The TSI history for the earlier investigations is available in DARRTS (look under SAFETY application 1404, 1405, or 1784); feel free to let me know if you have any additional questions about the records.

If the reporter is referring to the KHN article and public posting from 2017, I don't know if it's accurate to say that we made labeling updates based on review of that safety signal, since the seizures/psych reviews were ongoing at the time we were made aware of the KHN article.

Thanks,
Elisabeth

From: Kehoe, Theresa <Theresa.Kehoe@fda.hhs.gov>
Sent: Tuesday, January 25, 2022 12:25 PM
To: Sullivan, Shannon <Shannon.Sullivan@fda.hhs.gov>
Cc: Lowy, Naomi <Naomi.Lowy@fda.hhs.gov>; Hanan, Elisabeth <Elisabeth.Hanan@fda.hhs.gov>; Woronow, Daniel <Daniel.Woronow@fda.hhs.gov>
Subject: RE: [EXTERNAL] question on puberty blocking drugs

Ok, thank you
It seems we cannot talk about off label indications (transgender), so from a safety perspective: *Product labeling for GnRH agonists indicated for Central Precocious Puberty (CPP) was updated based on the 2017 safety review. We continue to monitor for adverse events and have recently posted about a potential signal of a serious risk regarding intercranial hypertension in children treated for CPP. That review is ongoing.*

I believe the NISS information is public, but cc'ing Elisabeth as well as Dan from OSE in case they have anything to add

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From: Sullivan, Shannon <Shannon.Sullivan@fda.hhs.gov>
Sent: Tuesday, January 25, 2022 12:12 PM
To: Kehoe, Theresa <Theresa.Kehoe@fda.hhs.gov>
Cc: Lowy, Naomi <Naomi.Lowy@fda.hhs.gov>
Subject: Re: [EXTERNAL] question on puberty blocking drugs

Hi Theresa,
DMEP did do a safety review of the GnRH agonist class in pediatric patients in 2016/2017, which was initiated after publication of an article by Kaiser Health News in which adults with histories of CPP attributed multiple complaints to prior use of a GnRH agonist. The complaints were extensive and variable, and included fibromyalgia type symptoms, infertility, PCOS, and weight gain, among others. Our review focused on suicidal ideation/depression, seizures, and bone health, and we reviewed all cases of these AEs in pediatric patients exposed to a GnRH agonist. Most of these patients had CPP but a handful were transgender kids using the drugs off-label. We found no effect on bone (after factoring in catch-up growth), including no

increase in fracture risk. We did find increased risk of depression and suicidality, as well as increased seizure risk and we issued SLCs to the entire class for these AEs (added to W&P in 2017).

Regarding use of GnRH agonists in the transgender population, no company has come in for this indication to date. DUOG has done a patient listening session with trans kids and separately with trans adults, which I participated in, and there is definitely a need for these drugs to be approved for gender transition, as they are typically not covered by insurance and are expensive out of pocket. It was my understanding that DUOG would take these applications if and when any do come in.

Let me know if I need to provide additional details on any of this.
Thanks
Shannon

Shannon Sullivan
Clinical Team Leader
Division of General Endocrinology

From: Kehoe, Theresa <Theresa.Kehoe@fda.hhs.gov>
Sent: Tuesday, January 25, 2022 11:02:54 AM
To: Sullivan, Shannon <Shannon.Sullivan@fda.hhs.gov>
Cc: Lowy, Naomi <Naomi.Lowy@fda.hhs.gov>
Subject: FW: [EXTERNAL] question on puberty blocking drugs

Hi Shannon
I am going to need some history here. See the inquiry below.

Theresa

From: Maynard, Janet <Janet.Maynard@fda.hhs.gov>
Sent: Tuesday, January 25, 2022 10:58 AM
To: Moore, Jennifer <Jennifer.Moore1@fda.hhs.gov>; Kehoe, Theresa <Theresa.Kehoe@fda.hhs.gov>
Cc: Grant, April <April.Grant@fda.hhs.gov>
Subject: RE: [EXTERNAL] question on puberty blocking drugs

I believe this would be in DGE in OCHEN. Theresa—is that correct?

From: Moore, Jennifer <Jennifer.Moore1@fda.hhs.gov>
Sent: Tuesday, January 25, 2022 10:09 AM
To: Maynard, Janet <Janet.Maynard@fda.hhs.gov>
Cc: Grant, April <April.Grant@fda.hhs.gov>
Subject: FW: [EXTERNAL] question on puberty blocking drugs

Hi Janet,

OMA received the below inquiry. Does this fall under ORPURM?

Thanks,
Jennifer

From: Grant, April <April.Grant@fda.hhs.gov>
Sent: Tuesday, January 25, 2022 9:56 AM
To: Moore, Jennifer <Jennifer.Moore1@fda.hhs.gov>
Subject: FW: [EXTERNAL] question on puberty blocking drugs

Hi Jenifer,

We are trying to figure out if this topic falls under ORPURM. Do you know?

Thank you!

April M. Grant
Press Officer

Office of Media Affairs
Office of External Affairs
U.S. Food and Drug Administration
Mobile: 202-657-8179
April.grant@fda.hhs.gov

From: Terhune, Chad (Reuters) <Chad.Terhune@thomsonreuters.com>
Sent: Monday, January 24, 2022 6:20:44 PM
To: Tantibanchachai, Chanapa <Chanapa.Tantibanchachai@fda.hhs.gov>
Subject: [EXTERNAL] question on puberty blocking drugs

Hello and hope you're doing well. I'm not sure if you're the right person for this one. I had a couple questions on puberty blocking drugs such as Lupron and Supprelin LA, approved for central precocious puberty but also used off-label for transgender children.

I saw mention of a 2017 FDA safety review of these drugs related to CPP. There are questions about bone health, brain development and fertility. Did anything come out of that?
Has FDA done anything in relation to their off-label use for gender dysphoria in children?
Just checking to see if I've missed something. Not on immediate deadline. Thanks, Chad

Chad Terhune
Health enterprise reporter
Reuters
213-769-9125
@chadterhune
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