EXHIBIT A

Table of Contents

TAB 1:

Documents showing FDA considered Firdapse's price when it approved Ruzurgi

From: Myers, James
To: Locicero, Colleen L
Subject: Fwd: Exclusivity Question regarding Firdapse (amifampridine)
Date: Wednesday, January 02, 2019 9:07:16 AM
Attachments: image002.png

FYI

From: Myers, James <James.Myers@fda.hhs.gov>
Date: December 19, 2018 at 8:31:00 AM EST
To: Flahive, James <James.Flahive@fda.hhs.gov>
Cc: Volpe, Carolyn <Carolyn.Volpe@fda.hhs.gov>, Becker, Carolyn E. <Carolyn.Becker@fda.hhs.gov>, Ashley, Donald <Donald.Ashley@fda.hhs.gov>, Stein, Peter <Peter.Stein@fda.hhs.gov>, Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>
Subject: RE: Exclusivity Question regarding Firdapse (amifampridine)

Hi James,

Thanks for your note. Apologies for the delay getting back to you. You're correct that there are a number of complicated factors associated with the two amifampridine NDAs.

As you noted below, Catalyst's NDA 208078 (Firdapse (amifampridine)) was recently approved and currently has 5-year NCE exclusivity. Jacobus's NDA (NDA 209321) was submitted in June 2018 and is currently pending before the Agency. Although 5-year NCE exclusivity often serves to block NDAs (and ANDAs) for products with the same active moiety, the statutory terms governing NCE exclusivity provide that NCE exclusivity blocks only the ***submission*** of an application for the same active moiety, not the approval of such an application. Because Jacobus's NDA was submitted prior to the approval of Catalyst's NDA, the NCE exclusivity should not have an affect on the approvability of Jacobus's NDA. (However, this NCE exclusivity would block the submission of any future (b)(2) NDAs or ANDAs.)

The more complicated issue here is that Catalyst's NDA likely is also eligible for orphan exclusivity. Although the Orange Book entry for Firdapse does not yet reflect this exclusivity, Firdapse has already been granted an orphan designation and (barring some unforeseen issue) should be granted orphan exclusivity (See orphan designation - https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=295309). Unlike NCE exclusivity, orphan exclusivity would block approval of Jacobus's NDA, unless Jacobus's NDA is proven to be clinically superior to Catalyst's NDA (which, based on my understanding, it's not) or if Jacobus's NDA is approved for an additional indication not covered by the scope of Firdapse's orphan exclusivity. My understanding is that the Division thinks that Jacobus's NDA may be able to be approved for a pediatric indication, which is separate from the adult indication approved under Catalyst's NDA (Firdapse) and thus potentially not blocked by Firdapse's orphan exclusivity. There are still some issues being discussed with respect to this indication, given that it's based on extrapolated data.

There are also a few other substantive issues with Jacobus's NDA, which could potentially result in a CR action by the February goal date or an extension of the goal date. As a result, it's not entirely clear whether this NDA will be approved or CR'd in the current review cycle, but the current thinking is that there may still be a path forward for Jacobus's NDA to be approved, despite Firdapse's orphan and NCE exclusivities.

I hope the above is helpful. I know these exclusivity issues can be complicated, so I'm more than happy to discuss any questions.

Thanks,
James

From: Flahive, James
Sent: Friday, December 14, 2018 4:53 PM
To: Myers, James <James.Myers@fda.hhs.gov>; Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>
Cc: Volpe, Carolyn <Carolyn.Volpe@fda.hhs.gov>; Becker, Carolyn E. <Carolyn.Becker@fda.hhs.gov>; Ashley, Donald <Donald.Ashley@fda.hhs.gov>
Subject: Exclusivity Question regarding Firdapse (amifampridine)

Hi Maarika and James,

Derek Griffing in OGD suggested that I reach out to you with this question regarding New Chemical Entity (NCE exclusivity).

Firdapse (amifampridine) was approved on 11/28/2018 (NDA 208078) to treat Lambert-Eaton Myasthenic Syndrome, a neuromuscular disorder. Dr. Throckmorton and others are concerned by an article stating that while patients who suffer this rare disorder have been able to access amifampridine treatment at low or no cost prior to approval, there is concern that the NDA holder intends to raise the price significantly. https://www.statnews.com/2018/11/30/fda-approval-lems-drug-costs/

Our understanding is that Catalyst, the approved NDA holder, has a 5 year NCE exclusivity. According to DARRTS, Jacobus Pharmaceuticals submitted an NDA application for 3,4-Diaminopyridine (amifampridine) in June 2018 with a PDUFA date of February 15, 2019. Based on the time of filing, would Jacobus's product be blocked by the Catalyst's NCE exclusivity?

Thanks,
Jim

James Flahive, J.D.
Branch Chief
Prescription Drugs Branch
Office of Unapproved Drugs and Labeling Compliance
CDER Office of Compliance
Food and Drug Administration

301-796-9293
james flahive@fda hhs.gov

From: Flahive, James
Sent: Friday, December 14, 2018 3:53 PM
To: Levy, Michael (CDER) <Michael.Levy@fda.hhs.gov>; Anderson, Kathleen R <Kathleen.Anderson@fda.hhs.gov>; Becker, Carolyn E. <Carolyn.Becker@fda.hhs.gov>
Cc: Bormel, Frances Gail <Frances.Bormel@fda.hhs.gov>; Ashley, Donald <Donald.Ashley@fda.hhs.gov>; Volpe, Carolyn <Carolyn.Volpe@fda.hhs.gov>
Subject: RE: High priced drugs - Firdapse (amifampridine)

Do you want me to set up a meeting to discuss Firdapse?

According to the orange book, Firdapse appears to have a 5-year new chemical entity exclusivity that expires on 11/28/2023. Derek Griffing in OGD confirmed that this is the only exclusivity (there is not an orphan exclusivity listed for this product) and there are no associated patents listed in the Orange Book.

While this is the first I'm aware of CDER Compliance hearing about the drug, this does seem to raise themes familiar from the Agency's experiences with Makena and may relate to the discussion we have started with Liz Dickinson about (b) (5) .

From: Levy, Michael (CDER)
Sent: Friday, December 14, 2018 2:51 PM
To: Anderson, Kathleen R <Kathleen.Anderson@fda.hhs.gov>; Becker, Carolyn E. <Carolyn.Becker@fda.hhs.gov>
Cc: Bormel, Frances Gail <Frances.Bormel@fda.hhs.gov>; Flahive, James <James.Flahive@fda.hhs.gov>; Ashley, Donald <Donald.Ashley@fda.hhs.gov>
Subject: RE: High priced drugs - Firdapse (amifampridine)

Can we get any handle on the compounding aspect of this today so we can get back to Dr. Throckmorton?

From: Levy, Michael (CDER)
Sent: Friday, December 14, 2018 2:28 PM
To: Anderson, Kathleen R <Kathleen.Anderson@fda.hhs.gov>; Becker, Carolyn E. <Carolyn.Becker@fda.hhs.gov>
Cc: Bormel, Frances Gail <Frances.Bormel@fda.hhs.gov>; Flahive, James <James.Flahive@fda.hhs.gov>; Ashley, Donald <Donald.Ashley@fda.hhs.gov>
Subject: FW: High priced drugs - Firdapse (amifampridine)

OUDLC may have to do a deeper dive on 3,4-DAP. The article indicates it's been compounded for years and is now approved. May be similar to the drug involved in litigation a few years ago.

https://www.statnews.com/2018/11/30/fda-approval-lems-drug-costs/

From: Throckmorton, Douglas C
Sent: Friday, December 14, 2018 2:08 PM
To: Ashley, Donald <Donald.Ashley@fda.hhs.gov>
Cc: Flahive, James <James.Flahive@fda.hhs.gov>; Levy, Michael (CDER) <Michael.Levy@fda.hhs.gov>; Carpenter, Courtney <Courtney.Carpenter@fda.hhs.gov>; CDER EXSEC <CDEREXSEC@cder.fda.gov>
Subject: FW: High priced drugs - Firdapse (amifampridine)

Don, need to have a little more background on this issue. I'm hoping your UDI folks have been engaged. I need to know any additional background you have, including if we've taken any actions against the unapproved product (as the article suggests) and if the company that just got the approval has asked us to do anything.

Please cc Courtney on all responses. We may need to fold this into the drug dislocation discussion…..

Thanks, Doug

Douglas C. Throckmorton MD
Deputy Director for Regulatory Programs
CDER FDA
240-402-5400

From: Carpenter, Courtney
Sent: Friday, December 14, 2018 12:20 PM
To: Throckmorton, Douglas C <Douglas.Throckmorton@fda.hhs.gov>
Cc: Dunn, Billy <Billy.Dunn@fda.hhs.gov>; McLatchy, Johanna <Johanna.McLatchy@fda.hhs.gov>; Bastings, Eric <Eric.Bastings@fda.hhs.gov>; Kozauer, Nicholas <Nicholas.Kozauer@fda.hhs.gov>
Subject: RE: High priced drugs - Firdapse (amifampridine)

Doug,

Here is a summary:

- Jacobus Pharmaceutical Co. has prescribed 3,4-DAP, a nearly identical treatment, off label since the 1980s at little or no cost to patients.
- On 11/28/18, FDA approved Catalyst Pharmaceuticals Firdapse (amifampridine) tablets for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults. This is the first FDA approval of a treatment for LEMS.
- Catalyst Pharmaceuticals is predicted to charge thousands of dollars for treatment.
- I was not able to unlock the article below (requires a subscription) - I did find a similar article discussing drug pricing. https://www.statnews.com/201L8/11/30/fda-approval-lems-drug-costs/

I am CC'ing Billy and DNP just in case they have more to add.

Thanks,
Courtney

Courtney Carpenter, MPH
Division of Executive Operations (CDER EXSEC)
CDER|OEP
301.796.4487 |(c)240.687.2804
Courtney.Carpenter@fda.hhs.gov

From: Throckmorton, Douglas C
Sent: Friday, December 14, 2018 7:55 AM
To: CDER EXSEC <CDEREXSEC@cder.fda.gov>
Cc: McLatchy, Johanna <Johanna.McLatchy@fda.hhs.gov>
Subject: HIgh priced drugs

We're in the middle of working up a proposal to address high priced drugs and I'm likely to get a call about this. Can someone find out more about the facts? I can't unlock the article. I assume the 'free' before was because it was available under expanded access?

Price Of Drug For Rare Neuromuscular Disorder Shoots Up Following FDA Approval.

STAT (12/13, 20K) reports last month, the Food and Drug Administration approved Firdapse (amifampridine) for the treatment of Lambert-Eaton myasthenic syndrome, "a rare, neuromuscular disorder," and the drug has been priced at $375,000. However, the article points out that before it was approved by the FDA, the drug was available to "hundreds of patients...for free."

Douglas C. Throckmorton MD
Deputy Director for Regulatory Programs
CDER FDA
240-402-5400

From: Locicero, Colleen L
To: Temkin, Eva
Subject: RE: Medical Policy and Program Review Council (MPPRC)
Date: Friday, January 04, 2019 3:45:00 PM

Thanks, Eva. I'm going to send you a brief backgrounder and then give you a call shortly after that….in about 10 minutes or so..does that work for you?

From: Temkin, Eva
Sent: Friday, January 04, 2019 3:42 PM
To: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>
Subject: RE: Medical Policy and Program Review Council (MPPRC)

Thanks, Colleen. I'm working at home today, but you can reach me at (b) (6) if it would be easier to talk about it.

From: Locicero, Colleen L
Sent: Friday, January 4, 2019 3:37 PM
To: Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>
Cc: Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>; Myers, James <James.Myers@fda.hhs.gov>; Sharma, Khushboo <Khushboo.Sharma@fda.hhs.gov>; Temkin, Eva <Eva.Temkin@fda.hhs.gov>
Subject: FW: Medical Policy and Program Review Council (MPPRC)

Hi Paul and all,

I started this (inserting some thoughts, in red, in Peter and Jacqueline's messages) when I thought Jacqueline might go ahead with the meeting this afternoon and I might have to participate by phone, which is never optimal. Since I started, I went ahead and finished it and am sharing it with you all, in case it is helpful, prior to our discussion Monday AM.

Eva- I'll follow up with you separately with some additional background. If you can only make half the meeting on Monday AM, that is better than none!!

Thanks,
Colleen

From: Corrigan-Curay, Jacqueline
Sent: Friday, January 04, 2019 8:17 AM
To: Stein, Peter <Peter.Stein@fda.hhs.gov>; Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>; Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>
Cc: Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>; Myers, James <James.Myers@fda.hhs.gov>; Faranda, David <David.Faranda@fda.hhs.gov>; Bickel, Lori <Lori.Bickel@fda.hhs.gov>

Subject: RE: Medical Policy and Program Review Council (MPPRC)

Dear Paul,

On your first point we certainly can reword that sentence as that is not my intent. Perhaps the following

(b) (5)

As for the second point, Peter has outlined our rationale. I would emphasize that the safety

(b) (5)

(b) (5)

I admit this is a difficult case, but more so perhaps because we know about the competition and price issues.

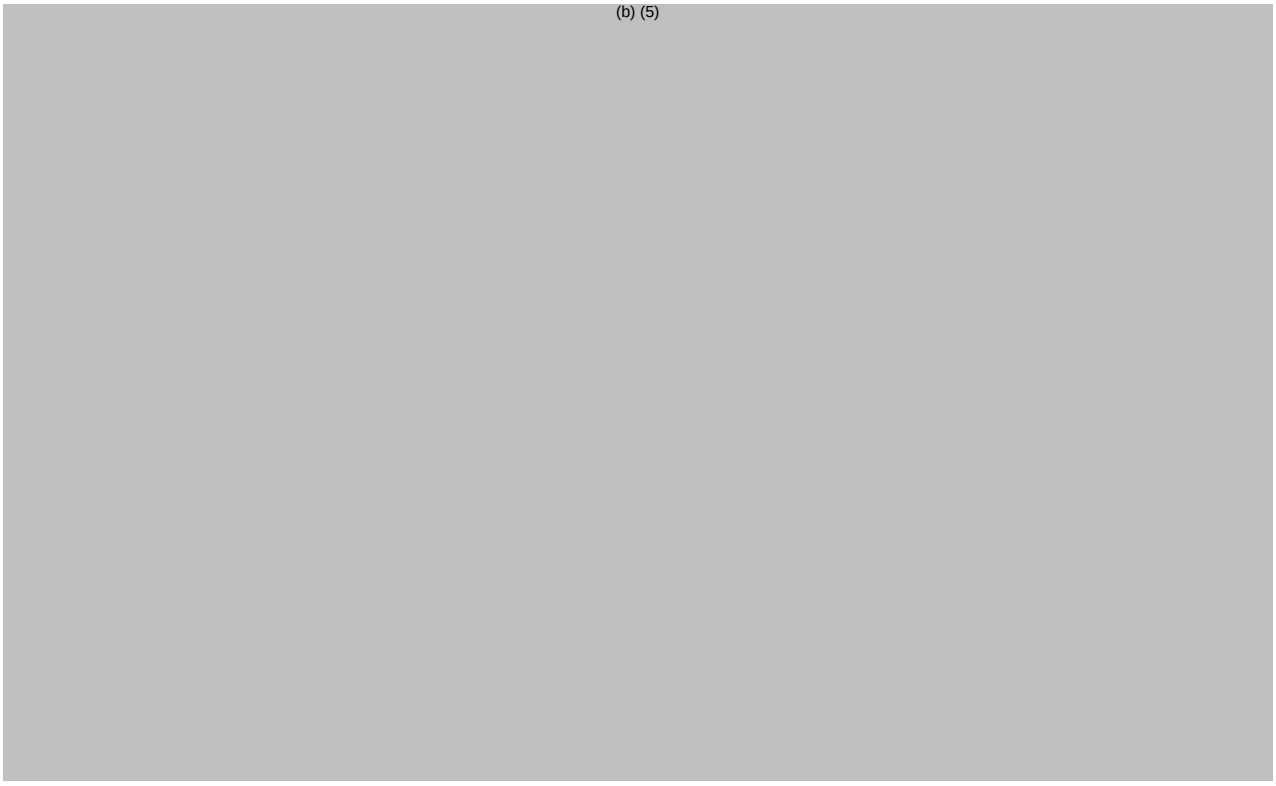
Best
Jacqueline

From: Stein, Peter <Peter.Stein@fda.hhs.gov>
Date: January 4, 2019 at 7:33:11 AM EST
To: Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>, Corrigan-Curay, Jacqueline <Jacqueline.Corrigan-Curay@fda.hhs.gov>, Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>
Cc: Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>, Myers, James <James.Myers@fda.hhs.gov>, Faranda, David <David.Faranda@fda.hhs.gov>, Bickel, Lori <Lori.Bickel@fda.hhs.gov>
Subject: RE: Medical Policy and Program Review Council (MPPRC)

Hi Paul,
You raise an important point – which was raised in the discussion at MPPRC – that once

(b) (5)

(b) (5)



Again, I think your framing of this is appropriate – and I do have some concerns here – so I would ask our OND policy folks to weigh in regarding this precedent to make sure we can both defend this decision – and remain consistent with it in future circumstances.

Regards,
Peter

From: Phillips, J. Paul
Sent: Thursday, January 3, 2019 10:56 PM
To: Corrigan-Curay, Jacqueline <Jacqueline.Corrigan-Curay@fda.hhs.gov>; Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>
Cc: Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>; Myers, James <James.Myers@fda.hhs.gov>; Faranda, David <David.Faranda@fda.hhs.gov>; Bickel, Lori <Lori.Bickel@fda.hhs.gov>; Stein, Peter <Peter.Stein@fda.hhs.gov>
Subject: RE: Medical Policy and Program Review Council (MPPRC)

Sorry, Jacqueline, one correction in red below for accuracy.
I really appreciate any time you take to help me better understand.

Warm regards,

Paul

From: Phillips, J. Paul
Sent: Thursday, January 03, 2019 10:43 PM
To: Corrigan-Curay, Jacqueline <Jacqueline.Corrigan-Curay@fda.hhs.gov>; Locicero, Colleen

L <Colleen.Locicero@fda.hhs.gov>
Cc: Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>; Myers, James <James.Myers@fda.hhs.gov>; Faranda, David <David.Faranda@fda.hhs.gov>; Bickel, Lori <Lori.Bickel@fda.hhs.gov>; Stein, Peter <Peter.Stein@fda.hhs.gov>
Subject: RE: Medical Policy and Program Review Council (MPPRC)

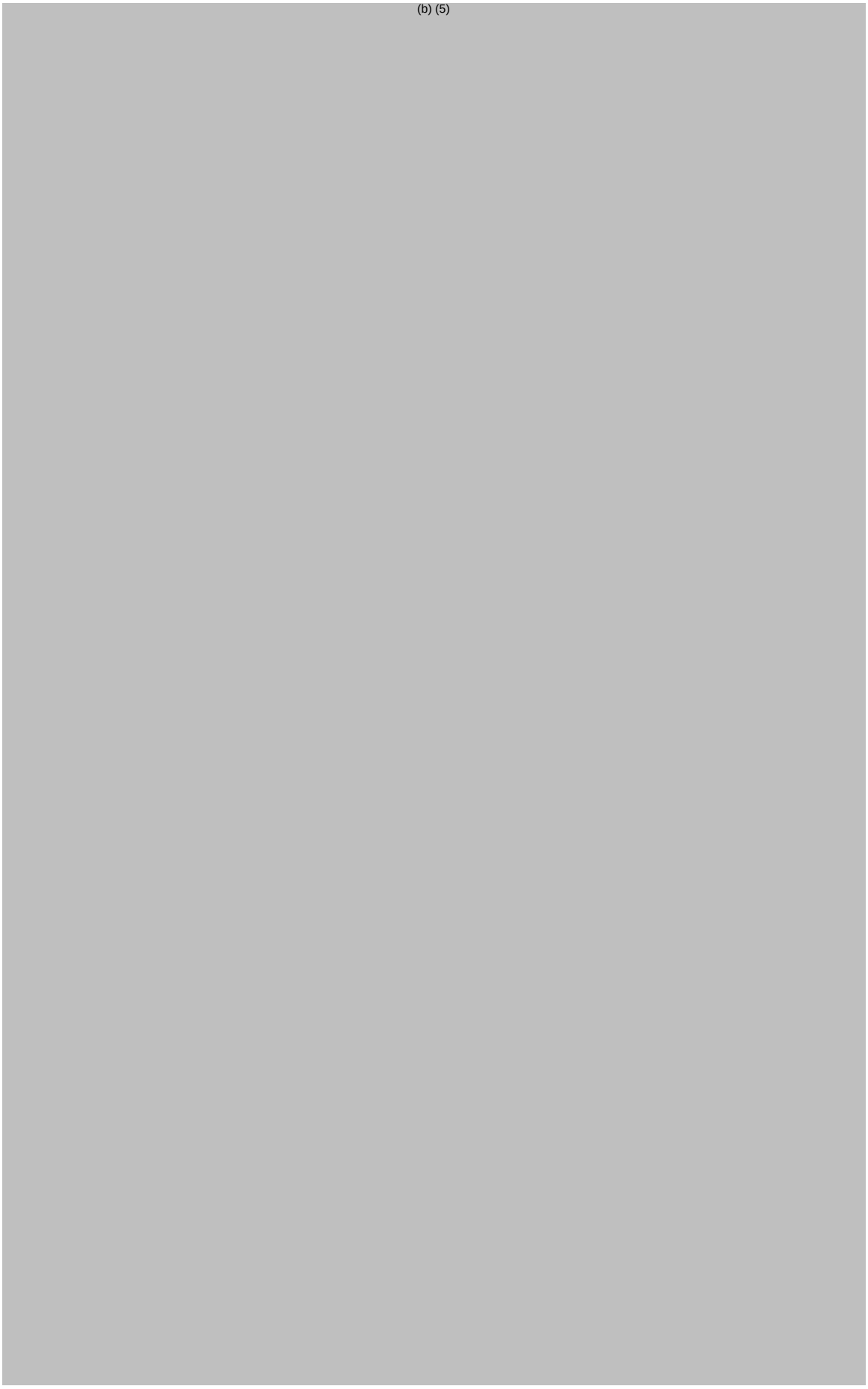
Jacqueline,

Just a thought for your consideration. (b) (5) [redacted]

Separately, I wondered if you would mind helping me to understand the basis for MPCs overall decision on the Jacobus case. This will help me as the OND EA program manager to consistently apply the policy decision that was made when the principle of the exception needs to be applied in other cases moving forward.

My understanding is the following, but please correct me where I am wrong:

(b) (5) [redacted]


(b) (5)

(b) (5)

Thank you so much,

Paul

From: Corrigan-Curay, Jacqueline
Sent: Thursday, January 03, 2019 6:36 PM
To: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>
Cc: Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>; Myers, James <James.Myers@fda.hhs.gov>; Faranda, David <David.Faranda@fda.hhs.gov>; Bickel, Lori <Lori.Bickel@fda.hhs.gov>; Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>; Stein, Peter <Peter.Stein@fda.hhs.gov>
Subject: RE: Medical Policy and Program Review Council (MPPRC)

Colleen
Here is a first draft of language to start the conversation. I have looped in Peter as well since he may have some edits to make. I have included something about the exclusivity for the LEMS indication. I am open to other opinions regarding whether that is appropriate.
Best,
Jacqueline

(b) (5)

From: Locicero, Colleen L
Sent: Thursday, January 3, 2019 12:49 PM
To: Corrigan-Curay, Jacqueline <Jacqueline.Corrigan-Curay@fda.hhs.gov>
Cc: Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>; Myers, James <James.Myers@fda.hhs.gov>; Faranda, David <David.Faranda@fda.hhs.gov>; Bickel, Lori <Lori.Bickel@fda.hhs.gov>; Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>
Subject: RE: Medical Policy and Program Review Council (MPPRC)

Hi Jacqueline,

Thanks so much for holding and leading this discussion at yesterday's MPPRC meeting. I apologize, up front, that I have a big favor to ask.

(b) (5)

Jacobus has submitted multiple requests for help on this EA issue, but here are the two that I think sum up their current questions the best:

> *We wondered if a possible solution would be for us to continue to support those patients whose dosing regimen, diagnosis and demographics fall outside of the Catalyst labeling and support the continued IND distribution based on the statutory language of "Clinical Superiority" within 21 CFR Part 316?*

and

> *Are we permitted to continue to support those patients receiving medication under the Jacobus compassionate distribution program who:*

1. *receive doses greater than the approved Firdapse® labeling?*
    a. *Example: ≥61 mg or 81 mg daily dose not to exceed 120 mg daily.*

2. *are less than 18 years of age?*
    a. *There are currently at least 3 who remain < 18 years of age.*

3. *are receiving our amifampridine 10 mg tablets for an indication other than LEMS?*

I would think (but could be wrong) that we'd want to say that, (b) (5) (b) (5) (b) (5) If so, it is the last part (a clear articulation of the rationale) that I am struggling with.

Thanks,
Colleen

From: Locicero, Colleen L
Sent: Tuesday, January 01, 2019 3:57 PM
To: Corrigan-Curay, Jacqueline <Jacqueline.Corrigan-Curay@fda.hhs.gov>; Faranda, David <David.Faranda@fda.hhs.gov>; Bickel, Lori <Lori.Bickel@fda.hhs.gov>; Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>
Subject: RE: Medical Policy and Program Review Council (MPPRC)

Hi All,

Just want to make sure it is clear for tomorrow's discussion that Jacobus is not only proposing to provide their drug for treatment under expanded access to patients who have myasthenic syndromes other than LEMS (other indications), but also to pediatric patients (Catalyst product is approved in adults only) and to patients currently on dosing regimens that are outside (higher than) that approved for the Catalyst product.

Also, I think there are two questions, especially in light of some of the recent emails to Jacobus from patients who have "failed" treatment with the Catalyst product, as follows:

1) Should FDA authorize expanded access for treatment with the Jacobus product in patients not covered by the conditions of use approved for the Catalyst product, including the following?
    a. patients with myasthenic syndromes other than LEMS
    b. pediatric patients
    c. patients on dosing regimens outside (e.g., higher than) that

approved for the Catalyst product

2) If the answer to Question 1 is NO, should FDA advise Jacobus that it will consider authorizing expanded access for treatment with the Jacobus product for patients who try the Catalyst product and fail (lack of or decreased effectiveness, adverse event on the Catalyst product, etc.)?

Thanks,
Colleen

-----Original Appointment-----
From: Garvin, Kayla
Sent: Wednesday, December 12, 2018 4:44 PM
To: Garvin, Kayla; Beaver, Julia; Beitz, Julie G; Cavazzoni, Patrizia; Corrigan-Curay, Jacqueline; Cox, Edward M; Dal Pan, Gerald; ElZarrad, M. Khair; Joffe, Hylton; Martin, Jewell; Permutt, Thomas J; Sacks, Leonard V; Stein, Peter; Temple, Robert; Thanh Hai, Mary; Woodcock, Janet; Zineh, Issam; Locicero, Colleen L; Faranda, David; Bickel, Lori; Phillips, J. Paul; Myers, James; Lowy, Naomi; Ware, Jacqueline H; Kozauer, Nicholas; Markert, David
Cc: Abrams, Thomas W; Albrecht, Renata; Alexander, John J; Amchin, Wayne; Askine, Mark W; Bennett, Carol; Bernstein, Ilisa; Birnkrant, Debra B; Blum, Michael; Blumenthal, Gideon; Borges, Silvana; Brugger, Kristiana; Buch, Barbara D; Buckman-Garner, ShaAvhrée; Budashewitz, Philip; Chong, Barbara; Christl, Leah A; Crentsil, Victor; Davis Bruno, Karen L; Dempsey, Mary; Dunn, Billy; Farley, John; Farrell, Ann T; Flanagan, Keith; Franklin, Joseph; Furlong, Lesley-Anne; Ganley, Charles J; Gebbia, Emily; Gray, Catherine; Hertz, Sharon H; Hewett, Jan; Karesh, Alyson; Keegan, Patricia; Kehoe, Theresa; Kimbrell, Maarika; Kraus, Stefanie; Lackey, Leila; Lauritsen, Kristina; Leptak, Christopher; Lindstrom, Jill; Loewke, Sally A; Lostritto, Richard T; Maloney, Diane; Maniwang, Janice; Marcus, Kendall; Marner, Juanita; Marzella, Libero; Masucci, Iris; Mathis, Mitchell; McKee, Amy; Michele, Theresa; Moeny, David; Muldowney, Laurie; Mullin, Theresa; Nambiar, Sumathi; Pacanowski, Michael A; Pazdur, Richard; Pearsall, Bryon; Popat, Vaishali; Rare Disease Program Meetings; Rawlings, Kimberly; Roberts, Rosemary; Roman, Dragos; Santiago, Jonas; Seymour, Sally; Shreeve, Chris; Shukla, Sunita; Sipes, Grail; Soule, Lisa; Southworth, Mary Ross; Stockbridge, Norman L; Stone, Heather; Taylor, Lockwood; Thompson, Aliza; Thompson, Graham; Throckmorton, Douglas C; Toigo, Theresa A; Unger, Ellis; Vasisht, Kaveeta; Witten, Celia (CBER); Woo, Jason; Yao, Lynne P; Zander, Judith; Zhang, Lillian Hua; Less, Joanne; Bastings, Eric; Buracchio, Teresa; Mathers, Michelle; Cleck Derenick, Jessica
Subject: Medical Policy and Program Review Council (MPPRC)

When: Wednesday, January 02, 2019 9:00 AM-10:00 AM (UTC-05:00) Eastern Time (US & Canada).
Where: Building 2 - Room 2046

Agenda:
9am to 10am – IND under Expanded Access issue

Please do not forward this meeting invite. If someone needs to be added, please contact Kayla Garvin.

-- Do not delete or change any of the following text. --

Join Webex meeting

Meeting number (access code): (b) (6)
Meeting password: (b) (6)

Join by phone

+1-877-465-7975 US Toll Free

+1-210-795-0506 US Toll

Global call-in numbers | Toll-free calling restrictions

Can't join the meeting?

If you are a host, go here to view host information.

IMPORTANT NOTICE: Please note that this Webex service allows audio and other information sent during the session to be recorded, which may be discoverable in a legal matter. By joining this session, you automatically consent to such recordings. If you do not consent to being recorded, discuss your concerns with the host or do not join the session.

From:	Sitlani, Jay
To:	Nduom, Kelley; Locicero, Colleen L
Cc:	Flores, Lars; Shah, Nisha
Subject:	RE: Discuss NDA 209321 Ruzurgi [Amifampridine (3,4-Diaminopyridine)] and Catalyst NDA-208078 Firdapse exclusivity for adult use
Date:	Monday, February 04, 2019 12:15:46 PM

FYI, Firdapse is the drug that is raising the ire of Senator Sanders and others in Congress, in part because of the cost of the drug touted to be $375,000. I'm guessing that when amifampridine was being marketed as an unapproved drug, it was sold for a fraction of that amount. So, our exclusivity discussions, while technical and legalistic as they always are, will by necessity have to occur against this backdrop.

From: Nduom, Kelley
Sent: Monday, February 04, 2019 9:58 AM
To: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>
Cc: Sitlani, Jay <Jay.Sitlani@fda.hhs.gov>; Flores, Lars <Lars.Flores@fda.hhs.gov>; Shah, Nisha <Nisha.Shah@fda.hhs.gov>
Subject: RE: Discuss NDA 209321 Ruzurgi [Amifampridine (3,4-Diaminopyridine)] and Catalyst NDA-208078 Firdapse exclusivity for adult use

Hi Colleen,

Thanks so much. Yes, I am working on drafting a background document and would definitely appreciate your review and comment. I'll send it to you once I'm finished.

Thanks!
Kelley

From: Locicero, Colleen L
Sent: Monday, February 04, 2019 9:53 AM
To: Nduom, Kelley <Kelley.Nduom@fda.hhs.gov>
Cc: Sitlani, Jay <Jay.Sitlani@fda.hhs.gov>; Flores, Lars <Lars.Flores@fda.hhs.gov>; Shah, Nisha <Nisha.Shah@fda.hhs.gov>
Subject: RE: Discuss NDA 209321 Ruzurgi [Amifampridine (3,4-Diaminopyridine)] and Catalyst NDA-208078 Firdapse exclusivity for adult use

Hi Kelley,

Definitely want the right people to attend, so if it needs to be moved, so be it.

Re – additional information….I was not sure if you needed any kind of summary document/background for the meeting, but wanted to let you know that if you did, I could help with it. If you don't, that's fine too. It is just that this one seems kind of complicated, so I wanted to let you know I am willing to help, however you need me to so do.

Thanks,
Colleen

From: Nduom, Kelley
Sent: Friday, February 01, 2019 3:06 PM
To: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>
Cc: Sitlani, Jay <Jay.Sitlani@fda.hhs.gov>; Flores, Lars <Lars.Flores@fda.hhs.gov>; Shah, Nisha <Nisha.Shah@fda.hhs.gov>
Subject: RE: Discuss NDA 209321 Ruzurgi [Amifampridine (3,4-Diaminopyridine)] and Catalyst NDA-208078 Firdapse exclusivity for adult use

Hi Colleen,

I think we're going to need to move this meeting again, since there are some key people who will be out of the office. If you're free at this time next week, however, I was hoping we could hold this time to touch base. You mentioned that you might have some additional background information that would be helpful for us to consider? If so, please let me know if you're available for a call at this time.

Many thanks,

Kelley

-----Original Appointment-----
From: Flores, Lars
Sent: Friday, January 25, 2019 7:51 AM
To: Flores, Lars; Locicero, Colleen L; Myers, James; Dunn, Billy; Mathers, Michelle; Buracchio, Teresa; Daugherty, Susan B (CSO); Ware, Jacqueline H; Kozauer, Nicholas; Unger, Ellis; Startzman, Henry; Szydlo, Roberta; Kimbrell, Maarika; Schumann, Katherine; Nduom, Kelley; Helms Williams, Emily; Khurana, Mona; Sachs, Hari; Vaid, Sonal; Bastings, Eric
Cc: Sitlani, Jay; Maynard, Janet; Shah, Nisha
Subject: Discuss NDA 209321 Ruzurgi [Amifampridine (3,4-Diaminopyridine)] and Catalyst NDA-208078 Firdapse exclusivity for adult use
When: Thursday, February 07, 2019 1:00 PM-2:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: WO-Bldg 32 Room 1215

Conference Call In
Dial In: **Toll Free** +1-877-465-7975
(b) (6) Host access code
Attendee access code
PIN: (b) (6)

From: Locicero, Colleen L
To: Kimbrell, Maarika; Schumann, Katherine; Unger, Ellis; Myers, James
Subject: amifampridine
Date: Wednesday, February 06, 2019 12:42:00 PM
Attachments: Jacobus Exclusivity Background.docx

Since the Catalyst/Jacobus amifampridine saga is getting a lot of press (Eva sent me this link yesterday:
https://www.facebook.com/7292655492/posts/10156122666440493/) and will be the subject of an upcoming X Board meeting, I put together a high level overview (which the division reviewed and edited/commented on) of
the applications and related activities. I sent this to ORP/Jay in case it helps in preparation for the X Board discussion and thought I'd send to you in case you might find it helpful.

Thanks,
Colleen

From: Locicero, Colleen L
To: Nduom, Kelley; Helms Williams, Emily; Buracchio, Teresa; Mathers, Michelle
Cc: Sitlani, Jay
Subject: RE: Question re: Jacobus product
Date: Tuesday, February 12, 2019 5:46:29 PM
Attachments: image003.jpg
image005.png

All except the OCC/ORP discussion with Peter Stein and Jacqueline Corrigan-Curay that was pretty much limited to lawyers and those two. I do, however, know the upshot of that discussion.

I'm going to talk to Emily tomorrow or Thursday about this.

Thanks,
Colleen

From: Nduom, Kelley
Sent: Tuesday, February 12, 2019 5:43 PM
To: Helms Williams, Emily <Emily.HelmsWilliams@fda.hhs.gov>; Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>
Cc: Sitlani, Jay <Jay.Sitlani@fda.hhs.gov>
Subject: RE: Question re: Jacobus product

I'm looping in Colleen, who may be able to speak to the discussions with OCC.

Colleen – have you been involved in those discussions?

Thanks!

Kelley

From: Helms Williams, Emily
Sent: Tuesday, February 12, 2019 2:02 PM
To: Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Nduom, Kelley <Kelley.Nduom@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>
Cc: Sitlani, Jay <Jay.Sitlani@fda.hhs.gov>
Subject: RE: Question re: Jacobus product

Thanks all! This is helpful. I understand that there have been extensive discussions recently, with OCC and others in the Agency, (b) (5)

(b) (5)

Thanks,

Emily

From: Buracchio, Teresa
Sent: Tuesday, February 12, 2019 1:53 PM
To: Nduom, Kelley <Kelley.Nduom@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>
Cc: Helms Williams, Emily <Emily.HelmsWilliams@fda.hhs.gov>; Sitlani, Jay <Jay.Sitlani@fda.hhs.gov>
Subject: RE: Question re: Jacobus product

Not on the (b) (4) per day regimen, but they have inquired about whether the (b) (4) (b) (4)

The clinical superiority for the Jacobus product would potentially come from pediatric dosing for LEMS. They are proposing an indication for LEMS down to (b) (4) (we think we may be able to indicate down to 6 years of age). This would be based on extrapolation of efficacy from adult patients and some dosing and safety data in pediatric patients. Firdapse only has adult dosing.

Teresa

From: Nduom, Kelley
Sent: Tuesday, February 12, 2019 1:48 PM
To: Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>
Cc: Helms Williams, Emily <Emily.HelmsWilliams@fda.hhs.gov>; Sitlani, Jay <Jay.Sitlani@fda.hhs.gov>
Subject: RE: Question re: Jacobus product

Hi Teresa,

Thanks so much for this. Do you know if Jacobus has made any claims of clinical superiority based on the (b) (4) daily dosing regimen (in contrast to the Catalyst product's 3-4 daily dosing regimen) or (b) (4) Or if there have been claims of clinical superiority based on other factors?

Thanks,
Kelley

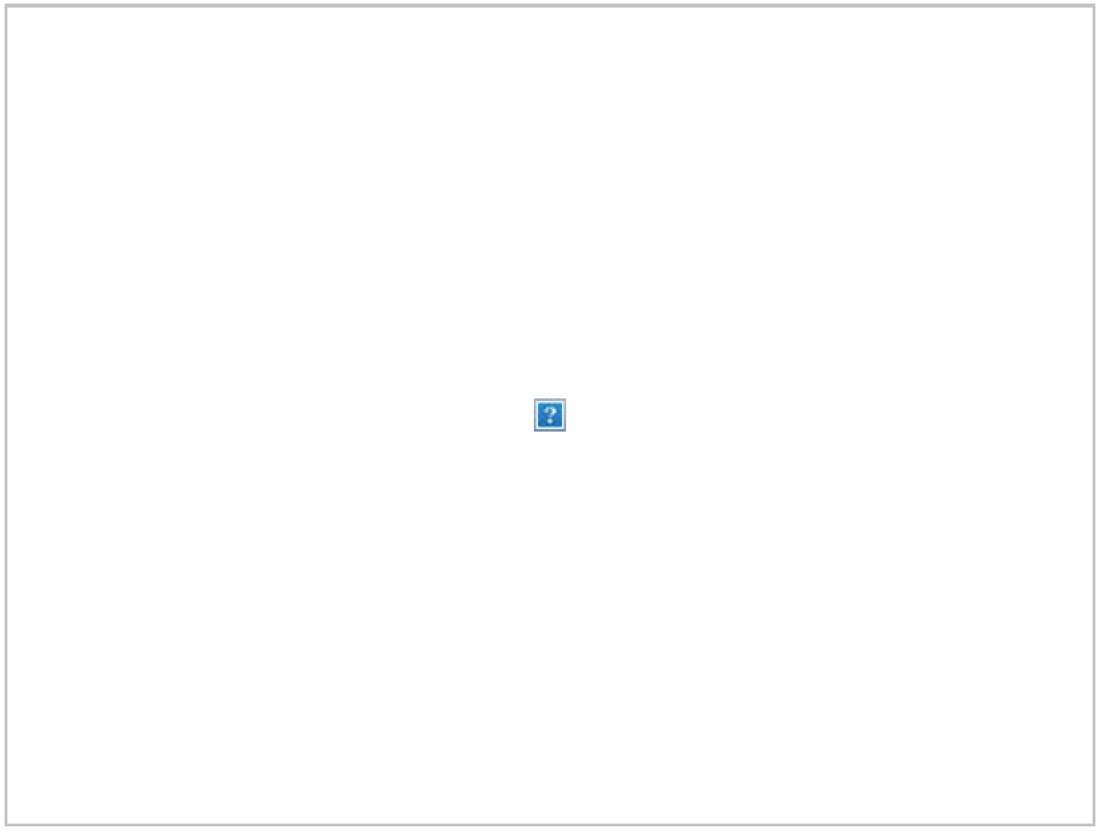
From: Buracchio, Teresa
Sent: Tuesday, February 12, 2019 1:13 PM
To: Nduom, Kelley <Kelley.Nduom@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>
Cc: Helms Williams, Emily <Emily.HelmsWilliams@fda.hhs.gov>; Sitlani, Jay <Jay.Sitlani@fda.hhs.gov>

Subject: RE: Question re: Jacobus product

Hi Kelley,
The Catalyst and Jacobus products have the same active moiety, amifampridine. The Jacobus product (Ruzurgi) is amifampridine base and the Catalyst product (Firdapse) is the phosphate salt, amifampridine phosphate. The two products have minor CMC differences that are outlined in the table below.

The two products have also studied slightly different dosing regimens in their clinical trials and expanded access program:
Firdapse is indicated for use in adult LEMS patients. Dosing regimen is 5-20 mg 3-4 times per day. Maximum dose is 80 mg/day.
Jacobus proposed dosing in adult LEMS patients (and what is being used in expanded access) is (b) (4) per day. Maximum dose is proposed to be (b) (4) mg/day.

Let me know if you have additional questions.
Teresa



From: Nduom, Kelley
Sent: Tuesday, February 12, 2019 10:40 AM
To: Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>

Cc: Helms Williams, Emily <Emily.HelmsWilliams@fda.hhs.gov>; Sitlani, Jay <Jay.Sitlani@fda.hhs.gov>
Subject: Question re: Jacobus product

Hi Teresa and Michelle,

I hope you're doing well. I'm coordinating the CDER Exclusivity Board discussions around the Jacobus application for Ruzurgi. As you know, this issue has been heating up in the news, and the Commissioner's office has raised some questions about the differences between the two drugs. News reports state that Catalyst's version doesn't require refrigeration, and Catalyst has suggested there are other differences. We're hoping you could help us with a few questions:

1. Are the Catalyst and Jacobus products different, if so how (any differences in active moiety/ingredient, or just excipients)?

2. Assuming they are different in some way, what is our justification for ending expanded access to the Jacobus product?

I'm happy to give you a call to discuss, if that would be easier. Thanks!

Kelley

Kelley Nduom, JD, MPH
Senior Regulatory Counsel
Acting Special Assistant to the Deputy Center Director for Regulatory Policy

Center for Drug Evaluation and Research
Office of Regulatory Policy
U.S. Food and Drug Administration
Tel: 301-796-8597
kelley.nduom@fda.hhs.gov

From:	Molnar, Danielle
To:	Locicero, Colleen L
Cc:	Chew, Catherine; Wagner, Lindsay; Kremzner, Mary E; Mathers, Michelle; Buracchio, Teresa
Subject:	RE: Firdapse Availability Discussion-(DDI &DNP)
Date:	Wednesday, February 13, 2019 9:25:13 AM

Hi Colleen,

I have a quick comment regarding the draft response to the (b) (6) emails.

When we drafted the response the day or two before 12/31/18, the only exclusivity type showing in the Orange Book was NCE. We mention that exclusivity in the letter. Soon after we sent the draft Orphan Drug Exclusivity was added to the Orange Book, so a minor correction would be needed in that part of the letter if it's decided during the clearance process to keep the mention of exclusivity.

Danielle

From: Locicero, Colleen L
Sent: Wednesday, February 13, 2019 8:49 AM
To: Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Chew, Catherine <Catherine.Chew@fda.hhs.gov>; Kremzner, Mary E <Mary.Kremzner@fda.hhs.gov>; Molnar, Danielle <Danielle.Molnar@fda.hhs.gov>; Wagner, Lindsay <Lindsay.Wagner@fda.hhs.gov>
Subject: RE: Firdapse Availability Discussion-(DDI &DNP)

Thanks, Teresa. Very helpful!!

Colleen

From: Buracchio, Teresa
Sent: Wednesday, February 13, 2019 8:39 AM
To: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Chew, Catherine <Catherine.Chew@fda.hhs.gov>; Kremzner, Mary E <Mary.Kremzner@fda.hhs.gov>; Molnar, Danielle <Danielle.Molnar@fda.hhs.gov>; Wagner, Lindsay <Lindsay.Wagner@fda.hhs.gov>
Subject: RE: Firdapse Availability Discussion-(DDI &DNP)

Hi Colleen,
Regarding question 2, I expect that the safety will be very similar in the label. It will not be identical because they have different safety datasets but it will be similar. Certainly, seizures, paresthesias, and gastrointestinal effects will be in there. I am not sure about the carcinogenicity because that depends on the results of the nonclinical studies.
Teresa

From: Locicero, Colleen L

Sent: Wednesday, February 13, 2019 6:31 AM
To: Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Chew, Catherine <Catherine.Chew@fda.hhs.gov>; Kremzner, Mary E <Mary.Kremzner@fda.hhs.gov>; Molnar, Danielle <Danielle.Molnar@fda.hhs.gov>; Wagner, Lindsay <Lindsay.Wagner@fda.hhs.gov>
Subject: RE: Firdapse Availability Discussion-(DDI &DNP)

All,

I have a couple more questions:

1) Has DDI or the division received directly from patients and/or healthcare providers (i.e., not via Jacobus) inquiries or complaints about not being able to obtain the Catalyst product or sufficient quantities of the Catalyst product (e.g., for patients on higher than 80 mg/day)? (My concern is that if we have only received this particular complaint/inquiry via Jacobus, we may not be able to or want to approach Catalyst about it. If, however, we've received direct patient/physician inquiries/complaints, approaching Catalyst seems more appropriate. I failed to ask this question yesterday and I think it is important for me to know this before today's meeting with OND and OMP management.)
2) For DNP – (b) (6) identifies a lot of safety concerns (carcinogenicity, seizures, other adverse effects) with Firdapse, because of information in the Firdapse approved labeling, that she believes are not concerns for the base product (Jacobus's product). However, when the Jacobus product is approved, its label will include all or most of the adverse effects, etc. that (b) (6) discusses – is that correct?

Much thanks!
Colleen

-----Original Appointment-----
From: Mathers, Michelle
Sent: Thursday, February 07, 2019 8:09 AM
To: Mathers, Michelle; Dunn, Billy; Bastings, Eric; Kozauer, Nicholas; Buracchio, Teresa; Locicero, Colleen L; Chew, Catherine; Kremzner, Mary E; Molnar, Danielle; Wagner, Lindsay; CDER 120 Calendar
Cc: Bullock, Heather; Daugherty, Susan B (CSO); Ware, Jacqueline H
Subject: Firdapse Availability Discussion-(DDI &DNP)
When: Tuesday, February 12, 2019 4:15 PM-4:45 PM (UTC-05:00) Eastern Time (US & Canada).
Where: WO22 Room 4270 (EMS Reservation 1245683)

Hi All,

I've scheduled a 30-minute meeting to discuss talking points for addressing

questions regarding the unavailability of the Jacobus amifampridine and the price of Firdapse. The attached outlook file contains a draft letter that DDI has provided for review in response to letters/e-mails received from patients and physicians.

A web-ex number is provided below. I've also booked room WO22/4270 for those who wish to attend in person.

Thanks,
Michelle

-- Do not delete or change any of the following text. --

Join Webex meeting

Meeting number (access code): (b) (6)
Meeting password: (b) (6)

Join by phone

+1-210-795-0506 US Toll

+1-877-465-7975 US Toll Free

Global call-in numbers | Toll-free calling restrictions

Can't join the meeting?

If you are a host, go here to view host information.

IMPORTANT NOTICE: Please note that this Webex service allows audio and other information sent during the session to be recorded, which may be discoverable in a legal matter. By joining this session, you automatically consent to such recordings. If you do not consent to being recorded, discuss your concerns with the host or do not join the session.

From: Locicero, Colleen L
To: Kimbrell, Maarika
Subject: RE: Discuss Jacobus inquiry about amifampridine higher dose/(Phillips)
Date: Wednesday, February 13, 2019 9:10:00 AM

No, I do. I just didn't know if I should start with her, but what you say makes complete sense!!

From: Kimbrell, Maarika
Sent: Wednesday, February 13, 2019 9:10 AM
To: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>
Subject: RE: Discuss Jacobus inquiry about amifampridine higher dose/(Phillips)

And do you really not know Val? How is that possible? I thought you knew everyone!

From: Locicero, Colleen L
Sent: Wednesday, February 13, 2019 9:09 AM
To: Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>; Schumann, Katherine <Katherine.Schumann@fda.hhs.gov>; Myers, James <James.Myers@fda.hhs.gov>
Subject: RE: Discuss Jacobus inquiry about amifampridine higher dose/(Phillips)

That sounds right. Thanks!!

Colleen

From: Kimbrell, Maarika
Sent: Wednesday, February 13, 2019 9:02 AM
To: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>; Schumann, Katherine <Katherine.Schumann@fda.hhs.gov>; Myers, James <James.Myers@fda.hhs.gov>
Subject: RE: Discuss Jacobus inquiry about amifampridine higher dose/(Phillips)

Val Jensen runs the group and she is great. I would start with her and she can pass this along to someone else in her staff. Given the amount of interest here (including from OC), it makes sense for Val to be aware herself.

From: Locicero, Colleen L
Sent: Wednesday, February 13, 2019 9:00 AM
To: Schumann, Katherine <Katherine.Schumann@fda.hhs.gov>; Myers, James <James.Myers@fda.hhs.gov>; Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>
Subject: RE: Discuss Jacobus inquiry about amifampridine higher dose/(Phillips)

I do not.

By the way, DDI and OMA have received inquiries/complaints directly from patients/physicians, so, it seems to me that it would be OK for FDA to reach out to Catalyst, but want to make sure everybody agrees at today's meeting. I think the division would like it if DSS could/would do the outreach (they just have so much going on with these two applications right now). Plus, I agree that it seems better to have a 3rd party do it. So, if you have a contact, that'd be great!

Thanks,

Colleen

From: Schumann, Katherine
Sent: Wednesday, February 13, 2019 8:22 AM
To: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>; Myers, James <James.Myers@fda.hhs.gov>; Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>
Subject: RE: Discuss Jacobus inquiry about amifampridine higher dose/(Phillips)

That seems like an important clarification to receive from DDI and the division before anyone reaches out to Catalyst. I agree that it is worth checking in with the drug shortage staff to see if they would be the appropriate group to inquire about availability of the product. Colleen, do you have a contact in DSS or do you need one?

From: Locicero, Colleen L
Sent: Wednesday, February 13, 2019 8:09 AM
To: Myers, James <James.Myers@fda.hhs.gov>; Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>
Cc: Schumann, Katherine <Katherine.Schumann@fda.hhs.gov>
Subject: RE: Discuss Jacobus inquiry about amifampridine higher dose/(Phillips)

I am trying to get clarification from DDI and the division as to whether they have received any complaints directly from patients/providers or only via Jacobus. If they have, then I think somebody (Drug Shortages of the division) could reach out to Catalyst, maybe, but if not…..?

From: Myers, James
Sent: Wednesday, February 13, 2019 8:01 AM
To: Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>; Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>
Cc: Schumann, Katherine <Katherine.Schumann@fda.hhs.gov>
Subject: RE: Discuss Jacobus inquiry about amifampridine higher dose/(Phillips)

I defer to Colleen and Katie here, but I think that's a good idea. My understanding is that they routinely reach out to companies to inquire about the marketing status of products. They might be able to do so on our behalf here.

From: Kimbrell, Maarika
Sent: Wednesday, February 13, 2019 7:57 AM
To: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>
Cc: Myers, James <James.Myers@fda.hhs.gov>; Schumann, Katherine <Katherine.Schumann@fda.hhs.gov>
Subject: RE: Discuss Jacobus inquiry about amifampridine higher dose/(Phillips)

On the question of why (some?) patients seem to have trouble

accessing the Catalyst product, would it make sense to check in with the shortage staff to see what they would normally do and we could consider doing the same/part of the same here?

From: Locicero, Colleen L
Sent: Wednesday, February 13, 2019 7:52 AM
To: Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>
Cc: Myers, James <James.Myers@fda.hhs.gov>; Schumann, Katherine <Katherine.Schumann@fda.hhs.gov>
Subject: RE: Discuss Jacobus inquiry about amifampridine higher dose/(Phillips)

Thanks, Maarika!

Colleen

From: Kimbrell, Maarika
Sent: Wednesday, February 13, 2019 7:47 AM
To: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>
Cc: Myers, James <James.Myers@fda.hhs.gov>; Schumann, Katherine <Katherine.Schumann@fda.hhs.gov>
Subject: RE: Discuss Jacobus inquiry about amifampridine higher dose/(Phillips)

Hey Colleen – Still wading through the substance here, but if you want to talk to someone in compounding, try Ruey Ju in the Compounding Staff within the OCD (which is run by Julie Dohm). That would be a good contact. We would need to coordinate with that staff anyway, if anyone is proving advice or guidance on compounding.

From: Locicero, Colleen L
Sent: Wednesday, February 13, 2019 7:00 AM
To: Stein, Peter <Peter.Stein@fda.hhs.gov>; Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>; Corrigan-Curay, Jacqueline <Jacqueline.Corrigan-Curay@fda.hhs.gov>; Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>; Myers, James <James.Myers@fda.hhs.gov>; Schumann, Katherine <Katherine.Schumann@fda.hhs.gov>
Subject: RE: Discuss Jacobus inquiry about amifampridine higher dose/(Phillips)

I am blissfully ignorant of much of anything to do with compounding, but am trying to identify somebody in

ORP who might be able to give me a quick briefer before we meet today, in case it would be helpful.

From: Stein, Peter
Sent: Tuesday, February 12, 2019 6:25 PM
To: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>; Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>; Corrigan-Curay, Jacqueline <Jacqueline.Corrigan-Curay@fda.hhs.gov>; Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>; Myers, James <James.Myers@fda.hhs.gov>; Schumann, Katherine <Katherine.Schumann@fda.hhs.gov>
Subject: RE: Discuss Jacobus inquiry about amifampridine higher dose/(Phillips)

(b) (5)

(b) (5)

I look forward to the discussion tomorrow,

Peter

From: Locicero, Colleen L
Sent: Tuesday, February 12, 2019 5:35 PM
To: Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>; Stein, Peter <Peter.Stein@fda.hhs.gov>; Corrigan-Curay, Jacqueline <Jacqueline.Corrigan-Curay@fda.hhs.gov>; Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>; Myers, James <James.Myers@fda.hhs.gov>;

Schumann, Katherine
<Katherine.Schumann@fda.hhs.gov>
Subject: RE: Discuss Jacobus inquiry about amifampridine higher dose/(Phillips)

All,

I just met with DDI and DNP and have a better idea of the scope of this issue now. Since tomorrow's discussion is scheduled for only a half hour and I will be on the phone, I want to provide a summary and identify three areas for discussion/consideration related to this issue.

Summary

DDI is receiving ***a lot*** of inquiries, as well as complaints, from individuals, physicians, the Commissioner's Office, the Patient Affairs Staff, Dr. Woodcock's office and others about amifampridine. These inquiries/complaints include complaints about the price of the Catalyst product, questions/complaints from physicians with patients (and patients themselves) on doses higher than 80 mg/day (although it is not clear whether the patients can't obtain sufficient quantities of the Catalyst product to meet their needs, are unable to get reimbursed for the higher doses, or both), and questions about compounding of amifampridine as an alternative to paying the Catalyst price. Ellis found Sigma-Aldrich's price for bulk 3,4 diaminopyridine that could be used by pharmacists to compound product for patients. Cost is $31.40 for what Ellis estimates would provide about a one month supply, which works out to an annual cost (excluding compounding fees) of less than $400, compared to the Catalyst price of $375,000.

While there seems to be some issue or problem regarding the availability of the Catalyst product, especially for patients on doses greater than 80 mg/day, it isn't clear to the division or DDI exactly what the problem is. If the Catalyst product is commercially available (which it was supposed to be as of 2/4), how is the supply to the high dose patients being limited? Or are these patients receiving the drug under the Catalyst Pathways program and the quantity being limited by Catalyst under that program? Or is it something else?

Questions/issues for discussion/consideration

1) It would be helpful to understand the situation with respect to the Catalyst product availability better. Can FDA

ask Catalyst for clarification about the availability of their product in general and for patients on higher than recommended doses (saying that we've received complaints and inquiries and would like to understand the situation)?

2) Do we want to ask OCC for (b) (4), (b) (5)

(b) (4), (b) (5)

3) What should DDI tell folks asking about the possibility of compounding the product to avoid the high cost of the Catalyst product?

I will be talking to Emily Helms Williams tomorrow or Thursday about the Catalyst/Jacobus amifampridine issues (exclusivity, expanded access, etc.). She's apparently on a detail in the Commissioner's office and I guess he wants some additional information/background.

Attached is a response that DDI has drafted to respond to correspondence sent (by the same individual) to DNP, Rare Diseases, the Center Director and Commissioner.

Thanks,
Colleen

<< Message: FW: Firdapse patient letters >>

-----Original Appointment-----
From: Phillips, J. Paul
Sent: Friday, February 08, 2019 5:19 PM
To: Phillips, J. Paul; Stein, Peter; Corrigan-Curay, Jacqueline; Kimbrell, Maarika; Myers, James; Locicero, Colleen L; Schumann, Katherine
Subject: Discuss Jacobus inquiry about amifampridine higher dose/(Phillips)
When: Wednesday, February 13, 2019 1:30 PM-2:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: WO22/ Room 1155

****UPDATE (2/12)- added WebEx info; please keep this invite (with red updated text) and delete the other duplicate mtg invite if it still exists on your calendar****

Purpose:

Discuss Jacobus inquiry regarding higher dose.

WebEx:

Join online

https://fda1.webex.com/fda1/j.php?MTID=m5169c61ddf1e3f564ac88dc9b05d40a7

Join by phone only

1-877-465-7975 US Toll Free

Access code: (b) (6)

Background & email

It is not clear whether Catalyst product is commercially available yet. They have been providing the approve product free of charge through a pathway program in the interim (between approval and marketing)—this may be how they are limiting the dose. Colleen will be attending a meeting with the Division (DNP) on Tuesday where she will hopefully learn more about the status of the situation.

From: Laura R. Jacobus [mailto:laura.jacobus@jacobus-pharmaceutical.com]
Sent: Wednesday, February 06, 2019 9:54 AM
To: Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>
Subject: on-going questions

Good morning

We continue to receive questions from physicians regarding their patients who require above 80 mg 3,4-dap daily.

Since Jacobus has ceased distribution to adult patients living with LEM we are unsure how to handle the issue. Catalyst has told the physicians (as told to us) that they will not provide additional medication above 80 mg / daily.

(b) (4)

Should they contact you if they have questions?

We are just stuck in a difficult position and fully recognize that any guidance must come from FDA.

Kind regards

Laura

Laura R. Jacobus

Jacobus Pharmaceutical Company, Inc

Office: 609-799-8221 ex 207

Mobile: (b) (6)

From: Locicero, Colleen L
To: Unger, Ellis
Subject: RE: EAP
Date: Tuesday, February 26, 2019 5:36:16 PM

You are welcome. This one is keeping everybody busy!!

From: Unger, Ellis
Sent: Tuesday, February 26, 2019 5:30 PM
To: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>
Subject: RE: EAP

Thanks for the update, Colleen!

Ellis

From: Locicero, Colleen L
Sent: Tuesday, February 26, 2019 5:27 PM
To: Dunn, Billy <Billy.Dunn@fda.hhs.gov>; Bastings, Eric <Eric.Bastings@fda.hhs.gov>; Kozauer, Nicholas <Nicholas.Kozauer@fda.hhs.gov>; Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Ware, Jacqueline H <Jacqueline.Ware@fda.hhs.gov>; Daugherty, Susan B (CSO) <Susan.Daugherty@fda.hhs.gov>; Unger, Ellis <Ellis.Unger@fda.hhs.gov>
Cc: Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>
Subject: RE: EAP

All,

OND Policy and ORP met with Jacqueline and Peter today to discuss these issues related to the amifampridine situation. Here is an update.

1) (b) (4), (b) (5)

2) Jacqueline and Peter would like an assessment from clinical and clinical pharmacology on the matter of whether differences between the two products could account for the Firdapse AEs (in patients previously treated with the Jacobus product) that have been reported. They have (b) (4), (b) (5) (b) (4), (b) (5) (b) (4), (b) (5) I will work with the clinical and clinical pharmacology teams on this request.

3) There was consensus that the division does not need to follow up with Catalyst on their EA program.

I will follow up with DDI on the matter of EA for the higher dose patients and ask them to send any requests/inquiries on this matter that require a response to me, so I can coordinate a response. If the division gets any, please do the same.

Thanks,
Colleen

From: Locicero, Colleen L
Sent: Friday, February 22, 2019 6:37 AM
To: Dunn, Billy <Billy.Dunn@fda.hhs.gov>; Stein, Peter <Peter.Stein@fda.hhs.gov>; Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>
Cc: Myers, James <James.Myers@fda.hhs.gov>
Subject: RE: EAP

I will be teleconferencing with Eleanor Mayer and Andrew Zacher from OCC at 3 pm today to hear OCC's conclusion on the higher dose matter. If anybody wishes to join me, please let me know.

I have a meeting scheduled for Tuesday afternoon with Peter, Jacqueline, Paul Phillips and my management to discuss

- the OCC determination
- (b) (4), (b) (5)
- Catalyst's EA program, which may still be providing their product to adult patients with LEMS – it isn't clear (if they are, do we need to tell them that needs to stop, since we told Jacobus that, keeping in mind that Jacobus specifically asked and Catalyst has never asked).

I have asked DSS to reach out to Catalyst to get clarity with respect to the complaints we have received from the higher dose patients who switched to Firdapse and claim they can't obtain sufficient amounts of Firdapse to meet their dosing needs. It isn't clear if/how the quantities of Firdapse are being limited by Catalyst if these patients are receiving the drug via usual commercial marketing of the drug. There are a few possible explanations and it seemed important to get a clearer picture of the situation to see if we can or should intervene.

Thanks,
Colleen

From: Dunn, Billy
Sent: Thursday, February 21, 2019 6:59 PM
To: Stein, Peter <Peter.Stein@fda.hhs.gov>; Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>; Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>
Subject: RE: EAP

Peter has described my current understanding of the state of affairs. I also am under the impression that OCC is in a contemplative state right now and we are waiting to hear from them – mainly about the higher than approved Catalyst dose. There have apparently been many ongoing discussions of the EA issue for this that have not involved DNP, so I may not have the latest update, but Colleen has been quite vigilant in staying on top of the various folks that are involved, so I have copied her on this.

Colleen – is there anything to add to what Peter noted below?

Billy

From: Stein, Peter
Sent: Thursday, February 21, 2019 1:52 PM
To: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>; Dunn, Billy <Billy.Dunn@fda.hhs.gov>
Subject: RE: EAP

My understanding was that we were (b) (4), (b) (5)

(b) (4), (b) (5)

Peter

From: Woodcock, Janet
Sent: Thursday, February 21, 2019 8:05 AM
To: Stein, Peter <Peter.Stein@fda.hhs.gov>; Dunn, Billy <Billy.Dunn@fda.hhs.gov>
Subject: FW: EAP

Do you know where we are with Jacobus? jw

From: Silvis, Lauren
Sent: Wednesday, February 20, 2019 10:15 PM

To: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>
Subject: EAP

https://www-m.cnn.com/2019/02/20/health/firdapse-expensive-drug-mom-bernie-sanders-eprise/index.html?r=https%3A%2F%2Fwww.google.com%2F

Janet, can I get your take on the EAP issue here? Happy to discuss tomorrow

From: Locicero, Colleen L
To: Corrigan-Curay, Jacqueline; Stein, Peter
Cc: Kimbrell, Maarika; Schumann, Katherine; Phillips, J. Paul; Myers, James
Subject: amifampridine update
Date: Thursday, March 07, 2019 3:39:00 PM
Attachments: SKM_C754e19030511480.pdf
Response to RFI drug supply info Son.pdf
FW Firdaps.msg
Firdapse AE.msg
Letter from Sen. Sanders to HHS and FDA on Firdapse.pdf

Jacqueline and Peter,

In follow up to our 2/26 meeting where you asked whether differences between the Jacobus and Catalyst products could account for the adverse events described in the emails received by DDI (a hypersensitivity type reaction and report of increased seizures), I obtained the following information from the clinical TL and the clinical pharmacology team.

The clinical TL provided the following very helpful table:

The only differences in chemistry between the two products seem to be 1) the phosphate salt and 2) the use of calcium stearate as an excipient in Firdapse.

The clinical TL concluded that it is possible that someone could have an allergic reaction to the phosphate salt or calcium stearate. She noted that amifampridine phosphate rapidly dissociates into amifampridine and phosphate, but it is unlikely that the phosphate increases phosphate levels enough to have any clinical significance. She also noted that both products have a risk of seizures.

Per the clinical pharmacology team, Catalyst conducted a relative BA study of the free base and phosphate salt formulations (not the final Jacobus/Catalyst products). Catalyst concluded that the base and salt formulations are BE for AUC, but not for Cmax.

Here are the results:

Please let me know your thoughts with respect to whether these differences might allow access to the Jacobus product for patients who report an AE on Firdapse.

On a related note, attached is Catalyst's response to inquiries they received from DSS about the Firdapse supply. According to Catalyst, they "have no knowledge of any patients or health care providers that have been "unable to obtain sufficient quantities" of Firdapse." They are not aware of a single patient who missed even a single dose in their transition to commercially

available Firdapse. They acknowledge that immediately after launch, they were focused on providing Firdapse to patients already on amifampridine, such that patients not previously treated with amifampridine (or who had adequate supplies) did not start to receive shipments of Firdapse until 2/4/19.

Prescriptions for doses that exceed 80 mg/day are referred to a specialty pharmacy that works with the prescriber to prepare letters of medical necessity for insurance coverage purposes. Catalyst is aware of 9 patients who have been covered by insurance at these doses and provides sufficient quantities of Firdapse to the specialty pharmacies to fill those prescriptions. The letter explains the Catalyst Pathways program and acknowledges that while participation in Pathways does not limit the patient's daily dose, patients on doses above 80 mg/day limits some Pathway services for those patients.

Also attached are Bernie Sanders' letter to Dr. Gottlieb and Catalyst's letter to Dr. Gottlieb regarding the Bernie Sanders letter.

Finally, I will be forwarding to you and the review division shortly the draft response to the Bernie Sanders letter that is being circulated for clearance.

Thanks,

Colleen

BERNARD SANDERS
VERMONT

COMMITTEES:
BUDGET, RANKING MEMBER
ENERGY AND NATURAL RESOURCES
ENVIRONMENT AND PUBLIC WORKS
HEALTH, EDUCATION, LABOR, AND PENSIONS
VETERANS' AFFAIRS

United States Senate
WASHINGTON, DC 20510–4504

332 SENATE DIRKSEN OFFICE BUILDING
WASHINGTON, DC 20510
(202) 224–5141

1 CHURCH STREET, 3RD FLOOR
BURLINGTON, VT 05401
(802) 862–0697
1 (800) 339–9834

www.sanders.senate.gov

February 26, 2019

The Honorable Alex M. Azar II
Secretary
U.S. Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, DC 20201

The Honorable Scott Gottlieb, M.D.
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Secretary Azar and Commissioner Gottlieb:

I understand that the Food and Drug Administration's (FDA) mission includes not only protecting the public health by ensuring medical products have benefits that outweigh their risks, but also "helping to speed innovations" to the public that are "more affordable."[1] FDA recently approved Firdapse to treat a rare neuromuscular disease called Lambert-Eaton myasthenic syndrome (LEMS), and in so doing, a drug that had been available to patients for free for decades through a compassionate use program is now being sold by Catalyst Pharmaceuticals at the outrageous annual list price of $375,000.

Since Firdapse's market entry my office has heard from patients who are unable to get the medicine they need because of this astronomical price. Without this medication, patients with LEMS will suffer and die.

Although I recognize FDA did not specifically intend for its approval of Firdapse to result in Catalyst setting this exorbitant price, FDA's approval of this drug nonetheless led to this result. Catalyst now has at least seven years of exclusive marketing rights during which time the company projects to make hundreds of millions of dollars in profit on a drug that has been available for decades.[2] In light of the drug's shocking price, I urge FDA to announce that it will not take enforcement action against pharmacies or manufacturers that were previously providing 3,4-DAP to patients and are able to resume the distribution of this drug, subject to the same requirements as the drug was available prior to the date of Firdapse's approval.

---

[1] U.S. Food & Drug Administration, "What We Do," (last accessed Feb. 26, 2019), (available at https://www.fda.gov/aboutfda/whatwedo/).
[2] "U.S. FDA approves Catalyst Pharma's rare disease drug," *Reuters* (Nov. 28, 2018), (available at https://www.reuters.com/article/us-catalyst-pharms-fda/us-fda-approves-catalyst-pharmas-rare-disease-drug-idUSKCN1NX2ZL).

Catalyst may be the most recent company to exploit their monopoly after receiving FDA approval for an inexpensive old drug, but they were certainly not the first. FDA's effort to bring older, unapproved drugs through the approval process may have some laudable benefits, but it has also led to instances where drugmakers use the grant of market exclusivity that accompanies FDA approval to fleece patients and taxpayers. The prices of very old and inexpensive drugs like colchicine, vasopressin, neostigmine, and others have been raised substantially by drugmakers following approval, causing needless suffering and adding to the cost of our health care system.[3]

It is absurd for FDA to claim affordability as central to its mission and tout policy activities that prioritize lower drug prices while simultaneously claiming the agency cannot take steps to lower drug prices.[4,5] You have said that "access to prescription drugs is a matter of public health."[6] I agree, and I also believe that the lack of access we have in this country to affordable prescription drugs is a public health crisis, a crisis that FDA must acknowledge its role in perpetuating and take action to address.

You have personally called out price gouging companies and said that "there's no moral imperative to price gouge and take advantage of patients. FDA will continue to promote competition so speculators and those with no regard to public health consequences can't take advantage of patients who need medicine."[7] Catalyst Pharmaceuticals' decision to set a price of $375,000 is a prime example of price gouging. This price was set without regard to public health and takes advantage of patients who need this medicine to survive.

For all of these reasons, I urge FDA to take action immediately. One action I suggest, an action for which there is similar agency precedent,[8] is to announce that FDA will not take enforcement action against pharmacies and manufacturers who were previously providing 3,4-DAP to patients and are able to resume the distribution of this drug. Thank you for your consideration.

Sincerely,

Bernard Sanders
United States Senator

---

[3] Michael Hiltzik, "The little-known FDA program that's driving drug prices higher," *LA Times* (Sept. 23, 2015), (available at https://www.latimes.com/business/hiltzik/la-fi-mh-the-little-known-fda-program-20150923-column.html).

[4] "Statement from FDA Commissioner Scott Gottlieb, M.D., on the Trump Administration's plan to lower drug prices," (May 11, 2018), (available at https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm607495.htm).

[5] "Statement from FDA Commissioner Scott Gottlieb, M.D. on new efforts to empower consumers by advancing access to nonprescription drugs," (July 17, 2018), (available at https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm613692.htm).

[6] *See* note 4.

[7] Scott Gottlieb, M.D., *Twitter* (Sept. 11, 2018), (available at https://twitter.com/SGottliebFDA/status/1039481679218401285).

[8] FDA Statement on Makena (Mar. 30, 2011), (available at http://web.archive.org/web/20110402072831/http:/www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm249025.htm).

From: Locicero, Colleen L
To: Kimbrell, Maarika; Myers, James; Schumann, Katherine
Subject: FW: Discussion of Sanders Letter Response
Date: Thursday, March 07, 2019 9:23:00 AM
Attachments: Firdapse Sanders draft response 352019 516 SJR.cllDOCX.DOCX
image001.png

Just FYI. I offered to handle the Sanders response for DNP and they accepted (otherwise, how are they going to get that application reviewed?!?)

Colleen

From: Locicero, Colleen L
Sent: Thursday, March 07, 2019 9:20 AM
To: Kempf, Lucas <Lucas.Kempf@fda.hhs.gov>
Cc: Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Bullock, Heather <Heather.Bullock@fda.hhs.gov>
Subject: RE: Discussion of Sanders Letter Response

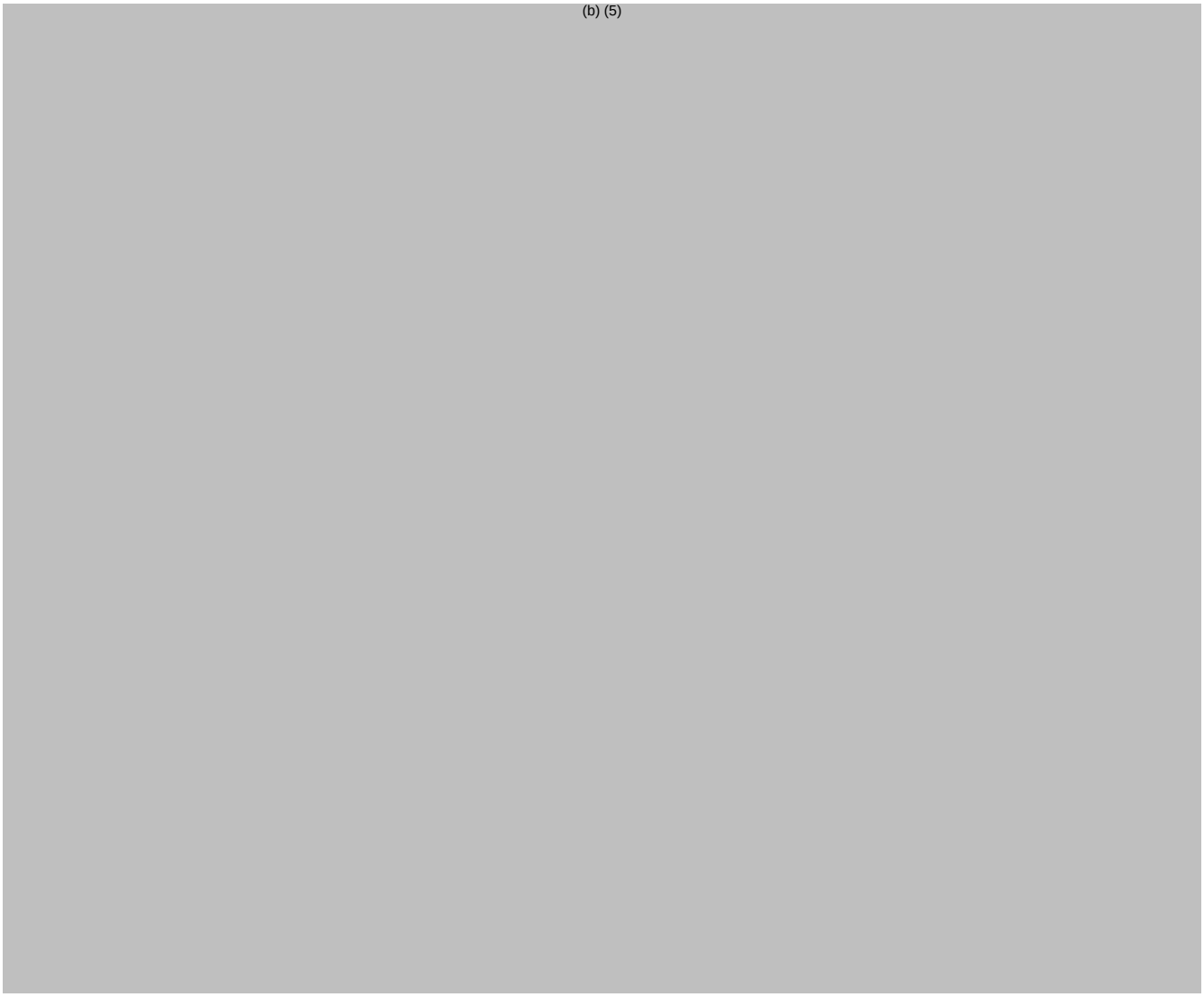
Hi Lucas,

Regarding the questions about expanded access to the Jacobus product, please note that Jacobus has never sponsored an expanded access IND or INDs for treatment use of their amifampridine product. They have, however, provided their product for treatment under physician-sponsored expanded access INDs. Jacobus has provided their product for treatment under these expanded access INDs for adult and pediatric patients with LEMS, as well as patients with other myasthenic syndromes. Because the differences between the Jacobus and Catalyst products (base versus phosphate salt and difference of a single excipient) are not expected to be clinically significant, Jacobus asked the division, a while back, whether they could continue to provide their product for treatment of LEMS under expanded access once the Catalyst product was approved and commercially available. The division advised Jacobus that they could not continue to do so, once the Catalyst product became commercially available, because the LEMS patients would have a satisfactory treatment available to them, at that time, and would therefore no longer meet the criteria for expanded access.

More recently, but prior to the commercial availability of Firdapse, Jacobus asked the division whether they could continue to provide their product for physician-sponsored expanded access programs once the Catalyst product was commercially available for patients not covered by the Firdapse approved labeling. Firdapse is approved only for the treatment of adult LEMS patients. Specifically, Jacobus asked whether they could continue to provide their product for expanded access for patients being treated for non-LEMS conditions, pediatric LEMS patients, and LEMS patients on doses of amifampridine higher than that recommended in the Firdapse approved labeling.

CDER consulted OCC on the general matter of (b) (5)
(b) (5)

(b) (5)



Also, attached is the draft response with a few high level edits/comments that I've made. I ask that once the letter is closer to final, I have the opportunity to have DNP and OND management review the letter for any comments/edits they may have.

If you have any questions, please let me know.

Much thanks,
Colleen

From: Locicero, Colleen L
Sent: Wednesday, March 06, 2019 11:18 AM
To: Kempf, Lucas <Lucas.Kempf@fda.hhs.gov>
Cc: Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Bullock, Heather <Heather.Bullock@fda.hhs.gov>
Subject: FW: Discussion of Sanders Letter Response

Hi Lucas,

I've been working very closely with DNP on the EA and other aspects of this situation, since

many of them involve policy decisions. Unfortunately, neither I nor members of the review team are available at 1:30 today. However, I'll get you an answer to the EA questions, including some background, and will also take a look at the letter and get back to you later this afternoon, but probably not before the 1:30 meeting because of other obligations. To ease the burden on the review team, who is working on the Jacobus application review, I will be the contact on the Sanders letter response and will involve the review division as needed. Does that work for you?

Thanks,
Colleen

From: Kempf, Lucas
Sent: Wednesday, March 06, 2019 8:45 AM
To: Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>
Subject: FW: Discussion of Sanders Letter Response

Hi Teresa,
Can you answer the question about the expanded access for firdapse that is highlighted below? There is a meeting at 1:30 pm in 32/3242 about the above response letter. I don't know if you are free or might be able to call in if they need technical assistance. If you know the answer and can brief me then I can respond otherwise. Sorry about the short turn around but for some reason HHS is asking for a super rapid turnaround on this response.
Thanks,
Lucas

From: Van Pool, Kendall
Sent: Wednesday, March 6, 2019 8:13 AM
To: Rothman, Sara <Sara.Rothman@fda.hhs.gov>; Kempf, Lucas <Lucas.Kempf@fda.hhs.gov>; Cosel, Gabrielle <Gabrielle.Cosel@fda.hhs.gov>; Becker, Carolyn E. <Carolyn.Becker@fda.hhs.gov>; Bennett, Carol <Carol.Bennett@fda.hhs.gov>; Ju, Ruey <Ruey.Ju@fda.hhs.gov>; OND Exec Ops <ONDExecops@fda.hhs.gov>
Cc: Anderson, Kathleen R <Kathleen.Anderson@fda.hhs.gov>; Bormel, Frances Gail <Frances.Bormel@fda.hhs.gov>; Dohm, Julie <Julie.Dohm@fda.hhs.gov>
Subject: RE: Discussion of Sanders Letter Response

Thanks so much for your work on this Sara! I really appreciate you taking a review of this to kick off the editing process.

Good catch on adding OND. I should have ensured they were on this from the start. I am adding OND's Exec Ops box on this and hopefully this can get routed to the right person.

OND – I have attached the original Sander's letter and Sara's edits to my original draft to get routed to the right person. We are planning a huddle today at 1:30 in Bldg 51 6157 to just get everyone in the room quickly to ensure we are covering the right bases on this and to map out an approval pathway. Hopefully you can have someone attend. Thanks and sorry

for the late notice!

Ken

From: Rothman, Sara
Sent: Tuesday, March 5, 2019 9:44 PM
To: Van Pool, Kendall <Kendall.VanPool@fda.hhs.gov>; Kempf, Lucas <Lucas.Kempf@fda.hhs.gov>; Cosel, Gabrielle <Gabrielle.Cosel@fda.hhs.gov>; Becker, Carolyn E. <Carolyn.Becker@fda.hhs.gov>; Bennett, Carol <Carol.Bennett@fda.hhs.gov>; Ju, Ruey <Ruey.Ju@fda.hhs.gov>
Cc: Anderson, Kathleen R <Kathleen.Anderson@fda.hhs.gov>; Bormel, Frances Gail <Frances.Bormel@fda.hhs.gov>; Dohm, Julie <Julie.Dohm@fda.hhs.gov>
Subject: Re: Discussion of Sanders Letter Response

Hi all,

Adding Ruey.

Attached are some revisions (which Kathy and Gail took a look at as well), with the caveat that the first few paragraphs may need to be revised based on information that OND can provide regarding the status of the Jacobus expanded access IND. If that IND remains in effect (for what I understand is a different salt than that which was approved), and if the existence of the IND is public, which I suspect it is, it would be important to address that in the response. Also, I suspect that what patients were receiving prior to the approval was 3,4-aminopyridine (without the phosphate) through the expanded access to IND program, or from compounding pharmacies (with or without the phosphate).

Ken, have you been in touch with OND about this? And thanks so much for preparing the first draft of the response -- it was very helpful!

Also, this has not, of course, been cleared through Compliance and is intended solely for discussion purposes at this point.

Best,

Sara

From: Van Pool, Kendall
Sent: Tuesday, March 5, 2019 5:36 PM
To: Kempf, Lucas; Rothman, Sara; Cosel, Gabrielle; Becker, Carolyn E.; Bennett, Carol
Cc: Anderson, Kathleen R; Bormel, Frances Gail
Subject: RE: Discussion of Sanders Letter Response

As noted in the calendar appointment I just sent. Here are the documents we can review tomorrow. I believe we should get edits from Sara on this so please keep an eye out for her edits.

Thanks All!!!

Ken

-----Original Appointment-----
From: Van Pool, Kendall
Sent: Tuesday, March 5, 2019 12:52 PM
To: Van Pool, Kendall; Kempf, Lucas; Rothman, Sara; Cosel, Gabrielle; Becker, Carolyn E.; Bennett, Carol
Cc: Anderson, Kathleen R; Bormel, Frances Gail
Subject: Discussion of Sanders Letter Response
When: Wednesday, March 6, 2019 1:30 PM-2:30 PM (UTC-05:00) Eastern Time (US & Canada).
Where: WO 51 6157 (near Mary Beth's office)

UPDATE – Attached is the draft letter and outline to be discussed. Also the room we will be in is a bit small, but I'm hoping that is ok since this meeting will be more of a huddle. I'm also adding a webex to this appointment.

As stated in my email - OL has greatly reduced the time to respond to the attached Sanders letter on Firdapse (COB Thursday). It is my understanding that the pressure is coming from HHS to get this drafted and FDA cleared. I am pushing back on them noting that clearance will be difficult to get done.

That said I am fairly far into my own drafting process on this response and I'm hoping that a way that we can expedite approval of the letter through CDER is to sit down

tomorrow afternoon. We were originally supposed to do this with a larger group on Thursday, but since the timing changed OL cancelled that meeting. If we can get this group together to ensure the draft (which I can share with the group later today) has all the appropriate points in it we may be able to at least jumpstart the letter through approval.

I know this is a bit of a different process for these things.

-- Do not delete or change any of the following text. --

Join Webex meeting

Meeting number (access code): (b) (6)

Meeting password (b) (6)

Join by phone

+1-210-795-0506 US Toll

+1-877-465-7975 US Toll Free

Global call-in numbers | Toll-free calling restrictions

Can't join the meeting?

If you are a host, go here to view host information.

IMPORTANT NOTICE: Please note that this Webex service allows audio and other information sent during the session to be recorded, which may be discoverable in a legal matter. By joining this session, you automatically consent to such recordings. If you do not consent to being recorded, discuss your concerns with the host or do not join the session.

(b) (5)

From: Locicero, Colleen L
To: Kempf, Lucas
Subject: RE: Discussion of Sanders Letter Response
Date: Thursday, March 07, 2019 10:55:00 AM
Attachments: image001.png

Hi Lucas,

Please see my comments in red.

Thanks,
Colleen

From: Kempf, Lucas
Sent: Thursday, March 07, 2019 9:32 AM
To: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>
Subject: RE: Discussion of Sanders Letter Response

Hi Colleen,
Can you give me a sense of when these conversations happened? I am trying to understand the timeline for when this all happened.
Thanks,
Lucas

From: Locicero, Colleen L
Sent: Thursday, March 7, 2019 9:20 AM
To: Kempf, Lucas <Lucas.Kempf@fda.hhs.gov>
Cc: Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Bullock, Heather <Heather.Bullock@fda.hhs.gov>
Subject: RE: Discussion of Sanders Letter Response

Hi Lucas,

Regarding the questions about expanded access to the Jacobus product, please note that Jacobus has never sponsored an expanded access IND or INDs for treatment use of their amifampridine product. They have, however, provided their product for treatment under physician-sponsored expanded access INDs. Jacobus has provided their product for treatment under these expanded access INDs for adult and pediatric patients with LEMS, as well as patients with other myasthenic syndromes. Because the differences between the Jacobus and Catalyst products (base versus phosphate salt and difference of a single excipient) are not expected to be clinically significant, Jacobus asked the division, a while back, whether they could continue to provide their product for treatment of LEMS under expanded access once the Catalyst product was approved and commercially available. The division advised Jacobus that they could not

continue to do so, once the Catalyst product became commercially available, because the LEMS patients would have a satisfactory treatment available to them, at that time, and would therefore no longer meet the criteria for expanded access. In July 2015, in response to questions from Jacobus about whether they could continue to provide their drug for expanded access if another company's marketing application for 3,4-DAP were approved, DNP informed Jacobus that if a drug product is approved that provides a comparable or satisfactory alternative to the Jacobus investigational drug for a patient or patients, it is unlikely the patient or patients would qualify or continue to qualify for expanded access to the Jacobus investigational drug.

More recently (Fall/Winter 2018), but prior to the commercial availability of Firdapse, Jacobus asked the division whether they could continue to provide their product for physician-sponsored expanded access programs once the Catalyst product was commercially available for patients not covered by the Firdapse approved labeling. Firdapse is approved only for the treatment of adult LEMS patients. Specifically, Jacobus asked whether they could continue to provide their product for expanded access for patients being treated for non-LEMS conditions, pediatric LEMS patients, and LEMS patients on doses of amifampridine higher than that recommended in the Firdapse approved labeling.

CDER consulted OCC on the general matter of (b) (5)

(b) (5)

(b) (4), (b) (5)

Also, attached is the draft response with a few high level edits/comments that I've made. I ask that once the letter is closer to final, I have the opportunity to have DNP and OND management review the letter for any comments/edits they may have.

If you have any questions, please let me know.

Much thanks,
Colleen

From: Locicero, Colleen L
Sent: Wednesday, March 06, 2019 11:18 AM
To: Kempf, Lucas <Lucas.Kempf@fda.hhs.gov>
Cc: Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Bullock, Heather <Heather.Bullock@fda.hhs.gov>
Subject: FW: Discussion of Sanders Letter Response

Hi Lucas,

I've been working very closely with DNP on the EA and other aspects of this situation, since many of them involve policy decisions. Unfortunately, neither I nor members of the review team are available at 1:30 today. However, I'll get you an answer to the EA questions, including some background, and will also take a look at the letter and get back to you later this afternoon, but probably not before the 1:30 meeting because of other obligations. To ease the burden on the review team, who is working on the Jacobus application review, I will be the contact on the Sanders letter response and will involve the review division as needed. Does that work for you?

Thanks,

Colleen

From: Kempf, Lucas
Sent: Wednesday, March 06, 2019 8:45 AM
To: Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>
Subject: FW: Discussion of Sanders Letter Response

Hi Teresa,
Can you answer the question about the expanded access for firdapse that is highlighted below? There is a meeting at 1:30 pm in 32/3242 about the above response letter. I don't know if you are free or might be able to call in if they need technical assistance. If you know the answer and can brief me then I can respond otherwise. Sorry about the short turn around but for some reason HHS is asking for a super rapid turnaround on this response.
Thanks,
Lucas

From: Van Pool, Kendall
Sent: Wednesday, March 6, 2019 8:13 AM
To: Rothman, Sara <Sara.Rothman@fda.hhs.gov>; Kempf, Lucas <Lucas.Kempf@fda.hhs.gov>; Cosel, Gabrielle <Gabrielle.Cosel@fda.hhs.gov>; Becker, Carolyn E. <Carolyn.Becker@fda.hhs.gov>; Bennett, Carol <Carol.Bennett@fda.hhs.gov>; Ju, Ruey <Ruey.Ju@fda.hhs.gov>; OND Exec Ops <ONDExecops@fda.hhs.gov>
Cc: Anderson, Kathleen R <Kathleen.Anderson@fda.hhs.gov>; Bormel, Frances Gail <Frances.Bormel@fda.hhs.gov>; Dohm, Julie <Julie.Dohm@fda.hhs.gov>
Subject: RE: Discussion of Sanders Letter Response

Thanks so much for your work on this Sara! I really appreciate you taking a review of this to kick off the editing process.

Good catch on adding OND. I should have ensured they were on this from the start. I am adding OND's Exec Ops box on this and hopefully this can get routed to the right person.

OND – I have attached the original Sander's letter and Sara's edits to my original draft to get routed to the right person. We are planning a huddle today at 1:30 in Bldg 51 6157 to just get everyone in the room quickly to ensure we are covering the right bases on this and to map out an approval pathway. Hopefully you can have someone attend. Thanks and sorry for the late notice!

Ken

From: Rothman, Sara

Sent: Tuesday, March 5, 2019 9:44 PM
To: Van Pool, Kendall <Kendall.VanPool@fda.hhs.gov>; Kempf, Lucas <Lucas.Kempf@fda.hhs.gov>; Cosel, Gabrielle <Gabrielle.Cosel@fda.hhs.gov>; Becker, Carolyn E. <Carolyn.Becker@fda.hhs.gov>; Bennett, Carol <Carol.Bennett@fda.hhs.gov>; Ju, Ruey <Ruey.Ju@fda.hhs.gov>
Cc: Anderson, Kathleen R <Kathleen.Anderson@fda.hhs.gov>; Bormel, Frances Gail <Frances.Bormel@fda.hhs.gov>; Dohm, Julie <Julie.Dohm@fda.hhs.gov>
Subject: Re: Discussion of Sanders Letter Response

Hi all,

Adding Ruey.

Attached are some revisions (which Kathy and Gail took a look at as well), with the caveat that the first few paragraphs may need to be revised based on information that OND can provide regarding the status of the Jacobus expanded access IND. If that IND remains in effect (for what I understand is a different salt than that which was approved), and if the existence of the IND is public, which I suspect it is, it would be important to address that in the response. Also, I suspect that what patients were receiving prior to the approval was 3,4-aminopyridine (without the phosphate) through the expanded access to IND program, or from compounding pharmacies (with or without the phosphate).

Ken, have you been in touch with OND about this? And thanks so much for preparing the first draft of the response -- it was very helpful!

Also, this has not, of course, been cleared through Compliance and is intended solely for discussion purposes at this point.

Best,

Sara

From: Van Pool, Kendall

Sent: Tuesday, March 5, 2019 5:36 PM
To: Kempf, Lucas; Rothman, Sara; Cosel, Gabrielle; Becker, Carolyn E.; Bennett, Carol
Cc: Anderson, Kathleen R; Bormel, Frances Gail
Subject: RE: Discussion of Sanders Letter Response

As noted in the calendar appointment I just sent. Here are the documents we can review tomorrow. I believe we should get edits from Sara on this so please keep an eye out for her edits.

Thanks All!!!

Ken

-----Original Appointment-----
From: Van Pool, Kendall
Sent: Tuesday, March 5, 2019 12:52 PM
To: Van Pool, Kendall; Kempf, Lucas; Rothman, Sara; Cosel, Gabrielle; Becker, Carolyn E.; Bennett, Carol
Cc: Anderson, Kathleen R; Bormel, Frances Gail
Subject: Discussion of Sanders Letter Response
When: Wednesday, March 6, 2019 1:30 PM-2:30 PM (UTC-05:00) Eastern Time (US & Canada).
Where: WO 51 6157 (near Mary Beth's office)

UPDATE – Attached is the draft letter and outline to be discussed. Also the room we will be in is a bit small, but I'm hoping that is ok since this meeting will be more of a huddle. I'm also adding a webex to this appointment.

As stated in my email - OL has greatly reduced the time to respond to the attached Sanders letter on Firdapse (COB Thursday). It is my understanding that the pressure is coming from HHS to get this drafted and FDA cleared. I am pushing back on them noting that clearance will be difficult to get done.

That said I am fairly far into my own drafting process on this response and I'm hoping that a way that we can expedite approval of the letter through CDER is to sit down tomorrow afternoon. We were originally supposed to do this with a larger group on Thursday, but since the timing changed OL cancelled that meeting. If we can get this group together to ensure the draft (which I can

share with the group later today) has all the appropriate points in it we may be able to at least jumpstart the letter through approval.

I know this is a bit of a different process for these things.

-- Do not delete or change any of the following text. --

Join Webex meeting

Meeting number (access code): (b) (6)

Meeting password: (b) (6)

Join by phone

+1-210-795-0506 US Toll

+1-877-465-7975 US Toll Free

Global call-in numbers | Toll-free calling restrictions

Can't join the meeting?

If you are a host, go here to view host information.

IMPORTANT NOTICE: Please note that this Webex service allows audio and other information sent during the session to be recorded, which may be discoverable in a legal matter. By joining this session, you automatically consent to such recordings. If you do not consent to being recorded, discuss your concerns with the host or do not join the session.

From: Kimbrell, Maarika
To: Locicero, Colleen L
Subject: RE: draft response to Bernie Sanders - amifampridine
Date: Friday, March 08, 2019 5:06:13 PM

Only add my comments if you think they are helpful. I think they might go part way to addressing Ellis's concerns, but really – you've got too many cats to herd here already. Don't keep things just to spare my feelings. Happy weekend, Colleen!

From: Locicero, Colleen L
Sent: Friday, March 08, 2019 4:52 PM
To: Corrigan-Curay, Jacqueline <Jacqueline.Corrigan-Curay@fda.hhs.gov>; Unger, Ellis <Ellis.Unger@fda.hhs.gov>; Dunn, Billy <Billy.Dunn@fda.hhs.gov>; Bastings, Eric <Eric.Bastings@fda.hhs.gov>; Kozauer, Nicholas <Nicholas.Kozauer@fda.hhs.gov>; Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>; Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>; Schumann, Katherine <Katherine.Schumann@fda.hhs.gov>; Myers, James <James.Myers@fda.hhs.gov>
Cc: Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Bullock, Heather <Heather.Bullock@fda.hhs.gov>; Stein, Peter <Peter.Stein@fda.hhs.gov>
Subject: RE: draft response to Bernie Sanders - amifampridine

Thanks so much everybody. I'll return to OEP this version and will add to it Jacqueline, Ellis's, and Maarika's comments for consideration.

Thanks again,
Colleen

From: Corrigan-Curay, Jacqueline
Sent: Friday, March 08, 2019 12:30 PM
To: Unger, Ellis <Ellis.Unger@fda.hhs.gov>; Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>; Dunn, Billy <Billy.Dunn@fda.hhs.gov>; Bastings, Eric <Eric.Bastings@fda.hhs.gov>; Kozauer, Nicholas <Nicholas.Kozauer@fda.hhs.gov>; Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>; Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>; Schumann, Katherine <Katherine.Schumann@fda.hhs.gov>; Myers, James <James.Myers@fda.hhs.gov>
Cc: Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Bullock, Heather <Heather.Bullock@fda.hhs.gov>; Stein, Peter <Peter.Stein@fda.hhs.gov>
Subject: RE: draft response to Bernie Sanders - amifampridine

I have made some smaller edits that do not speak to Ellis' concerns. However, to his point

(b) (5)

(b) (5)

Jcc

From: Unger, Ellis
Sent: Friday, March 8, 2019 10:28 AM
To: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>; Dunn, Billy <Billy.Dunn@fda.hhs.gov>; Bastings, Eric <Eric.Bastings@fda.hhs.gov>; Kozauer, Nicholas <Nicholas.Kozauer@fda.hhs.gov>; Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Corrigan-Curay, Jacqueline <Jacqueline.Corrigan-Curay@fda.hhs.gov>; Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>; Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>; Schumann, Katherine <Katherine.Schumann@fda.hhs.gov>; Myers, James <James.Myers@fda.hhs.gov>
Cc: Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Bullock, Heather <Heather.Bullock@fda.hhs.gov>; Stein, Peter <Peter.Stein@fda.hhs.gov>
Subject: RE: draft response to Bernie Sanders - amifampridine

All,

I could live with this letter, but in response to a very reasonable and understandable letter written by a politician, we've written something that sounds – well – political!

(b) (5)

Ellis

From: Locicero, Colleen L
Sent: Friday, March 08, 2019 9:02 AM
To: Dunn, Billy <Billy.Dunn@fda.hhs.gov>; Bastings, Eric <Eric.Bastings@fda.hhs.gov>; Unger, Ellis <Ellis.Unger@fda.hhs.gov>; Kozauer, Nicholas <Nicholas.Kozauer@fda.hhs.gov>; Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Corrigan-Curay, Jacqueline <Jacqueline.Corrigan-Curay@fda.hhs.gov>; Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>; Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>; Schumann, Katherine <Katherine.Schumann@fda.hhs.gov>; Myers, James <James.Myers@fda.hhs.gov>
Cc: Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Bullock, Heather <Heather.Bullock@fda.hhs.gov>; Stein, Peter <Peter.Stein@fda.hhs.gov>
Subject: RE: draft response to Bernie Sanders - amifampridine

And they are now asking for comments/clearance by end of today. Please let me know if that is a problem. Otherwise, if I don't hear from you, I'll assume this version, with my and Peter's edits/comments, is cleared and will send to OEP on Monday AM.

Thanks,
Colleen

From: Locicero, Colleen L
Sent: Friday, March 08, 2019 8:58 AM
To: Dunn, Billy <Billy.Dunn@fda.hhs.gov>; Bastings, Eric <Eric.Bastings@fda.hhs.gov>; Unger, Ellis <Ellis.Unger@fda.hhs.gov>; Kozauer, Nicholas <Nicholas.Kozauer@fda.hhs.gov>; Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Corrigan-Curay, Jacqueline <Jacqueline.Corrigan-Curay@fda.hhs.gov>; Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>; Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>; Schumann, Katherine <Katherine.Schumann@fda.hhs.gov>; Myers, James <James.Myers@fda.hhs.gov>
Cc: Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Bullock, Heather <Heather.Bullock@fda.hhs.gov>; Stein, Peter <Peter.Stein@fda.hhs.gov>
Subject: FW: draft response to Bernie Sanders - amifampridine

All,

Resending to include updated version of the draft response that includes comments from Peter. If you have any comments/concerns, please add them to this version.

Thanks,

Colleen

<< File: Firdapse Sanders draft response 372019 for Center Reviewcll.docx >>

From: Locicero, Colleen L
Sent: Thursday, March 07, 2019 4:27 PM
To: Dunn, Billy <Billy.Dunn@fda.hhs.gov>; Bastings, Eric <Eric.Bastings@fda.hhs.gov>; Unger, Ellis <Ellis.Unger@fda.hhs.gov>; Kozauer, Nicholas <Nicholas.Kozauer@fda.hhs.gov>; Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Stein, Peter <Peter.Stein@fda.hhs.gov>; Corrigan-Curay, Jacqueline <Jacqueline.Corrigan-Curay@fda.hhs.gov>; Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>; Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>; Schumann, Katherine <Katherine.Schumann@fda.hhs.gov>; Myers, James <James.Myers@fda.hhs.gov>
Cc: Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Bullock, Heather <Heather.Bullock@fda.hhs.gov>
Subject: draft response to Bernie Sanders - amifampridine

All,

Attached is the letter that Senator Sanders sent to Dr. Gottlieb and the draft response that was forwarded to OND for review/clearance. It includes a couple of edits and comment from me for your consideration. Please review and send me any edits/comment you may have (and please let me know if you disagree with my edits/comment). If you can send me your response by Monday, that would be great. If that's not enough time, please let me know.

Jacqueline – you probably received this directly, so if you want to handle your review/clearance separately, let me know.

Thanks,
Colleen

<< File: Letter from Sen. Sanders to HHS and FDA on Firdapse.pdf >> << File: Firdapse Sanders draft response 38 for OGD review 837.docx >>

From: Locicero, Colleen L
To: Stein, Peter
Subject: FW: Firdapse patient letters
Date: Monday, March 11, 2019 4:12:00 PM
Attachments: Firdapse (b) (6) draftOOPD_CLL_DNPCLEAN07March2019.doc.docx
image001.png
image002.jpg
image003.jpg
image004.jpg
image005.jpg
image006.jpg

Hi Peter,

My apologies for the constant emails on this issue. When you have the chance, could you let me know if the letter, as revised, is OK or if you'd like to further edit and/or discuss with the group?

Much thanks,
Colleen

From: Locicero, Colleen L
Sent: Friday, March 08, 2019 4:56 PM
To: Stein, Peter <Peter.Stein@fda.hhs.gov>; Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>; Corrigan-Curay, Jacqueline <Jacqueline.Corrigan-Curay@fda.hhs.gov>; Myers, James <James.Myers@fda.hhs.gov>; Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>; Schumann, Katherine <Katherine.Schumann@fda.hhs.gov>
Subject: FW: Firdapse patient letters

Thanks, Jacqueline!

Peter – if you are OK with this version, which includes Jacqueline's addition and the paragraph that I added that contains language from our website, I'll send this to DDI as cleared by DNP and this group.

Thanks,
Colleen

From: Corrigan-Curay, Jacqueline
Sent: Thursday, March 07, 2019 2:55 PM
To: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>; Stein, Peter <Peter.Stein@fda.hhs.gov>; Myers, James <James.Myers@fda.hhs.gov>; Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>; Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>; Schumann, Katherine <Katherine.Schumann@fda.hhs.gov>
Subject: RE: Firdapse patient letters

I have attempted to add something that may capture what Peter mentioned which is to highlight that the increased information on safety in the Catalyst label may in part be a result of having gone through the approval process. I know Peter noted this is an advantage of going through the approval process but I had trouble adding anything about the value which would seem to be congratulating the company for going through the approval process. If it misses the mark just delete or edit. I don't feel strongly.

Best,
Jacqueline

From: Locicero, Colleen L
Sent: Thursday, March 7, 2019 2:32 PM
To: Stein, Peter <Peter.Stein@fda.hhs.gov>; Myers, James <James.Myers@fda.hhs.gov>; Corrigan-Curay, Jacqueline <Jacqueline.Corrigan-Curay@fda.hhs.gov>; Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>; Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>; Schumann, Katherine <Katherine.Schumann@fda.hhs.gov>
Subject: RE: Firdapse patient letters

Thanks everybody. See attached version, edited based on your feedback. Does this work?

Thanks,
Colleen

From: Stein, Peter
Sent: Thursday, March 07, 2019 5:56 AM
To: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>; Myers, James <James.Myers@fda.hhs.gov>; Corrigan-Curay, Jacqueline <Jacqueline.Corrigan-Curay@fda.hhs.gov>; Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>; Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>; Schumann, Katherine <Katherine.Schumann@fda.hhs.gov>
Subject: RE: Firdapse patient letters

I put in some comments – it seems the major issue raised is the "safety" of the DAP Jacobus product vs the safety of the Catalyst product. I wonder if we can say something about the fact that often more safety information both preclinical and clinical is provided in labeling then may be known about a drug being used if it is an unapproved drug. We can point out that the more complete safety profile is one of the important values of having a drug go through the approval process. Of course we can't comment on the specifics, or if the drugs are comparable or not – but we could say something about how much more we know by requiring the range of studies and other information about a drug through an NDA.

Peter

From: Locicero, Colleen L
Sent: Wednesday, March 6, 2019 8:43 AM
To: Myers, James <James.Myers@fda.hhs.gov>; Stein, Peter <Peter.Stein@fda.hhs.gov>; Corrigan-Curay, Jacqueline <Jacqueline.Corrigan-Curay@fda.hhs.gov>; Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>; Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>; Schumann, Katherine <Katherine.Schumann@fda.hhs.gov>
Subject: RE: Firdapse patient letters

All,

Attached is the draft response to (b) (6) that DDI drafted and Orphan and DNP have cleared in response to (b) (6) multiple letters and emails to several FDA officials about Firdapse(attached). I will run this by DIDP to make sure all the information is disclosable. Please let me know if you have any concerns or edits/comments on the letter. DDI would like to send the response to (b) (6) by the end of this week/early next week, if possible. We are in receipt of several other emails/communications from patients and physicians and I hope to be able to use some of this language for those responses as well.

I have not yet seen the letter from Bernie Sanders or the response that is being drafted, but will forward those once I do.

I have obtained feedback from the clinical team leader and clinical pharmacology team in response to your request for their input on the differences between the two amifampridine products and whether these might account for some of the AEs about which we have heard. I have collated that information and am running it by DNP and ODE I management to make sure they agree and will then send to you for your consideration. At that time, I will also share with you Catalyst's response to DSS's outreach about the supply of Firdapse and Catalyst's letter to Dr. Gottlieb regarding the Bernie Sanders letter (Peter should already have a copy of that).

If you have any questions, please let me know.

Thanks,
Colleen

From: Locicero, Colleen L
Sent: Friday, March 01, 2019 4:43 PM
To: Myers, James <James.Myers@fda.hhs.gov>; Stein, Peter <Peter.Stein@fda.hhs.gov>; Corrigan-Curay, Jacqueline <Jacqueline.Corrigan-Curay@fda.hhs.gov>; Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>; Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>; Schumann, Katherine <Katherine.Schumann@fda.hhs.gov>
Subject: RE: Firdapse patient letters

Yes, I was going to send the letter to this group once DNP finished their review and clears. Is that OK?

Thanks,
Colleen

From: Myers, James
Sent: Friday, March 01, 2019 4:39 PM
To: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>; Stein, Peter <Peter.Stein@fda.hhs.gov>; Corrigan-Curay, Jacqueline <Jacqueline.Corrigan-Curay@fda.hhs.gov>; Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>; Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>; Schumann, Katherine <Katherine.Schumann@fda.hhs.gov>
Subject: Re: Firdapse patient letters

Thanks, Colleen. Have you seen a copy of whatever letters OOPD, Lucas or DDI are working on? Just want to make sure that we're all on the same page with what we are saying.

From: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>
Date: March 1, 2019 at 3:32:18 PM EST
To: Stein, Peter <Peter.Stein@fda.hhs.gov>, Corrigan-Curay, Jacqueline <Jacqueline.Corrigan-Curay@fda.hhs.gov>, Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>, Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>, Schumann, Katherine <Katherine.Schumann@fda.hhs.gov>, Myers, James <James.Myers@fda.hhs.gov>
Subject: FW: Firdapse patient letters

Just FYI

There's probably no way you haven't seen this article by now (this is the 3rd or 4th email I've seen about it), but in case you haven't…. I have not seen the Sanders letter yet.

I also heard from Emily Helms Williams in the Commissioner's Office today on (b) (4), (b) (5)

Thanks,
Colleen

From: Chew, Catherine
Sent: Friday, March 01, 2019 11:45 AM
To: Friedman, Aaron <Aaron.Friedman@fda.hhs.gov>; Maynard, Janet <Janet.Maynard@fda.hhs.gov>; Kremzner, Mary E <Mary.Kremzner@fda.hhs.gov>; Kempf, Lucas <Lucas.Kempf@fda.hhs.gov>
Cc: Dobbs, Donald <Donald.Dobbs@fda.hhs.gov>; Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>
Subject: RE: Firdapse patient letters

Colleen, just FYI-
https://www.reuters.com/article/us-usa-healthcare-catalyst/senator-sanders-urges-fda-to-allow-older-versions-of-375k-drug-idUSKCN1QH1LK?rpc=401&

Looks like Bernie Sander sent a letter to FDA too. The article says:

FDA spokeswoman Jennifer Rodriguez, in an emailed statement, said the FDA has received the letter and will respond directly to the senator. HHS also said it has received the letter and will respond.

From: Friedman, Aaron <Aaron.Friedman@fda.hhs.gov>
Date: March 1, 2019 at 10:29:49 AM EST
To: Chew, Catherine <Catherine.Chew@fda.hhs.gov>, Maynard, Janet <Janet.Maynard@fda.hhs.gov>, Kremzner, Mary E <Mary.Kremzner@fda.hhs.gov>, Kempf, Lucas <Lucas.Kempf@fda.hhs.gov>
Cc: Dobbs, Donald <Donald.Dobbs@fda.hhs.gov>, Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>
Subject: RE: Firdapse patient letters

My suggestions are highlighted in the attached version. We want to be sure the email to OOPD is acknowledged in the introduction, and orphan-drug exclusivity mentioned further down. I was probably not working off the latest version, so if you have trouble incorporating my edits into the current version, I'm happy to review and edit that version.

Thanks!
Aaron

From: Chew, Catherine
Sent: Thursday, February 28, 2019 3:22 PM
To: Maynard, Janet <Janet.Maynard@fda.hhs.gov>; Kremzner, Mary E <Mary.Kremzner@fda.hhs.gov>; Kempf, Lucas <Lucas.Kempf@fda.hhs.gov>
Cc: Dobbs, Donald <Donald.Dobbs@fda.hhs.gov>; Friedman, Aaron <Aaron.Friedman@fda.hhs.gov>; Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>
Subject: RE: Firdapse patient letters

Sure, no problem at all.

Colleen, do you know the latest status of the Firdapse letter?

If it hasn't been reviewed yet, Aaron can add language to the letter before it's completely cleared.

Thanks,
Cat

From: Maynard, Janet
Sent: Thursday, February 28, 2019 3:12 PM
To: Chew, Catherine <Catherine.Chew@fda.hhs.gov>; Kremzner, Mary E <Mary.Kremzner@fda.hhs.gov>; Kempf, Lucas <Lucas.Kempf@fda.hhs.gov>
Cc: Dobbs, Donald <Donald.Dobbs@fda.hhs.gov>; Friedman, Aaron <Aaron.Friedman@fda.hhs.gov>
Subject: RE: Firdapse patient letters

Hi Catherine—I wondered if it was possible to include Office of Orphan Products in the response letter because my office also received inquiries? In addition, the draft response letter doesn't include a discussion of orphan exclusivity, which was brought up and I wondered if we should add something about that? I'm copying Aaron Friedman who is regulatory council for Orphan Products and could assist with language regarding orphan exclusivity if that would be helpful. Thanks so much, Janet

---

From: Chew, Catherine
Sent: Sunday, February 24, 2019 6:37 PM
To: Maynard, Janet <Janet.Maynard@fda.hhs.gov>; Kremzner, Mary E <Mary.Kremzner@fda.hhs.gov>; Kempf, Lucas <Lucas.Kempf@fda.hhs.gov>
Cc: Dobbs, Donald <Donald.Dobbs@fda.hhs.gov>
Subject: RE: Firdapse patient letters

Hello Janet,

DDI has drafted a response to the Firdapse letter (attached), however after we met with the Billy Dunn and the review division and Colleen Locicero, our letter was taken to OCC for clearance. There is a lot surrounding this issue, so we are waiting right now. I can send you the latest email where Colleen asked the Drug Shortage Staff to contact Catalyst. Some of that information will impact our letter. Jacobus (the sponsor of the EA) has also asked to forward their inquiries to DDI, so there are many moving parts.

We'll keep you informed,
Cat

From: Maynard, Janet
Sent: Sunday, February 24, 2019 5:53 PM
To: Kremzner, Mary E <Mary.Kremzner@fda.hhs.gov>; Kempf, Lucas <Lucas.Kempf@fda.hhs.gov>

Cc: Chew, Catherine <Catherine.Chew@fda.hhs.gov>
Subject: RE: Firdapse patient letters

Hi—I just wanted to follow-up and see if a response had been generated in regards to the Firdapse letters? Thank you, Janet

---

From: Kremzner, Mary E
Sent: Tuesday, December 18, 2018 5:56 PM
To: Maynard, Janet <Janet.Maynard@fda.hhs.gov>; Kempf, Lucas <Lucas.Kempf@fda.hhs.gov>
Cc: Chew, Catherine <Catherine.Chew@fda.hhs.gov>
Subject: RE: Firdapse patient letters

That's very helpful. I received a preliminary "yes" from the letters lead in my division which means he is familiar with the topic.

We'll be in touch soon.
mK

From: Maynard, Janet <Janet.Maynard@fda.hhs.gov>
Date: December 18, 2018 at 4:29:42 PM EST
To: Kremzner, Mary E <Mary.Kremzner@fda.hhs.gov>, Kempf, Lucas <Lucas.Kempf@fda.hhs.gov>
Cc: Chew, Catherine <Catherine.Chew@fda.hhs.gov>
Subject: RE: Firdapse patient letters

Thank you very much. OOPD is also happy to help in anyway, especially related to the exclusivity questions. Thank you, Janet

---

From: Kremzner, Mary E
Sent: Tuesday, December 18, 2018 3:46 PM
To: Kempf, Lucas <Lucas.Kempf@fda.hhs.gov>
Cc: Chew, Catherine <Catherine.Chew@fda.hhs.gov>; Maynard, Janet <Janet.Maynard@fda.hhs.gov>
Subject: RE: Firdapse patient letters

Yes, I saw that and appreciate your willingness to help. We have worked with Billy in the past to clear responses from patient communities. .
We'll keep you posted on what we find and develop in response to (b) (6) (b) (6) emails.
mK

From: Kempf, Lucas
Sent: Tuesday, December 18, 2018 3:42 PM

To: Kremzner, Mary E <Mary.Kremzner@fda.hhs.gov>
Cc: Chew, Catherine <Catherine.Chew@fda.hhs.gov>; Maynard, Janet <Janet.Maynard@fda.hhs.gov>
Subject: RE: Firdapse patient letters

Billy Dunn said that he would be the lead for OND and he received multiple emails, along with the commissioner. I can review at it prior to posting.

From: Kremzner, Mary E
Sent: Tuesday, December 18, 2018 3:40 PM
To: Kempf, Lucas <Lucas.Kempf@fda.hhs.gov>
Cc: Chew, Catherine <Catherine.Chew@fda.hhs.gov>; Maynard, Janet <Janet.Maynard@fda.hhs.gov>
Subject: RE: Firdapse patient letters

Hi Lucas,
Thanks for the heads up on the letters from (b) (6). If you would be willing to edit and clear, I think we should try to reply. We may not answer all 6 of her questions directly, e.g., "Who was involved in the approval process for the FDA", but perhaps we could acknowledge her concerns and answer a few of the other questions. What do you think?

In the meantime, we will check to see if we have similar queries or comments on these drugs.
mK

Mary E. Kremzner, PharmD, MPH, BCGP
CAPT,USPHS
Director|Division of Drug Information
FDA|CDER|OCOMM
Hillandale Bldg., Room 4150
Silver Spring, MD 20993
301 796 3144
mary.kremzner@fda.hhs.gov

From: Kempf, Lucas
Sent: Tuesday, December 18, 2018 2:40 PM
To: Kremzner, Mary E <Mary.Kremzner@fda.hhs.gov>
Cc: Chew, Catherine <Catherine.Chew@fda.hhs.gov>; Maynard, Janet <Janet.Maynard@fda.hhs.gov>
Subject: Firdapse patient letters

Hi Mary,
It was suggested by Janet Maynard, the acting director of Orphan Products, to forward this letter to you so that your office would be aware (she received

similar ones) and perhaps coordinate a response if needed. I spoke to Billy Dunn today and he said that he would be the lead for any issue regarding ONDs response if you need to contact him. Please let me know where to forward future emails if needed

Bests,
Lucas

Lucas Kempf, MD
Associate Director (acting), Rare Diseases Program
Office of New Drugs – Immediate Office
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-1140
Lucas.Kempf@fda.hhs.gov

cid:image001.png@01D1C57E.DFA022A0

From: Chew, Catherine
To: Friedman, Aaron; Mathers, Michelle; Buracchio, Teresa; Startzman, Henry
Cc: Bullock, Heather
Subject: RE: Firdapse
Date: Monday, April 22, 2019 2:23:01 PM
Attachments: image029.png
image030.jpg
image031.jpg
image032.jpg
image033.jpg
image034.jpg
image035.png
image036.png
image037.png
image038.png
image039.png
image040.png
image041.jpg
image042.jpg

Thanks Aaron, that helps a lot. And we won't mention Jacobus unless asked.

Thank you all for the quick reply,
Cat

From: Friedman, Aaron <Aaron.Friedman@fda.hhs.gov>
Date: April 22, 2019 at 2:19:39 PM EDT
To: Chew, Catherine <Catherine.Chew@fda.hhs.gov>, Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>, Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>, Startzman, Henry <Henry.Startzman@fda.hhs.gov>
Cc: Bullock, Heather <Heather.Bullock@fda.hhs.gov>
Subject: RE: Firdapse

In terms of the Orphan Products Clinical Trials Grants Program, we have not provided funding to Catalyst for Firdapse. However (and I don't know if you need to include this in your response to HHS), we have funded a few studies for amifampridine, one of which has a connection to Jacobus.

Aaron

From: Chew, Catherine
Sent: Monday, April 22, 2019 1:43 PM
To: Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Startzman, Henry <Henry.Startzman@fda.hhs.gov>; Friedman, Aaron <Aaron.Friedman@fda.hhs.gov>
Cc: Bullock, Heather <Heather.Bullock@fda.hhs.gov>
Subject: RE: Firdapse

Great, thank you Michelle.

From: Unger, Ellis
To: Walsh, Sandy
Subject: RE: Early look at pediatric LEMS drug approval clips
Date: Tuesday, May 07, 2019 9:27:00 AM
Attachments: image002.png
image004.jpg
image006.jpg
image008.jpg
image010.jpg
image012.jpg

Good press! Thanks for sending. I like being crafty…

Too bad the Catalyst lawyers will be on our doorstep soon!

From: Walsh, Sandy
Sent: Tuesday, May 07, 2019 7:53 AM
To: Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>; Dunn, Billy <Billy.Dunn@fda.hhs.gov>; Bastings, Eric <Eric.Bastings@fda.hhs.gov>; Kozauer, Nicholas <Nicholas.Kozauer@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Unger, Ellis <Ellis.Unger@fda.hhs.gov>; Shah, Nisha <Nisha.Shah@fda.hhs.gov>; Myers, James <James.Myers@fda.hhs.gov>; Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>; Hayes, Nancy <Nancy.Hayes@fda.hhs.gov>; Friedman, Aaron <Aaron.Friedman@fda.hhs.gov>; Fuchs, Elissa <Elissa.Fuchs@fda.hhs.gov>; Nduom, Kelley <Kelley.Nduom@fda.hhs.gov>; Dettelbach, Kim <Kim.Dettelbach@fda.hhs.gov>; Sitlani, Jay <Jay.Sitlani@fda.hhs.gov>
Cc: Bolek, Michelle <Michelle.Bolek@fda.hhs.gov>
Subject: Early look at pediatric LEMS drug approval clips

Good morning,
Below are a few early news clips from the LEMS drug approval. You'll see that STAT/Pharmalot reporter did a deeper dive, speculating on issues around the action including pricing and exclusivity issues, etc. I'll keep an eye out for additional clips today.

Reuters
HEALTH NEWS
MAY 6, 2019 / 6:11 PM / UPDATED 13 HOURS AGO

FDA grants Jacobus Pharma approval for rare disease drug

(Reuters) - Jacobus Pharmaceutical Co Inc on Monday won U.S. approval for the first drug to treat children with Lambert-Eaton myasthenic syndrome, a rare autoimmune disorder.

The drug, Ruzurgi, was approved for use in patients aged between 6 and 17, the FDA said here.

Lambert-Eaton myasthenic syndrome, which affects about three people per million worldwide, affects the connection between nerves and muscles, disrupting the ability of nerve cells to send signals to muscle cells.

The treatment currently available has been approved only for adults.

Reporting by Tamara Mathias in Bengaluru; Editing by Anil D'Silva

STAT/Pharmalot

In a crafty move, FDA may have found a way to dampen controversy over a $375,000 rare-disease drug

By Ed Silverman @Pharmalot

May 6, 2019

The Food and Drug Administration just added an unexpected twist to a simmering controversy over a rare disease drug that earlier this year briefly became a poster child for high-priced medicines.

In a surprise move, the agency approved a medicine from Jacobus Pharmaceuticals, a small, family-run company, for treating a neuromuscular disorder called Lambert-Eaton myasthenic syndrome, or LEMS, for children ages 6 to 17. However, the approval potentially adds unforeseen competition for Catalyst Pharmaceuticals (CPRX), which only last December won an FDA endorsement to market its own treatment for adults.

In after-hours trading, Catalyst stock was down as much 44%.

The Food and Drug Administration just added an unexpected twist to a simmering controversy over a rare disease drug that earlier this year briefly became a poster child for high-priced medicines.

In a surprise move, the agency approved a medicine from Jacobus Pharmaceuticals, a small, family-run company, for treating a neuromuscular disorder called Lambert-Eaton myasthenic syndrome, or LEMS, for children ages 6 to 17. However, the approval potentially adds unforeseen competition for Catalyst Pharmaceuticals (CPRX), which only last December won an FDA endorsement to market its own treatment for adults.

In after-hours trading, Catalyst stock was down as much 44%.

Here's why: The FDA approval of the Catalyst drug, called Firdapse, set off a firestorm. Until then, a few hundred LEMS patients were able for years to obtain the Jacobus drug for free under a compassionate use program sanctioned by the FDA. But with its approval, Catalyst obtained seven years of market exclusivity, which meant Jacobus and compound pharmacies could no longer market their versions.

The move created an uproar because Catalyst decided to charge $375,000 list price, depending upon total patient dosing, for Firdapse. In February, U.S. Sen. Bernie Sanders (I-Vt.), who's made high drug prices a raison d'etre, accused the drug maker of "corporate greed" and

"immoral exploitation." And he asked the FDA to permit Jacobus and compounders to resume suppliers of their treatments.

"This sounds like a workaround."

Dr. Donald Sanders, a Duke University

The agency appears to have heeded the call. Jacobus has not yet disclosed a price for its drug, called Ruzurgi. But by approving it for children, the agency is making it possible for physicians to prescribe the Jacobus drug for any patient, regardless of age, because doctors are free to prescribe medicines for unapproved or so-called off-label uses. Interestingly, the FDA approval was predicated, in part, on data from studies involving adults.

"If it's on the market for children, it can be prescribed for adults," said Dr. Donald Sanders, a Duke University researcher who worked with the Jacobus family when they first developed their LEMS drug and later helped design the clinical trial that was submitted to the FDA. "I don't know of any drug that is approved for adults with LEMS other than Firdapse, but we already use many other medicines off label to treat LEMS. This sounds like a workaround."

An FDA spokeswoman sent us this: "The decision to treat a patient with a drug for an unapproved use is up to the treating health care professional and generally speaking, the practice of medicine is not regulated by the FDA. Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics, and devices according to their best knowledge and judgement."

Meanwhile, PiperJaffray analyst Joseph Catanzaro wrote this: "While this is a different label indication than Firdapse's adult LEMS label, it will no doubt raise questions around whether Ruzurgi will be used off-label in adult patients and whether Firdapse will be able to maintain the orphan drug price point it set at launch. However, we suspect that there will be legal questions around whether the approval of Ruzurgi infringes on Firdapse's orphan drug exclusivity in LEMS."

"We see this approval by the FDA simply as a way to combat the pricing rhetoric that has surrounded Firdapse since its approval late last year and bring a potential competitor to the market," he continued, adding that there are "questions around whether the adult and pediatric populations represent two distinct orphan diseases."

"Obviously, it will be less than what they're charging,"

Laura Jacobus, Jacobus Pharmaceuticals, when asked about price

The uncertainty helps explain investor reaction to the FDA approval, which was announced late Monday. A spokesman for Catalyst, which had indicated there are as many as 3,000 LEMS patients in the U.S., declined to comment.

However, there are some extenuating factors.

For one thing, a doctor may prescribe the Jacobus drug, but that doesn't mean an insurance company will automatically provide coverage. Sometimes, insurers will not cover off-label use, although in this instance, the price of the Catalyst drug may provide some impetus — if the Jacobus drug costs significantly less.

As of Monday night, Laura Jacobus, who runs the privately held company, said a final decision hasn't been made.

"I haven't given it much thought. This decision just came in, but obviously, it will be less than what they're charging," she told us. "But we're carrying over the last 27 years the research, development, the compassionate use manufacturing. We're probably $60 million in the hole. And the post-approval commitments are probably (going to cost) $10 million to $20 million."

However, she declined to discuss off-label usage. "We assume we can't take care of adult patients, but we'd like to take care of pediatric patients," she said. "That's a role we're pleased to provide."

One patient who had been taking the Jacobus drug under the compassionate use program but was forced to switch to Firdapse, told us she is excited by the approval. She is among several Firdapse patients who have complained the medicine is not as effective as the older Jacobus treatment.

"Oh my gosh, this is very good news," said Rebecca Hovde, who lives in Iowa. "I will definitely ask my doctor to switch to the Jacobus drug now."

Pharma Times

FDA approves Ruzurgi for children with Lambert-Eaton myasthenic syndrome

7th May 2019

By Anna Smith

The US Food and Drug Administration (FDA) has approved Jacobus' Ruzurgi (amifampridine) tablets for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in patients six to less than 17 years of age.

The approval marks the first FDA approval of a treatment specifically for paediatric patients with LEMS, as currently the only other treatment approved for LEMS is approved for use in adults.

The approval was based on a placebo-controlled withdrawal study of 32 adult patients in which patients were taking Ruzurgi for at least three months prior to entering the study, using pharmacokinetic modelling and simulation to identify the dosing regimen in paediatric patients and safety data from paediatric patients.

"We continue to be committed to facilitating the development and approval of treatments for rare diseases, particularly those in children," said Billy Dunn, director of the Division of Neurology Products in the FDA's Centre for Drug Evaluation and Research. "This approval will provide a much-needed treatment option for paediatric patients with LEMS who have significant weakness and fatigue that can often cause great difficulties with daily activities."

The FDA has also granted the application Priority Review and Fast Track designations, alongside its Orphan Drug designation, which provides incentives to assist and encourage the

development of drugs for rare diseases.

LEMS is a rare autoimmune disorder that affects the connection between nerves and muscles and causes weakness and other symptoms in affected patients. In people with LEMS, the body's own immune system attacks the neuromuscular junction - the connection between nerves and muscles - and disrupts the ability of nerve cells to send signals to muscle cells.

Sandy Walsh
Press Officer

Office of Media Affairs
Office of External Affairs
U.S. Food and Drug Administration
Tel: 301-796-4669
Sandy.Walsh@fda.hhs.gov

From: Ahmed, Mariam
To: Uppoor, Ramana S; Mehta, Mehul U; AbuAsal, Bilal
Subject: 34DAP_divisionMeeting_MA.pptx
Date: Wednesday, August 14, 2019 1:44:29 PM
Attachments: 34DAP_divisionMeeting_MA.pptx
ViewDocument.pdf

Hi all,
Please see attached the slides. I am also attaching the pre-NDA meeting minutes for Ruzurgi. You can see that we asked that they include information regarding hepatic and renal impairment in their NDA submission in response to their specific questions regarding renal and hepatic impairment (9 and 10) and we told them that they may receive a PMR for hepatic and renal. In the Sponsor-submitted slide presentation(included in the meeting minutes), they indicated that they are committed to conduct the hepatic and renal impairment studies as PMR if required.

Thanks,
Mariam

U.S. FOOD & DRUG ADMINISTRATION

Ruzurgi
NDA-209321

Amifampridine (3,4-diaminopyridine, 3,4-DAP)
for
treatment of (b) (4) Lambert-Eaton myasthenia Syndrome (LEMS)

Applicant
JACOBUS PHARMACEUTICAL COMPANY (JPC)

Clinical Pharmacology Team

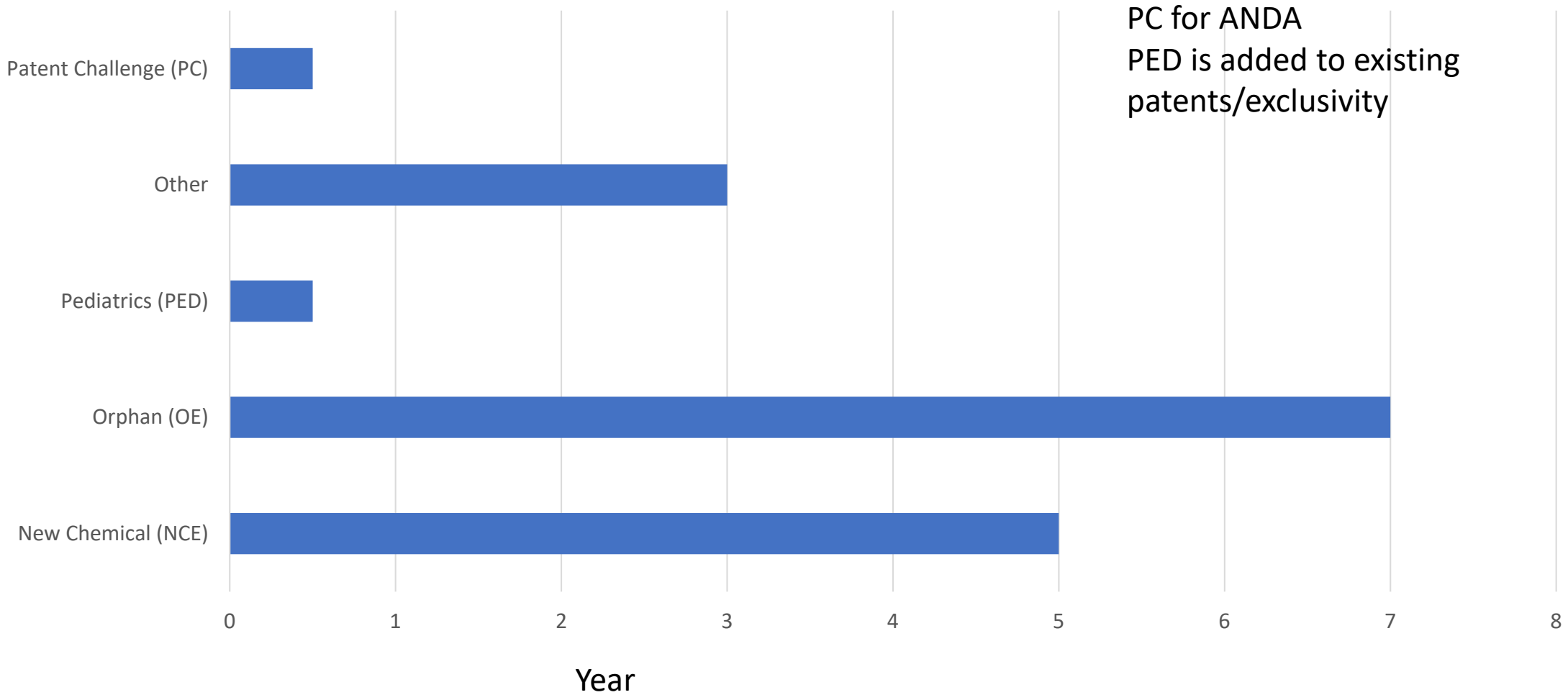
Primary Clinical Pharmacology/PM Reviewer: Mariam Ahmed
Primary PG Reviewer: Katarzyna Drozda
Team Leaders: Sabarinath Sreedharan, Kevin Krudys, and Christian Grimstein

Before we begin

Patency and Exclusivity

	Patency	Exclusivity
Definition	Granted by the United States Patent and Trademark Office (USPTO) anywhere along the development lifeline of a drug	Exclusive marketing rights granted by the FDA upon approval of a drug and may run concurrently with a patent but need not do so
length	20 years since filling	Varies depends on the type of exclusivity granted (starts since approval)

Exclusivity Length



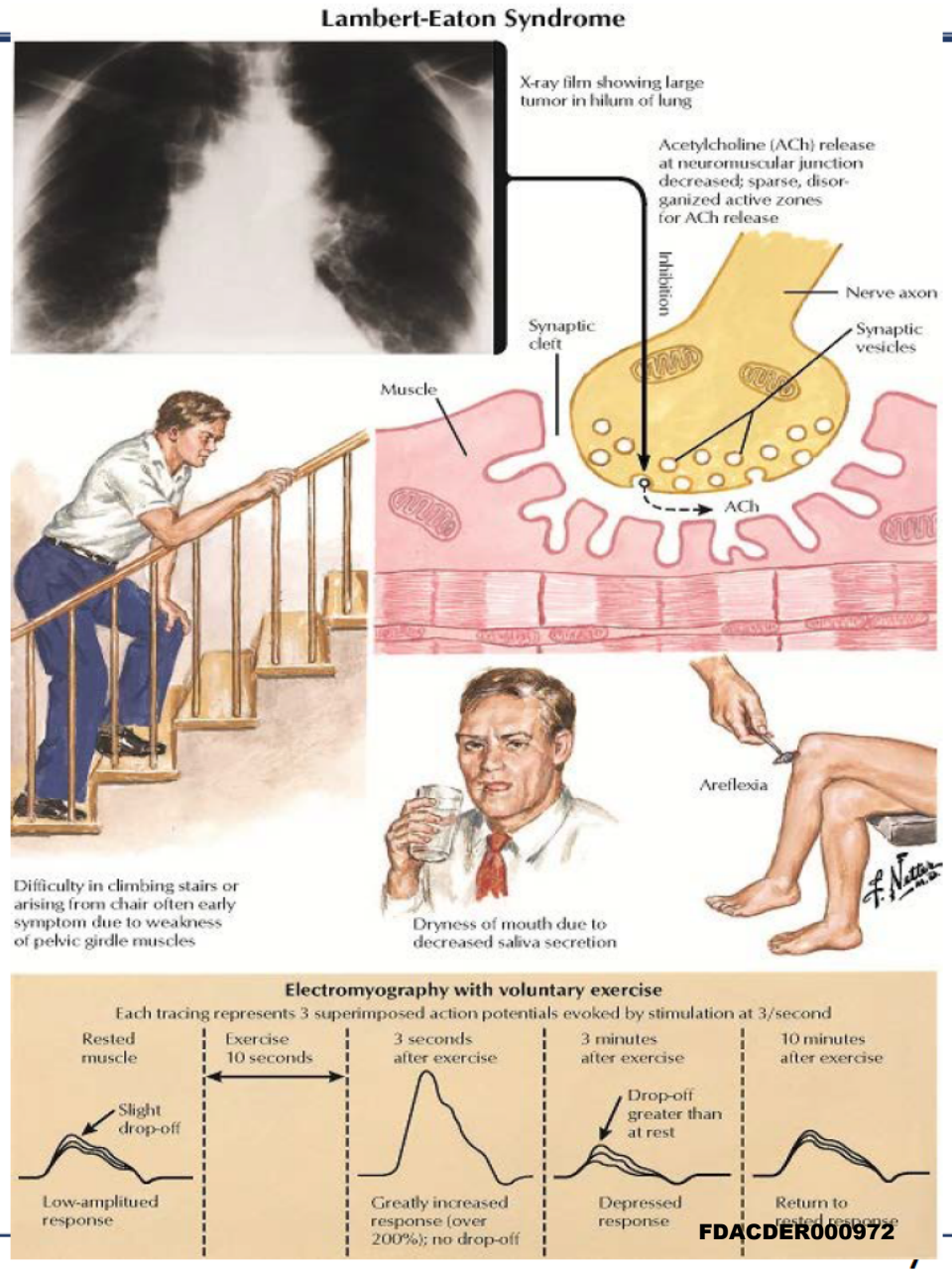

Lets Start

Outline

- Target Indication
- 3,4-DAP Background and History
- Regulatory History
- Program Overview
- Clinical Pharmacology
- Review Focus

LEMS Disease Pathophysiology

- LEMS is an ultra-rare, autoimmune, myasthenia like syndrome, caused by Antibodies to the voltage-gated calcium channel resulting in interference with the release of acetylcholine (Ach) at the motor nerve terminal.
- Age at onset: 50 years (1-76 years)
- Major clinical presentation:
  - Progressive proximal muscle weakness

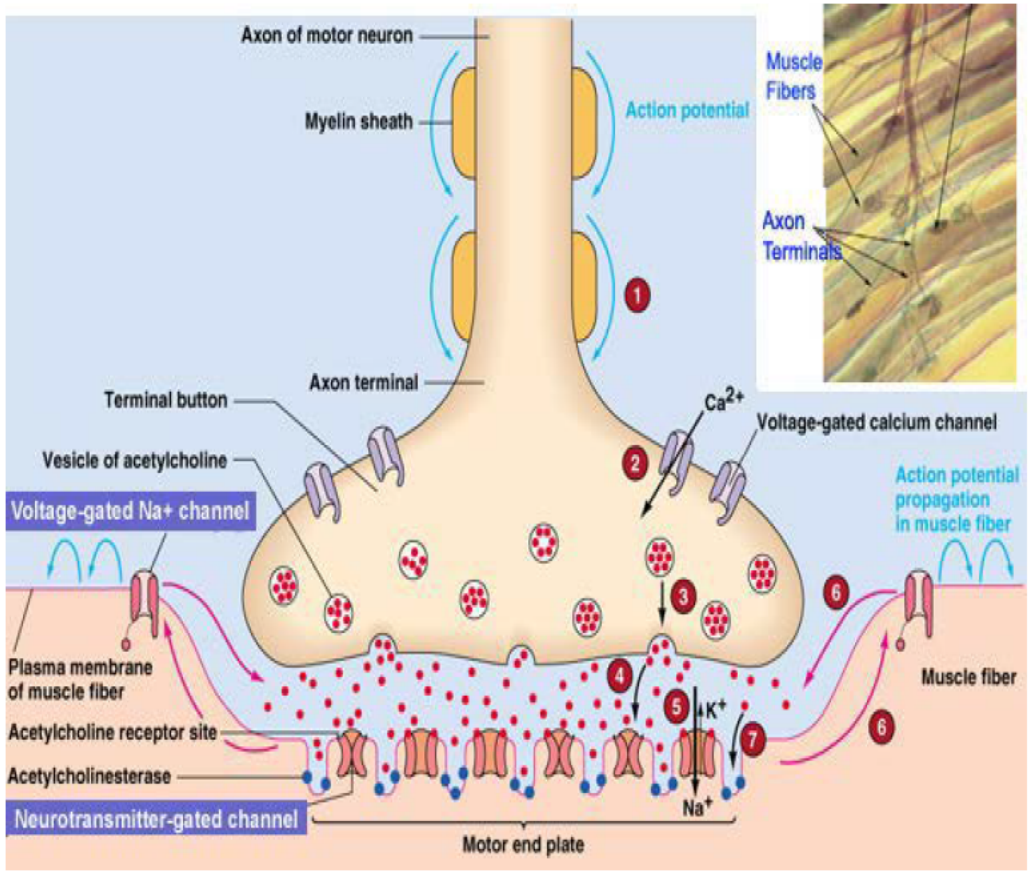


LEMS Management Options

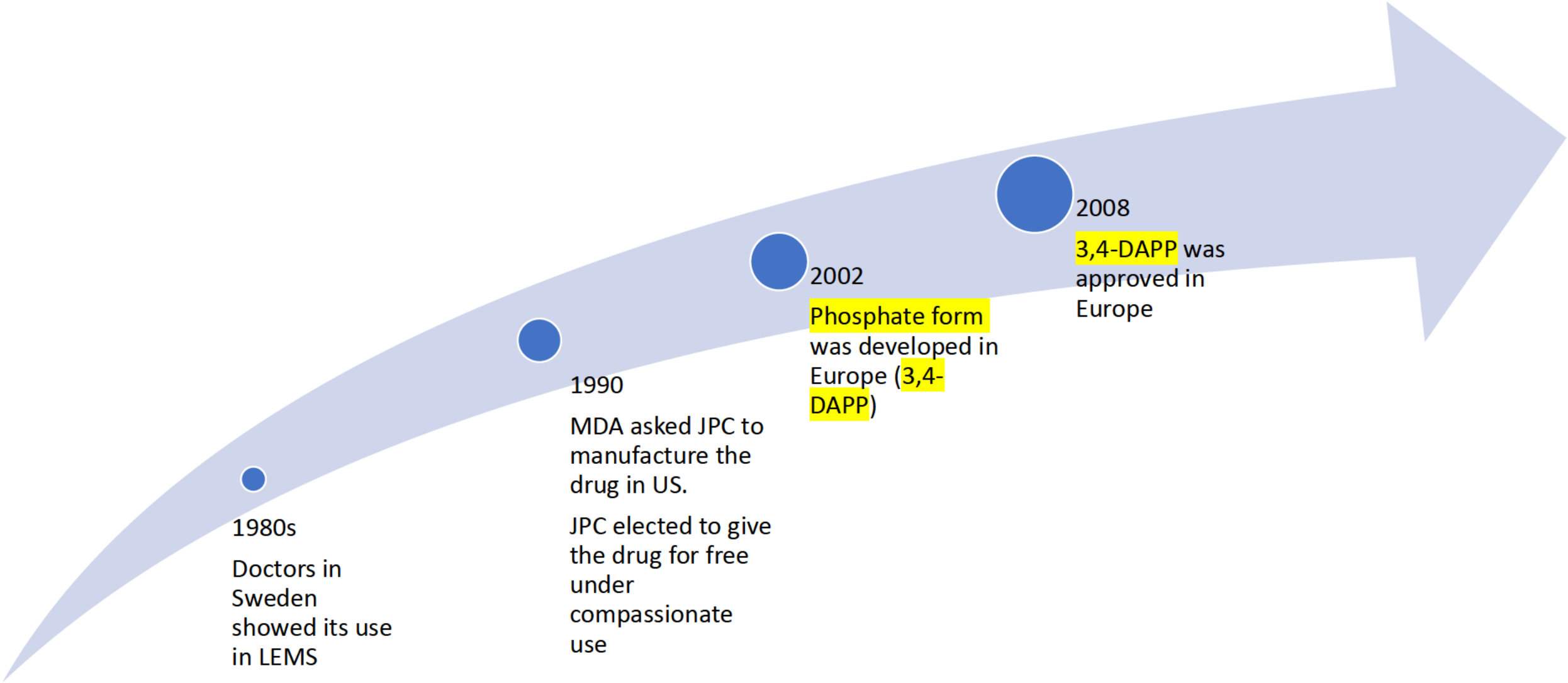
- Anti-tumor treatment in paraneoplastic LEMS
  - Chemotherapy
- Immunologic treatments to suppress anti-VCGG
  - Intravenous immunoglobulin
  - Plasma exchange
  - Prednisone
  - Azathioprine
- Symptomatic treatment acting at the NMJ
  - Pyridostigmine
  - 3,4-DAP

3,4-DAP: MoA

- 3,4-DAP blocks fast voltage-gated potassium channels, prolonging presynaptic depolarization and thus the action potential, resulting in increased release of acetylcholine
- Used for the treatment of Congenital myasthenic syndrome (CMS) and LEMS since 1990



3,4-DAP : History



MDA: muscular dystrophy association
LEMS: Lambert Eaton Myasthenia Syndrome

3,4-DAP and 3,4-DAPP in LEMS: Regulatory History with US FDA

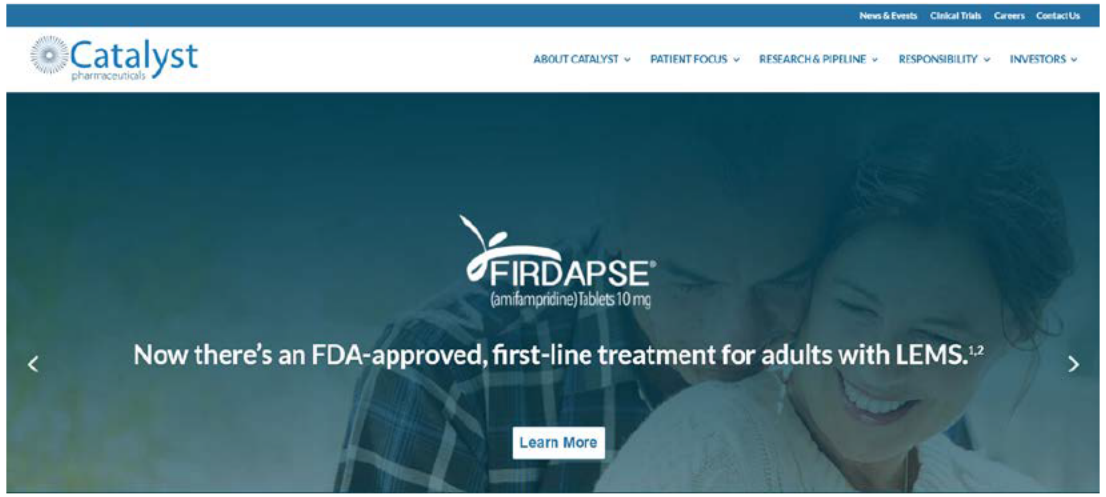
3,4-DAP: Ruzurgi by Jacobus

- **12/1990** — Orphan drug designation (compassionate use)
- **09/2010** — Pre-NDA meeting
- **06/2014** — DAPPER study result
- **12/2018** — RTF for the NDA for CMC reasons
- **06/2018** — NDA resubmission (priority review)
- **05/2019** — Approval for pediatrics with LEMS and tentative approval for adults with LEMS (priority review clock was extended by 3 months due to major amendments)

3,4-DAPP: Firdapse by Catalyst

- **06/2010** — pIND submission
- **12/2015** — RTF for the NDA for Efficacy reasons
- **04/2018** — NDA resubmission (priority review)
- **11/2018** — Approval for adults with LEMS (6 months clock)

Firdapse®: 3, 4 DAP Phosphate



FiercePharma

MANUFACTURING MARKETING PHARMA VACCINES

Pharma

Sanders escalates fight with Catalyst, asking FDA to allow unbranded copies of $375K Firdapse: report

by Angus Liu | Feb 28, 2019 11:38am

FIRDAPSE® (amifampridine) tablets, for oral use
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------

FIRDAPSE is a potassium channel blocker indicated for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults. (1)

----------DOSAGE AND ADMINISTRATION----------

- The recommended starting dosage is 15 mg to 30 mg daily taken orally in divided doses (3 to 4 times daily). (2.1)
  - Starting dosage is 15 mg daily for patients with renal impairment, hepatic impairment, and in known N-acetyltransferase 2 (NAT2) poor metabolizers (2.2, 2.3, 2.4)
- Dosage can be increased by 5 mg daily every 3 to 4 days. (2.1)
- Dosage is not to exceed a maximum of 80 mg daily. (2.1)
- The maximum single dose is 20 mg. (2.1)

Ruzurgi and Firdapse Clinical Development Program Overview

3,4-DAP: Ruzurgi by Jacobus

Phase 1

- SAD/FE
- TQT

Phase 3

- Study DAPPER — Primary endpoints is 3TUG
- Study Duke — Primary endpoints is QMG score
- RPV/compassionate use experience

3,4-DAPP: Firdapse by Catalyst

Phase 1

- SAD/MAD
- BA/BE
- FE
- RI
- TQT

Phase 3

- Study LMS-002
- Study LMS-003

Co-primary endpoints of **SGI and QMG** scores

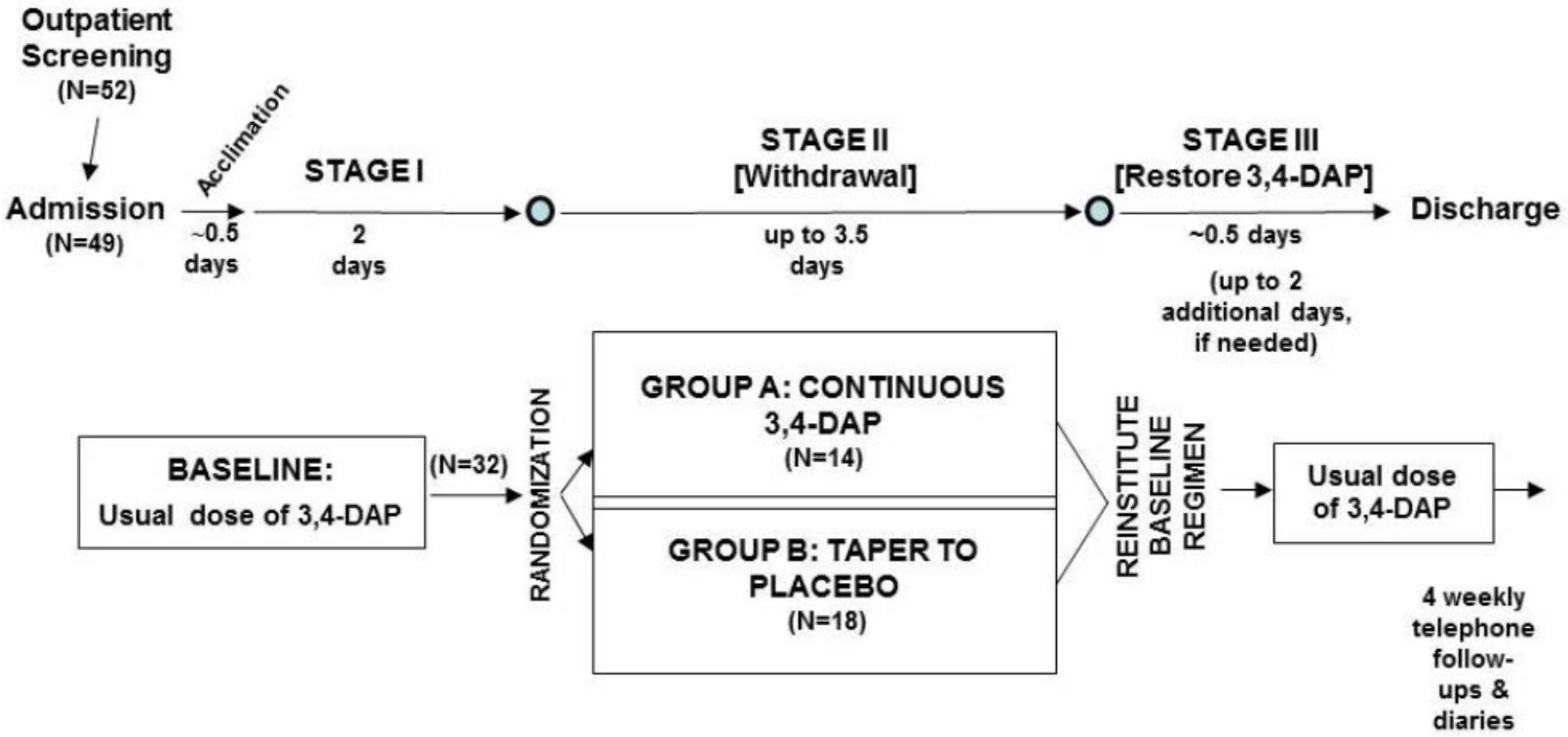
FE: Food effect
RPV: retrospective pharmacovigilance review
QMG: quantitative myasthenia gravis
SCI: subject global impression
3TUG: tripled time up and go

3,4-DAP: Clinical Pharmacology

- Absorption:
  - Tmax: 0.5 hour (fasted); 1 hour (fed)
  - Food Effect: Food ↓ AUC by ~ 23% and C_{max} by ~52%
- Distribution:
  - Plasma protein binding is 25 % for 3,4-DAP and 43 for 3-Ac-DAP.
- Metabolism:
  - ~80% through NAT (mainly NAT2)
  - Slow acetylators had ~6-8.5 fold higher AUC_{0-4h} than fast acetylators
- Excretion:
  - $t_{1/2}$ 3-4 hours
  - ~20% unchanged in urine
- DDI Potential:
  - Not substrate/inducer or inhibitor of major CYPs or transporters

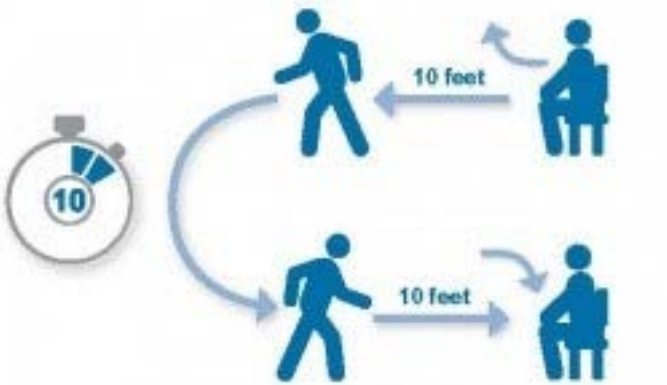
Evidence of Ruzurgi Efficacy: DAPPER Study

- **Key Inclusion:**
  - at least 18 years of age with known clinically active LEM
  - on a stable regimen of 3,4-DAP > 3 months and a stable daily regimen of other concomitant medications for > 1 month
  - Responsive to 3,4 DAP
- **Dose:**
  - TDD of 30-100 mg, with individual doses of 10 - 30 mg (3x-7x/d).



Evidence of Efficacy: DAPPER Study

- **Primary Endpoint**
  - The proportion of subjects with >30% deterioration in the 3TUG test upon withdrawal of active medication

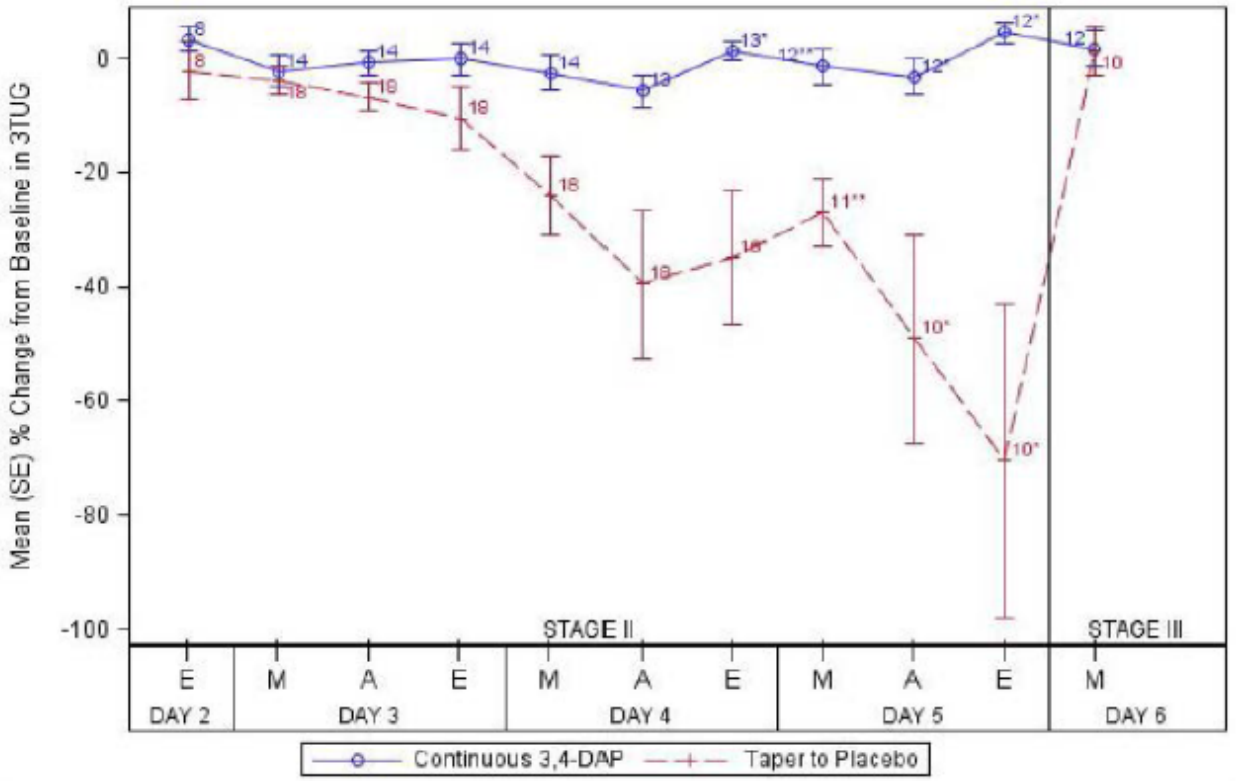


Primary Efficacy Endpoint: Summary of >30% Deterioration in the Final Timed Up & Go (3TUG) Test Upon Withdrawal of Study Drug (Stage II) – Efficacy, Intent-to-treat and Per protocol Populations

Triple Time UP and GO (3TUG)	Taper to Placebo N = 18 N (%)	Continuous 3,4-DAP N = 14 N (%)
No change or faster	5 (27.8)	14 (100)
>30% slower	13 (72.2)	0 (0.0)
p-value		<0.0001

Source: Study JPC 3,4-DAPPER CSR.

Dose Response Relationship: DAPPER Study



M: Morning
A: Afternoon
E: Evening

Supportive Evidence of Efficacy: Duke Study

NEUROLOGY

A randomized trial of 3,4-diaminopyridine in Lambert-Eaton myasthenic syndrome

Donald B. Sanders, Janice M. Massey, Linda L. Sanders and Lloyd J. Edwards

Neurology 2000;54;603

Supportive Evidence of Efficacy: Duke Study

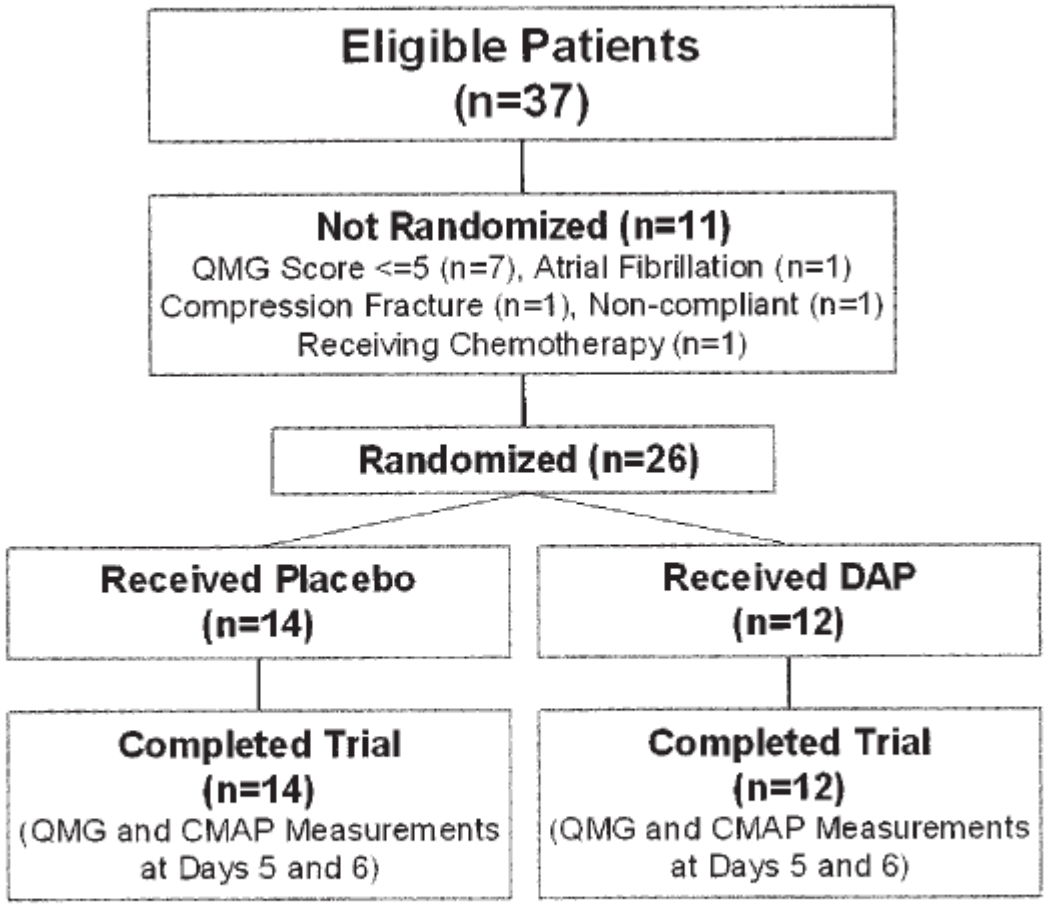


Figure. Flow diagram of trial. QMG = quantitative myasthenia gravis; DAP = 3,4-diaminopyridine; CMAP = compound muscle action potential.

- **Key Inclusion:**
  - at least 18 years of age with a confirmed diagnosis of LEM
  - undergone testing and treatment of any underlying malignancy
  - a QMG score of 5 or more
- **Key Exclusion:**
  - history of cardiac arrhythmia, seizures, known hepatic, renal, or hematologic disease
- **Dose:**
  - 10 or 20 mg (3x or 4x/d) for 6-9 days

Supportive Evidence of Efficacy: Duke Study

- Primary Endpoint:
  - QMG: quantitative examination of muscle strength with a scoring system ranging from 0 to 39, with a score of 0 indicative of normal muscular function and higher scores indicative of more severe disease

QMG Results from the Double-blind Portion of Duke RCT Study – Per-Protocol Population.

	Placebo (N=13)	3,4-DAP (N=12)	p-Value
QMG			
Baseline	11.5 (9.0 to 13.5)	8.5 (7.3 to 17.0)	0.806
Post-baseline	12.5 (9.0 to 13.5)	6.5 (5.0 to 14.3)	0.220
Change from baseline	-0.5 (-1.0 to 1.0)	-2.0 (-3.0 to 0.0)	0.015

The clinical significance of this 1.5-point difference on the 39-point QMG score is unclear.

Pediatric Data from the Compassionate Use Experience

- Safety information on pediatric use of RUZURGI is available from 22 subjects
  - 7 subjects with LEMS
  - 15 subjects with CMS

Patient Population	Age at the Start of 3,4-DAP (range)	Dose at the Start of 3,4-DAP (range)
LEMS (N=7)	9-16 years	40-95 mg/day
CMS (N=15)	13 months-14 years	5-120 mg/day

- No formal clinical study was performed to assess the efficacy of 3,4-DAP in pediatric LEMS patients
  - Only 1 subject had serial 3TUG assessments during treatment
  - Published reports of 3,4-DAP use in five pediatric LEMS patients, aged 11 to 16 years, describe clinical improvement in all cases but no objective measure

Proposed Indication and Dosing Recommendation: Jacobus Initial Proposal

----------INDICATIONS AND USAGE----------

TRADENAME is indicated for the (b) (4) (b) (4) Lambert-Eaton Myasthenia in patients (b) (4) (1)

Dose	(b) (4)	
Initial dose	(b) (4)	(b) (4)
Maximum Unit Dose		
Maximum Total Daily dose (TDD)		

Ruzurgi Formulation

- Available Dosage form: 10 mg scored, immediate release tablets
  - lowest available dosing strength is 5 mg
- For precision dosing in pediatric patients, patients unable to swallow the intact tablets, or patients using feeding tubes, sponsor proposes extemporaneous solution formulation:
  - dissolve 10 mg tablet in 10 cc sterile water
  - draw up appropriate dose into an oral syringe and administer directly into the mouth or feeding tube

This extemporaneous formulation was deemed acceptable by CMC and Bio-pharm reviewers

Review Focus

Important Clinical Pharmacology Review Questions

1. Is the proposed starting dose, maximum single dose, and maximum daily dose in adults and children acceptable?
   - Is the proposed age range for children acceptable

2. Is there a need for dose adjustments based on intrinsic and extrinsic factors?
   - Renal/hepatic impairments
   - Acetylation status
   - Food effect

Proposed and Recommended Dosing in Adults

(b) (4)

Pediatric Dosing Evaluation: Approach

- Efficacy data is limited
  - No formal analyses were performed to investigate similarity in response between adults and pediatrics

Based on the Medical Officer Review

Reviewer Comment: Efficacy can be extrapolated from adults to pediatric patients when it is reasonable to assume that children, compared with adults, have a similar progression of disease, similar response of disease to treatment, and similar exposure-response relationship.

1) The disease mechanism of LEMS, autoantibody-mediated removal of a subset of the P/Q-type Ca2+ channels at the neuromuscular junction, is the same in adults and children
2) It is reported that pediatric LEMS patients have a similar response to treatment as adults
3) A drug that is efficacious in adults by presynaptic potassium channel blockade would, therefore, also be expected to be efficacious in children
4) Based on simulation and modeling, the proposed doses for pediatric patients are expected to provide similar exposures to those found to be therapeutic in adult patients

Based on the overall data, it appears reasonable to extrapolate the effectiveness of amifampridine for the treatment of LEMS from adults to pediatric patients.

Pediatric Dosing Evaluation: Approach

- Safety information on pediatric use of RUZURGI is available from 22 subjects
  - 7 subjects with LEMS
  - 15 subjects with CMS

Patient Population	Age at the Start of 3,4-DAP (range)	Dose at the Start of 3,4-DAP (range)
LEMS (N=7)	9-16 years	40-95 mg/day[2]
CMS (N=15)	13 months-14 years	5-120 mg/day

doses ranging from 0.6 mg/kg/day to 1.1 mg/kg/day in the twelve patients for whom weight was reported

Pediatric Dosing Evaluation: Approach

- Exposure matching to adults
  - Only if safety permits
- Body weight and acetylator status are key predictors for exposure
  - PK data from adult NHVs and adult LEMS patients, aged 18-82 years and baseline body weight **45.8-132 kg**
  - Acetylator status is available for 81 subjects
- Relationship between body weight and PK is well-defined
- Adult PK model with allometric approach was used to predict exposure in pediatrics
  - NAT enzymes are mature by 6 years or less in children[1]
  - Sex and menstrual phase does not significantly affect NAT2 activity[2]

1. Based on a systematic review conducted by the reviewer

2. Clin Pharmacol Ther. 1998 May;63(5):540-51.

Evaluation of the Proposed Dosing in Pediatrics

(b) (4)

Recommended Dosing in Pediatrics

(b) (4)

Approved Final Label: Only Pediatric Indication

Initial Sponsor's Proposal

(b) (4)

Considering Firdapse® Label

Final Label

INDICATIONS AND USAGE

RUZURGI is a potassium channel blocker indicated for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in patients 6 to less than 17 years of age. (1)

DOSAGE AND ADMINISTRATION

- Patients 6 to less than 17 years of age weighing 45 kg or more:
  - Initial dosage is 15 mg to 30 mg daily, in divided doses
  - Increase daily in 5 mg to 10 mg increments, up to 5 doses daily
  - Maximum single dose is 30 mg; maximum daily dosage is 100 mg (2.1)
- Patients 6 to less than 17 years of age weighing less than 45 kg:
  - Initial dosage is 7.5 mg to 15 mg daily, in divided doses
  - Increase daily in 2.5 mg to 5 mg increments, up to 5 doses daily
  - Maximum single dose is 15 mg; maximum daily dosage is 50 mg (2.1)
- When patinets require a dosage in less than 5 mg increments, have difficulty swallowing, or require feeding tubes, a 1 mg/1 mL solution can be prepared. (2.2)
- For patients with renal or hepatic impairment or who are known N-acetyltransferase 2 poor metabolizers, use the lowest recommended initial dosage. (2.3, 2.4, 2.5)

FDA NEWS RELEASE

FDA approves first treatment for children with Lambert-Eaton myasthenic syndrome, a rare autoimmune disorder

More Press Announcements

For Immediate Release: May 06, 2019

Use of Ruzurgi in patients 6 to less than 17 years of age is supported by evidence from adequate and well-controlled studies of the drug in adults with LEMS, pharmacokinetic data in adult patients, pharmacokinetic modeling and simulation to identify the dosing regimen in pediatric patients and safety data from pediatric patients 6 to less than 17 years of age.

Dose Adjustments Based on Intrinsic and Extrinsic factors

DOSAGE AND ADMINISTRATION

- For patients with renal or hepatic impairment or who are known N-acetyltransferase 2 poor metabolizers, use the lowest recommended initial dosage. (2.3, 2.4, 2.5)

- Consistent with Firdapse® Label
  - Only starting dose is adjusted and the drug is titrated based on efficacy and tolerability
- PMR for hepatic Impairment
  - 3,4-DAP is primarily metabolized
- PMC for renal impairment using reduced design
  - ~20% unchanged in urine
- Drug can be administered with or without food
  - Consistent with both the food effect and pivotal efficacy studies

FDA undercuts $375,000 drug in surprise move

By Wayne Drash, CNN

Updated at 5:15 PM ET, Wed May 8, 2019

(CNN) — The US Food and Drug Administration created a workaround this week that effectively undercuts the $375,000 price tag of a drug that became the poster child for concerns about the pharmaceutical industry.

The FDA announced Monday that it was approving a separate drug for pediatric patients with a rare, painful neuromuscular disease called Lambert-Eaton myasthenic syndrome, also known as LEMS. The disease weakens and fatigues muscles, causing agonizing pain to the point at which patients struggle to walk.

The move sparked celebration in the LEMS community and tanked the stock of Catalyst Pharmaceuticals, maker of the $375,000 drug, called Firdapse. The company's stock price has dropped about 50% since Monday.

Catalyst Shares Plunge Following FDA Approval of Rival LEMS Drug

Published: May 07, 2019 | By Alex Keown

Shares of **Catalyst Pharmaceutical** fell more than 42 percent in after-hours trading Monday after the U.S. **Food and Drug Administration (FDA) approved a rival drug** for pediatric patients with Lambert-Eaton myasthenic syndrome (LEMS).

- Backup

FDA U.S. FOOD & DRUG ADMINISTRATION

APR 04 2019

The Honorable Bernard Sanders
United States Senate
Washington, D.C. 20510-4504

Dear Senator Sanders:

Thank you for your letter of February 26, 2019, regarding the U.S. Food and Drug Administration's (FDA) approval of Firdapse, also known chemically as 3,4-diaminopyridine phosphate (3,4-DAP). FDA shares your concern about situations in which manufacturers set drug prices that reduce affordability and access. However, FDA is limited in its ability to affect the price of such drugs. Further, as described in this letter, FDA has concerns with the use of unapproved drugs, which have not undergone premarket review for safety, effectiveness, and quality.

As you note in your letter, on November 28, 2018, FDA approved a new drug application (NDA) submitted by Catalyst Pharmaceuticals for Firdapse (amifampridine phosphate oral tablets) for the treatment of Lambert Eaton Myasthenic Syndrome (LEMS). FDA approved the NDA for Firdapse after a rigorous review of the evidence supplied by the applicant supported a conclusion of safety, effectiveness, and product quality. As you know, Americans rely on FDA to ensure that approved drugs are both safe and effective, including requiring the applicant's demonstration that its manufacturing processes can reliably produce drug products of expected identity, strength, quality, and purity. In addition, FDA's review of the applicant's labeling ensures that health care professionals and patients have the information necessary to understand a drug product's risks and its safe and effective use.

You note in your letter that a manufacturer previously provided LEMS patients with an investigational version of 3,4-diaminopyridine phosphate (3,4-DAP) under Expanded Access (also known as "compassionate use"). Expanded Access is a potential pathway for a patient with an immediately life-threatening condition or serious disease or condition to gain access to an investigational medical product (drug, biologic, or medical device) for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available. Investigational drugs, biologics, or medical devices have not yet been approved or cleared by FDA, and FDA has not found these products to be safe and effective for their specific use. Because there is now an approved comparable or satisfactory alternative to treat LEMS, Expanded Access is no longer permitted by law (21 CFR 312.305).

In your letter, you suggest that FDA refrain from pursuing enforcement action against pharmacies and manufacturers that provide 3,4-DAP. Although compounded drugs can serve an important medical need for certain patients, the Food Drug and Cosmetic Act Section 503A(b)(1)(D) (pharmacies) and Section 503B(a)(5) (outsourcing facilities) doesn't permit compounding of drugs that are essentially copies of a commercially available drug product. As applicable here, the statute defines the term "essentially a copy of an approved drug" to mean "a drug that is identical or nearly identical to an approved drug…unless . . . the drug appears on the drug shortage list in effect under Section 506E at the time of compounding, distribution, and

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

dispensing; ...." The Agency provided guidance to industry specific to this topic in January 2018.[1] At that time, in interpreting the applicable law, FDA advised that "factors such as a lower price are not sufficient to establish that the compounded product is not essentially a copy of the approved drug."

Compounded drugs do not undergo the same premarket review and thus lack an FDA finding of safety and efficacy and lack an FDA finding of manufacturing quality. Therefore, when an FDA-approved drug is commercially available, FDA recommends that practitioners prescribe the FDA-approved drug rather than a compounded drug unless the prescribing practitioner has determined that a compounded product is necessary for the particular patient and would provide a significant difference for the patient as compared to the FDA-approved commercially available drug product.

The 2011 statement that you referenced with respect to another drug, hydroxyprogesterone caproate, was superseded by an FDA statement on June 15, 2012, which clarified that FDA was "applying its normal enforcement policies for compounded drugs to compounded hydroxyprogesterone caproate." These actions occurred after testing revealed compounded versions of hydroxypregesterone caproate were sub-potent and contained impurities. FDA has investigated numerous serious adverse events associated with compounded drug products that were contaminated or otherwise compounded improperly, including the adverse events associated with the 2012 fungal meningitis outbreak in which contaminated injectable drug products resulted in more than 60 deaths and 750 cases of infection. Since then, FDA has investigated many serious adverse events associated with compounded products, including adverse events related to poor quality compounded oral tablets.

As noted above, the high cost of certain prescription drugs is an ongoing concern that the Agency shares. Too many patients are priced out of the medicines they need. However, providing patients with unapproved versions of approved drugs, which have not been subject to FDA premarket review for safety, effectiveness, and quality, is not the solution to this important problem.

Although FDA does not have a direct role in drug pricing, we have been taking new policy steps to support downward pressure on drug prices by facilitating generic competition. One of our key policy priorities is encouraging the timely development and approval of generics, and in 2017, FDA announced the Drug Competition Action Plan to further encourage robust and timely market competition for drugs and help bring greater efficiency and transparency to the generic drug review process, without sacrificing the scientific rigor underlying our drug review program. By ensuring that regulatory requirements are efficient, predictable, and science-based, we can help reduce the time, uncertainty, and cost of generic product development, fostering

---

[1] See:
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM510154.pdf (pharmacies) and
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM510153.pdf (outsourcing facilities)

competition in the marketplace and improving access to high quality, affordable treatment options for Americans.

We have been able to make significant progress over the past year in advancing efforts that have helped to strengthen and streamline the generic drug review process, enabling us to approve a record number of generic drugs in 2017 and 2018. To support the development of hard-to-develop complex generics, we have issued a number of guidance documents to provide greater scientific clarity, and we have called out potential abuses of the system where companies were using tactics to delay market entry of generic competitors. Bringing more drug competition to the market to increase the availability of lower-cost alternatives is a top priority of FDA, and we will continue to advance new efforts in the year ahead that support consumers getting access to the medicines they need at affordable prices.

Thank you for sharing your concerns with FDA on the pricing of Firdapse. We look forward to working with you and other interested parties on methods by which FDA can promote competition and otherwise engage on this important issue, within the scope of our statutory authorities.

Sincerely,

Karas Gross
Associate Commissioner for
Legislative Affairs

TAB 2:

Documents showing pediatric LEMS patients could receive treatment without a Ruzurgi approval

From: Buracchio, Teresa
To: Ahmed, Mariam; Mathers, Michelle; Locicero, Colleen L
Cc: Daugherty, Susan B (CSO); Ware, Jacqueline H; Bullock, Heather
Subject: RE: Exclusivity policy question
Date: Friday, October 05, 2018 10:09:00 AM
Attachments: image001.png
image002.jpg
image003.jpg
image004.jpg
image005.jpg
image006.jpg
Type C Meeting Minutes - 30 January 2018 - Resubmission.pdf
Type B Pre-NDA Meeting Minutes, 17 February 2016.pdf

There are no PSPs for either product.

Jacobus/Ruzurgi:
I reviewed the prior Jacobus meeting minutes and I do not see that we ever discussed pediatric extrapolation with them. In a preNDA meeting from 3/17/16, they did discuss including data from pediatric patients with LEMS in their safety dataset and indicated that they would seek inclusion in labeling but there was no detailed discussion of this strategy. I also asked Nick and he doesn't recall any informal discussions of pediatric extrapolation.

Catalyst/Firdapse:
I reviewed the prior Catalyst meeting minutes and we have not specifically discussed pediatric extrapolation of LEMs with them. However, in Type C Meeting Minutes from January 30, 2018, we did discuss and expressed openness to extrapolation of efficacy adult LEMS data to a **different indication**, congenital myasthenic syndrome (CMS); however, we stated that the sponsor would need to pediatric safety data from that indication or related indications to CMS. I believe that the sponsor only had published literature and did not have any actual pediatric data in hand so they chose not to pursue that indication at this time; however, I believe they recently started a study to collect that data.

I have attached the pertinent meeting minutes.

Teresa

From: Ahmed, Mariam
Sent: Friday, October 05, 2018 1:58 AM
To: Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>
Cc: Daugherty, Susan B (CSO) <Susan.Daugherty@fda.hhs.gov>; Ware, Jacqueline H <Jacqueline.Ware@fda.hhs.gov>; Bullock, Heather <Heather.Bullock@fda.hhs.gov>
Subject: RE: Exclusivity policy question

Hi Michelle,
Jacobus came with an indication down to (b) (4) and included pediatric data in the submission. We have to assess whether this data is enough or not based on scientific rationale. Catalyst came

with adult only indication and they didn't have any pediatric data at all.

I am not aware of any PSP.
Hope this answer your questions.

Mariam

Mariam Ahmed, B.Pharm, M.Sc., PhD
Clinical Pharmacology Reviewer

Center for Drug Evaluation and Research
OTS/OCP/DCPI
U.S. Food and Drug Administration
Phone: 301-796-7378
mariam.ahmed@fda hhs.gov

From: Mathers, Michelle
Sent: Thursday, October 04, 2018 8:00 PM
To: Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Ahmed, Mariam <Mariam.Ahmed@fda.hhs.gov>
Cc: Daugherty, Susan B (CSO) <Susan.Daugherty@fda.hhs.gov>; Ware, Jacqueline H <Jacqueline.Ware@fda.hhs.gov>; Bullock, Heather <Heather.Bullock@fda.hhs.gov>
Subject: FW: Exclusivity policy question

Hi Teresa and Mariam,

Jackie contacted Colleen regarding the exclusivity questions we had regarding competing Jacobus and Catalyst amifampridine applications. Collen had some follow-up questions that she added below in red. I know there is not a PSP for Jacobus since they have Orphan designation, so I'm guessing Catalyst doesn't either. However, for the extrapolation piece, I thought it was something we discussed on our end and not with Jacobus. Can you please confirm if that is indeed the case?

Thanks!
Michelle

We understand that the applicant who receives approval first (in adults) will block the other from approval because of orphan exclusivity. However, because the indication that Jacobus is pursuing includes patients (b) (4) (rather than just adults), and because approval of amifampridine for a pediatric population would be an advantage over currently approved therapies, we believe that the Jacobus NDA could potentially be approved AND receive exclusivity for a pediatrics only indication, if there is adequate support for the pediatric population. Support for the Jacobus pediatric indication would be based on Jacobus' own extrapolated adult data. Did the division suggest this extrapolation or is this something Jacobus initiated on their own? Was the division aware that Jacobus planned to do this (extrapolate pediatric efficacy/dosing from their adult data) prior to submission of their NDA? I assume Jacobus doesn't have a PSP, because of the orphan designation? However, if the Catalyst NDA is approved first (with an adult only indication) and receives 5-year NCE exclusivity, there is question whether Jacobus would be blocked from using in

labeling their own adult data in support of the pediatric only indication. Did Catalyst ever raise extrapolation with the division or the division with Catalyst, to your knowledge? I assume Catalyst doesn't have a PSP because of the orphan designation as well? Therefore, we have the following questions:

From: Locicero, Colleen L
Sent: Thursday, October 04, 2018 5:16 PM
To: Ware, Jacqueline H <Jacqueline.Ware@fda.hhs.gov>
Cc: Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Daugherty, Susan B (CSO) <Susan.Daugherty@fda.hhs.gov>; Bullock, Heather <Heather.Bullock@fda.hhs.gov>
Subject: RE: Exclusivity policy question

Sorry, please answer. Even though the NCE won't be an issue (confirmed by Jay Sitlani), the orphan exclusivity will, but Jay thinks a carve out may be possible to allow approval of the Jacobus NDA, but I need to look into this more.

Thanks,
Colleen

From: Locicero, Colleen L
Sent: Thursday, October 04, 2018 12:41 PM
To: Ware, Jacqueline H <Jacqueline.Ware@fda.hhs.gov>
Cc: Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Daugherty, Susan B (CSO) <Susan.Daugherty@fda.hhs.gov>; Bullock, Heather <Heather.Bullock@fda.hhs.gov>
Subject: RE: Exclusivity policy question

Ignore these questions for now. I am pretty sure, but will confirm with Jay Sitlani, that 5 year NCE only blocks approval of b2s and ANDAs. I do not believe it blocks approval of a b1 for the same NME. If that is the case, all your questions go away, right?

Thanks,
Colleen

From: Locicero, Colleen L
Sent: Thursday, October 04, 2018 11:59 AM
To: Ware, Jacqueline H <Jacqueline.Ware@fda.hhs.gov>
Cc: Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Daugherty, Susan B (CSO) <Susan.Daugherty@fda.hhs.gov>; Bullock, Heather <Heather.Bullock@fda.hhs.gov>
Subject: RE: Exclusivity policy question

Hi Jackie,

I have some questions in red.

Thanks,
Colleen

From: Ware, Jacqueline H
Sent: Monday, October 01, 2018 9:49 PM
To: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>
Cc: Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Bullock, Heather <Heather.Bullock@fda.hhs.gov>; Daugherty, Susan B (CSO) <Susan.Daugherty@fda.hhs.gov>; Ware, Jacqueline H <Jacqueline.Ware@fda.hhs.gov>
Subject: Exclusivity policy question

Hi Colleen,

As a first step, I'm reaching out to you for guidance. DNP has two interesting exclusivity questions related to two pending NDAs under review in our division. We understand and expect that OODP, ORP, and OCC will need to be informed and involved. However, we would appreciate guidance from OND Policy about how best to obtain input and advice from the appropriate FDA/CDER/OND policy groups on the questions below.

Summary:

DNP has received two NME New Drug Applications for amifampridine to treat Lambert-Eaton Myasthenic Syndrome, one from Catalyst Pharmaceuticals (NDA 20878) and the other from Jacobus Pharmaceutical Company (NDA 209321). Both products have orphan drug designation for the same indication and contain the same active moiety. The PDUFA Goal date for the Catalyst NDA is November 28, 2018, and the Goal date for the Jacobus application is February 15, 2018.

We understand that the applicant who receives approval first (in adults) will block the other from approval because of orphan exclusivity. However, because the indication that Jacobus is pursuing includes patients (b) (4) (b) (4) (rather than just adults), and because approval of amifampridine for a pediatric population would be an advantage over currently approved therapies, we believe that the Jacobus NDA could potentially be approved AND receive exclusivity for a pediatrics only indication, if there is adequate support for the pediatric population. Support for the Jacobus pediatric indication would be based on Jacobus' own extrapolated adult data. Did the division suggest this extrapolation or is this something Jacobus initiated on their own? Was the division aware that Jacobus planned to do this (extrapolate pediatric efficacy/dosing from their adult data) prior to submission of their NDA? I assume Jacobus doesn't have a PSP, because of the orphan designation? However, if the Catalyst NDA is approved first (with an adult only indication) and receives 5-year NCE exclusivity, there is question whether Jacobus would be blocked from using in labeling their own adult data in support of the pediatric only indication. Did Catalyst ever raise extrapolation with the division or the division with Catalyst, to your knowledge? I assume Catalyst doesn't have a PSP because of the orphan designation as well? Therefore, we have the following questions:

Questions:

1) Since both of these products are the same NME being developed under the 505(b)(1) pathway, the applicant who receives first approval will receive 5 year NCE exclusivity. Based on the PDUFA Goal dates, this most likely would be Catalyst. However, because the Jacobus indication includes patients (b) (4) (b) (4) whereas the Catalyst indication is for adults only, per MAPP 5018.2 regarding NDA classification codes, we believe that Jacobus could receive approval for a pediatric only indication as a Type 5 NDA since it would be a new indication with clinical data (although extrapolated from adult data). Thus, this pediatric approval would not be blocked by a Catalyst approval in adults. Do you agree that this scenario is a possibility?

2) If a Jacobus "pediatrics only" indication is approvable, we plan to use the Jacobus adult data in the labeling to support their pediatric indication. Since Catalyst would potentially have 5-year NME exclusivity on the adult indication, does this raise any concerns? Is there a way to write labeling to support the Jacobus pediatric only claim?

Pending Applications:

-

NDA 208078- Catalyst: Goal Date- November 28, 2018
Drug Product: Firdapse (amifampridine phosphate)
Dosage form: 10 mg tablets
Proposed Indication: Symptomatic treatment of Lambert-Eaton Myasthenic Syndrome (LEMS) in adults.
RPM: Heather Bullock

NDA 209321- Jacobus: Goal date- February 15, 2019
Drug Product: Ruzurgi (amifampridine)
Dosage form: 10 mg tablets
Proposed Indication: (b) (4) (b) (4) Lambert-Eaton myasthenia in patients (b) (4) (b) (4)
RPM: Michelle Mathers

-

I hope the scenario we are facing and our questions make sense. If not, please don't hesitate to reach out. Heather and Michelle will be most knowledgeable.

Many thanks,

Jackie

Jacqueline H. Ware, Pharm.D.
Captain, United States Public Health Service
Chief, Project Management Staff
Center for Drug Evaluation and Research
Office of Drug Evaluation I, Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-1160
Jacqueline.ware@fda.hhs.gov

From: Locicero, Colleen L
To: Locicero, Colleen L
Subject: FW: question - extrapolation of pediatric effectiveness
Date: Monday, October 28, 2019 10:59:22 AM

From: Locicero, Colleen L
Sent: Thursday, October 11, 2018 9:42 AM
To: Yao, Lynne P <Lynne.Yao@fda.hhs.gov>; Alexander, John J <John.Alexander@fda.hhs.gov>; Greeley, George <George.Greeley@fda.hhs.gov>; Addy, Rosemary <Rosemary.Addy@fda.hhs.gov>
Subject: RE: question - extrapolation of pediatric effectiveness

Thanks, Lynne. This is helpful. Doesn't sound like we typically initiate and in light of the pre-NDA discussions, doesn't sound like Catalyst could make an argument, if Jacobus' product would end up being approved for pediatric patients. You are correct, there are no iPSPs for either, because of the orphan designation. The products, one of which will be a NME, have been developed for LEMS (Lambert-Eaton Myasthenic Syndrome). CMS is congenital myasthenic syndromes. I am not terribly familiar with the applications (I'm just trying to determine if there might be any exclusivity issues at the request of the division), but as I understand it there are no pediatric effectiveness data, but there are pediatric safety data for the Jacobus product.

Thanks again,
Colleen

From: Yao, Lynne P
Sent: Thursday, October 11, 2018 6:33 AM
To: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>; Alexander, John J <John.Alexander@fda.hhs.gov>; Greeley, George <George.Greeley@fda.hhs.gov>; Addy, Rosemary <Rosemary.Addy@fda.hhs.gov>
Subject: RE: question - extrapolation of pediatric effectiveness

Hi Colleen,

So, the short answer to your question is that FDA would need to agree with any final plans to use pediatric extrapolation, whether initially planned by the sponsor or initially recommended by us. The use of pediatric extrapolation is a complicated scientific question and isn't generally a simple yes or no answer. Having said this, I have a few questions (happy to ask the division):

1. What is the indication or indications already approved for this drug? What is LEM and

CMS?

2. What is the current indication the sponsors are seeking?

3. What data in pediatric populations already exist for this drug?

It seems unlikely to me that the division would agree approval down to (b) (4) (b) (4) without any existing pediatric data (either in this indication or from another indication) that would support dosing and safety of the product. FDA generally requires at least some pediatric dosing and safety information even if we agree that adult efficacy data can be borrowed to support pediatric efficacy. Sounds like there may be some pediatric data that either Jacobus or Catalyst has previously collected.

If you provide the IND numbers for these applications, we can take a further look. Unfortunately, it appears that they have both received orphan designation which means that PREA does not apply and we probably don't have an agree iPSP to review.

Thanks,

Lynne

From: Locicero, Colleen L
Sent: Wednesday, October 10, 2018 5:17 PM
To: Yao, Lynne P <Lynne.Yao@fda.hhs.gov>; Alexander, John J <John.Alexander@fda.hhs.gov>; Greeley, George <George.Greeley@fda.hhs.gov>; Addy, Rosemary <Rosemary.Addy@fda.hhs.gov>
Subject: question - extrapolation of pediatric effectiveness

All,

If I sent this email already, my apologies. I've been having some laptop issues.

This is probably kind of an odd question, but, in your experience, does FDA typically or occasionally initiate with applicants the extrapolation of pediatric efficacy and related dosing information for a product from the adult data, or is this only considered at the request of an applicant/when the applicant proposes it?

The reason for my question is that OND Policy is looking into a few matters for the pending amifamprdine applications in DNP. While both amifampridine applications contain effectiveness data from adult patients only, one of the

applicants (Jacobus) extrapolated from their adult data to provide evidence of effectiveness and dosing information for pediatric patients, while the other (Catalyst) did not. At this time, therefore, DNP plans to approve Jacobus' product for adults and children down to (b) (4), while DNP plans to approve Catalyst's product for adults only (17 and above).

Catalyst's product will likely be approved first and its orphan exclusivity will block approval of the Jacobus product, but not entirely if Jacobus is found to be effective (from the extrapolated data) in patients (b) (4) Catalyst will likely not be happy about that (these two companies have been racing each other towards approval for a while), and we are concerned that Catalyst may make an argument that their product could have been approved in patients (b) (4) because it contains the adult data needed for the pediatric evidence/dosing extrapolation and that FDA should have initiated/suggested/raised this with Catalyst, because we have done that sort of thing in the past. So, my question is… to your knowledge, is extrapolation of pediatric efficacy and dosing limited to when the applicant requests/initiates it, or do we typically or occasionally initiate the extrapolation possibility ourselves?

(*Of note, the division did not discuss extrapolation with Jacobus (the company that did extrapolate), but did discuss extrapolation of efficacy data from one indication to another (LEMs to CMS) with Catalyst, but noted they could not extrapolate pediatric safety from adult safety data, so would need pediatric safety data; Catalyst chose not to pursue a CMS indication).*

Hopefully, this makes sense. If you have any questions, please let me know.

Thanks,
Colleen

From: Corrigan-Curay, Jacqueline
To: Choy, Fannie (Yuet)
Cc: Garvin, Kayla; Phillips, J. Paul; Locicero, Colleen L; Bickel, Lori
Subject: FW: 2018-12-20_CatalystJacobus policy considerations FINAL.docx
Date: Friday, December 21, 2018 8:33:38 PM
Attachments: 2018-12-20_CatalystJacobus policy considerations FINAL.DOCX

Dear Fannie,
Attached is the memo for the MPPRC discussion of the Catalyst-Jacobus EA. We propose to post the end of next week or Monday the 31st. If anyone needs to provide feedback please send your comments sometime by the end of next week
Thanks
Jacqueline.

From: Phillips, J. Paul
Sent: Friday, December 21, 2018 7:51 PM
To: Corrigan-Curay, Jacqueline <Jacqueline.Corrigan-Curay@fda.hhs.gov>; Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>; Bickel, Lori <Lori.Bickel@fda.hhs.gov>
Cc: Garvin, Kayla <Kayla.Garvin@fda.hhs.gov>
Subject: RE: 2018-12-20_CatalystJacobus policy considerations FINAL.docx

Jacqueline,

I had only one small edit. I apologize I did not get a chance to share with the division as I was extremely busy this week with contingency planning for the potential lapse in funding. Please feel free to share with the division directly if you would like.

Warm regards and happy holidays!

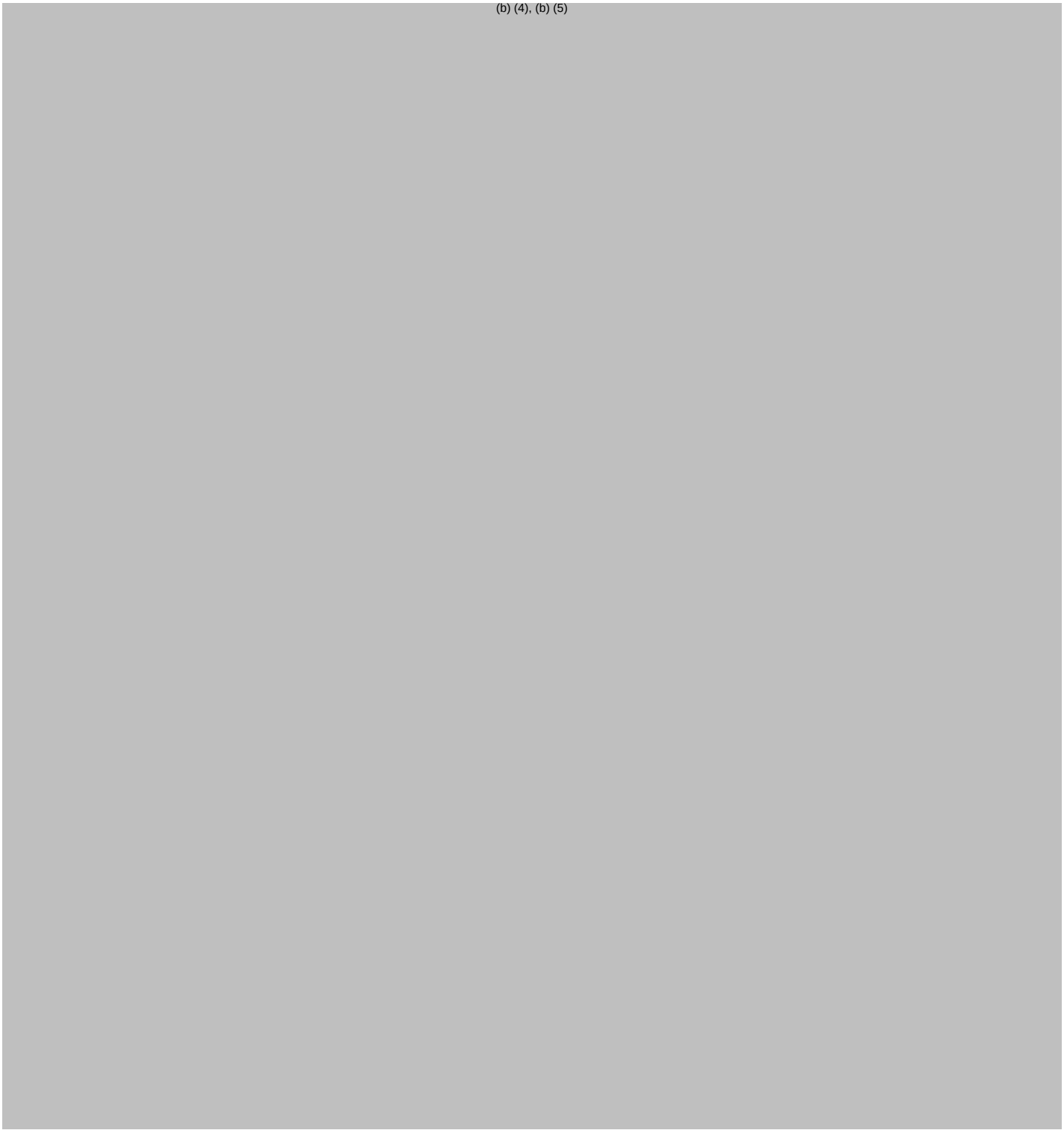
Paul

From: Corrigan-Curay, Jacqueline
Sent: Thursday, December 20, 2018 9:01 AM
To: Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>; Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>; Bickel, Lori <Lori.Bickel@fda.hhs.gov>
Cc: Garvin, Kayla <Kayla.Garvin@fda.hhs.gov>
Subject: 2018-12-20_CatalystJacobus policy considerations FINAL.docx

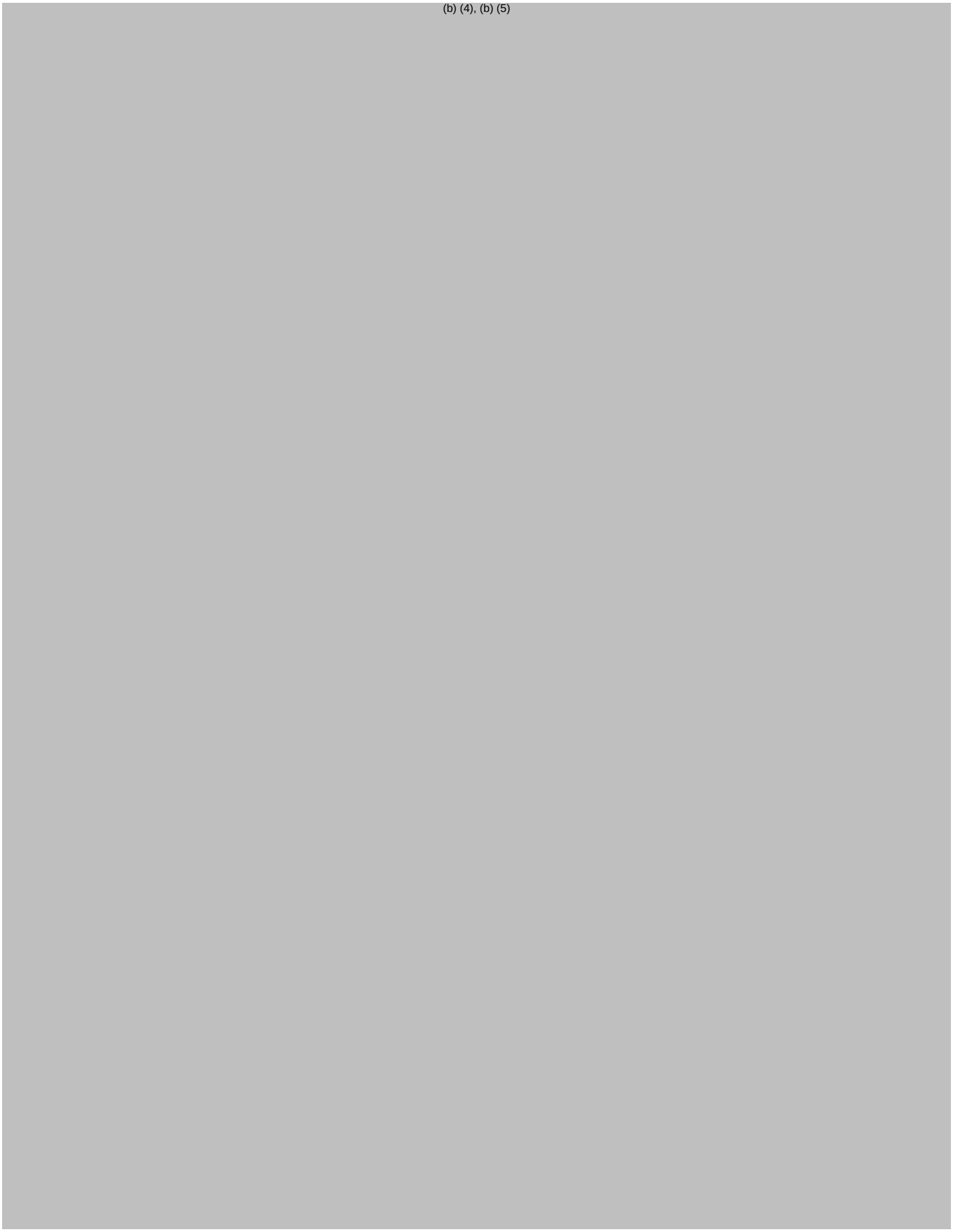
Paul,
Lori drafted the attached memo for the MPPRC and I made some edits. Can you review and if the division is around have them review as well but give to Kayla by Friday?
I will be intermittently on line today as I am officially on leave.
Best,
Jacqueline

Policy Implications for Catalyst/Jacobus Products and Expanded Access Use

(b) (4), (b) (5)



(b) (4), (b) (5)



(b) (4), (b) (5)

(b) (4), (b) (5)

From:	Dunn, Billy
To:	Locicero, Colleen L; Buracchio, Teresa; Mathers, Michelle
Cc:	Bastings, Eric; Kozauer, Nicholas; Phillips, J. Paul
Subject:	RE: IND distribution
Date:	Tuesday, January 15, 2019 11:55:54 AM

Great – thank you very much.

From: Locicero, Colleen L
Sent: Tuesday, January 15, 2019 11:49 AM
To: Dunn, Billy <Billy.Dunn@fda.hhs.gov>; Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>
Cc: Bastings, Eric <Eric.Bastings@fda.hhs.gov>; Kozauer, Nicholas <Nicholas.Kozauer@fda.hhs.gov>; Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>
Subject: RE: IND distribution

Thanks, Billy. Works for me.

Colleen

From: Dunn, Billy
Sent: Tuesday, January 15, 2019 11:48 AM
To: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>; Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>
Cc: Bastings, Eric <Eric.Bastings@fda.hhs.gov>; Kozauer, Nicholas <Nicholas.Kozauer@fda.hhs.gov>; Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>
Subject: RE: IND distribution

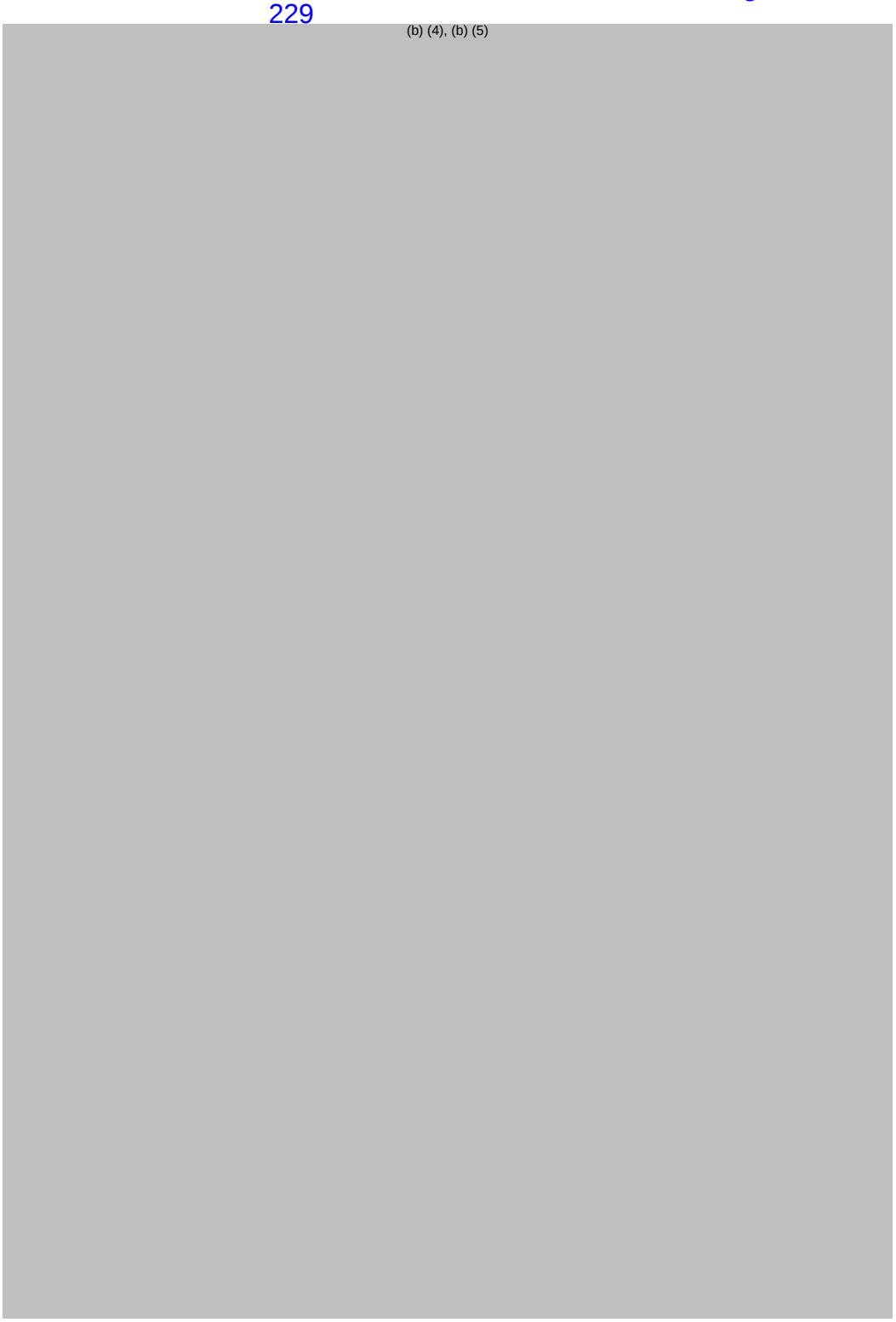
Yes, thank you. I might consider adding the word both (highlighted below) if acceptable to you?

From: Locicero, Colleen L
Sent: Tuesday, January 15, 2019 11:42 AM
To: Dunn, Billy <Billy.Dunn@fda.hhs.gov>; Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>
Cc: Bastings, Eric <Eric.Bastings@fda.hhs.gov>; Kozauer, Nicholas <Nicholas.Kozauer@fda.hhs.gov>; Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>
Subject: RE: IND distribution

Does this work?

(b) (4), (b) (5)

(b) (4), (b) (5)



From: Dunn, Billy
Sent: Tuesday, January 15, 2019 11:28 AM
To: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>; Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>
Cc: Bastings, Eric <Eric.Bastings@fda.hhs.gov>; Kozauer, Nicholas <Nicholas.Kozauer@fda.hhs.gov>; Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>
Subject: RE: IND distribution

OK – thanks. We'll want to clarify that in what we send them.

From: Locicero, Colleen L
Sent: Tuesday, January 15, 2019 9:52 AM
To: Dunn, Billy <Billy.Dunn@fda.hhs.gov>; Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>
Cc: Bastings, Eric <Eric.Bastings@fda.hhs.gov>; Kozauer, Nicholas <Nicholas.Kozauer@fda.hhs.gov>; Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>
Subject: RE: IND distribution

Billy,

Sorry (that isn't my language) - it means the latter, i.e., all (b) (4), (b) (5) (b) (4), (b) (5)

Colleen

From: Dunn, Billy
Sent: Tuesday, January 15, 2019 9:34 AM
To: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>; Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>
Cc: Bastings, Eric <Eric.Bastings@fda.hhs.gov>; Kozauer, Nicholas <Nicholas.Kozauer@fda.hhs.gov>; Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>
Subject: RE: IND distribution

Colleen – can you clarify if (b) (4), (b) (5) (b) (4), (b) (5)

From: Locicero, Colleen L
Sent: Tuesday, January 15, 2019 9:21 AM
To: Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>
Cc: Bastings, Eric <Eric.Bastings@fda.hhs.gov>; Kozauer, Nicholas <Nicholas.Kozauer@fda.hhs.gov>; Dunn, Billy <Billy.Dunn@fda.hhs.gov>; Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>
Subject: RE: IND distribution

Here is the language cleared by ORP/OCC and others. Please let me know if you have any concerns or questions.

Thanks, again, for your patience!!

Colleen

Response:

(b) (4), (b) (5)

(b) (4), (b) (5)

[redacted]

From: Locicero, Colleen L
Sent: Wednesday, January 09, 2019 10:39 AM
To: Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>
Cc: Bastings, Eric <Eric.Bastings@fda.hhs.gov>; Kozauer, Nicholas <Nicholas.Kozauer@fda.hhs.gov>; Dunn, Billy <Billy.Dunn@fda.hhs.gov>; Phillips, J. Paul <Paul.Phillips@fda.hhs.gov>
Subject: RE: IND distribution

Hi Teresa and Michelle,

There is a meeting of ORP/OCC and a few others this afternoon to discuss this matter. Therefore, if you are able to hold off on responding to this Jacobus email until after we learn the outcome of that meeting, it might be the preferred approach here. If you don't believe you can wait, however, for the response to this particular email from Jacobus (and any other EA-related emails from Jacobus you feel the need to respond to), this is the best we can do, at the moment:

(b) (5)

[redacted]

(b) (5)

I had thought I'd be able to provide you with something a little more substantive at this time, but in light of the emergency ORP/OCC meeting this afternoon, OND Policy has reconsidered and thinks this is the best we can do/say at this time, until we hear further from the lawyers.

(b) (5)

Again, much thanks to you all for your patience,
Colleen

From: Buracchio, Teresa
Sent: Tuesday, January 08, 2019 4:21 PM
To: Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>
Subject: RE: IND distribution

Colleen is working on responses. I think referring these patients to Catatlyst seems like the appropriate thing for her to do.

From: Mathers, Michelle
Sent: Tuesday, January 08, 2019 4:04 PM
To: Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>
Subject: FW: IND distribution

Hi Teresa and Colleen,

I received the below message from Laura regarding the expanded access issue. I know you were discussing this this afternoon- Is there anything else I can share with Jacobus at this point? I can acknowledge her e-mail but I'm not sure I can tell her much beyond that other than there are continued ongoing discussions and we will respond to her as soon as we can. Can they provide drug until the

Catalyst becomes available (which is actually next week)?

Thanks,
Michelle

From: Laura R. Jacobus [mailto:laura.jacobus@jacobus-pharmaceutical.com]
Sent: Tuesday, January 08, 2019 3:38 PM
To: Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>
Cc: kathy.ales@jacobus.pharmaceutical.com
Subject: IND distribution

Good afternoon,

(b) (4)

Kind regards
Laura

Laura R. Jacobus
Jacobus Pharmaceutical Company, Inc
Office: 609-799-8221 ex 207
Moble (b) (6)

From: Mathers, Michelle
To: Locicero, Colleen L; Buracchio, Teresa
Subject: FW: Question about NDA 209321 Jacobus" amifampridine
Date: Monday, March 04, 2019 11:52:07 AM

Hi Teresa and Colleen,

This request came from the office of compliance on Friday. I've drafted some high-level responses, please let me know if you would like to provide something more formal.

Thanks!

Michelle

1) Only approval of the adult indication is affected. A pediatric indication is under consideration and would not be blocked by Catalyst.

2) Jacobus has discontinued expanded access use of their product in adult LEMs patients, however may continue to provide product for other indications not covered by the Catalyst approval.

3) No, we have not discussed marketing plans with Jacobus as they would be able to market their product for pediatric use should that indication be approved.

From: Volpe, Carolyn
Sent: Friday, March 01, 2019 11:04 AM
To: Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>
Cc: Wilson, Kelly <Kelly.Wilson@fda.hhs.gov>; Maslov, Yelena <Yelena.Maslov@fda.hhs.gov>
Subject: Question about NDA 209321 Jacobus' amifampridine

Hi Michelle,

I see you are the project manager for this application. I am with the Office of Compliance/Office of Unapproved Drugs and Labeling Compliance. I know that Jacobus is/was supplying amifampridine under an expanded use IND and has also submitted this NDA for its product.

Because of the recent press for Catalyst's amifampridine approval, we have received several questions about Jacobus' marketing for its amifampridine and what happens to the Jacobus application/expanded use INDs now that Catalyst has received approval.

I was hoping that you could provide us some information:

1) I see that Catalyst's NDA now lists orphan drug exclusivity in the Orange Book. How does

this affect Jacobus' application? Can it be approved?

2) What will happen to the expand use INDs for Jacobus' amifampridine?

3) Has Jacobus given any indication that it would like to continue to market its product if it does not get exclusivity?

Also, would it be possible to invite me or one of my staff to the meetings for amifampridine so that we are aware of any issues with the application/discussions OND is having about the drug?

Thanks,

Carolyn Volpe, PharmD, MS
CDR, United States Public Health Service

Acting Branch Chief

Center for Drug Evaluation and Research
Office of Compliance/Office of Unapproved Drugs and Labeling Compliance

Prescription Drugs Branch
U.S. Food and Drug Administration
Tel: 301-796-5204
carolyn.volpe@fda.hhs.gov

From: Buracchio, Teresa
To: Locicero, Colleen L; Mathers, Michelle
Subject: RE: Question about NDA 209321 Jacobus" amifampridine
Date: Wednesday, March 06, 2019 8:22:00 AM

These look great!

Thanks, Colleen!

Teresa

From: Locicero, Colleen L
Sent: Wednesday, March 06, 2019 6:56 AM
To: Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>
Subject: RE: Question about NDA 209321 Jacobus' amifampridine

My suggested edits in red and mark up.

Thanks,
Colleen

From: Mathers, Michelle
Sent: Monday, March 04, 2019 11:52 AM
To: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>; Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>
Subject: FW: Question about NDA 209321 Jacobus' amifampridine

Hi Teresa and Colleen,

This request came from the office of compliance on Friday. I've drafted some high-level responses, please let me know if you would like to provide something more formal.

Thanks!

Michelle

1) While exclusivity determinations are made at the time of approval, it appears (based on preliminary discussions with the exclusivity board) that Only approval of the adult LEMS indication will be ~~is~~ affected (i.e., the Jacobus product cannot be approved with the adult LEMS indication until Catalyst's orphan exclusivity

expires). A pediatric indication is under consideration and, based on those preliminary discussions, would not likely be blocked by Catalyst's exclusivities.

2) Jacobus has discontinued providing their product to physicians for expanded access use ~~of their product~~ in adult LEMs patients, however we have advised Jacobus that they may continue to provide their product to physicians for treatment use under expanded access for other indications and for pediatric LEMS patients, since these uses are not covered in the Catalyst approved labeling. ~~by the Catalyst approval~~.

3) No, we have not discussed marketing plans with Jacobus. ~~as they would be able to market their product for pediatric use should that indication be approved.~~

From: Volpe, Carolyn
Sent: Friday, March 01, 2019 11:04 AM
To: Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>
Cc: Wilson, Kelly <Kelly.Wilson@fda.hhs.gov>; Maslov, Yelena <Yelena.Maslov@fda.hhs.gov>
Subject: Question about NDA 209321 Jacobus' amifampridine

Hi Michelle,

I see you are the project manager for this application. I am with the Office of Compliance/Office of Unapproved Drugs and Labeling Compliance. I know that Jacobus is/was supplying amifampridine under an expanded use IND and has also submitted this NDA for its product.

Because of the recent press for Catalyst's amifampridine approval, we have received several questions about Jacobus' marketing for its amifampridine and what happens to the Jacobus application/expanded use INDs now that Catalyst has received approval.

I was hoping that you could provide us some information:

1) I see that Catalyst's NDA now lists orphan drug exclusivity in the Orange Book. How does this affect Jacobus' application? Can it be approved?

2) What will happen to the expand use INDs for Jacobus' amifampridine?

3) Has Jacobus given any indication that it would like to continue to market its product if it does not get exclusivity?

Also, would it be possible to invite me or one of my staff to the meetings for

amifampridine so that we are aware of any issues with the application/discussions OND is having about the drug?

Thanks,

Carolyn Volpe, PharmD, MS
CDR, United States Public Health Service

Acting Branch Chief

Center for Drug Evaluation and Research
Office of Compliance/Office of Unapproved Drugs and Labeling Compliance

Prescription Drugs Branch
U.S. Food and Drug Administration
Tel: 301-796-5204
carolyn.volpe@fda.hhs.gov

BERNARD SANDERS
VERMONT

COMMITTEES:
BUDGET, RANKING MEMBER
ENERGY AND NATURAL RESOURCES
ENVIRONMENT AND PUBLIC WORKS
HEALTH, EDUCATION, LABOR, AND PENSIONS
VETERANS' AFFAIRS

United States Senate
WASHINGTON, DC 20510–4504

332 SENATE DIRKSEN OFFICE BUILDING
WASHINGTON, DC 20510
(202) 224–5141

1 CHURCH STREET, 3RD FLOOR
BURLINGTON, VT 05401
(802) 862–0697
1 (800) 339–9834

www.sanders.senate.gov

February 26, 2019

The Honorable Alex M. Azar II
Secretary
U.S. Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, DC 20201

The Honorable Scott Gottlieb, M.D.
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Secretary Azar and Commissioner Gottlieb:

I understand that the Food and Drug Administration's (FDA) mission includes not only protecting the public health by ensuring medical products have benefits that outweigh their risks, but also "helping to speed innovations" to the public that are "more affordable."[1] FDA recently approved Firdapse to treat a rare neuromuscular disease called Lambert-Eaton myasthenic syndrome (LEMS), and in so doing, a drug that had been available to patients for free for decades through a compassionate use program is now being sold by Catalyst Pharmaceuticals at the outrageous annual list price of $375,000.

Since Firdapse's market entry my office has heard from patients who are unable to get the medicine they need because of this astronomical price. Without this medication, patients with LEMS will suffer and die.

Although I recognize FDA did not specifically intend for its approval of Firdapse to result in Catalyst setting this exorbitant price, FDA's approval of this drug nonetheless led to this result. Catalyst now has at least seven years of exclusive marketing rights during which time the company projects to make hundreds of millions of dollars in profit on a drug that has been available for decades.[2] In light of the drug's shocking price, I urge FDA to announce that it will not take enforcement action against pharmacies or manufacturers that were previously providing 3,4-DAP to patients and are able to resume the distribution of this drug, subject to the same requirements as the drug was available prior to the date of Firdapse's approval.

---

[1] U.S. Food & Drug Administration, "What We Do," (last accessed Feb. 26, 2019), (available at https://www.fda.gov/aboutfda/whatwedo/).
[2] "U.S. FDA approves Catalyst Pharma's rare disease drug," *Reuters* (Nov. 28, 2018), (available at https://www.reuters.com/article/us-catalyst-pharms-fda/us-fda-approves-catalyst-pharmas-rare-disease-drug-idUSKCN1NX2ZL).

Catalyst may be the most recent company to exploit their monopoly after receiving FDA approval for an inexpensive old drug, but they were certainly not the first. FDA's effort to bring older, unapproved drugs through the approval process may have some laudable benefits, but it has also led to instances where drugmakers use the grant of market exclusivity that accompanies FDA approval to fleece patients and taxpayers. The prices of very old and inexpensive drugs like colchicine, vasopressin, neostigmine, and others have been raised substantially by drugmakers following approval, causing needless suffering and adding to the cost of our health care system.[3]

It is absurd for FDA to claim affordability as central to its mission and tout policy activities that prioritize lower drug prices while simultaneously claiming the agency cannot take steps to lower drug prices.[4,5] You have said that "access to prescription drugs is a matter of public health."[6] I agree, and I also believe that the lack of access we have in this country to affordable prescription drugs is a public health crisis, a crisis that FDA must acknowledge its role in perpetuating and take action to address.

You have personally called out price gouging companies and said that "there's no moral imperative to price gouge and take advantage of patients. FDA will continue to promote competition so speculators and those with no regard to public health consequences can't take advantage of patients who need medicine."[7] Catalyst Pharmaceuticals' decision to set a price of $375,000 is a prime example of price gouging. This price was set without regard to public health and takes advantage of patients who need this medicine to survive.

For all of these reasons, I urge FDA to take action immediately. One action I suggest, an action for which there is similar agency precedent,[8] is to announce that FDA will not take enforcement action against pharmacies and manufacturers who were previously providing 3,4-DAP to patients and are able to resume the distribution of this drug. Thank you for your consideration.

Sincerely,

Bernard Sanders
United States Senator

---

[3] Michael Hiltzik, "The little-known FDA program that's driving drug prices higher," *LA Times* (Sept. 23, 2015), (available at https://www.latimes.com/business/hiltzik/la-fi-mh-the-little-known-fda-program-20150923-column.html).

[4] "Statement from FDA Commissioner Scott Gottlieb, M.D., on the Trump Administration's plan to lower drug prices," (May 11, 2018), (available at https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm607495.htm).

[5] "Statement from FDA Commissioner Scott Gottlieb, M.D. on new efforts to empower consumers by advancing access to nonprescription drugs," (July 17, 2018), (available at https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm613692.htm).

[6] *See* note 4.

[7] Scott Gottlieb, M.D., *Twitter* (Sept. 11, 2018), (available at https://twitter.com/SGottliebFDA/status/1039481679218401285).

[8] FDA Statement on Makena (Mar. 30, 2011), (available at http://web.archive.org/web/20110402072831/http:/www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm249025.htm).

From: CDER DRUG INFO
To: (b) (6)
Subject: Firdapse
Date: Thursday, May 09, 2019 1:34:00 PM

Dear (b) (6)

This is in response to your March 8, 2019, letters to U.S. Department of Health and Human Services (HHS) Secretary Alex Azar and Dr. Scott Gottlieb, former Commissioner of the Food and Drug Administration (FDA) concerning the approval of Firdapse . Your letters were forwarded to the Division of Drug Information in FDA's Center for Drug Evaluation and Research (CDER) for a response.

We appreciate you taking the time to share your concerns with us.

As you are aware, on November 28, 2018, FDA approved a new drug application (NDA) submitted by Catalyst Pharmaceuticals for Firdapse (amifampridine phosphate oral tablets) for the treatment of Lambert Eaton Myasthenic Syndrome (LEMS). FDA approved the NDA for Firdapse after its rigorous review of the evidence supplied by the applicant supported a conclusion of safety, effectiveness, and product quality. As you know, Americans rely on the FDA to ensure that drugs are both safe and effective. An essential part of an application to support marketing approval is the applicant's demonstration that its manufacturing processes can reliably produce drug products of expected identity, strength, quality, and purity. In addition, FDA's review of the applicant's labeling ensures that health care professionals and patients have the information necessary to understand a drug product's risks and its safe and effective use. For reference, you can find on the FDA website reviews of the data that supported the approval of Firdapse (Drugs@FDA), and the Firdapse NDA approval letter.

The Agency has serious concerns that drugs distributed without FDA approval may not meet modern standards for safety, effectiveness, quality, and labeling. Unapproved drug products, including unapproved 3,4-DAP products, have not been through FDA's rigorous premarket review process, so patients do not have the same level of assurance about the quality of such products, or whether they are safe and effective in the treatment of their condition. Nor can patients or providers rely on the labeling associated with unapproved drugs as accurately conveying directions for use, warnings, or other important information. Therefore, unapproved drugs pose a higher risk to patients than FDA-approved drugs.

You also expressed concerns regarding the potential cost of Firdapse. The FDA is undertaking a series of policy and scientific initiatives that are intended to help increase competition in the market to address the multi-faceted problem of high drug costs. Although the FDA does not play a direct role in drug pricing — it is the responsibility of manufacturers, distributors, and retailers, among others, to establish these prices — the agency has noted that too many patients are being priced out of the medicines they need. To address this very important public health issue, former Commissioner Gottlieb announced the Drug Competition Action Plan in 2017 to help remove barriers to generic drug development and market entry to spur competition that could contribute to lower drug prices for patients. The FDA is similarly examining whether there are barriers to approval in the agency's other abbreviated approval pathways that could be addressed. In addition, the White House and Department of Health and Human Services have a blueprint for bringing down the high price of drugs and reducing out-of-pocket costs for American patients. You might wish to contact our colleagues at the Department of Health and Human Services and/or the Centers for Medicare & Medicaid Services for additional information on pricing issues.

As you probably now know, on May 7th, 2019, FDA approved Ruzurgi (amifampridine,

described chemically as 3,4-diaminopyridine) sponsored by Jacobus Pharmaceuticals. Ruzurgi is indicated for pediatric patients ages 6 to under 17 years of age with LEMS. Ruzurgi is the first approved treatment specifically for pediatric patients with LEMS. You can refer to the patient and doctor information and press release for more details. Please talk with your health care provider about the right treatment option for you.

Thank you for writing.

Sincerely,
/s/
Donald Dobbs
Division of Drug Information
Office of Communications
Center for Drug Evaluation and Research
Food and Drug Administration

TAB 3:

Documents showing that FDA intended that Ruzurgi be sold off-label to adult patients

From: Bastings, Eric
To: Kozauer, Nicholas (Nicholas.Kozauer@fda.hhs.gov)
Cc: Buracchio, Teresa
Subject: FW: For DNP review: Press release and QA for Ruzurgi (amifampridine) for LEMS - review by COB Friday
Date: Thursday, April 11, 2019 4:41:00 PM
Attachments: Reactive QA for Ruzurgi action.EAqdocx.docx
image001.png
image003.jpg
image004.jpg
image005.jpg
image006.jpg
image007.jpg

Nick,

I could not get to this. I assume Teresa is looking at it.

Eric

From: Locicero, Colleen L
Sent: Thursday, April 11, 2019 12:45 PM
To: Dunn, Billy <Billy.Dunn@fda.hhs.gov>; Bastings, Eric <Eric.Bastings@fda.hhs.gov>; Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>
Cc: Ware, Jacqueline H <Jacqueline.Ware@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Walsh, Sandy <Sandy.Walsh@fda.hhs.gov>
Subject: RE: For DNP review: Press release and QA for Ruzurgi (amifampridine) for LEMS - review by COB Friday

All,

Attached is the Q&A with the response to the question about expanded access revised (in mark up), based on feedback I received from the EACC.

Thanks,
Colleen

From: Walsh, Sandy
Sent: Tuesday, April 09, 2019 9:43 AM
To: Dunn, Billy <Billy.Dunn@fda.hhs.gov>; Bastings, Eric <Eric.Bastings@fda.hhs.gov>; Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>
Cc: Fuchs, Elissa <Elissa.Fuchs@fda.hhs.gov>; Ware, Jacqueline H <Jacqueline.Ware@fda.hhs.gov>; Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Kotz, Deborah <Deborah.Kotz@fda.hhs.gov>
Subject: For DNP review: Press release and QA for Ruzurgi (amifampridine) for LEMS - review by COB Friday

Good morning DNP,

Attached for DNP review is the draft press release and responsive QA for the Rizurgi approval. (ORP and OCC will need to weigh in on many of the Qs.) Please review by COB **Friday 4/12** if possible.

Also, do you have any update on potential timing for the action? Still planning for last week in April? (I'll be out the week of Monday April 15, my colleague Debbie Kotz, copied here, will be covering for me while I'm out so I'll brief her on the issues.)

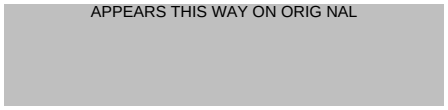
Sandy Walsh
Press Officer

Office of Media Affairs
Office of External Affairs
U.S. Food and Drug Administration
Tel: 301-796-4669
Sandy.Walsh@fda.hhs.gov

(b) (5)

(b) (5)

(b) (5)


APPEARS THIS WAY ON ORIG NAL

From:	Fuchs, Elissa
To:	Ware, Jacqueline H; Locicero, Colleen L; Mathers, Michelle; Kozauer, Nicholas; Dunn, Billy; Bastings, Eric; Walsh, Sandy; Buracchio, Teresa
Subject:	Cleared QA for Ruzurgi Approval
Date:	Monday, April 29, 2019 12:52:22 PM
Attachments:	Reactive QA for Ruzurgi approval OCC cleared 4.29.19.docx

Hi DNP,

Attached are the cleared QA for the Ruzurgi approval. Please let me know if you have any edits, questions or concerns.

Thanks,

Elissa

Responsive QAs for Ruzurgi and Firdapse

1. **Is the indication for Ruzurgi the same as Firdapse? Are they the same exact drug?**

   The indicated populations for the two drugs are different. Ruzurgi is indicated for pediatric patients ages 6 to under 17 years of age with Lambert-Eaton Myasthenic Syndrome (LEMS). Ruzurgi is the first approved treatment specifically for pediatric patients with LEMS. Firdapse is indicated only for adult patients with LEMS.

   The active ingredient is the same in both products, amifampridine.

2. **What clinical trial data enabled Ruzurgi to be approved for the pediatric population?**

   The FDA requires the drug company (sponsor) to have data demonstrating the effectiveness and safety of a product in pediatric patients to support approval of a pediatric indication. In this case, data was extrapolated from adult studies. It is common practice when designing pediatric development programs to consider the possibility of extrapolation of efficacy data from adult studies to pediatric ones. This approach is discussed in the following FDA guidance.

   Additionally, Ruzurgi's sponsor provided safety data from pediatric patients taking the drug through expanded access.

   Safety and effectiveness of Ruzurgi have been established in patients 6 to less than 17 years of age. Use in patients 6 to less than 17 years of age is supported by evidence from adequate and well-controlled studies of Ruzurgi in adults with LEMS, pharmacokinetic data in adult patients, pharmacokinetic modeling and simulation to identify the dosing regimen in pediatric patients, and safety data from pediatric patients 6 to less than 17 years of age. Safety and effectiveness in pediatric patients under age 6 have not been established.

   Please refer to the patient and doctor information and press release for more details.

3. **What are the differences between the pediatric and adult versions of the drugs?**

   In general, differences can exist between pediatric and adult versions of a medicine with respect to strength, dosage and safety issues.

   Firdapse is available in 10 mg tablets, functionally scored (meaning pill can be split), and the recommended starting dosage is 15 mg to 30 mg daily, taken orally in divided doses (three to four times a day). Additional dosage and administration considerations are described in the prescribing information. The most common adverse reactions for Firdapse include paresthesia (poor circulation), upper respiratory tract infection, abdominal pain, nausea, diarrhea, headache, elevated liver enzymes, back pain, hypertension, and muscle spasms.

   Ruzurgi will be available in 10 mg tablets, functionally scored. Dosage is based on weight and is described in detail in the prescribing information.

   The most common side effects for Ruzurgi include paresthesia/dysesthesia (abnormal sensations), abdominal pain, dyspepsia (indigestion), dizziness and nausea. Side effects reported in pediatric patients were similar to those seen in adult patients.

4. **How is it that Ruzurgi was allowed to be approved at this time? Wasn't it blocked by Firdapse's new chemical entity and orphan exclusivities?**

   Exclusivities are recognized for medicines upon or after approval, if the statutory requirements are met. Once exclusivity determinations are made, that information is published in the FDA's Orange Book.

   The agency recognized five-year new chemical entity (NCE) exclusivity and seven-year orphan drug exclusivity for Firdapse upon its approval. NCE exclusivity bars the submission and approval of abbreviated new drug applications (applications for generic versions of the innovator drug) and 505(b)(2) applications (applications where at least some of the information required for approval comes from studies not conducted by or for the applicant and to which it does not have a right of reference). However, the Ruzurgi application was a stand-alone application (neither a generic nor a 505b2 application), which relied on independent clinical evidence to support approval. Therefore, the submission and approval of Ruzurgi is unaffected by Firdapse's NCE exclusivity.

   Meanwhile, Firdapse's orphan exclusivity could block either type of application. However, because the indications for the treatments are different — Ruzurgi is indicated for children and teens and Firdapse is indicated for adults — both products could come to the market.

5. **When Firdapse came on the market, its price was exorbitantly high. *[insert comment about Ruzurgi when pricing becomes available]* What can FDA do to control drug prices?**

   The FDA is undertaking a series of policy and scientific initiatives that are intended to help increase competition in the market to address the multi-faceted problem of high drug costs. Although the FDA does not play a direct role in drug pricing — it is the responsibility of manufacturers, distributors, and retailers, among others, to establish these prices — the agency has noted that too many patients are being priced out of the medicines they need.

   To address this very important public health issue, former Commissioner Gottlieb announced the Drug Competition Action Plan in 2017 to help remove barriers to generic drug development and market entry to spur competition that could contribute to lower drug prices for patients. The FDA is similarly examining whether there are barriers to approval in the agency's other abbreviated approval pathways that could be addressed. In addition, the White House and Department of Health and Human Services have a blueprint for bringing down the high price of drugs and reducing out-of-pocket costs for American patients. You might wish to contact our colleagues at the Department of Health and Human Services and/or the Centers for Medicare & Medicaid Services for additional information on pricing issues.

6. **Patients were getting these treatments under the FDA's expanded access program before the drugs received FDA-approval. Can patients with LEMS still receive these treatments under the expanded access program?**

   Expanded access is a potential option for a patient with a serious or immediately life-threatening disease or condition to receive an investigational drug for treatment outside of clinical trials when there are no comparable or satisfactory alternative therapies.

   Now that Firdapse is FDA-approved to treat adult LEMS patients, and Ruzurgi is FDA-approved to treat pediatric LEMS patients, we expect patients with this disease will be able to access the

treatment approved for their age range in the same way they obtain other marketed prescription medicines.

7. Could patients potentially use either drug treatment off-label?

The decision to treat a patient with a drug for an unapproved use is up to the treating health care professional and generally speaking, the practice of medicine is not regulated by the FDA. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well-informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects.

Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgement.

8. Can patients still receive a compounded product through a pharmacy?

Although compounded drugs can serve an important medical need for certain patients, they do not undergo premarket review and thus lack FDA findings of safety, effectiveness and quality. Therefore, patients should only receive a compounded drug when an FDA-approved drug is not available or not medically suitable for a patient.

Draft, EFuchs, CDER OComm
Edits, SWalsh, OMA, 4/9/19
Edits, EFuchs, CDER OCOMM 4/9/19
Edits, CLocicero, TBurrachio, BDunn, DNP, 4/12/19
Minor Edits, EUnger, ODE-I, 4/12/19
Edits, KNduom, JSitlani, RRaman, GCheng, NShah, CBennett ORP, 4/16/19
Minor Edits EFUCHS CDER OCOMM 4/17/19
Edits: KBaumgartner, OCOMM, 4/17/19
Edits: EFuchs OCOMM 4/17/19
Cleared: CShreeve OCOMM 4/17/19
Edits: SPeddicord, OMA, 4/23/19
Edits, GYoung, OCC, 4/26/19
Clearance, LSilvis, OC, 4/29/19

From: Dobbs, Donald
To: Locicero, Colleen L
Cc: Kremzner, Mary E
Subject: LEMs Drugs
Date: Monday, April 29, 2019 3:30:22 PM
Attachments: image001.jpg
image002.jpg
image003.jpg
image004.jpg

Hi Colleen:

In anticipation of Ruzurgi's approval, attached is our (DDI's) draft response for patients that experienced potential ADRs and therapeutic failure while transitioning to Firdapse. You will find two examples of such complaints from (b) (6) and (b) (6) in the email trail below. The language we used came from the draft KMQA's and previously cleared language.

Can you please clear the draft for us.

Thanks much,

Don

From: Locicero, Colleen L
Sent: Friday, March 29, 2019 1:57 PM
To: Chew, Catherine <Catherine Chew@fda hhs gov>
Cc: Kremzner, Mary E <Mary Kremzner@fda hhs gov>; Kimbrell, Maarika <Maarika Kimbrell@fda hhs gov>; Phillips, J Paul <Paul Phillips@fda hhs gov>
Subject: RE: LEMs Drug

Hi Cat,

The Jacobus product is the product all of these folks had been taking, prior to the Firdapse approval, and while the Jacobus product, once approved, won t be labeled for use *in adults* with LEMS, healthcare providers will be able to prescribe it for adults off label under the practice of medicine The Jacobus approval should, therefore, take care of the situation

Your plan sounds good, because I am skeptical that we will be prepared to provide language to respond to the EA question after a single MPPRC discussion I suspect it may take several discussions However, if I would be able to provide cleared response language to you earlier, I will do so

Thanks and have a good weekend,
Colleen

From: Chew, Catherine
Sent: Friday, March 29, 2019 1:35 PM
To: Locicero, Colleen L <Colleen Locicero@fda hhs gov>
Cc: Kremzner, Mary E <Mary Kremzner@fda hhs gov>; Kimbrell, Maarika <Maarika Kimbrell@fda hhs gov>; Phillips, J Paul <Paul Phillips@fda hhs gov>
Subject: RE: LEMs Drug

Dear Colleen,

Thank you for all the time you re spending on this (and marijuana, and everything else we escalate to you) And thanks for confirming again that the Sanders letter has great language for compounding and EA because of price concerns Sorry, the email below was not a good example But below are two more emails where patients are interested in access to Jacobus amifampridine because of therapeutic failure more than price

Thank you for letting us know the outcome of the MPPRC discussion – however, (b) (5)
(b) (5)
(b) (5) Does that sound like a plan?

We do appreciate you, and thanks for YOUR patience,
Cat

From (b) (6)
Sent: Monday, March 4, 2019 11:14 AM
To: CDER DRUG INFO <DRUGINFO@fda hhs gov>
Subject: Firdapse

It was shared in a support group for individuals with Lambert Eaton Myasthenic Syndrome that we can report trouble transitioning from 3,4 DAP to Firdapse

I have taken 20 mg 3,4 DAP four times a day since 2015 It has been crucial for my regaining function I have been on Firdapse about 3 weeks and am having issues with the transition

The Firdapse has more intense tingling sensations and seems to cause vasoconstriction in the extremities within a half hour of taking a dose and it lasts an hour or more This makes it difficult to do outdoor activities I'm already on midodrine, for control of blood pooling, but nobody has any information as to whether it is okay to take both

As far as effectiveness, Firdapse seems to produce an earlier increase in strength but doesn't consistently maintain strength until the next dose On 3,4 DAP I was able to go 5-6 hours between doses Now I feel like it wears off after just 3 hours I'm nothing trouble walking in the morning, which was never the case on 3,4 DAP

It seems that there has been no comparison of the two treatments and that Firdapse has significant drawbacks over the prior standard of treatment

Thank you for your assistance

(b) (6)

From (b) (6)
Sent: Tuesday, March 19, 2019 1:18 AM
To: CDER DRUG INFO <DRUGINFO@fda hhs gov>
Subject: Firdapse

I have been taking firdapse for Lems since February 10,2019 I was on DAP for over 20 years and I never had the problems with DAP like I have had with firdapse My blood pressure has been all over the place and my INR has been too I have to go to a clinic once a week to have my clotting checked which is very hard for me My weakness has gotten bad enough that I have had to get help to get out of my chair and sometimes I need help getting dressed These things were never a problem before but since taking the firdapse I have noticed a great difference in my strength and stamina The price for firdapse is insane and since it doesn't work as good I would like my DAP back It doesn't work as long and as good as the DAP Thank You

(b) (6)

From: Locicero, Colleen L
Sent: Thursday, March 28, 2019 2:26 PM
To: Chew, Catherine <Catherine Chew@fda hhs gov>
Cc: Kremzner, Mary E <Mary Kremzner@fda hhs gov>; Kimbrell, Maarika <Maarika Kimbrell@fda hhs gov>; Phillips, J Paul <Paul Phillips@fda hhs gov>
Subject: RE: LEMs Drug

Hi Cat,

We discussed the matter of how to respond to inquiries about expanded access to the Jacobus amifampridine product and compounding of amifampridine today with Jacqueline Corrigan-Curay and Peter Stein (b) (5)

)

Thanks for your patience and sorry I can t provide anything more definitive at this time

Colleen

From: Chew, Catherine
Sent: Tuesday, March 26, 2019 9:55 AM
To: Locicero, Colleen L <Colleen Locicero@fda hhs gov>
Cc: Kremzner, Mary E <Mary Kremzner@fda hhs gov>
Subject: FW: LEMs Drug

Another request, after we replied about the pricing issue

From: Lal, Renu <Renu Lal@fda hhs gov>
Date: March 26, 2019 at 8:00 57 AM EDT
To: Chew, Catherine <Catherine Chew@fda hhs gov>
Subject: FW: LEMs Drug

Cat,

Here is an email I received asking for access to Jacobus product

Renu

From: (b) (6)
Sent: Monday, March 4, 2019 4:02 PM
To: CDER DRUG INFO <DRUGINFO@fda hhs gov>
Subject: Re: LEMs Drug

Good afternoon,

Would you please respond to my concerns about…

1. Allow Jacobus to continue producing 3-4 DAP as they seek FDA approval via the compassionate use program

2. Allow Compounding Pharmacies to produce 3-4 DAP

3. Break Catalyst's Orphan Drug Status given that Catalyst did not discover or develop the drug. They are licensing it from a European company, which seems to be a loophole in the well intentioned Orphan Drug program.

I just talked with (b) (6) I have asked that my prescription be run WithOut the Pathways program that require me to sign away my HIPPA rights. As of today, I have not signed page 2 of the Catalyst Pathways Programs for assistance. Each pill is $205.05 I need 8 pills per day that is $1640.00 per day. $1640 x 30days = $49,200 per month $49,200 X 12 months = $590,400 per year.... insane... I feel like a burden on society and my husbands job being in jeopardy due to my medical cost.

I look forward to hearing for you,
(b) (6)

On Monday, March 4, 2019, 3:35 26 PM EST, CDER DRUG NFO <DRUGINFO@fda.hhs gov> wrote:

Dear (b) (6)

Thank you for writing to the Division of Drug Information in the FDA's Center for Drug Evaluation and Research (CDER).

We would like to thank you for your comments and suggestions related to the recent approval of Catalyst's Firdapse. We understand this approval has frustrated and angered many people, due to the prior access to the active ingredient in the drug product.

We understand that high drug prices have a direct impact on patients—too many American patients are priced out of the medicines they need. However, the FDA has no legal authority to investigate or control the prices set by manufacturers, distributors and retailers. A number of factors can impact drug pricing, such as the costs of research and development and the amount of competition in the marketplace. Also, other factors, beyond FDA's purview can determine patient access to drugs.

You may also wish to contact the drug manufacturer to share your concerns, or you may contact the Federal Trade Commission (FTC). The FTC enforces a variety of federal antitrust and consumer protection laws, and seeks to ensure that the nation's markets function competitively, and are vigorous, efficient, and free of undue restrictions. Finally, consider reaching out to your elected US representatives to enact legislative change.

Best regards,
RL
Pharmacist
Division of Drug Information
Center for Drug Evaluation and Research
Tel: 855-543-DRUG (888-543-3784)
druginfo@fda hhs.gov

Follow us

This communication is consistent with 21 CFR 10.85(k) and constitutes an informal communication that represents our best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of the FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

From: (b) (6)
Sent: Monday March 4 2019 11:11 AM
To: CDER DRUG INFO <DRUGINFO@fda hhs gov>
Subject: LEMs Drug

(b) (6)

To Whom It May Concern:

I have a very rare disease, Lambert-Eaton Myasthenic Syndrome or LEMS for short. After many years, I was diagnosed at (b) (6) My doctor explained that an orphan drug from Jacobus Pharmaceutical's called 3,4 DAP was available on compassionate use. This is the primary drug that allows me to lead a pretty normal life. 3,4 DAP is no longer available to patients in the United States. Amifampridine (3,4 DAP) enabled me to move, eat, breathe, and live a normal good life. Some people have been on it for years and call it their miracle drug. As of November 2018, Catalyst pharmaceutical's drug - Firdapse has been approved for the treatment of LEMS by the FDA, and it was priced at $375,000 a year. The $375,000 price is based on 60mg daily. I will need 80mg so my price is more than half a million. At present, (b) (6) and some other insurance companies do not have this medication on their formulary list. And if I do get approval, how long will they be willing to pay for this medication at this price point? I will need this medication for the rest of my life. Vets that need this drug are having problems getting it through the VA. Because it is such a rare disease, there is not going to be large numbers of patients or family members asking for something to be done. We would like for the medicine to be available at an affordable price. The average American makes $55,000 per year. There are people who want both drugs to be available in this country as they are in some others countries because one drug may work better for some people. Why can't patient have the Choice of 3,4 DAP from Jacobus Pharmaceutical's and Firdapse from Catalyst's Pharmaceutical's. In December 2018, Catalyst Pharmaceuticals (CPRX) licensed a modified version (Amifampridine phosphate (Firdapse®) from European pharmaceutical Biomarin, received FDA approval through the Orphan Drug program, and changed the price from 0 to $375,000 per year for 60mg.

It is beyond me to understand why some human beings attempt to profit from the suffering of others, but here we are.

I know you believe in competitive markets, and I believe Catalyst's price gouging can be checked by each of the following ways:

1. Allow Jacobus to continue producing 3-4 DAP as they seek FDA approval via the compassionate use program

2. Allow Compounding Pharmacies to produce 3-4 DAP

3 Break Catalyst's Orphan Drug Status given that Catalyst did not discover or develop the drug They are licensing it from a European company, which seems to be a loophole in the well intentioned Orphan Drug program.

Here is an article where the FDA tool the unusual step and allowed a second company to continue producing a less expensive version of a drug, which had long been available at an affordable price.

https://www.washingtonpost.com/national/pharmaceutical_company_slashes_price_of_preterm_baby_drug_makena/2011/04/01/AFpP9hGC_story.html?fbclid=IwAR02bzCafycLMJ0EHRoWPiOv9-EWBMzCUTYNrt6zRmm3O6xhzzGmq4Flrt4&noredirect=on&utm_term=.55a7a8378dc8

Regards,
(b) (6)

From: Unger, Ellis
To: Walsh, Sandy
Subject: RE: Early look at pediatric LEMS drug approval clips
Date: Tuesday, May 07, 2019 9:27:00 AM
Attachments: image002.png
image004.jpg
image006.jpg
image008.jpg
image010.jpg
image012.jpg

Good press! Thanks for sending. I like being crafty…

Too bad the Catalyst lawyers will be on our doorstep soon!

From: Walsh, Sandy
Sent: Tuesday, May 07, 2019 7:53 AM
To: Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>; Dunn, Billy <Billy.Dunn@fda.hhs.gov>; Bastings, Eric <Eric.Bastings@fda.hhs.gov>; Kozauer, Nicholas <Nicholas.Kozauer@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Unger, Ellis <Ellis.Unger@fda.hhs.gov>; Shah, Nisha <Nisha.Shah@fda.hhs.gov>; Myers, James <James.Myers@fda.hhs.gov>; Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>; Hayes, Nancy <Nancy.Hayes@fda.hhs.gov>; Friedman, Aaron <Aaron.Friedman@fda.hhs.gov>; Fuchs, Elissa <Elissa.Fuchs@fda.hhs.gov>; Nduom, Kelley <Kelley.Nduom@fda.hhs.gov>; Dettelbach, Kim <Kim.Dettelbach@fda.hhs.gov>; Sitlani, Jay <Jay.Sitlani@fda.hhs.gov>
Cc: Bolek, Michelle <Michelle.Bolek@fda.hhs.gov>
Subject: Early look at pediatric LEMS drug approval clips

Good morning,
Below are a few early news clips from the LEMS drug approval. You'll see that STAT/Pharmalot reporter did a deeper dive, speculating on issues around the action including pricing and exclusivity issues, etc. I'll keep an eye out for additional clips today.

Reuters
HEALTH NEWS
MAY 6, 2019 / 6:11 PM / UPDATED 13 HOURS AGO

FDA grants Jacobus Pharma approval for rare disease drug

(Reuters) - Jacobus Pharmaceutical Co Inc on Monday won U.S. approval for the first drug to treat children with Lambert-Eaton myasthenic syndrome, a rare autoimmune disorder.

The drug, Ruzurgi, was approved for use in patients aged between 6 and 17, the FDA said here.

Lambert-Eaton myasthenic syndrome, which affects about three people per million worldwide, affects the connection between nerves and muscles, disrupting the ability of nerve cells to send signals to muscle cells.

The treatment currently available has been approved only for adults.

Reporting by Tamara Mathias in Bengaluru; Editing by Anil D'Silva

STAT/Pharmalot

In a crafty move, FDA may have found a way to dampen controversy over a $375,000 rare-disease drug

By Ed Silverman @Pharmalot

May 6, 2019

The Food and Drug Administration just added an unexpected twist to a simmering controversy over a rare disease drug that earlier this year briefly became a poster child for high-priced medicines.

In a surprise move, the agency approved a medicine from Jacobus Pharmaceuticals, a small, family-run company, for treating a neuromuscular disorder called Lambert-Eaton myasthenic syndrome, or LEMS, for children ages 6 to 17. However, the approval potentially adds unforeseen competition for Catalyst Pharmaceuticals (CPRX), which only last December won an FDA endorsement to market its own treatment for adults.

In after-hours trading, Catalyst stock was down as much 44%.

The Food and Drug Administration just added an unexpected twist to a simmering controversy over a rare disease drug that earlier this year briefly became a poster child for high-priced medicines.

In a surprise move, the agency approved a medicine from Jacobus Pharmaceuticals, a small, family-run company, for treating a neuromuscular disorder called Lambert-Eaton myasthenic syndrome, or LEMS, for children ages 6 to 17. However, the approval potentially adds unforeseen competition for Catalyst Pharmaceuticals (CPRX), which only last December won an FDA endorsement to market its own treatment for adults.

In after-hours trading, Catalyst stock was down as much 44%.

Here's why: The FDA approval of the Catalyst drug, called Firdapse, set off a firestorm. Until then, a few hundred LEMS patients were able for years to obtain the Jacobus drug for free under a compassionate use program sanctioned by the FDA. But with its approval, Catalyst obtained seven years of market exclusivity, which meant Jacobus and compound pharmacies could no longer market their versions.

The move created an uproar because Catalyst decided to charge $375,000 list price, depending upon total patient dosing, for Firdapse. In February, U.S. Sen. Bernie Sanders (I-Vt.), who's made high drug prices a raison d'etre, accused the drug maker of "corporate greed" and

"immoral exploitation." And he asked the FDA to permit Jacobus and compounders to resume suppliers of their treatments.

"This sounds like a workaround."

Dr. Donald Sanders, a Duke University

The agency appears to have heeded the call. Jacobus has not yet disclosed a price for its drug, called Ruzurgi. But by approving it for children, the agency is making it possible for physicians to prescribe the Jacobus drug for any patient, regardless of age, because doctors are free to prescribe medicines for unapproved or so-called off-label uses. Interestingly, the FDA approval was predicated, in part, on data from studies involving adults.

"If it's on the market for children, it can be prescribed for adults," said Dr. Donald Sanders, a Duke University researcher who worked with the Jacobus family when they first developed their LEMS drug and later helped design the clinical trial that was submitted to the FDA. "I don't know of any drug that is approved for adults with LEMS other than Firdapse, but we already use many other medicines off label to treat LEMS. This sounds like a workaround."

An FDA spokeswoman sent us this: "The decision to treat a patient with a drug for an unapproved use is up to the treating health care professional and generally speaking, the practice of medicine is not regulated by the FDA. Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics, and devices according to their best knowledge and judgement."

Meanwhile, PiperJaffray analyst Joseph Catanzaro wrote this: "While this is a different label indication than Firdapse's adult LEMS label, it will no doubt raise questions around whether Ruzurgi will be used off-label in adult patients and whether Firdapse will be able to maintain the orphan drug price point it set at launch. However, we suspect that there will be legal questions around whether the approval of Ruzurgi infringes on Firdapse's orphan drug exclusivity in LEMS."

"We see this approval by the FDA simply as a way to combat the pricing rhetoric that has surrounded Firdapse since its approval late last year and bring a potential competitor to the market," he continued, adding that there are "questions around whether the adult and pediatric populations represent two distinct orphan diseases."

"Obviously, it will be less than what they're charging,"

Laura Jacobus, Jacobus Pharmaceuticals, when asked about price

The uncertainty helps explain investor reaction to the FDA approval, which was announced late Monday. A spokesman for Catalyst, which had indicated there are as many as 3,000 LEMS patients in the U.S., declined to comment.

However, there are some extenuating factors.

For one thing, a doctor may prescribe the Jacobus drug, but that doesn't mean an insurance company will automatically provide coverage. Sometimes, insurers will not cover off-label use, although in this instance, the price of the Catalyst drug may provide some impetus — if the Jacobus drug costs significantly less.

As of Monday night, Laura Jacobus, who runs the privately held company, said a final decision hasn't been made.

"I haven't given it much thought. This decision just came in, but obviously, it will be less than what they're charging," she told us. "But we're carrying over the last 27 years the research, development, the compassionate use manufacturing. We're probably $60 million in the hole. And the post-approval commitments are probably (going to cost) $10 million to $20 million."

However, she declined to discuss off-label usage. "We assume we can't take care of adult patients, but we'd like to take care of pediatric patients," she said. "That's a role we're pleased to provide."

One patient who had been taking the Jacobus drug under the compassionate use program but was forced to switch to Firdapse, told us she is excited by the approval. She is among several Firdapse patients who have complained the medicine is not as effective as the older Jacobus treatment.

"Oh my gosh, this is very good news," said Rebecca Hovde, who lives in Iowa. "I will definitely ask my doctor to switch to the Jacobus drug now."

Pharma Times

FDA approves Ruzurgi for children with Lambert-Eaton myasthenic syndrome

7th May 2019

By Anna Smith

The US Food and Drug Administration (FDA) has approved Jacobus' Ruzurgi (amifampridine) tablets for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in patients six to less than 17 years of age.

The approval marks the first FDA approval of a treatment specifically for paediatric patients with LEMS, as currently the only other treatment approved for LEMS is approved for use in adults.

The approval was based on a placebo-controlled withdrawal study of 32 adult patients in which patients were taking Ruzurgi for at least three months prior to entering the study, using pharmacokinetic modelling and simulation to identify the dosing regimen in paediatric patients and safety data from paediatric patients.

"We continue to be committed to facilitating the development and approval of treatments for rare diseases, particularly those in children," said Billy Dunn, director of the Division of Neurology Products in the FDA's Centre for Drug Evaluation and Research. "This approval will provide a much-needed treatment option for paediatric patients with LEMS who have significant weakness and fatigue that can often cause great difficulties with daily activities."

The FDA has also granted the application Priority Review and Fast Track designations, alongside its Orphan Drug designation, which provides incentives to assist and encourage the

development of drugs for rare diseases.

LEMS is a rare autoimmune disorder that affects the connection between nerves and muscles and causes weakness and other symptoms in affected patients. In people with LEMS, the body's own immune system attacks the neuromuscular junction - the connection between nerves and muscles - and disrupts the ability of nerve cells to send signals to muscle cells.

Sandy Walsh
Press Officer

Office of Media Affairs
Office of External Affairs
U.S. Food and Drug Administration
Tel: 301-796-4669
Sandy.Walsh@fda.hhs.gov

From: CDER DRUG INFO
To: (b) (6)
Subject: Firdapse
Date: Thursday, May 09, 2019 1:34:00 PM

Dear (b) (6)

This is in response to your March 8, 2019, letters to U.S. Department of Health and Human Services (HHS) Secretary Alex Azar and Dr. Scott Gottlieb, former Commissioner of the Food and Drug Administration (FDA) concerning the approval of Firdapse . Your letters were forwarded to the Division of Drug Information in FDA's Center for Drug Evaluation and Research (CDER) for a response.

We appreciate you taking the time to share your concerns with us.

As you are aware, on November 28, 2018, FDA approved a new drug application (NDA) submitted by Catalyst Pharmaceuticals for Firdapse (amifampridine phosphate oral tablets) for the treatment of Lambert Eaton Myasthenic Syndrome (LEMS). FDA approved the NDA for Firdapse after its rigorous review of the evidence supplied by the applicant supported a conclusion of safety, effectiveness, and product quality. As you know, Americans rely on the FDA to ensure that drugs are both safe and effective. An essential part of an application to support marketing approval is the applicant's demonstration that its manufacturing processes can reliably produce drug products of expected identity, strength, quality, and purity. In addition, FDA's review of the applicant's labeling ensures that health care professionals and patients have the information necessary to understand a drug product's risks and its safe and effective use. For reference, you can find on the FDA website reviews of the data that supported the approval of Firdapse (Drugs@FDA), and the Firdapse NDA approval letter.

The Agency has serious concerns that drugs distributed without FDA approval may not meet modern standards for safety, effectiveness, quality, and labeling. Unapproved drug products, including unapproved 3,4-DAP products, have not been through FDA's rigorous premarket review process, so patients do not have the same level of assurance about the quality of such products, or whether they are safe and effective in the treatment of their condition. Nor can patients or providers rely on the labeling associated with unapproved drugs as accurately conveying directions for use, warnings, or other important information. Therefore, unapproved drugs pose a higher risk to patients than FDA-approved drugs.

You also expressed concerns regarding the potential cost of Firdapse. The FDA is undertaking a series of policy and scientific initiatives that are intended to help increase competition in the market to address the multi-faceted problem of high drug costs. Although the FDA does not play a direct role in drug pricing — it is the responsibility of manufacturers, distributors, and retailers, among others, to establish these prices — the agency has noted that too many patients are being priced out of the medicines they need. To address this very important public health issue, former Commissioner Gottlieb announced the Drug Competition Action Plan in 2017 to help remove barriers to generic drug development and market entry to spur competition that could contribute to lower drug prices for patients. The FDA is similarly examining whether there are barriers to approval in the agency's other abbreviated approval pathways that could be addressed. In addition, the White House and Department of Health and Human Services have a blueprint for bringing down the high price of drugs and reducing out-of-pocket costs for American patients. You might wish to contact our colleagues at the Department of Health and Human Services and/or the Centers for Medicare & Medicaid Services for additional information on pricing issues.

As you probably now know, on May 7th, 2019, FDA approved Ruzurgi (amifampridine,

described chemically as 3,4-diaminopyridine) sponsored by Jacobus Pharmaceuticals. Ruzurgi is indicated for pediatric patients ages 6 to under 17 years of age with LEMS. Ruzurgi is the first approved treatment specifically for pediatric patients with LEMS. You can refer to the patient and doctor information and press release for more details. Please talk with your health care provider about the right treatment option for you.

Thank you for writing.

Sincerely,
/s/
Donald Dobbs
Division of Drug Information
Office of Communications
Center for Drug Evaluation and Research
Food and Drug Administration

From: CDER DRUG INFO
To: (b) (6)
Subject: Firdapse
Date: Thursday, May 09, 2019 1:34:00 PM

Dear (b) (6)

This is in response to your March 8, 2019, letters to U.S. Department of Health and Human Services (HHS) Secretary Alex Azar and Dr. Scott Gottlieb, former Commissioner of the Food and Drug Administration (FDA) concerning the approval of Firdapse . Your letters were forwarded to the Division of Drug Information in FDA's Center for Drug Evaluation and Research (CDER) for a response.

We appreciate you taking the time to share your concerns with us.

As you are aware, on November 28, 2018, FDA approved a new drug application (NDA) submitted by Catalyst Pharmaceuticals for Firdapse (amifampridine phosphate oral tablets) for the treatment of Lambert Eaton Myasthenic Syndrome (LEMS). FDA approved the NDA for Firdapse after its rigorous review of the evidence supplied by the applicant supported a conclusion of safety, effectiveness, and product quality. As you know, Americans rely on the FDA to ensure that drugs are both safe and effective. An essential part of an application to support marketing approval is the applicant's demonstration that its manufacturing processes can reliably produce drug products of expected identity, strength, quality, and purity. In addition, FDA's review of the applicant's labeling ensures that health care professionals and patients have the information necessary to understand a drug product's risks and its safe and effective use. For reference, you can find on the FDA website reviews of the data that supported the approval of Firdapse (Drugs@FDA), and the Firdapse NDA approval letter.

The Agency has serious concerns that drugs distributed without FDA approval may not meet modern standards for safety, effectiveness, quality, and labeling. Unapproved drug products, including unapproved 3,4-DAP products, have not been through FDA's rigorous premarket review process, so patients do not have the same level of assurance about the quality of such products, or whether they are safe and effective in the treatment of their condition. Nor can patients or providers rely on the labeling associated with unapproved drugs as accurately conveying directions for use, warnings, or other important information. Therefore, unapproved drugs pose a higher risk to patients than FDA-approved drugs.

You also expressed concerns regarding the potential cost of Firdapse. The FDA is undertaking a series of policy and scientific initiatives that are intended to help increase competition in the market to address the multi-faceted problem of high drug costs. Although the FDA does not play a direct role in drug pricing — it is the responsibility of manufacturers, distributors, and retailers, among others, to establish these prices — the agency has noted that too many patients are being priced out of the medicines they need. To address this very important public health issue, former Commissioner Gottlieb announced the Drug Competition Action Plan in 2017 to help remove barriers to generic drug development and market entry to spur competition that could contribute to lower drug prices for patients. The FDA is similarly examining whether there are barriers to approval in the agency's other abbreviated approval pathways that could be addressed. In addition, the White House and Department of Health and Human Services have a blueprint for bringing down the high price of drugs and reducing out-of-pocket costs for American patients. You might wish to contact our colleagues at the Department of Health and Human Services and/or the Centers for Medicare & Medicaid Services for additional information on pricing issues.

As you probably now know, on May 7th, 2019, FDA approved Ruzurgi (amifampridine,

described chemically as 3,4-diaminopyridine) sponsored by Jacobus Pharmaceuticals. Ruzurgi is indicated for pediatric patients ages 6 to under 17 years of age with LEMS. Ruzurgi is the first approved treatment specifically for pediatric patients with LEMS. You can refer to the patient and doctor information and press release for more details. Please talk with your health care provider about the right treatment option for you.

Thank you for writing.

Sincerely,
/s/
Donald Dobbs
Division of Drug Information
Office of Communications
Center for Drug Evaluation and Research
Food and Drug Administration

From: CDER SBIA
To: (b) (6)
Subject: FW: FDA approves first treatment for children with Lambert-Eaton myasthenic syndrome, a rare autoimmune disorder
Date: Tuesday, May 14, 2019 9:03:00 AM
Attachments: image025.png
image030.png

Dear Zachary,
Thank you for your patience while we consulted agency experts to assist with responding to your inquiry.
Ruzurgi is approved for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in patients 6 to less than 17 years of age. In their marketing of Ruzurgi, Jacobus Pharmaceuticals, like any other applicant for an approved prescription drug product, is required to meet the criteria for Prescription Drug Marketing discussed in FDA's regulations at 21 CFR 203.1. The practice of medicine is not regulated by FDA, and the decision to treat a patient with a drug for an unapproved use is up to the treating health care professional.
If in the future you have additional questions, please feel free to contact us again at CDERSBIA@fda.hhs.gov.

Upcoming Training

- May 29-30, 2019 – SBIA Annual RedI Conference – Drugs|Devices with Drugs track ***Essentials of an NDA/BLA Submission***

Need additional training? Visit www.fda.gov/cdersbialearn.
Get the latest regulatory updates and notifications for webinars and conferences straight from the source - Follow SBIA on LinkedIn and sign-up for SBIA email updates.

Best regards,
Danielle
Pharmacist
Small Business and Industry Assistance | Division of Drug Information
Center for Drug Evaluation and Research
Tel: 866-405-5367
CDERSBIA@fda.hhs.gov
Follow us

This communication is consistent with 21 CFR 10.85(k) and constitutes an informal communication that represents our best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of the FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

From: CDER SBIA
Sent: Thursday, May 09, 2019 3:37 PM
To: (b) (6)
Subject: RE: FDA approves first treatment for children with Lambert-Eaton myasthenic syndrome, a rare autoimmune disorder

Dear Zachary,
Thank you for writing. Your email was forwarded to the Division of Drug Information, Small Business and Industry Assistance (SBIA) in the FDA's Center for Drug Evaluation and Research.

Your inquiry has been forwarded to experts within the Agency for input and assistance. When we receive a response we will forward it to you, or they may contact you directly. Please understand that response times may vary. Thank you in advance for your patience.
Best regards,

Danielle
Pharmacist
Small Business and Industry Assistance | Division of Drug Information
Center for Drug Evaluation and Research
Tel: 866-405-5367
CDERSBIA@fda.hhs.gov
Follow us

From: Zachary Prensky (b) (6)
Sent: Tuesday, May 7, 2019 8:18 AM
To: Walsh, Sandy <Sandy.Walsh@fda.hhs.gov>
Subject: FDA approves first treatment for children with Lambert-Eaton myasthenic syndrome, a rare autoimmune disorder

Mrs Walsh-
I read with interest the FDA press release yesterday entitled, "FDA approves first treatment for children with Lambert-Eaton myasthenic syndrome, a rare autoimmune disorder". I note that you are the press contact for this release. Can you comment as to whether or not there is any restriction placed upon the Sponsor (Jacobus) in distributing and/or marketing this approved pharmaceutical for **adults** suffering from LEMS given that the data utilized by the agency to approve the application was a randomized, double-blind, placebo-controlled withdrawal study of 32 adult patients in which patients were taking Ruzurgi for at least three months prior to entering the study as compared to patients switched to placebo?
Thanks in advance for your feedback--

Zachary Prensky, CEO
LB Pharmaceuticals Inc
o (212) 605-0230
c (b) (6)

From: CDER DRUG INFO
To: (b) (6)
Subject: RE: firdapse is not working for me at all compared to 3,4 dap
Date: Monday, June 03, 2019 10:40:45 AM
Attachments: image004.png

Dear (b) (6)

Thank you for writing to the Division of Drug Information in the FDA Center for Drug Evaluation and Research (CDER). This is in response to your email describing the problems experienced by the Lambert-Eaton myasthenic syndrome (LEMS) community while transitioning from amifampridine (3,4-DAP) to Firdapse (amifampridine phosphate, described chemically as 3,4-diaminopyridine [3,4-DAP] phosphate).

We are sorry to learn that the transition to Firdapse for treatment of LEMS has been problematic for the patient community. Drug safety and effectiveness are among our highest priorities. Before we approve any drug (including Firdapse), we make an assessment and take appropriate regulatory actions to ensure the drug works effectively and its benefits outweigh its risks. In addition, approval of a medication does not mean that there are no potential side effects from the drug. No drug is perfectly safe. Some patients may experience side effects, but some patients benefit from the product without side effects. The FDA expects that a patient and his or her health care provider should decide together if the benefits of Firdapse outweigh the risks for that patient.

If patients have not already done so, we urge them to report the problems experienced with Firdapse through the MedWatch program. This is FDA's mechanism for collecting reports of product problems and adverse effects from the public. Product problems include quality (such as potency and stability through the product's expiration date), performance, or formulation safety concerns. The voluntary reporting form can be accessed by going to the MedWatch homepage, clicking on the "Report a Problem" tab and then clicking on the "Consumer/Patient" button. Alternatively, they can download the appropriate paper reporting form and either fax it to 1-800-332-0178 or mail it to the address indicated on page 4 of the form.

On May 7th, 2019, FDA approved Ruzurgi (amifampridine, described chemically as 3,4-diaminopyridine) sponsored by Jacobus Pharmaceuticals. Ruzurgi is indicated for pediatric patients ages 6 to under 17 years of age with LEMS. Ruzurgi is the first approved treatment specifically for pediatric patients with LEMS. You can refer to the patient and doctor information and press release for more details. Patients may speak with their health care provider about the right treatment option for them.

If we can be of further help or you have drug related questions or concerns in the future, please do not hesitate to contact us.

Best regards,

SB
Drug Information Specialist
Division of Drug Information
Center for Drug Evaluation and Research

From: CDER DRUG INFO
To: (b) (6)
Subject: RE: Firdapse
Date: Thursday, May 23, 2019 9:24:48 AM
Attachments: image004.png

Dear (b) (6)

Thank you for writing to the Division of Drug Information in the FDA Center for Drug Evaluation and Research (CDER). This is in response to your email describing the problems you've experienced while transitioning from amifampridine (3,4-DAP) to Firdapse (amifampridine phosphate, described chemically as 3,4-diaminopyridine [3,4-DAP] phosphate).

We are sorry to learn that the transition to Firdapse for treatment of Lambert-Eaton myasthenic syndrome (LEMS) has been problematic for you. Drug safety and effectiveness are among our highest priorities. Before we approve any drug (including Firdapse), we make an assessment and take appropriate regulatory actions to ensure the drug works effectively and its benefits outweigh its risks. In addition, approval of a medication does not mean that there are no potential side effects from the drug. No drug is perfectly safe. Some patients may experience side effects, but some patients benefit from the product without side effects. The FDA expects that a patient and his or her health care provider should decide together if the benefits of Firdapse outweigh the risks for that patient.

If you have not already done so, we urge you to report the problems you experienced with Firdapse through the MedWatch program. This is FDA's mechanism for collecting reports of product problems and adverse effects from the public. Product problems include quality (such as potency and stability through the product's expiration date), performance, or formulation safety concerns. You can access the voluntary reporting form by going to the MedWatch homepage, click on the "Report a Problem" tab and then click on the "Consumer/Patient" button. Alternatively, you can download the appropriate paper reporting form and either fax it to 1-800-332-0178 or mail it to the address indicated on page 4 of the form.

As you may now be aware, on May 7th, 2019, FDA approved Ruzurgi (amifampridine, described chemically as 3,4-diaminopyridine) sponsored by Jacobus Pharmaceuticals. Ruzurgi is indicated for pediatric patients ages 6 to under 17 years of age with LEMS. Ruzurgi is the first approved treatment specifically for pediatric patients with LEMS. You can refer to the patient and doctor information and press release for more details. Please talk to your health care provider about the right treatment option for you.

If we can be of further help or you have drug related questions or concerns in the future, please do not hesitate to contact us.

Best regards,

SB
Drug Information Specialist
Division of Drug Information
Center for Drug Evaluation and Research

TAB 4:

Documents showing that FDA realized there were only very limited circumstances specified in the statute for departing from the "same drug, same disease" requirement

From: Myers, James
To: Locicero, Colleen L
Subject: Fwd: Exclusivity Question regarding Firdapse (amifampridine)
Date: Wednesday, January 02, 2019 9:07:16 AM
Attachments: image002.png

FYI

From: Myers, James <James.Myers@fda.hhs.gov>
Date: December 19, 2018 at 8:31:00 AM EST
To: Flahive, James <James.Flahive@fda.hhs.gov>
Cc: Volpe, Carolyn <Carolyn.Volpe@fda.hhs.gov>, Becker, Carolyn E. <Carolyn.Becker@fda.hhs.gov>, Ashley, Donald <Donald.Ashley@fda.hhs.gov>, Stein, Peter <Peter.Stein@fda.hhs.gov>, Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>
Subject: RE: Exclusivity Question regarding Firdapse (amifampridine)

Hi James,

Thanks for your note. Apologies for the delay getting back to you. You're correct that there are a number of complicated factors associated with the two amifampridine NDAs.

As you noted below, Catalyst's NDA 208078 (Firdapse (amifampridine)) was recently approved and currently has 5-year NCE exclusivity. Jacobus's NDA (NDA 209321) was submitted in June 2018 and is currently pending before the Agency. Although 5-year NCE exclusivity often serves to block NDAs (and ANDAs) for products with the same active moiety, the statutory terms governing NCE exclusivity provide that NCE exclusivity blocks only the ***submission*** of an application for the same active moiety, not the approval of such an application. Because Jacobus's NDA was submitted prior to the approval of Catalyst's NDA, the NCE exclusivity should not have an affect on the approvability of Jacobus's NDA. (However, this NCE exclusivity would block the submission of any future (b)(2) NDAs or ANDAs.)

The more complicated issue here is that Catalyst's NDA likely is also eligible for orphan exclusivity. Although the Orange Book entry for Firdapse does not yet reflect this exclusivity, Firdapse has already been granted an orphan designation and (barring some unforeseen issue) should be granted orphan exclusivity (See orphan designation - https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=295309). Unlike NCE exclusivity, orphan exclusivity would block approval of Jacobus's NDA, unless Jacobus's NDA is proven to be clinically superior to Catalyst's NDA (which, based on my understanding, it's not) or if Jacobus's NDA is approved for an additional indication not covered by the scope of Firdapse's orphan exclusivity. My understanding is that the Division thinks that Jacobus's NDA may be able to be approved for a pediatric indication, which is separate from the adult indication approved under Catalyst's NDA (Firdapse) and thus potentially not blocked by Firdapse's orphan exclusivity. There are still some issues being discussed with respect to this indication, given that it's based on extrapolated data.

There are also a few other substantive issues with Jacobus's NDA, which could potentially result in a CR action by the February goal date or an extension of the goal date. As a result, it's not entirely clear whether this NDA will be approved or CR'd in the current review cycle, but the current thinking is that there may still be a path forward for Jacobus's NDA to be approved, despite Firdapse's orphan and NCE exclusivities.

I hope the above is helpful. I know these exclusivity issues can be complicated, so I'm more than happy to discuss any questions.

Thanks,
James

From: Flahive, James
Sent: Friday, December 14, 2018 4:53 PM
To: Myers, James <James.Myers@fda.hhs.gov>; Kimbrell, Maarika <Maarika.Kimbrell@fda.hhs.gov>
Cc: Volpe, Carolyn <Carolyn.Volpe@fda.hhs.gov>; Becker, Carolyn E. <Carolyn.Becker@fda.hhs.gov>; Ashley, Donald <Donald.Ashley@fda.hhs.gov>
Subject: Exclusivity Question regarding Firdapse (amifampridine)

Hi Maarika and James,

Derek Griffing in OGD suggested that I reach out to you with this question regarding New Chemical Entity (NCE exclusivity).

Firdapse (amifampridine) was approved on 11/28/2018 (NDA 208078) to treat Lambert-Eaton Myasthenic Syndrome, a neuromuscular disorder. Dr. Throckmorton and others are concerned by an article stating that while patients who suffer this rare disorder have been able to access amifampridine treatment at low or no cost prior to approval, there is concern that the NDA holder intends to raise the price significantly. https://www.statnews.com/2018/11/30/fda-approval-lems-drug-costs/

Our understanding is that Catalyst, the approved NDA holder, has a 5 year NCE exclusivity. According to DARRTS, Jacobus Pharmaceuticals submitted an NDA application for 3,4-Diaminopyridine (amifampridine) in June 2018 with a PDUFA date of February 15, 2019. Based on the time of filing, would Jacobus's product be blocked by the Catalyst's NCE exclusivity?

Thanks,
Jim

James Flahive, J.D.
Branch Chief
Prescription Drugs Branch
Office of Unapproved Drugs and Labeling Compliance
CDER Office of Compliance
Food and Drug Administration

301-796-9293
james flahive@fda hhs.gov

From: Flahive, James
Sent: Friday, December 14, 2018 3:53 PM
To: Levy, Michael (CDER) <Michael.Levy@fda.hhs.gov>; Anderson, Kathleen R <Kathleen.Anderson@fda.hhs.gov>; Becker, Carolyn E. <Carolyn.Becker@fda.hhs.gov>
Cc: Bormel, Frances Gail <Frances.Bormel@fda.hhs.gov>; Ashley, Donald <Donald.Ashley@fda.hhs.gov>; Volpe, Carolyn <Carolyn.Volpe@fda.hhs.gov>
Subject: RE: High priced drugs - Firdapse (amifampridine)

Do you want me to set up a meeting to discuss Firdapse?

According to the orange book, Firdapse appears to have a 5-year new chemical entity exclusivity that expires on 11/28/2023. Derek Griffing in OGD confirmed that this is the only exclusivity (there is not an orphan exclusivity listed for this product) and there are no associated patents listed in the Orange Book.

While this is the first I'm aware of CDER Compliance hearing about the drug, this does seem to raise themes familiar from the Agency's experiences with Makena and may relate to the discussion we have started with Liz Dickinson about (b) (5) .

From: Levy, Michael (CDER)
Sent: Friday, December 14, 2018 2:51 PM
To: Anderson, Kathleen R <Kathleen.Anderson@fda.hhs.gov>; Becker, Carolyn E. <Carolyn.Becker@fda.hhs.gov>
Cc: Bormel, Frances Gail <Frances.Bormel@fda.hhs.gov>; Flahive, James <James.Flahive@fda.hhs.gov>; Ashley, Donald <Donald.Ashley@fda.hhs.gov>
Subject: RE: High priced drugs - Firdapse (amifampridine)

Can we get any handle on the compounding aspect of this today so we can get back to Dr. Throckmorton?

From: Levy, Michael (CDER)
Sent: Friday, December 14, 2018 2:28 PM
To: Anderson, Kathleen R <Kathleen.Anderson@fda.hhs.gov>; Becker, Carolyn E. <Carolyn.Becker@fda.hhs.gov>
Cc: Bormel, Frances Gail <Frances.Bormel@fda.hhs.gov>; Flahive, James <James.Flahive@fda.hhs.gov>; Ashley, Donald <Donald.Ashley@fda.hhs.gov>
Subject: FW: High priced drugs - Firdapse (amifampridine)

OUDLC may have to do a deeper dive on 3,4-DAP. The article indicates it's been compounded for years and is now approved. May be similar to the drug involved in litigation a few years ago.

https://www.statnews.com/2018/11/30/fda-approval-lems-drug-costs/

From: Throckmorton, Douglas C
Sent: Friday, December 14, 2018 2:08 PM
To: Ashley, Donald <Donald.Ashley@fda.hhs.gov>
Cc: Flahive, James <James.Flahive@fda.hhs.gov>; Levy, Michael (CDER) <Michael.Levy@fda.hhs.gov>; Carpenter, Courtney <Courtney.Carpenter@fda.hhs.gov>; CDER EXSEC <CDEREXSEC@cder.fda.gov>
Subject: FW: High priced drugs - Firdapse (amifampridine)

Don, need to have a little more background on this issue. I'm hoping your UDI folks have been engaged. I need to know any additional background you have, including if we've taken any actions against the unapproved product (as the article suggests) and if the company that just got the approval has asked us to do anything.

Please cc Courtney on all responses. We may need to fold this into the drug dislocation discussion…..

Thanks, Doug

Douglas C. Throckmorton MD
Deputy Director for Regulatory Programs
CDER FDA
240-402-5400

From: Carpenter, Courtney
Sent: Friday, December 14, 2018 12:20 PM
To: Throckmorton, Douglas C <Douglas.Throckmorton@fda.hhs.gov>
Cc: Dunn, Billy <Billy.Dunn@fda.hhs.gov>; McLatchy, Johanna <Johanna.McLatchy@fda.hhs.gov>; Bastings, Eric <Eric.Bastings@fda.hhs.gov>; Kozauer, Nicholas <Nicholas.Kozauer@fda.hhs.gov>
Subject: RE: High priced drugs - Firdapse (amifampridine)

Doug,

Here is a summary:

- Jacobus Pharmaceutical Co. has prescribed 3,4-DAP, a nearly identical treatment, off label since the 1980s at little or no cost to patients.
- On 11/28/18, FDA approved Catalyst Pharmaceuticals Firdapse (amifampridine) tablets for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults. This is the first FDA approval of a treatment for LEMS.
- Catalyst Pharmaceuticals is predicted to charge thousands of dollars for treatment.
- I was not able to unlock the article below (requires a subscription) - I did find a similar article discussing drug pricing. https://www.statnews.com/201L8/11/30/fda-approval-lems-drug-costs/

I am CC'ing Billy and DNP just in case they have more to add.

Thanks,
Courtney

Courtney Carpenter, MPH
Division of Executive Operations (CDER EXSEC)
CDER|OEP
301.796.4487 |(c)240.687.2804
Courtney.Carpenter@fda.hhs.gov

From: Throckmorton, Douglas C
Sent: Friday, December 14, 2018 7:55 AM
To: CDER EXSEC <CDEREXSEC@cder.fda.gov>
Cc: McLatchy, Johanna <Johanna.McLatchy@fda.hhs.gov>
Subject: HIgh priced drugs

We're in the middle of working up a proposal to address high priced drugs and I'm likely to get a call about this. Can someone find out more about the facts? I can't unlock the article. I assume the 'free' before was because it was available under expanded access?

Price Of Drug For Rare Neuromuscular Disorder Shoots Up Following FDA Approval.

STAT (12/13, 20K) reports last month, the Food and Drug Administration approved Firdapse (amifampridine) for the treatment of Lambert-Eaton myasthenic syndrome, "a rare, neuromuscular disorder," and the drug has been priced at $375,000. However, the article points out that before it was approved by the FDA, the drug was available to "hundreds of patients...for free."

Douglas C. Throckmorton MD
Deputy Director for Regulatory Programs
CDER FDA
240-402-5400

From: Buracchio, Teresa
To: Locicero, Colleen L; Bullock, Heather; Daugherty, Susan B (CSO); Ware, Jacqueline H; Mathers, Michelle
Subject: RE: amifampridine - favor to ask
Date: Wednesday, February 06, 2019 8:27:00 AM
Attachments: Jacobus Exclusivity Background (002).docx

Hi Colleen,

This looks accurate. I just put one note for your consideration. It seems like in several of these discussions that people are getting distracted by the proposed indication for Ruzurgi having different language than Firdapse. Once we have completed our labeling negotiations, the indication will be the same as Firdapse other than the age. So, the wording of the indication statement is not a relevant issue for consideration in the exclusivity discussion. It may be worth nothing that summary.

Teresa

From: Locicero, Colleen L
Sent: Wednesday, February 06, 2019 7:31 AM
To: Bullock, Heather <Heather.Bullock@fda.hhs.gov>; Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Daugherty, Susan B (CSO) <Susan.Daugherty@fda.hhs.gov>; Ware, Jacqueline H <Jacqueline.Ware@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>
Subject: amifampridine - favor to ask

All,

At the suggestion of my TL, I put together a brief background document on the Firdapse and Ruzurgi NDAs in case it is helpful for the X Board discussion or any other issues that arise related to these applications/this situation. Would you mind taking a look for accuracy and to make sure I didn't leave anything out that you might think important? In particular, could you look at the information about what will support the Jacobus peds indication to make sure it is accurate?

Also, what is your current anticipated date for being able to take an action?

Thanks,
Colleen

<< File: Jacobus Exclusivity Background.docx >>

From: Helms Williams, Emily
To: Locicero, Colleen L
Subject: FW: Question re: Jacobus product
Date: Tuesday, February 12, 2019 3:19:02 PM
Attachments: image003.jpg
image004.png

Hi Colleen! Hope you're doing well. I've just started a detail in the Commissioner's Office, and as you've likely heard, I'm working to track down some answers to questions that have been raised about the Catalyst/Jacobus issue. Are you the right person to talk to about the EA questions in the e-mail chain below? If so it'd be great if we could touch base briefly by phone today or tomorrow.

Thanks,
Emily

From: Mathers, Michelle
Sent: Tuesday, February 12, 2019 3:16 PM
To: Helms Williams, Emily <Emily.HelmsWilliams@fda.hhs.gov>
Cc: Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>
Subject: RE: Question re: Jacobus product

Hi Emily,

Have you been in touch with Colleen Locicero? We (DNP) have been working closely with her concerning the Jacobus expanded access questions.

Michelle

From: Helms Williams, Emily
Sent: Tuesday, February 12, 2019 2:02 PM
To: Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Nduom, Kelley <Kelley.Nduom@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>
Cc: Sitlani, Jay <Jay.Sitlani@fda.hhs.gov>
Subject: RE: Question re: Jacobus product

Thanks all! This is helpful. I understand that there have been extensive discussions recently, with OCC and others in the Agency, (b) (5)

(b) (5)

Thanks,
Emily

From: Buracchio, Teresa
Sent: Tuesday, February 12, 2019 1:53 PM
To: Nduom, Kelley <Kelley.Nduom@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>

Cc: Helms Williams, Emily <Emily.HelmsWilliams@fda.hhs.gov>; Sitlani, Jay <Jay.Sitlani@fda.hhs.gov>
Subject: RE: Question re: Jacobus product

Not on the (b) (4) per day regimen, but they have inquired about whether the (b) (4) (b) (4)

The clinical superiority for the Jacobus product would potentially come from pediatric dosing for LEMS. They are proposing an indication for LEMS down to (b) (4) (we think we may be able to indicate down to 6 years of age). This would be based on extrapolation of efficacy from adult patients and some dosing and safety data in pediatric patients. Firdapse only has adult dosing.

Teresa

From: Nduom, Kelley
Sent: Tuesday, February 12, 2019 1:48 PM
To: Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>
Cc: Helms Williams, Emily <Emily.HelmsWilliams@fda.hhs.gov>; Sitlani, Jay <Jay.Sitlani@fda.hhs.gov>
Subject: RE: Question re: Jacobus product

Hi Teresa,

Thanks so much for this. Do you know if Jacobus has made any claims of clinical superiority based on the (b) (4) daily dosing regimen (in contrast to the Catalyst product's 3-4 daily dosing regimen) or (b) (4) dose? Or if there have been claims of clinical superiority based on other factors?

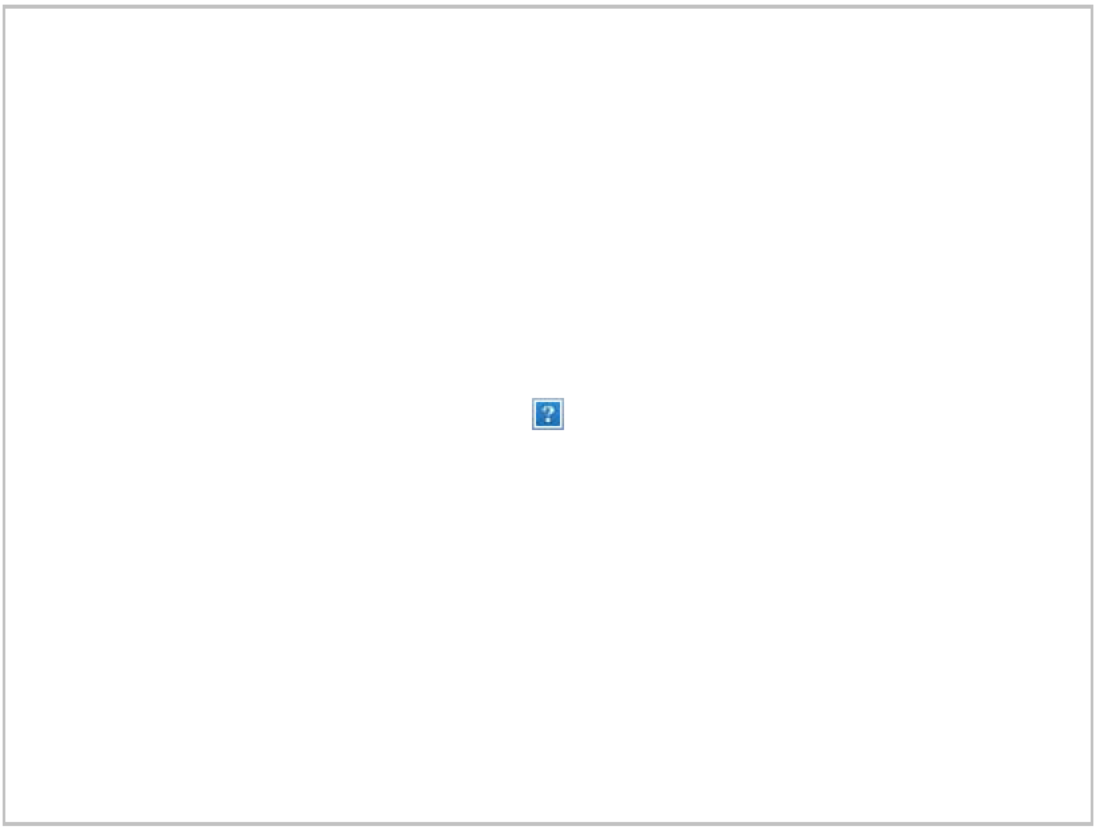
Thanks,
Kelley

From: Buracchio, Teresa
Sent: Tuesday, February 12, 2019 1:13 PM
To: Nduom, Kelley <Kelley.Nduom@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>
Cc: Helms Williams, Emily <Emily.HelmsWilliams@fda.hhs.gov>; Sitlani, Jay <Jay.Sitlani@fda.hhs.gov>
Subject: RE: Question re: Jacobus product

Hi Kelley,
The Catalyst and Jacobus products have the same active moiety, amifampridine. The Jacobus product (Ruzurgi) is amifampridine base and the Catalyst product (Firdapse) is the phosphate salt, amifampridine phosphate. The two products have minor CMC differences that are outlined in the table below.

The two products have also studied slightly different dosing regimens in their clinical trials and expanded access program:
Firdapse is indicated for use in adult LEMS patients. Dosing regimen is 5-20 mg 3-4 times per day. Maximum dose is 80 mg/day.
Jacobus proposed dosing in adult LEMS patients (and what is being used in expanded access) is (b) (4) (b) (4) per day. Maximum dose is proposed to be (b) (4) mg/day.

Let me know if you have additional questions.
Teresa



From: Nduom, Kelley
Sent: Tuesday, February 12, 2019 10:40 AM
To: Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>
Cc: Helms Williams, Emily <Emily.HelmsWilliams@fda.hhs.gov>; Sitlani, Jay <Jay.Sitlani@fda.hhs.gov>
Subject: Question re: Jacobus product

Hi Teresa and Michelle,

I hope you're doing well. I'm coordinating the CDER Exclusivity Board discussions around the Jacobus application for Ruzurgi. As you know, this issue has been heating up in the news, and the Commissioner's office has raised some questions about the differences between the two drugs.

News reports state that Catalyst's version doesn't require refrigeration, and Catalyst has suggested there are other differences. We're hoping you could help us with a few questions:

1. Are the Catalyst and Jacobus products different, if so how (any differences in active moiety/ingredient, or just excipients)?

2. Assuming they are different in some way, what is our justification for ending expanded access to the Jacobus product?

I'm happy to give you a call to discuss, if that would be easier. Thanks!

Kelley

Kelley Nduom, JD, MPH
Senior Regulatory Counsel
Acting Special Assistant to the Deputy Center Director for Regulatory Policy

Center for Drug Evaluation and Research
Office of Regulatory Policy
U.S. Food and Drug Administration
Tel: 301-796-8597
kelley.nduom@fda.hhs.gov

From: Nduom, Kelley
To: Locicero, Colleen L
Cc: Sitlani, Jay
Subject: RE: Discuss NDA 209321 Ruzurgi [Amifampridine (3,4-Diaminopyridine)] and Catalyst NDA-208078 Firdapse exclusivity for adult use
Date: Tuesday, February 12, 2019 9:01:53 AM

Hi Colleen,

Thanks again for this. As you know, this issue has been heating up in the news, and the Commissioner's office has some questions about the differences between the two drugs. News reports state that Catalyst's version doesn't require refrigeration, and Catalyst says there are other differences. Do you know who would be the best person in the Division to ask about these nuances? Is Teresa Buracchio the lead medical reviewer?

Thanks,

Kelley

From: Locicero, Colleen L
Sent: Wednesday, February 06, 2019 12:33 PM
To: Nduom, Kelley <Kelley.Nduom@fda.hhs.gov>
Cc: Sitlani, Jay <Jay.Sitlani@fda.hhs.gov>
Subject: RE: Discuss NDA 209321 Ruzurgi [Amifampridine (3,4-Diaminopyridine)] and Catalyst NDA-208078 Firdapse exclusivity for adult use

Here it is. Please feel free to use as much or as little from the document as you want.

Thanks,
Colleen

From: Locicero, Colleen L
Sent: Wednesday, February 06, 2019 7:25 AM
To: Nduom, Kelley <Kelley.Nduom@fda.hhs.gov>
Cc: Sitlani, Jay <Jay.Sitlani@fda.hhs.gov>
Subject: RE: Discuss NDA 209321 Ruzurgi [Amifampridine (3,4-Diaminopyridine)] and Catalyst NDA-208078 Firdapse exclusivity for adult use

Hi Kelley,

In case it is helpful, I've put together a brief summary of the Jacobus and Catalyst NDA histories and related background (e.g., the expanded access issues/decision) in case it would be of any help to the XB discussion. I'm running it by the division now (to QC) and can send to you once they have reviewed, hopefully today or tomorrow.

Thanks,
Colleen

From: Locicero, Colleen L
Sent: Monday, February 04, 2019 2:40 PM
To: Nduom, Kelley <Kelley.Nduom@fda.hhs.gov>
Subject: RE: Discuss NDA 209321 Ruzurgi [Amifampridine (3,4-Diaminopyridine)] and Catalyst NDA-208078 Firdapse exclusivity for adult use

Hi Kelley,

I think these are the essential folks.

Thanks,
Colleen

DNP
Billy Dunn and Eric Bastings, but if you can't get both and you can get Billy, that would probably be OK
Teresa Buracchio

ODE I
Ellis Unger

ONDP
Colleen LoCicero
Maarika Kimbrell and James Myers, but if you can't get both, one or the other would be OK

OOPD
Henry (Chip) Startzman
Roberta Szydlo

DPMH
Lynne Yao and John Alexander, but if you can't get both or one of them, Hari and Mona would probably be OK

I'll leave the rest up to you.

From: Nduom, Kelley
Sent: Monday, February 04, 2019 2:00 PM
To: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>
Subject: RE: Discuss NDA 209321 Ruzurgi [Amifampridine (3,4-

Diaminopyridine)] and Catalyst NDA-208078 Firdapse exclusivity for adult use

Hi Colleen – I'm working with Lars to find a time for this meeting. Sorry, I didn't realize he rescheduled for a day you're out of the office. I was wondering if you could help me identify the essential individuals from each group. I know we won't get everyone, so I want to have him look for the windows where the key people are available.
I've copied the invitees below. I know we'll want to have Sonal available for OCC. Are there others that you think are essential? I can give you a call to discuss quickly, if that's easier. Thank you!

DNP
Billy Dunn
Eric Bastings
Michelle Mathers
Teresa Buracchio
Susan Daugherty
Jacqueline Ware
Nicholas Kozauer

ODE I
Ellis Unger

ONDP
Colleen Locicero
James Myers
Maarika Kimbrell
Katherine Schumann

OOPD
Henry (Chip) Startzman
Roberta Szydlo
Janet Maynard

DPMH
Lynne Yao (tentative for last 30 minutes)
John Alexander
Hari Sachs (for second half)
Mona Khurana

OCC
Sonal Vaid

ORP

Emily Helms Williams
Jay Sitlani
Nisha Shah
Kelley Nduom

-----Original Appointment-----
From: Flores, Lars
Sent: Monday, February 04, 2019 9:16 AM
To: Flores, Lars; Myers, James; Dunn, Billy; Bastings, Eric; Mathers, Michelle; Buracchio, Teresa; Daugherty, Susan B (CSO); Ware, Jacqueline H; Kozauer, Nicholas; Unger, Ellis; Startzman, Henry; Szydlo, Roberta; Kimbrell, Maarika; Schumann, Katherine; Nduom, Kelley; Helms Williams, Emily; Khurana, Mona; Sachs, Hari; Vaid, Sonal; Sitlani, Jay; Locicero, Colleen L
Cc: Maynard, Janet; Shah, Nisha; CDER 120 Calendar
Subject: Discuss NDA 209321 Ruzurgi [Amifampridine (3,4-Diaminopyridine)] and Catalyst NDA-208078 Firdapse exclusivity for adult use
When: Friday, February 15, 2019 11:00 AM-12:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: WO-Bldg 51 Room 6300

Conference Call In
Dial In: **Toll Free** +1-877-465-7975
(b) (6) Host access code
Attendee access code
PIN: (b) (6)

From: Locicero, Colleen L
To: Myers, James
Subject: FW: OCC determination summary
Date: Monday, February 25, 2019 4:59:00 PM

FYI.

From: Phillips, J. Paul
Sent: Friday, February 22, 2019 5:58 PM
To: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>
Subject: Re: OCC determination summary

Perfect!

From: "Locicero, Colleen L" <Colleen.Locicero@fda.hhs.gov>
Sent: Friday, February 22, 2019 5:42 PM
To: "Phillips, J. Paul" <Paul.Phillips@fda.hhs.gov>
Subject: OCC determination summary

Is this what you heard?

OCC believes (b) (4), (b) (5)

(b) (4), (b) (5)

Thanks,
Colleen

From: Son, Hyun
To: Locicero, Colleen L
Cc: Chew, Catherine; Buracchio, Teresa; Mathers, Michelle; Molnar, Danielle; Wagner, Lindsay; Saliba, Jouhayna; Jensen, Valerie E
Subject: RE: Firdapse availability
Date: Monday, March 04, 2019 5:57:50 PM
Attachments: Response to RFI drug supply info Son.pdf
image001.jpg
image002.png
image003.jpg
image004.jpg
image005.jpg
image006.jpg
image007.jpg

---

apologies

Thanks
Hyun

From: Son, Hyun
Sent: Monday, March 04, 2019 5:20 PM
To: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>
Cc: Chew, Catherine <Catherine.Chew@fda.hhs.gov>; Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Molnar, Danielle <Danielle.Molnar@fda.hhs.gov>; Wagner, Lindsay <Lindsay.Wagner@fda.hhs.gov>; Saliba, Jouhayna <Jouhayna.Saliba@fda.hhs.gov>; Jensen, Valerie E <Valerie.Jensen@fda.hhs.gov>
Subject: RE: Firdapse availability

Hello Colleen et al,

I've just received the attached correspondence from Catalyst.
They ensure that there is plenty of product available and with no foreseeable supply issues.
They also state that they have had 9 patients treated with greater than 80 mg/day dose (working outside Catalyst pathway, with specialty pharmacy and clinicians to provide information to insurance co).
They've also provided an explanation of how the Pathway works and other information regarding their product.

Please let me know if you have clarifying questions or additional questions for the company.

Thank you.
Hyun

Hyun J. Son, Pharm.D.
CDR, US Public Health Service

Senior Program Management Officer
CDER Drug Shortage Staff
10903 New Hampshire Ave
BLDG 22, Room 6200
Silver Spring, MD 20993
☎ 301-796-1939
202-510-4146
301-796-9887
Hyun.Son@fda.hhs.gov

Please consider the environment before printing this e-mail.

From: Jensen, Valerie E
Sent: Thursday, February 21, 2019 4:40 PM
To: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>
Cc: Chew, Catherine <Catherine.Chew@fda.hhs.gov>; Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Molnar, Danielle <Danielle.Molnar@fda.hhs.gov>; Wagner, Lindsay <Lindsay.Wagner@fda.hhs.gov>; Son, Hyun <Hyun.Son@fda.hhs.gov>
Subject: RE: Firdapse availability

Thanks, and Hyun Son, cc'd above said she will check and get back to you. Thanks Hyun!

From: Locicero, Colleen L
Sent: Thursday, February 21, 2019 4:36 PM
To: Jensen, Valerie E <Valerie.Jensen@fda.hhs.gov>
Cc: Chew, Catherine <Catherine.Chew@fda.hhs.gov>; Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Molnar, Danielle <Danielle.Molnar@fda.hhs.gov>; Wagner, Lindsay <Lindsay.Wagner@fda.hhs.gov>
Subject: RE: Firdapse availability

Terrific. Thanks so much, Val! I know your staff is always extremely busy, so I appreciate it.

Colleen

From: Jensen, Valerie E
Sent: Thursday, February 21, 2019 4:32 PM
To: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>
Cc: Chew, Catherine <Catherine.Chew@fda.hhs.gov>; Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Molnar, Danielle <Danielle.Molnar@fda.hhs.gov>; Wagner, Lindsay <Lindsay.Wagner@fda.hhs.gov>
Subject: RE: Firdapse availability

So sorry, Colleen, I was out of the office last week and missed this email somehow – thanks for following up. And yes, will have someone on my team contact Catalyst and get you this info. Best, - Val

---

CAPT Valerie Jensen R.Ph.
Associate Director
CDER Drug Shortage Staff, FDA
Building #22/Room 6204
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone 301-796-0737
Fax 301-796-9887

From: Locicero, Colleen L
Sent: Thursday, February 21, 2019 4:13 PM
To: Jensen, Valerie E <Valerie.Jensen@fda.hhs.gov>
Cc: Chew, Catherine <Catherine.Chew@fda.hhs.gov>; Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Molnar, Danielle <Danielle.Molnar@fda.hhs.gov>; Wagner, Lindsay <Lindsay.Wagner@fda.hhs.gov>
Subject: RE: Firdapse availability

Hi Val,

Following up on this to see if you think DSS may be able to reach out to Catalyst about this?

Thanks,
Colleen

From: Locicero, Colleen L
Sent: Thursday, February 14, 2019 3:48 PM
To: Jensen, Valerie E <Valerie.Jensen@fda.hhs.gov>
Cc: Chew, Catherine <Catherine.Chew@fda.hhs.gov>; Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>; Molnar, Danielle <Danielle.Molnar@fda.hhs.gov>; Wagner, Lindsay <Lindsay.Wagner@fda.hhs.gov>
Subject: Firdapse availability

Hi Val,

Catalyst Pharmaceuticals' NDA 208078 for Firdapse (amifampridine phosphate) 10 mg. tablets was approved in November of 2018. Catalyst launched the product the first week of February 2019. The product is indicated for patients with LEMS (Lambert Eaton Myasthenic Syndrome), which is a rare disease. Prior to the approval and launch of Firdapse, many LEMS patients were receiving an amifampridine base product developed by Jacobus Pharmaceuticals under expanded access. Once Catalyst's product became commercially available, treatment with the Jacobus product under expanded access had to stop. Some of those patients were on doses higher than 80 mg/day, which is the maximum daily dose recommended in the Firdapse labeling.

FDA has been receiving complaints and inquiries from patients (and their healthcare providers) who had been on more than 80 mg of fampridine a day under expanded access that they are not able to obtain sufficient quantities of the Catalyst product to meet their dosing needs. We don't understand how this is possible if Firdapse is commercially available and there is an adequate drug supply. Catalyst has a Pathways program (see blurb from their website) and we are thinking maybe availability is being restricted to patients who elect to enroll in that program? Or maybe patients are saying they can't get obtain sufficient supplies of the Catalyst product because their insurance won't cover the higher than recommended doses (and they can't afford to pay for these doses themselves)? We just don't know and have not heard anything from Catalyst.

It seems important for us to have a clear understanding of what is going on with respect to the availability of Firdapse to these higher dose patients. As I understand it, the Drug Shortage Staff often reaches out to companies when FDA receives complaints about patients not being able to obtain drug (or enough drug), so we are

wondering whether it might be appropriate for the DSS to reach out to Catalyst to get a better understanding of what is going on?

I've included some of the folks from DDI who have been seeing these complaints and inquiries, in case you need more specific information about the nature of the complaints/inquiries.

Appreciate any help you may be able to provide.

Thanks,
Colleen

Catalyst Pathways™ is an optional, free, personalized program that offers patients and their families one-on-one support throughout their treatment journey with a dedicated team of specialists to help them manage their unique challenges. The support team for each enrolled patient at Catalyst Pathways includes a Care Coordinator, with extensive experience in health care; an Insurance Navigator, to help them understand their insurance coverage and the prescription drug benefit process; a Patient Assistance Liaison, to assist them in understanding their disease and their prescription, and a specialty pharmacy experienced in supporting rare disease patients to provide direct-to-patient delivery of prescriptions. The Catalyst Pathways support team also helps enrolled patients understand and access financial assistance options for qualifying patients, including a copay support program designed to minimize the patient's burden of out-of-pocket costs. For more information on Catalyst Pathways click here.

Catalyst pharmaceuticals

March 4, 2019

Via Electronic Mail
Hyun J. Son, Pharm.D.
CDR, US Public Health Service
Senior Program Management Officer
CDER Drug Shortage Staff
10903 New Hampshire Ave
BLDG 22, Room 6200
Silver Spring, MD 20993

Re: Firdapse (amifampridine phosphate) tablets: product availability

Dear Dr. Son:

Set forth below are our responses to the questions in your email dated February 27, 2019. For clarity, your questions are set out in italics, followed by our responses.

> *The agency has received complaints and inquiries from patients (and their healthcare providers) unable to obtain sufficient quantities of your product, Firdapse. Can you update me on your supply situation and if you are seeing an increased demand? If so, are you able to keep up with demand for the product.*

Catalyst has no knowledge of any patients or health care providers that have been "unable to obtain sufficient quantities" of Firdapse®. Catalyst has on hand a sufficient supply of both finished drug product and amifampridine API. Thus, Catalyst's "supply situation" is such that it firmly believes it can adequately provide Firdapse® to all patients that need it. The only "increased demand" is from patients that were or are transitioning from the Jacobus amifampridine product, but Catalyst fully accounted for those patients in considering demand for the product prior to and after FDA's approval of Firdapse®. As of February 28, 2019, Catalyst has supplied 240 patients with Firdapse®. This includes 24 new patients who did not previously have any access to amifampridine. To the best of the Company's knowledge, not a single patient who wanted to remain on amifampridine therapy has missed a single dose during the transition to commercially-available Firdapse®.

More specifically, there are two qualified contract tablet manufacturers included in our NDA to ensure a reliable, uninterrupted supply of Firdapse®. Catalyst has enough finished drug product and API on hand to supply all current Firdapse® patients, and those we anticipate for the remainder of 2019, for at least 18 months. In addition, orders have been placed for more API to ensure a long-term uninterrupted supply of Firdapse® for all patients, including additional new patients. Our program ships Firdapse® to a patient within five business days, once all required prescriber and patient information is received on a completed Catalyst Pathways enrollment form, unless a patient is in danger of running out of available product prior to five days (in which case the patient shipment is expedited to ensure continued therapy). In summary, Catalyst has no difficulty in meeting patient demand for Firdapse® and anticipates absolutely no difficulties in the future.

355 Alhambra Circle, Suite 1250 | Coral Gables, FL 33134 | Phone (305) 420-3200 | Fax (305) 569-0233

During the very beginning commercial availability of Firdapse® (i.e., around January 15, 2019), patients or providers may have had a misperception of delayed drug supply. Initially, we informed patients that Catalyst would focus first on distribution to those already in compassionate use programs (both Jacobus and Catalyst patients) and patients in short supply of medication to prevent any lapses in therapy. As such, patients who had never had access to amifampridine, or who had adequate supplies, were instructed that Firdapse® shipments would begin for them on February 4, 2019. This prioritization is complete; currently medication is shipped to patients within five business days of receiving completed patient enrollment form with all necessary information, as noted above.

> *Also, we have received information that before the availability of Firdapse, many patients who were on amifampridine phosphate, received doses higher than 80mg/day, which is the maximum daily dose recommended in the Firdapse labeling. Would this have some issues with patient obtaining product (through insurance)?*

Catalyst is aware that some patients were receiving amifampridine doses higher than 80 mg/day, which is the maximum labeled dose for FDA-approved Firdapse®. While prescribers are permitted, in their medical judgment, to prescribe any dose they choose, Catalyst will not promote this because it is inconsistent with the current FDA-approved labeled indication, and there is no objective data to show that doses above 80 mg/day are more efficacious. There is evidence that an increased risk of seizures occurs at higher doses. If a prescriber nevertheless writes a prescription for more than 80 mg/day, the prescription is referred to specialty pharmacy, outside of the Catalyst Pathways process and the specialty pharmacy works with the prescriber to prepare letters of medical necessity for insurance approval purposes (rather than being supported by Catalyst Pathways in this activity). At each step of the process the prescriber is advised that the dose exceeds the maximum in the FDA approved labeling. We are aware that nine such patients have already been approved by their payers for doses beyond the FDA-approved label, and Catalyst is therefore providing sufficient quantities of Firdapse® to the Specialty Pharmacy to fill those prescriptions.

> *Also, would I be able to get some more information or understanding of how the Catalyst Pathways works? Would this also limit the patient's daily dose?*

To facilitate patient access to Firdapse®, we have created "Catalyst Pathways," a free, personalized program that offers patients and families one-on-one support covering all aspects of living with LEMS, including reimbursement. treatment journey. It includes a dedicated team of specialists that can help manage patients' unique questions, challenges and needs. Among many other services, Catalyst Pathways aids patients in navigating the complicated world of health insurance and accessing therapy with as much financial support as legally possible. Participation in the Catalyst Pathways program does not "limit that patient's daily dose," as that dosage amount is determined by the patient's prescriber, but a dose above the FDA-approved label maximum will limit some services available through Catalyst Pathways. As stated above, Catalyst does not promote a dosage amount that is inconsistent with the FDA-approved label.

A broad array of assistance is available to <u>all</u> eligible adult LEMS patients to ensure affordable access to Firdapse. A detailed description of Catalyst Pathways services is described below.

Patient Service Center – A group of dedicated experts focused on helping the patient understand their insurance, copay and deductible amounts, who can direct patients to additional resources if needed. They can also provide medication and disease information.[1] Each patient within Catalyst Pathways has assigned resources within these groups:

Care Coordinators – Care coordinators have extensive experience in healthcare who will provide one-on-one phone support to help manage prescription logistics. They will explain insurance coverage and benefits, outline potential sources of financial assistance, coordinate shipping with the specialty pharmacy, and answer questions as they arise.

Insurance and Reimbursement Experts – These experts work "behind the scenes" using the information on the Enrollment Form to conduct a "benefits investigation" with the insurance company, determine if "prior authorization" information is required from the insurer, educate the provider/physician on specific insurance plan requirements, monitor prior authorization status and communicate coverage decisions to the patient.

Patient Access Liaisons (PAL) for in-person support needed – A PAL possesses both insurance and clinical expertise who has knowledge of LEMS, the medication, insurance benefits and the financial support programs available. They can meet with a patient in person to review the support programs and answer any questions.

Free "Bridge" Medication – If insurance coverage is not determined or confirmed within five business days of submitting a completed Enrollment Form, we will arrange for 30 days (and up to 60 days total) of "bridge" medication to be shipped to the patient, free of charge, while insurance coverage is determined. If the insurance company does not provide coverage within that 60-day period, or if the patient does not have insurance coverage, the patient may be eligible for additional charitable, free, long-term medication via our Patient Assistance Program (PAP) until coverage is determined or obtained. We anticipate that most all patients will meet the eligibility requirements for PAP if necessary.

Financial Assistance Programs – Catalyst Pathways has different types of financial assistance programs to help patients with their out-of-pocket deductible and copay costs. For patients that participate in government insurance programs such as Medicare, Medicaid or Tricare, we have successfully directed the patients to several qualified and independent non-profit organizations who financially support LEMS patients experiencing difficulty with their out-of-pocket costs as a result of their care and treatment. Additionally, for patients with commercial (non-government) insurance, Catalyst Pathways offers two types of programs, which patients may be eligible for:

1) Copay Assistance to decrease out-of-pocket costs to $10/month
2) Our PAP also provides free, long-term medication for qualifying commercial (non-government) patients with denied coverage, for as long as it is needed.

Catalyst Pathways also has engaged an exclusive specialty pharmacy partner, AnovoRX Specialty Pharmacy, that is experienced in dispensing rare disease medications through its dedicated pharmacists. AnovoRx will deliver medication, overnight, directly to the patient's house or desired delivery location. Pharmacy staff is always available to answer patients' questions about their medication. Additional information about the Patient Management Program is also provided with medication delivery.

---

[1] For instance, a new patient who is titrating to an optimal effective dose will be provided information and follow up to help facilitate an optimal titration through informed communications with the patient's physician

* * * * *

We believe the above information fully responds to your questions. Please let us know if you would like additional information.

A few final points:

Catalyst Pharmaceuticals undertook the development of Firdapse® because, at the time, only about 200 LEMS patients had access to an unapproved, investigational amifampridine product to treat their disease. The estimated prevalence of LEMS in the United States is about 1,500 diagnosed patients and a total of 3,000 patients, with the majority having no access to an amifampridine product. With FDA approval, all adult LEMS patients now have affordable access to Firdapse®, and we are positioned to supply those who choose treatment using amifampridine. In fact, as noted earlier, we can confirm that there are at least 24 new patients who have affordable access who have never had access to the product before with another five or so in progress.

In preparation for the commercial availability of Firdapse®, Catalyst reached out to Jacobus, the other supplier of investigational amifampridine to treatment IND holders. We sought to coordinate with Jacobus and provide smooth patient transitions to Firdapse®, specifically to avoid any misunderstandings about how to obtain Firdapse® or delay continuation of treatment. Jacobus repeatedly declined to collaborate with Catalyst so that we could provide information about Catalyst Pathways and make information about accessing Firdapse® available to Jacobus' IND holders. Understandably, this lack of information likely amplified the natural prescriber and patient anxiety about obtaining Firdapse® in a timely manner before depleting their Jacobus product after FDA approval of Firdapse®. Nevertheless, as noted above, to the best of our knowledge Catalyst has supplied every interested transitioning amifampridine patient so that none has involuntarily missed a single dose since the commercial availability of Firdapse.

Lastly, you should also be aware that we are informed and believe there is a small subset of Jacobus patients who are generally hostile to Catalyst – to the point where some have said on a restricted-access LEMS Facebook page that they would do anything in their power to destroy Catalyst To be clear, we are not seeking to discount patient communications, but when reviewing patient reports we all need to be conscious of the fact that a very few individuals may be motivated by something other than good faith reporting.

Sincerely,

Gary Ingenito, MD, PhD
Chief Medical and Regulatory Officer
Catalyst Pharmaceuticals, Inc.

From: Locicero, Colleen L
To: Corrigan-Curay, Jacqueline; Stein, Peter
Cc: Kimbrell, Maarika; Schumann, Katherine; Phillips, J. Paul; Myers, James
Subject: amifampridine update
Date: Thursday, March 07, 2019 3:39:00 PM
Attachments: SKM_C754e19030511480.pdf
Response to RFI drug supply info Son.pdf
FW Firdaps.msg
Firdapse AE.msg
Letter from Sen. Sanders to HHS and FDA on Firdapse.pdf

Jacqueline and Peter,

In follow up to our 2/26 meeting where you asked whether differences between the Jacobus and Catalyst products could account for the adverse events described in the emails received by DDI (a hypersensitivity type reaction and report of increased seizures), I obtained the following information from the clinical TL and the clinical pharmacology team.

The clinical TL provided the following very helpful table:

The only differences in chemistry between the two products seem to be 1) the phosphate salt and 2) the use of calcium stearate as an excipient in Firdapse.

The clinical TL concluded that it is possible that someone could have an allergic reaction to the phosphate salt or calcium stearate. She noted that amifampridine phosphate rapidly dissociates into amifampridine and phosphate, but it is unlikely that the phosphate increases phosphate levels enough to have any clinical significance. She also noted that both products have a risk of seizures.

Per the clinical pharmacology team, Catalyst conducted a relative BA study of the free base and phosphate salt formulations (not the final Jacobus/Catalyst products). Catalyst concluded that the base and salt formulations are BE for AUC, but not for Cmax.

Here are the results:

Please let me know your thoughts with respect to whether these differences might allow access to the Jacobus product for patients who report an AE on Firdapse.

On a related note, attached is Catalyst's response to inquiries they received from DSS about the Firdapse supply. According to Catalyst, they "have no knowledge of any patients or health care providers that have been "unable to obtain sufficient quantities" of Firdapse." They are not aware of a single patient who missed even a single dose in their transition to commercially

available Firdapse. They acknowledge that immediately after launch, they were focused on providing Firdapse to patients already on amifampridine, such that patients not previously treated with amifampridine (or who had adequate supplies) did not start to receive shipments of Firdapse until 2/4/19.

Prescriptions for doses that exceed 80 mg/day are referred to a specialty pharmacy that works with the prescriber to prepare letters of medical necessity for insurance coverage purposes. Catalyst is aware of 9 patients who have been covered by insurance at these doses and provides sufficient quantities of Firdapse to the specialty pharmacies to fill those prescriptions. The letter explains the Catalyst Pathways program and acknowledges that while participation in Pathways does not limit the patient's daily dose, patients on doses above 80 mg/day limits some Pathway services for those patients.

Also attached are Bernie Sanders' letter to Dr. Gottlieb and Catalyst's letter to Dr. Gottlieb regarding the Bernie Sanders letter.

Finally, I will be forwarding to you and the review division shortly the draft response to the Bernie Sanders letter that is being circulated for clearance.

Thanks,

Colleen

From:	Buracchio, Teresa
To:	Dunn, Billy; Bastings, Eric; Kozauer, Nicholas
Subject:	FW: Ruzurgi Exclusivity Memo-- comments requested by 10 am Monday
Date:	Friday, April 26, 2019 11:37:02 AM
Attachments:	Ruzurgi Exclusivity Memo (4-25-19 revised).DNP.docx image001.png
Importance:	High

We received the draft exclusivity memo. I made a few edits. Please review and let me know if you have any additional edits or comments by Monday morning.
Thanks,
Teresa

From: Nduom, Kelley
Sent: Thursday, April 25, 2019 4:23 PM
To: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>; Dettelbach, Kim <Kim.Dettelbach@fda.hhs.gov>; Friedman, Aaron <Aaron.Friedman@fda.hhs.gov>; Buracchio, Teresa <Teresa.Buracchio@fda.hhs.gov>; Mathers, Michelle <Michelle.Mathers@fda.hhs.gov>
Cc: Hayes, Nancy <Nancy.Hayes@fda.hhs.gov>; Sitlani, Jay <Jay.Sitlani@fda.hhs.gov>; Shah, Nisha <Nisha.Shah@fda.hhs.gov>; Flores, Lars <Lars.Flores@fda.hhs.gov>; Ligon, Sharnell (CDER) <Sharnell.Ligon@fda.hhs.gov>
Subject: Ruzurgi Exclusivity Memo
Importance: High
All – Please find attached the draft exclusivity memo for Ruzurgi's approval.
This memorandum addresses whether the unexpired new chemical entity (NCE) and orphan drug exclusivities the FDA recognized for Firdapse (amifampridine phosphate) tablets (NDA 208078) (Firdapse) block the approval of Ruzurgi (amifampridine) tablets (NDA 209321) (Ruzurgi).
The memo and background materials are in sharepoint.
The PDUFA date is May 15th, but the Division would like to take action on the application on April 30th (this coming Tuesday). Given the time crunch, please provide any comments **by 10 am on Monday** (or sooner, if possible), so that we can revise/resolve any issues for approval on Tuesday.
Feel free to contact me with any questions.
Many thanks,
Kelley

Kelley Nduom, JD, MPH
Senior Regulatory Counsel
Acting Special Assistant to the Deputy Center Director for Regulatory Policy

Center for Drug Evaluation and Research
Office of Regulatory Policy
U.S. Food and Drug Administration
Tel: 301-796-8597
kelley.nduom@fda.hhs.gov

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

TAB 5:

Key FDA decision-makers in the Firdapse and Ruzurgi approvals

From: Locicero, Colleen L
To: Buracchio, Teresa; Mathers, Michelle
Cc: Dunn, Billy; Bastings, Eric; Daugherty, Susan B (CSO); Choy, Fannie (Yuet); Bullock, Heather; Ware, Jacqueline H; Temple, Robert; Unger, Ellis; Kozauer, Nicholas; Lowy, Naomi
Subject: amifampridine
Date: Wednesday, December 12, 2018 1:33:33 PM

Teresa and Michelle,

Thanks so much for your patience while I have been looking into the Jacobus amifampridine exclusivity and expanded access issues. Here is an update:

Exclusivity

Jay Sitlani is working on getting the Jacobus NDA on the agenda for an upcoming exclusivity board meeting to start the discussion about Catalyst's orphan exclusivity, a possible pediatric indication for the Jacobus product (which the Catalyst product does not have), etc. I will let you know when that discussion will be once I hear from Jay.

Expanded Access

I have been consulting with Jacqueline Corrigan-Curay, David Faranda, Lori Bickel, and Paul Phillips on the expanded access issues. Jacqueline, in turn, discussed them with Janet at her 1:1 this week.

> Regarding Jacobus' question about having to recall any of their product distributed under expanded access, once the Catalyst product is on the market, please assure Jacobus that we will not require or ask them to recall any of their product and try to leave it at that. If Jacobus continues to raise the 3-month supply issue, such that you have to respond to that, please continue to tell them (as I understand you did at yesterday's meeting) that we generally don't get involved in these types of administrative details pertaining to expanded access.
>
> Regarding Jacobus' questions about continuing to provide EA to their product for conditions not covered by the Catalyst approval (pediatric patients, treatment of non-LEMS patients, patients receiving higher than the Catalyst approved doses), it appears we are leaning towards a determination that we could not continue to authorize EA to their product, once the Catalyst product is marketed, unless a patient has tried and failed on the Catalyst product or had an adverse reaction to the Catalyst product and the division believes the patient may have success with the Jacobus product. That said, we are not certain and Janet believes a discussion is warranted. Therefore, Jacqueline is adding this issue to the agenda for the January 2nd MPPRC meeting. I realize many folks may be on leave, but we are trying to be sensitive to the need to get a response to Jacobus before the

I am CC'ing Billy and DNP just in case they have more to add.

Thanks,
Courtney

Courtney Carpenter, MPH
Division of Executive Operations (CDER EXSEC)
CDER|OEP
301.796.4487 |(c)240.687.2804
Courtney.Carpenter@fda.hhs.gov

From: Throckmorton, Douglas C
Sent: Friday, December 14, 2018 7:55 AM
To: CDER EXSEC <CDEREXSEC@cder.fda.gov>
Cc: McLatchy, Johanna <Johanna.McLatchy@fda.hhs.gov>
Subject: HIgh priced drugs

We're in the middle of working up a proposal to address high priced drugs and I'm likely to get a call about this. Can someone find out more about the facts? I can't unlock the article. I assume the 'free' before was because it was available under expanded access?

Price Of Drug For Rare Neuromuscular Disorder Shoots Up Following FDA Approval.

STAT (12/13, 20K) reports last month, the Food and Drug Administration approved Firdapse (amifampridine) for the treatment of Lambert-Eaton myasthenic syndrome, "a rare, neuromuscular disorder," and the drug has been priced at $375,000. However, the article points out that before it was approved by the FDA, the drug was available to "hundreds of patients...for free."

Douglas C. Throckmorton MD
Deputy Director for Regulatory Programs
CDER FDA
240-402-5400

Cc: Helms Williams, Emily <Emily.HelmsWilliams@fda.hhs.gov>; Sitlani, Jay <Jay.Sitlani@fda.hhs.gov>
Subject: Question re: Jacobus product

Hi Teresa and Michelle,

I hope you're doing well. I'm coordinating the CDER Exclusivity Board discussions around the Jacobus application for Ruzurgi. As you know, this issue has been heating up in the news, and the Commissioner's office has raised some questions about the differences between the two drugs. News reports state that Catalyst's version doesn't require refrigeration, and Catalyst has suggested there are other differences. We're hoping you could help us with a few questions:

1. Are the Catalyst and Jacobus products different, if so how (any differences in active moiety/ingredient, or just excipients)?

2. Assuming they are different in some way, what is our justification for ending expanded access to the Jacobus product?

I'm happy to give you a call to discuss, if that would be easier. Thanks!

Kelley

Kelley Nduom, JD, MPH
Senior Regulatory Counsel
Acting Special Assistant to the Deputy Center Director for Regulatory Policy

Center for Drug Evaluation and Research
Office of Regulatory Policy
U.S. Food and Drug Administration
Tel: 301-796-8597
kelley.nduom@fda.hhs.gov

Thanks,
Colleen

From: Locicero, Colleen L
Sent: Monday, February 04, 2019 2:40 PM
To: Nduom, Kelley <Kelley.Nduom@fda.hhs.gov>
Subject: RE: Discuss NDA 209321 Ruzurgi [Amifampridine (3,4-Diaminopyridine)] and Catalyst NDA-208078 Firdapse exclusivity for adult use

Hi Kelley,

I think these are the essential folks.

Thanks,
Colleen

DNP
Billy Dunn and Eric Bastings, but if you can't get both and you can get Billy, that would probably be OK
Teresa Buracchio

ODE I
Ellis Unger

ONDP
Colleen LoCicero
Maarika Kimbrell and James Myers, but if you can't get both, one or the other would be OK

OOPD
Henry (Chip) Startzman
Roberta Szydlo

DPMH
Lynne Yao and John Alexander, but if you can't get both or one of them, Hari and Mona would probably be OK

I'll leave the rest up to you.

From: Nduom, Kelley
Sent: Monday, February 04, 2019 2:00 PM
To: Locicero, Colleen L <Colleen.Locicero@fda.hhs.gov>
Subject: RE: Discuss NDA 209321 Ruzurgi [Amifampridine (3,4-