685-96. [PubMed 16234530]*
15. *Follows GA, Ardeshna KM, Barrington SF, et al. Guidelines for the first line management of classical Hodgkin lymphoma. Br J Haematol. 2014;166(1):34-49. [PubMed 24712411]*
16. *Griggs JJ, Mangu PB, Anderson H, et al, "Appropriate Chemotherapy Dosing For Obese Adult Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline," J Clin Oncol, 2012, 30(13):1553-61. [PubMed 22473167]*
17. *Horning SJ, Hoppe RT, Breslin S, et al, "Stanford V and Radiotherapy for Locally Extensive and Advanced Hodgkin's Disease: Mature Results of a Prospective Clinical Trial," J Clin Oncol, 2002, 20(3):630-7. [PubMed 11821442]*
18. *Horning SJ, Williams J, Bartlett NL, et al, "Assessment of the Stanford V Regimen and Consolidative Radiotherapy for Bulky and Advanced Hodgkin's Disease: Eastern Cooperative Oncology Group Pilot Study E1492," J Clin Oncol, 2000, 18(5):972-80. [PubMed 10694546]*
19. *Hoskin PJ, Lowry L, Horwich A, et al, "Randomized Comparison of the Stanford V Regimen and ABVD in the Treatment of Advanced Hodgkin's Lymphoma: United Kingdom National Cancer Research Institute Lymphoma Group Study ISRCTN 64141244," J Clin Oncol, 2009, 27(32):5390-6. [PubMed 19738111]*
20. *Huang TT, Hudson MM, Stokes DC, et al, "Pulmonary Outcomes in Survivors of Childhood Cancer: A Systematic Review," Chest, 2011, 140(4): 881-901. [PubMed 21415131]*
21. *Hutchinson RJ, Fryer CJ, Davis PC, et al, "MOPP or Radiation in Addition to ABVD in the Treatment of Pathologically Staged Advanced Hodgkin's Disease in Children: Results of the Children's Cancer Group Phase III Trial," J Clin Oncol, 1998, 16(3):897-906. [PubMed 9508171]*
22. *Ibrahimi OA and Anderson RR, "Images in Clinical Medicine. Bleomycin-Induced Flagellate Hyperpigmentation," N Engl J Med, 2010, 363(24):e36. [PubMed 21142531]*
23. *Johnson P, Federico M, Kirkwood A, et al. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. N Engl J Med. 2016;374(25):2419-2429. [PubMed 27332902]*
24. *Johnson PW, Radford JA, Cullen MH, et al, "Comparison of ABVD and Alternating or Hybrid Multidrug Regimens for the Treatment of Advanced Hodgkin's Lymphoma: Results of the United Kingdom Lymphoma Group LY09 Trial (ISRCTN97144519)," J Clin Oncol, 2005, 23(36):9208-18. [PubMed 16314615]*
25. *King PD and Perry MC, "Hepatotoxicity of Chemotherapy," Oncologist, 2001, 6(2):162-76. [PubMed 11306728]*
26. *Kintzel PE and Dorr RT, "Anticancer Drug Renal Toxicity and Elimination: Dosing Guidelines for Altered Renal Function," Cancer Treat Rev, 1995, 21(1):33-64. [PubMed 7859226]*
27. *Kung FH, Schwartz CL, Ferree CR,et al, "POG 8625: A Randomized Trial Comparing Chemotherapy With Chemoradiotherapy for Children and Adolescents With Stages I, IIA, IIIA1 Hodgkin Disease: A Report From the Children's Oncology Group," J Pediatr Hematol Oncol, 2006, 28(6):362-8. [PubMed 16794504]*

28. *Lam MS, "The Need for Routine Bleomycin Test Dosing in the 21st Century," Ann Pharmacother, 2005, 39(11):1897-902. [PubMed 16219896]*

29. *Lauritsen J, Kier MG, Bandak M, et al. Pulmonary function in patients with germ cell cancer treated with bleomycin, etoposide, and cisplatin. J Clin Oncol. 2016;34(13):1492-1499. [PubMed 26903578]*

30. *Morgan C, Tillett T, Braybrooke J, et al, "Management of Uncommon Chemotherapy-Induced Emergencies," Lancet Oncol, 2011, 12(8):806-14. [PubMed 21276754]*

31. *Nichols CR, Catalano PJ, Crawford ED, et al, "Randomized Comparison of Cisplatin and Etoposide and Either Bleomycin or Ifosfamide in Treatment of Advanced Disseminated Germ Cell Tumors: An Eastern Cooperative Oncology Group, Southwest Oncology Group, and Cancer and Leukemia Group B Study," J Clin Oncol, 1998, 16(4):1287-93. [PubMed 9552027]*

32. *O'Sullivan JM, Huddart RA, Norman AR, et al, "Predicting the Risk of Bleomycin Lung Toxicity in Patients With Germ-Cell Tumours," Ann Oncol, 2003, 14(1):91-6. [PubMed 12488299]*

33. *Peccatori FA, Azim HA Jr, Orecchia R, et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24(Suppl 6):vi160-170. [PubMed 23813932]*

34. *Perry MC. Chemotherapeutic agents: bleomycin. The Chemotherapy Source Book. 5th ed. Philadelphia, PA: 2012. [PubMed 12488299]*

35. *Sleijfer S, "Bleomycin-Induced Pneumonitis," Chest, 2001, 120(2):617-24. [PubMed 11502668]*

36. *Stefanou A, MacCallum P, and Siderov J. Errors due to bleomycin nomenclature. BMJ 2001;322(7299):548.*

37. *Straus DJ, Portlock CS, Qin J, et al, "Results of a Prospective Randomized Clinical Trial of Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine (ABVD) Followed by Radiation Therapy (RT) Versus ABVD Alone for stages I, II, and IIIA Nonbulky Hodgkin Disease," Blood, 2004, 104(12):3483-9. [PubMed 15315964]*

38. *Tobias JS, Monson K, Gupta N, et al, "Chemoradiotherapy for Locally Advanced Head and Neck Cancer: 10-year Follow-Up of the UK Head and Neck (UKHAN1) Trial," Lancet Oncol, 2010, 11(1):66-74. [PubMed 19875337]*

39. *US Department of Health and Human Services; Centers for Disease Control and Prevention; National Institute for Occupational Safety and Health. NIOSH list of antineoplastic and other hazardous drugs in healthcare settings 2016. http://www.cdc.gov/niosh/topics/antineoplastic/pdf/hazardous-drugs-list_2016-161.pdf. Updated September 2016. Accessed October 5, 2016.*

40. *Wiernik PH, Hong F, Glick JH, et al, "Radiation Therapy Compared With Chemotherapy for Consolidation of Chemotherapy-Induced Remission of Advanced Hodgkin Lymphoma: A Study by the Eastern Co-Operative Oncology Group (E1476) With >20 Years Follow-Up," Leuk Lymphoma, 2009, 50(10):1632-41. [PubMed 19863338]*

41. *Williams S, Blessing JA, Liao SY, et al, "Adjuvant Therapy of Ovarian Germ Cell Tumors With Cisplatin, Etoposide, and Bleomycin: A Trial of the Gynecologic Oncology Group," J Clin Oncol, 1994, 12(4):701-6. [PubMed 7512129]*

Topic 9160 Version 144.0