CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209844Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 16, 2018
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 209844
Product Name and Strength:	LymePak (doxycycline hyclate); 100 mg per tablet
Applicant/Sponsor Name:	Chartwell Pharmaceuticals LLC
FDA Received Date:	May 14, 2018
OSE RCM #:	2017-1727-2
DMEPA Safety Evaluator:	Sevan Kolejian, Pharm D, MBA
DMEPA Team Leader:	Otto L. Townsend, Pharm D

1 PURPOSE OF MEMORANDUM

The Division of Anti-Infective Products (DAIP) requested that we review the revised container labels and carton labeling for LymePak (doxycycline hyclate), 100 mg per tablet (Appendix A), to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels and carton labeling for LymePak (doxycycline hyclate), 100 mg per tablet is acceptable from a medication error perspective.

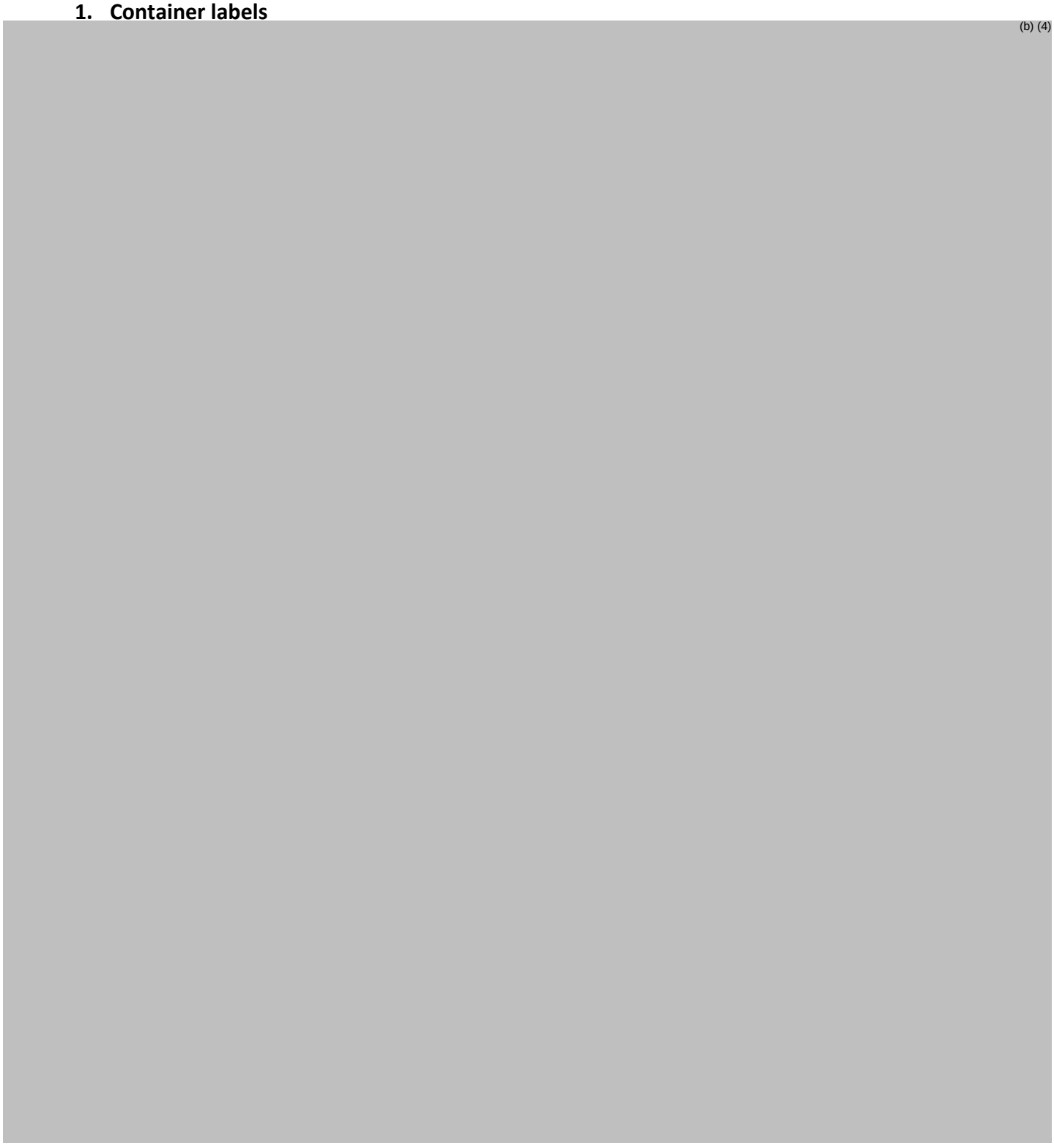
We have no further recommendations at this time.

[a] Kolejian, S. Label and Labeling MEMO for LymePak (NDA 209844). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAY 2. RCM No.: 2017-1727-1.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON MAY 14, 2018

1. Container labels

(b) (4)



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/s/

SEVAN H KOLEJIAN
05/16/2018

OTTO L TOWNSEND
05/16/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
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Division of Pediatric and Maternal Health Review

Date: 5/10/2018 **Date consulted:** 4/11/2018

From: Miriam Dinatale, D.O., Team Leader Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Lynne P. Yao, M.D., OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Anti-Infective Products (DAIP)

Drug: LymePak (doxycycline hyclate, USP) tablets, 100mg

NDA: 209844

Applicant: Chartwell Pharma NDA B2 Holdings, LLC

Subject: Pregnancy and Lactation Labeling

Indication: Treatment of early Lyme disease (as evidenced by erythema migrans) due to Borrelia burgdorferi

Materials Reviewed:

- DPMH consult request for NDA 209844
- Applicant's submission for LymePak (doxycycline hyclate, USP) tablets, 100mg, NDA 209844
- DPMH Review on Xyrosa (doxycycline hyclate) tablets, NDA 209259. Leyla Sahin, MD 2/13/2017.[1]
- Vibramycin approved labeling (reference drug relied upon)

[1] The Xyrosa review was part of the materials reviewed by was not a source relied upon for the labeling recommendations below.

- **Consult Question**: DAIP is requesting comments/edits for proposed labeling recommendations for the pregnancy and lactation related sections in Highlights and the Full Prescribing Information (sections 5.1, 8.1, 8.2, 8.3 and 17).

INTRODUCTION AND BACKGOUND

On August 18, 2017, the applicant (Chartwell Pharma NDA B2 Holdings, LLC) submitted a 505(b)(2) new drug application for LymePak (doxycycline hyclate, USP) for the proposed indication of treatment of early Lyme disease (as evidenced by erythema migrans) due to Borrelia burgdorferi. LymePak is referring to Vibramycin (doxycycline hyclate), NDA 050007 as the referenced drug relied upon.

DAIP consulted DPMH on April 11, 2018 to assist with the Pregnancy and Lactation subsections of labeling.

Doxycycline and Drug Characteristics

Mechanism of action	inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit. Doxycycline has bacteriostatic activity against a broad range of Gram-positive and Gram-negative bacteria.
Molecular weight	1025.89
Half-life	18-22 hours
Protein Binding	readily absorbed and bound to plasma proteins in varying degrees
Serious Adverse Reactions	Discoloration and Enamel Hypoplasia, Clostridium-Difficile associated diarrhea, photosensitivity, severe skin reactions (exfoliative dermatitis, erythema multiforme, Stevens-Johnsons syndrome, toxic epidermal necrolysis), Jarisch-Herxheimer reaction, intracranial hypertension
Other adverse reactions	Anorexia, nausea/vomiting, diarrhea, glossitis, dysphagia, entercolitis, pancreatitis, rash, rise in BUN, hemolytic anemia, thrombocytopenia, neutropenia, eosinophilia

Current State of Labeling for Reference Drug Relied Upon (Vibramycin)

Initial Approval Date	2/6/2008
Labeling Format	Non-Physician Labeling Rule (PLR)
Pregnancy Information	-Warnings section: Information regarding tetracycline class and effects on tooth discoloration during last half of pregnancy. Animal studies demonstrate evidence of embryofetal toxicity. If any tetracycline is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus -Precautions section: includes human information regarding use of doxycycline during pregnancy.
Lactation Information	-notes that short-term use is not contraindicated -Includes the statement: "Because of the potential for serious adverse reactions in nursing infants from doxycycline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother."
Fertility Information	-No effects on animal fertility -Concurrent use of tetracycline may render oral contraceptives less effective.

REVIEW

PREGNANCY

Lyme Disease and Pregnancy

Although several early case reports and small studies suggested a link between maternal Lyme disease and congenital malformations, in particular cardiac malformations, or fetal demise, more recent studies of over 3500 pregnant women and 1500 offspring have not supported an association between treated Lyme disease in pregnancy and adverse fetal outcomes, including congenital malformations, prematurity, intrauterine death or decreased birth weight with Lyme disease occurring within three months before or during pregnancy. Current evidence suggests that there is no definable congenital Lyme disease syndrome.[2, 3,4]

Women with Lyme disease are treated with amoxicillin, cefuroxime, azithromycin or ceftriaxone. Doxycycline, which is the antibiotic of choice for the treatment of Lyme disease in nonpregnant women, is avoided during pregnancy.[5]

Reviewer comment

Although the applicant cited the National Organization for Rare Disorders (2009) and noted that Lyme disease contracted during pregnancy is associated with adverse fetal outcomes, more recent published literature does not support an associated between Lyme's disease and adverse pregnancy outcomes. Therefore, DPMH does not recommend adding a (b) (4) *as proposed by the applicant.*

Nonclinical Experience

No additional animal reproduction studies were performed for this NDA. Please refer to the pharmacology/toxicology review by Tessie Alapatt, PhD for further details.

Applicant's Review of Literature

The applicant conducted a PubMed database search regarding doxycycline and pregnancy. Fifteen articles were found, but the applicant noted that there was no report of specific maternal adverse reactions. The applicant did reference Vibramycin labeling, which describes the results of a case-control study that showed a "weak but marginally statistically significant association with total malformations and use of doxycycline anytime during pregnancy… This association was not seen when the analysis was confined to maternal treatment during the period of organogenesis… with the exception of a marginal relationship with neural tube defect based on only two exposed cases."[6]

[2] Clinical manifestations of Lyme disease in adults. UpToDate. Accessed 4/21/2018.

[3] Lakos A and Solymosi, N. Maternal Lyme borreliosis and pregnancy outcome. Int J Infect Dis. 2010; 14(6): e494-8.

[4] Mullegger, R et al. Skin infections in pregnancy. Clinics in Dermatology. 2016; 34: 368-377.

[5] https://www.cdc.gov/lyme/resources/toolkit/factsheets/10_508_Lyme-disease_PregnantWoman_FACTSheet.pdf. Accessed 4/21/2018

[6] Vibramycin Hyclate (doxycycline hyclate capsules) Labeling: Pregnancy: Teratogenic Effects. Recent labeling approved 2017.

DPMH Review of Literature:

In the DPMH review by Leyla Sahin, MD, [7] the reviewer concluded that:

> "Available published data on doxycycline exposure in the first trimester of pregnancy have not shown a difference in major malformation risk compared to unexposed pregnancies. Permanent discoloration of deciduous teeth following exposure in the second and third trimesters and reversible inhibition of bone growth seen with tetracycline appear to be a theoretical risk with doxycycline."

The reader is referred to the previous DPMH review for details of the published studies that describe doxycycline use during pregnancy. The studies are also summarized in Appendix A. In addition, the reader is referred to the previous DPMH review of doxycycline for a discussion of "Tetracycline effects on fetal teeth and bones and implications for doxycycline."

DPMH conducted a review of the literature using PubMed, and Micromedex[8] using the search terms, "doxycycline and pregnancy and fetal malformations/birth defects/ miscarriage/ spontaneous abortion/stillbirth" from 1/1/2017 to present. The following additional published article was reviewed.

In a population-based cohort study in Quebec, Canada (1998-2008), 139, 938 liveborn singleton infants whose mothers were exposed to antibiotics during the first trimester and who had a major congenital malformation were identified within the first year of life. Of the 15,469 women exposed to antibiotics during the first trimester of pregnancy, 410 were exposed to tetracyclines only and 164 women were exposed to doxycycline. The authors noted that doxycycline exposure increased the risk of circulatory system malformation, cardiac malformations and ventricular/atrial septal defect (aOR 2.38, 95% CI 1.21–4.67, 9 exposed cases; aOR 2.46, 95% CI 1.21–4.99, 8 exposed cases; aOR 3.19, 95% CI 1.57–6.48, 8 exposed cases, respectively).[9]

Reviewer comments:
There have been several studies that have evaluated the effects of doxycycline during pregnancy. A previous study reviewed by DPMH suggested an increased risk of cleft lip with or without cleft palate; however, DPMH was unable to draw a conclusion based on only two exposed cases.[10]
The study by Muanda et al. reviewed above suggests that doxycycline may be associated with an increased risk for cardiac defects. However, the study is limited by small sample size, patients taking other medications (type unknown), and no information regarding tobacco, alcohol or illicit drug use. In addition, although we know that the drug was dispensed, we do not know if the patient actually took the drug.

[7] DPMH Review on Xyrosa (doxycycline hyclate) tablets, NDA 209259. Leyla Sahin, MD 2/13/2017.
[8] Truven Health Analytics information, http://www micromedexsolutions.com/. Accessed 4/4/2018.
[9] Muanda, et al. Use of antibiotics during pregnancy and the risk of major congenital malformations: a population based cohort study. British Journal of Clinical Pharmacology. 2017; 83: 2557-2571.
[10] Molgaard-Nielsen D, Hviid A. Maternal use of antibiotics and the risk of orofacial clefts: a nationwide cohort study. Pharmacoepidemiol Drug Saf. 2012;21(3):246-53.

Although there are two studies that suggest a potential increased risk for fetal malformations with use of doxycycline during pregnancy, both studies have significant limitations. In addition, other larger published studies have not shown an increased risk of major fetal malformation with first trimester use of doxycycline.[11,12,13,14]

LACTATION

Nonclinical Experience

Animal lactation studies were not performed.

Lyme Disease and Lactation

There are no reports of Lyme disease transmission from breast milk.[2]

Applicant's Review of Literature

The applicant relied upon Vibramycin labeling for language included in lactation and did not conduct their own review of published literature.

DPMH Review of Literature:

In the DPMH review by Leyla Sahin, MD[3], the reviewer concluded that:

> "Available limited data show that doxycycline levels in milk are 30-40 % of serum levels; however milk levels were not assessed at steady state, which is 5 half-lives, and equal to 3.5 days. These data may underestimate drug levels in breast milk; therefore DPMH recommends not adding these data to labeling. There are no reports of adverse reactions in breastfeeding infants. There are no data that inform drug levels in milk or the safety following exposure through breastfeeding. Lactation experts recommend avoiding breastfeeding for longer than a month due to the theoretical potential risk of dental staining and inhibition of bone growth."

DPMH conducted a review of the literature using the Drugs and Lactation Database (LactMed),[15] Micromedex, and of the published literature in PubMed using the search terms, "doxycycline and lactation/breastfeeding" from 1/1/2017 to present. There were no additional published studies regarding doxycycline and lactation.

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[11] Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, et al: Antibiotics potentially used in response to bioterrorism and the risk of major congenital malformations. Paediatr Perinat Epidemiol. 2009;23(1):18-28. PMID: 19228311.

[12] Kazy Z, Puho EH, Czeizel AE. Effect of doxycycline treatment during pregnancy for birth outcomes. Reprod Toxicol 2007;24:279-280.

[13] Czeizel AE, Rockenbauer M. Teratogenic study of doxycycline. Obstet Gynecol 1997;89:524-8.

[14] Horne HW Jr, Kundsin RB. The role of mycoplasma among 81 consecutive pregnancies: a prospective study. Int J Fertil 1980;25:315-17.

[15] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

LactMed did have an updated "Summary of Use during Lactation" statement that noted the following:

> "A number of reviews have stated that tetracyclines are contraindicated during breastfeeding because of possible staining of infants' dental enamel or bone deposition of tetracyclines. However, a close examination of available literature indicates that there is not likely to be harm in short-term use of doxycycline during lactation because milk levels are low and absorption by the infant is inhibited by the calcium in breastmilk. Short-term use of doxycycline is acceptable in nursing mothers. As a theoretical precaution, avoid prolonged or repeat courses during nursing. Monitor the infant for rash and for possible effects on the gastrointestinal flora, such as diarrhea or candidiasis (thrush, diaper rash)."

Micromedex[16] notes the following about doxycycline and lactation:

> "Infant risk cannot be ruled out…Conflicting information in regards to the use of doxycycline in lactating women is available. The World Health Organization (WHO) advises to avoid giving doxycycline to lactating women, if possible …The manufacturer suggests that due to the potential for serious adverse reactions in nursing infants from doxycycline, the risks and benefits of therapy must be assessed. Either nursing should be discontinued or doxycycline should be discontinued; the importance of therapy to the mother should be taken into consideration."

The previous DPMH review[3] included conclusions from the American Academy of Pediatrics[17] and Dr. Hale (a breastfeeding expert)[11] which noted that breastfeeding is compatible with use of doxycycline but to limit use to less than four weeks due to the potential for dental staining.

Reviewer comment:
There is no new information regarding doxycycline and use during lactation. Although there are reports of doxycycline being present in human milk, there is not a clear understanding of how much doxycycline will be present. Given LymePak's long half-life and the fact that the drug will be used for 21 days, there is a potential for drug accumulation in human milk and a potential for serious adverse reactions, including tooth discoloration and inhibition of bone growth.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Doxycycline administered orally at dosage levels as high as 250 mg/kg/day had no apparent effect on the fertility of female rats. Effect on male fertility has not been studied.[18] Please refer to the pharmacology/toxicology review by Tessie Alapatt, PhD for further details.

[16]http://www micromedexsolutions.com/micromedex2/librarian/CS/0DE4C2/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/392D64/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/evidencexpert.DoIntegratedSearch?SearchTerm=Doxycycline&fromInterSaltBase=true&false=null&false=null&=null#. Accessed 4/18/2018

[17] American Academy of Pediatrics Committee on Drugs The Transfer of Drugs and Other Chemicals into Human Milk. Pediatrics 2001;108:776-789.

Applicant's Review of Literature

The applicant conducted a PubMed database search regarding doxycycline and infertility and found 91 studies. The applicant noted that "none of the studies reported specific adverse effects of doxycycline to males or female reproductive potential."

DPMH Review of Literature:

In the DPMH review by Leyla Sahin, MD[3], the reviewer concluded that:

> "There are no human data available on doxycycline and infertility effects."

DPMH conducted a review of the literature in PubMed using the search terms, "doxycycline and infertility/fertility/contraception" from 1/1/2017 to present. No additional published studies were located.

Tetracyclines and Oral Contraceptives

Current labeling for tetracyclines includes language about tetracyclines reducing the effectiveness of low dose oral contraceptives. Although a 2001 review by Dickinson et al. notes that individual patients have been identified who have experienced decreases in plasma concentrations of combined OC components when administered tetracyclines,[19] there is a recent published article that suggests that clinical and pharmacokinetic outcomes studies do not support the existence of drug interactions between hormonal contraception and non-rifamycin antibiotics.[20] The December 2017 Labeling for Combined Hormonal Contraceptives Draft Guidance includes a list of drug interactions but does not include tetracycline antibacterials.[21]

Reviewer comment:
DPMH discussed the effects of combined oral contraceptives and tetracyclines with the Division of Bone, Reproductive and Urologic Products (DBRUP) who noted that language about tetracyclines affecting low dose contraceptives is no longer correct based on new data and should be removed from tetracycline labeling. DPMH agrees with this assessment.

DISCUSSION AND CONCLUSIONS

Pregnancy

Since the last DPMH review of doxycycline in February of 2017, there was one additional study that suggested a potential increased risk with use of doxycycline during the first trimester of pregnancy. Overall, there have been several studies that have evaluated the effects of doxycycline during pregnancy. Although there are two studies that suggest a potential increased risk for fetal malformations with use of doxycycline during the first trimester of pregnancy, these studies have limitations as noted above. Other larger published studies have not shown an increased risk of major fetal malformations with first trimester use of doxycycline.

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[18] Applicant's currently proposed labeling for LymePak, NDA 209844. Section 13.1

[19] Dickinson BD et al. Drug interactions between oral contraceptives and antibiotics. 2001. Obstetrics & Gynecology. 98(5;1):853-860.

[20] Simmons, et al. Drug Interactions between non-rifamycin antibiotics and hormonal contraception: a systemic review. American Journal of Obstetrics and Gynecology. 2018. 88-97.

[21] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590673.pdf

Doxycycline is a tetracycline antibiotic, and tetracyclines, as a class, are known to cause staining of primary dentition and reversible inhibition of bone growth in fetuses exposed during the second and third trimesters. Therefore, DPMH agrees with maintaining language in the labeling about the potential for tooth discoloration and reversible inhibition of bone growth.

Lactation

Since the last DPMH review of doxycycline in February of 2017, there is no new information about doxycycline use during lactation. Based on published literature, doxycycline is present in human milk; however, there are no data regarding the drug levels in milk. Based on the drug's half- life (18-22 hours), there is the potential for drug accumulation in human milk. Because of the potential risk of dental staining and inhibition of bone growth and because there are other antibacterial options that are available to treat Lyme disease, DPMH recommends that LymePak is not used during breastfeeding and for five days (5 half-lives) after the last dose.

Females and Males of Reproductive Potential

Since the last DPMH review of doxycycline in February of 2017, there is a new systemic review of literature[20] and a new FDA Guidance on combined hormonal contraceptives[21] that does not support the existence of drug interactions between hormonal contraception and non-rifamycin antibiotics. Given new information in published literature and the recent FDA guidance, DPMH recommends that language about (b) (4) is removed from LymePak labeling. In addition, there is no new information about doxycycline use and effects on fertility. Therefore, subsection 8.3 will be omitted from LymePak labeling.

LABELING RECOMMENDATIONS

DPMH revised sections 5.1, 5.2, 8.1, 8.2, and 17 of LymePak labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling for LymePak (doxycycline)

HIGHLIGHTS OF PRESCRIBING INFORMATION
----------WARNINGS AND PRECAUTIONS----------

- The use of LYMEPAK during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown) and enamel hypoplasia. (5.1, 8.1, 8.4)
- The use of LYMEPAK use during the second and third-trimester of pregnancy, infancy and childhood up to the age of 8 years may cause reversible inhibition of bone growth (5.2, 8.1, 8.4).:

----------USE IN SPECIFIC POPULATIONS----------
Lactation: Breastfeeding is not recommended (8.2)

FULL PRESCRIBING INFORMATION
5 WARNINGS AND PRECAUTIONS
5.1 Tooth Discoloration and Enamel Hypoplasia
The use of drugs of the tetracycline class during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction is more common during long-term use of the drugs, but it has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Advise the patient of the potential risk to the fetus if LYMEPAK is used during the second or third trimester of pregnancy *[see Use in Specific Populations (8.1, 8.4)]*.

5.2 Inhibition of Bone Growth
(b) (4). A decrease in fibula growth rate has been observed in premature infants given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued. Advise the patient of the potential risk to the fetus if LYMEPAK is used during the second or third trimester of pregnancy *[see Use in Specific Populations (8.1, 8.4)]*.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
LYMEPAK, like other tetracycline-class antibacterial drugs, may cause discoloration of deciduous teeth and reversible inhibition of bone growth when administered during the second and third trimester of pregnancy *[see Warnings and Precautions (5.1, 5.2), Data, Use in Specific Populations (8.4)]*. Available data from published studies over decades have not shown a difference in major birth defect risk compared to unexposed pregnancies with doxycycline exposure in the first trimester of pregnancy *(see Data).*There are no available data on the risk of miscarriage following exposure to doxycycline in pregnancy.

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 to 4% and 15 to 20%, respectively.

Data

Human Data

A retrospective cohort study of 1,690 pregnant patients who received doxycycline prescriptions in the first trimester of pregnancy compared to an unexposed pregnant cohort showed no difference in the major malformation rate. There is no information on the dose or duration of treatment, or if the patients actually ingested the doxycycline that was prescribed.

Other published studies on exposure to doxycycline in the first trimester of pregnancy have small sample sizes; however, these studies have not shown an increased risk of major malformations.

The use of tetracycline during tooth development (second and third trimester of pregnancy) can cause permanent discoloration of (b) (4) teeth (yellow-gray-brown). This adverse reaction is more common during long-term use of the drug but has been observed following repeated short-term courses.

Animal Data

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity also has been noted in animals treated early in pregnancy

8.2 Lactation

Risk Summary

Based on available published data, doxycycline is present in human milk. There are no data that inform the levels of doxycycline in breastmilk, the effects on the breastfed infant, or the effects on milk production. Because there are other antibacterial drug options available to treat Lyme disease in lactating women and because of the potential for serious adverse reactions, including tooth discoloration and inhibition of bone growth, advise patients that breastfeeding is not recommended during treatment with LymePak and for 5 days after the last dose.

17 PATIENT COUNSELING INFORMATION

(b) (4)

Advise the patient that LymePak, like other tetracycline-class drugs, may cause permanent tooth discoloration of deciduous teeth and reversible inhibition of bone growth when administered during the second and third trimesters of pregnancy *[see Warnings and Precautions (5.1, 5.2) and Use in Specific Populations (8.1, 8.4)]*.

Lactation

Advise women not to breastfeed during treatment with LymePak and for 5 days after the last dose *[see Use in Specific Populations (8.2)]*

Appendix A: Summary of Published Studies on Doxycycline Use In Pregnancy

Author	Study Design	N doxycycline	N comparator	Findings
Molgaard-Nielsen 2012[10] Denmark	Danish Birth Register Record linkage study to assess risk of orofacial clefts	945 doxycycline or tetracycline exposed	707, 159 unexposed	-Increased risk of cleft lip with or without cleft palate (n=2 exposed cases) Adj OR 7.3;95% CI, 1.81-29.46 -Unable to draw conclusions based on 2 cases of tetracycline and doxycycline
Cooper 2009[11]	Retrospective US cohort study using Tennessee Medicaid claims data	1, 690 1st trimester (1,843 exposed anytime)	3, 400 unexposed 26,649 exposed to other antibiotics	No increased risk of major malformations overall
Kazy 2007[12] Hungary	Case-control study to assess birth outcomes	78	38,073	-Exposure in the 1st or 2nd trimester decreased the preterm birth rate (3.8% in treated group vs. 9.2% in untreated group; adj OR 0.4; 95% CI, 0.4-1.4) -No difference in birth weight
Ceizel 1997[13] Hungary	Case-control	56 exposed	63 unexposed controls (no malformations)	No increased risk of major malformations overall in 1st trimester exposed pregnancies
Horne 1980[14] US	Prospective follow- up of women treated for mycoplasma in the 1st trimester of pregnancy	43	None	No major malformations at birth through 1 year of age
Muanda 2017[9] Canada	Population-based cohort study	164 exposed during the first trimester	15,305 were exposed to other antibiotics during the first trimester	Increased the risk of circulatory system malformation, cardiac malformations and ventricular/atrial septal defect (aOR 2.38, 95% CI 1.21–4.67, 9 exposed cases; aOR 2.46, 95% CI 1.21–4.99, 8 exposed cases; aOR 3.19, 95% CI 1.57–6.48, 8 exposed cases, respectively).

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/s/

MIRIAM C DINATALE
05/09/2018

LYNNE P YAO
05/14/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 2, 2018
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 209844
Product Name and Strength:	LymePak (doxycycline hyclate); 100 mg per tablet
Applicant/Sponsor Name:	Chartwell Pharmaceuticals LLC
FDA Received Date:	April 30, 2018
OSE RCM #:	2017-1727-1
DMEPA Safety Evaluator:	Sevan Kolejian, Pharm D, MBA
DMEPA Team Leader:	Otto L. Townsend, Pharm D

1 PURPOSE OF MEMORANDUM

The Division of Anti-Infective Products (DAIP) requested that we review the revised container labels and carton labeling for LymePak (doxycycline hyclate), 100 mg per tablet (Appendix A), to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

We note that Chartwell has removed the (b) (4) packaging configuration from the proposed labeling and revised the carton labeling for 14 tablet blister card packaging to reflect 3 blister cards per carton to support the 21 day dosing regimen. The revised carton labeling is unacceptable from a medication error perspective. The proposed carton does not reflect the net quantity of the tablets (42 tablets) in the carton nor the total days' supply (21 days). We also note the carton labeling includes the statement, (b) (4) (b) (4)

The inclusion of this statement on this prescription drug product could misleadingly suggest this product does not require a prescription.

3 RECOMMENDATIONS FOR CHARTWELL PHARMACEUTICALS LLC

We recommend the following be implemented prior to approval of this NDA:

Carton labeling

1. Revise the quantity statement "Contains 3 cards each card with: 14 tablets (b) (4) day supply" on the carton labeling to read "Contains (b) (4) 3 cards of 14 tablets) | 21 day supply" per 21 CFR 201.51, to accurately reflect the quantity of tablets in the carton.

2. Delete the statement, (b) (4) from the back panel. The title, (b) (4) (b) (4) Inclusion of this statement could misleadingly suggest this product does not require a prescription.

[a] Kolejian, S. Label and Labeling Review for LymePak (NDA 209844). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 APR 16. RCM No.: 2017-1727.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON APRIL 30, 2018

1. Container labels

(b) (4)

2. Carton labeling

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/s/

SEVAN H KOLEJIAN
05/02/2018

OTTO L TOWNSEND
05/02/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: April 23, 2018

To: Shabnam Naseer, M.D.
Division of Anti-Infective Products (DAIP)

Kristine Park, Regulatory Project Manager, (DAIP)

Abimbola Adebowale, Associate Director for Labeling, (DAIP)

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for LYMEPAK (doxycycline hyclate) tablets, for oral use

NDA: 209844

In response to DAIP's consult request dated October 4, 2017, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for LYMEPAK.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAIP on April 11, 2018, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on August 18, 2017, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

22 pages of draft labeling have been withheld in full as b4 (CCI/TS) immediately following this page

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/s/

DAVID F FOSS
04/23/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	April 16, 2018
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 209844
Product Name and Strength:	LymePak (doxycycline hyclate); 100 mg per tablet
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Chartwell Pharmaceuticals LLC
Submission Date:	August 18, 2017 and November 22, 2017
OSE RCM #:	2017-1727
DMEPA Safety Evaluator:	Sevan Kolejian, Pharm D, MBA
DMEPA Team Leader:	Otto L. Townsend, Pharm D

1 PURPOSE OF REVIEW VS REASON FOR REVIEW

As part of the approval process for LymePak (doxycycline hyclate); 100 mg per tablet, the Division of Anti-Infective Products (DAIP) requested that we review the proposed packaging, label and labeling for areas that may lead to medication errors.

2 1.1 BACKGROUND/REGULATORY HISTORY (IF APPLICABLE) MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B (N/A)
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted packaging, label and labeling, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Division of Anti-Infective Products

Prescribing Information			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Highlights of Prescribing Information/ Dosage and Administration section			
1.	Use of the non-metric unit, pound, to express the Pediatric weight based dose.	It is now customary for medications that are dose based on patient's weight to be expressed in the	Express the pediatric dose in metric units (i.e., mg/kg).

		metric unit Kilogram (kg) as most clinicians are now documenting patient weight using the kilogram unit of measurement. Ensure that patient weights are presented in metric (e.g., kilograms) instead of the British Imperial System pounds to prevent dosing confusions.	
2.	The strength, 100 mg, (b) (4) [redacted]	[redacted] (b) (4)	

Table 3: Identified Issues and Recommendations for Chartwell Pharmaceuticals LLC (entire table to be conveyed to Applicant)

Container Labels			
1.	When folded, the 14 tablet blister card and the [redacted] (b) (4)	[redacted] (b) (4)	[redacted] (b) (4) 14 tablet [redacted] (b) (4) tablet blister cards.
2.	[redacted] (b) (4)		

			(b) (4)
3.	(b) (4)		
Carton Labeling (carton containing (b) (4) blister cards)			
1.	(b) (4)		
2.	(b) (4)		To further identify the outer carton as containing several blister cards and to insure that the correct product and quantity is dispensed, (b) (4) Additionally, 1. To address the risk of dispensing the entire carton, remove (b) (4) from the outer carton labeling. This includes the (b) (4)

			and the "Keep this and all medication out of the reach of children" statement. 2. [redacted], the net quantity statement "14 tablets [redacted] day supply" [redacted] Revise the net quantity statement by using the same net quantity statement that is used on the front and back panels [redacted] Each Card with: 14 Tablets [redacted] Day Supply). 3. Increase the prominence of the net quantity statement and ensure that this statement is prominently displayed on the front, top, and side panels of the carton labeling.

4 CONCLUSION

Our evaluation of the proposed packaging, labels and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to the Applicant so that recommendations are implemented prior to approval of this NDA.

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for LymePak that Chartwell Pharmaceuticals LLC submitted on November 20, 2017 and the listed drug (LD).

Table 4. Relevant Product Information for Listed Drug and LymePak		
Product Name	LymePak	Vibramycin
Initial Approval Date	N/A	NDA # 050007 approved on 12/05/1967
Active Ingredient	doxycycline hyclate	doxycycline hyclate
Indication	Treatment of early Lyme disease (as evidenced by erythema migrans) due to *Borellia burgdorferi*	• Doxycycline is indicated for the treatment of the following infections: ○ Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox, and tick fevers caused by Rickettsiae. ○ Respiratory tract infections caused by Mycoplasma pneumoniae. ○ Lymphogranuloma venereum caused by Chlamydia trachomatis. ○ Psittacosis (ornithosis) caused by Chlamydophila psittaci. ○ Trachoma caused by Chlamydia trachomatis, although the infectious agent is not always eliminated, as judged by immunofluorescence. ○ Inclusion conjunctivitis caused by Chlamydia trachomatis.

		○ Uncomplicated urethral, endocervical, or rectal infections in adults caused by Chlamydia trachomatis. ○ Nongonococcal urethritis caused by Ureaplasma urealyticum. ○ Relapsing fever due to Borrelia recurrentis. Doxycycline is also indicated for the treatment of infections caused by the following gram-negative microorganisms: ○ Chancroid caused by Haemophilus ducreyi. ○ Plague due to Yersinia pestis. ○ Tularemia due to Francisella tularensis. ○ Cholera caused by Vibrio cholerae. ○ Campylobacter fetus infections caused by Campylobacter fetus. ○ Brucellosis due to Brucella species (in conjunction with streptomycin). ○ Bartonellosis due to Bartonella bacilliformis. ○ Granuloma inguinale caused by Klebsiella granulomatis. Because many strains of the following groups of microorganisms have been shown to be resistant to doxycycline, culture and susceptibility testing are recommended. Doxycycline is indicated for treatment of infections caused by the following gram-negative bacteria, when

		bacteriologic testing indicates appropriate susceptibility to the drug: ○ Escherichia coli. ○ Enterobacter aerogenes. ○ Shigella species. ○ Acinetobacter species. ○ Respiratory tract infections caused by Haemophilus influenzae. ○ Respiratory tract and urinary tract infections caused by Klebsiella species. Doxycycline is indicated for treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug: ○ Upper respiratory infections caused by Streptococcus pneumoniae. ○ Anthrax due to Bacillus anthracis, including inhalational anthrax (post-exposure): to reduce the incidence or progression of disease following exposure to aerosolized Bacillus anthracis. When penicillin is contraindicated, doxycycline is an alternative drug in the treatment of the following infections: ○ Uncomplicated gonorrhea caused by Neisseria gonorrhoeae.

		○ Syphilis caused by Treponema pallidum. ○ Yaws caused by Treponema pallidum subspecies pertenue. ○ Listeriosis due to Listeria monocytogenes. ○ Vincent's infection caused by Fusobacterium fusiforme. ○ Actinomycosis caused by Actinomyces israelii. ○ Infections caused by Clostridium species. – In acute intestinal amebiasis, doxycycline may be a useful adjunct to amebicides. – In severe acne, doxycycline may be useful adjunctive therapy. **PROPHYLAXIS** Doxycycline is indicated for the prophylaxis of malaria due to Plasmodium falciparum in short-term travelers (<4 months) to areas with chloroquine and/or pyrimethamine-sulfadoxine resistant strains. (See DOSAGE AND ADMINISTRATION section and Information for Patients subsection of the PRECAUTIONS section.)
Route of Administration	oral	oral
Dosage Form	tablet	capsule
Strength	100 mg	100 mg
Dose and Frequency	- ***Adults*** - Administer 100 mg every 12 hours, for (b) (4) 21 days, (b) (4)	– Adults: The usual dose of oral doxycycline is 200 mg on the first day of treatment (administered 100 mg every 12 hours) followed by a maintenance dose of 100

	[redacted] (b) (4) - [redacted] (b) (4) .	mg/day. In the management of more severe infections (particularly chronic infections of the urinary tract),100 mg every 12 hours is recommended. [redacted] (b) (4) – Uncomplicated gonococcal infections in adults (except anorectal infections in men): 100 mg, by mouth, twice a day for 7 days. As an alternate single visit dose, administer 300 mg stat followed in one hour by a second 300 mg dose. The dose may be administered with food, including milk or carbonated beverage, as required. – Uncomplicated urethral, endocervical, or rectal infection in adults caused by *Chlamydia trachomatis:* 100 mg, by mouth twice a day for 7 days. – Nongonococcal urethritis (NGU) caused by *C. trachomatis* or *U. urealyticum:* 100 mg by mouth,twice a day for 7 days.

		– Syphilis – early: Patients who are allergic to penicillin should be treated with doxycycline 100 mg, by mouth, twice a day for 2 weeks. Syphilis of more than one year's duration: Patients who are allergic to penicillin should be treated with doxycycline 100 mg, by mouth, twice a day for 4 weeks. – Acute epididymo-orchitis caused by *N. gonorrhoeae:* 100 mg, by mouth, twice a day for at least 10 days. – Acute epididymo-orchitis caused by *C. trachomatis:* 100 mg, by mouth, twice a day for at least 10 days. – For prophylaxis of malaria: For adults, the recommended dose is 100 mg daily. For children over 8 years of age, the recommended dose is 2 mg/kg given once daily up to the adult dose. Prophylaxis should begin 1–2 days before travel to the malarious area. Prophylaxis should be continued daily during travel in the malarious area and for 4 weeks after the traveler leaves the malarious area. – Inhalational anthrax (post-exposure): ▪ ADULTS: 100 mg of doxycycline, by mouth, twice a day for 60 days. ▪ CHILDREN: weighing less than (b) (4) (45 kg); (b) (4) (b) (4) (2.2 mg/kg) of body weight by mouth, twice a day for 60 days. Children weighing (b) (4) or more should receive the adult dose.

How Supplied	NDC # 62135-596-01: is supplied as a child-resistant blister card containing 14 tablets (b) (4)	*100 mg doxycycline capsules* bottles of 50 (b) (4)
Storage	Store at 20°C to 25°C (68°F to 77°F) excursions permitted to 15° to 30°C (59° to 86°F)	Stored below 86°F (30°C) and dispensed in tight, light-resistant containers (USP).
Container Closure	carton containing child resistant blister card	bottles

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following LymePak labels and labeling submitted by Chartwell Pharmaceuticals LLC on November 20, 2017.

- Container label
- Carton labeling
- Prescribing Information (Image not shown) See EDR: \\cdsesub1\evsprod\nda209844\0002\m1\us\draft-labeling-text.doc

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.


(b) (4)


(b) (4)


(b) (4)

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/s/

SEVAN H KOLEJIAN
04/16/2018

OTTO L TOWNSEND
04/16/2018