Implications of the National BCG Drug Shortage

End Drug Shortages Alliance

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SUMMARY

Since 2019, Bacillus Calmette-Guerin (BCG), used in the treatment of bladder cancer, has experienced a significant supply disruption due to a reduction in the number of pharmaceutical manufacturers in the market. Currently, Merck & Co. is the sole manufacturer of this product globally. The End Drug Shortages Alliance along with two of its members, Vizient, a healthcare performance improvement company, and Angels for Change, a patient advocacy group, conducted a Vizient member survey to better characterize the implications of the BCG shortage on the treatment of patients with bladder cancer. The most significant findings of the Vizient member survey showed that all respondents reported implementing at least one mitigation strategy in the face of the ongoing BCG drug shortage and more than a third of respondents noted having to reduce dosages below the standard treatment dose. Notably, 20% of the organizations reported not being able to provide any BCG to patients who were eligible for therapy. This paper presents current BCG market trends and insights from the findings of the Vizient member survey.

Background

TICE® BCG has successfully treated bladder tumors since 1976.[1] BCG is approved by the U.S. Food and Drug Administration (FDA) for the treatment and prophylaxis of non-muscle invasive bladder cancer (NMIBC).[2] This medication is an attenuated, live culture preparation and instilled into the bladder weekly for six weeks and continued monthly for at least six to 12 months per national guidelines.[3,4] The use of BCG for intermediate- and high-risk NMIBC is the standard of care in the U.S.

In 2023, approximately 82,000 cases of bladder cancer will be diagnosed in the U.S., with approximately 17,000 deaths per the American Cancer Society.[5] An increase in the incidence of bladder cancer cases over the next five years is anticipated globally due to aging population and additional risk factors.[6] Additional details regarding bladder cancer incidence and projected growth rates can be found in Appendix 1.

Shortage history and current demand

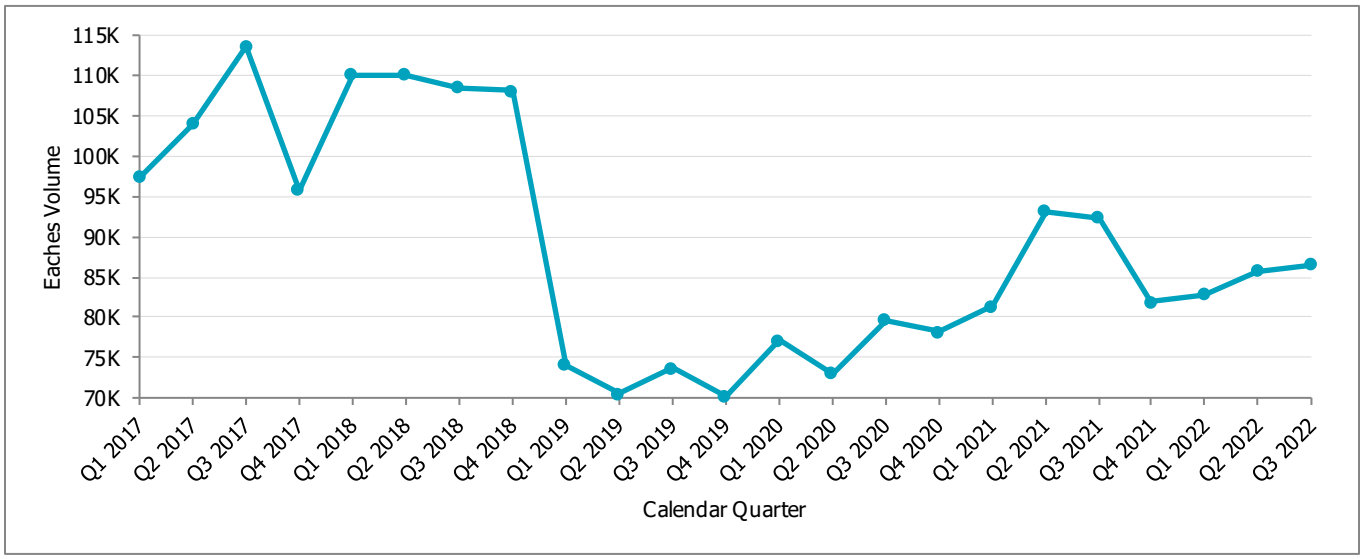
In the 1990s and early 2000s, BCG was supplied to the U.S. market by Sanofi Pasteur (TheraCys®) and Merck (TICE® BCG). Beginning in 2012, Sanofi Pasteur began to experience production challenges.[7] Ultimately, Sanofi Pasteur announced on Nov. 21, 2016, they would be discontinuing production mid-2017.[8]

As a result of Sanofi exiting the market, Merck increased production of their BCG vaccine to the fullest extent of their manufacturing capacity, approximately double of their historical production. However, despite the increase in production by Merck, demand has continued to outpace supply since 2020.[9]

Given supply chain constraints of this life-saving drug, multiple leading national organizations met with Merck to craft a joint statement in September 2020 to facilitate patient management during this global shortage.[10,11] Additional mitigation strategies suggested by other national organizations can be found in Appendix 2.

From 2017 to 2022, the volume of BCG vials sold in the U.S. through all distribution channels is displayed in Figure 1. The immediate drop in sales in 2019 is representative of the beginning of the drug shortage event. Since that time, the supply provided by Merck slightly increases throughout 2020 to 2022.

Figure 1: BCG units sold nationally between 2017-2022 from IQVIA[12]



Through Vizient data analytics, the pharmacy member fill rate for BCG can be seen in Figure 2 for the period of January 2021 through December 2022. The image indicates a consistent supply from Merck despite increased member demand continuing throughout this timeframe.

Figure 2: BCG units ordered and sold to Vizient members Jan. 2021 – Dec. 2022[13]

As evidenced by the widening gap between orders placed and fulfilled for Vizient members, demand continues to increase while supply is constrained. Worldwide, the incidence of bladder cancer is increasing. The predicted annual growth rate is estimated to be 2.21% globally and 2.58% in the U.S. between 2018 and 2028.[6]

To quantify the gap in the marketplace of the amount of BCG required to treat eligible patients, pre-shortage historical values were used as a baseline to establish population volume. A projection model was developed based on the total U.S. volume in 2018 and the U.S. annual growth rate of 2.5% for bladder cancer. Based on these projection calculations, there was a difference of greater than 150,000 vials between estimated market demand and supply availability for 2022. The current standard of care treatment for BCG incorporates induction therapy for six weeks then monthly maintenance therapy for approximately one year. This dosing schedule is equivalent to 18 vials per patient for full treatment. The impact of 150,000 vials short in the market would affect more than 8,300 patients from receiving full dose treatment per year.

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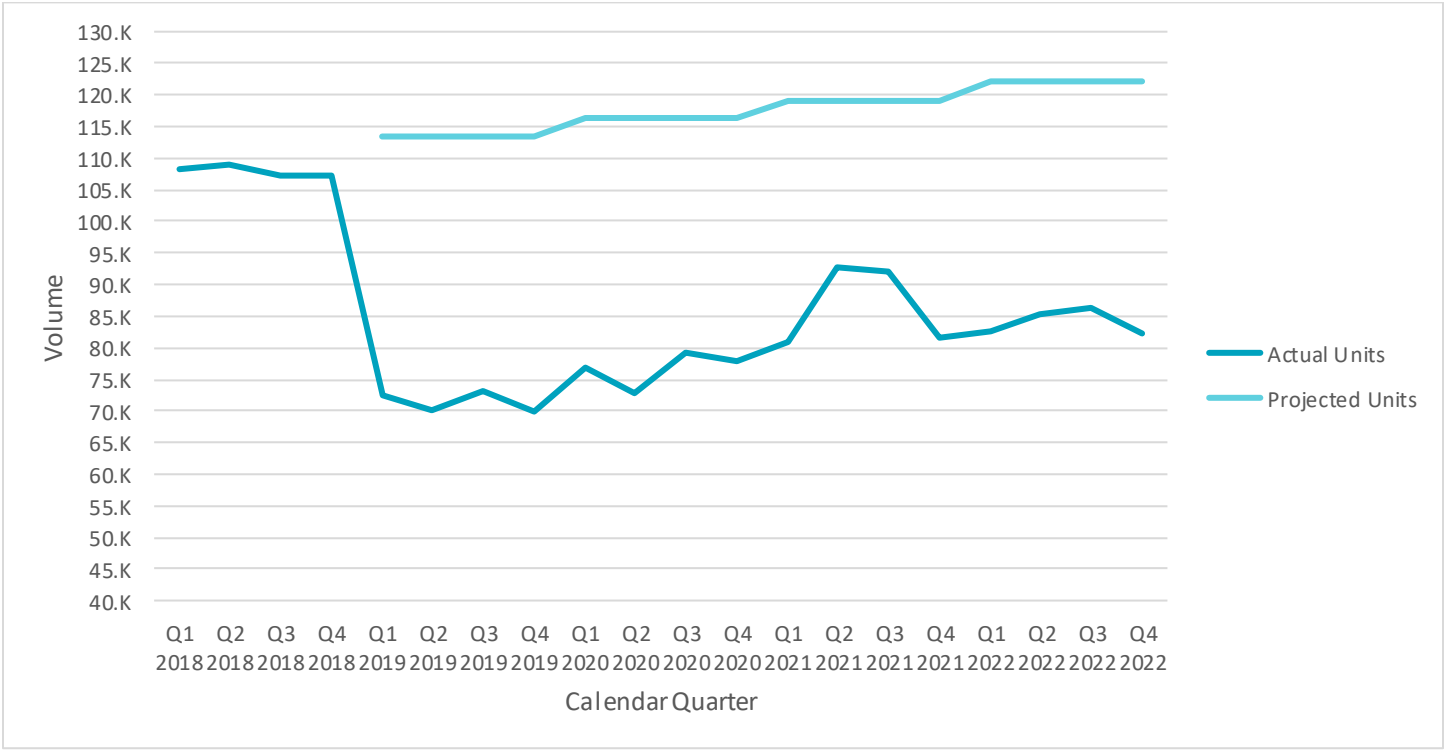
The current market is only producing 69% of the estimated BCG need based on 2018 baseline volume and an assumed annual bladder cancer growth rate of 2.5%. [6, 12]

Figure 3: Comparison of actual BCG supply to projected market volume[12]



Note: Q4 2022 actual units were estimated based on previous years' quarterly fluctuations and 2022 sales to date.

The national impact on patient care

The Hematology/Oncology Pharmacists Association (HOPA) conducted a nationwide survey of their membership and published the findings in May 2022.[14] The National Survey on the Effect of Oncology Drug Shortages in Clinical Practice: A Hematology Oncology Pharmacy Association Survey listed BCG as the most difficult agent to obtain behind vincristine, vinblastine, IVIG and leucovorin. Institutions reported having to delay treatments, reduce doses or use alternative treatment regimens based on oncology drug shortages.

The implications of the BCG shortage on the treatment of patients: Vizient member survey

In November 2022, Vizient conducted a survey of its health system and hospital members to better characterize the implications of the BCG shortage on the treatment of patients with bladder cancer. A seven-question survey was developed and distributed to Vizient members with greater than $50,000 in BCG purchases during January 2019 to September 2022 time frame.

Survey results

A total of 20 academic medical centers, health systems and physician practices provided complete responses to the survey for analysis (15.5% response rate). The respondents included four National Comprehensive Cancer Center (NCCN) institutions. Vizient members reported almost 4,000 total patients with new diagnoses of NMIBC in 2021, with a median of 50 patients per institution (average: 246). Of the newly diagnosed patients, the majority (75%) were classified as intermediate- or high-risk patients that are eligible for BCG therapy.

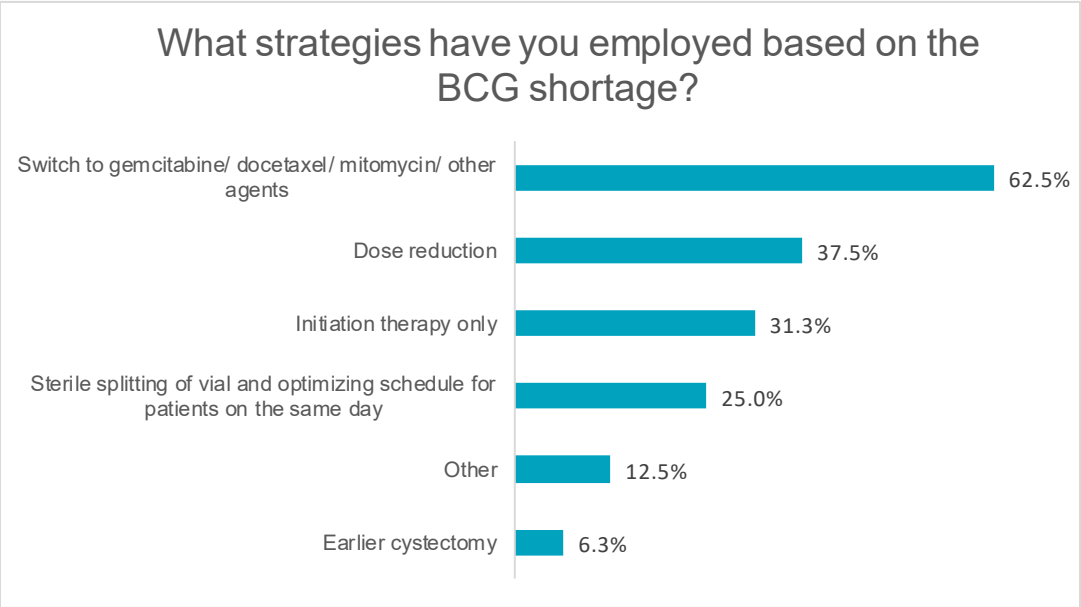
Members were asked to indicate their ability to provide national guideline-based treatment regimens comprised of BCG. The responses were divided into full- or partial-dose therapy for both induction and maintenance treatment. The ability to adhere to guideline-based therapy varied widely among institutions. Of note, four respondents (20%) indicated they could not provide any BCG therapy to patients who were eligible.

The consensus guidelines created in 2020 provided alternative treatment strategies in the case of insufficient BCG supply.[10] Alternative therapies to BCG include traditional antineoplastic chemotherapy, dose-reduction strategies, alteration of therapy duration and earlier surgical intervention. The majority of Vizient members (62.5%) documented switching patients to gemcitabine, docetaxel, mitomycin or other alternative agents where appropriate, followed by dose reduction (37.5%) and reserving BCG for initiation therapy only (31.3%) [Figure 3].

Most notably, 100% of respondents were required to use at least one mitigation strategy during the BCG shortage.

Ref. Vizient member survey November 2022

Figure 3: Drug mitigation strategies employed for BCG shortage by Vizient members



The Vizient survey also assessed how many respondents had a formulary restriction or protocol outlining the use of BCG therapy during a shortage. Nearly 80% of respondents do not have a formulary restriction or drug shortage mitigation strategy in place at their institution, which could potentially lead to a faster decline in stock due to a lack of conservation to regulate supply and applying inconsistent practices per patient.

Summary

The ongoing drug shortage for BCG has had a significant impact on Vizient members and the patients they serve. BCG is the standard of care for the treatment of patients with NMIBC. Vizient member survey results show that 100% of respondents were required to provide alternate therapy options to patients and were unable to adhere to guideline-based therapy. Alternatives to BCG therapy are associated with many negative consequences, including substantial adverse effects from traditional chemotherapeutic agents, risks of disease progression with reduced-dose BCG instillations and premature loss of an organ with earlier cystectomy. The standard of care for the treatment of bladder cancer is being compromised by the insufficient supply of BCG.

Relief of the current BCG shortage is not within sight. Until additional suppliers come to the market, the shortage will continue to disrupt the ability to provide this life-saving therapy. In late 2020, Merck announced plans for a new manufacturing facility in North Carolina that could triple their current production of BCG.[15] The most recent update from Merck in January 2023 indicates they are still expecting to complete their facility in three to four years.[9]

Together, EDSA, Vizient and Angels for Change implore manufacturers to investigate their ability to bring additional supply of this life-saving drug to the market.

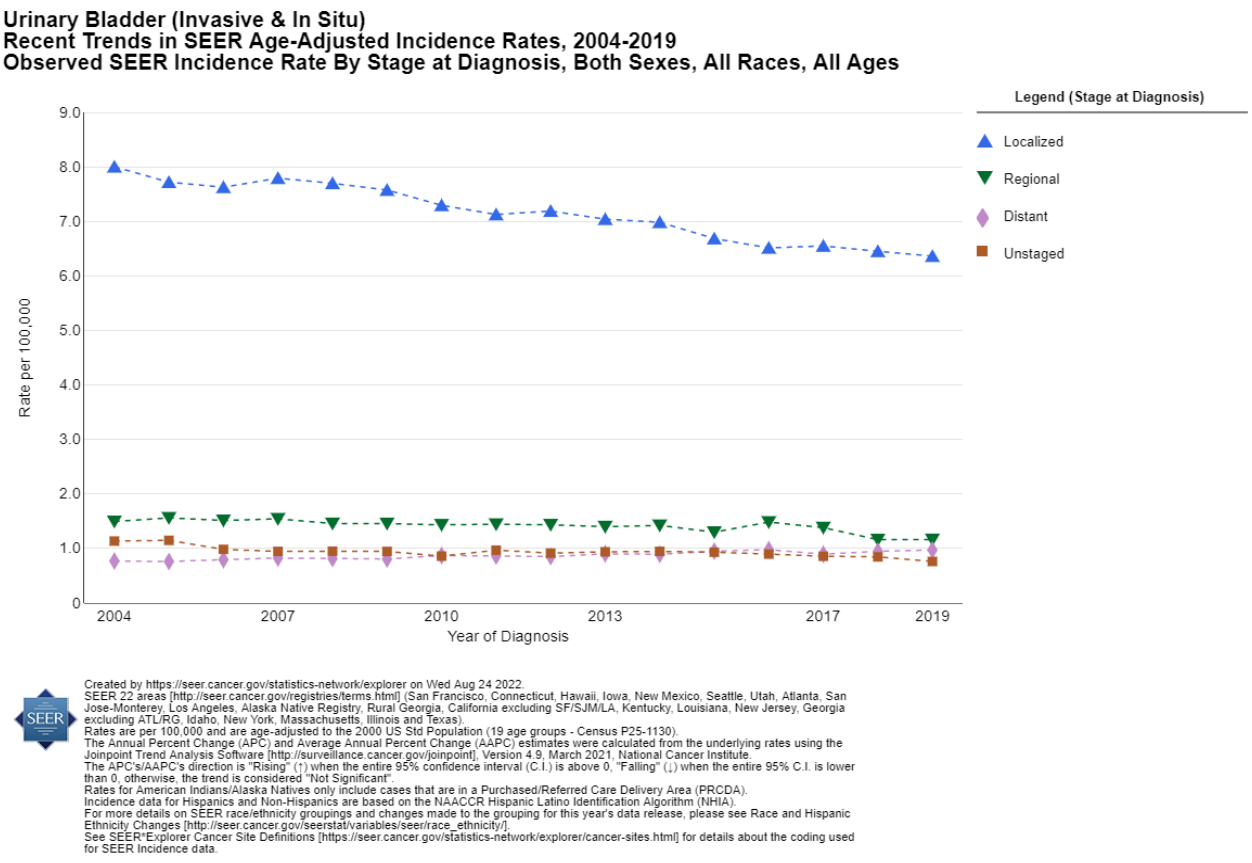
Appendix 1: Bladder Cancer Epidemiology

Per the American Cancer Society, approximately 82,290 cases of bladder cancer (62,420 in men and 19,870 in women) will be diagnosed in 2023, with approximately 16,710 deaths resulting from bladder cancer.[5] Among men, bladder cancer is the sixth most common and nineth most deadly neoplasm. Non-muscle-invasive bladder cancer represents approximately 75% of all new bladder cancer diagnoses in the U.S.[3]

The survival rates of bladder cancer, overall, is approximately 77%; however, survival rates can differ depending on the type and stage of disease.[6] Bladder cancer diagnosed at Stage IV with distant metastasis occurs in 4% of patients and has a five-year survival rate of 5%.[6]

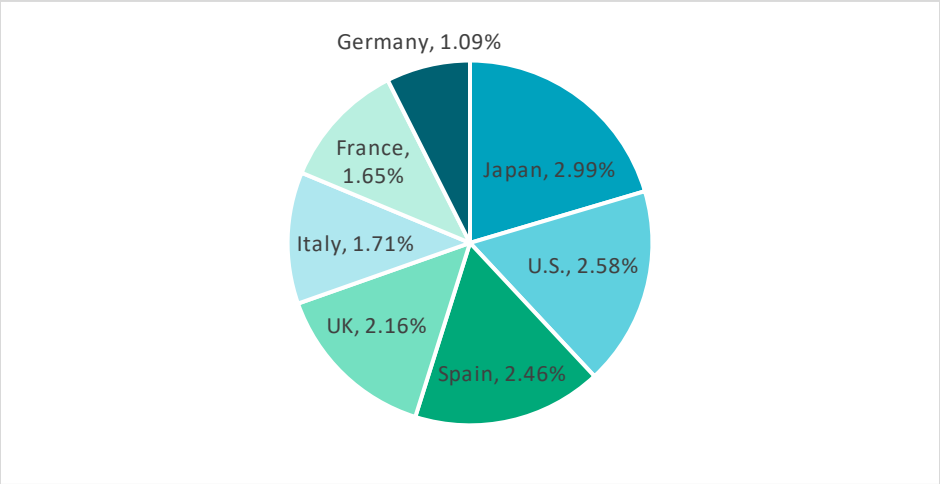
Nationally, data from the Surveillance, Epidemiology, and End Results Program (SEER) database regarding urinary bladder cancer between 2004 and 2019 is presented in Figure 4.[16] There has been a modest decline in the rates of localized bladder cancer during this period encompassing Ta and Tis subtype of NMIBC. Subtype T1 can be classified as regional disease and is shown to have a flat incidence rate over this time period.

Figure 4: Urinary bladder cancer incidence rates 2004-2019[16]



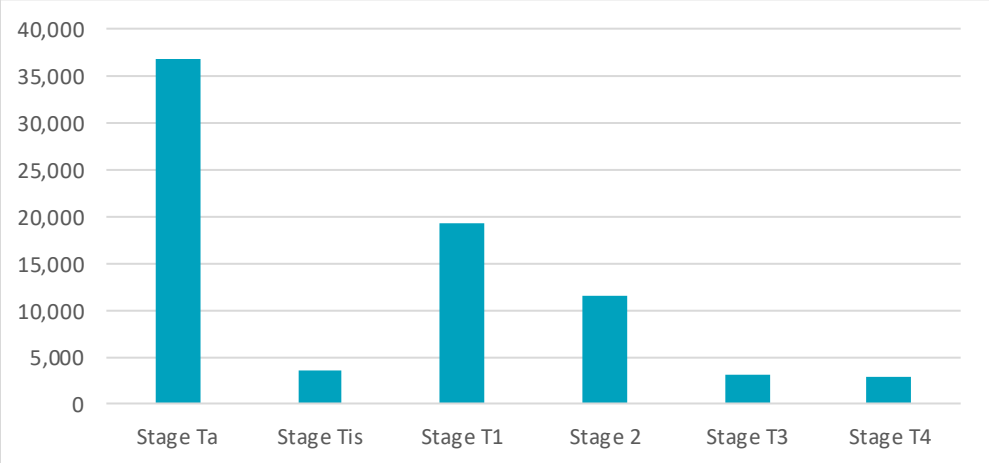
Globally, across the seven major markets including the U.S., United Kingdom, France, Spain, Italy, Germany and Japan, the incidence rates of bladder cancer in both sexes for patients greater than 18 years of age is below in Figure 5.[6] In 2018, the highest percent of cases was in Japan, followed by the U.S. and Spain.

Figure 5: Global incidence cases of bladder cancer in 2018[6]



In 2018, the stage at diagnosis in both men and women ages 18 years and above are identified in Figure 6.[6] In the U.S., the highest number of cases of bladder cancer were diagnosed in stage Ta followed by stage T1. GlobalData reports high-grade tumors account for 6.9% of Ta cases and have a 20-25% chance of developing into muscle invasive bladder cancer.[7]

Figure 6: Diagnosed incident cases of bladder cancer by stage at diagnosis[6]



An increase in the incidence of bladder cancer cases over the next five years is anticipated globally due to an aging population and population changes with varying influences of risk factors. A recent publication on bladder cancer from GlobalData provides a comprehensive epidemiological forecast for bladder cancer for 2018 through 2028. Based on their analyses, the number of diagnosed bladder cases will have an annual growth rate of 2.21% through 2028; the U.S.-specific bladder cancer growth rate for this same period is predicted to be 2.58% annually.[6]

Appendix 2. BCG shortage mitigation strategies

American Urological Association (AUA) recommendations[10]

1. BCG should not be used for patients with low-risk disease.
2. Intravesical chemotherapy should be used as the first-line option for patients with intermediate-risk NMIBC. Patients with recurrent/multifocal low-grade Ta lesions who require intravesical therapy should receive intravesical chemotherapy such as mitomycin, gemcitabine, epirubicin or docetaxel instead of BCG.
3. If BCG would be administered as second-line therapy for patients with intermediate-risk NMIBC, an alternative intravesical chemotherapy should be used rather than BCG in the setting of this BCG shortage.
4. For patients with high-risk NMIBC, high-grade T1 and CIS patients receiving induction therapy, they should be prioritized for use of full-strength BCG. If not available, these patients and other high-risk patients may be given a reduced one-half to one-third dose, if feasible.
5. If supply exists for maintenance therapy for patients with NMIBC, limit BCG dose to one year.
6. In the event of BCG supply shortage, maintenance therapy should not be given and BCG naïve patients with high-risk disease should be prioritized for induction BCG.
7. If BCG is not available, alternatives to BCG such as gemcitabine, epirubicin, docetaxel, valrubicin, mitomycin or sequential gemcitabine/docetaxel or gemcitabine/mitomycin may also be considered with an induction and possible maintenance regimen.
8. Patients with high-risk features (i.e., high-grade T1 with additional risk factors such as concomitant CIS, lymphovascular invasion, prostatic urethral involvement or variant histology) who are not willing to take any potential oncologic risks with alternative intravesical agents, should be offered initial radical cystectomy, if they are surgical candidates.

American Society of Health-System Pharmacists (ASHP) recommendations[17]

1. The choice of an alternative agent must be patient-specific and based on renal function, liver function and the neoplasm type and location. No single agent can be substituted for BCG live.
2. The optimal dose, schedule and duration of BCG live therapy in non-muscle invasive bladder cancer is not fully established. Recent trials have evaluated the use of reduced (one-third dose) dosing regimens.
3. Several urologic associations created recommendations on how to manage the shortage in patients with non-muscle invasive bladder cancer (NMIBC). These included alternatives for treatment, rationing dosing or administering reduced doses. The recommendations can be found at: https://bcan.org/wp-content/uploads/2020/09/2020-joint-letter-re-BCG-shortage-with-signatures-and-logos-FINAL-BCAN.pdf.

National Comprehensive Cancer Network (NCCN) recommendations[4]

The NCCN guidelines state BCG should be prioritized for induction of high-risk patients (e.g., high-grade T1 and CIS). Preferable alternatives to BCG include mitomycin or gemcitabine. Guideline authors note that other options include the following: sequential gemcitabine/ docetaxel, epirubicin, valrubicin, docetaxel or sequential gemcitabine/ mitomycin. If feasible, the dose of BCG may be split (one-third or one-half dose) so that multiple patients may be treated with a single vial in the event of a shortage.

NCCN recommends maintenance therapy with BCG should be prioritized for high-risk patients, especially in the early maintenance period (i.e., three- and six-months post-induction) and continued for one year for intermediate-risk and three years for high-risk NMIBC due to the decreased rate of recurrence for NMIBC.

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For more information:

To learn more, please contact pharmacyquestions@vizientinc.com.

Formed in December, 2021, the End Drug Shortages Alliance brings together health systems, manufacturers, industry and other stakeholders across the supply chain who are dedicated to solving pharmaceutical supply challenges by collaborating to increase visibility, access and advocacy. Collectively we will end drug shortages through focus on transparency, communication, quality, redundancy and supply readiness to achieve measurable and sustainable results. Learn more at enddrugshortages.com.

Vizient, Inc., the nation's largest health care performance improvement company, serves more than 60% of the nation's acute care providers, which includes 97% of the nation's academic medical centers, and more than 20% of ambulatory care providers. Vizient provides expertise, analytics and advisory services, as well as a contract portfolio that represents more than $130 billion in annual purchasing volume. Vizient's solutions and services improve the delivery of high-value care by aligning cost, quality and market performance. Headquartered in Irving, Texas, Vizient has offices throughout the United States. Learn more at www.vizientinc.com

Angels for Change is a volunteer-supported charitable organization on a mission to end drug shortages through advocacy, awareness, and resilient supply chain. Founder Laura Bray, a business professor and consultant, established Angels for Change after her own daughter's Leukemia treatment was disrupted by drug shortages.

Laura believes lifesaving medicines must be in supply and available at the right place and right time, ensuring access to patients. Angels for Change works with healthcare leaders to help end all health crises created by drug shortages. Learn more at www.angelsforchange.org.