Lassman Law+Policy
— FDA Regulatory Expertise —

Scott M. Lassman
+1 202-248-5426
scott@lassmanfdalaw.com

1717 K Street, NW
Suite 900
Washington, D.C. 20006

October 11, 2019

VIA ELECTRONIC SUBMISSION

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2019-P-1679; Supplemental Information in Further Support of Braeburn, Inc.'s Citizen Petition and in Response to the July 24, and October 1, 2019 Comments Submitted by Indivior Inc.

Dear Sir or Madam:

On behalf of Braeburn, Inc. ("Braeburn"), and in accordance with 21 C.F.R. § 10.30(g), the undersigned hereby submits supplemental information in support of Braeburn's petition and in response to the comments submitted on July 24, and October 1, 2019 by Indivior, Inc. ("Indivior"). This submission provides further support from newly obtained documents for Braeburn's position that Sublocade™ (buprenorphine extended-release) injection was never eligible for orphan drug designation ("ODD") because Indivior, Inc. ("Indivior") failed to submit a new ODD request for that specific "drug" as required by the Orphan Drug Act and Food and Drug Administration ("FDA") regulations.[1]

In its July 24 comments, Indivior asserted that it was not required to submit a new ODD request for Sublocade because FDA's "longstanding orphan-drug regulations" have "for decades" established the relevant drug for ODD purposes as the active moiety, not any particular formulation or drug product. Indivior July 24 Comments, pp. 23-24. Indivior, however, failed to identify a single FDA regulation to support its position. In its October 1 submission, Indivior again fails to identify any such regulation and instead cites various court cases, Federal Register preambles and FDA letter decisions addressing an entirely different issue and statutory provision. Indivior October 1 Comments, p. 9. These precedents address whether FDA can interpret the term "same drug" (or "such drug") to mean a different drug product containing the same active moiety as a previously approved drug product for purposes of orphan drug exclusivity ("ODE") under 21 U.S.C. § 360cc(a). As such, they are not relevant to the issue presented here, *which concerns ODD under section 360bb*.

Contrary to Indivior's claim, FDA's longstanding position has been that a sponsor seeking a new ODE period for a product reformulation must first seek and obtain ODD for the specific

[1] Indivior's October 1, 2019 comments fail to present any serious challenge to Braeburn's prior arguments and comments and thus will not be further addressed here. Braeburn, however, believes it is important to include some new documents in the administrative record and to provide some context for them in these additional comments.

follow-on drug product or formulation based upon a plausible hypothesis of clinical superiority. This is particularly the case where, as here, the sponsor's first drug previously received both ODD and ODE, and the ODE period has expired.

In new documents Braeburn just received under the Freedom of Information Act regarding Nutropin Depot, FDA explained that "*the formulation is the essential element in defining this product*." *See* Supervisors Memo (Designation #98-1150), p. 2 (Oct. 21, 1999) (emphasis added) (Exhibit 1). FDA further explained that because ODE had already expired for the active ingredient (r-human growth hormone), "no exclusivity would be granted to the active ingredient alone; therefore, for this product, it is necessary to specify *both the formulation and the duration of action as essential to the designation*." *Id*. (emphasis added). In other words, FDA explicitly designated the long-acting *drug product*, not the active moiety or active ingredient, and did so only after the sponsor provided a plausible hypothesis of clinical superiority to the previously approved r-human growth hormone products (*e.g.*, Protropin and Nutropin). Until FDA amended its policy in 2016, FDA took the exact same position in similar circumstances with respect to Tyvaso and Orenitram.[2] For the reasons set forth in Braeburn's prior submissions, FDA's change of position is unlawful and cannot be applied to Sublocade.

Moreover, although Indivior again seeks to undermine the Nutropin Depot precedent by suggesting the Nutropin was not really approved and/or designated before Nutropin Depot, Indivior misinterprets the regulatory record. Both Protropin (somatrem) and Nutropin (somatropin) were designated as orphan drugs and approved individually and on different dates. Protropin was designated on December 9, 1985, and approved October 17, 1995. *See* Protropin ODD Record (Exhibit 2). Nutropin, by contrast, was designated on March 6, 1987, and approved for the relevant orphan indication in March 1994. *See* Genentech Press Release (March 8, 1994) (Exhibit 3) and Drugs@FDA.com Listing (Exhibit 4). While Indivior makes much of the fact that FDA's orphan drug database lists the marketing approval date for Nutropin as October 17, 1985 and the ODE expiration date as October 17, 1992 (the same as for Protropin), this simply reflects the fact that FDA appears to have considered Nutropin and Protropin to be the "same drug" for purposes of ODE despite the fact that they differ slightly in amino acid sequence and thus have different non-proprietary names (somatrem versus somatropin). *See* 21 C.F.R. § 316.3(b)(14)(ii)(A) (considering protein drugs the "same" even if they have minor differences in amino acid sequence); *see also* 57 Fed. Reg. 62076, 62079 (Dec. 29, 1992) (rejecting argument that one amino acid difference results in a different drug). As a result, Nutropin's ODE period ran concurrently with Protropin's, which was approved first, and in fact expired before Nutropin was even approved.

Nutropin Depot thus remains a valid precedent that is consistent with all of the prior precedents identified by Braeburn, including glatiramer acetate, Tyvaso, and Orenitram. Nutropin Depot also supports that argument that if Sublocade and Subutex are considered to be the "same drug," as Indivior contends, then any ODE granted to Sublocade must run concurrently with Subutex's ODE and, as such, has already expired. If, on the other hand, Sublocade is clinically

[2] Contrary to Indivior's assertion, FDA has designated specific drug products or formulations on multiple occasions, including vincristine sulfate liposome injection (Jan. 8, 2007), metronidazole 10% ointment (Nov. 8, 2007), lidocaine patch 5% (Oct. 24, 1995), acetylcysteine effervescent tablets for oral solution (Feb. 24, 2015), and riluzole orally dissolving tablets (Nov. 30, 2016), among many, many other examples.

superior to Subutex (which it is not), then Sublocade is not now and never was the "same drug" as Subutex, which provides additional grounds for revoking ODD under 21 C.F.R. § 316.29(a)(3). In other words, Indivior cannot have it both ways: either Sublocade is the same drug as Subutex, in which case its ODE has already expired, or it is not the same drug as Subutex, in which case it was never properly designated as an orphan drug in the first place.

In sum, because Sublocade is a distinct drug (drug product) from Subutex under FDA's clear and unambiguous regulations, it was not eligible for ODD unless Indivior submitted a separate request to FDA prior to submission of its New Drug Application. Indivior concedes that it did not do so. Because Indivior failed to submit a designation request for Sublocade, it was not eligible under the statute or FDA regulations to receive ODD, and that ODD thus must be revoked now. 21 C.F.R. § 316.29.

Thank you for your consideration of these supplemental comments, and please do not hesitate to contact me directly if you have any questions.

Sincerely,

Scott M. Lassman
Counsel to Braeburn, Inc.

cc: Dr. Janet Maynard, Director, Office of Orphan Product Development
Elizabeth Dickinson, Office of Chief Counsel
Sharon Hertz, M.D., Director, DAAAP

Exhibits

EXHIBIT 1

FILE COPY

Supervisors Memo

Designation #98-1150

Drug Name:
code name:
generic name: sustained-release Recombinant human growth hormone somatropin (rDNA origin)
trade name: ProLease rhGH

Sponsor's Name:
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

Proposed Designation:
Long term treatment of children who have growth failure due to lack of adequate endogenous growth hormone secretion.

Regulatory Status:
This product is being studied under IND 47177

Disease/Condition Background Information:
Growth hormone is a product which was first designated as an orphan in 1985 and at present the exclusivity for "the long tern treatment of children who have growth failure due to lack of adequate endogenous growth hormone secretion" has expired. The sponsor has reformulated their product to allow for once monthly administration and are claiming that the reformulation constitutes a major contribution to patient care and therefore a different product which would also be entitled to seven years of exclusivity.

While this office has resisted using the number of administrations as a criteria for determining a major contribution to patient care Sandostatin LAR was found to be a superior product when it demonstrated that one injection per month could be substituted for three injections per day. We are now looking at one injection per day as opposed to one per month or a thirty to one advantage. In addition the drug is administered to children.

The reviewer has pointed out that other growth hormone products are labeled for three times a week administration and this product is proposed for use once a month, or twice a month depending on the volume that needs to be administered, reducing the numerical advantage from thirty to one to five to one.

Evaluation and Recommendation:
There are a number of difficulties with evaluating this product, one of which is deciding when a significant contribution to patient care become a MAJOR CONTRIBUTION TO PATIENT CARE in that the contribution represents such benefit that it warrants either breaking or granting exclusivity. The general consensus of the OOPD is that thirty to one qualifies; however, the majority of the office also has concluded that five to one is not sufficient to qualify. Most patients receiving growth hormone get daily injections and if the sponsor can demonstrate that most patients treated with sustained release recombinant human growth hormone do well on one injection per month then they have met the burden of proof required to establish that the product is a Major Contribution to Patient Care and therefore clinically superior.

Another difficulty in dealing with this application is the concept of active ingredient which the regulations use as the standard for defining a drug. The regulations state that formulation changes do not constitute a new drug unless the formulation changes are shown to be clinically superior. With sustained-release Recombinant human growth hormone somatropin, the formulation is the essential element in defining this product, and since the exclusivity on r-human growth hormone has expired, no exclusivity would be granted to the active ingredient alone; therefore, for this product, it is necessary to specify both the formulation and the duration of action as essential to the designation. The sponsor should be informed that long term administration will be defined as one injection per month, and exclusivity for this product would accrue only to the long acting formulation.

John J McCormick, M.D.
Medical Reviewer, Office of
Orphan Products Development
(HF-35)

Concur: Marlene E. Haffner Date: 10/21/99

Marlene E. Haffner, M.D., M.P.H.
RADM USPHS
Director, Office of Orphan Products Development

cc:
HF-35/Designation File #98-1150
HF-35/Chron File
c:somatrop.150

EXHIBIT 2

FDA

Search Orphan Drug Designations and Approvals

Generic Name:	Somatrem for injection
Trade Name:	Protropin
Date Designated:	12/09/1985
Orphan Designation:	1. Long-term treatment of children who have growth failure due to a lack of adequate endogenous growth hormone secretion (prevalence 15,000) 2. Treatment of short stature associated with Turner's syndrome (prevalence 8000).
Orphan Designation Status:	Designated/Approved
Marketing Approval Date:	10/17/1985
Approved Labeled Indication:	
Exclusivity End Date:	10/17/1992
Sponsor:	Genentech, Inc. 1 DNA Way South San Francisco, California 94080 USA

The sponsor address listed is the last reported by the sponsor to OOPD.

Links on this page:

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3. https://www.fda.gov/
4. http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm

U.S. Food and Drug Administration
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Silver Spring, MD 20993
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EXHIBIT 3

Tuesday, Mar 8, 1994

FDA Grants Genentech License to Market Nutropin for Growth Hormone Deficiency in Children

Only human growth hormone (hGH) product with two indications

South San Francisco, Calif. -- March 8, 1994 --

Genentech, Inc. announced today that it received permission from the Food and Drug Administration (FDA) to market Nutropin (somatropin [rDNA origin] for injection) hGH for the treatment of children with growth failure due to inadequate levels of the natural hormone in their bodies.

This marketing approval is the second to be granted by the FDA for Nutropin, occurring less than four months after Genentech received approval to market Nutropin for treating growth failure in children due to chronic renal insufficiency prior to kidney transplantation. Nutropin is the only hGH product approved for more than one indication.

"Nutropin's development and these approvals demonstrate both Genentech's and the FDA's commitment to treating serious growth disorders," said G. Kirk Raab, Genentech's president and chief executive officer.

Genentech, Inc. is a leading biotechnology company that discovers, develops, manufactures and markets human pharmaceuticals for significant unmet medical needs. The company has headquarters in South San Francisco, Calif., and is traded on the New York and Pacific Stock Exchanges under the symbol GNE.

EXHIBIT 4

Drugs@FDA: FDA Approved Drug Products

SHARE (HTTPS://WWW.FACEBOOK.COM/SHARER/SHARER.PHP?U=HTTPS://WWW.ACCESSDATA.FDA.GOV/SCRIPTS/CDER/DAF/INDEX.CFM?EVENT=OVERVIEW.PROCESS&APPLNO=019676)

TWEET (HTTPS://TWITTER.COM/INTENT/TWEET/?TEXT=DRUGS@FDA: FDA APPROVED DRUG PRODUCTS&URL=HTTPS://WWW.ACCESSDATA.FDA.GOV/SCRIPTS/CDER/DAF/INDEX.CFM?EVENT=OVERVIEW.PROCESS&APPLNO=019676)

EMAIL (MAILTO:?SUBJECT=DRUGS@FDA: FDA APPROVED DRUG PRODUCTS&BODY=HTTPS://WWW.ACCESSDATA.FDA.GOV/SCRIPTS/CDER/DAF/INDEX.CFM?EVENT=OVERVIEW.PROCESS&APPLNO=019676)

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New Drug Application (NDA): 019676
Company: GENENTECH

EMAIL (MAILTO:?SUBJECT=DRUGS@FDA: FDA APPROVED DRUG PRODUCTS&BODY=HTTP://WWW.ACCESSDATA.FDA.GOV/SCRIPTS/CDER/DAF/INDEX.CFM?EVENT=OVERVIEW.PROCESS%26VARAPPLNO=019676)

- Additional Label (http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/019676s020,021_rel2_lbl.pdf)
- Additional App Ltr (http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2005/019676s020,021,020522s021,022_letter2.pdf)

Products on NDA 019676

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Drug Name	Active Ingredients	Strength	Dosage Form/Route	Marketing Status	TE Code	RLI
NUTROPIN	SOMATROPIN [rDNA origin]	N/A	Injectable; Injection	Prescription	None	No

Showing 1 to 1 of 1 entries

Approval Date(s) and History, Letters, Labels, Reviews for NDA 019676

Original Approvals or Tentative Approvals

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Action Date	Submission	Action Type	Submission Classification	Review Priority; Orphan Status	Letters, Reviews, Labels, Patient Package Insert	
03/09/1994	ORIG-1	Approval		STANDARD; Orphan		L n a o si

Showing 1 to 1 of 1 entries

Supplements

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Action Date	Submission	Supplement Categories or Approval Type	Letters, Reviews, Labels, Patient Package
12/13/2016	SUPPL-44	Labeling-Package Insert	**Label (PDF) (https://www.accessdata.fda.gov/dru Letter (PDF) (https://www.accessdata.fda.gov/drugsatfda_doc**
04/10/2012	SUPPL-42	Labeling-Package Insert	**Label (PDF) (https://www.accessdata.fda.gov/dru Letter (PDF) (https://www.accessdata.fda.gov/drugsatfda_doc**
02/15/2007	SUPPL-30	Labeling	**Label (PDF) (https://www.accessdata.fda.gov/dru Letter (PDF) (https://www.accessdata.fda.gov/dru 020522s033ltr.pdf)**
02/23/2006	SUPPL-26	Efficacy-Labeling Change With Clinical Data	**Label (PDF) (https://www.accessdata.fda.gov/dru Letter (PDF) (https://www.accessdata.fda.gov/dru**