DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: 07/31/2015

TO: Office of Orphan Products Designation and CDER's Division of Neurology Products in the Office of Drug Evaluation I

FROM: CDER Exclusivity Board

SUBJECT: Determination of Whether SD-809 (Dutetrabenazine) and Tetrabenazine are Different Active Moieties

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SUMMARY

This memorandum documents the recommendation of the Exclusivity Board (Board) within the Center for Drug Evaluation and Research (CDER) regarding whether the investigational new drug, SD-809 (d_6-tetrabenazine or dutetrabenazine), a deuterated version of tetrabenazine, being developed by Auspex Pharmaceuticals (Auspex) has a different active moiety from tetrabenazine. Tetrabenazine was previously approved under the trade name Xenazine on August 15, 2008 (NDA 021894).

This recommendation was based on a review of the regulatory documents related to SD-809 and submissions from Auspex, as well as consultation with the Division of Neurology Products (DNP or the Division) in CDER, the Office of Pharmaceutical Quality in CDER, and the Office of Orphan Products Designation (OOPD). The Board concluded that tetrabenazine and dutetrabenazine are not the same active moiety under FDA's regulations and precedent. Therefore, dutetrabenazine and tetrabenazine are not the "same drug" under the statute and regulations governing orphan drugs and it is appropriate to grant orphan drug designation to dutetrabenazine without a plausible theory of superiority to tetrabenazine. In addition, we concluded that the active moiety dutetrabenazine has not yet been previously approved in any new drug application (NDA).[1]

A discussion of the Board's reasoning follows.

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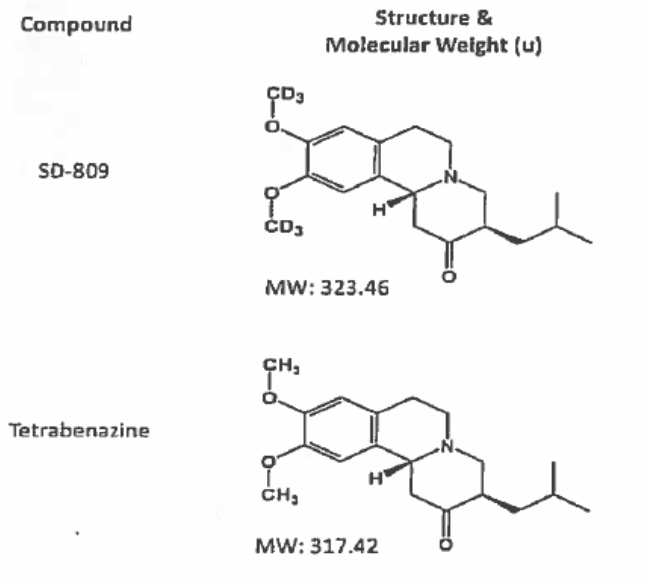
[1] Decisions about whether a particular drug product is entitled to 5-year new chemical entity (NCE) exclusivity are generally made at the time of approval of an NDA.

I. FACTUAL AND PROCEDURAL BACKGROUND

FDA approved Xenazine (tetrabenazine) on August 15, 2008, for the treatment of chorea associated with Huntington's disease (NDA 021894). Xenazine received 5-year new chemical entity (NCE) exclusivity, which expired on August 15, 2013, and is protected by 7-year orphan drug exclusivity until August 15, 2015.

Auspex requested orphan drug designation for the use of its investigational new drug, SD-809, a deuterated version of tetrabenazine also for the treatment of chorea associated with Huntington's disease. As shown in the figures below, the difference between the two products is that the deuterated tetrabenazine has deuterium instead of hydrogen on the two methoxy methyl groups present in tetrabenazine. Deuterium is a nonradioactive isotope of hydrogen that is different from hydrogen in that it also contains a neutron in addition to the single proton and single electron present in hydrogen. The deuterium atom in SD-809 is covalently linked to the carbon atom.



As a result of this substitution, dutetrabenazine has a higher molecular weight (323.46 Da) than tetrabenazine (317.43 Da) and a different empirical formula that reflects the substitution of six deuterium atoms for the hydrogens in the methyl groups ($C_{19}H_{21}D_6NO_3$ in contrast to $C_{19}H_{27}NO_3$ for tetrabenazine).

In a letter dated August 15, 2013, OOPD informed Auspex that after consultation with the Division, it considered tetrabenazine and dutetrabenazine to be the "same drug"[2] under the Agency's orphan drug regulations.[3] OOPD also informed Auspex that it would have to submit a plausible hypothesis of "clinical superiority"[4] in order to seek and obtain orphan drug

[2] See section II of this memorandum for a discussion on the regulatory definition of the term "same drug."
[3] Letter from Gayatri R. Rao, OOPD, to (b) (4) (on behalf of Auspex), at 1(Aug. 15, 2013).
[4] 21 CFR 316.20(a), (b)(5).

designation, and must demonstrate clinical superiority in order to receive orphan exclusivity upon marketing approval.[5]

Auspex disagreed with OOPD's conclusions and asserted that tetrabenazine and its deuterated isotope, dutetrabenazine, are different active moieties, and thus not the same drug.[6] Auspex offered the following reasons (among others) for its assertion:[7]

1. The deuterium atom in dutetrabenazine is covalently linked to the carbon atom and cannot be removed from the carbon or exchanged with hydrogen.

2. The replacement of specific covalent C-H bonds in tetrabenazine with C-D bonds results in the formation of a novel drug candidate that is neither an ester, nor a salt, nor a non-covalent derivative of a non-deuterated compound.

Auspex has also stated that when metabolized, dutetrabenazine is converted to other metabolites, but cannot revert to tetrabenazine.[8] Moreover, Auspex has claimed that the molecular changes in dutetrabenazine prolong the half-life of the α- and β-active metabolites, which are themselves deuterium containing molecules α- and β-dihydrodutetrabenazine, thereby reducing dosing frequency and improving the drug's pharmacokinetics vis-à-vis tetrabenazine.[9]

OOPD sought additional input from the Board and a meeting of the Board was held on June 9, 2014, to discuss this issue.

II. STATUTORY AND REGULATORY BACKGROUND

The Orphan Drug Act of 1983 (Pub.L. 97-414) (ODA) amended the FD&C Act to authorize FDA to grant orphan-drug designation to a drug or biological product that treats a rare disease or condition. Congress has explained that drugs for rare diseases or conditions are "commonly referred to as 'orphan drugs,'" because "[t]hey generally lack a sponsor to undertake the necessary research and development activities to attain their approval by the [FDA]."[10] For a product to qualify for orphan-drug designation, both the drug and the disease or condition must meet certain criteria specified in the ODA and FDA's implementing regulations at 21 CFR part 316. Orphan-drug designation qualifies the sponsor of the drug for various development incentives, including tax credits for qualified clinical testing.

Another incentive available under the ODA and FDA's regulations is a 7-year exclusivity period to the first sponsor who obtains approval of a marketing application for an orphan drug for an orphan-designated disease or condition.[11] Upon approval of such a marketing application, the

[5] 21 CFR 316.34(c).
[6] Letter from Kurt R. Karst, Counsel to Auspex Pharmaceuticals, to Gayatri R. Rao and Eric Bastings, FDA, Re. Orphan Drug Designation No. 12-3822; "Sameness" Determination (Nov. 25, 2013) ("Karst Letter"), at 2.
[7] Letter from Kurt R. Karst, Counsel to Auspex Pharmaceuticals, to Shannon N. Bacote, FDA, Re. SD-809 (Dutetrabenazine) – Request for NCE Determination (May 28, 2014).
[8] Karst Letter at 4.
[9] Id.
[10] H.R. Rep. 97-840, Pt. 1, at 6 (1982).
[11] Section 527 of the FD&C Act.

ODA instructs FDA not to approve another marketing application for "such drug" for the same disease or condition[12] for 7 years, with certain exceptions not relevant here.[13] Congress provided no guidance on what "such drug" means in this context.[14]

After extensive consideration of the Orphan Drug Act's text and purpose, FDA defined "such drug" through implementing regulations defining sameness.[15] FDA's orphan drug regulations at 21 CFR part 316 largely parallel the statutory design of the ODA. In describing the scope of the 7-year exclusivity period, the regulations state that "FDA will not approve another sponsor's marketing application *for the same drug* for the same use or indication" rather than the term "such drug" that is used in the statute.[16]

For small molecules, FDA's regulations define "same drug" as "a drug that contains the same active moiety as a previously approved drug and is intended for the same use as the previously approved drug, even if the particular ester or salt (including a salt with hydrogen or coordination bonds) or other noncovalent derivative such as a complex, chelate or clathrate has not been previously approved," with the exception "that if the subsequent drug can be shown to be clinically superior to the first drug, it will not be considered to be the same drug."[17]

Active moiety is defined in the orphan drug regulations as:

> the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.[18]

This is the same definition of "active moiety" found in the Agency's regulations governing 5-year New Chemical Entity (NCE) exclusivity under the Hatch-Waxman Amendments to the FD&C Act.[19] Therefore, FDA has applied the same analysis to determine a drug's "active moiety" under the 5-year NCE exclusivity provisions and under the orphan drug regulations for small molecule drugs.[20] Given this structure-centric definition in the regulations, FDA's

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[12] Section 527(a) of the FD&C Act.
[13] See Section 527(b) of the FD&C Act.
[14] See 57 Fed. Reg. 62076, 62078 (Dec. 29, 1992); Baker Norton Pharms. v. FDA, 132 F. Supp. 2d 30, 36 (D.D.C. 2001) ("Given the multiple definitions of the term 'drug,' and the different purposes that various statutory provisions can serve, the Court cannot find that the definition of 'drug' in § 360cc(a) is clear and unambiguous."). But see Depomed, Inc. v. HHS, No. 12-CV-1592 (KBJ), 2014 WL 4457225, at *11 (D.D.C. Sept. 5, 2014) ("[T]he term 'such drug' in the exclusivity provision operates only to define the scope of the limit on the FDA's approval authority once a "designated drug" has been "approved" as required for exclusivity to attach.").
[15] See 56 Fed. Reg. 3341 (Jan. 29, 1991); 57 Fed. Reg. 62076.
[16] 21 CFR 316.31.
[17] 21 CFR 316.3(b)(14)(i).
[18] 21 CFR 316.3(b)(2).
[19] See 21 CFR 314.108(a).
[20] We note that a district court recently announced a decision that raises questions about the Agency's interpretation of the term "active ingredient" to mean "active moiety" as applied to Amarin's drug Vascepa in the five-year New Chemical Entity Exclusivity context. See Amarin Pharm. Ireland Ltd. v. FDA, No. 14-CV-00324 (RDM), 2015 WL 3407061, at *1 (D.D.C. May 28, 2015). We note it here only to point out that Amarin involved interpretation of a different statutory provision with different statutory language and does not appear to impact the Agency's structure-centric approach to defining the "same drug" for ODE purposes. See infra note 21.

evaluation of an "active moiety" in the context of 5-year NCE exclusivity has focused on the structure of the moiety, rather than the activity of the moiety, regardless of which portions of the active ingredient contribute to the overall therapeutic effect of the drug.[21] FDA's interpretation of its "active moiety" regulations is that "drug derivatives containing non-ester covalent bonds are, on the whole, distinct from other types of derivative drugs such that the former" and latter are considered different active moieties.[22] Under this interpretation, FDA "has consistently focused on the specific chemical structure of the drug under consideration."[23] Further, FDA has stated that under the regulatory definition of active moiety, "although neither esters nor salts will be a unique active moiety . . . covalently bonded molecules that are not esters will be considered separate active moieties."[24]

III. DISCUSSION

The Board reviewed the submissions from Auspex regarding whether tetrabenazine and dutetrabenazine should be considered the "same drug" under 21 CFR part 316 and also discussed this issue on June 9, 2014. The Board applied FDA's "structure-based" approach to determine the active moiety for each molecule and considered whether there are any structural differences between tetrabenazine and dutetrabenazine that involve non-ester covalent bonds. The only structural difference between tetrabenazine and dutetrabenazine molecules is that the latter contains deuterium instead of hydrogen on the two methyl groups present in tetrabenazine. The deuterium atoms in dutetrabenazine are covalently bonded to the carbon atom. Thus, based on the different structures of the two molecules and FDA's structural approach to determining "active moiety," tetrabenazine and dutetrabenazine are different active moieties, and thus not the "same drug" under the statute and regulations governing orphan drugs.

IV. CONCLUSION

Based on our findings above, the Board concludes that a) tetrabenazine and dutetrabenazine are different active moieties, and b) therefore are not the "same drug" under the orphan drug regulations.[25]

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[21] See generally, FDA, Vyvanse Exclusivity Decision Letter, Docket No. FDA-2009-N-0184 (Oct. 23, 2009). This decision was upheld in Actavis Elizabeth, LLC v. FDA, 689 F. Supp. 2d 174 (D.D.C. 2010), aff'd 625 F.3d 760 (D.C. Cir. 2010).

[22] Actavis Elizabeth, 625 F.3d at 765.

[23] Letter from Keith Webber, FDA, to Kurt R. Karst, Counsel for Sandoz, re. NDA 022088, May 29, 2012, at 6.

[24] Id. at 8.

[25] Based upon the analysis and conclusions reached at the Board meeting on June 9, 2014, as well as consultations with CDER leadership, OOPD designated dutetrabenazine as an orphan drug consistent with the Board's recommendations explained in this memorandum on November 5, 2014. Therefore, Auspex does not need to advance a plausible theory under which dutetrabenazine is clinically superior to tetrabenazine.