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UPS EXPRESS MAIL

Division of Dockets Management
Food and Drug Administration
5630 Fishers lane, Room 1061 (HFA-305)
Rockville, MD 20852

CITIZEN PETITION
(ANDA SUITABILITY PETITION)

Sandoz Inc., hereby submits this petition under Section 505 (j) (2) (c) of the Federal Food, Drug and Cosmetic Act and pursuant to 21 CFR 314.93 to request that the Commissioner of Food and Drug Administration permit the filing of an Abbreviated New Drug Application for a drug that has the same active ingredient and dosage form listed in FDA's publication entitled, Approved Drug Products with Therapeutic Equivalence Evaluations, current Internet edition but differs in its dosage strength (total quantity of active ingredient in the package).

A. Action Requested

By this petition, we hereby request the Agency to permit the filing of an Abbreviated New Drug Application for Cefazolin for Injection, USP 2 g Vials, or a supplemental application, if appropriate. This drug differs from the reference listed drug filed under NDA 50-461 for GlaxoSmithKline's Ancef® 1 g.

B. Statement of Grounds

In accord with Section 505 (j) (2) (c) of the Federal Food, Drug, and Cosmetic Act a petition may be filed, with the Agency, seeking permission to file an Abbreviated New Drug Application for a new drug, which differs from a "listed" drug in dosage strength. The Act stipulates that such a petition must be approved by the Agency, unless there is a finding that investigations are needed to demonstrate the safety and effectiveness of the proposed drug product.

The reference listed drug product, GlaxoSmithKline's Ancef® (Cefazolin for Injection) 1 g Vial, is identified in the Prescription Product List of the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book). A printout of this listing by active ingredient details is provided in Attachment 1.

2007P-0214 CPI

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We propose to develop a Cefazolin for Injection 2g vial.

Cefazolin is a 1st generation cephalosporin for parenteral use in various infections caused by susceptible organisms as well as for perioperative prophylaxis. Sandoz markets its Cefazolin for Injection, USP drug formulation in the USA in vials containing 0.5 g (NDC 0781-9338-95) or 1.0 g cefazolin (NDC 0781-9339-96). However, in clinical practice for a considerable number of indications, daily doses up to 12 g cefazolin (divided into 3 or 4 doses applied every 6 or 8 h) are applied. Moreover, in patients with higher body weight (> 80 kg) the dose in standard indications such as preoperative infection prophylaxis is 2.0 g as a single dose according to US recommendations. Therefore, an additional formulation providing 2.0 g cefazolin per vial appears highly valuable in clinical practice. A related 2 g formulation of cefazolin is already marketed in European countries and Canada.

The cefazolin 2.0 g per vial formulation allows an easier handling of the drug in the higher dosing range, as only half the number of vials has to be reconstituted with solvent. This reduction in vial handlings minimizes the risk for handling errors, such as choice of inappropriate fluid volume or (partly) missed doses. Moreover, the reduced number of sterile vials to be reconstituted reduces to the same amount the risk for inadvertent non-sterile drug application. The bulk formulations already available in the USA from other marketing authorization holders containing 10 or 20 g of cefazolin per vial are intended for the use in hospital pharmacy and cannot be applied directly in clinical practice. Therefore these formulations are not to be considered an alternative to the intended new 2 g cefazolin formulation for direct clinical use, e.g. in emergency departments or during night.

The new 2 g formulation might be dissolved in a reduced solvent volume compared to 2 vials of the 1 g formulation. As cefazolin in the higher dose range relevant for the new 2 g formulation is frequently applied via infusion, the concentration of the final solution for application to the patient will not be influenced by the new drug preparation. The drug is typically transferred from the reconstituted vials in a container with the solute for infusion (such as sodium chloride injection, USP, lactated Ringer's, invert sugar 5%/10%, 5% sodium bicarbonate, or Dextrose 5% or 10% with or without lactated Ringer's or sodium chloride). Therefore, the new formulation is not considered to represent any new safety issues (i.e. local tolerance), as the new formulation does not result in clinically relevant higher concentrations of cefazolin in the ready-to-use solution for infusion.

As there are already two different dose strengths of Cefazolin for Injection, USP available in clinical practice, the hospital staff is sufficiently aware of different dose strengths for this medication. Therefore, no inappropriate risk for confusing the different dose strengths is introduced by the new 2.0 g per vial formulation of Cefazolin for Injection, USP.

In the following, the clinical properties of cefazolin will be presented to support the proposed new 2 g dose strength of Cefazolin for Injection, USP.

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Clinical Pharmacology of Cefazolin

Cefazolin is poorly absorbed from the gastrointestinal tract and is therefore given by the intramuscular or intravenous routes (slow intravenous injection over 3 to 5 minutes, or by intravenous infusion). Following a 0.5 g or 1.0 g dose given intramuscularly, peak plasma concentrations of 30 or 64 µg/ml are obtained after 1 hour, respectively. A single dose of 2 g cefazolin has been found to result in peak plasma levels of 122 ± 45.3 µg/ml. No accumulation was observed in patients treated with 2 g cefazolin every 8 over 5 days (n = 4). The mean maximum plasma level on day 5 (136 ± 52.5 µg/ml) was comparable to the value observed after the first dose (122 ± 45.3 µg/ml). Moreover, the trough levels were also indistinguishable on day 1 (18.65 ± 13.90 µg/ml) and day 5 (16.98 ± 6.67 µg/ml), respectively. The only adverse reaction observed was fatigue in one case[1].

About 85% of cefazolin is bound to plasma proteins. The plasma half-life of cefazolin is about 1.8 h, and is prolonged in patients with renal impairment. In one study, half-life was 6.8 h in 1 adult with a creatinine clearance of 26 ml/minute, 12 h in 3 adults with creatinine clearances of 12-17 ml/minute, and 57 h in 3 adults with creatinine clearances less than 5 ml/minute. Cefazolin diffuses into bone and into ascitic, pleural, and synovial fluid but not appreciably into the CSF. Moreover, the compound is excreted unchanged in the urine, mainly by glomerular filtration with some renal tubular secretion, at least 80% of a dose given intramuscularly being excreted within 24 h. Peak urine concentrations of more than 2 and 4 mg/ml have been reported after intra-muscular doses of 0.5 and 1 g respectively. High biliary concentrations have been reported, although the amount excreted by this route is small. Cefazolin usually is preferred among the first-generation cephalosporins because it can be administered less frequently owing to its longer half-life[2].

The pharmacokinetic profile of a single i.v. dose as high as 4 g cefazolin (infusion in 100 ml of sterile water over 60 min) has been characterized in 25 volunteers. Even at this dose level, no adverse reactions were observed. By a bioassay method (agar diffusion assay with *B. subtilis* as test germ), the terminal half-life of cefazolin was determines as 87 min in the study population, in line with other published results[3]

Clinical Use of Cefazolin

Cefazolin is a 1st generation cephalosporin antibacterial used in the treatment of a variety of infections by susceptible organisms, including biliary-tract infections, endocarditis (staphylococcal), and peritonitis (associated with continuous ambulatory peritoneal dialysis). It is also used for surgical infection prophylaxis, including prophylaxis of endometritis at caesarean

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[1] Cox VC, Zed PJ. Once-daily cefazolin and probenecid for soft tissue infections. Ann Pharmacother 2004;38:458-63.

[2] B Sweetman S (Ed), Martindale: The complete drug reference. London: Pharmaceutical Press. Electronic version, (Edition 1. September 2004) and Brunton LL, Lazo JS, Parker KL. Goodman & Gillman'S The Pharmacological Basis of Therapeutics. New York: McGraw-Hill. 11th Edition 2006.

[3] Adam D, Patzold J. Serumkonzentrationen und Kinetik nach Kurzzeitinfusion von vier Gramm Cefazolin. Inf 1977;5(4):228-31.

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section[2] . The compound has good activity against gram-positive bacteria and relatively modest activity against gram-negative microorganisms. Most gram-positive cocci (with the exception of enterococci, methicillin-resistant *S. aureus*, and *S. epidermidis*) are susceptible. Most oral cavity anaerobes are sensitive, but the *B. fragilis* group is resistant. Activity against *Moraxella catarrhalis*, *E. coli*, *K. pneumoniae*, and *P. mirabilis* is good. However, cefazolin is more susceptible to hydrolysis by β-lactamase from *S. aureus* than for example cephalothin[4].

Cefazolin has been effective when used perioperatively to reduce the incidence of infection in patients undergoing surgical procedures classified as contaminated or potentially contaminated (e.g., vaginal hysterectomy, high-risk cesarean section, cholecystectomy in high-risk patients) and in those undergoing surgical procedures in which the development of infection at the surgical site would represent a serious risk (e.g., cardiac surgery, prosthetic arthroplasty). The compound is broadly used for perioperative infection prophylaxis in the USA according to Infection Control Guidelines as well as recommendations by the US Surgical Care Improvement Project (SCIP). The Surgical Care Improvement Project (SCIP) is a US quality partnership of organizations focused on improving surgical care by significantly reducing surgical complications. The goal of this initiative is to reduce the incidence of surgical complications nationally by 25 percent by the year 2010. To obtain this goal the initiative provides quality assurance tools, recommendations and information on relevant issues to improve clinical practices under routine conditions. According to these quality assurance documents, the indication "perioperative infection prophylaxis" covers cardiovascular, abdominal, neurological, obstetric/gynecological, orthopedic, urological as well as trauma surgeries, sometimes in combination with metronidazole[5,6]. For example the clinical efficacy of the 2 g in prophylaxis for laparotomic gynecologic surgery has been found to be comparable to amoxicillin/clavulanic acid (2.2 g) in a clinical trial in 511 patients[7]. Therefore the CDC recommends the use of cefazolin (2 g i.v. initially followed by 1 g i.v. every 8 h until delivery) in women with penicillin allergy (without risk of anaphylaxis) when intrapartum antibiotic prophylaxis considered necessary[8]. Moreover, the clinical efficacy of cefazolin in complicated skin and skin structure infections even positively compares with highly effective comparator drugs such as vancomycin or

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[4] Brunton LL, Lazo JS, Parker KL. Goodman & Gillman's The Pharmacological Basis of Therapeutics. New York: McGraw-Hill. 11th Edition 2006.

[5] Guidelines for Surgical Prophylaxis at the University of Louisville Hospital, as outlined in: Bratzler, Houck, et al. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. CID 2004; 38:1706-15. Access at: http://www.medqic.org

[6] St. Claire Regional Medical Center, Morehead, Kentucky Form: Surgical Pre OP Orders as promoted by the Medicare Quality Improvement Community. Access at: http://www.medqic.org

[7] Cormio G, Di Fazio F, Lorusso F, Di Gesu G, Cacciapuoti C, Loverro G, Nappi L, Selvaggi L. Antimicrobial prophylaxis in laparotomic gynecologic surgery: a prospective randomized study comparing amoxicillin-clavulanic acid with cefazolin. J Chemother. 2002 Dec;14(6):618-22.

[8] AHFS Monograph on Cefazolin Inj. Available at: http:\www.medscape.com

SANDOZ

quinupristin/dalfopristin[9]. Therefore cefazolin is considered a valuable alternative to the empirical use of vancomycin, e.g. in the treatment of sepsis associated to chronic haemodialysis[10].

Dosing of Cefazolin

The typical doses in adults described in the SPC of Cefazoiln Sandoz are as follows:

Type of Infection	Dose	Frequency
Moderate to severe infections	500 mg to 1 gram	every 6 to 8 hrs.
Mild infections caused by susceptible gram-positive cocci	250 mg to 500 mg	every 8 hours
Acute, uncomplicated urinary tract infections	1 gram	every 12 hours
Pneumococcal pneumonia	500 mg	every 12 hours
Severe, life-threatening infections (e.g., endocarditis, septicemia)*	1 gram to 1.5 grams	every 6 hours

*In rare instances, doses of up to 12 grams of Cefazolin for Injection per day have been used.

Doses are expressed in terms of the equivalent amount of cefazolin, as 1.05 g of cefazolin sodium is approximately equivalent to 1 g of cefazolin. The usual adult dose is the equivalent of 0.5 to 1 g of cefazolin every 6 to 12 h. The usual maximum daily dose is 6 g (i.e. 2 g every 8 h), although up to 12 g has been used in severe life-threatening infections. Cefazolin is relatively well tolerated after either intramuscular or intravenous administration.

Recently the good clinical success rate (84.7%) with cefazolin 2 g bid home treatment in the management of cellulitis (66.2% of lower limb) has been documented in 123 patients. Only one case of diarrhea and no other adverse drug reactions were observed over the mean treatment period of 6.24 d[11].In the treatment of bacterial endocarditis the typical dose has been described as 2 g i.v. every 8 h[12]. Moreover, cefazolin is broadly used in perioperative infection prophylaxis in North America. In the indication perioperative infection prophylaxis the clinical practice guidelines recommend a standard dose of 1 g per application, but in patients with bodyweight >80 kg the standard dose is 2 g per application[13]. For patients with very high body weight even higher doses might be necessary in this indication. A study in 38 patients with morbid obesity

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[9] Nichols RL. Optimal treatment of complicated skin and skin structure infections. J Antimicrob Chemother 1999;44:19-23.

[10] Kuypers D, Vanwalleghem J, Maes B, Messiaen T, Vanrenterghem Y and Peetermans WE. Cefazolin serum concentrations with fixed intravenous dosing in patients on chronic hemodialysis treatment. Nephrol Dial Transplant (1999) 14: 2050-1.

[11] Donald M, Marlow N, Swinburn E, Wu E. Emergency department management of home intravenous antibiotic therapy for cellulitis. Emerg Med J 2005;22:715-7.

[12] Giessel BE, Koenig CJ, Blake RL Jr. Management of bacterial endocarditis. Am Fam Physician. 2000 Mar 15;61(6):1725-32. Available at: http://www.aafp.org/afp/20000315/1725.html

[13] Guidelines for Surgical Prophylaxis at the University of Louisville Hospital, as outlined in: Bratzler, Houck, et al. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. CID 2004; 38:1706-15.

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(BMI >40) reported on the tissue concentrations of cefazolin following a dose of 2 g applied 1 h preoperative and a second dose of 2 g at 3 h during operation. While this dose regimen resulted in serum levels above the break point (i.e. 32 µg/ml) up to 1 h after incision in patients with a BMI up to 59, in the patient group with BMI >60 only up to 15 min serum concentrations in this range were observed. However, in all patients tissue concentrations of cefazolin were substantially lower, indicating that in this population with extreme obesity higher doses might be necessary. The authors cited other studies employing higher doses of cefazolin in this patient group, such as 3 g bolus followed by continuous infusion[14].

Moreover the safety of a single dose of 2 g cefazolin has been confirmed in 15 patients on chronic haemodialysis (8 of these completely anuric). In this patient population an extremely diminished clearance for cefazolin has been found, as the plasma concentrations 48 h after administration (i.e. 47 to 130 µg/ml) were still in the range typically found as maximum plasma levels in healthy volunteers. However, even following 3 consecutive doses (48 h dosing interval), the very good safety profile of 2 g cefazolin in this vulnerable population could be documented, as only a single case of transient urticaria, one case of mouth ulceration, one case of *Clostridium difficile* colitis and one of vomiting (later diagnosed with reflux oesophagitis) was reported[15].

Conclusion

Overall the data presented support the conclusion that the proposed new 2 g Cefazolin for Injection, USP formulation provides significant benefit for clinical practice in the USA, as it supports a well-established and broadly used dose regimen. The 2 g cefazolin dose is frequently used e.g. in patients with high body weight as well as in the treatment of severe infections according to published scientific information. The new 2 g formulation allows much easier handling of the higher doses clinically used, reduces the risk on non-sterile application and provides more flexibility to the treating health care professional with higher convenience.

Considering the pharmacokinetic data and safety information available from clinical practice, no risk is related to the new dose strength of cefazolin, which is already broadly established in clinical practice. The lack of safety issues for the 2 g per single dose formulation of cefazolin is supported by the broad clinical experience with this compound, indicating lack of significant, unacceptable adverse event profile for higher doses and the successful use of 2 g formulations of cefazolin in other countries such as Canada and the European Union. Therefore the proposed new 2 g formulation for cefazolin offers considerable clinical benefit particularly regarding handling of higher doses, which are well established in clinical practice. At the same time the well known tolerability of the drug remains unchanged.

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[14] Edmiston CE, Krepel C, Kelly H, Larson J, Andris D, Hennen C, Nakeeb A, Wallace JR. Perioperative antibiotic prophylaxis in the gastric bypass patient: do we achieve therapeutic levels? Surgery 2004;136(4):738-47.

[15] Kuypers D, Vanwalleghem J, Maes B, Messiaen T, Vanrenterghem Y and Peetermans WE. Cefazolin serum concentrations with fixed intravenous dosing in patients on chronic hemodialysis treatment. Nephrol Dial Transplant (1999) 14: 2050-1.

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Proposed physician labeling is provided in attachment 2. The current labeling for the 500 mg and 1 gram Cefazolin for Injection USP would be amended to include the 2 gram product.

For convenience purposes, copies of the cited references are provided directly behind Attachment 3.

C. Environmental Impact

An environmental impact analysis report is not required for this petition per 21 CFR 25.24.

D. Economic Impact

This information will be provided upon request from the Agency.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

If you have any questions or need additional information, please feel free to contact me.

Sincerely yours,

Sandoz Inc.

Beth Brannan /jep

Beth Brannan, Director
Drug Regulatory Affairs

/jep