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RESEARCH**

APPLICATION NUMBER:

208083Orig1s000

MEDICAL REVIEW(S)

Clinical Review

NDA	208083
Applicant	Celerity Pharmaceuticals, LLC (Celerity)
Date of Submission	June 30, 2016
PDUFA Goal Date	April 30, 2017
Established Name	Clindamycin Injection, USP
Referenced Licensed Drug	Celerity's Clindamycin in 0.9% Sodium Chloride Injection is therapeutically equivalent to the Reference Listed Drug (RLD), CLEOCIN PHOSPHATE IV Solution (clindamycin injection in 5% dextrose) in the GALAXY plastic container (300 mg/50 mL, 600 mg/50 mL, and 900 mg/50 mL). CLEOCIN was approved under NDA 050639 by Pharmacia Upjohn, which is now Pfizer.
Dosage forms / Strength	Clindamycin in 0.9% Saline Injection (300mg/50ML, 600mg/50mL, and 900mg/mL) in a GALAXY plastic container
Proposed Indication	Treatment of serious infections caused by susceptible anaerobic bacteria
Medical Officer	Maria Allende, MD
Medical Team Leader	Thomas Smith, MD
Recommendation	Approval

Introduction

Using the 505(b)2 pathway, Celerity is seeking approval of a premixed, Clindamycin in 0.9% Saline Injection (300mg/50ML, 600mg/50mL, and 900mg/mL) in a GALAXY plastic container for the indication of treatment of serious infections caused by susceptible anaerobic bacteria. Celerity Pharmaceuticals, LLC (Celerity) is relying on FDA's previous findings of safety and efficacy for the 6 mg/mL, 12 mg/mL, and 18 mg/mL CLEOCIN PHOSPHATE IV SOLUTION (Clindamycin phosphate Injection) marketed by Pfizer under NDA 050639 (approved on August 30, 1989 and April 10, 1991 [Pharmacia and Upjohn (now Pfizer)]). As such, Celerity intends to maintain the same indications and usage statements as the 6 mg/mL, 12 mg/mL, and 18 mg/mL Pfizer drug product. Because of the comparability to the approved Pfizer product, the Applicant argues that no new clinical studies are warranted. There are no new clinical studies or new clinical data submitted with this application.

The proposed drug product is a premixed, sterile, nonpyrogenic solution supplied in GALAXY plastic containers and intended for intravenous administration. The route of administration, dosage form, dosing regimen, and strengths (i.e., total drug content) of the proposed drug product are the same as those of the Pfizer drug products, with the exception that the proposed drug product contains sodium chloride, USP as the tonicity adjuster, in the same strength as the Reference Listed Drug (RLD) that is the subject of an approved New Drug Application (NDA). Per 21 CFR § 314.94(a)(9)(iii), Inactive ingredient changes permitted in drug products intended for parenteral use: *“Generally, a drug product intended for parenteral use shall contain the same inactive ingredients and in the same concentration as*

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the reference listed drug identified by the applicant under paragraph (a)(3) of this section. However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.”

(b) (4) issued a Letter of Authorization granting the Food and Drug Administration (FDA) authority to cross-reference and review their Type II Drug Master File (DMF) number (b) (4) for Clindamycin Phosphate. Baxter Healthcare Corporation issued a Letter of Authorization granting the FDA authority to cross-reference and review their Type III DMF number (b) (4) for Production of (b) (4) (b) (4) Plastic Containers (GALAXY Container Closure System). Copies of (b) (4) and Baxter’s DMF letters of authorization are provided within Module 1.4.2 of this NDA.

Background

Clindamycin is a lincosamide antibacterial drug product indicated for the treatment of serious infections caused by susceptible anaerobic bacteria. Clindamycin for Injection was first approved in 1972 (Cleocin Phosphate, NDA 050441). The non-clinical and clinical safety data of Clindamycin for Injection have been reviewed for the listed drug (LD), Cleocin Phosphate (Pharmacia and Upjohn, NDA 050639).

Celerity intends to maintain the same dosing regimen described in the package insert of CLEOCIN PHOSPHATE IV SOLUTION, which is currently approved as a premixed, (b) (4) sterile solution containing clindamycin phosphate, USP equivalent to 300 mg, 600 mg, and 900 mg of clindamycin in the GALAXY plastic container under NDA 050639.

The Applicant contends that the administration of clindamycin 0.9% Sodium Chloride is not expected to impact drug product performance.

The Applicant has submitted a Request for Waiver of In-vivo Bioavailability Studies with detailed comparisons between the proposed drug product and the Pfizer drug product. It is included in Module 1.12.15, along with a review of the non-clinical literature of clindamycin. The Biopharmaceutical team reviewer, Dr. Kaushalkumar Dave, has approved this waiver request on 01/17/2017 as follows:

*“..... In conclusion, consistent with 21 CFR § 320.24(b)(6) the FDA deems that the bridge (bioavailability/bioequivalence) between the proposed drug product and the listed drug product is established, and therefore the reliance of NDA 208083 on the Agency’s finding of safety and effectiveness of the listed drug is justified. From a Biopharmaceutics perspective, NDA 208083 for Clindamycin in 0.9% Sodium Chloride Injection, 300 mg/50 mL, 600 mg/50 mL and 900 mg/50 mL, is recommended for **APPROVAL**”.*

The proposed indications are the same as those for the equivalent product under NDA 50639. The table below outlines the indications sought.

Proposed Indication(s)	<p>Clindamycin in 0.9% sodium chloride injection products are indicated in the treatment of serious infections caused by susceptible anaerobic bacteria.</p> <p>Clindamycin in 0.9% sodium chloride injection products are also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci. Its use should be reserved for penicillin-allergic patients or other patients for whom, in the judgment of the physician, a penicillin is inappropriate.</p> <p>Clindamycin in 0.9% sodium chloride injection is indicated in the treatment of serious infections caused by susceptible strains of the designated organisms in the conditions listed below:</p> <ul style="list-style-type: none">• Lower respiratory tract infections including pneumonia, empyema, and lung abscess caused by anaerobes, <i>Streptococcus pneumoniae</i>, other streptococci (except <i>E. faecalis</i>), and <i>Staphylococcus aureus</i>.• Skin and skin structure infections caused by <i>Streptococcus pyogenes</i>, <i>Staphylococcus aureus</i>, and anaerobes.• Gynecological infections including endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal cuff infection caused by susceptible anaerobes.• Intra-abdominal infections including peritonitis and intra-abdominal abscess caused by susceptible anaerobic organisms.• Septicemia caused by <i>Staphylococcus aureus</i>, streptococci (except <i>Enterococcus faecalis</i>), and susceptible anaerobes.• Bone and joint infections including acute hematogenous osteomyelitis caused by <i>Staphylococcus aureus</i> and as adjunctive therapy in the surgical treatment of chronic bone and joint infections due to susceptible organisms.
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M.O.comment: Based on the package insert for clindamycin, these indications are the same.

CMC

Celerity noted the following:

“The active pharmaceutical ingredient (API), clindamycin phosphate, USP, and inactive ingredients (edetate disodium, hydrochloric acid, sodium hydroxide, and water for injection) for Celerity’s Clindamycin in 0.9% Sodium Chloride (b) (4) CLEOCIN PHOSPHATE IV Solution, marketed by Pfizer, with the exception that the proposed drug product contains sodium chloride, USP as the tonicity adjuster”.

Celerity provided the following table comparing Celerity’s Clindamycin in 0.9% Sodium Chloride Injection to the CLEOCIN PHOSPHATE IV Solution from Pfizer’s NDA 050639.

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Table 1. Side-by-Side Comparison of Proposed and Reference Listed Drug Products

Parameter	Reference Listed Drug	Proposed Drug Product
Name	CLEOCIN PHOSPHATE IV Solution	Clindamycin in 0.9% Sodium Chloride Injection
Conditions of Use (Indications)	<p>CLEOCIN PHOSPHATE products are indicated in the treatment of serious infections caused by susceptible anaerobic bacteria.</p> <p>CLEOCIN PHOSPHATE products are also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci.</p> <p>CLEOCIN PHOSPHATE is indicated in the treatment of serious infections caused by susceptible strains of the designated organisms in the conditions listed below:</p> <p>Lower respiratory tract infections including pneumonia, empyema, and lung abscess caused by anaerobes, <i>Streptococcus pneumoniae</i>, other streptococci (except <i>E. faecalis</i>), and <i>Staphylococcus aureus</i>.</p> <p>Skin and skin structure infections caused by <i>Streptococcus pyogenes</i>, <i>Staphylococcus aureus</i>, and anaerobes.</p> <p>Gynecological infections including endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal cuff infection caused by susceptible anaerobes.</p> <p>Intra-abdominal infections including peritonitis and intra-abdominal abscess caused by susceptible anaerobic organisms.</p>	<p>Clindamycin in 0.9% Sodium Chloride Injection, (b) (4) indicated (b) (4) the treatment of serious infections caused by susceptible anaerobic bacteria.</p> <p>Clindamycin in 0.9% Sodium Chloride Injection, (b) (4) indicated (b) (4) the treatment of serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci.</p> <p>(b) (4)</p> <p>Lower respiratory tract infections including pneumonia, empyema, and lung abscess caused by anaerobes, <i>Streptococcus pneumoniae</i>, other streptococci (except <i>E. faecalis</i>), and <i>Staphylococcus aureus</i>.</p> <p>Skin and skin structure infections caused by <i>Streptococcus pyogenes</i>, <i>Staphylococcus aureus</i>, and anaerobes.</p> <p>Gynecological infections including endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal cuff infection caused by susceptible anaerobes.</p> <p>Intra-abdominal infections including peritonitis and intra-abdominal abscess caused by susceptible anaerobic organisms.</p>

Nonclinical Pharmacology/Toxicology, Clinical Pharmacology, Microbiology

No new nonclinical studies were conducted for this application. The Applicant provided a nonclinical overview in the NDA that contained an updated literature review since June 29, 2001 (the last ANDA approval date for a clindamycin parenteral drug product). No new pharmacology, clinical microbiology and clinical efficacy or statistical analysis information was included in the current application. The studies conducted in support of the original approval of clindamycin were detailed in the original NDA.

M.O.comment: *This Medical Officer refers the reader to previous non-clinical and clinical information from NDA 050639, and to the current reviews of the Pharmacology/Toxicology, Clinical Pharmacology and Microbiology review teams, filed in DARRTS.*

Safety

Review of Proposed Label

The Applicant has submitted as reference the current label from CLEOCIN PHOSPHATE, the RLD product under NDA 050639 (b) (4). This label has been updated several times during the past two years. Please refer to the label reviews filed in DARRTS over the past year. The last revision was in (b) (4) 2016.

Since this is a new NDA, the proposed label submitted by the Applicant for their product is in the format described in the Pregnancy and Lactation Labeling (Drugs) Final Rule:

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>

The change to PLLR format is the only change as compared to the RLD reference label from Pfizer. None of the contents have been changed other than organizational structure.

The Safety sections from the proposed label are copied below:

5 WARNINGS AND PRECAUTIONS

5.1 *Clostridium difficile* Associated Diarrhea

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Clindamycin in 0.9% Sodium Chloride Injection, and may range in severity from mild diarrhea to fatal colitis.

Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

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

If CDAD is suspected or confirmed, ongoing (b) (4) use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, (b) (4) treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated [see *Boxed Warning*].

5.2 Anaphylactic and Severe Hypersensitivity Reactions

Anaphylactic shock and anaphylactic reactions have been reported [see *Adverse Reactions (6)*].

Severe hypersensitivity reactions, including severe skin reactions such as toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and Stevens-Johnson syndrome (SJS), some with fatal outcome, have been reported [see *Adverse Reactions (6)*].

In case of such an anaphylactic or severe hypersensitivity reaction, discontinue treatment permanently and institute appropriate therapy.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens.

5.3 Diarrhea in Elderly Patients with Associated Severe Illness

(b) (4) patients with associated severe illness may (b) (4) diarrhea (b) (4). When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency.

5.4 Use (b) (4) in Patients with Gastrointestinal Disease

Clindamycin in 0.9% Sodium Chloride Injection products should be (b) (4) in individuals with a history of gastrointestinal disease, particularly colitis.

5.5 Use (b) (4) in Atopic Individuals

Clindamycin in 0.9% Sodium Chloride Injection should be (b) (4) in atopic individuals.

5.6

5.7 Laboratory Tests

During prolonged therapy periodic liver and kidney function tests and blood counts should be performed. Clindamycin dosage modification may not be necessary in patients with renal disease. In patients with moderate to severe liver disease, prolongation of clindamycin half-life has been found. However, it was postulated from studies that when given every eight hours, accumulation should rarely occur. Therefore, dosage modification in patients with liver disease may not be necessary. However, periodic liver enzyme determinations should be made when treating patients with severe liver disease.

5.8 Overgrowth of Nonsusceptible Organisms

The use of Clindamycin in 0.9% Sodium Chloride Injection may result in overgrowth of nonsusceptible organisms—particularly yeasts. (b) (4) appropriate measures should be taken as indicated by the clinical situation.

5.9

5.10 Development of Drug-Resistant Bacteria

Prescribing Clindamycin in 0.9% Sodium Chloride Injection 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.

6 ADVERSE REACTIONS

The following serious adverse reactions to clindamycin are described below and elsewhere in the labeling:

- *Clostridium difficile* Associated Diarrhea [see *Warnings and Precautions* (5.1)]
- Anaphylactic and Severe Hypersensitivity Reactions [see *Warnings and Precautions* (5.2)]

The following adverse reactions associated with the use of clindamycin were identified in clinical trials or postmarketing reports. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency, reliably, or to establish a causal relationship to drug exposure.

Infections and Infestations

Clostridium difficile colitis

Gastrointestinal

Antibiotic-associated colitis [see *Warnings and Precautions* (5.1)], pseudomembranous colitis, abdominal pain, nausea, and vomiting. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment [see *Warnings and Precautions* (5.1)]. An unpleasant or metallic taste has been reported after intravenous administration of the higher doses of clindamycin phosphate.

Hypersensitivity Reactions

Maculopapular rash and urticaria have been observed during drug therapy. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions.

Severe skin reactions such as Toxic Epidermal Necrolysis, some with fatal outcome, have been reported [see *Warnings and Precautions* (5.2)]. Cases of Acute Generalized Exanthematous Pustulosis (AGEP), erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. Anaphylactic shock, anaphylactic reaction and hypersensitivity have also been reported [see *Warnings and Precautions* (5.2)].

Skin and Mucous Membranes

Pruritus, vaginitis, angioedema and rare instances of exfoliative dermatitis have been reported [see *Warnings and Precautions* (5.2)].

Liver

Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy.

Renal

Renal dysfunction as evidenced by azotemia, oliguria, and/or proteinuria has been observed.

Hematopoietic

Transient neutropenia (leukopenia) and eosinophilia have been reported. Reports of agranulocytosis and thrombocytopenia have been made.

Immune System

Drug reaction with eosinophilia and systemic symptoms (DRESS) cases have been reported.

Local Reactions

Thrombophlebitis has been reported after intravenous infusion. (b) (4) avoid (b) (4) prolonged use of indwelling intravenous catheters.

Musculoskeletal

Polyarthritis cases have been reported.

Cardiovascular

Cardiopulmonary arrest and hypotension have been reported following too rapid intravenous administration. [see *Dosage and Administration (2)*].

7 DRUG INTERACTIONS

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, it should be (b) (4) in patients receiving such agents.

Antagonism has been demonstrated between clindamycin and erythromycin *in vitro*. Because of possible clinical significance, the two drugs should not be administered concurrently.

M.O.comment: *The adverse reactions listed in the proposed label are consistent with the most updated CLEOCIN PHOSPHATE label from Pfizer, the RLD.*

Literature Review

I have reviewed PubMed and Embase databases for additional safety data related to the use of the clindamycin intravenous and oral products. The search conducted used the following strategies:

PubMed search strategy:

("Clindamycin/adverse effects"[Mesh] OR "Clindamycin/poisoning"[Mesh] OR "Clindamycin/toxicity"[Mesh])
Filters: published in the last 5 years; limited to English

Embase search strategy:

'clindamycin'/mj/dd_ae,dd_to AND [2012-2017]/py AND [english]/lim

This search yielded 57 references in PubMed and 85 in Embase in the last 5 years up to 02/27/2017. Further limiting the search by adding "clinical trial" to the search strategy yielded one publication during the time frame.

M.O.comment: *The reported adverse events are consistent with the adverse reactions listed in the current Pfizer CLEOCIN label. None of these articles provided new or additional adverse event information related to the use of clindamycin that is not addressed in the current label. None of the data described in the trials or case reports provided additional information that would inform the safety of this dosing regimen. Therefore, a label change is not warranted at this time.*

Recommendations

From a clinical standpoint, the recommendation is to approve this product.

No new data from clinical or nonclinical studies were included in this submission. A waiver of bioequivalence studies was granted. This formulation of clindamycin was assessed as bioequivalent to Pfizer's CLEOCIN for Injection in Galaxy Container, under NDA 050639. No new safety information was presented or identified in the literature that would alter the favorable risk/benefit assessment of clindamycin in the current labeled indications.

No postmarketing risk evaluation and management strategies or postmarketing requirements or commitments are recommended. We are in the process of reviewing the updates to the label, and it is

not final at the current time. Please refer to the final approved label at the time of the NDA approval date.

References

- Baumann, L. S., et al. (2013). "Comparison of clindamycin 1% and benzoyl peroxide 5% gel to a novel composition containing salicylic acid, capryloyl salicylic acid, HEPES, glycolic acid, citric acid, and dioic acid in the treatment of acne vulgaris." J Drugs Dermatol **12**(3): 266-269.
- Bawany, M. Z., et al. (2013). "Acute liver failure: an uncommon complication of commonly used medication." Am J Ther **20**(5): 566-568.
- Ben-Ami, R., et al. (2012). "Antibiotic exposure as a risk factor for fluconazole-resistant *Candida* bloodstream infection." Antimicrob Agents Chemother **56**(5): 2518-2523.
- Bradshaw, C. S., et al. (2012). "Efficacy of oral metronidazole with vaginal clindamycin or vaginal probiotic for bacterial vaginosis: randomised placebo-controlled double-blind trial." PLoS ONE **7**(4): e34540.
- Callender, V. D. (2012). "Fitzpatrick skin types and clindamycin phosphate 1.2%/benzoyl peroxide gel: efficacy and tolerability of treatment in moderate to severe acne." J Drugs Dermatol **11**(5): 643-648.
- Chang, A. L., et al. (2012). "A randomized, double-blind, placebo-controlled, pilot study to assess the efficacy and safety of clindamycin 1.2% and tretinoin 0.025% combination gel for the treatment of acne rosacea over 12 weeks." J Drugs Dermatol **11**(3): 333-339.
- Chen, B. K., et al. (2012). "Root discolouration following short-term application of steroid medicaments containing clindamycin, doxycycline or demeclocycline." Aust Endod J **38**(3): 124-128.
- Cook-Bolden, F. E. (2012). "Treatment of moderate to severe acne vulgaris in a Hispanic population: a post-hoc analysis of efficacy and tolerability of clindamycin phosphate 1.2%/benzoyl peroxide 2.5% gel." J Drugs Dermatol **11**(4): 455-459.
- da Silva, J. R., et al. (2014). "Esophagitis dissecans superficialis associated with severe clindamycin toxicity." J Gastrointestin Liver Dis **23**(4): 363.
- De Cruz, R., et al. (2015). "Acute localised exanthematous pustulosis (ALEP) induced by clindamycin in pregnancy." Australas J Dermatol **56**(3): e55-58.
- Dhaliwal, G. and D. Hsu (2016). "Tramadol Ultra Rapid Metabolizers at Risk for Respiratory Depression." Pain Physician **19**(2): E361.
- Draeos, Z. D., et al. (2012). "A multicenter, double-blind study to evaluate the efficacy and safety of 2 treatments in participants with mild to moderate acne vulgaris." Cutis **89**(6): 287-293.
- Dreno, B., et al. (2014). "Efficacy and safety of clindamycin phosphate 1.2%/tretinoin 0.025% formulation for the treatment of acne vulgaris: pooled analysis of data from three randomised, double-blind, parallel-group, phase III studies." Eur J Dermatol **24**(2): 201-209.
- Eichenfield, L. F. and A. C. Krakowski (2012). "Moderate to severe acne in adolescents with skin of color: benefits of a fixed combination clindamycin phosphate 1.2% and benzoyl peroxide 2.5% aqueous gel." J Drugs Dermatol **11**(7): 818-824.

Fortuna, G. and A. Pollio (2012). "Comment: probable clindamycin-induced ageusia, xerostomia, and burning mouth syndrome." Ann Pharmacother **46**(11): 1577-1578; author reply 1578.

Freeman, S. A., et al. (2012). "Clindamycin phosphate 1.2% and tretinoin 0.025% gel for rosacea: summary of a placebo-controlled, double-blind trial." J Drugs Dermatol **11**(12): 1410-1414.

Giugno, C. S., et al. (2013). "Daily dose of clindamycin versus standard divided doses in obstetrical and gynecological infections: a retrospective cohort study." Int J STD AIDS **24**(11): 893-898.

Gold, L. S. (2013). "Efficacy and tolerability of fixed-combination acne treatment in adolescents." Cutis **91**(3): 152-159.

Gonzalez, P., et al. (2012). "The tolerability profile of clindamycin 1%/benzoyl peroxide 5% gel vs. adapalene 0.1%/benzoyl peroxide 2.5% gel for facial acne: results of a randomized, single-blind, split-face study." J Cosmet Dermatol **11**(4): 251-260.

Goshi, R., et al. (2012). "A double-blind, randomized, bilateral comparison of skin irritancy following application of the combination acne products clindamycin/tretinoin and benzoyl peroxide/adapalene." J Drugs Dermatol **11**(12): 1422-1426.

Grove, G., et al. (2013). "Tolerability and irritation potential of four topical acne regimens in healthy subjects." J Drugs Dermatol **12**(6): 644-649.

Harper, J. C. (2012). "Gender as a clinically relevant outcome variable in acne: benefits of a fixed combination clindamycin phosphate (1.2%) and benzoyl peroxide (2.5%) aqueous gel." J Drugs Dermatol **11**(12): 1440-1445.

Harper, J. C. (2015). "The efficacy and tolerability of a fixed combination clindamycin (1.2%) and benzoyl peroxide (3.75%) aqueous gel in patients with facial acne vulgaris: gender as a clinically relevant outcome variable." J Drugs Dermatol **14**(4): 381-384.

Heslop, O. D., et al. (2013). "A unique strain of community-acquired *Clostridium difficile* in severe complicated infection and death of a young adult." BMC Infect Dis **13**: 299.

Jarratt, M. T. and T. Brundage (2012). "Efficacy and safety of clindamycin-tretinoin gel versus clindamycin or tretinoin alone in acne vulgaris: a randomized, double-blind, vehicle-controlled study." J Drugs Dermatol **11**(3): 318-326.

Kawashima, M., et al. (2015). "Clindamycin phosphate 1.2%-benzoyl peroxide 3.0% fixed-dose combination gel has an effective and acceptable safety and tolerability profile for the treatment of acne vulgaris in Japanese patients: a phase III, multicentre, randomised, single-blinded, active-controlled, parallel-group study." Br J Dermatol **172**(2): 494-503.

Kim, Y. G., et al. (2014). "Gut dysbiosis promotes M2 macrophage polarization and allergic airway inflammation via fungi-induced PGE(2)." Cell Host Microbe **15**(1): 95-102.

Kiser, C. J., et al. (2014). "Development of *Clostridium septicum* gas gangrene as an adverse effect of clindamycin-induced *Clostridium difficile* infection in a pediatric patient." J Pediatr Orthop **34**(6): e19-21.

Koban, I., et al. (2012). "Clinical use of the antiseptic polihexanide for genital tract infections." Skin Pharmacol Physiol **25**(6): 298-304.

Kronman, M. P., et al. (2012). "Antibiotic exposure and IBD development among children: a population-based cohort study." Pediatrics **130**(4): e794-803.

Llamas-Velasco, M., et al. (2013). "Acute generalized exanthematous pustulosis with histopathologic findings of lymphomatoid drug reaction." Am J Dermatopathol **35**(6): 690-691.

Miller, L. G., et al. (2015). "Clindamycin versus trimethoprim-sulfamethoxazole for uncomplicated skin infections." N Engl J Med **372**(12): 1093-1103.

Miller Quidley, A., et al. (2012). "Fatal clindamycin-induced drug rash with eosinophilia and systemic symptoms (DRESS) syndrome." Pharmacotherapy **32**(12): e387-392.

Mohyuddin, G. R., et al. (2013). "Acute generalized exanthematous pustulosis with multiple organ dysfunction syndrome." Am J Crit Care **22**(3): 270-273.

Morales-Cabeza, C., et al. (2015). "SDRIFE-like reaction induced by an intradermal skin test with clindamycin: A case report." J Allergy Clin Immunol Pract **3**(6): 976-977.

Murray, J. and A. Potts (2014). "The phototoxic and photoallergy potential of clindamycin phosphate 1.2%/ tretinoin 0.025% gel for facial acne: results of two single-center, evaluator-blinded, randomized, vehicle-controlled phase 1 studies in healthy volunteers." J Drugs Dermatol **13**(1): 16-22.

Nakamura, Y., et al. (2013). "Drug-induced hypersensitivity syndrome induced by clindamycin." Acta Derm Venereol **93**(1): 83-84.

Navarini, A. A., et al. (2013). "Rare variations in IL36RN in severe adverse drug reactions manifesting as acute generalized exanthematous pustulosis." J Invest Dermatol **133**(7): 1904-1907.

Pool, C., et al. (2016). "Increased Surgical Site Infection Rates following Clindamycin Use in Head and Neck Free Tissue Transfer." Otolaryngol Head Neck Surg **154**(2): 272-278.

Prasad, S., et al. (2012). "Efficacy and safety of a nano-emulsion gel formulation of adapalene 0.1% and clindamycin 1% combination in acne vulgaris: a randomized, open label, active-controlled, multicentric, phase IV clinical trial." Indian J Dermatol Venereol Leprol **78**(4): 459-467.

Richardson, W. L. and W. C. Hammert (2014). "Adverse effects of common oral antibiotics." J Hand Surg Am **39**(5): 989-991.

Rosen, S., et al. (2012). "Probable clindamycin-induced ageusia, xerostomia, and burning mouth syndrome." Ann Pharmacother **46**(7-8): 1119-1120.

Schmidt, R. S. and E. R. Reiter (2012). "Clindamycin-induced neutropenia following major head and neck surgery." Ear Nose Throat J **91**(9): E27-29.

Stein Gold, L. (2015). "Efficacy and Tolerability of a Fixed Combination of Clindamycin Phosphate (1.2%) and Benzoyl Peroxide (3.75%) Aqueous Gel in Moderate and Severe Acne Vulgaris Subpopulations." J Drugs Dermatol **14**(9): 969-974.

Sullivan, T. (2014). "Antibiotic overuse and Clostridium difficile: a teachable moment." JAMA Intern Med **174**(8): 1219-1220.

Thornhill, M. H., et al. (2015). "Incidence and nature of adverse reactions to antibiotics used as endocarditis prophylaxis." J Antimicrob Chemother **70**(8): 2382-2388.

Ting, W. (2012). "Randomized, observer-blind, split-face study to compare the irritation potential of 2 topical acne formulations over a 14-day treatment period." Cutis **90**(2): 91-96.

Varada, N. L., et al. (2015). "Agranulocytosis with ceftaroline high-dose monotherapy or combination therapy with clindamycin." Pharmacotherapy **35**(6): 608-612.

Wargo, K. A., et al. (2015). "Vancomycin Combined With Clindamycin for the Treatment of Acute Bacterial Skin and Skin-Structure Infections." Clin Infect Dis **61**(7): 1148-1154.

Wu, G., et al. (2015). "A Costly Lesson: Fatal Respiratory Depression Induced by Clindamycin during Postoperative Patient Controlled Analgesia." Pain Physician **18**(3): E429-431.

Wu, H. and G. Wu (2016). "In Response: The Cause of Fatal Respiratory Depression Is Combination of Clindamycin and Fentanyl, Rather than Tramadol." Pain Physician **19**(2): E362.

Xie, H., et al. (2013). "Clindamycin-induced acute kidney injury: large biopsy case series." Am J Nephrol **38**(3): 179-183.

Zaenglein, A. L., et al. (2013). "A phase IV, open-label study evaluating the use of triple-combination therapy with minocycline HCl extended-release tablets, a topical antibiotic/retinoid preparation and benzoyl peroxide in patients with moderate to severe acne vulgaris." J Drugs Dermatol **12**(6): 619-625.

Zeichner, J. A. (2012). "Optimizing topical combination therapy for the treatment of acne vulgaris." J Drugs Dermatol **11**(3): 313-317.

Zeichner, J. A., et al. (2012). "Efficacy and safety of a ceramide containing moisturizer followed by fixed-dose clindamycin phosphate 1.2%/benzoyl peroxide 2.5% gel in the morning in combination with a ceramide containing moisturizer followed by tretinoin 0.05% gel in the evening for the treatment of facial acne vulgaris." J Drugs Dermatol **11**(6): 748-752.

Zeichner, J. A., et al. (2013). "Efficacy and safety of tretinoin 0.025%/clindamycin phosphate 1.2% gel in combination with benzoyl peroxide 6% cleansing cloths for the treatment of facial acne vulgaris." J Drugs Dermatol **12**(3): 277-282.

Zhang, Z., et al. (2014). "Culture-inappropriate antibiotic therapy decreases quality of life improvement after sinus surgery." Int Forum Allergy Rhinol **4**(5): 403-410.

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/s/

MARIA C ALLENDE
03/14/2017

THOMAS D SMITH
03/15/2017
I concur with Dr. Allende's review