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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	208083
Supporting document/s:	4
Sponsor's letter date:	June 30, 2016
CDER stamp date:	June 30, 2016
Product:	Clindamycin in 0.9% Sodium Chloride Injection
Indication:	Treatment of serious infections caused by susceptible anaerobic bacteria
Sponsor:	Celerity Pharmaceuticals, LLC
Review Division:	Division of Anti-Infective Products
Reviewer:	Tessie P. Alapatt, Ph.D.
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Introduction

Celerity Pharmaceuticals is seeking approval of Clindamycin in 0.9% Sodium Chloride Injection using the 505(b)2 pathway. Clindamycin in 0.9% Saline Injection (300, 600mg, and 900mg) is a premixed solution supplied in GALAXY plastic containers for the treatment of serious infections caused by susceptible anaerobic bacteria. The Applicant plans to rely on the FDA's prior findings of safety and efficacy, which includes clinical and nonclinical data from previously approved Clindamycin drug product (Cleocin phosphate®, NDA 050639) for parenteral use. The route of administration (intravenous or IV), dosage form, dosage strength, dosing regimen, and indications for the proposed drug product are the same as those of the reference listed drug (RLD). However, the formulation differs from the RLD as it contains 0.9% sodium chloride instead of 5% dextrose. Given that clindamycin phosphate is marketed currently, no new nonclinical studies were submitted for this NDA. This is acceptable as there are no unqualified impurities or degradants up to a shelf-life of 18 months.

Recommendations:

Pharmacology/Toxicology has no objection to the approval of Clindamycin in 0.9% Sodium Chloride Injection considering the acceptance of the Chemistry review team of the Applicant's latest proposed impurity specifications for this drug product.

Labeling:

Section 8.1 and 8.2 of the PI were modified to comply with current Pregnancy and Lactation Labeling Rule (PLLR) standards. The animal data were edited to include dosing days and general comparisons to human equivalent dose. There were no changes to section 13 of the label. Based on the recommendations of the review team, Sections 8.1 and 8.2 are recommended to read as follows:

8.1 Pregnancy

Risk Summary

In limited published clinical trials with pregnant women, the systemic administration of clindamycin during the second and third trimesters has not been associated with an increased frequency of major birth defects.

The limited published data on use of clindamycin in pregnant women with exposure during the first trimester are insufficient to inform a drug-associated risk of pregnancy-related adverse outcomes *[see Data].* In animal reproduction studies, no evidence of any adverse developmental outcomes was observed when oral or subcutaneous doses of clindamycin were administered to pregnant rats and mice during organogenesis at doses half to twice the highest clinically relevant dose based on body surface area comparison *[see Data].* The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the

estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Human Data

In limited published trials in pregnant women administered clindamycin during the first trimester of pregnancy, there was no difference in the rate of major birth defects reported among in utero exposed infants compared to unexposed infants. From these observational data, it is not possible to draw any conclusions on the rate of specific major birth defects associated with clindamycin. These data cannot definitely establish or exclude any clindamycin-associated risk during pregnancy.

Animal Data

Reproduction studies performed during organogenesis (gestational days 6-15) in pregnant rats and mice that were administered oral doses of clindamycin up to 600 mg/kg/day (twice or equivalent to the highest recommended adult human dose based on a body surface area comparison, respectively) or subcutaneous doses of clindamycin up to 250 mg/kg/day (equivalent to or half the highest recommended adult human dose based on a body surface area comparison, respectively) revealed no evidence of teratogenicity.

8.2 Lactation

Risk Summary

Clindamycin is present in breast milk in the range of 0.7 to 3.8 mcg/mL at dosages of 150 mg orally to 600 mg intravenously. Clindamycin has the potential to cause adverse effects on the breastfed infant's gastrointestinal flora. There is no information on the effects of clindamycin on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for clindamycin and any potential adverse effects on the breast-fed child from clindamycin or from the underlying maternal condition.

Clinical Considerations

Clindamycin may cause intestinal flora alteration. Advise a woman to monitor the breastfed infant for diarrhea, candidiasis (thrush, diaper rash) and bloody stools.

Information from the NDA Submission:

Drug

CAS Registry Number:

24729-96-2

Generic Name

Clindamycin in 0.9% Sodium Chloride Injection

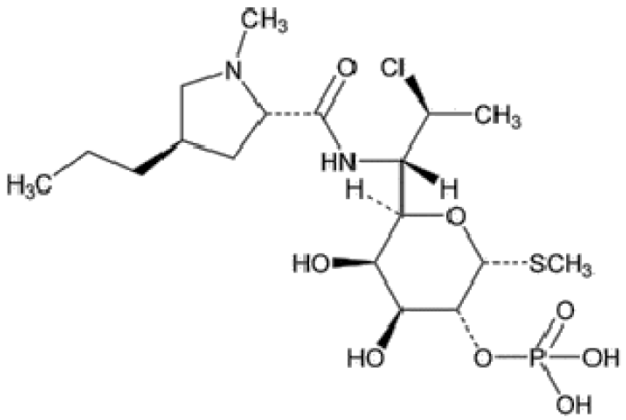
Chemical Name

1. L-*threo*-α-D-*galacto*-Octopyranoside, methyl-7-chloro-6,7,8-trideoxy-6-[[(1-methyl-4-propyl-2-pyrrolidinyl)carbonyl]amino]-1-thio-, 2-(dihydrogen phosphate), (2*S*-*trans*)-
2. (b) (4)

Molecular Formula/Molecular Weight: 504.96

$C_{18}H_{34}ClN_2O_8PS$

Structure or Biochemical Description



Pharmacologic Class

Clindamycin in 0.9% Sodium Chloride Injection is a lincosamide antibacterial drug product.

Relevant NDAs and DMFs

NDA 050639, DMF (b) (4) (drug substance), DMF (b) (4) (Galaxy container PL 2501)

Drug Formulation

Table 1: Formulation of Clindamycin in 0.9% Sodium Chloride Injection.

Component	Concentration (g/L)	Dose		
		300 mg/50 mL[c]	600 mg/50 mL[c]	900 mg/50 mL[c]
Clindamycin Phosphate, USP[a]	Equivalent to Clindamycin: 300 mg (b) (4) 600 mg - 900 mg -	Equivalent to 300 mg Clindamycin	Equivalent to 600 mg Clindamycin	Equivalent to 900 mg Clindamycin
Sodium Chloride, USP	(b) (4)			
Edetate Disodium Dihydrate, USP	(b) (4)	2 mg		
Hydrochloric Acid, NF[d]	For pH adjustment[b]			
Sodium Hydroxide, NF[e]	For pH adjustment[b]			
Water for Injection, USP	QS			

USP = United States Pharmacopeia; NF = National Formulary; QS = Quantity Sufficient

[a] The amount required is calculated based on the potency of the drug substance.

[b] Solution is adjusted to pH (b) (4) during batch manufacture. The product limits are pH 5.5 – 7.0.

[c] (b) (4)

[d] Added as (b) (4) hydrochloric acid solution, if necessary, to adjust pH.

[e] Added as (b) (4) sodium hydroxide solution to adjust pH.

Comments on Novel Excipients

There are no novel excipients in the drug product.

Comments on Impurities/Degradants of Concern

Impurities: The impurities of concern, RLD impurity limits, FDA recommended limits and proposed impurity limits are listed in the table below (Table 2). The USP monograph of the RLD does not have limits specified for these impurities. However, the proposed limits of these impurities in the current drug product were determined to be higher than levels in the RLD when tested by the Applicant. The Agency recommended lowering the impurity limits (b) (4) Although the Applicant proposed lowering the impurity levels, (b) (4) the Applicant requested a shelf-life of 18 months (b) (4) Further, the Applicant provided nonclinical and chemistry data to justify their proposed impurity limits, summarized here.

(b) (4) in the Clindamycin in 0.9% Sodium Chloride Injection drug product. (b) (4) (b) (4) The maximum recommended daily dose for intravenous administration is (b) (4) (FDA approved drug). Therefore, the TDI of lincomycin resulting from intravenous administration of Clindamycin in 0.9% Sodium Chloride Injection drug product is (b) (4) imes lower than the maximum recommended daily dose of (b) (4). In a nonclinical study referenced by the Applicant[1] in which pregnant rats were administered (b) (4) subcutaneously, the NOAEL was determined to be 300 mg/kg. This is equivalent to a human equivalent dose (HED) of 48 (b) (4) for a 60 kg adult. This estimated systemic HED is (b) (4) greater than (b) (4) Clindamycin in 0.9% Sodium Chloride Injection drug product.

(b) (4) is a degradation product in the Clindamycin in 0.9% Sodium Chloride Injection drug product. (b) (4) The TDI of (b) (4) resulting from the proposed impurity limit of (b) (4) % (in Clindamycin in 0.9% Sodium Chloride Injection) is (b) (4) mg/day. In nonclinical studies referenced by the Applicant[2], an oral dose of 300 mg/kg was well tolerated in both rats and dogs for up to 1 year. The NOAEL was determined to be 300 mg/kg in rats and dogs, and the corresponding HEDs would be (b) (4) respectively. For a 60 kg adult, the HEDs would be (b) (4) respectively, which is (b) (4) than the TDI for (b) (4) from Clindamycin in 0.9% Sodium Chloride Injection drug product.

From a Pharmacology/Toxicology perspective, with concurrence with the Chemistry Review team, the revised impurity limits for (b) (4) appear acceptable with the justification provided by the Applicant, for a shelf-life of 18 months.

(b) (4)

Table 2: Proposed Limits/FDA Recommended Limit/Applicant's Counter Proposal limits

Impurity	Stability limits Proposed in the initial NDA submission (%)	NDA Registration Stability batch limits (%)	RLD Batch stability limi (b) (4) As tested by the applicant (%)	RLD Batch stability limit (b) (4) As tested by the applicant (%)	FDA recommended stability limit (based on RLD data submitted by the applicant) (%)	Applicant's counter proposal stability limits (%)		
						1st IR	2nd IR	3rd IR
(b) (4)								
Any single Unknown								
Total Unspecified Impurities								
Total								

Leachables: (b) (4) GALAXY PL 2501 container closure system used for the proposed drug product. (b) (4) Clindamycin in 0.9% Sodium Chloride Injection drug product would be (b) (4) mcg/day. A daily intake of up to (b) (4) mcg/day is acceptable for impurities when duration of treatment is (b) (4) The expected daily intake of (b) (4) is therefore, approximately (b) (4) lower than the acceptable daily intake of (b) (4) mcg/day. Hence, from a Pharmacology/Toxicology

perspective, [redacted] (b) (4) is acceptable.

Proposed Clinical Population and Dosing Regimen

In adults, the proposed IV dose is 600–1200 mg/day. For more severe infections up to 2700 mg/day is recommended. In pediatric patients, 1 month of age to 16 Years, 20 to 40 mg/kg/day, whereas in neonates (less than 1 month of age), 15 to 20 mg/kg/day is recommended. Alternative dosing for pediatric patients for serious and severe infections are 350 and 450 mg/m^2/day respectively.

Integrated Summary

The sponsor intends to rely on the Agency's findings of safety and efficacy for approved clindamycin products to support an NDA for the current product, Clindamycin in 0.9% Sodium Chloride Injection. The proposed drug product is a premixed, sterile, non-pyrogenic solution supplied in GALAXY plastic containers and intended for IV administration. The drug product is composed of clindamycin phosphate equivalent to 300 mg, 600 mg, and 900 mg of clindamycin. The impurity limits, although higher than that of the RLD, were ultimately found acceptable by the Chemistry review team up to a shelf-life of 18 months. The predominant leachable compound from GALAXY containers PL 2501 with the drug product is [redacted] (b) (4) which was determined to be at an acceptable level of [redacted] (b) (4). The Applicant did not conduct any additional nonclinical studies with Clindamycin Injection in 0.9% Sodium Chloride in the Galaxy container. No additional nonclinical toxicology studies are needed for approval of this 505(b)(2) application.

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/s/

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04/13/2017

TERRY J MILLER
04/14/2017