Xellia Pharmaceuticals, ApS

Advisory Committee Background Document

Meeting of the Antimicrobial Drugs Advisory Committee (AMDAC)

on Safety and Efficacy of Bacitracin for Intramuscular Injection

BACITRACIN for Injection (bacitracin)

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACLS	Advanced cardiac life support
ADR	Adverse drug reaction
ANDA	Abbreviated New Drug Application
ASHP	American Society of Health-System Pharmacists
BID	Twice daily
CDAD	Clostridium difficile associated diarrhea
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
COPD	Chronic obstructive pulmonary disease
CSF	Cerebrospinal fluid
CT	Computerized tomography
ECG	Electrocardiogram
FDA	Food and Drug Administration
HR	Hazard ratio
ICSR	Individual Case Safety Report
IDSA	Infectious Diseases Society of America
IM	Intramuscular
IV	Intravenous
L	Liter
mL	mililiter
PBRER	Periodic Benefit Risk Evaluation Report
PEA	Pulseless electrical activity
PADER	Periodic Adverse Event Report
PSUR	Periodic Safety Update Report
PO	Peroral
RSI	Reference Safety Information
QD	Every day
qxh	Every x hours
SHEA	Society for Healthcare Epidemiology of America
SIS	Surgical Infection Society
SOC	System Organ Class
SSI	Sugical Site Infections
TID	Three times a day
U	Units
US	United States
USPI	United States Prescribing Information
WHO	World Health Organisation
VRE(F)	Vancomycin resistant Enterococcus (faecium)

1 EXECUTIVE SUMMARY

The United States (US) Food and Drug Administration (FDA) is convening a Meeting of the Antimicrobial Drugs Advisory Committee on April 26, 2019 to discuss 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 injection (vials for intramuscular administration). The committee will also consider whether there are alternate uses for Bacitracin for Intramuscular injection that could be studied. Xellia Pharmaceuticals ApS (the Sponsor), which markets a product BACITRACIN for Injection® (bacitracin) appreciates the opportunity to participate in this important dialogue and provides this briefing package to provide data and perspective that could prove helpful in the Committees' deliberation. Importantly, the Sponsor is committed to actively participate in helping to ensure that patients and society benefit optimally from the use of its products.

Briefing package will include Sponsor's view of currently approved indication of Bacitracin for injection, based on published literature data, and also alternate use of bacitracin that has been described in published papers. Initial search was done on 11 March 2019 by PubMed search, using keyword "bacitracin" and selection of those which are relevant for assessment of bacitracin efficacy and safety after intramuscular administration or alternate uses.

It has been realized that there is paucity of data related to bacitracin in approved indication - staphylococcal pneumonia or empyema in infants, while more literature data was found on alternate routes of administration, mostly in the prophylaxis or treatment of wound infections of different anatomical structures (neurological, cardiac, ophthalmic and orthopedic surgery), and in much less extent and of older dates, for oral administration for *Clostridium difficile* caused pseudomembranous enterocolitis. Nephrotoxicity dominates in safety profile of bacitracin - as well known feature which is properly listed in Prescribing information of Bacitracin for intramuscular administration. Published literature, in addition, reveals predominantly anaphylactic reactions as a consequence of wound irrigation, particularly in patients who were already sensitized to bacitracin, either by widely-used bacitracin formulations for dermal application (either as monotherapy or in combinations, mostly with polymyxin B and neomycin), or previous systemic exposure to bacitracin. The extracted data from FAERS database were in line with these findings.

Overall, from the Sponsor perspective, we find the risk benefit balance for bacitracin use still positive for approved indication under conditions and limitations listed in current Prescribing Information (last updated in June 2018). In addition, there are some evidence on its alternate uses, which needs to be further explored in terms of efficacy and safety, indications, formulations and dosing standardization in order to explore further utility of this antibiotic in the era of increased microbial resistance and scarce pipeline of novel antimicrobial drugs.

2 INTRODUCTION

Bacitracin is a polypeptide antibiotic of natural origin, produced by *Bacillus licheniformis*. It was discovered in 1943 and introduced into clinical practice back in 1948. This antibiotic is principally active against Gram-positive cocci and is suitable for various routes of administration including topical, local to the site of infection, oral (for local action in gastrointestinal tract), and systemic, the latter *via* intramuscular (IM) route. During the 1950's, bacitracin had an important place in therapy because of activity against penicillin-resistant staphylococci and was life-saving for many patients with severe staphylococcal infections like sepsis, pneumonia, endocarditis, osteomyelitis, and similar.[1,2] Owing to nephrotoxicity, which occurs after systemic administration, and the advent of vancomycin and penicillinase-resistant penicillins, the IM use of bacitracin ceased in the early 1960's. Topical formulations however gained popularity, especially fixed combinations with neomycin and/or polymyxin B, and are nowadays still widely used for the prevention and treatment of superficial skin infections.

Bacitracin exerts antimicrobial activity through tight binding to C_{55}-isoprenyl pyrophosphate (also called undecaprenyl pyrophosphate), a lipid carrier responsible for translocation of bacterial cell envelope precursors from the cytosol to the extracellular surface of the cytoplasmic membrane. This results in inhibition of peptidoglycan biosynthesis and cell lysis.[3,4] Recent data indicate that bacitracin also degrades nucleic acids, in particular ribonucleic acids,[5] and directly inhibits certain bacterial toxins.[6]

Bacitracin is highly active against most Gram-positive bacteria, particularly *Staphylococcus aureu*s and *Streptococcus pyogenes*. Group C and G beta-hemolytic streptococci are generally less susceptible, and group B streptococci are usually resistant. Susceptibility of *Enterococcus* species, *Clostridium difficile* and anaerobic bacteria is variable. *Corynebacterium diphteriae* is susceptible. With exception of *Neisseria meningitidis, N. gonorrhoeae* and *Haemophilus influenzae,* other Gram-negative bacteria are resistant. *Treponema pallidum* is susceptible.[7] It should be noted that contemporary information on bacterial susceptibility to bacitracin is fairly limited. Resistance among staphylococci and streptococci is thought to be very low but is occasionally reported.[8,9,10] Resistance is often related to the activity of ATP-binding cassete (ABC) transporters that may mediate active efflux of bacitracin.[4,9]

Absorption of bacitracin is poor from skin, skin wounds, pleura, synovia, and mucous membranes, including the gut and the bladder, but can occur during peritoneal or mediastinal lavage, leading to serum levels comparable to those after IM administration. Following IM dosing, peak concentration in blood

occurs after 1 to 2 hours. Plasma protein binding is minimal. From blood, bacitracin readily diffuses into the pleural and ascitic fluid but does not penetrate into the cerebrospinal fluid (CSF), even if the meninges are inflamed. Less than 40% of the dose is excreted in urine within 24 hours. A considerable proportion of the dose cannot be accounted for and is thought to be either degraded or retained in the body.[7,11]

3 CLINICAL DATA ON EFFECTIVENESS OF BACITRACIN FOR INJECTION

3.1 APPROVED INDICATION: STAPHYLOCOCCAL PNEUMONIA AND EMPYEMA IN INFANTS

Bacitracin for Injection is nowadays exclusively approved for IM injection in the treatment of infants with pneumonia and empyema caused by staphylococci shown to be susceptible to the drug. Recommended daily dose is 900 units/kg for infants under 2,500 grams, and 1,000 units/kg for those over 2,500 grams, which should be administered in two or three doses per day.

No clinical data on IM bacitracin in approved indication could be found in the literature.

Such use is briefly mentioned in a retrospective review of 176 cases of pediatric staphylococcal pneumonia and 35 cases of empyema, observed in the period from 1954 to 1960 at St. Paul's Hospital, Vancouver, Canada. The author states that bacitracin was given on the top of other antibiotics (chloramphenicol and erythromycin) in patients who were desperately ill, but no further details are provided.[12]

Likewise, in a review paper on antibiotics from 1968, it is just mentioned that some pediatricians employ the IM injection of bacitracin, 1,000 units/kg/day, for the treatment of staphylococcal pneumonia in infants.[13] Also, a review paper on pediatric antimicrobial therapy from 1978 states that bacitracin has found little use except for topical application because of nephrotoxicity, but represents an interesting illustration of age-related differences in toxicity because adverse renal effects were rarely found when it was employed in a dosage of 900 to 1,000 units/kg/day for the treatment of severe staphylococcal infections of early infancy.[14] Potentially, some additional information may be contained in a paper from 1964[15] which we are still waiting to obtain in full article.

3.1.1 Supporting data on the treatment of lung infections in adults

A case report on successful treatment of staphylococcal lung abscess with bacitracin in a 62-year old man was published in 1952.[16] The patient was unsuccessfully treated with various antibiotics over five weeks and promptly responded after initiation of bacitracin at a dose of 10,000 units q4h IM (other antibiotics were discontinued at that point). After one week, the dose was reduced to 10,000 q8h because of signs of nephrotoxicity (erythrocyturia, proteinuria and polyuria), and q8h dosing was continued for the following 14 days. Renal function recovered within three weeks after discontinuation of bacitracin and the patient was discharged as cured.

There are no further data on bacitracin efficacy in staphylococcal pneumonia, but it was effective in pneumococcal pneumonia which illustrates sufficient penetration into lungs. In respective study,[17] fourteen adult patients with lobar pneumonia were treated with IM bacitracin at a dose of 30,000 to 99,000 units q6h. In most patients the causative pathogen was *Streptococcus pneumoniae*. Twelve patients (86%) recovered, one had to be treated with penicillin, and one died of bacterial endocarditis (pneumonia responded well to the treatment). In patients who recovered, bacitracin blood levels were at least 10 times above the sensitivity of the organism. All patients exhibited moderate albuminuria, casts, and impairment of concentrative power of the kidney and phenolsulfonphthalein excretion, however, there was no elevation of non-protein nitrogen and renal function spontaneously recovered in several weeks after treatment cessation.

3.1.2 Data on intrapleural administration in infants and children with empyema

Intrapleural administration of bacitracin for the treatment of staphylococcal pneumonia in infancy and childhood was reported in 1958.[18] Out of 24 patients with staphylococcal pneumonia treated at the Boston City Hospital, 19 had empyema with or without pneumothorax. Most patients were treated with penicillin, alone or in combination with streptomycin, and few with chloramphenicol and erythromycin. Surgical treatment was carried out in 17 (71%) patients; needle aspiration of empyema in four and thoracotomy with closed intercostal drainage in 13. Bacitracin was instilled into pleural cavity in seven (29%) patients, in a total dosage of 5,000 to 10,000 units; this was given once or twice daily for a period of 2 to 8 days, depending upon the patient's condition and the extent of the empyema. Overall, 15 patients (62.5%) survived. Intrapleural administration of bacitracin was well tolerated, and instillation

of 5,000 to 10,000 units of bacitracin at the time of the initial thoracentesis became standard practice at the study site for patients with empyema.

In 1961, Jawetz reported that early drainage of the pleural space by a closed system is widely recommended for the treatment of acute staphylococcal pneumonia of infants and children. In addition to such drainage, the intermittent instillation of bacitracin solution (2,000 to 10,000 units) could contribute to rapid sterilization of the area and the prevention of empyema.[1]

In 1972, Gelley confirmed that bacitracin proved to be an excellent local antibiotic in the treatment of empyema.[19]

3.2 ALTERNATE USES FOR BACITRACIN FOR INJECTION

3.2.1 Surgical Site Infection (SSI) Prophylaxis

SSIs continue to be one of the most significant burdens on the health care system, both in the US and abroad. It is estimated that approximately 500,000 SSIs occur annually in the US alone with associated cost of $10 billion.[20] Surgical wound irrigation has long been debated as a critical intraoperative measure taken to prevent the development of SSI, however, there is no clear consensus on appropriate type of irrigation solution (water, saline, antiseptics, antibiotics, surfactants), its mode of delivery (continuous, pulsatile, pressure), and volume needed during the surgery.[20,21] Surveys conducted in recent years indicate that 35-46% surgeons regularly use antibiotics intraoperatively, either in the form of irrigation solution or powder.[22]

In 2013, the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Surgical Infection Society (SIS), and the Society for Healthcare Epidemiology of America (SHEA) jointly concluded that use of topical antibiotics for intraoperative wound irrigation cannot be recommended because of insufficient evidence.[23] The World Health Organization (WHO) guideline on SSI prevention also advises against antibiotics in irrigation solutions, with a note that the strength of recommendation is conditional due to the low quality of the evidence.[24] In 2017, the Centers for Disease Control and Prevention (CDC) abstained from any recommendation related to intraoperative antimicrobial irrigation of intra-abdominal, deep or subcutaneous tissues because of uncertain trade-offs between the benefits and harms, however, concluded that antimicrobial ointments, solutions or powders should not be applied to the surgical incision for the prevention of SSI.[25]

The predominant organisms causing SSIs after clean surgical procedures are skin flora, including *S. aureus* and coagulase-negative staphylococci. In clean-contaminated procedures, like abdominal procedures and heart, kidney, and liver transplantations, Gram-negative rods and enterococci occur in addition to skin flora.[23] Literature data on bacitracin use for SSI prophylaxis are summarized below.

3.2.1.1 Neurosurgery

Following the first report by Teng in 1951 on local prophylactic use of bacitracin in 28 patients who underwent various neurosurgery procedures,[26] the first data on effectiveness of bacitracin-containing prophylactic regimen were published by Gibson 1958.[27] In this study, bacitracin was administered in combination with neomycin and polymyxin B. The three antibiotics (37,500 units bacitracin, 49,000 units neomycin and 150,000 units polymyxin B) were suspended in dichlorotetrafluoroethane and kept in a pressurized container allowing for spraying the antibiotic mixture. The spray was used in 250 consecutive neurosurgical procedures performed over five months, and was administered by spraying each tissue layer encountered on wound opening and closing. Compared to preceding series of 250 consecutive neurosurgeries performed at the same department without local antibiotic, the incidence of SSIs was reduced from 8.4 to 1.2%. Importantly, the frequency of deep infections was reduced 18 folds, from 7.2 to 0.4%.

Beckman et al. evaluated the efficacy and safety of bacitracin powder for SSI prophylaxis in cranial shunt surgery in the retrospective cohort study which included 539 shunt operations (both initial and revision surgeries) performed by a single surgeon in the period from 2001 to 2013.[28,29] From 2008 onwards, bacitracin dry powder was applied to all shunt wounds prior to closure. The powder was applied by tucking powder chunks under wound edges with forceps. For children of adult size, one vial of bacitracin powder (50,000 units) was commonly used to fill all of the wounds. Smaller doses were used in infants, but a strict weight-dependent formula was not used. The wound was then closed in the typical fashion. Other procedures did not differ between the two study periods and included: minimal hair removal using clippers, pre-preparation with topical chlorhexidine and 3% isopropyl alcohol, wound infiltration with local anesthetic containing epinephrine, skin preparation with either povidone-iodine gel or Prevail solution (CareFusion), use of povidone-iodine–impregnated adhesive drapes over all exposed skin, the use of double gloves by all staff, multiple wound irrigations with bacitracin solution (50,000 units in 1 L of lactated ringers solution), and application of antibiotic ointment to the closed wound at the end of the procedure with rare use of any sort of surgical dressing. Shunt surgeries were

performed using antibiotic-impregnated or standard nonantibiotic systems, with pressure-controlled or programmable valves. Endoscopy and/or neuronavigation were intermittently used for catheter placement after 2008. The primary outcome measure was shunt infection within 1 year of the surgery. The infection rate dropped from 13% in the first study period (2001 to 2007) to 1% in the second study period (2008 to 2103). Bacitracin powder use was associated with a reduced risk of shunt infection in both univariate analysis (HR 0.11, 95% CI 0.03-0.34, p = 0.0002) and multivariate analysis (HR 0.12, 95% CI 0.04-0.41, p = 0.0006), which included covariates that were associated with infection in the univariate analysis. Bacitracin powder was well tolerated and was not associated with anaphylaxis (none occurred), an increase in wound breakdown (five in the control group and none in bacitracin powder group), or renal dysfunction.

It should be noted that wound irrigation with bacitracin solution was not effective in this study, which can be partly attributed to relatively low bacitracin concentration in the irrigation solution used (50 units/mL). In 1981, Savitz and Katz have reported the results of the antimicrobial prophylaxis program for neurosurgical patients implemented at three community hospitals, which employed wound irrigation with higher concentration of bacitracin (1,000 units/mL).[30] The program was tailored according to the level of the risk and consisted of: a) for clean cases - a single IV dose of 2 g cephalotin at the time of incision; b) for clean contaminated cases (i.e., when a paranasal sinus or mastoid was entered) - cephalotin plus wound irrigation before closure with 50,000 units bacitracin in 50 mL saline; c) for contaminated cases (e.g., grossly infected scalp wounds or compound depressed fractures of the scull) - the same type of wound irrigation with bacitracin plus 2 g cephalotin q6h until sutures removal; and d) for cases with implanted foreign bodies like ventriculoperitonal shunt or cranioplasty - 1 g methicillin IV q6h, switched to 500 mg oxacillin q6h orally as soon as possible and continued until sutures removal. With this protocol no primary wound infection occurred in a series of 1000 consecutive operations which included 817 clean cases, 20 clean contaminated cases, 62 contaminated cases, and 101 foreign body implantation.

Irrigation solution with higher concentration of bacitracin (250 units/mL) was also evaluated in a non-randomized, partly prospective comparative trial in neurotologic procedures that transgress the posterior cranial fossa dura (translabyrinthine resection of an acoustic neuroma and retrolabyrinthine vestibular nerve resection).[31] Of the 236 patients included in this study, 87 received no antibiotic prophylaxis (retrospective cohort of patients operated between 1979 and 1983), 34 received IV antibiotic (1 g

cephalosporin q8h starting immediately before surgery, five doses in total; prospective cohort treated in 1984), 49 received bacitracin irrigation intraoperatively (50,000 units in 200 mL normal saline; prospective cohort treated in 1985), and 66 received both IV antibiotic and bacitracin irrigation (prospective cohort treated in 1986). End points were the incidence of wound infection, CSF leak and meningitis. The incidence of wound infection in the 1st, the 2nd, the 3rd and the 4th cohort was 9, 9, 0 and 3%, CSF leak 14, 9, 6 and 5%, meningitis 2, 3, 2 and 2%, and all targeted complications combined 24, 12, 8 and 9%, respectively. When bacitracin-treated groups were pooled and compared with remaining two groups that received no irrigation, the incidence of wound infection was reduced from 9 to 2% ($p < 0.05$), CSF leak from 12 to 5% ($p < 0.04$), and all complications combined from 22 to 9% ($p < 0.006$); there was no effect on the incidence of meningitis (2% in both groups). No untoward effects of either IV antibiotics or bacitracin irrigation were observed.

3.2.1.2 Orthopedic and spinal surgery

Anglen compared the efficacy and safety of bacitracin irrigation solution (33.3 units/mL saline) and castile soap solution (2.6% v/v in saline) a randomized trial involving 400 patients with an open fracture of the lower extremity (458 open fractures in total).[32] Fractures were graded according to the Gustilo-Anderson scale, and patients with grade I or II fractures were randomized separately from those with grade III. Patients with more than one open fracture were randomized only once, on the basis of the most severe injury. Each patient was initially treated with irrigation (3, 6 or 9 L of irrigation solution for grade I, II or III fracture, respectively) and debridement. Depending on the fracture grade, one, two or three irrigation-debridement procedures were performed. Decisions regarding the type of implant used for fixation, timing of fixation, and wound closure or coverage were made by the attending physician. Patients with a grade I or II fracture were to be treated with a 3-day course of cephalosporin and those with a grade III fracture with a 5-day course of cephalosporin and aminoglycoside. The actual selection and duration of antibiotics was frequently modified by either the orthopedic or the general trauma team on the basis of other clinical criteria and conditions. Patients were followed until an infectious or healing complication developed or until they were discharged from care with a healed fracture and restored soft-tissue envelope. Overall, 192 patients were randomized to receive bacitracin and 208 castile soap. Outcomes were available for 171 patients (199 fractures in total) in the bacitracin group and 180 patients (199 fractures in total) in the castile soap group. Mean duration of follow-up was 500 days. There was no difference between the groups in terms of gender, fracture grade, the time between the injury and the

irrigation, smoking, or alcohol use. There were significant differences in the mean age (38 vs. 42 years, p = 0.01), duration of follow-up (560 vs. 444 days, p = 0.01), prevalence of hypotension (23 vs. 14%, p = 0.04), and duration of treatment with IV antibiotics (11 vs. 9 days, p = 0.02). There was no difference between the groups in the incidence of infection or bone healing. Infection occurred at 35 (18%) fracture sites treated with bacitracin and 26 (13%) sites treated with castile soap (p = 0.2). Bone healing was delayed for 49 (25%) and 46 (23%) fractures, respectively (p = 0.72). Wound healing problems were more common in the bacitracin group; these were observed in 19 (9.5%) vs. 8 (4%) fractures (p = 0.03).

With respect to clean spinal surgery, Savitz et al. reported a zero infection rate in 50 consecutive patients undergoing spinal surgery (22 arthroscopic microdiscectomy, 18 lumbar laminotomy, and 10 anterior cervical discectomy) who received 1 g cefazolin IV at the incision and constant wound irrigation with bacitracin/polymyxin dissolved in saline (50,000 units/L each).[33] Intraoperative wound culture was positive in one case only (2%). This was a significant improvement compared to historical incidence of 64%, observed at one of the two study sites at the time when wounds were irrigated with saline only.

In contrast to the study mentioned above, Michels and Agger reported no difference between antibiotic irrigation and normal saline in prevention of surgical wound infections after laminectomy.[34] Of the 2823 clean surgical procedures included in their retrospective study there were 941 laminectomies. Out of these, 470 were irrigated with standard antibiotic solution and 471 with normal saline. Antibiotic solution consisted of bacitracin (250 units/mL) and 1% neomycin in 200 mL normal saline. It was rapidly flushed into the body cavity, without a standardized dwell time, prior to wound closing. Most patients also received 2 g cefazolin IV within two hours of the incision. Post-discharge surveillance of surgical wound was performed by the clinic nurse, approximately two weeks after the surgery. There were 23 (4.9%) surgical wound infections in the group irrigated with bacitracin/neomycin and 17 (3.7%) in the group irrigated with normal saline. The difference was not statistically significant.

The International Consensus Group on Orthopedic Infections has recently concluded that surgical site irrigation with antibiotic solutions should not be performed in orthopedic surgery.[35]

3.2.1.3 Cardiothoracic surgery

The Michels and Agger study mentioned above[34] also included 1464 coronary artery bypass grafts (CABGs) and 418 pacemaker implantations. Prophylactic treatment and follow-up were performed in the same manner as described for laminectomy. The only difference was a slightly shorter post-discharge

follow-up period in patients who underwent pacemaker implantation, which was seven to ten days. Of the 1464 CABG procedures, 475 were irrigated with bacitracin/neomycin, and 989 with normal saline. There were 23 (4.8%) chest wound infections, deep and superficial combined, in the antibiotic irrigation group and 66 (6.7%) in the saline group. The difference was not statistically significant. Of the 418 pacemaker implantations, 98 were irrigated with bacitracin/ neomycin, and 320 with normal saline. One infection (1%) occurred in the antibiotic solution group and none in the saline group. This was not statistically different. Pooled data for all 2823 procedures, including laminectomies, confirmed no difference between irrigation with antibiotic solution and normal saline. The overall infection rate was 4.5 vs. 4.6% respectively (chi square 0.04, p = 0.85).

Miller et al. retrospectively evaluated the efficacy of local administration of antibiotics in prevention of deep-seated infectious complications of pneumectomy.[36] In 47 out of 93 patients, 1 L of saline containing 5 million units penicillin G, 50,000 units bacitracin and 60 mg gentamycin was intraoperatively instilled into the post-pneumectomy cavity and left in the chest after the surgery. The remaining 46 patients did not receive local antibiotics. All patients perioperatively received three IV doses of 1 g cefazolin q8h or alternative prophylactic antibiotic in case of beta-lactam allergy. The occurrence of empyema and/or bronchial fistula was the primary outcome of interest. The two groups were comparable in terms of age, gender, diagnosis, and length of hospital stay. Empyema occurred in six (13%) patients from the control group (in five it was accompanied with bronchial fistula), and none in the group that received intracavitary antibiotics (p = 0.012). Four patients (9%) in each group died (p = 0.63).

3.2.1.4 Abdominal surgery

Pancreaticoduodenectomy is historically associated with incisional SSI rates between 15% and 20%. A prospective cohort study in 300 patients undergoing this surgery was undertaken to evaluate the impact of a 4-part perioperative bundle on the occurrence of incisional SSI.[37] The bundle consisted of a double-ring wound protector, gown/glove and drape change before fascial closure, irrigation of the wound with 500 mL bacitracin solution in saline before skin closure (no data on bacitracin concentration are provided), and a negative-pressure wound dressing that was left in place until postoperative day 7 or day of discharge. The first cohort of 150 patients was treated before, and the second, equally sized cohort, after implementation of the bundle. The primary end point was development of incisional SSI within 30 days of operation. Organ/space SSIs and incisional SSIs associated with these were not

included in final analysis. The cohorts were similar with respect to age, sex, body mass index, use of neoadjuvant therapy, median operative time, and presence of a preoperative stent. Implementation of the 4-part bundle decreased the incisional SSI rate from 22 to 11%.

3.2.2 Bacitracin Irrigation in the Treatment of Surgical Site/Implant Infection

3.2.2.1 Periprosthetic joint infection

In 2017, Duque at al. have reported the results of a specific protocol for the treatment of acute periprosthetic infection of the knee that allows for retention of total knee arthroplasty components.[38] It was retrospectively evaluated in 67 consecutive patients who had less than three weeks of symptoms at presentation, no immunologic compromise, intact soft tissue sleeve, and well-fixed components. The protocol consists of a) polyethylene liner removal and extensive synovectomy; b) irrigation with 3 L each of betadine, Dakin's solution, bacitracin solution (concentration not stated), and normal saline; c) implantation of the new polyethylene liner; and d) postoperative treatment with IV antibiotics selected by an infectious disease specialist. The infection was considered eradicated if the wound healed without persistent drainage and there was no residual pain or evidence of infection. Out of 67 patients who underwent the procedure, 46 (69%) had successful infection eradication. The success rate in case of MRSA and *Pseudomonas aeruginosa* infection was low (20 and 33%, respectively), but for other pathogens it was as high as 85%.

3.2.2.2 Infection of other types of implanted medical devices

Infection occurring after implantation of an implantable cardioverter defibrillator (ICD) is a serious complication because it requires removal of all hardware, including the generator, leads and myocardial patches. Lee at al. have reported successful salvage of the ICD in four patients with infected ICD generator pocket.[39] This was achieved with a) wide debridement of the pocket; b) placement of a closed irrigation system consisting of irrigation and drainage catheters for continuous irrigation of the pocket with antibiotics; c) irrigation of the pocket with antibiotic solution containing 50,000 units/L bacitracin, 40 mg/L neomycin and 100,000 units/L polymyxin, at a rate of 40 mL/h for at least five days; and d) culture-specific systemic antibiotic therapy. All four patients were free of infection at a mean follow-up of 25.0 +/- 17.3 months with no recurrence.

Ortler et al. reported a salvage of infected vagus nerve stimulator in a patient who developed local signs of deep cervical wound infection five weeks after implantation of the device.[40] After open wound

debridement and thorough rinsing with bacitracin-containing solution (concentration not specified), the wound was packed with 3% iodoformized gauze with stimulator left in place, and systemic antibiotic therapy with fosfomycin and cefmenoxim was started. The wound was rinsed daily with 3% hydrogen peroxide solution and 5% saline until cultures were sterile and granulation tissue started to fill the wound. Delayed primary closure was performed two weeks later.

3.2.2.3 Surgical site infection

Strider at al. retrospectively reviewed nine patients who underwent betadine/bacitracin continuous irrigation for the treatment of vascular graft infection in the groin.[41] Wound irrigation was performed after explantation of the graft and consisted of continuous infusion of 0.25% betadine in normal saline at 0.3 mL/kg/h for 48 hours, followed by bacitracin infusion (50,000 units/L normal saline) at 0.3 mL/kg/h for 72 hours. All patients also received at least 6 weeks of IV antibiotics followed by oral antibiotic suppression therapy for life. All patients healed their groin wounds except for an 81-year-old patient with aortobifemoral bypass graft who developed ischemic bowel and expired.

Continuous irrigation of antibiotic solution was also reported by Bryant et al. in five patients who developed infection and dehiscency of median sternotomy incision following cardiac surgery.[42] Treatment included reoperation, debridement of the mediastinum, placement of a plastic catheter in the mediastinum for antibiotic infusion with two separate intercostal tubes for drainage in the right pleural cavity and the mediastinum, primary closure of the sternotomy incision with wire sutures, irrigation of the mediastinum with neomycin, bacitracin and/or polymyxin B solution, and appropriate systemic antibiotics. In one patient the mediastinum was irrigated with all three antibiotics, two received bacitracin and neomycin, one neomycin and polymyxin B, and one neomycin only. Bacitracin concentration in irrigation solution ranged from 50 to 500 units/mL, neomycin was given at 1 to 2 mg/mL, and polymyxin B at 500 units/mL. Antibiotic solution was continuously infused at a rate of 41.5 to 100 mL/h. Two patients were switched to intermittent instillation of 60 mL q4h or 100 mL q6h, respectively. Mediastinal irrigation lasted for six to 22 days. Four of the five patients survived. Death in one patient resulted from a ruptured mycotic aneurysm of the aorta. Infection did not extend to the cardiotomy incisions or to the intracardiac prostheses in any patient.

3.2.3 Local administration in the treatment of life-threatening infections

3.2.3.1 Local administration into the central nervous system (CNS)

In the period 1950-1953, Teng described 43 cases of severe CNS infections that were treated by intrathecal, intracerebroventricular, intracerebral, epidural and/or subdural administration of bacitracin, in combination with IM bacitracin and other systemic antibiotics.[26,43] Infections included 17 cases of purulent meningitis (mainly staphylococcal and streptococcal), eight brain abscesses (one with subdural empyema), six epidural abscesses with chronic osteomyelitis of the scull, four infected craniotomy wounds, and eight infected laminectomy wounds. Thirty-eight (88%) patients were cured, while five with meningitis one with brain abscess died. The series also included 31 neurosurgery patient (17 contaminated and 14 clean procedures) who locally received bacitracin for SSI prophylaxis. No SSI occurred. Based on experience gained with local administration of bacitracin, Teng suggested that in adults 5,000 to 20,000 units dissolved in 3 to 5 mL of normal saline could be safely injected intraspinally once or twice a day for two weeks. For intracerebroventricular application, 3,000 to 10,000 units in 10 mL normal saline could be repeatedly injected into the lateral ventricle at 12 hour intervals. He further stressed that no ill effects were produced when 5,000 to 10,000 units in 10 mL normal saline were applied to a freshly cut cortical surface of the cerebral hemisphere in the prefrontal region as a postoperative prophylactic measure, and that a dose as large as 50,000 units in 5 mL of normal saline has been given to a patient by intracerebral and intraventricular injection or applied to an ablated cortical surface with no side effects.[44]

3.2.3.2 Regional perfusion for necrotizing fasciitis

In 1964, Baker reported a case of necrotizing fasciitis in a 40 years old man, which over six days spread from the ankle to within three inches of the inguinal ligament. This occurred despite three debridements and treatment with several systemic antibiotics and local administration of bacitracin and neomycin. The disease promptly responded to one hour regional perfusion of the leg with 300,000 units bacitracin in the extracorporeal circuit.[45]

3.2.4 Oral administration

Oral bioavailability of bacitracin low and variable,[46] however, 25 to 30% of the oral dose may be recovered from the stool.[47] This allows for bacitracin use as a non-absorbable oral antibiotic with local action in the gut. Consequently, PubMed search revealed a number of small studies related to evaluation

of oral bacitracin in the treatment of enterocolitis, amebiasis, oral antimicrobial prophylaxis before colorectal surgery, and suppression of intestinal flora in patients with hematologic malignancies. In most of these studies, bacitracin was administered in combination with neomycin or other antibiotics, and with variable results. Considering bacitracin spectrum of activity and current views on importance of preservation of gut microbiota, only data related to high-priority pathogens, *Clostridium difficile* and vancomycin-resistant *Enterococcus* (VRE) are summarized below.

3.2.4.1 C. difficile associated diarrhea (CDAD)

Following initial reports on successful treatment of CDAD with oral bacitracin,[48,49] two randomized, double-blind studies were undertaken to evaluate its efficacy and safety in CDAD.

In the first study,[50] 42 patients with microbiologically confirmed CDAD were randomized to receive either 20,000 units bacitracin or 125 mg vancomycin orally, q6h over seven days. Study medication was provided in capsules filled with antibiotic powder. Patients who responded to the treatment (<3 stools per day at the end of treatment) were followed-up for four weeks. Non-responders or those with symptomatic relapse were crossed-over to alternative treatment arm in the blinded manner and were followed-up in the same way as initial patients. The clinical response rate after initial treatment was similar for bacitracin and vancomycin (76 vs. 86%), including the mean time for a 50% reduction in stool frequency (4.1 vs. 4.2 days), and clinical relapse rate (42 vs. 33%). The percentage of patients with a negative stool culture at the end of treatment (52 vs. 81%; p = 0.02) or with *C. difficile* cytotoxin cleared (53 vs. 83%, p = 0.04) was higher in the vancomycin group. During follow-up, *C. difficile* reappeared in 50% of patients in each group irrespective of symptoms. Non-responders tended to be refractory to the alternative treatment as well, and most patients with a clinical relapse, also relapsed after crossover.

These results were confirmed in the second trial,[51] where 62 CDAD patients were randomized to receive either bacitracin (25,000 units) or vancomycin (500 mg) four times daily over 10 days. Antibiotics were provided in solution, 10 mL per dose. Diarrhea was considered resolved when less than four loose stools were passed per day on two consecutive days. Patients were followed-up during hospitalization and were instructed to contact the investigator if symptoms recur after discharge. Patients who did not respond to initial treatment were crossed over to alternative drug; the first recurrence was treated by repeating a course of initial drug, and the second one by the alternative drug. Blinding was maintained throughout the study. Out of 62 patients included, 15 patients in each group were evaluable for efficacy; others were

mainly non-evaluable because of a negative stool culture at baseline. Bacitracin was as effective as vancomycin in resolving diarrhea (response rate 80 vs. 100%), but was less effective in eradicating *C. difficile* and its toxin in the stool; at the end of treatment both were negative in 3/10 (30%) and 10/14 (71%) patients, respectively. Five patients receiving bacitracin and three receiving vancomycin had at least one recurrence. Low, nontoxic concentrations of bacitracin were detected in serum samples collected from 11 patients.

Recent random effects network meta-analysis has shown that bacitracin is clinically as effective as vancomycin and other drugs used in the treatment of CDAD with exception of fidaxomicin and teicoplanin, which are superior.[52] Another, Bayesian network meta-analysis, has yielded a conflicting result, indicating that bacitracin is comparable to metronidazole (with or without rifampicin) and fusidic acid, but inferior to other drugs.[53]

3.2.4.2 VRE decolonization from the gut

Intestinal colonization with VRE is considered a major risk factor for VRE infection in immunocompromised patients and may contribute to nosocomial spread of these difficult-to-treat pathogens. Several small studies were undertaken to explore if bacitracin can be useful for VRE eradication from the gut.

Donovan et al. assessed the effectiveness of oral vancomycin (125 mg q6h/10 days) in eliminating vancomycin-resistant *Enterococcus faecium* (VREF) from the stool.[54] Microbiologic response was defined as the absence of VREF in three consecutive stool cultures within 15 days after the treatment. Patients who did not respond to vancomycin were to be treated with oral bacitracin (25,000 units q6h/10 days). Vancomycin was effective in 8/19 (42%) patients and bacitracin in 8/8 (100%), $p < 0.01$. The organism recurred in two bacitracin patients (25%), eight and 20 days after the treatment.

Chia et al. performed a small non-comparative study and found that VREF was eliminated from stool in five out of eight (63%) colonized patients after one course of bacitracin treatment (25,000 units q12h/10 days), and in additional patient after the second course. In one of these VREF recurred after two months.[55]

Mondy et al. performed a randomized, placebo-controlled trial of oral zinc bacitracin (50,000 units q6h/10 days) in 12 patients colonized with VREF.[56] At three weeks after the treatment, stool culture was negative in two (33%) patients in each group. Of the remaining eight patients who had a positive stool

culture at three weeks, five (62%) had later evidence of spontaneous eradication at eight weeks. Further testing of VREF isolates revealed that 76% had bacitracin MIC ≥ 64 μg/mL (3.2 units/mL) and that patients may have been colonized with multiple different VREF strains.

A combination of bacitracin (75,000 units q6h) and doxycycline (100 mg q24h) given orally over 14 days was tested by Weinstein et al. in a prospective observational cohort study.[57] Fifteen VREF-colonized patients were treated and 24 served as control. Rectal swabs were collected for qualitative culture at days 0, 7, and 14, then biweekly for 6 weeks, and monthly for 4 months. Stool samples were collected at the same time points or within a 2-day range. Patients were considered eligible for evaluation if >3 stool cultures were performed and follow-up was >3 weeks. On day 14, cultures of rectal swabs were negative for 15 (100%) antibiotic-treated vs. eight (33.3%) untreated patients ($p < 0.001$). However, follow-up for a mean of 127 and 130 days revealed that 60% of treated and 63% of untreated patients carried VREF intermittently or persistently. Quantitative VREF stool cultures in the treated cohort revealed an initial 3.1 $\log_{10}$/g decrease in bacterial burden, but there was an increase to pretreatment levels at 2–4 and 5–7 weeks post-treatment (7.8 and 7.4 $\log_{10}$/g).

While these data indicate that VREF decolonization is a futile intervention, a case report from 2015 well illustrates that individual patients may benefit from VREF elimination. [58] A 25-year-old patient with leukemia and neutropenia after chemotherapy presented with *Klebsiella pneumoniae* and *Escherichia coli* bacteremia, which was successfully treated with doripenem. Subsequently, VREF resistant to ampicillin and daptomycin but susceptible to linezolid and quinupristin-dalfopristin was isolated from patient's blood. Catheters were changed multiple times, but blood cultures continued to grow VREF despite combinations of tigecycline, rifampin, quinupristin-dalfopristin, linezolid, and ampicillin. Transthoracic echocardiography was normal and an indium white blood cell scan revealed uptake consistent with focal pericecal colitis. A perirectal swab grew VREF, so oral bacitracin (25,000 units q6h) begun. Forty-eight hours later, stool cultures were negative for VREF as were blood cultures for the first time in 17 days.

4 SAFETY OVERVIEW

4.1 POST-MARKETING SAFETY SURVEILLANCE

Xellia has an authorization of Bacitracin for Injection USP (50,000 units/vial). [ANDA 203177] in United States (US) since 25-Aug-2014. This report has been prepared for the purpose of safety review of Bacitracin for Injection USP, concerning adverse drug reactions (ADRs). Since authorization and launch (30 September 2014) approx. 2.5 million Bacitracin for Injection, USP (50,000 units/vial) have been sold by Xellia Pharmaceuticals ApS. Xellia continually monitors the safety profile of Bacitracin for Injection, USP to ensure that updated safety information is available for physicians. The safety information provided in the USPI addresses the risks associated with the product, which continues to have a favorable benefit-risk profile when used in the approved indications.

The company reviews and assesses all data reported, as well as reviewing the published literature, for bacitracin during a specific defined period in the Periodic Adverse Drug Experience Report (PADER). Although the analysis in the PADER is not focused on specific indications, potential safety issues or concerns pertaining to a specific indication would be reviewed and discussed in the PADER, if such issues or concerns were identified.

Based on review of the data available to Xellia Pharmaceuticals ApS during the periods covered by the 13 PADERs (12 quarterly PADERs and 1 annual PADER), there were no identified safety issues that were required to be addressed and updated in the product label accordingly. A literature review conducted in preparation for the aforementioned 13 PADERs is consistent with the safety profile outlined in the Applicant's USPI and/or reflects the background incidence of adverse events in the target population.

4.1.1 Bacitracin safety review report provided by pharmacovigilance service provider (Lambda)

Method of evaluation:

- Pharmacovigilance safety database (PvEdge) search was performed to retrieve the ICSRs covering the duration from 25-Aug-2014 to 11-Mar-2019.
- PubMed search was performed to retrieve the significant safety information for bacitracin. The search criterion was broad, and it included the term 'bacitracin' and the reporting interval of this report (25-Aug-2014 to 11-Mar-2019).

Result:

- **ICSR**

From the inception of authorization of Bacitracin for Injection USP (50,000 units/vial) in USA to till date, total 02 cases were reported for bacitracin. Both the cases were received from published literature and were medically confirmed cases. Both these cases were reported for "Bacitracin ointment". There was no case received for "Bacitracin for Injection". In both the cases, patient received bacitracin ointment for scalp irritation secondary to seborrhea and mild folliculitis and developed xanthoma, hair color change, and hypersensitivity. In both the case, causal role of bacitracin was confounded with other co-suspect drugs (polymyxin B, neomycin and selenium sulfide) for the reported events. There was no significant safety or efficacy information was reported from both these cases.

Moreover, during reporting interval, no cases were reported for the bacitracin used in the treatment of infants with pneumonia and empyema caused by staphylococci. Furthermore, no case of off label use and lack of efficacy were reported during this period.

- **Literature**

A search of the world-wide medical and scientific literature was carried out for the interval covered by this PSUR and following articles reporting significant safety information were identified. The searches were made via 'PubMed' for the duration of 25-Aug-2014 to 11-Mar-2019. The search criterion was broad and it included the term 'bacitracin' and the reporting interval.

Anaphylactic shock

PMID: 28841484

Desai M, Castells M. Anaphylactic shock to bacitracin irrigation during breast implant surgery. Ann Allergy Asthma Immunol. 2019 Feb; 122(2):217-218.

A 28 year old woman with a history of congenital breast deformity presented to the allergy/immunology clinic 4 weeks after experiencing anaphylactic shock in the operating room during breast saline implant replacement surgery. She had no drug allergies recorded in her medical record on the day of the surgery. The initial breast augmentation surgery was done ten years prior using general anesthesia, intravenous cefazolin, and an antibiotic solution for irrigation (specific agents unknown) and was uneventful. During

the surgery, the patient received 2g of intravenous cefazolin for antibiotic prophylaxis and anesthesia induction with midazolam, fentanyl, propofol and succinylcholine and maintenance with propofol and remifentanil. Vital signs remained stable. The surgeon then incised the breast tissue bilaterally and removed the existing saline implants. Approximately 15 minutes into the surgery, an antibiotic solution of bacitracin and cefazolin was used to irrigate breast tissue pockets on both sides. Within a minute, the patient experienced tachycardia and then an undetectable blood pressure by a non-invasive blood pressure cuff. The patient was noted to be in pulseless electrical activity arrest. She received brief chest compressions, multiple vasopressors and four IV boluses of epinephrine 1000mcg before return of spontaneous circulation. No rash or bronchospasm was noted. The surgery was terminated and the surgical wounds were rapidly stapled closed. The patient was transferred to the hospital and other causes of hypotension were ruled out (normal ECG, echocardiogram, CT angiogram) A serum tryptase level, drawn within 2.5 hours of the episode, came back elevated at 17.4 μg/L (reference range ≤10.9 μg/L). Anaphylactic shock was felt to be the most likely diagnosis. The patient underwent a comprehensive drug allergy evaluation. Upon questioning she reported localized, immediate hives after topical exposure to triple antibiotic ointment (bacitracin, neomycin, polymyxin and pramoxine) a few weeks prior and recalled a similar reaction more than a year ago. Sequential skin testing with dilutions of bacitracin ointment was used to confirm IgE-mediated drug allergy to bacitracin. IgE-mediated hypersensitivity to bacitracin was determined to be the cause of anaphylaxis based on history, timing of reaction and positive testing. She returned to the operating room for completion of the breast implant surgery. Pre-operatively she received hydrocortisone 100mg IV, diphenhydramine 25mg IV, and 2g of intravenous ampicillin. General anesthetic agents were used (midazolam, fentanyl, ketamine, propofol, remifentanil, succinylcholine) and breast pocket washout was performed using an ampicillin solution. The breast implant surgery was successful.

Medical review comment:

Authors reported a case of severe intra-operative anaphylactic shock immediately following irrigation of breast tissue with bacitracin solution. Based on reasonable temporal association, the causal role of bacitracin could not be excluded in the event. The patient's medical history included immediate hives after topical exposure to triple antibiotic ointment (bacitracin, neomycin, polymyxin and pramoxine) a few weeks prior and a similar reaction more than a year ago. As per RSI, this drug is contraindicated in

those individuals with a history of previous hypersensitivity or toxic reaction to it. Based on available information, no further actions are recommended at present.

Anaphylaxis and cardiovascular collapse

PMID: 29367094

Burnett GW, Meisner J, Hyman JB, Levin EJ. Bacitracin irrigation leading to anaphylaxis and cardiovascular collapse in the ambulatory surgery center setting. J Clin Anesth. 2018 May; 46:35-36.

Author presented a case of 28-year-old female with no significant past medical history presented to an ambulatory surgery center for bilateral breast implant exchange. The patient had an uncomplicated breast augmentation 10 years prior. She denied any known drug allergies or previous problems with anesthesia. General endotracheal anesthesia was induced with midazolam, fentanyl, propofol, and succinylcholine and maintained with propofol and remifentanil infusion. Preoperative antibiotic profphylaxis withcefazolin 2 g IV was administered and vital signs remained stable following induction and surgical incision. The in-situ breast implants were removed and both pockets were irrigated with bacitracin solution. Within 1 min of irrigation, the patient's heart rate increased from 65 beats per minute to 130 beats-per-minute and the non-invasive blood pressure cuff was unable to obtain a reading. Additionally, the end-tidal carbon dioxide decreased from 33 mmHg to 10 mmHg. A blood pressure was unable to be obtained despite boluses of phenylephrine and ephedrine. Anesthetic infusions were stopped and additional help was called for. No signs of urticaria or bronchospasm were present. The patient was noted to be in pulseless electrical activity (PEA) and advanced cardiac life support (ACLS). Four doses of epinephrine 1000 mg IV were administered and return of spontaneous circulation was obtained after approximately 10 min. An arterial line was placed and the patient was transferred to the inpatient hospital for further workup and monitoring. The patient was extubated 30 min after arrival in the postanesthesia care unit. Approximately 2 h following cardiac arrest, the patient's tryptase was found to be elevated to 17.4 μg/L (reference range ≤10.9 μg/L). A CT angiogram to evaluate for pulmonary embolus was negative. Echocardiogram and electrocardiogram was unremarkable. The patient remained stable postoperatively with no sequelae of cardiovascular collapse. She followed up with an allergist and was found to have a markedly positive bacitracin skin test and a normal baseline tryptase (2.3 μg/L). She returned to an inpatient facility four months later for completion of her procedure in order to have

additional support staff and resources in case of emergency. The procedure was uncomplicated and utilized ampicillin for antibiotic prophylaxis.

Medical review comment:

Authors describe a case of intraoperative anaphylaxis due to bacitracin irrigation with significant cardiovascular collapse without cutaneous or pulmonary manifestations. Based on reasonable temporal association, the causal role of bacitracin could not be excluded in the events. As per RSI, this drug is contraindicated in those individuals with a history of previous hypersensitivity or toxic reaction to it. Based on available information, no further actions are recommended at present.

Conclusion on bacitracin safety

Based on the evaluation of the safety data and the benefit-risk analysis, current risk-benefit ratio for Bacitracin for Injection USP (50,000 units/vial) remains unchanged.

4.1.2 Literature Data on Bacitracin Safety

Besides the safety report provided by Lambda (Xellia's PV provider) several additional literature references reported adverse events associated with bacitracin uses in different indications and administration routes. The reports found in the PubMed search by using keywords bacitracin revealed 12 articles (predominantly case reports) describing adverse events upon bacitracin administration as irrigation of wounds as solution of different concentrations or IM injection as presented in the Table 1 below.

The most common adverse events after systemic (intramuscular) administration of bacitracin is nephrotoxicity. It is listed in prescribing information of bacitracin (warning box) and also reported in several literature reports (69, 70, 71).

Another important and dramatic adverse reaction that requires prompt safety measures is anaphylaxis. There are several reports described in the literature where anaphylaxis was noted after irrigation of wounds and inner body spaces (mediastinum, peritoneum, pericardium etc.) (59,. Anaphylactic reaction is the clinical manifestation of immunoglobulin E (IgE) dependent systemic mast- cell degranulation and mediator release. There are several published reports on bacitracin-induced anaphylaxis (59, 60, 62-67), but the most serious reaction occurred during general anesthesia after antibiotic wound irrigation, where protracted shock, edema, and rash of the face and upper

chest are often noted. Marked elevation of serum histamine and IgE levels in conjunction with this clinical presentation are consistent with the diagnosis of anaphylaxis.

Caraballo J et al, 2017[59]reported an anaphylactic reaction in 63-year old man with a history of retinal detachment in the right eye repaired by scleral buckle presented with decreased peripheral vision in the left eye and was found to have a macula-sparing retinal detachment in the left eye, for which urgent repair by scleral buckle was recommended. The patient did not take any routine outpatient medications. During placement, the patient experienced a severe drop of arterial blood pressure (50/30 mm Hg), oxygen saturation (to 85%), and end-tidal carbon dioxide concentration (to 12 mm Hg). Physical examination revealed wheezing, mottled extremities, and urticarial rash. Surgery was halted, and the patient received intravenous epinephrine (total dose, 2.4 mg), diphenhydramine (50 mg), and hydrocortisone (100 mg), which achieved hemodynamic stability within 30 minutes. The previously placed scleral buckle was then explanted and replaced with a new scleral buckle soaked in betadine solution rather than bacitracin. After successful retinal detachment repair, the patient was transferred to the surgical intensive care unit for recovery and was extubated approximately 2 to 3 hours later. His initial tryptase level, measured within 3 hours of symptom onset, was 74.6 mg/L (reference range, _10.9 mg/L), consistent with diagnosis of anaphylaxis. Ten hours after symptom onset, the tryptase level decreased to 24.9 mg/L. He was discharged Preoperative evaluation revealed no history of anesthetic complications, and he denied any drug allergies. He did not receive any preoperative prophylactic antibiotics.

Damm S et al, 2011[60] described three cases of severe anaphylactic reactions associated with prophylactic bacitracin irrigation during cardiac procedures. In all three cases, bacitracin irrigation was concentrated at 50,000 units per 10 mL and applied directly to the pacemaker pocket. The first case described involved an 88-year-old woman undergoing pacemaker insertion to correct bradycardia. Within 10 minutes of bacitracin irrigation, she lost consciousness and developed apnea, diffuse erythema, and hypotension. In the second case, a 69-year-old man receiving a cardiac resynchronization defibrillator implant developed apnea, hypotension, decreased pulse, erythema of the extremities, and a maculopapular rash within 15 minutes of bacitracin administration. The third case involved an 83-year-old woman undergoing a dual pacemaker battery change; she became agitated and was noted to have hypotension, anxiety, and other symptoms 8 minutes after bacitracin irrigation. Two of the three cases involved apnea and loss of consciousness, and all three patients developed erythema or rash. Application of the adverse

drug reaction probability scale developed by Naranjo et al. yielded a score of 3 (indicating a possible after bacitracin irrigation) in all three cases. As in other published reports of anaphylactic reactions associated with bacitracin irrigation, development of hypotension within 15 minutes of bacitracin administration was the first sign of an adverse reaction in these cases. Three patients developed severe adverse reactions after prophylactic bacitracin irrigation, two during pacemaker insertions and one during a cardiac resynchronization defibrillator implantation.

Greenberg SB et al, 2008[61] reported about a patient with a history of T12 burst fracture caused by a fall, and with progressive weakness and sensory loss in the left leg, survived a cardiac arrest after pulsed saline bacitracin lavage irrigation during a posterior spinal fusion.

Freiler JF et al, 2005[62] described a 72-year-old woman with anaphylaxis after irrigation and packing of an infected pacemaker pocket with a bacitracin solution. Skin prick testing to bacitracin and latex; serum tryptase, serum histamine, serum IgE to latex, and serial cardiac enzyme measurements; blood cultures, transthoracic echocardiograms, and venograms were performed to characterize the reaction. RESULTS: Six hours after the anaphylactic event, the patient had an elevated serum tryptase level of 49 ng/mL (reference range, 2-10 ng/mL), which normalized the next morning. She had immediate-type skin prick test reactions to full-strength bacitracin ointment (500 U/g) and bacitracin solution (150 U/mL). Serum IgE level to latex was undetectable, and results of skin testing to latex were negative.

Antevil JL et al, 2003[63] described intraoperative anaphylactic shock associated with bacitracin irrigation during revision after total knee arthroplasty in sixty-two-year-old woman. *Staphylococcus aureus* and *Pseudomonas aeruginosa* grew on subsequent culture of specimens obtained from the wound. After removal of the implants, the tourniquet was released and the surgical site was copiously irrigated with several liters of saline solution, followed by 1 L of saline solution containing 50,000 units of bacitracin. During the course of irrigation, a precipitous drop in the systolic blood pressure was noted from 101 to 62 mm Hg and a concomitant increase in the pulse from 72 to 116 beats per minute. The hypotension did not respond adequately to administration of fluid and boluses of Neo-Synephrine (phenylephrine). Transesophageal echocardiography revealed a hyperdynamic volume-deplete left ventricle and mild mitral regurgitation. Erythema of the face, trunk, and upper extremities developed, and an anaphylactic cause was proposed for the hemodynamic instability. Aggressive crystalloid fluid resuscitation was instituted and guided by the continuous use of transesophageal echocardiography. Epinephrine (50 μg) was administered in addition to intravenous hydrocortisone, ranitidine, and diphenhydramine. The blood

pressure and pulse normalized over the course of thirty minutes after a total of 7 L of crystalloid fluid had been given. The patient recovered uneventfully and was discharged on the fourth postoperative day. Outpatient skin testing was performed three weeks postoperatively and demonstrated a marked IgE response to bacitracin.

Blas M, et al, 2000[64] reported an interesting case of anaphylaxis after mediastinal irrigation with a bacitracin solution A 65-yr-old man presented for elective sternal debridement and rewiring. He had a history of mitral valve replacement with a Bjork-Shiley prosthetic valve implanted 1 yr earlier for severe mitral regurgitation. Other medical problems included hypertension, diabetes mellitus, and hiatal hernia. He had an allergy to penicillin, which produced a systemic rash, nausea, and vomiting. Surgical findings consisted of a localized pocket of serous fluid (approximately 20 mL), and the entire mediastinum was subsequently washed with bacitracin irrigation (approximately 25 U/mL). Immediately after the placement of the first sternal wire (approximately 40 min after the induction of anesthesia and 10 min after wound irrigation), the arterial blood pressure decreased precipitously from 120/70 to 65/40 mm Hg. The mediastinum was inspected and showed no evidence of hemorrhage or cardiac injury. The electrocardiogram showed an increased rate from 70 to 80 bpm with no S-T segment changes. IV fluid resuscitation was begun while breath and cardiac sounds were auscultated. The anesthetics were discontinued, and 100% oxygen was given. The mechanical sounds from the prosthetic valve were unchanged, and breath sounds were equal bilaterally. The patient was placed in steep Trendelenburg position, and ephedrine (total dose 50 mg IV) was given incrementally with minimal response. The end-tidal CO_2 decreased from 35 to 31 mmHg, which coincided with the onset of hypotension. Esophageal temperature was unchanged at 36.5°C. Arterial blood pressure began to improve after several small IV boluses of epinephrine (4 mg/bolus) and a total of 2 L of fluid given IV A transesophageal echocardiography (TEE) probe was placed to further evaluate cardiac function. There were no segmental wall motion abnormalities as viewed in the gastric short-axis, mid papillary view. The prosthetic mitral valve appeared competent, with normal bileaflet motion. There was no significant mitral regurgitation and no signs of cardiac tamponade. The left-ventricular end-diastolic area was normal, but the end-systolic area was significantly reduced, compatible with a decrease in afterload. At this time, it was also noted that the patient's face and upper extremities were flushed red. As a result of the TEE findings and the patient's flushed color, the diagnosis of an anaphylactoid reaction was made. IV fluid resuscitation and boluses of epinephrine were given in addition to diphenhydramine (50 mg), hydrocortisone (100 mg), and famotidine (20 mg). After approximately 20 min from onset of flushing, arterial blood pressure

was 120/75 mm Hg, and the cutaneous flushing had resolved. A small-dose epinephrine infusion was rapidly titrated and discontinued. Examination of the anesthesia back table revealed no ampules or bottles of medication suspicious for a drug error. The remainder of the surgery was uneventful. The patient awoke at the end of surgery, was tracheally extubated, and was transferred to the recovery room. Later examination of the patient's history revealed rash after using an over-the-counter antibiotic ointment, Neosporin ® (Burroughs Wellcome, Research Triangle Park, NC; a triple antibiotic ointment consisting of polymixin B, bacitracin, and neomycin). No other complications had developed at that time, and the patient discontinued further use. Based on the patient's previous adverse reaction and the temporal association to bacitracin exposure in the operating room, the diagnosis of a bacitracin allergy was made.

Carver ED et al 2000[65] described two episodes of anaphylaxis in a 9-year child undergoing revision of a ventriculoperitoneal shunt. Initially, the anaphylaxis was attributed to either vancomycin or latex allergy; however, after the second episode, the child was found to be sensitive to bacitracin that had been used to soak the shunt tubing before insertion on both occasions. Clinical symptoms immediately after insertion of the ventriculoperitoneal shunt into the ventricle, included systolic blood pressure decrease to 65 mmHg, associated with widespread erythema, and hemoglobin oxygen saturation decreased to 86%; these resolved with administration of 70 mg epinephrine, 200 mg hydrocortisone, and 40 mg diphenhydramine intravenously. Further inquiry revealed that the neurosurgeons had soaked the shunt tubing in a bacitracin solution prepared in a dilution of 2,500 U/mL. Skin-prick testing underwent later on revealed an allergic reaction to bacitracin.

Sprung J, et al. 1990[66] noted Intraoperative Anaphylactic Shock after Bacitracin Irrigation report a patient who, after bacitracin wound irrigation, developed protracted shock, edema, and rash of the face and upper chest, while bronchospastic symptoms were conspicuously absent. Marked elevation of serum histamine and IgE levels in conjunction with this clinical presentation are consistent with the diagnosis of anaphylaxis.

Netland PA, et al. 1987[67] reported a case of intraoperative anaphylaxis that occurred after irrigation with a solution containing bacitracin during lumbar laminectomy in 67-year-old man. During the operation, an irrigating solution containing bacitracin (50,000 units/litre) was used without complication. His arm strength and sensation improved postoperatively, but the low back pain, lower extremity weakness, and paresthesias gradually progressed. At operation, general endotracheal anesthesia was induced with

thiopental and isoflurane: there was no significant instability of blood pressure or pulse. No perioperative antibiotics were administered. As the first lamina was drilled after removal of the spinous processes from L2 to LS, the operative field was irrigated with approximately 100 mL of lactated Ringer's solution containing bacitracin (50.000 units/L). Within 2 min. the patient's systolic blood pressure dropped precipitously to 40 to 50 mm Hg. the skin on his arms and trunk turned bright red and wheals formed. Cardiac arrhythmias. ST-segment elevation and ventricular tachycardia were noted and the operation was aborted. The patient received incremental doses of phenylephrine hydrochloride ephedrine diphenhydramine hydrochloride, and epinephrine intravenously and aggressive fluid replacement: an epinephrine drip was given during rapid wound closure. When the patient was turned supine, it was noted that the carotid pulse was absent and the cardiac monitor showed ventricular fibrillation. He received cardio-pulmonary resuscitation for about 5 min. and was defibrillated twice. Normal sinus rhythm was restored after the intravenous administration of lidocaine and an additional defibrillation. He was transferred to the intensive care unit.

In the intensive care unit, the patient had elevated creatine phosphokinase and was MB-positive: his renal function was normal. He was extubated and recovered uneventfully. Lumbar laminectomy was performed without complication s during a subsequent operation in which bacitracin irrigation was not used.

Westerman EL, 1983[68] reported a case of a 70-year-old man with severe chronic obstructive lung disease underwent a coronary artery bypass. The postoperative course was complicated by respiratory difficulties, and, on the14th postoperative day, sternal dehiscence occurred. The patient was taken back to surgery, where sternal closure was performed. Because of the possibility of mediastinitis, three irrigation tubes were inserted with three sump drains. Through each irrigation tube, normal saline containing bacitracin, 50.000 units/L, was infused at 100 mL/h for a total of three days. On the second day, a serum bacitracin level was measured at 10.7 units/mL. During this period, the serum urea nitrogen level rose from 16 mg/dL to 30 mg/dL. The serum creatinine level remained unchanged at 0.6mg/dL, and urine output remained good.

Genkins G, et al. 1954[69] described a case of 57-y old women who developed bacitracin-related nephropathy with acute renal failure and death. The treatment with bacitracin was initiated after several courses of antibiotic therapies in attempt to solve her endocarditis. The patient transiently improve after 3 days of bacitracin therapy (50000 Units IM divided in 5 daily doses for 6 days), but then developed

rapidly progressive renal nephropathy with proteinuria, oliguria, and azotemia. Simultaneous with the fall of the urinary output to 100 cc. per day, the blood urea nitrogen rose to 44 mg. per 100 ml. Because of the severe impairment amounting to almost complete renal shutdown, bacitracin therapy was discontinued after six days of treatment. The patient remained oliguric, voiding less than 300 cc. per day, and the blood urea nitrogen level continued to rise, reaching 76 mg. per 100 ml. two days after cessation of bacitracin therapy. As a supportive measure, three small transfusions of packed red blood cells were administered without incident. The patient failed to respond and became lethargic. A pericardial friction rub developed, and the woman died 10 days after the institution of bacitracin therapy.

Miller JH et al. (1950)[70] investigated renal effects of bacitracin in 12 normotensive male subjects, who showed no clinical evidence of cardiovascular or renal disease and free of infectious disease, were studied before and after the parenteral administration of bacitracin. Parenteral administration of bacitracin, in therapeutic doses is followed uniformly by the occurrence of proteinuria and the appearance of renal tubular epithelial cells in the urine, and frequently by the occurrence of glycosuria in the post-absorptive state. During the period of proteinuria an acute depression of tubular function and probably also of glomerular function have occurred, as manifested by a decrease in the clearances of inulin and p-aminohippurate (PAH), a decrease in the tubular excretory capacity for PAH, a decrease in the tubular reabsorptive capacity for glucose, and a decrease in the renal extraction of PAH at low plasma levels. Although proteinuria was present for only 6 to 10 days following two injections of 1,500 units of bacitracin per kilogram body weight, both glomerular and tubular function remain depressed over a period of weeks, returning only gradually to baseline levels at seven to nine weeks.

Michie AJ et al 1949[71] also reporting on nephrotoxicity of bacitracin after IM administration.

Table 1 - Summary of literature data on bacitracin safety after irrigation or intramuscular use.

Reference	**Cases (N)**	**Age (y)**	**Description**	**RoA**	**Dosing form**	**Adverse event**	**Reversibility of adverse events (y/n)**
Caraballo J, (2017)	1	63 y	A 63-year-old man with a history of retinal detachment in the right eye repaired by scleral buckle soaked with bacitracin presented with symptoms of anaphylaxis within 24 hours of surgery with no other complications during his admission.	Irrigation (bucklet soaked in bacitracin solution)	Solution (150 U/mL)	Anaphylaxis	Y (24h)
Damm S. (2011)	3	88y 69 y 83y	Three cases of severe anaphylactic reactions associated with prophylactic bacitracin irrigation during cardiac procedures (irrigation of the cardiac pocket).	Irrigation	Solution (50,000 U bacitracin per 10 mL)	Anaphylaxis	Y (w24 h)

Greenberg SB, (2008)	1	62 y	A patient with a history of history of Graves' disease and T12 burst fracture caused by a fall, and with progressive weakness and sensory loss in the left leg, survived a cardiac arrest after pulsed saline bacitracin lavage irrigation during a posterior spinal fusion.	Irrigation	Solution (1:50,000 saline:bacitracin)	Anaphylaxis	Y (48h)
Freiler JF, (2005)	1	72 y	Woman experienced anaphylaxis after irrigation and packing of an infected pacemaker pocket with a bacitracin solution. Immediate type skin prick test reactions to full-strength bacitracin ointment (500 U/g) and bacitracin solution (150 U/mL): Serum IgE level to latex was undetectable, and	Irrigation	Solution (150 U/mL):	Anaphylaxis (skin sensitisation to bacitracin history).	Y (24h)

			results of skin testing to latex were negative.				
Antevil JL, (2003)	1	62 y	Woman w. revision of a left total knee arthroplasty Upon implants removal, was copiously irrigated with several liters of saline solution, followed by bacitracin irrigation	Irrigation	Solution (50,000 U/L bacitracin in saline).	Anaphylaxis	Y (24h)
Blas M et al. (2000)	1	65 y	Unique case of acute anaphylaxis in man after mediastinal irrigation with a dilute bacitracin solution.	Irrigation	Solution (25 U/mL)	Anaphylaxis (skin sensitization history)	Y (24h)
Carver ED, et al (2000)	1	9 y	Not available; Two episodes in a child after soaking of the shunt tubing into bacitracin before insertion	Soaked graft	Solution (2,500 U/mL)	Anaphylaxis (skin sensitization history)	Y (?)
Sprung J, et al (1990)	1	36	Intraoperative anaphylactic shock after bacitracin irrigation with 2000 mL of a solution	Irrigation	Solution (100,000 U/L bacitracin)	Anaphylaxis	Y (w72h)

			that contained 1 g kanamycin and 100,000 U/L bacitracin				
Netland PA, (1987)	1	67	Case report of anaphylaxis caused by irrigation with a bacitracin solution during lumbar laminectomy.	Irrigation	Solution (50,000 U/L of lactated Ringer's solution)	Anaphylaxis (history of systemic baci tracin exposure 3 mo ago)	Y (?)
Westerman EL. (1983)	1	70	Man with severe COPD underwent a coronary artery bypass. The postoperative course was complicated by respiratory difficulties, and, on the 14th postoperative day, sternal dehiscence Occurred, reoperated, sternal closure was performed.Bacitracin irrigation was performed for mediastinitis prophyaxis	Irrigation	Solution Through each irrigation tube, normal saline containing bacitracin, 50,000 units/L, was infused at 100 mL/hr for a total of 3 days.	On the second day, a serum bacitracin level was measured at 10.7 U/mL. Serum urea nitrogen level rose from 16 mg/dL to 30 mg/dL. The serum creatinine level remained	Y

						unchanged at 0.6 mg/dL, and urine output remained good	
Genkins G, et al (1954).	1	57 y	Bacitracin nephropathy: report of a case of acute renal failure and death.	IM	Solution 50,000 U/day IM in five divided doses, added to the regimen containing. penicillin, streptomycin and dihydrostreptomycin	Nephrotox (proteinuria, oliguria, and azotemia developed)	N
Miller JH et al. (1950)	12	?	Parenteral administration of the 1500 mg/kg bacitracin, for 2d followed uniformly by the occurrence of. 2. During the period of proteinuria there occurs an acute depression of tubular function and..	IM	1,500 U/kg BID	Nephrotox (proteinuria and the appearance of renal tubular epithelial cells in the urine, and glycosuria in the post-absorptive state)	Y (proteinuria 6—10 d; Tubularfunction 7-9-weeks)

Michie AJ, et al (1949)	?	?	Not available (Full article pending)	IM		Nephrotox	

4.1.3 FAERS data

A search of FDA Adverse Events Reporting System (FAERS) was conducted to identify post marketing safety findings associated with the use of bacitracin.

These analyses focused on safety findings associated with use of the marketed bacitracin for intramuscular injection products covering the time period since inception 1969 through the most recent available data in the FAERS quarterly report Dec 31, 2018.

A total of 637 reports containing bacitracin adverse events were identified in FAERS for the time period 1969 through Dec 31, 2018. These reports included 637 total adverse events, including 216 events from cases identified as serious, and 421 events from cases identified as non-serious. However it should be taken into account that FAERS comprise mainly serious adverse events from 15-days reports, therefore the database probably does not represent accurate incidence of non-serious events.

Since there are local treatments containing bacitracin only besides bacitracin for IM use and therefore it is not possible to count the exact number of cases exclusively related to Bacitracin vials for intramuscular injection. However, cases which, based on published literature data, are most probably associated with systemic administration are related to intramuscular, intraperitoneal or wound irrigation administration are anaphylactic reactions and nephrotoxicity. Therefore, they have been evaluated as most probably adverse events related to systemic exposure.

Since 1969, of 637 reports identified in FAERS for bacitracin, 37 were related to bacitracin immune system disorders. Among them, there were 25 related to Anaphylactic reaction, 11 Anaphylactoid reactions and 1 Anaphylactic shock.

Table 2 - Immune System Disorders for Bacitracin (FAERS), 1969-2018

Reaction Group and Reaction

Reaction Group	Reaction	Number of Cases
Total Cases		**37**
Immune System Disorders	**Number of Cases**	**37**
	Anaphylactic Reaction	25
	Anaphylactoid Reaction	11
	Anaphylactic Shock	1

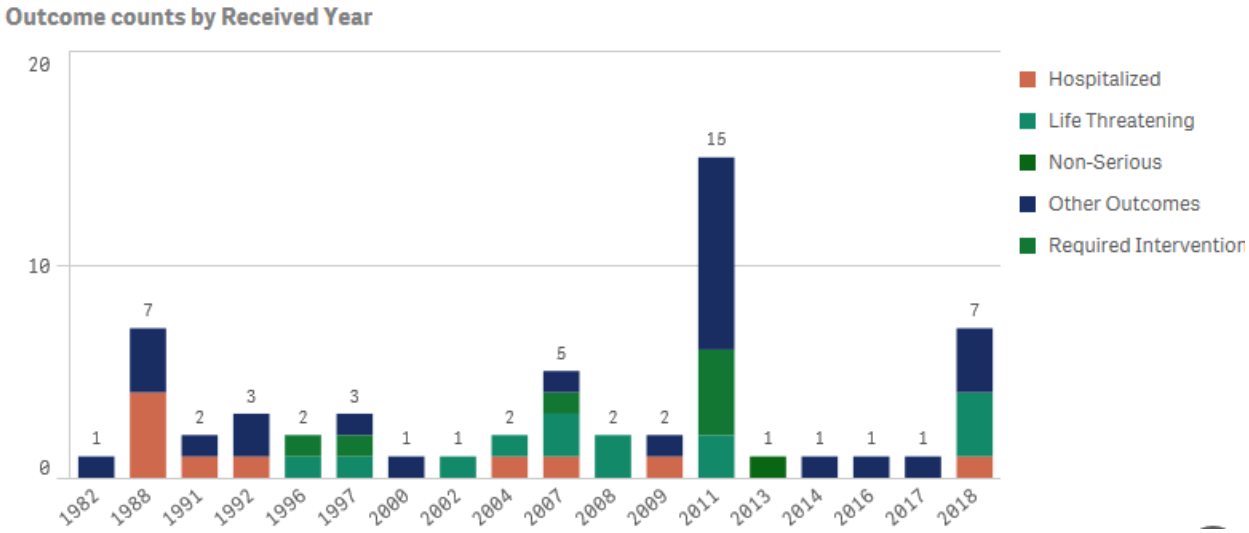


Figure 1 - Distribution of Anaphylactic reaction, Anaphylactoid reaction and Anaphylactic Shock case count by year received and outcome (FAERS), 1982-2018

Nephrotoxicity related adverse events

Data provided in FAERS database for bacitracin, unspecified formulation, related to renal disorders revealed 9 reports related to renal and urinary disorders. Relatively small number of cases are reported since inception of bacitracin in relation to 2,5 mil unit packages sold for Xellia only since entering US market in 2014.

Table 3 - Renal and Urinary Disorders for Bacitracin (FAERS), 1969-2018

Reaction Group and Reaction

Reaction Group	Reaction	Number of Cases
Total Cases		**9**
Renal And Urinary Disorders	**Number of Cases**	**9**
	Renal Failure	4
	Pollakiuria	2
	Renal Tubular Necrosis	1
	Acute Kidney Injury	1
	Urinary Tract Disorder	1
	Anuria	1
	Renal Tubular Disorder	1

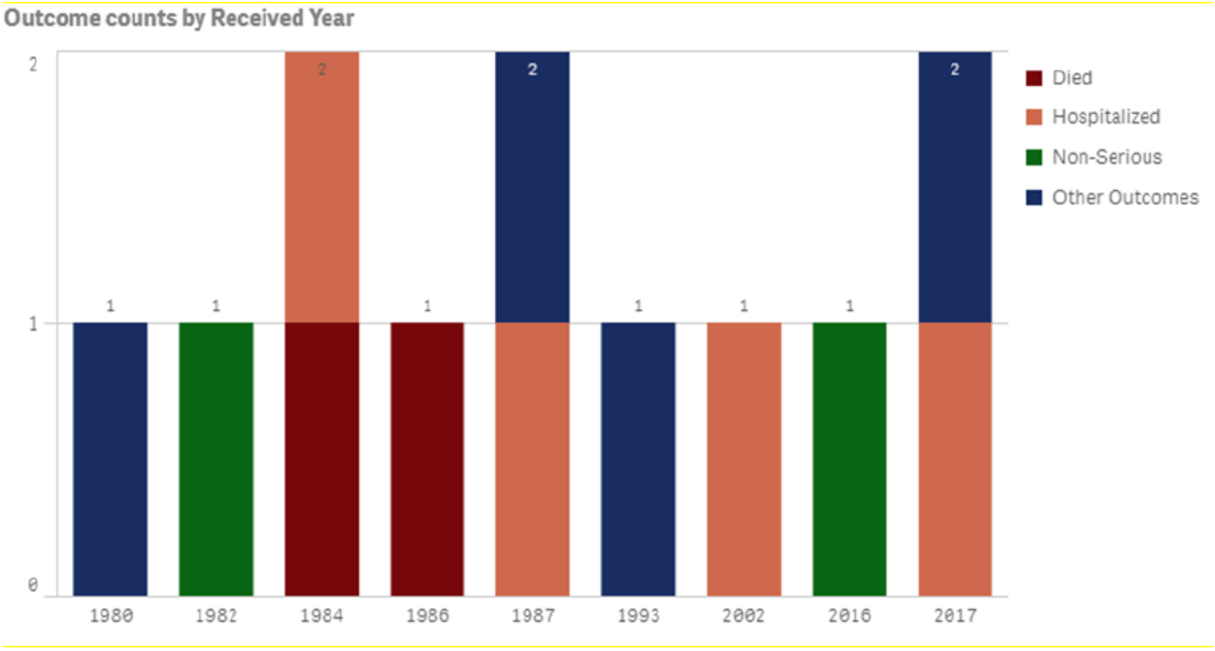


Figure 2 - Distribution of renal disorders count by year received and outcome (FAERS), 1980 – 2017

4.2 OVERALL RISK BENEFIT CONCLUSION

Based on available evidence, although the Sponsor is aware that the evidence is scarce for approved indication, it still considers bacitracin continues to maintain a positive benefit-risk profile for the treatment of infections when used appropriately according to the product labeling. Regarding alternate uses of bacitracin (wound irrigation across different body cavities) is some interventions, like neurological surgeries, the risk-benefit in prevention in post-surgical wound infection prevention seems positive, however it is difficult to estimate the risk of toxicity to bacitracin against the benefits of wound prophylaxis in other body regions, like orthopedic surgeries, cardiac interventions, due to differences in study designs, concentrations of solutions containing different concentrations of bacitracin, and different duration of bacitracin exposure before wound closing. The definite conclusion could potentially be done upon collecting data on standardized use of bacitracin solutions.

Xellia pharmacovigilance data provided by PV provider Lambda, literature overview and FAERS database search suggests that anaphylactic reactions are an uncommon but potentially disastrous complication of intraoperative pharmacological manipulations, requiring prompt pharmacological intervention. Although dramatic, the symptoms are usually reversible after prompt and adequate medical intervention and resolve without sequelae within 24-48h. Anaphylaxis could result from irrigation with a solution that contained bacitracin. Bacitracin solutions have been shown to produce high serum drug levels rapidly during wound irrigation. Absorption of bacitracin through wounds, body cavities and bone may have led to the rapid development of a high serum drug level, facilitating an anaphylactic response.

The intramuscular administration of bacitracin has been condemned because of potential renal toxicity. The possibility of rapid systemic absorption of bacitracin from wound irrigating solutions suggests that it would be prudent not to use such solutions in patients with impaired renal function. On the basis of presently available evidence, the risk-benefit balance on bacitracin use in approved indication is still considered positive.

The Sponsor welcomes the opportunity to participate in the dialogue and looks forward to the Committees' discussion to identify opportunities to balance the availability of safe and effective medication for patients in need.

5 ATTACHMENT 1. US PRESCRIBING INFORMATION

xellia PHARMACEUTICALS

Rx only

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

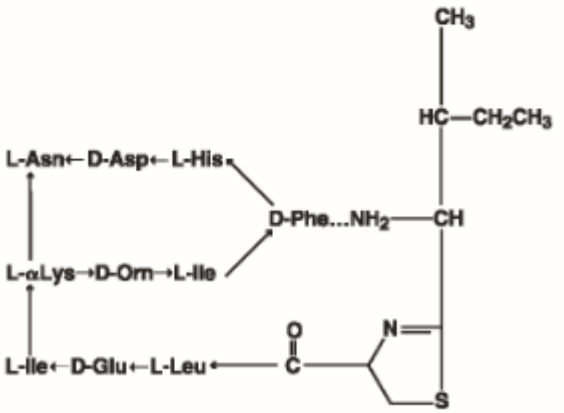
Nephrotoxicity: Bacitracin in parenteral (intramuscular) therapy may cause renal failure due to tubular and glomerular necrosis. Its use should be restricted to infants with staphylococcal pneumonia and empyema when due to organisms shown to be susceptible to bacitracin. It should be used only where 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 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:



bacitracin A

The molecular formula is: $C_{66}H_{102}N_{17}O_{16}S$. 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.

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

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

xellia
PHARMACEUTICALS

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