

Drug Shortage Stewardship

Alprostadil injection, Amikacin injection, Bleomycin injection, Dacarbazine injection, Idarubicin injection, Ifosfamide injection, Mitoxantrone injection, Octreotide injection, Streptozocin injection, Topotecan injection

Situation

Recently Teva closed a manufacturing plant in Irvine, California. This document provides a market analysis of the affected products and is also intended to aid in understanding the current supply chain. Additionally, *abbreviated* mitigation strategies are included for clinical and operational recommendations for frontline staff and pharmacy leadership. The *abbreviated* mitigation strategies are high-level, not all inclusive, and should be used in conjunction with clinical expertise and resources.

Background

The products manufactured at the closed Teva location in Irvine, California, with any relevant market share (e.g., $\geq 15\%$) were injectable presentations of alprostadil, amikacin, bleomycin, dacarbazine, idarubicin, ifosfamide, mitoxantrone, octreotide, streptozocin, and topotecan. Products identified with $<15\%$ market share and not further addressed in this document include injectable presentations of adenosine, daunorubicin, desmopressin, epoprostenol and epoprostenol diluent, etoposide, haloperidol decanoate, leucovorin, medroxyprogesterone, methylprednisolone acetate, metoclopramide, norepinephrine, vecuronium, and vincristine. The included market analysis ([Table 1](#)) and *abbreviated* mitigation strategies ([Appendix 1](#)) are intended to provide guidance for present and future shortages, as well as limit the severity of potential shortages. Please review the [ASHP Drug Shortages](#) for the most current information.

End Drug Shortages Alliance: Assessment and recommendation

Manufacturers and wholesalers

The End Drug Shortages Alliance recommends that manufacturers of impacted products evaluate their ability to ramp up production and shift or increase manufacturing capacity as able. Wholesalers should communicate with manufacturers and establish protective allocations for medications to ensure product is available for patient care.

Group Purchasing Organizations

The End Drug Shortages Alliance encourages Group Purchasing Organizations (GPOs) to pursue novel sourcing strategies to provide additional redundancy for essential medications to minimize potential patient care disruption. See [Table 1](#) for an abbreviated analysis of the market as it currently stands.

Clinical and provider recommendations

The End Drug Shortages Alliance encourages providers and clinicians to exercise a stewardship mindset when ordering, prescribing and administering medications affected by supply constraints to preserve availability for vulnerable patient populations.

Table 1. Market analysis of affected products

Drug ^a	Essential medication ^b	Additional suppliers	Estimated supplier market share ^f	Shortage per ASHP ^h	Estimated level of impact (national) ⁱ
Alprostadir	Yes ^c	Pfizer	Teva (~20%)	No	Medium ^j
Amikacin	No	Avet, Fresenius Kabi, Hikma, Sagent	Teva (~16%)	No	Low
Bleomycin	Yes	Fresenius Kabi, Hikma, Meitheal, Northstar Rx, Pfizer	For 15 IU: Teva (~16%)	No	Low
Dacarbazine	Yes	Fresenius Kabi, Hikma	Teva (~19%)	Yes	Medium ^j
Idarubicin	No	Pfizer, Hikma	Teva (~24%)	No	Low
Ifosfamide	Yes	Baxter, Fresenius Kabi, Hikma	Teva (~17%)	No	Low
Mitoxantrone	No	Fresenius Kabi, Pfizer	Teva (~16%)	No	Low
Octreotide	Yes	Fresenius, Hikma, Novartis, Sagent, Viartis	For 100 mcg/mL: Teva (~27%)	Yes	Medium ^j
Streptozocin	No	N/a	Teva (100%)	No	High ^k
Topotecan	No	Accord, Fresenius, Novartis, Pfizer, Viartis	Teva (~15%)	No	Low

^aInjectable presentations

^bIdentified essential medications. To access the latest update, please visit https://www.vizientinc.com/-/media/documents/sitecorepublishingdocuments/public/essential_meds.pdf.

^cIdentified as having a disproportionate impact on the pediatric population in times of supply disruption

^fIQVIA; 2022 data encompasses Jan-Feb only; 0% market share if unspecified

^gSpecific to the 200 mg vials

^hAs of April 2020

ⁱEstimated level of impact is based upon an analysis of fill rates, market share, contract status, therapeutic alternatives, and additional market insights

^jSuppliers indicate being able to meet current market demands and/or are potentially increasing production to manage any impact

^kThe FDA is working to potentially introduce additional supply of streptozocin to the US market through importation of international formulation

Appendix 1. Abbreviated mitigation strategies of affected products

Alprostadil injection

Assessment

For neonatal patients, IV alprostadil is utilized for maintenance of ductus arteriosus patency. For adults, IV alprostadil is utilized for erectile dysfunction and treatment of Raynaud's phenomenon.

Recommendation

Clinical

- 1) Reserve IV alprostadil for ductus arteriosus patency maintenance in ductal dependent neonates.
- 2) Utilize alprostadil urethral suppository for erectile dysfunction in adults.

Operational

1. Implement changes in the electronic health record to restrict usage to neonatal patients.
2. Prioritize and mitigate clinical barriers to scheduling congenital heart disease surgeries to reduce duration of usage of IV alprostadil.
3. Evaluate utilization trends in automatic dispensing cabinets and shift inventory as able to prevent expiration and maximize availability where needed most. If inventory becomes critically low, pull available stock to inpatient pharmacy for inventory control. Limit transport inventory to smallest, reasonable quantity.
4. For IV alprostadil, batch doses if multiple patients are on this therapy to reduce wastage. Pharmacy should compound all doses in the inpatient pharmacy when possible. Use smallest syringe/bag size depending on the rate of infusion to minimize waste.

Amikacin injection

Assessment

Amikacin is an aminoglycoside antibiotic that is primarily used for the treatment of serious infections caused by gram-negative organisms. Amikacin also has activity against *Mycobacterium* species.

Recommendation

Clinical

- 1) Utilize alternative antibiotic (e.g., tobramycin, gentamicin, 3rd or 4th generation cephalosporin, anti-pseudomonal penicillin, carbapenem) for empiric or directed therapy based on typical pathogens or culture & susceptibilities.
- 2) Consider restricting use of amikacin based on susceptibility.

Operational

- 1) Implement changes in the electronic health record to direct providers to utilize alternative antibiotics as clinically appropriate.

Bleomycin injection

Assessment

Bleomycin is utilized for treatment of head and neck cancers, Hodgkin's lymphoma, malignant pleural effusion, and testicular cancer. There are also data to support its use in germ cell tumors and refractory, high-risk gestational trophoblastic neoplasia.

Recommendation

Clinical

- 1) Evaluate and assess the use of other chemotherapy agents on a patient-to-patient basis, as clinically appropriate.
- 2) Prioritize inventory for ongoing therapy and evaluate other regimens for new starts.
- 3) Consult with institutional oncology specialists to determine appropriate course of action.

Operational

- 1) Schedule doses for patients at similar times to maximize vial usage and reduce wastage.

Dacarbazine injection

Assessment

Dacarbazine is utilized for Hodgkin's lymphoma, metastatic malignant melanoma, and advanced or metastatic soft-tissue sarcomas. There is also data to support its use in advanced or metastatic medullary thyroid cancer, advanced pancreatic neuroendocrine tumors, and malignant pheochromocytoma.

Recommendation

Clinical

- 1) Evaluate and assess the use of other chemotherapy agents on a patient-to-patient basis, as clinically appropriate.
- 2) Prioritize inventory for ongoing therapy and evaluate other regimens for new starts.
- 3) Consult with institutional oncology specialists to determine appropriate course of action.

Operational

- 1) Schedule doses for patients at similar times to maximize vial usage and reduce wastage.

Idarubicin injection

Assessment

Idarubicin is utilized for treatment of acute myeloid leukemia, in combination with other chemotherapy agents.

Recommendation

Clinical

- 1) Evaluate and assess the use of other chemotherapy agents, such as daunorubicin, on a patient-to-patient basis, as clinically appropriate.
- 2) Prioritize inventory for ongoing therapy and evaluate other regimens for new starts.
- 3) Consult with institutional oncology specialists to determine appropriate course of action.

Operational

- 1) Schedule doses for patients at similar times to maximize vial usage and reduce wastage.

Ifosfamide injection

Assessment

Ifosfamide is utilized as 3rd-line treatment for germ cell testicular cancer, in combination with other chemotherapy agents. To be administered in combination with mesna for prophylaxis of hemorrhagic cystitis.

Recommendation

Clinical

- 1) Evaluate and assess the use of other chemotherapy agents, on a patient-to-patient basis, as clinically appropriate.
- 2) Prioritize inventory for ongoing therapy and evaluate other regimens for new starts.
- 3) Consult with institutional oncology specialists to determine appropriate course of action.

Operational

- 1) Schedule doses for patients at similar times to maximize vial usage and reduce wastage.

Mitoxantrone injection

Assessment

Mitoxantrone is utilized for treatment of acute myeloid leukemia, relapsing or secondary progressive multiple sclerosis, and prostate cancer. There are also data to support its use in relapsed or refractory acute lymphoblastic leukemia, relapsed or refractory acute myeloid leukemia, newly diagnosed acute promyelocytic leukemia, conditioning regimen of autologous hematopoietic stem cell transplantation, Hodgkin's lymphoma, and relapse or refractory non-Hodgkin's lymphoma.

Recommendation

Clinical

- 1) For relapsing or secondary progressive multiple sclerosis, consider other disease-modifying therapies such as monoclonal antibodies (e.g., ocrelizumab, rituximab, natalizumab, ofatumumab, and alemtuzumab), oral options (e.g., siponimod, fingolimod, ozanimod, ponesimod, dimethyl fumarate, diroximel fumarate, monomethyl fumarate, teriflunomide, and cladribine), and others.
- 2) Evaluate and assess the use of other chemotherapy agents, on a patient-to-patient basis, as clinically appropriate.
- 3) Prioritize inventory for ongoing therapy and evaluate other regimens for new starts.
- 4) Consult with institutional oncology specialists to determine appropriate course of action.

Operational

- 1) Schedule doses for patients at similar times to maximize vial usage and reduce wastage.

Octreotide injection

Assessment

Octreotide is primarily utilized for acute gastroesophageal variceal hemorrhage, hepatorenal syndrome (HRS), high-output gastroenteropancreatic fistulas, prevention and treatment of carcinoid crisis, sulfonylurea-induced hypoglycemia, vasoactive intestinal peptide-secreting gastroenteropancreatic neuroendocrine tumors (VIPomas), and acromegaly.

Recommendation

Clinical

- 1) Reserve octreotide for IV administration to treat acute gastroesophageal variceal hemorrhage.
- 2) Reserve octreotide for SUBQ administration to treat HRS, high-output gastroenteropancreatic fistulas, prevention and treatment of carcinoid crisis, and sulfonylurea-induced hypoglycemia (not responsive to dextrose or glucagon).
- 3) Utilize LAR depot for vasoactive intestinal peptide-secreting gastroenteropancreatic neuroendocrine tumors (VIPomas) and acromegaly.

Operational

- 1) Implement changes in the electronic health record to restrict IV usage to acute gastroesophageal variceal hemorrhage and SUBQ usage to the indications above.
- 2) Evaluate utilization trends in automatic dispensing cabinets and shift inventory as able to prevent expiration and maximize availability where needed most.
- 3) For IV or SUBQ octreotide, batch doses in the inpatient pharmacy to reduce wastage.
- 4) If inventory becomes critically low, pull available stock to inpatient pharmacy for inventory control.

Streptozocin injection

Assessment

For adults, streptozocin is utilized for pancreatic neuroendocrine tumors. There is also data to support its use in metastatic adrenocortical carcinoma and gastrointestinal neuroendocrine tumors.

Recommendation

Clinical

- 1) Reserve streptozocin for patients with metastatic islet cell carcinoma of the pancreas.
- 2) Evaluate and assess the utilization of dacarbazine and temozolomide-based regimens, and oxaliplatin-containing regimens, as clinically appropriate.
- 3) Prioritize inventory for ongoing therapy and evaluate other regimens for new starts.
- 4) Consult with institutional oncology specialists to determine appropriate course of action.

Operational

- 1) Implement changes in the electronic health record to restrict usage to pancreatic neuroendocrine tumors.
- 2) Assess inventory and determine expiration dating of product on-hand.
- 3) Monitor for potential short-term importation of an international formulation of streptozocin.

Topotecan injection

Assessment

Topotecan is utilized for treatment of recurrent or persistent cervical cancer, metastatic ovarian cancer, relapsed or progressive small cell lung cancer. There are also data to support its use for Ewing sarcoma, high-risk myelodysplastic syndromes, metastatic ovarian cancer, relapsed or refractory primary CNS lymphoma, and rhabdomyosarcoma.

Recommendation

Clinical

- 1) Reserve IV topotecan for patients unable to utilize oral therapy, or for whom oral therapy may not be clinically appropriate.
- 2) Assess and evaluate once weekly dosing of IV topotecan, as clinically appropriate, to conserve inventory.
- 3) Evaluate and assess the use of other chemotherapy agents, on a patient-to-patient basis, as clinically appropriate.
- 4) Prioritize inventory for ongoing therapy and evaluate other regimens for new starts.
- 5) Consult with institutional oncology specialists to determine appropriate course of action.

Operational

- 1) Implement changes in the electronic health record to direct providers to utilize oral therapy, as clinically appropriate.
- 2) Schedule doses for patients at similar times to maximize vial usage and reduce wastage.

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