FDA Briefing Document

Bacitracin for Intramuscular Injection

Meeting of the Antimicrobial Drugs Advisory Committee (AMDAC)

April 26, 2019

The committee will discuss the safety and effectiveness of bacitracin for intramuscular injection for the treatment of infants with pneumonia and empyema caused by staphylococci shown to be susceptible to the drug, which is the only approved indication for bacitracin for intramuscular injection. The committee will also consider whether there are other uses for bacitracin for intramuscular injection that could be studied. The Federal Register notice for this AMDAC is dated 03/25/2019.
The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought bacitracin for injection to this Advisory Committee in order to gain the Committee’s insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.
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1 Introduction

This briefing document describes the review of safety and efficacy of bacitracin for injection, prepared by the FDA for the panel members of the Advisory Committee. We would like the committee to discuss the safety and effectiveness of bacitracin for injection for the treatment of infants with pneumonia and empyema caused by staphylococci shown to be susceptible to the drug, the only approved indication for bacitracin for injection. We would also like the committee to consider whether there are other uses for bacitracin for injection that could be studied. Topical and ophthalmic formulations of bacitracin are not subject to the discussion of this advisory committee.

2 Product Information

Bacitracin is a mixture of peptides and acts by interfering with bacterial cell wall synthesis. The drug is active in vitro against several gram-positive organisms including Staphylococcus aureus. Bacitracin is available as sterile powder in vials each containing 50,000 units of the drug. It is to be dissolved in sodium chloride for injection containing 2% procaine hydrochloride and administered intramuscularly (IM) in 2 or 3 divided doses over 24 hours based on the infant’s weight.

3 Regulatory History

In July 1948, The Upjohn Company’s (Upjohn) application for bacitracin sterile powder; 10,000 and 50,000 units per vial, became effective. In July 1949, Congress amended section 507 of the Federal Food, Drug, and Cosmetic (FD&C) Act, which provided for the certification of batches of antibiotics, to add bacitracin. In 1950, the Charles Pfizer & Company’s (Pfizer) application for bacitracin sterile powder; 50,000 units per vial, became effective.

In 1962, Congress amended the FD&C Act to require that a new drug be proven effective, as well as safe, to obtain FDA approval. This amendment also required FDA to conduct a retrospective evaluation of the effectiveness of the drug products that FDA had approved as safe between 1938 and 1962 through the new drug approval process. FDA contracted with the National Academy of Sciences/National Research Council (NAS/NRC) to make an initial evaluation of the effectiveness of over 3,400 products that were approved only for safety between 1938 and 1962. The NAS/NRC created 30 panels of 6 professionals each to conduct the review, which was broken down into specific drug categories. The NAS/NRC reports for these drug products were submitted to FDA in the late 1960s and early 1970s. The Agency reviewed and re-evaluated the findings of each panel and published its findings in Federal Register notices. FDA’s administrative
implementation of the NAS/NRC reports was called the Drug Efficacy Study Implementation (DESI).

On June 24, 1970, FDA published a DESI notice announcing the FDA’s conclusions based on its evaluation of reports received from the NAS/NRC Drug Efficacy Study Group, for the bacitracin drug products referenced above and for one other product, bacitracin sterile powder; 50,000 units per vial, marketed by Philadelphia Laboratories, Inc. (Philadelphia) [1]. In this notice, FDA concluded that bacitracin sterile powder was “probably effective” “[i]ntramuscularly for the treatment of infants with pneumonia and empyema caused by staphylococci shown to be sensitive to the drug; and topically (in solution form) for superficial infections caused by micro-organisms shown by sensitivity studies to be susceptible.” The NAS/NRC Panel on Anti-Infective Drugs cited two publications [2, 3] to support the Panel’s initial conclusion that bacitracin sterile powder was “probably effective” for this indication. In its notice, FDA explained that applicants had 12 months “to obtain and submit data to provide substantial evidence of effectiveness of the drug for use in these conditions for which it has been evaluated as probably effective.”

FDA also concluded based on its evaluation of the NAS/NRC reports that bacitracin sterile powder was “possibly effective” “in conjunction with intramuscular administration, by intrathecal, intraventricular, intracisternal, or intracerebral injection in the treatment of susceptible nonsurgical or neurosurgical infections, including osteomyelitis of the skull, septic coccal meningitis, brain abscess, and postoperative infections; surgical infections of tissue and bones; topically in the treatment of susceptible infections of the skin, the eye, and the nose and throat, and in the form of compresses or instillations, may be used in secondarily infected wounds, ulcers, and pyodermas.” FDA explained that applicants had 6 months “to obtain and submit data to provide substantial evidence of effectiveness of the drug for use in these conditions for which it has been evaluated as possibly effective.”

On February 12, 1972, FDA published an amended DESI notice finding Upjohn’s NDA 6-483, Pfizer’s NDA 60-282, and Philadelphia’s NDA 60-350 bacitracin sterile powder products to be effective for the indication of “intramuscularly for the treatment of infants with pneumonia and empyema caused by staphylococci shown to be sensitive to the drug” [4]. The reevaluation determination was based on data and information, including a letter from Dr. Heinz F. Eichenwald, who had chaired the NAS/NRC Panel on Anti-Infective Drugs that had determined bacitracin for injection was “probably effective,” supporting the effectiveness determination for this single, limited indication: “[w]e have used it in two such instances in the past year and, as might be expected, the drug performed quite well. No other medication presently available would have fulfilled this role since vancomycin is too toxic for use in small children.” The other indications previously found to be probably effective and possibly effective were found to be lacking substantial evidence of effectiveness since no new evidence of effectiveness was submitted. The indication of intramuscular bacitracin is limited to “the treatment of infants with pneumonia and empyema caused by staphylococci shown to be sensitive to
the drug,” and is the only indication currently included in the bacitracin for injection labeling [5].

On January 30, 1984, the Anti-Infective Drugs Advisory Committee recommended that bacitracin for injection be withdrawn from certification because of an unfavorable risk benefit assessment. The committee noted the significant risk of nephrotoxicity and the adequacy of alternatives for the treatment of staphylococcal infections for the approved indication. When put to a vote none of the five committee members believed that intramuscular administration of bacitracin was safe and effective for the approved indication.

Bacitracin for injection 50,000 units/vial continues to be marketed under several approved abbreviated new drug applications (ANDAs): ANDA 60733 held by Pharmacia and Upjohn LLC, ANDA 64153 held by X-Gen Pharmaceuticals, ANDA 65116 held by Fresenius Kabi USA, LLC, ANDA 203177 held by Xellia Pharmaceuticals ApS, and ANDA 206719 held by Akorn, Inc.

4 Drug Utilization

According to a drug utilization review for the period from 2015 through 2018, an estimated 2.3 million patients received bacitracin injection annually in the hospital setting (see Appendix 1); 97-98% of the patients who were administered bacitracin for injection were adults 17 years and older, suggesting very limited use in infants. Use was highest in the operating room location compared to other locations of care in the hospital. However, data on the clinical conditions for which bacitracin for injection was used are not available to the Agency.

The review of the literature and the analysis of the current use of bacitracin for injection indicate that the product, usually in combination with other antimicrobials, is mainly used in solutions for intraoperative irrigation of surgical wounds.

FDA found no data that bacitracin for injection is currently used for its labeled indication of intramuscular administration for the treatment of infants with pneumonia and empyema caused by staphylococci.

5 Safety and Effectiveness Data

As indicated above, bacitracin for injection is approved solely for the treatment of infants with pneumonia and empyema caused by staphylococci shown to be susceptible to the drug and is to be administered intramuscularly only. The product labeling includes a boxed warning stating that the drug may cause renal failure due to tubular and glomerular necrosis, should be restricted to infants with staphylococcal pneumonia and empyema when due to organisms shown to be susceptible to bacitracin, and should be used only where adequate laboratory facilities are available and when constant supervision of the
patient is possible [5]. The WARNINGS and PRECAUTIONS section states that there have been reports of anaphylaxis and/or allergic contact dermatitis in patients exposed to bacitracin in non-approved indications. Nephrotoxic reactions, nausea, vomiting, pain at the injection site, and skin rashes are listed in the ADVERSE REACTIONS section. Repeated intramuscular administration in infants of a product for the treatment of staphylococcal pneumonia and empyema is not consistent with the current standard of care.

We performed a literature search for publications addressing either the safety or effectiveness of bacitracin for injection for the treatment of staphylococcal pneumonia and empyema in infants. Publications identified in addition to the two publications [2, 3] considered by the NAS/NRC Panel on Anti-Infective Drugs supporting the 1970 DESI notice include four case series published between 1957 and 1972 [6-9]. Two of the case series [7, 9] report only intrapleural administration of bacitracin, one reports intramuscular administration [8] and the other [6] does not report the route of administration. No conclusions about the efficacy of bacitracin for injection for the treatment of staphylococcal pneumonia and empyema can be drawn from these publications. We found no relevant publications after 1972 addressing either the safety or effectiveness of bacitracin for injection for the treatment of staphylococcal pneumonia and empyema in infants.

The current Pediatric Infectious Diseases Society – Infectious Diseases Society of America clinical practice guidelines for the management of community-acquired pneumonia in infants and children list several FDA-approved antimicrobial therapies for the treatment of staphylococcal pneumonia, including anti-staphylococcal penicillins (e.g., oxacillin), first-generation cephalosporins (e.g., cefazolin), vancomycin, linezolid, and clindamycin [10]. Bacitracin for injection is not included as a treatment option in these guidelines. Other antibacterial drugs approved for the treatment of pneumonia caused by *Staphylococcus aureus* in infants (excluding neonates) include ceftaroline and cefepime [11, 12].

A review of the FDA Adverse Event Reporting System (FAERS) database through 2018 and the medical literature by the Office of Surveillance and Epidemiology (OSE) (see Appendix 2) identified reports of adverse events following the use of irrigation solutions containing bacitracin. The reported adverse events were primarily allergic reactions (including anaphylaxis) and nephrotoxicity. There were also reports of medication errors in the surgical setting in which irrigation solutions were inadvertently administered intravenously.

In conclusion, it appears bacitracin for injection is not currently used for its approved indication, the treatment of infants with pneumonia and empyema caused by staphylococci susceptible to the drug. We believe the reasons why bacitracin for injection is not currently used for its approved indication include the risk of nephrotoxicity, need for repeated intramuscular administrations, and the availability of numerous effective alternative treatments that are safer.
6 Other Clinical Uses

Below we provide a summary of the information in the published literature and clinical guidelines regarding the current clinical uses of bacitracin for injection. The existing literature is mostly comprised of retrospective, observational, single-center studies, reporting on the use of bacitracin for injection for unapproved indications [13-18]. The most commonly identified use of bacitracin for injection is as a component of intraoperative irrigation solutions for the prevention of surgical site infections.

An antibacterial solution that includes cefazolin, bacitracin, and gentamicin is reported to be used by plastic surgeons during breast reconstruction procedures to reduce postoperative breast implant infection and periprosthetic capsular contracture (CC), although inconsistent efficacy results are reported in the literature [17]. A recent meta-analysis found that irrigation of implant pockets fails to reduce the propensity for CC [19].

Intraoperative irrigation is used during clean orthopedic procedures to prevent surgical site infection (SSI). A recent consensus paper advises against the inclusion of antimicrobial agents, including bacitracin, in irrigation solutions for the prevention of SSI, citing concerns for hypersensitivity and antimicrobial resistance [20]. Irrigation solutions that include bacitracin have also been used for the treatment of prosthetic joint infections.

Antimicrobial agents, including bacitracin, are also used for pocket irrigation of cardiovascular implantable electronic devices (CIED). In its scientific statement on the management of CIED infection, the American Heart Association acknowledges the use of irrigation of CIED pockets with antimicrobial solutions and did not mention bacitracin [21].

The published vascular surgery literature describes case series on the use of irrigation solutions, including those with bacitracin, during the postoperative period following graft surgery, but the data are limited [16, 18].

Joint clinical practice guidelines for antimicrobial prophylaxis in surgery from the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Surgical Infection Society, and the Society for Healthcare Epidemiology of America note that there is no additional benefit of topically administered antimicrobial irrigation solutions, pastes, or washes when used as adjuncts to parenteral antimicrobial prophylaxis, and that additional data are needed to support this practice [22]. In a 2016 guideline update, the American College of Surgeons and Surgical Infection Society state that there is insufficient evidence to recommend routine use of topical antimicrobial therapy to decrease the risk of SSI [23]. The Centers for Disease Control and Prevention guideline for the prevention of SSI states that there are uncertain trade-offs between the benefits and harms of intraoperative antimicrobial irrigation and that no recommendation could be made regarding its use [24].
7 Points for Advisory Committee Discussion

1. Do the benefits of bacitracin for injection outweigh the risks for its approved indication of the treatment of infants with pneumonia and empyema caused by staphylococci shown to be susceptible to the drug?

   - If yes, please provide any recommendations concerning labeling.
   - If no, please provide your rationale.
   - Please provide any additional comments or thoughts on your vote.

2. Are there uses for bacitracin for intramuscular injection other than for treatment of infants with pneumonia and empyema caused by staphylococci that could be studied?
8 References


Appendix 1. FDA Bacitracin for Injection Drug Utilization Review

Appendix 2. FDA Pharmacovigilance Review

Appendix 3. Labeling
Appendix 1. FDA Bacitracin for Injection Drug Utilization Review
Drug Name(s): Bacitracin Injection 50,000 Units/Vial
Application Type/Number: ANDA 60282
ANDA 60733
ANDA 62696
ANDA 64153
ANDA 65116
ANDA 90211
ANDA 203177
ANDA 206719
Applicant/sponsor: Multiple Sponsors
OSE RCM #: 2018-2472

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EXECUTIVE SUMMARY

On April 26, 2019, a meeting of the Antimicrobial Drugs Advisory Committee (ADAC) will be held to discuss the safety and effectiveness of the only FDA approved use of bacitracin for intramuscular injection, the treatment of infants with pneumonia and empyema caused by staphylococci shown to be susceptible to the drug. The committee will also consider whether there are other uses for bacitracin for intramuscular injection that have been or could be studied. The Division of Anti-Infective Products (DAIP) requested the Division of Epidemiology II (DEPI II) to provide utilization data on bacitracin injection as well as the use of other products; chlorhexidine gluconate and povidone-iodine from 2015 through 2017. This information will be used to provide context and background information for the advisory committee discussions.

An estimated 2.3 million patients annually received bacitracin injection from the hospital setting over the 3 years examined. Adults 17 years and older accounted for majority of the patients who were administered bacitracin injection. The proportion of bacitracin injection use was highest in the operating room (OR) location compared to other locations of care in the hospitals which may suggest that bacitracin injection was possibly used as an irrigation solution in surgical procedures. However, data on indications for the use of IV bacitracin are not accessible in the resources available to the Agency.

1 INTRODUCTION

1.1 BACKGROUND

In 2016, the Division of Anti-Infective Products (DAIP) requested the Division of Epidemiology II (DEPI II) to provide utilization data on bacitracin injection. This request was prompted by the Office of Regulatory Policy (ORP) for a safety and efficacy determination of bacitracin for intramuscular injection (USP 50,000 Units/vial). The only labeled indication for bacitracin injection is for the treatment of infants with pneumonia and empyema caused by bacitracin-susceptible staphylococci. In preparation for the upcoming April 26, 2019 Antimicrobial Drugs Advisory Committee meeting, DAIP has requested DEPI II to provide more recent utilization data to determine extent of use for bacitracin injection.

1.2 PRODUCT INFORMATION

Bacitracin is an antibiotic that inhibits bacterial cell wall synthesis by preventing transfer of mucoproteptides into the growing cell wall.

Table 1. Product information for bacitracin injection

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Strength</th>
<th>Dosage Form/Route</th>
<th>Application Number</th>
<th>Applicant</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacitracin</td>
<td>50,000 Units/Vial</td>
<td>Injectable/Intramuscular</td>
<td>ANDA 60282</td>
<td>Pfizer</td>
<td>September 6, 1950</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ANDA 60733</td>
<td>Pharmacia and Upjohn</td>
<td>July 29, 1948</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ANDA 62696</td>
<td>Quad Pharm</td>
<td>April 17, 1987</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ANDA 64153</td>
<td>X Gen Pharmaceuticals, Inc</td>
<td>May 9, 1997</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ANDA 65116</td>
<td>Fresenius Kabi USA</td>
<td>December 3, 2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ANDA 90211</td>
<td>Mylan ASI</td>
<td>May 11, 2010</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ANDA 203177</td>
<td>Xellia Pharm AS</td>
<td>August 25, 2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ANDA 206719</td>
<td>Akorn</td>
<td>October 20, 2017</td>
</tr>
</tbody>
</table>
2 METHODS AND MATERIALS

Proprietary drug utilization databases available to the Agency were used to conduct this analysis. (See Appendix 2 for a detailed description of the databases used).

2.1 DATA SOURCES USED

The IQVIA, National Sales Perspectives™ (NSP) database was used to determine the number of bacitracin injection vials/packages sold to U.S. non-retail settings, stratified by manufacturers from 2015 through 2018, annually.

The IQVIA, Hospital Visit Analyzer (HVA) database was used to obtain the nationally estimated number of patients with a hospital discharge billing for bacitracin injection from U.S. non-federal hospitals, stratified by patient age (less than 1, 1-16, and 17 years and older), from January 2015 through December 2017, annually. In addition, the national estimates of unique patients with a hospital discharge billing for chlorhexidine gluconate and povidone-iodine (other commonly used surgical irrigation solutions) were reported to provide a comparison of use to bacitracin injection. The database was also used to obtain the nationally estimated number of patients with a hospital discharge billing for bacitracin injection, stratified by location of care; such as, operating room (OR), emergency room (ER), intensive care unit (ICU) etc., from U.S. non-federal inpatient hospitals in 2017. Of note, the IQVIA hospital sample does not include federal hospitals and other specialty hospitals (including children's hospitals and other standalone specialty hospitals).

3 RESULTS

3.1 SETTING OF CARE

Sales data in 2018 showed that approximately 99% of bacitracin injection vials/packages were sold to U.S. non-retail settings (primarily non-federal hospitals), and less than 1% to mail-order/specialty and outpatient retail pharmacy settings combined. As a result, only non-retail pharmacy utilization patterns were examined for bacitracin injection.

3.2 SALES DATA

Figure 1 below provides the sales data by the number of vials of bacitracin injection distributed to non-retail channels of distribution, stratified by manufacturers from 2015 through 2018, annually. The total number of bacitracin vials sold to non-retail settings remained stable at approximately 5 million vials annually in the examined time. In 2018, of all the manufacturers, Pfizer distributed the most at approximately 3 million vials, followed by X-Gen Pharm Inc and Fresenius Kabi USA at approximately 991,000 and 849,000 vials, respectively.
3.3 PATIENT DATA

Figure 2 below and Table 2 in Appendix 1 provide the nationally estimated number of patients who had a hospital discharge billing for bacitracin injection, stratified by patient age (less than 1, 1-16, and 17+), from U.S. non-federal hospitals from 2015 through 2017, annually. The total number of patients with a hospital billing for bacitracin injection remained stable at approximately 2.3 million patients annually in the examined time. Adults 17 years and older accounted for approximately 97-98% of the total patients, annually. Pediatric patients 0-16 years accounted for approximately 2-3% of the total patients, annually. Of the pediatric patients, approximately 12-16% were infants less than one year old and 84-89% were patients 1-16 years of age.

Figure 2

Nationally estimated number of patients with a hospital discharge billing for bacitracin injection\(^{a}\), stratified by patient age, from U.S. non-federal hospitals, 2015-2017


\(^a\) Single agent bacitracin injection.
Figure 3 below and Table 3 in Appendix 1 provide the nationally estimated number of patients who had a hospital discharge billing for bacitracin injection, chlorhexidine gluconate and povidone-iodine solutions, from U.S. non-federal hospitals from 2015 through 2017, annually.

In 2017, approximately 2.3 million patients had a hospital billing for bacitracin injection, followed by approximately 515,000 and 417,000 patients who had a hospital billing for povidone-iodine and chlorhexidine gluconate solution, respectively. During the examined time, the number of patients with a hospital billing for bacitracin injection remain stable but the number of patients with a hospital billing for chlorhexidine gluconate and povidone-iodine solutions decreased.

**Figure 3**

Nationally estimated number of patients with a hospital discharge billing for bacitracin injection\(^a\), chlorhexidine gluconate solution\(^b\), and povidone-iodine solution\(^c\) from U.S. non-federal hospitals, 2015 – 2017

![Graph showing the number of patients with hospital discharge billing for bacitracin, chlorhexidine, and povidone-iodine solutions from 2015 to 2017.]


\(^a\) Single agent bacitracin injection.

\(^b\) Include only topical forms. Excludes the mouth/throat products such as Periogard, Peridex, and Paroex and all strengths of 0.12%.

\(^c\) Include topical surgical products.

### 3.4 Location of Care Data

Table 4 below provides the nationally estimated number of patients who had a hospital discharge billing for bacitracin injection, stratified by location of care, from U.S. non-federal inpatient hospitals in 2017. During the examined time, approximately 2.3 million patients had a hospital discharge billing for bacitracin injection. Of the total patients, approximately 90% (2 million) of these patients were billed for bacitracin injection from the OR, followed by approximately 44% (1 million) of these patients from general units. Other hospital locations of care where these patients were billed for bacitracin injection included the ICU (11% of patients), unknown (6% of patients), ER (5% of patients), telemetry (4% of patients), CCU (3% of patients), and other (< 1% of patients).
Table 3
Nationally estimated number of patients who had a hospital discharge billing for bacitracin injection, stratified by location of care, from U.S. non-federal inpatient hospitals, 2017

<table>
<thead>
<tr>
<th>Location</th>
<th>Patient Count</th>
<th>Share %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Bacitracin Patients</strong></td>
<td>2,264,333</td>
<td>100.0%</td>
</tr>
<tr>
<td>OR</td>
<td>2,037,585</td>
<td>90.0%</td>
</tr>
<tr>
<td>General†</td>
<td>986,500</td>
<td>43.6%</td>
</tr>
<tr>
<td>ICU</td>
<td>242,724</td>
<td>10.7%</td>
</tr>
<tr>
<td>Unknown††</td>
<td>126,124</td>
<td>5.6%</td>
</tr>
<tr>
<td>ER</td>
<td>111,907</td>
<td>4.9%</td>
</tr>
<tr>
<td>Telemetry</td>
<td>82,977</td>
<td>3.7%</td>
</tr>
<tr>
<td>CCU</td>
<td>76,717</td>
<td>3.4%</td>
</tr>
<tr>
<td>Other†††</td>
<td>8,844</td>
<td>0.4%</td>
</tr>
</tbody>
</table>


Note: Location is the area in the hospital where the patient was on the day of treatment. Because a patient can be in multiple locations on the same day or across multiple days during the same inpatient visit, the sum of patients or hospital visits across locations is much higher than the total unique patients or hospital visits in each age group. The total percentage across locations within each age group is more than 100%.

† Single agent bacitracin injection.
† General unit or general floor is described as a private or semi-private hospital room or bed.
††Unknown means the categories for blank entries in the claim.
††† Other means grouping of locations with very few entries.
CCU = coronary care unit, ER = emergency room, ICU = intensive care unit, OR = operating room

4 DISCUSSION

Drug utilization analyses show that approximately 5 million vials of bacitracin injection were distributed to non-retail settings in 2018. Pfizer was the top manufacturer in the market and distributed approximately 63% (3.1 million) of the product. Findings from this analysis should be interpreted in the context of the known limitations of the databases used. These data do not provide a direct estimate of patient use but do provide a national estimate of units sold from the manufacturer to various channels of distribution.

National estimates of use in the non-federal hospitals were provided in this review. During the examined time, our findings show that approximately 2.2 million adult patients (17 years and older), annually were discharged with a billing for bacitracin injection from the hospital setting, which accounted for 97% of total patients. Moreover, DEPII was requested to provide a comparison of the extent of use between bacitracin injection against chlorhexidine gluconate and povidone-iodine solutions. The analysis shows that bacitracin injection accounted for the largest proportion of use in the non-federal hospital setting with approximately 2.3 million patients with a hospital billing for bacitracin injection in 2017.

Hospital location of care may also serve as a surrogate for possible use of bacitracin injection for different patient populations (e.g. NICU, surgical, etc.). Our analyses show that the use of bacitracin injection was highest in the operating room (OR) setting (~90%), which may suggest off-label use as an irrigation solution in surgical procedures. Published literature on bacitracin injection also suggest off-label use as surgical irrigations, particularly in neurosurgical, orthopedic and cardiac
procedure\textsuperscript{4,5,6}. No data was captured for the use of bacitracin injection either in the pediatric intensive care unit (PICU) or the neonatal intensive care unit (NICU); although the drug is only indicated for treatment of bacitracin-susceptible staphylococci for infants.

Of note, the pediatric utilization identified in our analyses is likely an underestimation of total pediatric utilization of bacitracin injection in all hospital settings. The IQVIA hospital sample does not include federal hospitals and other specialty hospitals (including children's hospitals and other standalone specialty hospitals) and does not necessarily represent all acute care hospitals in the U.S. across in all markets. Caveats of the IQVIA hospital data source are common to this type of hospital charge information but are mostly limited to limitations of charge descriptions and what is actually entered by the sample hospitals. However, validations of IQVIA hospital CDM data using both the National Hospital Discharge Survey (NHDS) and the AHRQ HCUP data have shown IQVIA’s patient level data to be representative and accurate across multiple therapeutic areas.

5 CONCLUSION

Although there are limitations to the databases used in this review, the data findings suggest that bacitracin injection is used to a large extent in the hospital setting, primarily in adults and in the OR (operating rooms). Published literature on bacitracin injection suggests use as surgical irrigations, particularly in neurosurgical, orthopedic and cardiac procedure. The findings in this review are consistent with these published reports, however, data on indications for use are not available in the analyses provided.

APPENDICES
### APPENDIX 1: TABLES

**Table 2**

Nationally estimated number of patients with a hospital discharge billing for bacitracin injection\(^a\), stratified by patient age, from U.S. non-federal hospitals, 2015-2017

<table>
<thead>
<tr>
<th>Age Category</th>
<th>2015 Patients (N)</th>
<th>2015 Share (%)</th>
<th>2016 Patients (N)</th>
<th>2016 Share (%)</th>
<th>2017 Patients (N)</th>
<th>2017 Share (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>2,273,167</td>
<td>100.0%</td>
<td>2,342,203</td>
<td>100.0%</td>
<td>2,279,870</td>
<td>100.0%</td>
</tr>
<tr>
<td>0 - 16 years</td>
<td>71,439</td>
<td>3.1%</td>
<td>80,933</td>
<td>3.5%</td>
<td>51,266</td>
<td>2.2%</td>
</tr>
<tr>
<td>Less than 1 year</td>
<td>8,759</td>
<td>12.3%</td>
<td>13,296</td>
<td>6.4%</td>
<td>7,878</td>
<td>15.4%</td>
</tr>
<tr>
<td>1-16 years</td>
<td>62,735</td>
<td>87.8%</td>
<td>67,919</td>
<td>33.9%</td>
<td>43,453</td>
<td>84.8%</td>
</tr>
<tr>
<td>17 years and older</td>
<td>2,201,821</td>
<td>96.9%</td>
<td>2,261,316</td>
<td>96.5%</td>
<td>2,228,081</td>
<td>97.8%</td>
</tr>
</tbody>
</table>

*Subtotals may not sum exactly, due to rounding. Patients may have received multiple administrations of drug during the study period and due to aging of patients during the study period, patients may be counted more than once in the individual categories. For this reason, summing is not advisable and will result in overestimates of patient counts.  
\(^a\) Single agent bacitracin injection.

**Table 3**

Nationally estimated number of patients with a hospital discharge billing for bacitracin injection\(^a\), chlorhexidine gluconate solution\(^b\), and povidone-iodine solution\(^c\) from U.S. non-federal hospitals, 2015 – 2017

<table>
<thead>
<tr>
<th></th>
<th>2015 Patients N</th>
<th>2015 Share %</th>
<th>2016 Patients N</th>
<th>2016 Share %</th>
<th>2017 Patients N</th>
<th>2017 Share %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>3,496,937</td>
<td>100.0%</td>
<td>3,201,357</td>
<td>100.0%</td>
<td>3,089,008</td>
<td>100.0%</td>
</tr>
<tr>
<td>Bacitracin</td>
<td>2,273,157</td>
<td>65.0%</td>
<td>2,342,203</td>
<td>73.2%</td>
<td>2,279,870</td>
<td>73.8%</td>
</tr>
<tr>
<td>Chlorhexidine</td>
<td>662,332</td>
<td>18.9%</td>
<td>476,952</td>
<td>14.9%</td>
<td>416,535</td>
<td>13.5%</td>
</tr>
<tr>
<td>Povidone-Iodine</td>
<td>745,585</td>
<td>21.3%</td>
<td>521,777</td>
<td>16.3%</td>
<td>514,704</td>
<td>16.7%</td>
</tr>
</tbody>
</table>

*Subtotals may not sum exactly, due to rounding. Patients may have received multiple administrations of drug during the study period and due to aging of patients during the study period, patients may be counted more than once in the individual categories. For this reason, summing is not advisable and will result in overestimates of patient counts.  
\(^a\) Single agent bacitracin injection.  
\(^b\) Include only topical forms. Excludes the mouth/throat products such as Periogard, Peridex, and Paroex and all strengths of 0.12%.  
\(^c\) Include topical surgical products.
APPENDIX 2: DATABASE DESCRIPTIONS

**IQVIA National Sales Perspectives™: Retail and Non-Retail**

The IQVIA National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

**IQVIA Hospital Visit Analyzer**

The Hospital Visit Analyzer (HVA) provides hospital inpatient and outpatient encounter transactions and patient level data drawn from hospital operational files and other reference sources. Encounter information is available from 2002, is collected weekly and monthly and is available 10 weeks after the end of each monthly period. This robust data set includes >700 hospitals with hospital inpatient and outpatient encounter data linked to each appropriate patient as well as to select individual hospital departments by anonymized, consistent, longitudinal patient identifiers. These data include over 13 million patients and 60 million visits per year projected to approximately 37 million inpatient visits and 560 million outpatient (including Emergency Department) visits per year, representing acute care, short-term hospital inpatient sites, and their associated hospital emergency departments in order to measure and track the near-term health care utilization of hospitalized patients. Each hospital patient encounter includes detailed drug, procedure, device, diagnosis, and applied charges data as well as location of initiation of each service within the hospital setting of care (e.g. Pediatric, ICU) by day for each patient's entire stay, as well as patient demographics and admission/discharge characteristics. HVA is representative geographically and across payer types such as commercial insurers, Medicare and Medicaid.
REFERENCES


5 Beckman JM, Amankwah EK, Tetreault LL, Tuite GF. Reduction in CSF shunt infection over a 10-year period associated with the application of concentrated topical antibiotic powder directly to surgical wounds prior to closure. J Neurosurg Pediatr. 2015 Dec;16(6):648-61.

Appendix 2. FDA Pharmacovigilance Review
Pharmacovigilance Review

Date: February 27, 2019

Reviewer: Ronald Wassel, PharmD, Safety Evaluator
Division of Pharmacovigilance II (DPV II)

Medical Officer: Karen Konkel, MD
DPV II

Team Leader: Kelly Cao, PharmD
DPV II

Division Director: S. Christopher Jones, PharmD, MS, MPH
DPV II

Product Names: Bacitracin for Injection, USP, 50,000 Units/vial

Subject: Safety review

Application Type/Numbers: ANDA #s 060733, 064153, 065116, 090211, 203177, 206719

Applicant/Sponsor:
- Pharmacia & Upjohn (ANDA 060733)
- X Gen Pharmaceuticals (ANDA 064153)
- Fresenius Kabi USA (ANDA 065116)
- Mylan ASI (ANDA 090211)
- Xellia Pharmaceuticals APS (ANDA 203177)
- Akorn (ANDA 206719)

OSE RCM #: 2018-2473
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EXECUTIVE SUMMARY

This review summarizes the FDA Adverse Event Reporting System (FAERS) data and the medical literature concerning adverse events associated with the use of bacitracin injection in irrigation and intravenous solutions. The Division of Anti-Infective Products (DAIP) requested this review in preparation for an Advisory Committee meeting to discuss the current use of bacitracin injection. This review is one of multiple reviews DAIP and the Office of Surveillance and Epidemiology (OSE) are conducting (i.e., drug use analysis, literature review of efficacy in off-labeled indications such as use as an irrigation solution) to inform the FDA and the Advisory Committee in the deliberation on the continued need for a bacitracin injectable product.

Our review of the FAERS database and the medical literature found that the adverse events described following the use of irrigation solutions containing bacitracin were typical of those known to occur with the drug, primarily allergic reactions (including anaphylaxis) and nephrotoxicity, which are well-characterized in the current Bacitracin for Injection labeling.

We did not find any new safety issues with the use of bacitracin irrigation, with the possible exception of medication errors in the surgical setting in which irrigation solutions are inadvertently administered intravenously.
1 INTRODUCTION

This review summarizes the FDA Adverse Event Reporting System (FAERS) data and the medical literature concerning adverse events associated with the use of bacitracin injection in irrigation and intravenous solutions. The Division of Anti-Infective Products (DAIP) requested this review in preparation for an Advisory Committee meeting to discuss the current use of bacitracin injection.

1.1 BACKGROUND

In 2016, FDA’s Office of Regulatory Policy (ORP) consulted DAIP to conduct a Safety and Efficacy Relisting Determination for Abbreviated New Drug Application (ANDA) 060282 for Bacitracin for Injection, USP, 50,000 Units/vial for Intramuscular (IM) use to determine whether it was withdrawn from the market in 1996 for reasons of safety and effectiveness. ORP generated the consult request in response to a request by FDA’s Office of Generic Drugs (OGD) because there were believed to be one or more approved ANDAs for which ANDA 060282 was the reference listed drug. There are currently six active approved ANDAs, and two ANDAs (ANDA 060282 and one other) that were discontinued in 1996 with an official Federal Register Notice.

Bacitracin, approved by the FDA in 1948, is a polypeptide antibiotic with activity in vitro against some gram-positive bacteria, including staphylococci (e.g., Staphylococcus aureus) and group A β-hemolytic streptococci (Streptococcus pyogenes). Bacitracin ointment is used topically and ophthalmically alone or in combination with other anti-infectives for the prevention or treatment of superficial infections of the skin and eye caused by susceptible organisms. Systemically, bacitracin’s use has been limited because it is nephrotoxic and may cause renal failure due to renal tubular and glomerular necrosis. As such, the only approved indication for intramuscular bacitracin is the treatment of infants with pneumonia and empyema caused by staphylococci shown to be susceptible to the drug. Despite the approved indication, bacitracin is rarely (if at all) given by this route and for this indication in contemporary medicine.

During their review in 2016, DAIP concluded that ANDA 060282 was not withdrawn from sale because of safety or effectiveness. However, from their research, DAIP noted that an FDA Anti-Infective Drugs Advisory Committee (AC) meeting in 1984 recommended that Bacitracin for Injection, USP be withdrawn from certification because of an unfavorable risk and benefit assessment. The committee noted that the risk of nephrotoxicity outweighed any benefit because of the availability of numerous alternatives for the treatment of staphylococcal infections. The committee also concluded that the earlier studies demonstrating efficacy in infants were conducted at a time when the quality of the science was not sufficiently rigorous to satisfactorily demonstrate efficacy. However, it appears no action was taken following the 1984 AC meeting and Bacitracin for Injection has remained on the market except for the two ANDAs withdrawn in 1996.

DAIP determined that the drug product would not be considered safe and effective if it were reintroduced to the market today, because preclinical or clinical studies would first need to be
conducted to address relevant safety signals or efficacy concerns. However, before recommending withdrawal of the drug, DAIP obtained drug use data that showed considerable non-FDA approved use, primarily in surgical settings as an irrigation solution in surgical incisions for prophylaxis of wound infections, the prevention of capsular contracture in breast augmentation surgery, pocket irrigation for cardiovascular implantable electronic device infection prophylaxis, and to soak medical implants prior to insertion, such as scleral buckles.1-4 Typically, these solutions are prepared by reconstituting the bacitracin 50,000 unit vial and adding the resulting mixture to a quantity of saline or lactated Ringer’s solution. In some cases, one or more additional antibiotics such as neomycin, polymyxin B, vancomycin, cefazolin, and gentamicin are added to the irrigation solution.

DAIP has requested another AC meeting to address the continued need of Bacitracin for Injection since its approved indication is not considered safe and effective, but withdrawal from the market may create unintended consequences since it is being used extensively off-label in the surgical setting and there may be no alternatives for surgeons to use that they consider as effective.

This review is one of multiple reviews DAIP and the Office of Surveillance and Epidemiology (OSE) are conducting (i.e., drug use analysis, literature review of efficacy in off-labeled indications such as use as an irrigation solution) to inform the FDA and the Advisory Committee in the deliberation on the continued need for a bacitracin injectable product.

1.2 PRODUCT LABELING

The current Bacitracin for Injection label contains a Boxed Warning describing bacitracin’s potential for nephrotoxicity. The Boxed Warning notes that its use should be restricted to infants with staphylococcal pneumonia and empyema when due to organisms shown to be susceptible to bacitracin.

Additional Warnings and Precautions include the potential for Clostridium difficile-associated diarrhea (CDAD); the overgrowth of nonsusceptible organisms, including fungi; and the risk of the development of drug-resistant bacteria.

The following statement is also included in the Warnings and Precautions section:

There have been reports of anaphylaxis and/or allergic contact dermatitis in patients exposed to bacitracin for injection in non-approved indications.

The Adverse Reactions section describes nephrotoxic reactions including albuminuria, cylindruria, azotemia and rising blood levels without any increase in dosage; and other reactions including nausea and vomiting, pain at the site of injection, and skin rashes.
2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 1. We used the Report Input Control to exclude non-parenteral routes of administration, which included Cutaneous, Intraocular, Nasal, Ophthalmic, Oral, Topical, Transplacental, and Vaginal. Those reports coded as Other or Unknown underwent a hands-on review to determine if any described a parenteral route of administration. The objective of this search strategy was to identify adverse events that have been reported with the use of bacitracin as an irrigation solution or when injected intravenously.

<table>
<thead>
<tr>
<th>Table 1. FAERS Search Strategy*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Date of Search</strong></td>
</tr>
<tr>
<td><strong>Time Period of Search</strong></td>
</tr>
<tr>
<td><strong>Search Type</strong></td>
</tr>
<tr>
<td><strong>Product Terms</strong></td>
</tr>
<tr>
<td><strong>Report Input Control</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

* See Appendix A for a description of the FAERS database.

2.2 LITERATURE SEARCH

DPV searched the medical literature for articles related to adverse events associated with the use of bacitracin in irrigation solutions or in the context of surgical procedures.

DPV searched the medical literature with the strategy described in Table 2.

<table>
<thead>
<tr>
<th>Table 2. Literature Search Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Date of Search</strong></td>
</tr>
<tr>
<td><strong>Database</strong></td>
</tr>
<tr>
<td><strong>Search Terms</strong></td>
</tr>
<tr>
<td><strong>Years Included in Search</strong></td>
</tr>
</tbody>
</table>
3 RESULTS

3.1 FAERS CASE SELECTION

The FAERS search retrieved 621 reports. After applying the Report Input Control, there were 66 reports available for a hands-on review. Following the hands-on review, we excluded 30 cases because they involved a topical or ophthalmic route of administration and 1 non-case (report of potential medication error because of similar packaging), leaving 35 cases for the case series of adverse events associated with the use of bacitracin injection in irrigation and intravenous solutions (see Figure 1). There were no reports of adverse events associated with bacitracin given by intramuscular injection.

Figure 1. FAERS Case Selection

Table 3 summarizes the 35 FAERS cases of adverse events reported with the use of bacitracin injection in irrigation and intravenous solutions for this case series.

Appendix B contains a line listing of the 35 cases in this case series.
Table 3. Descriptive Characteristics of Adverse Events Reported with the Use of Bacitracin Injection in Irrigation and Intravenous Solutions, Received by FDA Through December 12, 2018  
(N=35)

<table>
<thead>
<tr>
<th>Route</th>
<th>Irrigation (N=24)</th>
<th>Intravenous (N=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 to &lt; 17 years</td>
<td>1</td>
<td>1 to &lt; 3 years</td>
</tr>
<tr>
<td>17 to &lt; 65 years</td>
<td>9</td>
<td>7 to &lt; 17 years</td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>5</td>
<td>17 to &lt; 65 years</td>
</tr>
<tr>
<td>Not reported</td>
<td>9</td>
<td>≥ 65 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10</td>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>Female</td>
</tr>
<tr>
<td>Not reported</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td><strong>Country</strong></td>
<td>United States</td>
<td>United States</td>
</tr>
<tr>
<td><strong>Most Frequently Reported MedDRA Preferred Terms (n&gt;1)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>10</td>
<td>Accidental Overdose</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>9</td>
<td>Headache</td>
</tr>
<tr>
<td>Application Site Reaction</td>
<td>8</td>
<td>Medication Error</td>
</tr>
<tr>
<td>Anaphylactic Reaction</td>
<td>4</td>
<td>Photophobia</td>
</tr>
<tr>
<td>Anaphylactoid Reaction</td>
<td>3</td>
<td>Pyrexia</td>
</tr>
<tr>
<td>Hypotension</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Serious Outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>3</td>
<td>Death</td>
</tr>
<tr>
<td>Life-threatening</td>
<td>4</td>
<td>Life-threatening</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>5</td>
<td>Hospitalization</td>
</tr>
<tr>
<td>Other serious</td>
<td>9</td>
<td>Other serious</td>
</tr>
<tr>
<td><strong>Cases by Event Years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1971</td>
<td>1</td>
<td>1978</td>
</tr>
<tr>
<td>1982</td>
<td>1</td>
<td>1982</td>
</tr>
<tr>
<td>1988</td>
<td>8</td>
<td>1986</td>
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<td>1990</td>
<td>2</td>
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<td>1991</td>
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<td>1991</td>
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<tr>
<td>1992</td>
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<td>1995</td>
</tr>
<tr>
<td>1994</td>
<td>1</td>
<td>1997</td>
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<tr>
<td>1995</td>
<td>1</td>
<td>2012</td>
</tr>
<tr>
<td>1996</td>
<td>1</td>
<td>2013</td>
</tr>
<tr>
<td>2000</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>2017</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2018</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events. Cases may have reported more than one outcome.
3.2 Literature Search

The literature search retrieved 12 relevant citations published between 1979 and 2017.\textsuperscript{4, 6-16} Ten of the 12 citations are case reports involving 12 patients (nine individual reports and one report describing three patients). Six of the literature case reports are in FAERS.

Of the 12 cases, 11 reported an anaphylactic reaction (9 following the use of bacitracin irrigation, 1 in which bacitracin solution was used to soak a medical device, and 1 of bacitracin-soaked gauze to pack the surgical cavity).\textsuperscript{4, 6, 8-14} The twelfth case in which the patient received bacitracin by mediastinal irrigation, reported an increase in the serum bacitracin level to 10.7 units/mL (typically 0.3 to 3 units/mL after IM injection) with an increase in the serum urea nitrogen from 16 mg/dL to 30 mg/dL, while serum creatinine and urine output remained normal.\textsuperscript{15}

The other two literature reports were retrospective analyses. One involved a review of 597 pediatric patients undergoing cerebral spinal fluid shunt procedures, 208 of which had bacitracin powder packed into the surgical wound prior to closing.\textsuperscript{7} The authors found no association between the use of bacitracin and anaphylaxis, wound breakdown, or renal dysfunction. The other review found 8 of 41 patients undergoing total hip replacement surgery developing acute renal failure following use of a bacitracin-neomycin-polymyxin irrigation solution.\textsuperscript{16}

4 DISCUSSION

Our review of the FAERS database and the medical literature found that the adverse events described following the use of irrigation solutions containing bacitracin were typical of those known to occur with the drug, primarily allergic reactions (including anaphylaxis) and nephrotoxicity. Allergic reactions related to bacitracin are not surprising as the drug is cited as the eighth most frequent allergen in North America.\textsuperscript{17}

While only 2 of the 11 cases involving intravenous administration of bacitracin were coded as medication errors, most appeared to be medication errors on review of the narratives. These cases included:

- 2 cases in which bacitracin solutions were prepared specifically for irrigation
- 2 cases in which bacitracin solutions used during surgery were suctioned into a cell saver unit with red blood cells that got infused into the patients
- 1 case in which the nurse administered the wrong antibiotic
- 1 case in which the solution was intended to flush an intracranial pressure monitoring line
- 1 case in which an IV fluid bag looked suspicious and was found to contain bacitracin
- 3 cases in which the product that should have been given, or how the bacitracin product was intended to be given was not provided
- 1 case in which a bacitracin/polymyxin B preparation was given by drip through a peripherally inserted central catheter line

Reference ID: 4396763
The adverse events reported in these cases included three cases of acute kidney injury (coded as Renal Tubular Disorder, Renal Failure, and Blood Creatinine Increased), but were otherwise non-serious.

There were four deaths reported, three following irrigation and one after intravenous administration. However, two cases were related to complications of infection (meningitis in a 75-year-old female, and pneumonia in a 75-year-old male). One case described sudden death in a 34-year-old female following surgery in which bacitracin was used to irrigate an unspecified wound, but no additional information was provided to allow an adequate assessment. The fourth case involved a mixture of neomycin, polymyxin B, and bacitracin mistakenly given intravenously resulting in renal failure in a male patient of unknown age who had suspected osteomyelitis following a spondylo-lumbar fusion. The patient died from respiratory failure after an unknown period of time.

5 CONCLUSION

In conclusion, we find that the reported adverse events following the use of bacitracin irrigation are consistent with the drug’s safety profile. We did not find any new safety issues with the use of bacitracin irrigation, with the possible exception of medication errors in the surgical setting in which irrigation solutions are inadvertently administered intravenously.

6 REFERENCES


7 APPENDICES

7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.
### 7.2 Appendix B. Line Listing of Adverse Event Reports with the Use of Bacitracin Injection in Irrigation and Intravenous (IV) Solutions, Received by FDA Through December 12, 2018

<table>
<thead>
<tr>
<th>Initial FDA Received Date</th>
<th>FAERS Case #</th>
<th>Version #</th>
<th>Manufacturer Control #</th>
<th>Route Description</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Serious Outcome(s)*</th>
<th>Adverse Event(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Ref. 12)</td>
<td>11/3/2000</td>
<td>3566402</td>
<td>1</td>
<td>Irrigation (mediastinal)</td>
<td>65</td>
<td>Male</td>
<td>OT</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>2</td>
<td>3/29/2004</td>
<td>4103592</td>
<td>2</td>
<td>Irrigation (abdominal cavity)</td>
<td>50</td>
<td>Male</td>
<td>HO, RI, OT</td>
<td>Peritoneal adhesions</td>
</tr>
<tr>
<td>3</td>
<td>5/1/1971</td>
<td>4255051</td>
<td>1</td>
<td>Irrigation (right buttock drain)</td>
<td>22</td>
<td>Male</td>
<td>OT</td>
<td>Pruritis</td>
</tr>
<tr>
<td>4</td>
<td>11/1/1980</td>
<td>4339826</td>
<td>1</td>
<td>IV</td>
<td>77</td>
<td>Female</td>
<td>OT</td>
<td>Impairment of renal function (solution with neomycin to be used as irrigation)</td>
</tr>
<tr>
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<td>IV</td>
<td>Male</td>
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<td>Acute renal failure (solution with neomycin and polymyxin to be used as irrigation)</td>
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<tr>
<td>7</td>
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<td>4529252</td>
<td>1</td>
<td>IV</td>
<td>24</td>
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<td>Febrile reaction, Metabolic acidosis (solution to soak bone chips for bone graft surgery; solution suctioned into a cell saver unit that was used to infuse red blood cells)</td>
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<td>60</td>
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<td>Deafness, Tinnitus, Kidney Injury (irrigation solution with neomycin; concomitant gentamicin)</td>
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<tr>
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<td>Version #</td>
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<td>Route Description</td>
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<td>Sex</td>
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<td>Adverse Event(s)</td>
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<tr>
<td>8/8/1989</td>
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<td>4418</td>
<td>Irrigation (brain probe for tumor incision)</td>
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<td>34</td>
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<td>Anaphylaxis (irrigation solution with kanamycin)</td>
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<td>Version</td>
<td>Manufacturer Control #</td>
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<td>Sex</td>
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<td>Manufacturer Control #</td>
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<td>Sex</td>
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<td>Adverse Event(s)</td>
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<tr>
<td>27 2/15/1996</td>
<td>5368712</td>
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<td>14</td>
<td>Male</td>
<td>LT,RI</td>
<td>Allergic reaction, Hypotension, Bronchospasm (irrigation solution with polymyxin B)</td>
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<tr>
<td>28 9/10/1996</td>
<td>5456452</td>
<td>1</td>
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<td>31</td>
<td>Female</td>
<td>LT,OT</td>
<td>Erythema at injection site, Headache, Photophobia (irrigation solution given IV)</td>
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<tr>
<td>30 (Ref. 10) 7/1/2011</td>
<td>8038535</td>
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<td>Soaked gauze (pacemaker pocket)</td>
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<td>OT</td>
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<td>8038537</td>
<td>1</td>
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<td>RI,OT</td>
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<td>8856461</td>
<td>2</td>
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<td>47</td>
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<td>OT</td>
<td>Photophobia, Nausea, Headache, Muscle pain and stiffness (drip solution with polymyxin B through PICC line following hip replacement surgery)</td>
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<td>33 8/1/2013</td>
<td>9436615</td>
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<td>IV</td>
<td>85</td>
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<td>HO</td>
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<td>34 (Ref. 4) 1/5/2018</td>
<td>14355157</td>
<td>1</td>
<td>US-MYLANLABS-2017M1082596</td>
<td>Soaked scleral buckle</td>
<td>63</td>
<td>Male</td>
<td>LT,OT</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Initial FDA Received Date</td>
<td>FAERS Case #</td>
<td>Version #</td>
<td>Manufacturer Control #</td>
<td>Route Description</td>
<td>Age (years)</td>
<td>Sex</td>
<td>Serious Outcome(s)*</td>
<td>Adverse Event(s)</td>
</tr>
<tr>
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<td>35 (Ref. 6)</td>
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<td>1</td>
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<td>Irrigation (breast pockets)</td>
<td>28</td>
<td>Female</td>
<td>HO,LT,OT</td>
<td>Anaphylaxis</td>
</tr>
</tbody>
</table>

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. This outcome should not be confused with the clinical outcome of the reported adverse drug experience. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A report may have more than one serious outcome.

Abbreviations: DE= Death, HO= Hospitalization, LT= Life-threatening, CA= Congenital anomaly, RI= Required intervention, OT=Other medically significant
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

------------------------------------------------------------
RONALD T WASSEL
02/27/2019 03:41:25 PM

KAREN E KONKEL
02/27/2019 03:50:00 PM

KELLY Y CAO
02/27/2019 05:05:28 PM

STEVEN C JONES
02/27/2019 05:39:14 PM
Appendix 3. Labeling

The drug labels represent the most recent drug listing information companies have submitted to the FDA as found on https://labels.fda.gov. (See 21 CFR part 207.) The drug labeling and other information has been reformatted to make it easier to read but its content has neither been altered nor verified by FDA. The drug labeling may not be the labeling on currently distributed products or identical to the labeling that is approved.
WARNING

Nephrotoxicity: Bacitracin in parenteral (intramuscular) therapy may cause renal failure due to tubular and glomerular necrosis. Its use should be restricted to infants with staphylococcal pneumonia and empyema when due to organisms shown to be susceptible to bacitracin. It should be used only when adequate laboratory facilities are available and when constant supervision of the patient is possible.

Renal function should be carefully determined prior to and daily during therapy. The recommended daily dose should not be exceeded and fluid intake and urinary output maintained at proper levels to avoid kidney toxicity. If renal toxicity occurs the drug should be discontinued. The concurrent use of other nephrotoxic drugs, particularly streptomycin, kanamycin, polymyxin B, polymyxin E (colistin), and neomycin should be avoided.

DESCRIPTION:

Bacitracin for Injection, USP is an antibiotic for intramuscular administration. Bacitracin is derived from cultures of *Bacillus licheniformis*. It is a white to pale buff, hygroscopic powder, odorless or having a slight odor. It is freely soluble in water; insoluble in acetone, chloroform, and ether. While soluble in alcohol, methanol, and glacial acetic acid, there is some insoluble residue. It is precipitated from its solutions and inactivated by many of the heavy metals.

The structural formula is:

\[
\begin{align*}
\text{bacitracin A} \\
C_{66}H_{103}N_{17}O_{16}S \\
\text{M.W. 1422.71}
\end{align*}
\]

Bacitracin is comprised of a polypeptide complex and Bacitracin A is the major component in this complex.
CLINICAL PHARMACOLOGY:

Bacitracin, an antibiotic substance derived from cultures of *Bacillus licheniformis* exerts pronounced antibacterial action *in vitro* against a variety of gram-positive and a few gram-negative organisms. However, among systemic diseases, only staphylococcal infections qualify for consideration of bacitracin therapy. Bacitracin is assayed against a standard and its activity is expressed in units, 1 mg having a potency of not less than 50 units.

*Susceptibility plate testing*

If the Kirby-Bauer method of disk susceptibility is used, a 10 unit bacitracin disk should give a zone of over 13 mm when tested against a bacitracin-susceptible strain of *Staphylococcus aureus*. Absorption of bacitracin following intramuscular injection is rapid and complete. A dose of 200 or 300 units/kg every 6 hours gives serum levels of 0.2 to 2 mcg/mL in individuals with normal renal function. The drug is excreted slowly by glomerular filtration. It is widely distributed in all body organs and is demonstrable in ascitic and pleural fluids after intramuscular injection.

INDICATIONS AND USAGE:

In accord with the statements in the “Warning Box” the use of intramuscular bacitracin is limited to the treatment of infants with pneumonia and empyema caused by staphylococci shown to be susceptible to the drug.

CONTRAINDICATIONS:

This drug is contraindicated in those individuals with a history of previous hypersensitivity or toxic reaction to it.

PRECAUTIONS:

See “Warning Box” for precautions in regard to kidney toxicity associated with intramuscular use of bacitracin.

Adequate fluid intake should be maintained orally, or if necessary, by parenteral method.

As with other antibiotics, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be instituted.

ADVERSE REACTIONS:

*Nephrotoxic reactions*

Albuminuria, cylindruria, azotemia. Rising blood levels without any increase in dosage.

*Other reactions*


DOSAGE AND ADMINISTRATION:

TO BE ADMINISTERED INTRAMUSCULARLY ONLY

*Infant dose*

For infants under 2,500 grams - 900 units/kg/24 hours, in 2 or 3 divided doses. For infants over 2,500 grams - 1,000 units/kg/24 hours, in 2 or 3 divided doses. Intramuscular injections of the solution should
be given in the upper outer quadrant of the buttocks, alternating right and left and avoiding multiple injections in the same region because of the transient pain following injection.

**Preparation of Solutions**

Should be dissolved in sodium chloride injection containing 2 percent procaine hydrochloride. The concentration of the antibiotic in the solution should not be less than 5,000 units per mL nor more than 10,000 units per mL.

Diluents containing parabens should not be used to reconstitute bacitracin; cloudy solutions and precipitate formation have occurred.

Reconstitution of the 50,000 unit vial with 9.8 mL of diluent will result in a concentration of 5,000 units per mL.

Solutions are stable for one week when stored in a refrigerator 2° to 8°C (36° to 46°F).

**HOW SUPPLIED:**

<table>
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<th>Product No.</th>
<th>NDC No.</th>
<th>Description</th>
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<tr>
<td>302930</td>
<td>63323-329-30</td>
<td>Bacitracin for Injection, USP, 50,000 units per vial, packaged individually.</td>
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<tr>
<td>302931</td>
<td>63323-329-31</td>
<td>Bacitracin for Injection, USP, 50,000 units per vial, 10 vials per tray.</td>
</tr>
</tbody>
</table>

The container closure is not made with natural rubber latex.

Store the unreconstituted product in a refrigerator 2° to 8°C (36° to 46°F).

[www.fresenius-kabi.us](http://www.fresenius-kabi.us)

45960E/Revised: December 2016

**PACKAGE LABEL - PRINCIPAL DISPLAY - Bacitracin 50,000 Units Vial Label**

**Bacitracin** for Injection, USP

**50,000 Units**

For Intramuscular Use

Rx only
For Intramuscular Use

Rx only
Bacitracin
for Injection, USP
50,000 Units

For Intramuscular Use

Rx only
# Active Ingredient/Active Moiety

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<th>Ingredient Name</th>
<th>Basis of Strength</th>
<th>Strength</th>
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<tr>
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<td>BACITRACIN</td>
<td>50000 [iu]</td>
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## Packaging

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<td>NDC:63323-329-31</td>
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<td>01/28/2003</td>
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<tr>
<td>1</td>
<td></td>
<td>1 in 1 VIAL; Type 0: Not a Combination Product</td>
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## Marketing Information

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<td>ANDA065116</td>
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## Labeler

Labeler - Fresenius Kabi USA, LLC (608775388)

## Establishment

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<th>Address</th>
<th>ID/FEI</th>
<th>Business Operations</th>
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<td>Fresenius Kabi USA, LLC</td>
<td></td>
<td>023648251</td>
<td>MANUFACTURE(63323-329)</td>
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</table>

Revised: 7/2017

Fresenius Kabi USA, LLC
To reduce the development of drug-resistant bacteria and maintain the effectiveness of bacitracin and other antibacterial drugs, bacitracin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

**For Intramuscular Use**

**WARNING**

Nephrotoxicity: Bacitracin in parenteral (intramuscular) therapy may cause renal failure due to tubular and glomerular necrosis. Its use should be restricted to infants with staphylococcal pneumonia and empyema when due to organisms shown to be susceptible to bacitracin. It should be used only where adequate laboratory facilities are available and when constant supervision of the patient is possible.

Renal function should be carefully determined prior to and daily during therapy. The recommended daily dose should not be exceeded and fluid intake and urinary output should be maintained at proper levels to avoid kidney toxicity. If renal toxicity occurs the drug should be discontinued. The concurrent use of other nephrotoxic drugs, particularly streptomycin, kanamycin, polymyxin B, polymyxin E (colistin), neomycin, and vancomycin, should be avoided.

**DESCRIPTION**

Bacitracin for Injection, USP is a sterile antibiotic for intramuscular administration. Bacitracin is derived from cultures of Bacillus subtilis (Tracey). It is a white to pale buff, hygroscopic powder, odorless or having a slight odor. It is freely soluble in water; insoluble in acetone, chloroform, and ether. While soluble in alcohol, methanol, and glacial acetic acid, there is some insoluble residue. It is precipitated from its solutions and inactivated by many of the heavy metals.

Each vial contains 50,000 units of bacitracin.

The structural formula is:
The molecular formula is: $C_{66}H_{103}N_{17}O_{16}S$

Bacitracin is comprised of a polypeptide complex and Bacitracin A is the major component in this complex. The molecular weight of Bacitracin A is 1422.71.

**CLINICAL PHARMACOLOGY**

Bacitracin exerts pronounced antibacterial action *in vitro* against a variety of gram-positive and a few gram-negative organisms. However, among systemic diseases, only staphylococcal infections qualify for consideration of bacitracin therapy. Bacitracin is assayed against a standard and its activity is expressed in units, 1 mg having a potency of not less than 50 units.

Susceptibility plate testing: If the Kirby-Bauer method of disk susceptibility is used, a 10 unit bacitracin disk should give a zone of over 13 mm when tested against a bacitracin-susceptible strain of *Staphylococcus aureus*. Absorption of bacitracin following intramuscular injection is rapid and complete. A dose of 200 or 300 units/kg every 6 hours gives serum levels of 0.2 to 2 mcg/mL in individuals with normal renal function. The drug is excreted slowly by glomerular filtration. It is widely distributed in all body organs and is demonstrable in ascitic and pleural fluids after intramuscular injection.

**INDICATIONS AND USAGE**

In accord with the statements in the “Warning Box” the use of intramuscular bacitracin is limited to the treatment of infants with pneumonia and empyema caused by staphylococci shown to be susceptible to the drug.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of bacitracin and other antibacterial drugs, bacitracin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

**CONTRAINDICATIONS**

This drug is contraindicated in those individuals with a history of previous hypersensitivity or toxic reaction to it.

**WARNINGS and PRECAUTIONS**

See "Warning Box"; for precautions in regard to kidney toxicity associated with intramuscular use of bacitracin.

*Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

*C. difficile* produces toxins A and B which contribute to the development of CDAD. Hyp toxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic
treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Adequate fluid intake should be maintained orally, or if necessary, by parenteral method.

As with other antibiotics, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be instituted.

Prescribing bacitracin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

There have been reports of anaphylaxis and/or allergic contact dermatitis in patients exposed to bacitracin in non-approved indications.

*Information for Patients*

Patients should be counseled that antibacterial drugs, including bacitracin, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When bacitracin is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by bacitracin or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

**ADVERSE REACTIONS**

*Nephrotoxic reactions.* Albuminuria, cylindruria, azotemia. Rising blood levels without any increase in dosage.

*Other reactions.* Nausea and vomiting. Pain at site of injection. Skin rashes.

**DOSAGE AND ADMINISTRATION**

**TO BE ADMINISTERED INTRAMUSCULARLY ONLY**

Infant dose: For infants under 2500 grams – 900 units/kg/24 hours in 2 or 3 divided doses. For infants over 2500 grams – 1,000 units/kg/24 hours, in 2 or 3 divided doses. Intramuscular injections of the solution should be given in the upper outer quadrant of the buttocks, alternating right and left and avoiding multiple injections in the same region because of the transient pain following injection.

*Preparation of Solutions* – Should be dissolved in sodium chloride injection containing 2 percent procaine hydrochloride. The concentration of the antibiotic in the solution should not be less than 5,000 units per mL nor more than 10,000 units per mL.

Diluents containing parabens should not be used to reconstitute bacitracin; cloudy solutions and precipitate formation have occurred.

Reconstitution of the 50,000 unit vial with 9.8 mL of diluent will result in a concentration of 5,000 units per mL.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

**HOW SUPPLIED**
Bacitracin for Injection, USP is available in vials containing 50,000 units.

Store the unreconstituted product in a refrigerator 2° to 8°C (36° to 46°F).
Solutions are stable for one week when stored in a refrigerator 2° to 8°C (36° to 46°F).

Manufactured for:
X-Gen Pharmaceuticals, Inc.
Big Flats, 14814
Revised June 2012
BIM-P04

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL
NDC 39822-0277-5
BACiiM
(Bacitracin for Injection, USP)
50,000 Units/vial
For Intramuscular Use
Rx Only
1 Vial
X-GEN Pharmaceuticals, Inc

NDC 39822-0277-2
BACiiM
(Bacitracin for Injection, USP)
50,000 Units/vial
For Intramuscular Use
Rx Only
10 Vial/Carton
X-GEN Pharmaceuticals, Inc
BACIIM
bacitracin injection, powder, lyophilized, for solution

Product Information

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**Labeler** - X-GEN Pharmaceuticals, Inc. (790169531)

Revised: 1/2013

X-GEN Pharmaceuticals, Inc.
To reduce the development of drug-resistant bacteria and maintain the effectiveness of Bacitracin and other antibacterial drugs, Bacitracin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

For Intramuscular Use

WARNING

Nephrotoxicity

Bacitracin in parenteral (intramuscular) therapy may cause renal failure due to tubular and glomerular necrosis. Its use should be restricted to infants with staphylococcal pneumonia and empyema when due to organisms shown to be susceptible to bacitracin. It should be used only where adequate laboratory facilities are available and when constant supervision of the patient is possible.

Renal function should be carefully determined prior to and daily during therapy. The recommended daily dose should not be exceeded and fluid intake and urinary output maintained at proper levels to avoid kidney toxicity. If renal toxicity occurs the drug should be discontinued. The concurrent use of other nephrotoxic drugs, particularly streptomycin, kanamycin, polymyxin B, polymyxin E (colistin), and neomycin should be avoided.

DESCRIPTION

Sterile Bacitracin, USP is an antibiotic for intramuscular administration. Bacitracin is derived from cultures of Bacillus subtilis (Tracey). It is a white to pale buff, hygroscopic powder, odorless or having a slight odor. It is freely soluble in water; insoluble in acetone, chloroform, and ether. While soluble in alcohol, methanol, and glacial acetic acid, there is some insoluble residue. It is precipitated from its solutions and inactivated by many of the heavy metals.

The structural formula is:

\[
\text{bacitracin A}
\]

The molecular formula is: C_{66}H_{103}N_{17}O_{16}S. Bacitracin is comprised of a polypeptide complex and Bacitracin A is the major component in this complex. The molecular weight of Bacitracin A is 1422.71.

CLINICAL PHARMACOLOGY

Bacitracin exerts pronounced antibacterial action in vitro against a variety of gram-positive and a few
gram-negative organisms. However, among systemic diseases, only staphylococcal infections qualify for consideration of bacitracin therapy. Bacitracin is assayed against a standard and its activity is expressed in units, 1 mg having a potency of not less than 50 units.

Absorption of bacitracin following intramuscular injection is rapid and complete. A dose of 200 or 300 units/kg every 6 hours gives serum levels of 0.2 to 2 mcg/mL in individuals with normal renal function. The drug is excreted slowly by glomerular filtration. It is widely distributed in all body organs and is demonstrable in ascitic and pleural fluids after intramuscular injection.

Susceptibility Testing

For specific information regarding susceptibility test criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: www.fda.gov/STIC.

INDICATIONS AND USAGE

In accordance with the statements in the "Warning Box" the use of intramuscular bacitracin is limited to the treatment of infants with pneumonia and empyema caused by staphylococci shown to be susceptible to the drug.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Bacitracin and other antibacterial drugs, Bacitracin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

This drug is contraindicated in those individuals with a history of previous hypersensitivity or toxic reaction to it.

PRECAUTIONS

See "Warning Box" for precautions in regard to kidney toxicity associated with intramuscular use of bacitracin.

Adequate fluid intake should be maintained orally, or if necessary, by parenteral method.

As with other antibiotics, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be instituted.

Prescribing Bacitracin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Information for patients

Patients should be counseled that antibacterial drugs including Bacitracin should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Bacitracin is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Bacitracin or other antibacterial drugs in the future.
ADVERSE REACTIONS

Nephrotoxic reactions. Albuminuria, cylindruria, azotemia. Rising blood levels without any increase in dosage.


To report SUSPECTED ADVERSE REACTIONS, contact Xellia Pharmaceuticals USA, LLC at safety@xellia.com or 1-855-642-2594, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DOSAGE AND ADMINISTRATION

TO BE ADMINISTERED INTRAMUSCULARLY ONLY

Infant dose

For infants under 2500 grams-900 units/kg/24 hours in 2 or 3 divided doses. For infants over 2500 grams-1,000 units/kg/24 hours, in 2 or 3 divided doses. Intramuscular injections of the solution should be given in the upper outer quadrant of the buttocks, alternating right and left and avoiding multiple injections in the same region because of the transient pain following injection.

Preparation of Solutions

Should be dissolved in sodium chloride injection containing 2 percent procaine hydrochloride. The concentration of the antibiotic in the solution should not be less than 5,000 units per mL nor more than 10,000 units per mL.

Diluents containing parabens should not be used to reconstitute bacitracin; cloudy solutions and precipitate formation have occurred.

Reconstitution of the 50,000 unit vial with 9.8 mL of diluent will result in a concentration of 5,000 units per mL.

Solutions are stable for one week when stored in a refrigerator 2° to 8°C (36° to 46°F).

HOW SUPPLIED

Sterile Bacitracin, USP is available in a vial (1's) containing 50,000 units (NDC 70594-026-01) and as pack of ten (10's) each containing 50,000 units (NDC 70594-026-02).

Store the unreconstituted product in a refrigerator 2° to 8°C (36° to 46°F).

Rx only

Manufactured for:
Xellia Pharmaceuticals USA, LLC
Raleigh, NC 27616

Made in India
LEA-019548-00

Revised: June 2018

PRINCIPAL DISPLAY PANEL - 1 Vial Carton

NDC 70594-026-01
Rx Only
For Intramuscular Use
Bacitracin
BACITRACIN
bacitracin injection, powder, for solution
## Product Information

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**Labeler** - Xellia Pharmaceuticals USA LLC (079459964)

**Registrant** - Xellia Pharmaceuticals ApS (305814345)

Revised: 7/2018
Bacitracin for Injection, USP

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Bacitracin and other antibacterial drugs, Bacitracin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

For Intramuscular Use

WARNING

Nephrotoxicity

Bacitracin in parenteral (intramuscular) therapy may cause renal failure due to tubular and glomerular necrosis. Its use should be restricted to infants with staphylococcal pneumonia and empyema when due to organisms shown to be susceptible to bacitracin. It should be used only where adequate laboratory facilities are available and when constant supervision of the patient is possible.

Renal function should be carefully determined prior to and daily during therapy. The recommended daily dose should not be exceeded and fluid intake and urinary output should be maintained at proper levels to avoid kidney toxicity. If renal toxicity occurs the drug should be discontinued. The concurrent use of other nephrotoxic drugs, particularly streptomycin, kanamycin, polymyxin B, polymyxin E (colistin), and neomycin should be avoided.

DESCRIPTION

Sterile Bacitracin USP is an antibiotic for intramuscular administration. Bacitracin is derived from cultures of Bacillus subtilis (Tracey). It is a white to pale buff, hygroscopic powder, odorless or having a slight odor. It is freely soluble in water; insoluble in acetone, chloroform, and ether. While soluble in alcohol, methanol, and glacial acetic acid, there is some insoluble residue. It is precipitated from its solutions and inactivated by many of the heavy metals.

The structural formula is:
The molecular formula is: C_{66}H_{103}N_{17}O_{16}S. Bacitracin is comprised of a polypeptide complex and Bacitracin A is the major component in this complex. The molecular weight of Bacitracin A is 1422.71.

**CLINICAL PHARMACOLOGY**

Bacitracin exerts pronounced antibacterial action *in vitro* against a variety of gram-positive and a few gram-negative organisms. However, among systemic diseases, only staphylococcal infections qualify for consideration of bacitracin therapy. Bacitracin is assayed against a standard and its activity is expressed in units, 1 mg having a potency of not less than 50 units.

Absorption of bacitracin following intramuscular injection is rapid and complete. A dose of 200 or 300 units/kg every 6 hours gives serum levels of 0.2 to 2 mcg/mL in individuals with normal renal function. The drug is excreted slowly by glomerular filtration. It is widely distributed in all body organs and is demonstrable in ascitic and pleural fluids after intramuscular injection.

**Susceptibility Testing**

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC.

**INDICATIONS AND USAGE**

In accordance with the statements in the "Warning Box" the use of intramuscular bacitracin is limited to the treatment of infants with pneumonia and empyema caused by staphylococci shown to be susceptible to the drug.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Bacitracin and other antibacterial drugs, Bacitracin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

**CONTRAINDICATIONS**

This drug is contraindicated in those individuals with a history of previous hypersensitivity or toxic reaction to it.

**WARNINGS and PRECAUTIONS**

See "Warning Box" for precautions in regard to kidney toxicity associated with intramuscular use of bacitracin.

*Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

*C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxic producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.
Adequate fluid intake should be maintained orally, or if necessary, by parenteral method.

As with other antibiotics, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be instituted.

Prescribing Bacitracin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

There have been reports of anaphylaxis and/or allergic contact dermatitis in patients exposed to Bacitracin in non-approved indications.

Information for Patients

Patients should be counseled that antibacterial drugs, including Bacitracin should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Bacitracin is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Bacitracin or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

ADVERSE REACTIONS

Nephrotoxic reactions. Albuminuria, cylindruria, azotemia. Rising blood levels without any increase in dosage.


DOSAGE AND ADMINISTRATION

TO BE ADMINISTERED INTRAMUSCULARLY ONLY

Infant dose

For infants under 2500 grams–900 units/kg/24 hours in 2 or 3 divided doses. For infants over 2500 grams–1,000 units/kg/24 hours, in 2 or 3 divided doses. Intramuscular injections of the solution should be given in the upper outer quadrant of the buttocks, alternating right and left and avoiding multiple injections in the same region because of the transient pain following injection.

Preparation of Solutions

Should be dissolved in sodium chloride injection containing 2 percent procaine hydrochloride. The concentration of the antibiotic in the solution should not be less than 5,000 units per mL or more than 10,000 units per mL.

Diluents containing parabens should not be used to reconstitute bacitracin; cloudy solutions and precipitate formation have occurred.

Reconstitution of the 50,000 unit vial with 9.8 mL of diluent will result in a concentration of 5,000 units per mL.

Solutions are stable for one week when stored in a refrigerator 2° to 8°C (36° to 46°F).
Sterile Bacitracin USP is available in a vial (1's) containing 50,000 units (NDC 0009-0233-44) and as a pack of ten vials (10's) each containing 50,000 units (NDC 0009-0233-45).

Store the unreconstituted product in a refrigerator 2° to 8°C (36° to 46°F).

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com

Rx only

Distributed by
Pharmacia & Upjohn Co
Division of Pfizer Inc
New York, NY 10017

LAB-0389-4.0
Revised: 04/2018

PRINCIPAL DISPLAY PANEL - 50,000 Unit Vial Label

NDC 0009-0233-44

One Vial

Bacitracin for
Injection, USP

50,000 Units

For Intramuscular Use

Rx only

Distributed by Pfizer Inc, NY, NY 10017

Amerinet Choice®
PRINCIPAL DISPLAY PANEL - 50,000 Unit Vial Carton

NDC 0009-0233-44

One Vial
Bacitracin for Injection, USP
50,000 Units
For Intramuscular Use
Rx only
Amerinet Choice®
Store unconstituted product in a refrigerator 2-8°C (36-46°F).

DOSAGE AND USE:
See accompanying prescribing information.

Reconstitution with 9.8 mL of sodium chloride injection containing 2 percent procaine hydrochloride will result in a concentration of 5,000 units per mL. Diluents containing parabens should not be used.

Lyophilized in container.
Store solution in a refrigerator 2-8°C (36-46°F).

Discard after 1 week.
Each vial contains 50,000 units Bacitracin.
Contains 10 of NDC 0009-0233-44

10 Vials
Bacitracin for Injection, USP
50,000 Units
For Intramuscular Use
Amerinet Choice®
Rx only
## BACITRACIN

bacitracin injection, powder, for solution

### Product Information

- **Product Type**: HUMAN PRESCRIPTION DRUG
- **Route of Administration**: INTRAMUSCULAR
- **Item Code (Source)**: NDC:0009-0233

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- **Marketing Category**: ANDA
- **Application Number or Monograph Citation**: ANDA060733
- **Marketing Start Date**: 07/29/1948
- **Marketing End Date**: 07/29/1948

### Labeler

- Pharmacia and Upjohn Company LLC (618054084)

### Registrant

- Pfizer Inc (113480771)

### Establishment

| Name | Address | ID/FEI | Business Operations |
|------|---------|--------|---------------------|---------------------|

Each vial contains 50,000 units Bacitracin 70.
Bacitracin for Injection, USP

To reduce the development of drug-resistant bacteria and maintain the effectiveness of bacitracin for injection and other antibacterial drugs, bacitracin for injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

For Intramuscular Use

WARNING

Nephrotoxicity: Bacitracin in parenteral (intramuscular) therapy may cause renal failure due to tubular and glomerular necrosis. Its use should be restricted to infants with staphylococcal pneumonia and empyema when due to organisms shown to be susceptible to bacitracin. It should be used only where adequate laboratory facilities are available and when constant supervision of the patient is possible.

Renal function should be carefully determined prior to and daily during therapy. The recommended daily dose should not be exceeded and fluid intake and urinary output should be maintained at proper levels to avoid kidney toxicity. If renal toxicity occurs the drug should be discontinued. The concurrent use of other nephrotoxic drugs, particularly streptomycin, kanamycin, polymyxin B, polymyxin E (colistin), and neomycin should be avoided.

DESCRIPTION

Bacitracin for Injection, USP is a sterile antibiotic for intramuscular administration. Bacitracin is derived from cultures of Bacillus subtilis (Tracey). It is a white to pale buff, hygroscopic powder, odorless or having a slight odor. It is freely soluble in water; insoluble in acetone, chloroform, and ether. While soluble in alcohol, methanol, and glacial acetic acid, there is some insoluble residue. It is precipitated from its solutions and inactivated by many of the heavy metals.

The structural formula is:

\[
\text{bacitracin A}
\]
The molecular formula is: C_{66}H_{103}N_{17}O_{16}S. Bacitracin is comprised of a polypeptide complex and bacitracin A is the major component in this complex. The molecular weight of bacitracin A is 1422.71.

CLINICAL PHARMACOLOGY

Bacitracin exerts pronounced antibacterial action in vitro against a variety of gram-positive and a few gram-negative organisms. However, among systemic diseases, only staphylococcal infections qualify for consideration of bacitracin therapy. Bacitracin is assayed against a standard and its activity is expressed in units, 1 mg having a potency of not less than 50 units.

Susceptibility plate testing: If the Kirby-Bauer method of disk susceptibility is used, a 10 unit bacitracin disk should give a zone of over 13 mm when tested against a bacitracin-susceptible strain of Staphylococcus aureus. Absorption of bacitracin following intramuscular injection is rapid and complete. A dose of 200 or 300 units/kg every 6 hours gives serum levels of 0.2 to 2 mcg/mL in individuals with normal renal function. The drug is excreted slowly by glomerular filtration. It is widely distributed in all body organs and is demonstrable in ascitic and pleural fluids after intramuscular injection.

INDICATIONS AND USAGE

In accordance with the statements in the "Warning Box", the use of intramuscular Bacitracin for Injection, USP is limited to the treatment of infants with pneumonia and empyema caused by staphylococci shown to be susceptible to the drug.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Bacitracin for Injection, USP and other antibacterial drugs, Bacitracin for Injection, USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

This drug is contraindicated in those individuals with a history of previous hypersensitivity or toxic reaction to it.

WARNINGS AND PRECAUTIONS

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS

See "Warning Box" for precautions in regard to kidney toxicity associated with intramuscular use of bacitracin.
Adequate fluid intake should be maintained orally, or if necessary, by parenteral method.

As with other antibiotics, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be instituted.

Prescribing bacitracin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

There have been reports of anaphylaxis and/or allergic contact dermatitis in patients exposed to bacitracin for injection in non-approved indications.

Information for Patients

Patients should be counseled that antibacterial drugs, including bacitracin, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When bacitracin for injection is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by bacitracin for injection or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibacterial drugs which usually ends when the drug is discontinued. Sometimes patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibacterial drug. If this occurs, patients should contact their physician as soon as possible.

ADVERSE REACTIONS

Nephrotoxic reactions—Albuminuria, cylindruria, azotemia. Rising blood levels without any increase in dosage.

Other reactions—Nausea and vomiting. Pain at site of injection. Skin rashes.

DOSAGE AND ADMINISTRATION

TO BE ADMINISTERED INTRAMUSCULARLY ONLY

Infant dose: For infants under 2500 grams—900 units/kg/24 hours in 2 or 3 divided doses. For infants over 2500 grams—1,000 units/kg/24 hours, in 2 or 3 divided doses. Intramuscular injections of the solution should be given in the upper outer quadrant of the buttocks, alternating right and left and avoiding multiple injections in the same region because of the transient pain following injection.

Preparation of Solutions

Should be dissolved in sodium chloride injection containing 2 percent procaine hydrochloride. The concentration of the antibiotic in the solution should not be less than 5,000 units per mL or more than 10,000 units per mL.

Diluents containing parabens should not be used to reconstitute bacitracin; cloudy solutions and precipitate formation have occurred. Reconstitution of the 50,000 unit vial with 9.8 mL of diluent will result in a concentration of 5,000 units per mL.

Solutions are stable for one week when stored in a refrigerator 2° to 8°C (36° to 46°F).

HOW SUPPLIED

Bacitracin for Injection, USP is available in a vial containing 50,000 units bacitracin.
NDC 17478-608-30        Carton of 1 vial

Store the unreconstituted product in a refrigerator 2° to 8°C (36° to 46°F).

**Rx Only**

**AKORN**

Manufactured By:

**Akorn, Inc.**
Lake Forest, IL 60045

BC00N Rev. 10/17

Principal Display Panel Text for Container Label:

NDC 17478-608-30

Bacitracin

for Injection, USP

50,000 Units Per Vial

For Intramuscular Use

Sterile

Rx only

Principal Display Panel Text for Carton Label:

NDC 17478-608-30

Bacitracin

for Injection, USP

50,000 Units Per Vial

For Intramuscular Use

Sterile

1 x 50,000 Unit Vial

Rx only Akorn Logo
**BACITRACIN**

bacitracin injection, powder, for solution

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**Product Information**

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<tr>
<td>INTRAMUSCULAR</td>
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**Active Ingredient/Active Moiety**

- **Usual Dosage:** See package insert for dosage information.
- **Route of Administration:** INTRAMUSCULAR
- **Active Ingredient:** Bacitracin
- **Active Moiety:** powder
- **Product Type:** HUMAN PRESCRIPTION DRUG
- **Item Code:** NDC:17478-608
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<th>Ingredient Name</th>
<th>Basis of Strength</th>
<th>Strength[^7]</th>
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<tr>
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<td>Bacitracin A</td>
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### Packaging
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### Marketing Information
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**Labeler** - Akorn, Inc. (062649876)

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