CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207844Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

Division of Anti-Infective Products
Clinical Microbiology Review

NDA: 207844

Date Company Submitted: 06/19/2014
Date received by CDER: 06/19/2014
Date Assigned: 08/15/2014
Date Completed: 11/21/2014
Reviewer: Lynette Y. Berkeley

NAME AND ADDRESS OF APPLICANT:

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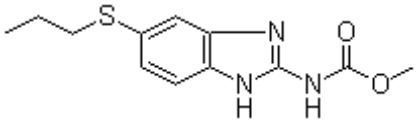
DRUG PRODUCT NAME

Proprietary: Albenza
Established: Albendazole
Chemical name: (5-(propylthio)-1H-benzimidazol-2-yl)carbamic acid methyl ester

Chemical Structure



Molecular formula: $C_{12}H_{15}N_3O_2S$
Molecular weight : 265.34 Da

PROPOSED INDICATION

Treatment of neurocysticercosis and hydatid disease.

PROPOSED DOSAGE FORM, STRENGTH, ROUTE OF ADMINISTRATION AND DURATION OF TREATMENT

Dosage form: Tablets
Route of Administration: Oral
Dosage: (b) (4)
Strength: 200 mg.
Duration of treatment: (b) (4)

DISPENSED:

Rx

RELATED DOCUMENTS:

NDA # 20666

REMARKS:

This protocol for the treatment of neurocysticercosis and hydatid disease does not have any microbiology attached to the submission . The objective is to assess bioequivalence between two formulations of albendazole -chewable tablets and tablets (swallowed) both at 200 mg.

SUMMARY

This is a 505 (b) (1) application that concerns the drug Albenza (albendazole). Albenza is a synthetic drug belonging to the class of broad spectrum antiparasitic drugs called the benzimidazoles which are active against helminthes and protozoa.
The objective of this application is to show bioequivalence between two formulations of the drug – chewable tablets and the approved tablets that can be swallowed . The concentration of the drug is 200 mg.

The indications are for neurocysticercosis caused by infection with *Taenia solium* and hydatid disease caused by *Echinococcus granulosus*.
The mechanism of action of the drug Albenza is that it inhibits the production of energy by the adult and larval forms of the parasites causing the parasite to eventually die. Resistance is caused by mutations in the β-tubulin protein to which the drug binds.

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1. INTRODUCTION

This ia a 505(b)(1) Albenza (albendazole) is a synthetic drug belonging to the class of broad spectrum antiparasitic drugs called the benzimidazoles active against helminthes and protozoa.
Albenza has been approved for the treatment of the larval forms of the pork tape worm *Tinea solium* in neurocysticerosis and the larval forms of the dog tapeworm *Echinococcus granulosus* but is used as an investigational drug for many other parasitic diseases. The primary metabolite albendazole sulfoxide is responsible for the antihelmintic activity.

This protocol for the treatment of neurocysticercosis and hydatid disease does not have any microbiology attached to the submission . The objective is to assess bioequivalence between two formulations of albendazole-chewable tablets and tablets (swallowed) both are administered at 200 mg. so that the chewable tablet can be used as a therapeutic equivalent.

2. BACKGROUND

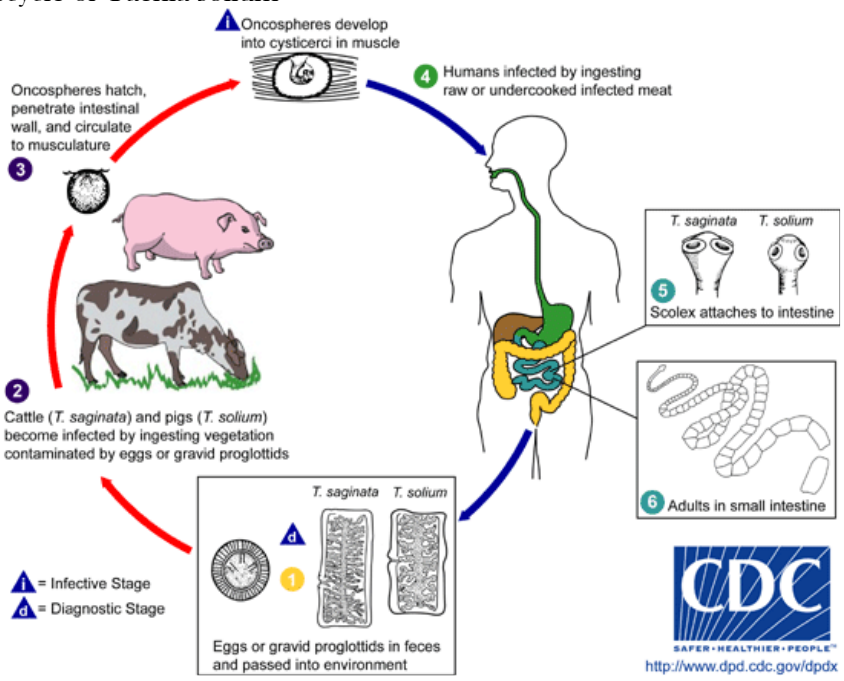
The NDA for Albenza Tablets was approved by FDA in 1996. Orphan drug status was granted by the Office of Orphan Products Development on January 17 and January 18, 1996 , for the indications approved under NDA 20666 which are the same for NDA 207844. No additional safety or efficacy data were collected for either the NDA 20666 or this NDA 207844. This NDA is cross-referenced with NDA20666. Microbiology was submitted Dec 8, 1995 of NDA 20666 vol.1.103 – 1.106

3. IN VITRO INFORMATION

3.1 Pork tapeworm – Neurocysticercosis

Albenza (albendazole) is indicated for the treatment of parenchymal neurocysticercosis due to active lesions caused by larval forms of the pork tapeworm, *Taenia solium.* Humans are infected by eating uncooked pork with cysterici. The larvae live in the small intestine and attach to the mucosa by four scolex (head). After approximately 2 months post infection, segments (proglottids) begin to detach from the distal end of the worm and are excreted in the feces. Each proglottid may have as many as 50, 000 eggs. Figure 1 shows the lifecycle of *Taenia solium.*
Lesions considered responsive to albendazole therapy appear as nonenhancing cysts with no surrounding edema on contrast-enhanced computerized tomography. Clinical studies in patients with lesions of this type demonstrate a 74% to 88% reduction in number of cysts; 40% to 70% of albendazole-treated patients showed resolution of all active cysts

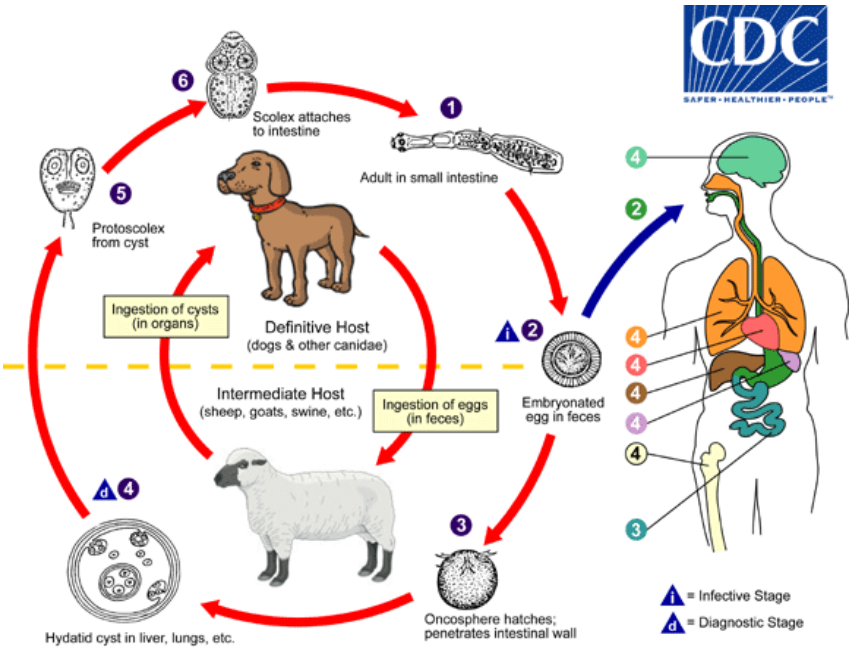
Figure 1: Lifecycle of *Taenia solium*



3.2 Echinococcus granulosus -*Hydatid disease*

The efficacy of albendazole in the therapy of alveolar hydatid disease caused by *Echinococcus granulosus*. This parasite is also a tapeworm. Disease is caused by the ingestion of infectious eggs from the feces of sheep and dogs.

Figure 2: Lifecycle of *Echinococcus granulosus*



4. NON-CLINICAL INFORMATION

4.1 Antimicrobial spectrum of activity

active against the larval forms of the following organisms:

Cestodes	Nematodes
Echinococcus granulosus	*Ascaris lumbricoides,*
	Taenia solium,
	Necator americanus/Ancyclostoma duodenale, Trichuris trichuria,
	Giardia lamblia
IntestinalProtozoa	*Loa Loa,*
Microsporidium spp.	*Enterobius vermicularis*
Intestinal Ascarid	
Toxocara spp.	

5. MECHANISM(S) OF ACTION

Albenza binds to the colchicine-sensitive site of ß-tubulin inhibiting their polymerization into microtubules. The decrease in microtubules in the intestinal cells of the parasites decreases their absorptive function, especially the uptake of glucose by the adult and larval forms of the parasites, and also depletes glycogen storage. Insufficient glucose

results in insufficient energy for the production of adenosine triphosphate (ATP) and the parasite eventually dies.

6. MECHANISM(S) OF RESISTANCE

Parasitic resistance to albendazole is caused by changes in amino acids that result in changes in the β-tubulin protein. This causes reduced binding of the drug to β-tubulin.

7. REFERENCES

1. Centers for Disease Control and Prevention (CDC). (2013) Parasites – enterobiasis (also known as pinworm infection): epidemiology and risk factors; www.cdc.gov/parasites/ pinworm/epi.html accessed September 26, 2013.
2. Centers for Disease Control and Prevention (CDC). (2013) Parasites – trichuriasis (also known as whipworm infection); www.cdc.gov/parasites/whipworm/index.html accessed September 26, 2013.
3. Cook, G. C. (1994) *Enterobius vermicularis* infection. Gut. 35:1159-1162.
4. Harhay MO, Horton J, Olliaro PL. (2010) Epidemiology and control of human gastrointestinal parasites in children. Expert Rev Anti Infect Ther. 8(2):219-234.

Lynette Y. Berkeley, Ph.D., M.T. (A.S.C.P.)
Microbiologist,
DAIP,
Nov. 22, 2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LYNETTE Y BERKELEY
12/01/2014

KERRY SNOW
12/01/2014

MEMORANDUM

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

DATE: 13 November 2014

TO: NDA 207844

FROM: Erika Pfeiler, Ph.D.
Microbiologist
CDER/OPS/NDMS

THROUGH: Stephen Langille, Ph.D.
Senior Review Microbiologist
CER/OPS/NDMS

cc: Gregory DiBernardo
Senior Regulatory Health Project Manager
CDER/OND/OAP/DAIP

SUBJECT: Product Quality Microbiology assessment of Microbial Limits for Albenza Chewable Tablet [Submission Date: 11 August 2014]

The NDA for Albenza Chewable Tablets proposes a waiver for microbial limits testing for product release, and the applicant provides a suitable rationale for the exclusion of this testing. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

The drug product is a chewable tablet for oral administration, and is packaged [redacted] (b) (4) in [redacted] (b) (4) blister packs.

The applicant proposes a waiver of microbial limits testing for product release, and presents information related to the product manufacturing, microbiological specifications for excipients, finished [redacted] (b) (4) to support this proposal. The product is manufactured with a [redacted] (b) (4) [redacted] (b) (4) The applicant states that environmental monitoring is performed at the manufacturing site. Acceptance criteria were provided for the drug product excipients, and all were generally within limits described in USP <1111> for nonaqueous preparations for oral use. Finished product [redacted] (b) (4) when packaged [redacted] (b) (4) in blister packs.

The applicant has not performed microbial limits testing on the product to date, but commits to

performing tests on upcoming process validation batches and providing the results in an annual report. Additionally, the applicant commits to performing microbial limits at the initial stability time point for commercial batches. The drug product will be tested for microbial limits using a method consistent with USP Chapter <61> (Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests) and <62> (Microbiological Examination of Non-sterile Products: Tests for Specified Microorganisms). These methods will be verified for use with the drug product.

The Microbial Limits acceptance criteria are consistent with USP Chapter <1111> (Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use).

ADEQUATE

Reviewer Comments – The applicant's proposal to waive microbial limits testing for product release is acceptable.

Filing Communication Information Request
Your application proposes a waiver of microbial limits testing for drug product release and stability. Your proposal may be acceptable; however, more information on your process and controls is needed. Address the following points:

1. *Identify and justify critical control points in the manufacturing process that could affect* [redacted] (b) (4) *of the drug product, including the* [redacted] (b) (4)

2. *Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.*

    a. *Your application provides a list of excipients for which microbiological testing is performed by your supplier, but you do not provide acceptance criteria. Provide the microbiological acceptance criteria for these excipients.*

3. *Describe activities taken when microbiological acceptance criteria are not met at control points.*

In addition to these points, address the following:

1. *Provide the results of microbial limits testing performed on exhibit or stability batches of the drug product.*

2. *Your application states that historical data from the lead product Albenza® supports a low risk of microbiological growth. These data may be used to support a waiver of microbial limits testing for the chewable tablets, but you should provide these data and a rationale for why they are adequate to represent the microbiological risks of the chewable tablet.*

3. *Verify the suitability of any microbiological testing methods for use with your drug product.*

4. *You should minimally perform microbial limits testing at the initial stability testing time point. Provide an updated stability schedule to reflect this testing.*

MEMORANDUM

06 November 2014 Response

The applicant provided a response, which was incorporated into the text of the review. A follow-up information request was sent to clarify the method used for microbial limits testing.

07 November 2014 Information Request

Your 05 November 2014 information request response contains information to support a waiver of microbial limits release testing for your drug product. You state that microbial limits testing will be performed on process validation batches and stability batches using methods described in USP (b) (4) *Microbial limits testing is typically performed using methods described in USP <61> and USP <62>. Clarify which methods you will use for microbial limits testing.*

12 November 2014 Response

The applicant clarified that USP <61> and <62> will be used for microbiological testing.

END

MEMORANDUM

Erika A. Pfeiler -S

Digitally signed by Erika A. Pfeiler -S
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Date: 2014.11.13 10:15:32 -05'00'

Stephen E. Langille -A

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