CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207987Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABELS 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:	June 7, 2018
Requesting Office or Division:	The Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 207987
Product Name and Strength:	Ablysinol (Dehydrated Alcohol) injection, USP, Each mL contains ≥ 99 % by volume ethyl alcohol
Applicant/Sponsor Name:	Belcher Pharmaceuticals LLC. (Belcher)
FDA Received Date:	May 25, 2018
OSE RCM #:	2018-6-1
DMEPA Safety Evaluator:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the revised Ablysinol container labels and carton labeling (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 labels and labeling review.[a]

2 CONCLUSION

Belcher implemented the majority of our previous recommendations for the container labels and carton labeling, except for our recommendation to remove the (b) (4) statement from the container labels and carton labeling. Therefore, we provide the recommendation again in section 3 below. We also have recommendations related to the strength expression on the container labels and the route of administration presentation on the container labels and carton labeling to help promote the safe use of Ablysinol.

[a] Thomas S. Labels and Labeling Review for Ablysinol (NDA 207987). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 APRIL 23. RCM No.: 2018-6.

3 RECOMMENDATIONS FOR BELCHER PHARMACEUTICALS

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

A. Container Labels and Carton Labeling

1. Remove the [redacted] (b) (4) statement from the container labels and carton labeling to ensure consistency with storage information provided in the Prescribing Information.
2. We note inconsistency in the presentation of the route of administration on the container labels and carton labeling versus in the Prescribing Information. Revise the route of administration on the container labels and carton labeling from [redacted] (b) (4) to "For Cardiac Septal Branch Intra-Arterial Use."

B. Container Labels

1. Revise the strength expressions on the container labels (e.g., 1 mL ≥99% by volume ethyl alcohol; 5 mL ≥99% by volume ethyl alcohol) to be consistent with the strength expression on the carton labeling (e.g., 1 mL **of** ≥99% by volume ethyl alcohol; 5 mL **of** ≥99% by volume ethyl alcohol). (Bolding and underlining intended to show the requested change and not for implementation.)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SARAH E THOMAS
06/07/2018

CHI-MING TU
06/07/2018

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Memo

Date:	05/23/2018
Reviewer(s):	Marie Bradley, PhD, MSc.PH, MPharm Division of Epidemiology II
Acting Team Leader:	Efe Eworuke, PhD Division of Epidemiology II
Division Director:	Lockwood Taylor, PhD Division of Epidemiology II
Subject:	ARIA Sufficiency Memo
Drug Name(s):	Dehydrated Alcohol (Ablysinol)
Application Type/Number:	NDA 207987
Applicant/sponsor:	Belcher Pharmaceutics, LLC
OSE RCM #:	2018-5

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	X
-No	
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	
-Exposure	
-Outcome(s) of Interest	
-Covariate(s) of Interest	
-Surveillance Design/Analytic Tools	

A. General ARIA Sufficiency Template

1. BACKGROUND INFORMATION

1.1. Medical Product

Dehydrated alcohol is used in percutaneous transluminal septal myocardial ablation (PTSMA), a procedure used to induce controlled cardiac septal myocardial infarction. PTSMA is indicated to improve (b) (4) exercise capacity in patients with symptomatic, (b) (4) in hypertrophic obstructive cardiomyopathy (HOCM). HOCM occurs when the myocardium of the heart becomes abnormally thick, defined as > 1.5 cm without an identifiable cause. The main causes of LV hypertrophy include long-standing hypertension, amyloidosis, aortic stenosis. HOCM most commonly presents in the second or third decade of life, but may present at any age. It is the most frequent cause of stress-induced syncope or sudden cardiac death in patients aged less than 30 years old.[1] Therapeutic approaches aim to reduce the extent of the outflow tract obstruction, thus improving clinical symptoms.

PTSMA, a nonsurgical technique, introduced by Professor Ulrich Sigwart at the Royal Brompton Hospital, UK, in 1994, [2] involves injection of 1 to 4 mL of 96% ethanol, over 5-10 minutes, into the first septal perforator branch of the coronary artery. This produces a localized basal septal myocardial infarction in the area overlying the left ventricular outflow tract ultimately remodeling the outflow tract. Currently unapproved dehydrated alcohol is utilized in all PTMSA procedures conducted in the US.[3]

Belcher Pharmaceuticals, LLC (Belcher) submitted the 505(b)(2) literature-based New Drug Application (NDA) 207987 for Ablysinol (Dehydrated Alcohol Injection, USP) on February 12, 2015. They intended to develop dehydrated alcohol for use in PTSMA, in patients with (b) (4) symptomatic hypertrophic obstructive cardiomyopathy (HOCM). On December 9, 2016, Belcher received a Complete Response Letter (CRL) due to chemistry, manufacturing, and controls (CMC) issues. A resubmission followed on December 22nd 2017.

The literature-based application was supported by 38 studies on various aspects of PTMSA efficacy and safety: 4 randomized controlled trials (RCTS), 3 meta-analyses, 1 systematic review, and 30 retrospective studies. Most retrospective studies showed improvement in subjective and objective measures of functional capacity after PTMSA. However, the over-riding concern is the lack of prospective randomized trial safety data and the limited safety data reported in the literature.

1.2. Describe the Safety Concern

The Division of Cardiovascular and Renal products (DCRP) are concerned that approval of Ablysinol might result in aggressive marketing of the product by the sponsor. This in turn may result in more PTSMA procedures being conducted by inexperienced physicians and lead to an increased complication rate.

Prior to the advent of PTSMA in 1994, septal myectomy, a type of open-heart surgery, which involves removal of a portion of the septum obstructing the flow of blood from the left ventricle to the aorta,

was the gold standard treatment for symptomatic HOCM. However, as PTSMA avoids the recovery time with loss of work, residual discomfort, and anxiety associated with myectomy surgery it was enthusiastically embraced and heavily promoted by many clinicians and interventional cardiologists.[3] Nevertheless, the American College of Cardiology and the European Society of Cardiology stated that: (1) surgical myectomy is the preferred (gold standard) and safest septal reduction procedure for most severely symptomatic obstructive HOCM patients, and (2) PTSMA is not regarded as the primary treatment option for such patients with a similar severity but rather as a useful, alternative to myectomy for patients of advanced age, patients at high operative risk as a result of important comorbidities, or those with a strong personal preference to avoid surgery.[4] However, the degree to which the guidelines have influenced practice patterns is uncertain, and a mismatch between the two is likely. A major factor contributing to the high volume of PTSMA procedures is the limited number of centers with sufficient surgical expertise for septal myectomy.[5]

Both PTSMA and myectomy are associated with non-fatal procedural complications such as heart block requiring permanent pacemaker insertion, arrhythmias such as ventricular fibrillation (VF), bradycardia and asystole, and myocardial infarction. However, much attention has been given to the heart block produced by the administration of alcohol, during PTSMA as the septal perforator artery serves the conduction system. Transient heart block is common in up to 50% of patients in the first 24 hours after PTSMA, and permanent complete heart block, requiring lifelong permanent pacemaker dependency, is reported in around 10% to 15% of patients. Permanent pacing, however, is a very rare consequence of myectomy surgery.[6]

Sorajja et al, in a study conducted in a tertiary hypertrophic cardiomyopathy referral center, reported that the procedural complication rate associated with PTSMA exceeded that of myectomy. The combined rate of post-procedural ventricular arrhythmia, pacemaker insertion, tamponade, and death in the myectomy patients was 5% compared to 26% among those who had PTSMA, ($p<0.001$). In this study, one patient developed VF after myectomy and compared to four after PTSMA. Three patients developed complete heart block and required permanent pacemaker implantation after myectomy compared with twenty eight patients after PTSMA.[7]

Some studies have reported that overall procedural mortality is largely similar between the two interventions, although other reports suggest a higher death rate with PTSMA compared to myectomy at the most experienced centers.[8] However, such comparisons between surgery and PTSMA are difficult, given the likely differences in operator expertise and patient selection. For example, PTSMA is performed in a multitude of individual laboratories with diverse (and sometimes limited) experience, but outcome data are reported only from the few most established centers and practices. Therefore, the true PTSMA-related complication rate is not known. Procedure inexperience also promotes a lower likelihood of success and an increased complication risk. [3]

- FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

1.3. Statement of Purpose

The purpose of the proposed descriptive safety assessment is to answer the questions: "Is there an increase in the number of PTSMA procedures being conducted after the approval of Ablysinol and have the rates of PTSMA associated non-fatal complications, repeat procedures and mortality increased after approval?" DCRP anticipate that approval of the product and subsequent marketing by the sponsor may increase the number of procedures being conducted, especially among less experienced practitioners, which may increase complication rates, mortality and repeat procedure rates. We will not be conducting direct comparisons between PTSMA and myectomy surgeries as we are interested in changes in PTSMA procedures only. To answer these questions, we will examine numbers of PTSMA procedures conducted from 30 June 2013- 30 June 2018 (before approval of Ablysinol), and after approval (01 July 2018+). The crude rates of the most common complications of PTSMA, all-cause mortality rates and repeat procedure rates (see table 1 below) will be examined both before and after approval.

Table 1. Study outcomes

Outcomes
1. Number of PTSMA procedures conducted before and after the approval
2. Hospitalization for a new ventricular arrhythmia up to one year after the index PTSMA procedure.
3. Hospitalization for new episode of heart failure up to one year after the index PTSMA procedure.
4. New episode AV block (categorize as 1st, 2nd [type 1 or 2], or 3rd degree AV block) up to 30 days after the index alcohol ablation procedure.
5. Any repeat alcohol ablation procedure, septal myectomy surgery or permanent pacemaker placement, up to one year after the index PTSMA procedure.
6. Mortality up to one year after the index PTSMA procedure.

1.4. Effect Size of Interest or Estimated Sample Size Desired

Given only crude incidence rates are to be calculated, a desired sample size is not relevant.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

The surveillance population will include patients over the age of 18 with a procedure or diagnosis code for PTSMA. Despite increasing popularity compared to myectomy, PTSMA is still a rare procedure. To help us understand how rare the procedure is, a preliminary count of ICD 9 procedure codes and current procedural terminology (CPT) codes for PTSMA, occurring between 2000-2015, in the Sentinel Distributed Database (SDD), were obtained (See table 2) (Note ICD-9 Procedure code: 37.34 will be combined with ICD-9- diagnosis code 425.1 hypertrophic cardiomyopathy, according to an algorithm used to identify PTSMA in a recently published study[9]). Therefore, the count shown in Table 2 reflects only 37.34 alone not in combination with 425.1. The combination is expected to result in a much smaller code count. DCRP were satisfied with the number of procedures identified using CPT codes and the ICD 10 procedure code.

Table 2. Code counts for PTSMA procedures conducted from 2000-2015, in the SDD.

Codes and description	Code counts 2000-2015
ICD-9 Procedure code: 37.34 Excision or destruction of other lesion or tissue of heart, endovascular approach	245,993
ICD-10 Procedure codes: 025M3ZZ Destruction of Ventricular Septum, Percutaneous Approach and	119
CPT code: 93583 Percutaneous transcatheter septal reduction therapy (eg, alcohol septal ablation) including temporary pacemaker insertion when performed	650

2.2 Is ARIA sufficient to assess the intended population?

ARIA was judged to be sufficient to assess the intended population. Based on the preliminary search in the SDD, described above, we identified an adequate number of PTSMA procedures using ICD 10 procedure codes and CPT codes to proceed with a study. A recent study using the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project Nationwide Inpatient Sample (NIS), a national inpatient database applied a combination of (ICD-9-CM) procedure code 37.34 for PTSMA and ICD-9 diagnosis code 425.1 for hypertrophic cardiomyopathy to identify PTSMA procedures.[9] We will also apply this in our study and anticipate that we identify additional procedures in this way. To examine the accuracy of our coding approach for identification of PTSMA procedures in the SDD we have arranged a consultation with expert procedure coders at (b) (4) which is a specialist and training center for PTSMA. No studies have been conducted to test the validity of our approach for identifying PTSMA procedures in US claims databases, given the procedure is rare.

EXPOSURES

2.3 Treatment Exposure(s)

The exposure is PTSMA which involves the use of dehydrated alcohol injection. Procedures conducted before Ablysinol approval date will have used regular unregulated dehydrated alcohol but after that date there may be a mix of Ablysinol and unregulated dehydrated alcohol use.

2.4 Comparator Exposure(s)

There will be no comparator exposure since the objective of the study will be to study changes in the number of procedures performed and to provide incidence rates for the outcomes (Table 1) before and after Ablysinol approval.

2.5 Is ARIA sufficient to identify the exposure of interest?

Yes, ARIA was judged to be sufficient. See section 2.2.

3 OUTCOME(S)

3.1 Outcomes of Interest

As discussed in section 1.2, PTSMA is associated with a number of non-fatal complications and mortality. The most important of these complications are listed below and will be included as outcomes in this study:

1. Hospitalization for a new ventricular arrhythmia up to one year after the index PTSMA procedure.
2. Hospitalization for new episode of heart failure up to one year after the PTSMA procedure.
3. New episode AV block (categorized as 1st, 2nd [type 1 or 2], or 3rd degree AV block) up to 30 days after the index PTSMA procedure.

4. Mortality up to one year after the index PTSMA procedure.

Given that DCRP are concerned about a possible increase in the number of PTSMA procedures conducted by inexperienced practitioners after Ablysinol approval we will also examine:

5. Any repeat PTSMA procedure, septal myectomy surgery or permanent pacemaker insertion, up to one year after the index PTSMA procedure.
6. Number of PTSMA procedures conducted before and after the approval

Outcome rates will first be assessed both in the Ablysinol pre-approval period (June 2013-June 2018) and after approval (July 2018+).

3.2 Is ARIA sufficient to assess the outcome of interest?

Heart Failure

Yes. A systematic review on the validity of heart failure (HF) diagnoses in administrative databases, published in 2014 described nineteen validation studies published from 1999–2009.[10] Nine of the studies (47%) were from the United States, six (32%) were from Canada, three (16%) from Europe, and one was from Australia. HF was determined in the individual studies using ICD-9 428, and ICD-10 I50 codes. Specificity for HF was >95% in all studies and PPV was >87% in the majority. However, sensitivity was lower at ≥ 69% in around half of the studies. In a meta-analysis of the 11 studies reporting sensitivity and specificity values, the pooled sensitivity was 75.3% (95% CI: 74.7–75.9) and specificity was 96.8% (95% CI: 96.8–96.9). A US based study (not included in the systematic review described above)[11] examined the validity of CMS Medicare HF diagnostic codes against medical records for those enrolled in the Atherosclerosis Risk in Communities (ARIC) study. Within matched records, HF diagnostic codes from CMS Medicare showed excellent agreement with HF diagnostic codes obtained from medical record abstraction. Specifically, ICD-9 code 428 showed a PPV for acute decompensated HF with a diagnosis in the primary position of 87.3% 95% CI (86.6, 88.1) and specificity was 98.3% (97.9, 98.6). These PPVs for heart failure ICD 9 and 10 codes are deemed acceptable therefore ARIA is judged as sufficient to determine HF.

Ventricular fibrillation

Yes. Ventricular fibrillation is indicated by ICD 9 code 427.4 and ICD 10 code 149.0. A systematic review of validation studies for identifying ventricular arrhythmias, using administrative and claims data, published in 2012, [12]found that among the nine identified studies the use of ICD-9 code 427.x alone in the principal position was appropriate for the identification of ventricular arrhythmias in claims databases. Of the nine studies, one evaluated claims data from a national health insurance company, two evaluated private state/local health plans, while the remaining evaluated Medicare and Medicaid databases. The use of ICD-9 code 427.x alone yielded high PPV in the studies ranging from 78%–100%. A higher PPV was seen when both ICD-9codes 427.x and 798.x (sudden cardiac death) were used in combination (92%). The same codes yielded the highest PPV when found in the principal diagnosis position (100%). ICD 10 codes were not evaluated in the review, however, trend analyses to evaluate algorithm performance in identifying atrial fibrillation (AF), another cardiovascular arrhythmia, across ICD 9 and 10 data eras, in the SDD, showed that the prevalence

trend pre- and post- transition was consistent. This indicates that the prevalence of AF remained constant across time irrespective of using either ICD 9 or 10 codes. ARIA is therefore judged as sufficient to determine VF.

AV block

Yes. AV block is indicated by ICD 9 code 426.0 and ICD 10 code I44.2. First degree AV block is indicated by ICD 9 code 426.11 and ICD 10 code I44.0 , second degree heart block type I is indicated by ICD 9 code 426.13 (Mobitz type I) and second degree heart block type II 426.12 (Mobitz type II) and ICD 10 code 144.1, third degree heart block is indicated by ICD 9 code 426.0 and ICD 10 code 144.2. There have been no previous validation studies conducted in US claims databases for AV block. However, a previous study[13] used ICD 9 codes to identify AV block in a large inpatient database from Veterans administration hospitals. Given that the key focus of this study is related to changes in complication rates and number of procedures before and after approval of Ablysinol the validity of outcome ascertainment is not as critical and is unlikely to change across the study period. DCRP have been made aware of and accept that there may be a level of error in outcome ascertainment given the absence of validation studies. A cardiologist from DCRP will assist with reviewing the outcome codes to help ensure that the most accurate ascertainment algorithm will be applied. Therefore, ARIA is sufficient.

Permanent pacemaker insertion

Yes. Permanent pacemaker insertion (PPI) can be identified in claims databases using a combination of ICD diagnosis and procedure codes, HCPCS codes and CPT codes (Table 2). A previous study has identified PPI in Truven MarketScan database from 2009-2013 using a mixture of these codes [14]. However, no studies to date have validated the approach. Given that PPI is an expensive procedure, it might be expected that records of these in claims databases would be highly reliable. As stated above given the focus of this study is change in outcome rates and numbers of procedures conducted the validity of the outcome may be less important and so ARIA judged to be sufficient.

Table 2. Codes to identify PPI in claims databases.

Primary Permanent pacemaker insertion
CPT codes
33216
33217
33206
33207
33208
ICD diagnosis codes
ICD 9 V45.01
ICD 10 Z95.0
ICD procedure codes
ICD-9 proc 37.96
ICD 10 proc 0JH636Z
ICD 10 proc 02H63JZ
ICD 10 proc 2HK3JZ
HCPCS codes
C1785

C1786
C2619
C2620

Septal myectomy

To date no study has validated codes for septal myectomy in US claims databases. One study[9] used a combination of ICD 9 procedure code 37.33 "excision or destruction of other lesion or tissue of heart, open approach" and ICD 9 diagnosis code 425.1 "Hypertrophic cardiomyopathy" to identify septal myectomy among those with HOCM in a national inpatient database. As explained above the absence of validation studies is not a major limitation given the focus, in this study, of examining changes in outcomes rates across time.

Mortality

All-cause mortality will be determined using a combination of ICD 9 and 10 codes. A previous study[15] which validated sudden death (SD) diagnoses in Medicare and Medicaid data against medical records, using ICD 9 codes 798, 798.1 and 798.2, found that SD claims codes had a high PPV for verbatim statement of SD or cardio-respiratory arrest (96.9% 95% CI 89.3–99.6), and also a high PPV for first-listed SD diagnosis (92.3%).[15]

A recent study[16] aimed at developing algorithms for identifying fatal cardiovascular disease in Medicare Claims linked Medicare claims to the reasons for geographic and racial differences in stroke (REGARDS) study. Events adjudicated by the REGARDS study investigators were used as the gold standard. Using a cut-point that provided the closest observed-to-predicted number of fatal CVD events, a specificity of 0.90 (95% CI 0.88-0.91), PPV of 0.65 (95%CI 0.61-69) and sensitivity of 0.64 (95%CI 0.61, 0.68) for fatal CVD events recorded in Medicare was reported.

An FDA study, which is currently under review by a peer review journal, evaluated the feasibility of using all-cause and cause-specific mortality as outcomes for pharmacoepidemiologic studies in the SDD. Rates of all-cause mortality and rates and proportional mortality for completed suicide, among the participating data partners of the SDD, from 2004 to 2012, were calculated, and compared to national estimates exported from the CDC Wide-ranging ONline Data for Epidemiologic Research (CDC WONDER), an online query tool maintained by CDC, which provides public access to datasets covering a variety of public health research topics, including Cause of Death among US residents.[17] It was found that data partner-level death and suicide rates were generally similar to national estimates within age and sex subgroups and that, among participating data partners, Sentinel appeared well suited investigation of all-cause mortality as a safety outcome.

4 COVARIATES

4.1 Covariates of Interest

The purpose of this analysis is to calculate crude rates for the outcomes of interest, and therefore no formal statistical covariate adjustment will be required. However, stratification of rates by factors prognostic for the study outcomes, such as age at first PTSMA procedure, gender, comorbidities, and previous invasive cardiac treatment may be calculated.

5 SURVEILLANCE DESIGN / ANALYTIC TOOLS

5.1 Surveillance or Study Design

A retrospective longitudinal cohort study design will be used to calculate crude incidence rates for the outcomes. The cohort will comprise all patients who have had a PTSMA procedure either before the date of Ablysinol approval (pre-approval Jun 2013- Jun2018) and after its approval (estimated post approval July 2018 +). PTSMA is used exclusively in HOCM so there is no need for an inclusion criteria related to HOCM. Patients will be followed from the date of their index PTSMA procedure until the occurrence of study outcomes, disenrollment from their health plan, evidence of death or the end of the study period, whichever comes first. The incidence of the study outcomes (per 1000 person-years) will be calculated and the rates from the pre-and post-approval periods will be compared. The numbers of PTSMA procedures conducted in the pre-and post-approval setting will also be calculated and compared.

Methods which allow near real-time active surveillance of consequences of the approval of Ablysinol using sequential analysis may also be applied in this project. Sequential analysis is used when there are repeated queries of the data over time, on a periodic basis (e.g., monthly, quarterly). These methods have been applied in a previous study to investigate the consequences of FDA warnings on suicidal risk with antidepressants and may be adapted for the present question.[18]

5.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

The L1 Sentinel modular program will be sufficient for providing crude rates for most of the study outcomes and for providing the numbers of procedures conducted. For the all-cause mortality outcome, some custom programming will be required, although we expect it to be minimal, which will elevate the query to an L2 +. The sequential analysis, if applicable, will likely to require L3.

6 NEXT STEPS

ARIA is considered sufficient to examine changes in the rates of complications associated with PTSMA procedures in the pre- and post-approval period for Ablysinol. While some of the outcomes (AV Block and PPI) have not been validated in US claims data, this should not affect the validity of the study findings as the overall aim is to examine trends in the rates of complications across time. DCRP have accepted that there may be some error in outcome ascertainment. The next step will be to write a protocol for the study and submit a concept brief to SOC to begin work on establishing rates of complications in the pre-approval period.

References

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/s/

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

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

Memorandum

Date: May 4, 2018

To: Brian Proctor, Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCaRP)

Michael Monteleone, MS, Associate Director for Labeling, DCaRP

From: Puja Shah, Pharm.D., RAC, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Pharm.D., RAC, CPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for ABLYSINOL® (dehydrated alcohol) injection for cardiac septal branch intra-arterial use

NDA: 207987

In response to DCaRP's consult request dated February 26, 2018, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for ABLYSINOL® (dehydrated alcohol) injection for cardiac septal branch intra-arterial use.

PI: OPDP's review of the proposed labeling is based on the attached draft PI received by electronic mail from DCaRP (Brian Proctor) on April 23, 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 December 21, 2017, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Puja Shah at (240) 402-5040 or Puja.Shah@fda.hhs.gov.

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/s/

PUJA J SHAH
05/04/2018

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

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

Memorandum

Date: March 22, 2016

To: Anna Park, R.Ph.
Regulatory Health Project Manager
Division of Cardiology and Renal Products (DCaRP)

Brian Proctor
Regulatory Health Project Manager, DCaRP

From: Puja Shah, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 207987
ABLYSINOL (dehydrated alcohol injection, USP)

OPDP acknowledges the receipt of DCaRP's March 18, 2015, labeling consult request for the proposed package insert and the carton/container labeling for ABLYSINOL (dehydrated alcohol injection, USP). OPDP notes that a Complete Response letter was issued on December 9, 2015. Therefore, OPDP will close out this labeling consult request and requests that DCaRP submit a new labeling consult request during the subsequent review cycle.

If you have any questions, please contact Puja Shah at 240-402-5040.

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/s/

PUJA J SHAH
03/22/2016

M E M O R A N D U M

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

DATE: November 9, 2015

TO: File for NDA 207987

FROM: Sharon K. Gershon, Pharm.D.
Good Clinical Practice Enforcement Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Memo To File NDA #207987
Cancellation of Inspection
Josef Veselka, M.D.
Czech Republic

Drug: Ablysinol™ (Dehydrated Alcohol Injection, USP)

Protocol: Alcohol Septal Ablation for Hypertrophic Obstructive Cardiomyopathy

Cancelation of Inspection:

This memo confirms that OSI is cancelling the inspection of Dr. Josef Veselka's site in the Czech Republic for NDA 207987. This Memo to File contains a copy of the email from Dr. Shari Targum in the Division of Cardiorenal Drug Products (DCRP) confirming the decision to cancel the inspection.

Background:
The Applicant, Belcher Pharmaceuticals, LLC (Belcher) submitted NDA 207987 for the use of Ablysinol™ (Dehydrated Alcohol Injection, USP) (b) (4) to improve (b) (4) exercise capacity in patients with symptomatic, (b) (4) hypertrophic obstructive cardiomyopathy (b) (4)

Belcher obtained a database of patient-level outcomes for 100 patients with hypertrophic obstructive cardiomyopathy (HOCM) treated by percutaneous transluminal septal myocardial ablation (PTSMA) at Motol University Hospital, Prague, Czech Republic, between May 1998 and December 2013. The data were obtained from Josef Veselka, M, D. Ph.D., who performed the procedures.

The rationale for requesting an OSI audit of Dr. Josef Veselka was that the critical data and majority of the publications, as well as the only database supporting the Applicant's NDA, originated from his site. The total database was approximately 180 subjects; the database for the remaining 80 patients was requested by DCRP, but Dr. Veselka declined.

According to Belcher, the referenced data is not part of an ICH controlled study trial, nor was it

ever intended to be part of a study As part of a limited agreement between Dr. Veselka and Belcher, Dr. Veselka agreed to provide patient level data on 100 of his hospital registry patients. Because of this agreement, OSI does not have the authority to inspect the site, nor mandate Dr. Veselka provide the data for the remaining 80 patients.

Below is the email from OSI notifying DCRP of the cancellation of the inspection of Dr. Veselka's site and the DCRP response:

From: Targum, Shari
Sent: Tuesday, November 03, 2015 2:57 PM
To: Thompson, Susan (CDER)
Cc: Senatore, Fortunato; Stockbridge, Norman L; Gershon, Sharon; Ayalew, Kassa
Subject: RE: FW: Dr. Josef Veslka - Czech Republic

I concur that an inspection of the sponsor won't be helpful. Since clinical information was submitted to us from Dr. Veselka, it would have been helpful to inspect Dr. Veselka's site; however, I understand your email that the Agency does not have the authority to do so.

Shari

Shari L. Targum, M.D., M.P.H.
Clinical Team Leader
Division of Cardiovascular and Renal Products
Center for Drug Evaluation and Research
Food and Drug Administration
20903 New Hampshire Avenue, WO22-4124
Silver Spring, Maryland 20993
(301) 796-1151
shari.targum@fda.hhs.gov

From: Thompson, Susan (CDER)
Sent: Monday, November 02, 2015 12:00 PM
To: Targum, Shari
Cc: Senatore, Fortunato; Stockbridge, Norman L; Gershon, Sharon; Ayalew, Kassa
Subject: RE: FW: Dr. Josef Veslka - Czech Republic
Importance: High

Hi Shari,

I am following up on the email below regarding Dr. Veslka's site inspection. If you are in agreement, we will cancel the inspection, since there was no clinical study at the site. Since ORA has instituted the planning process for the inspection, we would like to cancel as soon as the decision is made in order to conserve resources.

Our understanding is that you did not feel that a sponsor inspection would be beneficial for this

application. Please let us know if that is still the case.

Thank you-

Susan

No further investigation of this matter is warranted for the following reason:

☒ Not under FDA/CDER/OSI authority to inspect

{See electronic signature below}

_____

OSI Reviewer's Name and Title

CONCURRENCE:

{See electronic signature below}

Concur: _____ Date: _____

Nonconcur: _____ Date: _____

(See attached supervisory comments regarding nonconcurrence)

Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Electronic Signatures:

Cc:
OSI Complaint File #
Support Staff
Reviewer
Branch Chief
D. Walters

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/s/

SHARON K GERSHON
11/09/2015

SUSAN D THOMPSON
11/09/2015

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:	October 2, 2015
Requesting Office or Division:	Division of Cardiovascular & Renal Products (DCRP)
Application Type and Number:	NDA 207987
Product Name and Strength:	Ablysinol (dehydrated alcohol injection, USP), ≥ (b) (4)% by volume
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Belcher Pharmaceuticals, LLC
Submission Date:	February 12, 2015
OSE RCM #:	2015-645
DMEPA Primary Reviewer:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

As part of this new drug application evaluation, this review evaluates the proposed container label, carton labeling, and Prescribing Information for Ablysinol (dehydrated alcohol injection, USP) for areas of vulnerability that can lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C- N/A
Human Factors Study	D- N/A
ISMP Newsletters	E
Other	F- N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA performed a risk assessment of the proposed prescribing information (PI), container label, and carton labeling to identify deficiencies that may lead to medication errors and areas for improvement. We note the absence of a primary strength expression on the proposed PI, container label, and carton labeling. We also note that important information for the appropriate storage of the product lacks prominence.

Thus, we provide our recommendations to mitigate confusion and promote the safe use of this product on Section 4.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed container label and carton labeling can be improved to increase the readability and prominence of important information on the label and labeling to promote the safe use of the product and to mitigate the risk of confusion.

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

4.1 RECOMMENDATIONS FOR THE DIVISION

General Comments

There is no primary strength expression on the proposed container label, proposed carton labeling, or in the proposed Prescribing Information (PI). Instead, there is a volume expression on the container label and carton labeling in the customary location for the strength expression. The *Dosage Forms and Strengths* section of the proposed PI also expresses the strength in terms of volume. We defer to Chemistry, Manufacturing, and Controls (CMC) for the appropriateness of the volume expression versus a strength expression. In addition, we note there is a secondary strength expression on the proposed container label, carton labeling, and PI stated as "(b) (4)% by volume". We defer to CMC for the acceptable expression(s) of strength for this product.

In addition, the product storage information indicates the product must be (b) (4) (b) (4) We will discuss this issue with CMC further to determine if amber bottles or individual carton labeling are needed to help prevent wrong storage of the product.

4.2 RECOMMENDATIONS FOR THE APPLICANT/SPONSOR

Container Label and Carton Labeling

1. Revise the statements "Usual Dose: (b) (4)" on container label and "Usual Dose: (b) (4)" on carton labeling to "Usual Dose: See Prescribing Information".

Carton Labeling

1. Revise the statement "(b) (4)" to read "(b) (4)" followed underneath by "(b) (4)". Then relocate the statements to the right side of the principal display panel underneath the "Usual Dose color block" to increase the prominence of this important storage information.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ablysinol that Belcher Pharmaceuticals, LLC submitted on February 12, 2015.

Table 2. Relevant Product Information for Dehydrated Alcohol	
Initial Approval Date	Not Applicable
Active Ingredient	dehydrated alcohol injection, USP
Indication	To improve (b) (4) exercise capacity in patients with symptomatic, (b) (4), hypertrophic obstructive cardiomyopathy (b) (4)
Route of Administration	Percutaneous Injection
Dosage Form	Solution for Injection
Strength	(b) (4)% by volume
Dose and Frequency	(b) (4)
How Supplied	Box of 10-(b) (4) ampules containing 1 mL of (b) (4)% by volume ethyl alcohol in each clear glass ampule.
Storage	Store at room temperature, between 20°C and 25°C (68°F and 77°F). (b) (4) Do not refrigerate. (b) (4) Highly flammable, store away from any heat source.

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on September 1, 2015 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter[2]

Table 3: FAERS Search Strategy	
Date Range	**September 1, 2010 to September 1, 2015**
Drug Names	**Alcohol, Dehydrated; Dehydrated Alcohol** [product name]
MedDRA Search Strategy	**Medication Errors** [HLGT] **Product Packaging Issues** [HLT] **Product Label Issues** [HLT] **Product Quality Issues** (NEC)[HLT]

B.2 Results

Our search identified zero (0) cases.

[2] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L: Drive and AIMS on September 1, 2015 using the terms, dehydrated alcohol to identify reviews previously performed by DMEPA.

C.2 Results

Our search identified 0 (zero) reviews.

APPENDIX E. ISMP NEWSLETTERS

E.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on September 1, 2015 using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s) Searched	Acute Care, Community and Nursing
Search Strategy and Terms	Match Exact Word or Phrase: Dehydrated Alcohol

E.2 Results

Our search identified zero (0) newsletters.

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,[1] along with postmarket medication error data, we reviewed the following Ablysinol labels and labeling submitted by Belcher Pharmaceuticals, LLC on February 12, 2015.

- Container label
- Carton labeling

G.2 Label and Labeling Images

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

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/s/

JANINE A STEWART
10/02/2015

CHI-MING TU
10/03/2015