CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215430Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 5, 2022
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 215430
Product Name and Strength:	Auvelity (dextromethorphan HBr and bupropion HCl) extended-release tablets, 45 mg/105 mg
Applicant/Sponsor Name:	Axsome Therapeutics, Inc.
OSE RCM #:	2021-377-1
DMEPA 1 Safety Evaluator:	Loretta Holmes, BSN, PharmD
Acting DMEPA 1 Team Leader:	Madhuri R. Patel, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted a revised container label, received via email on August 3, 2022, for NDA 215430. The Division of Psychiatry (DP) requested that we review the revised container label for Auvelity (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review[a] and follow-up recommendations communicated to the Applicant via email on August 3, 2022.

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Holmes, L. Label and Labeling Review for Auvelity (NDA 215430). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 Jul 14. RCM No.: 2021-377.

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/s/

LORETTA HOLMES
08/05/2022 01:46:53 PM

MADHURI R PATEL
08/05/2022 02:18:53 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Addendum to DPMH PLLR Review

Date: 4/1/2022 **Date consulted:** 3/4/2021

From: Tamara Johnson, MD, MS, Team Leader, Maternal Health, Division of Pediatrics and Maternal Health (DPMH)

Through: Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Psychiatry (DP)

Drug: AXS-05 (dextromethorphan hydrobromide & bupropion hydrochloride) tablet

NDA: 215430

Applicant: Axsome Therapeutics

Subject: Pregnancy and Lactation Labeling

Indication: Treatment of major depressive disorder (MDD)

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 215430.
- DPMH PLLR Review of AXS-05 NDA 215430, Niquiche Guity, Ph.D., dated July 20, 2021, DARRTS Reference ID# 4827543.

Consult Question:

The review team requests DPMH's input on the section 8 of labeling.

PURPOSE

The purpose of this addendum is to update the DPMH labeling recommendations and PMR clinical lactation study description for AXS-05 based on recent discussion with the DP Review Team regarding

the concern for fetal and neonatal/infant neurotoxicity based on inadequate animal data. The original application cycle review clock was extended. The new action date is April 29, 2022.

REVIEW ISSUE

In recent discussion, the DP review team shared with DPMH that there remains concern for potential neurotoxicity to the developing fetus and neonate/infant. The DP integrated review notes that dextromethorphan at high doses is known to produce psychedelic-like and dissociative effects, and the applicant's submission of a published nonclinical study fails to address the neurotoxic potential of dextromethorphan on the developing brain due to the study being conducted in an inappropriate animal age group. Neurotoxic findings are described in the labeling for the reference listed drug, Nuedexta (dextromethorphan hydrobromide/quinidine sulfate) capsules, NDA 021879: "When dextromethorphan/quinidine was orally administered (0/0, 5/50, 15/50, 25/50 mg/kg) to male and female rats on postnatal day (PND) 7, the highest dose resulted in neuronal death in brain (thalamus and medulla oblongata)." These findings are confounded by the effect of quinidine on the offspring, such that the separate dextromethorphan effect cannot be determined.

In addition, there is need for adequate nonclinical embryofetal development and pre- and post-natal development studies in a second species to appropriately evaluate the combined effect of bupropion and dextromethorphan, because the levels of dextromethorphan with bupropion might be higher with this combination than with Nuedexta. Multiple PMRs will be sought to address deficiencies of the nonclinical developmental toxicity studies. Therefore, the DP review team and leadership determined to include a *Warnings & Precautions* subsection in labeling to recommend against use of AXS-05 during pregnancy and lactation based on the limits of the available data and concern for the developing fetus and neonate/infant. Subsection 8.3 is also to be added to labeling.

The discussion with DP and DPMH also led to modification of the proposed PMR clinical lactation study population from (b) (4) to healthy lactating females (or lactating patients who are stopping breastfeeding for other reasons) to assess dextromethorphan concentrations in breastmilk following AXS-05 dosing. Their breastfed infants would not be exposed to the breastmilk following AXS-05 dosing as this would be a research risk. However, a 2-step approach to this PMR is recommended due to concern for neurotoxicity, such that if the amount of dextromethorphan in breastmilk is possibly clinically important, a follow up mother-infant pair study may be required to assess the amount reaching the infant systemically and any adverse effects on the breastfed infant.

RECOMMENDATIONS

DPMH recommends the following revised language for the PMR:

> Perform a lactation study (milk only) in lactating women who have received AXS-05 to assess concentrations of dextromethorphan and its metabolites in breast milk using a validated assay. A mother-infant pair study may be required in the future depending on the results of this milk-only study.

DPMH edited the labeling language in the draft AXS-05 labeling Highlights, subsections 5.X, 8.1, 8.2, 8.3, and section 17 (see below). DP clinical and nonclinical team inputs are reflected in the below labeling recommendations. DPMH refers to the final NDA action for final labeling.

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/s/

TAMARA N JOHNSON
04/01/2022 03:41:31 PM

LYNNE P YAO
04/19/2022 06:40:16 AM

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

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

Memorandum

Date: April 19, 2022

To: David Millis, M.D., Clinical Reviewer
Division of Psychiatry (DP)

Simran Parihar, PharmD, Regulatory Project Manager, (DP)

Kimberly Updegraff, PharmD, MS, Associate Director for Labeling, (DP)

From: Domenic D'Alessandro, PharmD, MBA, BCPS, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for PROPRIETARY NAME (dextromethorphan hydrobromide and bupropion hydrochloride) extended-release tablets, for oral use

NDA: 215430

In response to DP's consult request dated March 5, 2021, OPDP has reviewed the proposed product labeling (PI) for the original NDA submission for PROPRIETARY NAME (dextromethorphan hydrobromide and bupropion hydrochloride) extended-release tablets, for oral use.

PI: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DP (Simran Parihar) on April 14, 2022, and are provided below.

Thank you for your consult. If you have any questions, please contact Domenic D'Alessandro at (301) 796-3316 or domenic.dalessandro@fda.hhs.gov.

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/s/

DOMENIC G DALESSANDRO
04/19/2022 12:01:24 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	March 7, 2022
To:	Simran Parihar, PharmD Senior Regulatory Health Project Manager **Division of Psychiatry (DP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Domenic D'Alessandro, PharmD, MBE, CDE Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	AUVELITY (dextromethorphan HBr and bupropion HCl)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 215430
Applicant:	Axsome Therapeutics

1 INTRODUCTION

On February 21, 2021, Axsome Therapeutics submitted for the Agency's review an original New Drug Application (NDA) for AUVELITY (dextromethorphan HBr and bupropion HCl) tablets, for oral use, for the proposed indication of treatment of major depressive disorder (MDD) in adults.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Psychiatry (DP) on January 24, 2022 and March 5, 2021 respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for AUVELITY (dextromethorphan HBr and bupropion HCl) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft AUVELITY (dextromethorphan HBr and bupropion HCl) MG received on March 1, 2022 and received by DMPP and OPDP on February 24, 2022.
- Draft AUVELITY (dextromethorphan HBr and bupropion HCl) Prescribing Information (PI) received on February 22, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 24, 2022.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SUSAN W REDWOOD
03/07/2022 01:41:20 PM

DOMENIC G DALESSANDRO
03/07/2022 01:42:40 PM

BARBARA A FULLER
03/07/2022 02:09:38 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

REVIEW DEFERRAL MEMORANDUM

Date:	August 23, 2021
To:	Simran Parihar, PharmD Senior Regulatory Health Project Manager **Division of Psychiatry (DP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Medication Guide (MG)
Drug Name (established name):	TRADENAME (dextromethorphan HBr and bupropion HCl)
Dosage Form and Route:	Tablets, for oral use
Application Type/Number:	NDA 215430
Applicant:	Axsome Therapeutics

1 INTRODUCTION

On February 22, 2021, Axsome Therapeutics submitted for the Agency's review an Original New Drug Application (NDA) for TRADENAME (dextromethorphan HBr and bupropion HCl), tablets, for oral use, for the proposed indication use for the treatment of major depressive disorder (MDD) in adults. On March 4, 2021, the Division of Psychiatry (DP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for TRADENAME (dextromethorphan HBr and bupropion HCl), tablets, for oral use.

This memorandum documents the DMPP review deferral of the Applicant's proposed MG for TRADENAME (dextromethorphan HBr and bupropion HCl), tablets, for oral use.

2 CONCLUSIONS

Due to outstanding clinical deficiencies, DP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

SHAWNA L HUTCHINS
08/23/2021 01:52:06 PM

LASHAWN M GRIFFITHS
08/23/2021 02:06:12 PM

M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: May 2021, Year

To: Tiffany Farchione, M.D., Director
Division of Psychiatry Products

Through: Dominic Chiapperino, Ph.D., Director
Controlled Substance Staff

From: Chad J. Reissig, Ph.D., Supervisory Pharmacologist
Controlled Substance Staff

Subject: AXS-05 (dextromethrophan-bupropion), NDA 215430
(b) (4) **(45 mg dextromethorphan/105 mg bupropion, oral tablets twice daily (BID))**
IND Number: 124813
Indication(s): Major Depressive Disorder (MDD)
Sponsor: Axsome Therapeutics
PDUFA Goal Date: August 22, 2021

Materials Reviewed:

Abuse-related preclinical and clinical data in NDA submission 215430
Prior CSS reviews in DARRTS (J. Randall-Thompson, 4/17/2019 and K. Bonson, 6/11/2020)

Table of Contents

I. SUMMARY

1. Background

This memorandum responds to a consult request by the Division of Psychiatry Products (DPP) to evaluate AXS-05 in NDA 215430, submitted by Axsome Therapeutics Inc. for (b) (4) (dextromethorphan and bupropion). This product is being submitted under the 505(b)(2) regulatory pathway, referencing Nuedexta® (dextromethorphan HBr/quinidine sulfate), Wellbutrin SR® (bupropion HCL), and Contrave® (naltrexone HCL/bupropion HCL). The drug product is an oral capsule indicated for Major Depressive Disorder (MDD). The recommended dose is a fixed-dose combination of 45 mg dextromethorphan and 105 mg bupropion. CSS has previously reviewed this product under IND 124813 and recommended that the Sponsor perform assessments of withdrawal and dependence, as well as collect abuse-related adverse events (AEs). AXS-05 is not marketed anywhere in the world and none of the drug components are scheduled under the Controlled Substances Act.

Dextromethorphan (DXM) has been marketed for over 40 years and is the active pharmaceutical ingredient (API) in several over-the-counter (OTC) cough suppressant medications. Despite its OTC availability and non-scheduled status, DXM is a known drug of abuse (Nordt, 1998; Tomczak et al., 2012). The primary mechanism of action of DXM is antagonism of *N*-methyl-D-aspartate (NMDA) receptors, a mechanism of action similar to ketamine and phencyclidine (PCP) (Church et al., 1994; Church et al., 1991). Consistent with this mechanism of action, high dose DXM studies in humans have demonstrated that DXM produces hallucinogenic effects and acute cognitive impairment (Carter et al., 2013; Reissig et al., 2012), though the subjective effects can be differentiated from classic serotonergic hallucinogens under select circumstances (Barrett et al., 2018; Carbonaro et al., 2020; Carbonaro et al., 2018).

NMDA antagonists have been shown efficacious in the treatment of major depressive disorder (MDD) and treatment resistant depression (TRD) (e.g., Spravato® C-III). According to the Sponsor, the NMDA antagonism produced by DXM is relevant to the treatment of MDD. AXS-05 includes bupropion, which is also indicated for the treatment of MDD and is available in several formulations, including an extended release formulation. The Sponsor asserts that the inclusion of bupropion in AXS-05 increases exposure to DXM via inhibition of CYP2D6 metabolism, an assertion supported by pharmacokinetic (PK) studies.

2. Conclusions

- Neither component of AXS-05 (dextromethorphan or bupropion) are scheduled under the Controlled Substances Act (CSA).

- High doses of dextromethorphan (DXM) produce psychedelic-like and dissociative effects that are associated with its abuse potential and recreational use.

- The bupropion component of AXS-05 inhibits CYP2D6 and the metabolism of DXM to its primary metabolite dextrorphan (DXO). Limited data suggest that relative to DXO, DXM is less reinforcing and produces increased dysphoric effects (Zawertailo et al., 1998; Zawertailo et al., 2010). This may decrease the abuse potential of AXS-05 relative to single-entity DXM products.

- Relative to highly concentrated and flavored DXM products that are available over-the-counter (OTC) and appear to be expressly marketed for recreational purposes (e.g., https://robocough.com/), AXS-05 does not appear to present an increased abuse liability.

3. Recommendations

Based on our findings in the Conclusions section, we recommend the following:

1. AXS-05 should not be controlled under the Controlled Substances Act (CSA).

2. NMDA antagonists such as esketamine can produce dependence and a withdrawal syndrome. The Division should consider whether a tapering schedule for subjects that discontinue AXS-05 is necessary.

3. Because each of the reference listed drugs (Nuedexta and Wellbutrin) contain a section 9 ("Drug Abuse and Dependence"), AXS-05 should also contain a section 9. However, section 9 of the Nuedexta label does not adequately describe the abuse-related risks of DXM and should be revised. In addition, the results of self-administration studies with bupropion are included in the Wellbutrin label, but do not appear in the proposed AXS-05 labeling.

II. DISCUSSION

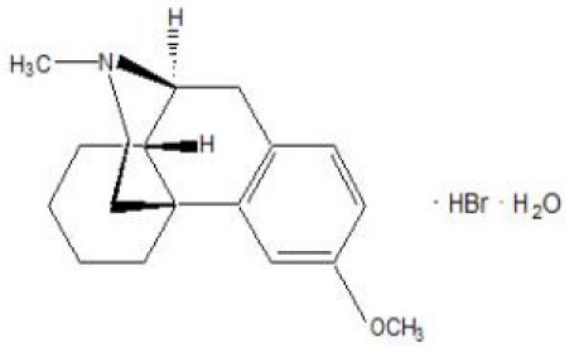
1. Chemistry

According to the Sponsor, AXS-05 is an oral, fixed dose combination of dextromethorphan hydrobromide and bupropion hydrochloride. The drug is formulated into round film-coated bilayer tablets. The bupropion component is formulated for extended release while the DXM component is formulated for immediate release.

The molecular formula of dextromethorphan is $C_{18}H_{25}NO \cdot HBr \cdot H_2O$ and it has a molecular weight of 370.3 g/mol. The CAS number for dextromethorphan is 6700-34-1 and the chemical names are:

- Ent-3-Methoxy-9a-methylmorphinan hydrobromide monohydrate
- 3-Methoxy-17-methyl-9α, 13α, 14α-morphinan hydrobromide monohydrate and
- (+)-3-Methoxy-9a-methylmorphinan hydrobromide monohydrate

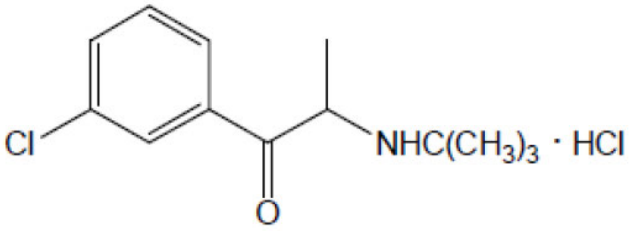
The structure of dextromethorphan appears below:



The molecular formula of bupropion hydrochloride is $C_{13}H_{18}ClNO$ HCl and it has a molecular weight of 276.21 g/mol. The CAS number of bupropion is 31677-93-7 and the chemical names are:

- 1-(3-Chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride
- (±)-2-(*tert*-Butylamine)-3'-chloropropionphenone hydrochloride
- m-chloro-α-(*tert*-butylamino)propiophenone hydrochloride
- Amfebutamone hydrochloride

The structure of bupropion appears below:



2.2 Safety Pharmacology/Metabolites

The Sponsor states DXM produces the metabolites dextrorphan (DXO) and dextrorphan-O-glucuronide. The published literature mentions three major metabolites: DXO, 3-hydroxymorphinan, and 3-methoxymorphinan (Barnhart, 1980). The metabolites of DXM are significant, notably, DXO (see section 2.4 below).

2.4 Animal Behavioral Studies

Both DXO and DXM are self-administered in PCP-trained monkeys (Nicholson et al., 1999; Young et al., 1981) and each substitute for PCP in PCP-trained rodents in drug discrimination studies. Similarly, PCP was able to completely substitute for DXM in DXM-trained rats (Holtzman, 1994). However, some human studies suggest that the subjective effects of DXM and DXO differ (Zawertailo et al., 1998; Zawertailo et al., 2010). These data suggest that DXM and PCP produce similar subjective effects a finding consistent with DXM's NMDA antagonist properties.

3. Clinical Pharmacology

According to the Sponsor, dextromethorphan is an uncompetitive antagonist of the NMDA receptor (an ionotropic glutamate receptor), and a sigma-1 receptor agonist (Nuedexta® product label). Blockade of

the NMDA receptor and agonism of the sigma-1 receptor modulate glutamate signaling in the central nervous system. Bupropion is a norepinephrine and dopamine reuptake inhibitor and its ability to inhibit CYP2D6 prevents the metabolism of DXM and enhances its pharmacological effects.

The Sponsor states that the pharmacokinetics of AXS-05 have been evaluated in 11 clinical pharmacology studies, including single- and multiple-dose PK, drug interaction, renal and hepatic impairment, CYP2D6 metabolizer status, thorough QT (TQT), and food effect studies. In addition, PK data were collected from MDD subjects treated with AXS-05 as part of efficacy and safety trials.

Only one study compared AXS-05 to dextromethorphan given alone (AXS-05-101). This was a phase 1 study with the goal of examining the pharmacokinetics of DXM when DXM was administered with bupropion. A total of 32 healthy, adult non-smokers were included in four treatment groups, with eight subjects (n=8) in each group. The treatment groups were as follows:

> **Treatment A:** 1 x 150 mg Zyban bupropion sustained-release (SR) tablet once daily (QD) Days 1-3 and twice daily (BID) Days 4-8 co-administered with 1 x 30 mg Stopex DM tablet, BID, Days 1-8.
> **Treatment B:** 1 x 150 mg Zyban bupropion sustained-release (SR) tablet once daily (QD) Days 1-3 and twice daily (BID) Days 4-8 co-administered with 1 x 30 mg and 1 x 15 mg Stopex DM tablets, BID, Days 1-8.
> **Treatment C:** 1 x 150 mg Zyban bupropion sustained-release (SR) tablet once daily (QD) Days 1-3 and twice daily (BID) Days 4-8 co-administered with 2 x 30 mg Stopex DM tablets, BID, Days 1-8.
> **Treatment D:** 2 x 30 mg Stopex DM tablets, BID, Days 1-8.

Repeated blood samples were collected following dosing and a variety of PK parameters were assessed. On day 1 of dosing, 60 mg of oral DXM resulted in peak DXM plasma levels (i.e., Cmax) of 2971.71 pg/mL. By way of contrast, when 60 mg of DXM was administered in combination with 150 mg of bupropion, the Cmax was 8698.31, almost three times higher than 60 mg of DXM alone. The AUC increased as well, from approximately 20063 pg*hr/mL following 60 mg of DXM to 56535 following the combination of 150 mg bupropion + 60 mg DXM. After eight days of dosing, the bupropion induced increases in DXM were more pronounced. DXM Cmax values were increased ~ 42-fold when comparing 60 mg of DXM alone to 150 mg bupropion + 60 mg DXM. AUC values were increased more than 100-fold, from 38661 pg*hr/mL following 60 mg of DXM alone to 3960124 pg*hr/mL following the combination of 150 mg bupropion + 60 mg DXM.

The Sponsor states they are utilizing the existing clinical pharmacology data from the label of Wellbutrin SR to support the NDA filing, and that reliance on Nuedexta (DXM and quinidine) is not necessary. Table 1 demonstrates the pharmacokinetic bridge from the bupropion component of AXS-05 to Wellbutrin SR. The Sponsor notes both single-dose and steady state concentrations of bupropion are lower after the administration of AXS-05 relative to bupropion SR.

Table 2. Pharmacokinetic bridge from AXS-05 to commercial bupropion. Data show PK values for bupropion. Taken from Table 2 of the Sponsor's clinical pharmacology summary.

	Mean (SD)		
	AXS-05[c] (45 mg dextromethorphan-105 mg bupropion)	AXS-05[b] (45 mg dextromethorphan + 150 mg bupropion)	Bupropion[b] (150 mg)
Single Dose			
AUC_{0-12} (ng*hr/mL)	406.44 (146.70)	470.87 (79.40)	490.41 (152.95)
C_{max} (ng/mL)	70.16 (36.17)	84.75 (24.35)	75.22 (21.28)
Steady State[a]			
AUC_{0-12} (ng*hr/mL)	600.31 (211.79)	699.55 (150.45)	798.75 (292.49)
C_{max} (ng/mL)	75.92 (28.12)	92.26 (23.84)	103.38 (33.26)

[a] Steady state was Day 8 for bupropion 150 mg and Day 10 for AXS-05 (45 mg-105 mg).
[b] From Study AXS-05-102, bupropion 150 mg given as Zyban®.
[c] From Study AXS-05-103
Source: Study AXS-05 103 Table 11.4.2.3-9; Study AXS-05-103 Table 11.4.2.3-10; Study AXS-05-102 Table 11.4.2.3-5; Study AXS-05-102 Table 11.4.2.3-6

From a CSS perspective the increase in DXM exposure is of particular interest. As an NMDA receptor antagonist, DXM has been associated with recreational use for its ability to produce hallucinations. Based on the single dose data presented above, bupropion increased the DXM Cmax values approximately 3-fold. Thus, it appears that AXS-05 produces DXM Cmax values roughly equivalent to 180 mg DXM. Assuming linear pharmacokinetic effects, two capsules of AXS-05 may be equivalent to ~ 360 mg DXM, a dose that was found to produce substantial drug effects (Reissig et al., 2012).

4.1 Human Abuse Potential Studies

The Sponsor did not perform a human abuse potential (HAP) study or conduct dedicated abuse potential studies (i.e., self-administration or drug discrimination studies).

However, the Sponsor assessed abuse-related treatment emergent adverse events (TEAEs) from the integrated safety data set (n=1114). The Sponsor states that overall rates of abuse-related TEAEs was low, and only dizziness (13.8%) and somnolence (4.4.%) were experienced by greater than 1% of subjects (see section 4.2).

4.2 Adverse Event Profile Through all Phases of Development

No Phase 1 studies were placebo controlled, and only one examined DXM administered alone (study AXS-05-101).

Study AXS-05-101 was an open-label, parallel group study with 29 (n=29) completers. The study examined DXM alone (60 mg), and 150 mg bupropion in combination with 30, 45, and 60 mg of DXM.

According to the Sponsor, a total of 141 TEAEs were reported by 23 of the 32 subjects who received at least one dose of the study medication. "Disturbance in Attention" was reported by 12.5% of subjects (n=1) in the low dose DXM arms (i.e., 30 and 45 mg DXM + 150 bupropion) and by 25% (n=2) of subjects at the highest dose of DXM (i.e., 60 mg DXM + 150 mg bupropion). Dizziness and somnolence were also reported.

Abuse-related AEs from study AXS-05-101				
Adverse Event PT	**Bupropion 150 mg + DXM 30 mg (N=8)**	**Bupropion 150 mg + DXM 45 mg (N=8)**	**Bupropion 150 mg + DXM 60 mg (N=8)**	**DXM 60 mg (N= 8)**
Disturbance in attention	1 (12.5%)	1 (12.5%)	2 (50%)	0
Dizziness	3 (37.5%)	4 (50.0%)	4 (50.0%)	0
Somnolence	1 (12.5%)	1 (12.5%)	0	0

Study AXS-05-102 was a single-center, randomized, multiple-dose, open-label, parallel-group study examining the following treatments:

- Bupropion 100 mg + DXM 30 mg
- Bupropion 75 mg + DXM 45 mg
- Bupropion 100 mg + DXM 45 mg
- Bupropion 150 mg + DXM 45 mg
- Bupropion 150 mg

35 subjects completed the study (n=35). A total of 160 TEAEs were reported by 30 of the 40 subjects who received at least one dose of the study medication. The only abuse-related AE reported by subjects was "dizziness" which was not reported by any subjects in the bupropion only group and reported by 12.5% - 50% of subjects receiving the combination of bupropion and DXM.

Adverse Event PT	**Bupropion 100 mg + DXM 30 mg (N=8)**	**Bupropion 75 mg + DXM 45 mg (N=8)**	**Bupropion 100 mg + DXM 45 mg (N=8)**	**Bupropion 150 mg + DXM 45 mg (N=8)**	**Bupropion 150 mg (N=8)**
Dizziness	3 (37.5%)	4 (50%)	1 (12.5%)	4 (50%)	0

Study AXS-05-103 was a single-center, randomized, multiple-dose, double-blind, parallel-group study. AXS-05 (105 mg bupropion and DXM 45 mg) and bupropion (150 mg) were administered to thirty (n=30) healthy subjects. According to the Sponsor, a total of 93 TEAEs were reported by 19 of the 30 subjects who received at least one dose of the study medication. "Dizziness" was reported by 6 (n=6) subjects, and two (13.3%) were in the AXS-05 group. No other abuse-related AEs were observed.

Study AXS-05-104 was an open-label, parallel-group, multiple-dose study in subjects with moderate renal impairment. An oral tablet of AXS-05 (105 mg bupropion and 45 mg DXM) was administered after an overnight fast with no comparator. Thirteen (n=13) subjects completed the study and a total of five TEAES were reported by four (30.8%) subjects with moderate renal impairment. None of the AEs were abuse-related and included diarrhea, flatulence, and orthostatic hypotension.

Study AXS-05-105 was open-label, 2-part, parallel-group, multiple-dose study to examine the PK of AXS-05 in hepatically impaired subjects. AXS-05 (105 mg bupropion and 45 mg DXM) was administered to eight subjects with moderate hepatic impairment, and seven healthy controls for a total of 15 subjects (N=15). No drug comparator was included in the study. A total of 11 TEAEs were reported by 5 (33.3%) of the 15 subjects who received at least one dose of the study medication. "Dizziness" was reported by one subject (14.3%). No other abuse-related AEs were observed.

Study AXS-05-106 was a randomized, open-label, parallel-group, multiple-dose study. The goal was to examine the PK of AXS-05 in CYP2D6 poor metabolizers and examine the PK of lower dose and alternative AXS-05 formulations. Forty-three (n=43) subjects completed the study across five cohorts that received the following treatments:

- Cohort 1: 210 mg bupropion and 90 mg DXM
- Cohort 2: 210 mg bupropion and 90 mg DXM
- Cohort 3: 105 mg bupropion and 30 mg DXM
- Cohort 4: 105 mg bupropion and 45 mg DXM
- Cohort 5: 105 mg bupropion and 45 mg DXM

Cohort 5 consisted of subjects identified as poor metabolizers. Each subject in each cohort received AXS-05 for eight days. The Sponsor notes gastrointestinal disorders and nervous system disorders were the most common SOCs. Euphoria was not observed in any subject. There was no placebo comparator. As seen below, dizziness was the most common abuse-related AE, followed by somnolence and feeling drunk.

Abuse-related AEs from study AXS-05-106					
Adverse Event PT	**Cohort 1**	**Cohort 2**	**Cohort 3**	**Cohort 4**	**Cohort 5**
Dizziness	2 (16.7%)	2 (18.2%)	2 (16.7%)	3 (27.3%)	2 (66.7%)
Somnolence	3 (25.0%)	0	1 (8.3%)	3 (27.3%)	2 (66.7%)
Feeling drunk	1 (8.3%)	0	0	1(9.1%)	0

Study AXS-05-107 was a randomized, open-label, 2-treatment (fed vs. fasted), 2-period, 2-way crossover, single-dose study to examine food effects of AXS-05 bioavailability. 105 mg bupropion and 45 mg DXM were administered to 12 healthy subjects that completed the study (n=12). Each dose of AXS-05 was separated by eight days. The fasted state was defined as 10 hrs without food and the fed state was dosing after an 800-1000 calorie meal. According to the Sponsor, three TEAEs were reported by a single subject. None of the TEAEs were abuse-related and included ear discomfort and two reports of nausea.

Study AXS-05-108 was a randomized, open-label, parallel-group study in healthy subjects. This was a drug-drug interaction (DDI) study to examine the PK effects of paroxetine on AXS-05. Twenty six (n=26) healthy subjects completed the study. Subjects received AXS-05 (105 mg bupropion and 45 mg DXM), AXS-05 in combination with 20 mg paroxetine, or paroxetine alone (20 mg). According to the Sponsor, A total of 46 TEAEs were reported by 21 of the 29 subjects who received at least one dose of

the study medication. The only abuse-related TEAE reported was "dizziness," which was reported by 1 subject in the AXS-05 alone group (7.1%), one subject in the paroxetine alone group (6.7%) and three subjects in the AXS-05 + paroxetine group (11.1%).

Study AXS-05-109 was a randomized, double-blind and open-label, 3-period, 6-way cross-over study. The study compared AXS-05 (105 mg bupropion and 45 mg DXM) to moxifloxacin (MOX, 400 mg) and placebo. The purpose of the study was to evaluate the effects of AXS-05 on the QT/QTc interval in healthy subjects. A total of 37 subjects (n=37) completed the study. The Sponsor describes the dosing sequences as follows:

> "Within each sequence, subjects participated in 3 Periods, AXS-05, Placebo and Moxifloxacin. In order to test both a therapeutic dose and supratherapeutic dose of AXS-05, the dose of AXS-05 was increased during the AXS-05 and Placebo Periods. On the 6th dosing day within each Period (once sufficient inhibition of CYP2D6 has occurred, thus increasing dextromethorphan concentrations to therapeutic levels), the subject received a single AM dose of AXS-05 or placebo and underwent continuous ECG evaluation and PK sampling."

Drugs were administered after an overnight fast. According to the Sponsor, a total of 150 TEAEs were reported by 32 of the 42 subjects who received at least one dose of any study drug or placebo. "Dizziness" was the only abuse-related AE experienced and was reported by 5 (11.9%) subjects who received AXS-05 (therapeutic dose), 6 (15.4%) subjects who received AXS-05 (supratherapeutic dose), 1 (2.6%) subject who received moxifloxacin, and 1 (2.6%) subject who received placebo. Though not considered an abuse-related AE, 3 subjects (7.1%) receiving the therapeutic dose of AXS_05 and 2 (5.15) of subjects receiving the supratherapeutic dose of AXS-05 experienced "vision blurred." Though speculative, this AE may represent the hallucinogenic like effects of DXM at high doses.

Study AXS-05-110 was a randomized, open-label, 2-period, 2-way cross-over study. The study was a drug-drug interaction (DDI) study to examine the effects of clopidogrel (a CYP 2B6 inhibitor) on the PK of AXS-05. In this study the effects of AXS-05 (105 mg bupropion + 45 mg DXM) were compared against the effects of AXS-05 + clopidogrel (75 mg). Doses were administered after an overnight fast and 20 (n=20) subjects completed the study. According to the Sponsor A total of 22 TEAEs were reported by 8 of the 23 subjects who received at least one dose of the study medication (safety population). Headache and insomnia were the only TEAEs reported. No abuse-related AEs occurred.

Study AXS-05-111 was an Open-label, single-arm study. The study was a drug-drug interaction (DDI) study to examine the effects of carbamazepine (a CYP 2B6 inhibitor) on the PK of AXS-05. In this study the effects of AXS-05 (105 mg bupropion + 45 mg DXM) + carbamazepine (200 mg) were compared against the effects of carbamazepine alone. Doses were administered after an overnight fast and 24 (n=20) subjects completed the study. According to the Sponsor A total of 35 TEAEs were reported by 15 of the 24 subjects who received at least one dose of the study medication (safety population). Two subjects (8.3%) in the AXS-05 alone group experienced dizziness. Two subjects (8.7%) in the carbamazepine alone group experienced somnolence. No other abuse-related AEs were observed.

Phase 2 and 3 studies were pooled and assessed for abuse-related AEs. Analysis of abuse-related TEAEs is was summarized by the Sponsor in Table 83 of the integrated safety of summary and appears below. Similar to the AE profile observed in Phase 1 studies, a small number of reports of "euphoric mood" were observed, suggesting minimal abuse liability.

Table 83: Assessment of Abuse-Related Treatment-Emergent Adverse Events by Term Category and Preferred Term (Safety Population)

Term Category Preferred Term	No. of Subjects (%)	
	AXS-05 Overall (N=1114)	Placebo (N=164)
Euphoria-related terms		
Dizziness	154 (13.8)	10 (6.1)
Feeling abnormal	11 (1.0)	1 (0.6)
Euphoric mood	4 (0.4)	0
Hallucination, visual	3 (0.3)	0
Thinking abnormal	1 (0.1)	0
Feeling drunk	0	0
Feeling of relaxation	0	0
Inappropriate affect	0	0
Terms indicative of impaired attention, cognition, and mood		
Somnolence	49 (4.4)	5 (3.0)
Memory impairment	6 (0.5)	0
Mental impairment	2 (0.2)	1 (0.5)
Mood swings	1 (0.1)	0
Dissociative / psychotic terms		
Confusional state	4 (0.4)	0
Disorientation	3 (0.3)	0
Autoscopy	2 (0.2)	0
Anger	1 (0.1)	0
Aggression	0	0
Psychotic disorder	0	0
Related terms not captured elsewhere		
Drug tolerance	0	0
Habituation	0	0
Drug withdrawal	0	0
Substance-related disorders	0	0

No.=number; TEAE=treatment-emergent adverse event. Source: ISS Table 4.1.1

4.5 Tolerance and Physical Dependence Studies in Humans

Dissociative symptoms were assessed prospectively in study AXS-05-301 (STRIDE) using the Brief Psychiatric Rating Scale (BPRS) Factor 1 items that measure reality distortion. The Sponsor asserts there was no evidence of dissociation when comparing AXS-05 to bupropion. There was no comparison to placebo, as the study was not placebo-controlled. The study was a randomized, double-blind, active controlled trial to assess the efficacy and safety of AXS-05 (45 mg DXM and 105 mg bupropion) administered orally to subjects with treatment resistant major depressive disorder. The study was 12 weeks in duration and consisted of a six week, open-label run in period (period 1) followed by a six week double blind period (period 2). A total of n=309 subjects were included in the modified intent to treat population. The BPRS was assessed at screening, then again at day 42 when subjects began treatment with AXS-05 (week 6, day of randomization) and then at weeks 7, 8, 10 and 12.

At the request of CSS, withdrawal was assessed in study AXS-05-MDD-301 (GEMINI). This was a phase 3 safety and efficacy study to assess the efficacy of AXS-05 in the treatment of MDD. In this six week trial, subjects received either AXS-05 (105 mg bupropion + 45 mg DXM), or placebo. At the end of the trial when subjects discontinued treatment, the Physicians Withdrawal Criteria (PWC-20) was administered to assess withdrawal symptoms. According to the Sponsor, The 20-item Physician Withdrawal Criteria (PWC-20) was conducted at Visit 9/Day 49 during the 1-week follow-up call to identify symptoms indicative of withdrawal. With the exception of nausea/vomiting and dizziness/lightheadedness, similar proportions of subjects in the AXS-05 and placebo groups reported symptoms. It's notable, however, that the PWC-20 was conducted after subjects had been "off drug" for seven days. Thus, withdrawal symptoms may have subsided by then, thought the questionnaire was retrospective.

5. Regulatory Issues and Assessment

The Sponsor has proposed a Section 9 ("Drug Abuse and Dependence") based on the RLD labels. Because the RLD drugs contain a section 9, this section will be necessary to include if AXS-05 is approved. However, this section will require substantial revision if approved.

Specifically, the proposed section 9 of the label appears below:

> 9. DRUG ABUSE AND DEPENDENCE
>
> 9.1. Controlled Substance
>
> PROPRIETARY NAME (b) (4)
>
> 9.2. Abuse
>
> While clinical (b) (4) with PROPRIETARY NAME did not reveal drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this experience the extent to which PROPRIETARY NAME will be misused, diverted, and/or abused once marketed. Therefore, patients with a history of drug abuse should be observed closely for signs of misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).
>
> Dextromethorphan

Dextromethorphan (b) (4) has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. However, cases of dextromethorphan abuse have been reported, predominantly in adolescents.

Bupropion
Controlled clinical trials conducted in normal volunteers, in subjects with a history of multiple drug abuse, and in depressed subjects showed some increase in motor activity and agitation/excitement, often typical of central stimulant activity.

In a population of individuals experienced with drugs of abuse, a single oral dose of 400 mg of bupropion produced mild amphetamine-like activity as compared with placebo on the Morphine-Benzedrine Subscale of the Addiction Research Center Inventories (ARCI) and a score (b) (4) (b) (4) on the Liking Scale of the ARCI. These scales measure general feelings of euphoria and drug liking which are often associated with abuse potential

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Division of Pediatric and Maternal Health Review

Date: 7/16/2021 **Date consulted:** 3/4/2021

From: Niquiche Guity, Ph.D, Clinical Analyst, Maternal Health
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Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
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Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Psychiatry (DP)

Drug: AXS-05 (45mg dextromethorphan hydrobromide & 105 mg bupropion Hydrochloride) tablet

NDA: 215430

Applicant: Axsome Therapeutics

Subject: Pregnancy and Lactation Labeling

Indication: Treatment of major depressive disorder (MDD)

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 215430
- DPMH Review of WELLBUTRIN (bupropion) NDA 18644, Leyla Sahin, M.D., Medical Officer, July 16, 2013. DARRTS Reference ID# 3342043.

- DPMH Review of WELLBUTRIN (bupropion), WELLBUTRIN SR (bupropion) NDA 18644 and 20358, Catherine Roca, M.D., Medical Officer, April 20, 2018. DARRTS Reference ID# 4251915.
- DPMH Review of CONTRAVE (8 mg naltrexone HCl and 90 mg bupropion HCl) extended-release tablets, NDA 200063, Carrie Ceresa, Pharm D., MPH, June 23, 2020. DARRTS Reference ID# 4629472.
- Pregnancy and Lactation Labeling Rule (PLLR) Review memo of Nuedexta (Dextromethorphan/Quinidine) NDA 021879/S14, Sally Yasuda, M.D., Division of Neurology I (DN1), May 22, 2019. DARRTS Reference ID# 4437400

Consult Question: Review section 8 of PI

INTRODUCTION AND BACKGROUND

On February 22, 2021, the applicant (Axsome Therapeutics) submitted a 505(b)(2) New Drug Application (NDA) for AXS-05 (dextromethorphan hydrobromide & bupropion hydrochloride) for the treatment of major depressive disorder (MDD). The Division of Psychiatry (DP) consulted the Division of Pediatric and Maternal Health (DPMH) on March 4, 2021, to assist with the Pregnancy and Lactation subsections of labeling.

Regulatory History

- This 505(b)(2) NDA application is relying on the safety and efficacy of two Reference Listed Drugs, Nuedexta (Dextromethorphan hydrobromide/Quinidine sulfate Capsules, NDA 021879, Avanir Pharmaceuticals, Inc), and Wellbutrin SR (Bupropion hydrochloride Sustained-Release Tablets, NDA 020358, GlaxoSmithKline).
    - Nuedexta (Dextromethorphan hydrobromide 20 mg/quinidine sulfate 10 mg), NDA 021879 was approved on October 29, 2010, and is currently approved for the treatment of pseudobulbar affect (PBA).
    - Wellbutrin SR (Bupropion hydrochloride Sustained-Release Tablets), NDA 020358 was approved on October 4, 1996 and is currently approved for the treatment of major depressive disorder (MDD).
- AXS-05 was granted Breakthrough Therapy Designation on March 25, 2019 based on the positive topline results from Study AXS-05-MDD-201 which demonstrated a significant reduction in depressive symptoms versus the active comparator bupropion.

Table 1: Drug Characteristics[1,2]

Drug class	Dextromethorphan: • uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist • sigma-1 receptor agonist Bupropion: • aminoketone

[1] WELLBUTRIN SR (bupropion hydrochloride) sustained-release tablets, approved labeling, Drugs@FDA, accessed 3/31/2020

[2] NUEDEXTA (dextromethorphan hydrobromide and quinidine sulfate) capsules, approved labeling, Drugs@FDA, accessed 3/31/2020

	• Bupropion is metabolized to three metabolites: hydroxybupropion (OHBUP), erthrohydroxybupropion and threohydrobupropion (TB).
Mechanism of action	Dextromethorphan: • is an uncompetitive antagonist of the NMDA receptor, an ionotropic glutamate receptor, and a sigma-1 receptor agonist. Bupropion: • is an aminoketone and a CYP2D6 inhibitor.
Molecular weight	Dextromethorphan: 370.33 Daltons Bupropion: 276.2 Daltons
Half-life	Dextromethorphan: 22 hours Bupropion: 21 (±9) hours after chronic dosing
Plasma protein binding	Dextromethorphan: 60-70% protein bound Bupropion: 84% bound to plasma proteins

AXS-05 Dosage and Adverse Reactions:

Dose and administration:

- Starting dose: one tablet daily by mouth for 3 days.
- After 3 days, one tablet twice daily, separated by at least 8 hours.
- Renal impairment: One tablet by mouth once daily in the morning.
- Concomitant use of CYP2D6 inhibitors: One tablet by mouth once daily in the morning
- CYP2D6 poor metabolizers: One tablet by mouth once daily in the morning

Common adverse reactions:

Dizziness, nausea, headache, dry mouth, somnolence, diarrhea, decreased appetite, anxiety, insomnia and constipation.

Current State of the Labeling

For the relied upon drugs WELLBUTRIN SR (bupropion hydrochloride) and NUEDEXTA (dextromethorphan hydrobromide and quinidine sulfate), the current labelings are in the Physician Labeling Rule/ Pregnancy and Lactation Labeling Rule (PLLR) format.

- WELLBUTRIN SR and NUEDEXTA
  - There is not a boxed warning on embryofetal toxicity.
  - There is no contraindication for pregnancy or lactation.
  - There are no existing pregnancy testing/contraception recommendations
  - There are no listed drug interactions with hormonal contraceptives.
- NUEDEXTA
  - Highlights section under "Use in Specific Populations", states *"Pregnancy: Based on animal data, may cause fetal harm."*
  - Nonclinical data is provided for NUEDEXTA, developmental toxicity was seen in rats and rabbits including embryolethality (rats) and teratogenicity (rabbits).
  - Not known whether dextromethorphan is excreted in human milk.
- WELLBUTRIN SR
  - Pregnancy exposure registry for antidepressants.

- Data from epidemiological studies of pregnant women exposed to bupropion in the first trimester have not identified an increased risk of congenital malformations overall.
- Embryofetal toxicity studies did not show any evidence of fetal malformations in rats at highest dose (11 times the maximum recommended human dose (MRHD)), however non-dose–related increases in incidence of fetal malformations, and skeletal variations were observed in rabbits at doses approximately equal to the MRHD and greater. Decreased fetal weights in rabbits were seen at doses twice the MRHD and greater.
- Bupropion and its active metabolites are present in human milk. Postmarket reports have described seizures in breastfed infants. The relationship of bupropion exposure and these seizures is unclear.

REVIEW

PREGNANCY

Major Depressive Disorder (MDD) and Pregnancy[3]

- MDD is diagnosed in patients who have suffered at least one major depressive episode and have no history of mania or hypomania[4]. An episode is a period lasting at least two weeks, with five or more of the following nine symptoms: depressed mood, loss of interest or pleasure in most or all activities, insomnia or hypersomnia, change in appetite or weight, psychomotor retardation or agitation, low energy, poor concentration, guilt or thoughts of worthlessness, and recurrent thoughts about death or suicide.
- MDD is common in pregnant women and is often not treated. It affects up to 10% of pregnant women, with higher rates in low- and middle-income countries. Of the 10%, only 20% of pregnant women with depression receive adequate treatment[5].
- Untreated depression causes maternal suffering and is associated with poor nutrition, comorbid substance use disorders, poor adherence with prenatal care, postpartum depression, impaired relationships between the mother and her infant and other family members, and an increased risk of suicide.[6] A recent meta-analysis (n=25,663) concluded that untreated depression among pregnant women resulted in preterm birth (odds ratio [OR], 1.56; 95% CI, 1.25-1.94; 14 studies; I2, 39%) and low birth weight (OR, 1.96; 95% CI, 1.24-3.10; 8 studies; I2, 48%).[7]
- Treatment:
  - Antidepressant medication (e.g. selective serotonin reuptake inhibitors (SSRIs)) is recommended as initial treatment. SSRIs have been used and studied more often in

[3] https://www.uptodate.com/contents/severe-antenatal-unipolar-major-depression-choosing-treatment?topicRef=1725&source=see_link

[4] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), American Psychiatric Association, Arlington, VA 2013.

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depressed, pregnant patients than other types of antidepressants and are not associated with specific patterns of birth defects.

- For refractory patients, serotonin-norepinephrine reuptake inhibitors (SNRI) (e.g. venlafaxine, duloxetine) are recommended. SNRI's are the second most frequently prescribed antidepressants in pregnant women.
- Psychotherapy is nearly always indicated as an adjuvant to pharmacotherapy, unless symptoms render the patient incapable of participating.

Nonclinical Experience

The Applicant performed embryo-toxicity studies for the combination of bupropion hydrochloride and dextromethorphan hydrobromide (BUP/DM) using the mouse model. BUP/DM was administered by oral gavage in doses of 57/26, 75/34, or 150/68 mg/kg once daily from GD 6 to 15. Treatment with (BUP/DM) at doses up to 150/68 mg/kg had no effect on body weights, body weight changes, food consumption, gross pathology findings, uterine data, fetal weights, or fetal examination data. Maternal toxicity including mortality and/or neurological signs were observed in two dams administered (BUP/DM) at 150/68 mg/kg/day and in two dams at 75/34 mg/kg/day. Mortality occurred on GD 8 in three dams (two at 75/34 mg/kg/day and one at 150/68 mg/kg/day) and a single dam (150/68 mg/kg/day) exhibited neurological signs such as ataxic, slightly languid, and exhibited minimal convulsions on GD 10.

This mouse study was based on the recommendation of the combination guidance to conduct the study in one of the most relevant species as a bridging study for the effect of the combination on the fetus. However, per DP Nonclinical reviewers, the mouse model should not have been used to conduct the embryo-toxicity studies. The most relevant species for the combination effect of bupropion and dextromethorphan appears to be the rabbit, as reproduction toxicity studies in the rabbit conducted separately for bupropion and dextromethorphan/quinidine demonstrated fetal malformations. Further, the embryofetotoxicity findings of the dextromethorphan/quinidine animal reproduction toxicity study are confounded by the effect of quinidine on the offspring, such that the separate dextromethorphan effect cannot be determined.

A reproduction toxicity study in rabbit would better inform the combination effect of bupropion and dextromethorphan for the AXS-05 labeling. Non-clinical will request the embryo-toxicity studies with the rabbit model.

For further details, refer to the Pharmacology/Toxicology review by Arippa (Ravi) Ravindran, PhD, and Ikram Elayan, PhD.

Review of Pharmacovigilance Database

Seven subjects became pregnant while taking AXS-05 during clinical trials. Upon identification of pregnancy, subjects were discontinued from the study drug. Three pregnancies resulted in full-term deliveries of healthy infants (2 vaginal, 1 Cesarean). One pregnancy is ongoing with no complications to date, and the outcomes of three pregnancies are unknown (2 lost to follow-up, 1 withdrawal of consent).

Review of Literature

DPMH has previously reviewed published literature regarding bupropion use during pregnancy in 2013[8] and 2018[9]. In 2018 review, DPMH concluded that data from published sources and the applicant's database have not definitively demonstrated an association of bupropion and major congenital malformations. The 2018 review also covered the final bupropion pregnancy registry study and concluded that there was no increase in birth defects with use of bupropion during the first trimester. In 2019, DN1[10]conducted a literature review to update Nuedexta's (Dextromethorphan/Quinidine) labeling sections that address the Pregnancy and Lactation Labeling Rule (PLLR) and did not find an association or increased risk of congenital defects[11,12]. DN1 concluded that the available data regarding the effects of dextromethorphan or quinidine separately were not sufficient to inform guidance on usage during pregnancy.

Applicant's Review of the literature

As the Agency has previously reviewed these drug components' effects on pregnancy, lactation, and fertility[13], the sponsor was asked to provide an update on any new data from publications from 2018 to present.

The applicant performed a search of the literature using EMBASE using the following search string:

('amfebutamone'/exp OR 'amfebutamone' OR 'bupropion' OR 'bupropion'/exp OR bupropion OR 'dextromethorphan'/exp OR 'dextromethorphan' OR 'axs 05' OR 'wellbutrin' OR 'wellbutrin'/exp OR wellbutrin OR 'zyban' OR 'zyban'/exp OR zyban OR 'aplenzin' OR 'aplenzin'/exp OR aplenzin) AND ('pregnant woman'/exp OR 'pregnant woman' OR 'pregnancy'/exp OR 'pregnancy' OR 'pregnancy outcome'/exp OR 'pregnancy outcome' OR 'pregnancy complication'/exp OR 'pregnancy complication' OR 'pregnancy disorder'/exp OR 'pregnancy disorder' OR 'lactating women' OR 'lactation'/exp OR 'lactation' OR 'lactation exposure' OR 'feeding'/exp OR 'feeding' OR 'breastfeeding'/exp OR 'breastfeeding' OR (('milk human'/exp OR 'milk human') AND ('secretion'/exp OR 'secretion')) OR 'fertility'/exp OR 'fertility' OR 'reproduction'/exp OR 'reproduction' OR 'congenital disorder'/exp OR 'congenital disorder') AND ([humans]/lim OR [clinical study]/lim) AND [1-7-2018]/sd NOT [19-3-2021]/sd

This search string yielded 294 articles. Of those, seven articles regarding the use of bupropion in pregnancy were identified as relevant. No new articles regarding the use of dextromethorphan in pregnancy were identified as relevant during the 2018-2021 timeframe. However, the Applicant summarized the 2001 publication by Einarson et al. within their annotated labeling document regarding the use of dextromethorphan in pregnancy. The Einarson et al. paper concluded that

[8] DPMH Review of WELLBUTRIN (bupropion) NDA 18644, Leyla Sahin, M.D., Medical Officer, July 16, 2013. DARRTS Reference ID# 3342043.

[9] DPMH Review of WELLBUTRIN (bupropion), WELLBUTRIN SR (bupropion) NDA 18644 and 20358, Catherine Roca, M.D., Medical Officer, April 20, 2018. DARRTS Reference ID# 4251915.

[10] Pregnancy and Lactation Labeling Rule (PLLR) Review memo of Nuedexta (Dextromethorphan/Quinidine) NDA 021879/S14, Sally Yasuda, M.D., Division of Neurology I, May 22, 2019. DARRTS Reference ID# 4437400

[11] Einarson A, Lyszkiewicz, Koren G. The safety of dextromethorphan in pregnancy: a prospective controlled study. Chest 2001;119:466-9.

[12] Martinez-Frias M-L, Rodriques-Pinilla E: Epidemiologic analysis of prenatal exposure to cough medicines containing dextromethorphan: no evidence of human teratogenicity. Teratology63:38-41, 2001.

[13] See "Materials Reviewed" section above for more details

dextromethorphan use during pregnancy did not increase the rates of major malformations above the expected baseline rates of 1% to 3%.

The bupropion search identified included two meta-analyses of previously published literature, two population-based cohort studies, and one case-control study, which are presented in Tables 1 to 3 (Appendix A, pages 24–27). Additionally, two individual case reports of bupropion and polypharmacy during pregnancy are described separately in Table 4 (Appendix A, pages 28).

The most relevant literature finding is the final analysis of the National Birth Defects Prevention Study (NBDPS; Anderson et al., 2020[14]) (Appendix A, Tables 2–3, pages 25–27for which interim results are described in the current bupropion product labeling (Wellbutrin SR, 2019). The NBDPS study was a population-based, multicenter, case-control study which included cases with selected birth defects and randomly sampled live-born infants without major birth defects. Mothers of cases and controls were interviewed after the expected delivery date and self-reported antidepressant exposure. A total of 30,630 case and 11,478 control mothers were included in the analysis.

Early pregnancy bupropion use (1st trimester) was reported by 149 case mothers (0.5%) and 45 control mothers (0.4%). All events were adjusted for maternal race/ethnicity, pre-pregnancy body mass index, education, and early pregnancy smoking and alcohol use. Meaningful associations were defined as an adjusted odds ratio (adjusted OR) of 2.0 or greater and a lower confidence interval bound of 0.8 or greater. In the final NBDPS analysis, elevated adjusted ORs for an association between bupropion and 3 birth defects were identified: diaphragmatic hernia (n=9; adjusted OR=2.77; 95% confidence interval [CI]: 1.34, 5.71), intestinal atresia/stenosis (n=4; adjusted OR=2.69; 95% CI: 0.96, 7.59), and hypoplastic left heart syndrome (n=5; adjusted OR=2.08; 95% CI: 0.82, 5.28) (Appendix A, Table 2 page 25 – 26). However, after accounting for underlying maternal conditions, bupropion was only associated with diaphragmatic hernia (n=9; adjusted OR=6.5; 95% CI, 1.85, 22.8) (Anderson et al., 2020[17]) (Appendix A, Table 3, pages 26-27).

These results build on the 2010 paper by Alwan et al. which reported on the interim analysis of the NBDPS (1997-2004) that included 64 case mothers and 26 control mothers exposed to bupropion in the 1st trimester of pregnancy. In the interim analysis, left ventricular outflow track obstruction (LVOTO) defects, including hypoplastic left heart and coarctation of aorta, was identified as having a positive association with bupropion (n=10; adjusted OR=2.6; 95%CI: 1.2, 5.7) (Alwan et al., 2010[15]). With the increased number of exposures in the final analysis, the adjusted OR was reduced to 1.59 (n=14; 95% CI: 0.87, 2.91) for any LVOTO defect. The interim results did not report on diaphragmatic hernia.

[14] Anderson KN, Lind JN, Simeone RM, et al. Maternal Use of Specific Antidepressant Medications During Early Pregnancy and the Risk of Selected Birth Defects. JAMA Psychiatry. 2020;77(12):1246-1255.
[15] Alwan S, Reefhuis J, Botto LD, et al. Maternal use of bupropion and risk for congenital heart defects. Am J Obstet Gynecol. 2010;203(1):52.

An additional recently published meta-analysis evaluated the association of congenital heart defects and antidepressant use during pregnancy (DeVries et al., 2021[16]). This study analyzed three published studies related to use of bupropion during pregnancy: the interim results from the NBDPS study (Alwan et al., 2010[16]), the Sloan Epidemiology Center's Birth Defects Study (BDS; Louik and Mitchell, 2014[17]) and a cohort study using data from the Medicaid Analytic eXtract (Huybrechts et al., 2014[18]). Two of these three studies are currently described in the bupropion product label (NBDPS and BDS). This analysis weighted each study based on the number of exposures: the Medicaid study (Huybrecht et al., 2014[19]) carried 73.6% weight, followed by the NBDPS interim analysis (14.5% weight) and the BDS (11.9% weight). The resulting odds ratio from the meta-analysis for all congenital heart defects following bupropion use during pregnancy (OR=1.23; 95% CI: 1.01,1.49) was similar to that observed in the NBDPS study (adjusted OR=1.24; 95% CI: 0.83, 1.84).

Two of the literature findings evaluated smoking cessation therapies during pregnancy. The results of a cohort study evaluating the use of smoking cessation pharmacotherapies during pregnancy did not identify any increased risk of perinatal events between bupropion-exposed and unexposed pregnant smokers (Tran et al., 2020[19]). A meta-analysis of 18 studies published between 1990 and May 25, 2017 (Turner et al., 2019[20]) similarly concluded that there was no strong evidence that either positive or negative outcomes were associated with gestational use of bupropion. While these studies support the safety of bupropion as a smoking cessation treatment during pregnancy, the alternative of continuing to smoke during pregnancy also carries a significant risk which puts limitations on the interpretability of the control mothers who smoked during pregnancy.

The final article (Patrick et al, 2021[21]) reported on a retrospective cohort study to develop and validate clinical risk prediction tools for neonatal abstinence syndrome (NAS). Data was collected on maternal medication use during the last 30 days of pregnancy and suggest a possible association of bupropion use with NAS.

The Applicant updated the labeling with the new findings identified by the literature search.

Reviewer comment:
Based upon the review of the literature, the information presented by the applicant appears to be sufficient. The literature search presented by the applicant has identified two potential safety

[16] De Vries C, Gadzhanova S, Sykes MJ, Ward M, Roughead E. A Systematic Review and Meta-Analysis Considering the Risk for Congenital Heart Defects of Antidepressant Classes and Individual Antidepressants. Drug Saf. 2021;44(3):291-312.
[17] Louik C, Kerr S, Mitchell AA. First-trimester exposure to bupropion and risk of cardiac malformations. Pharmacoepidemiol Drug Saf. 2014;23(10):1066-1075.
[18] Huybrechts KF, Palmsten K, Avorn J, et al. Antidepressant use in pregnancy and the risk of cardiac defects. N Engl J Med. 2014;370(25):2397-2407.
[19] Tran DT, Preen DB, Einarsdottir K, et al. Use of smoking cessation pharmacotherapies during pregnancy is not associated with increased risk of adverse pregnancy outcomes: a population-based cohort study. BMC Med. 2020;18(1):15. Published 2020 Feb 5.
[20] Turner E, Jones M, Vaz LR, Coleman T. Systematic Review and Meta-Analysis to Assess the Safety of Bupropion and Varenicline in Pregnancy. Nicotine Tob Res. 2019;21(8):1001-1010.
[21] Patrick SW, Slaughter JC, Harrell FE Jr, et al. Development and Validation of a Model to Predict Neonatal Abstinence Syndrome. J Pediatr. 2021;229:154-160.e6.

signals. One related to bupropion use and diaphragmatic hernia and the other related to the development of neonatal abstinence syndrome (NAS).

The Anderson et. al 2020 publication used the data from the multicenter case-control the National Birth Defects Prevention Study (October 1997–December 2011) to examine associations between individual antidepressants and specific birth defects with and without attempts to partially account for potential confounding underlying conditions. To account for potential confounding underlying conditions, the authors compared mothers who were exposed to each antidepressant during early pregnancy (e.g. month before conception through the third month of pregnancy) to mothers who were only exposed to an antidepressant (s) outside of early pregnancy (e.g. exposed to an antidepressant 2–3 months before pregnancy and/or in the second or third trimesters of pregnancy). This strategy was used to control for nonmedication related factors that could influence outcome. This comparison only identified diaphragmatic hernia as a possible association (n=9; aOR=6.5; 95% CI, 1.85, 22.8) after bupropion use during early pregnancy.

The NBDPS is one of the largest case-control studies conducted worldwide that examined the risk factors for specific birth defects after use of specific antidepressant across several antidepressant classes during pregnancy with a surveillance system in place adjudicated by clinical geneticists and other clinicians. Having this verification system allowed the authors to examine associations with specific defects more accurately than is possible with administrative information. The authors also provided a method to partially account for underlying conditions that could influence the outcome of the study. Limitations of this study includes small sample size for bupropion (149 case mothers (0.5%) and 45 control mothers (0.4%)) during the 1st trimester, not accounting for diagnosis associated with drug treatment as bupropion is also used to treat smoking cessation, differences in disease severity or clinical differences among the women, did not include important comparisons such as women that continue using anti-depressants during pregnancy compared with those who discontinue treatment before pregnancy, recall bias because of the retrospective data collection, and the study did not adjust for multiple testing in considering whether a medication and birth defect association met the criteria for an elevated association. The authors also note that each medication and birth defect association should be confirmed in other samples. As mentioned above, the Anderson et al. 2020 paper did not account for diagnosis associated with drug treatment. Consequently, there is a possibility that diaphragmatic hernia identified in this study reflects that association between smoking during early pregnancy and congenital diaphragmatic hernia.[22] Bupropion is also used to treat smoking cessation. Additionally, literature search for bupropion use during pregnancy and diaphragmatic hernia yielded no results.

Patrick et al. developed predictive models for NAS based on a set of 30 demographic and antenatal exposure covariates collected during pregnancy. One of the antenatal exposure covariates collected during the last 30 days of pregnancy included bupropion use. The general population predictive model identified a possible association with bupropion use and developing

[22] Caspers KM, Oltean C, Romitti PA, Sun L, Pober BR, Rasmussen SA, Yang W, Druschel C; National Birth Defects Prevention Study. Maternal periconceptional exposure to cigarette smoking and alcohol consumption and congenital diaphragmatic hernia. Birth Defects Res A Clin Mol Teratol. 2010 Dec;88(12):1040-9. doi: 10.1002/bdra.20716. Epub 2010 Sep 14.

NAS. This study had numerous limitations, including medication compliance assumptions, models were not validated on different populations, and small sample size among bupropion subjects (n=3). Additionally, the author states the data to validate the NAS risk is sparse and a literature search for an association with bupropion use and NAS was not found. The findings of this study do not clearly outline a potential safety risk.

No new data regarding congenital heart defects and bupropion use during pregnancy were identified. The DeVries et al.[17] paper revisited information from published studies that were already reviewed in the 2018 DPMH review and the Tran et al.[20] and Turner et al.[21] (meta - analysis) paper did not identify any increased risk of perinatal events for bupropion use during pregnancy. The recent study regarding bupropion use during the 2nd trimester also did not identify any adverse safety effects.[23] Additionally, the case reports of bupropion use in pregnancy presents confounding data as the case subjects were also taking other anti-depressants which makes it difficult to attribute any adverse findings specifically to bupropion.

DPMH Review of Literature
DPMH conducted a search of published literature search for "bupropion hydrochloride", "dextromethorphan hydrobromide" and "pregnancy" and "congenital defects/congenital anomalies/teratogenicity/prematurity/stillbirth/spontaneous abortion/miscarriage" in PubMed, Embase and the TERIS and ReproTox databases.

Bupropion hydrochloride
A search of the published literature revealed one new study since the last DPMH review in 2018 beyond those already listed above in the applicant's review.

- Kranzler et al[23]. conducted a multi-site, placebo-controlled, randomized clinical trial of bupropion for tobacco use among pregnant women (N = 129). Pregnant women during the second trimester (13-26 weeks of gestation) were randomly assigned to receive 10 weeks of treatment with bupropion (300mg/day) (n=64) or placebo (n=65), accompanied by a total of 6 smoking cessation counseling sessions (4 during treatment and 2 post-partum). Safety measures included maternal treatment-related adverse events, gestational age, the rate of overall and spontaneous preterm births, infant birth weight and size for gestational age, head circumference, and 5-minute Apgar scores. There were no significant differences between treatment arms on safety measures. While this placebo-controlled trial of bupropion in pregnant women showed no adverse safety effects additional studies are needed to verify results due to the study limitations. Study limitations include relatively small samples size and discrepancies with reporting medication adherence.

Reprotox also mentioned Anderson et al., 2020 and noted that the NBDPS case control study used 25 individual malformations or malformation groups and reported an association of bupropion use with diaphragmatic hernia. This association with diaphragmatic hernia has not

[23] Kranzler HR, Washio Y, Zindel LR, Wileyto EP, Srinivas S, Hand DJ, Hoffman M, Oncken C, Schnoll RA. Placebo-controlled trial of bupropion for smoking cessation in pregnant women. Am J Obstet Gynecol MFM. 2021 Jan 22:100315. doi: 10.1016/j.ajogmf.2021.100315. Epub ahead of print. PMID: 33493703.

been confirmed elsewhere and may have arisen due to multiple comparisons. There was no increase in left ventricular outflow tract defects. (Reviewer's comment is above, page 9)

Dextromethorphan hydrobromide
Review of the relevant databases did not provide any new articles of studies involving dextromethorphan hydrobromide and pregnancy/abortion/ miscarriage/newborn/ neonatal since 2019 (DN1 PLLR review memo). According to Micromedex/ReproTox/TERIS, the two most recent studies which were also mentioned in DN1's 2019 review found no significant association with maternal use of dextromethorphan and major congenital anomalies during the first trimester.

- Einarson et al[24] concluded from a retrospective survey that the frequency of major congenital anomalies was no greater than expected among the children of 128 women who took dextromethorphan compared to a control group (n=56) during the first trimester of pregnancy. This study did not reveal an increase in the rates of major malformations above the baseline rate of 1% to 3%. This study is limited due to its small sample size.
- Martinez-Frias & Rodriguez-Pinilla[25] concluded from the Spanish Collaborative Study of Congenital Malformations, a large case-control study, that there were no significant association with maternal use of dextromethorphan during the first trimester of pregnancy There were 70 cases exposed to dextromethorphan during the first trimester of pregnancy, as well as 26,696 nonexposed cases, with 48 exposed controls and 26,249 not exposed controls. Newborn infants were examined in the first 3 days of life and those with major and/or minor congenital defects were identified and described. The authors found that the 95% confidence intervals for the adjusted odds ratios[26] included 1 suggesting a nonsignificant result for neural tube defects, CNS defects, hydrocephaly, congenital heart defects, and oral clefts. They concluded that drugs containing dextromethorphan does not seem to be teratogenic agents for the human embryo.

ReproTox also included two studies that were published more than 30 years ago that did not find an association with congenital defects and dextromethorphan use during pregnancy[30, 31]. One study included 300 women who used dextromethorphan during the first four months of pregnancy and another study included a cohort study involving 184 women. These were not case-controlled studies. Reprotox summarizes that epidemiology studies, in aggregate, involving about 600 dextromethorphan-exposed pregnancies have not identified an increase in congenital anomalies.

Reviewer comment:
There has been no recent studies of dextromethorphan and pregnancy. Earlier studies looking at frequencies of malformations of women who took dextromethorphan such as the Collaborative Perinatal Project during pregnancy did not demonstrate an increase above the baseline

[24] Einarson A, Lyszkiewicz, Koren G. The safety of dextromethorphan in pregnancy: a prospective controlled study. Chest 2001;119:466-9.
[25] Martinez-Frias M-L, Rodriques-Pinilla E: Epidemiologic analysis of prenatal exposure to cough medicines containing dextromethorphan: no evidence of human teratogenicity. Teratology63:38-41, 2001.
*1tsp=5mls
[26] Adjusted by maternal age, fever, drugs other than dextromethorphan, flu/cold, first degree relatives with same defects.

malformation rates[27,28]. The strength/dosage of dextromethorphan in AXS-05 to is somewhat higher than the listed drug Nuedexta, 45mg and 20 mg, respectively. However, over-the-counter (OTC) preparations of cough syrup in the studies summarized above containing dextromethorphan is dispensed as either 15mg/5ml or 30mg/5ml dosage that is administered to adults and children 10 mL every 12 hours, with 12 years of age and over not to exceed 20 mL (120 mg) in 24 hours. In Einarson et al, the women were grouped into three categories, low dose (< 4 tsp, ~75 mg), medium dose (4 to 10 tsp, ~75mg to 150 mg) and high dose (> 10 tsp, ~ > 150 mg) dextromethorphan dosages since many of the women did not remember the exact amount of dextromethorphan used during their pregnancy (n=128, used during 1st trimester). Martinez-Frias & Rodriguez-Pinilla et al. estimated the mean of dosage of dextromethorphan among pregnant women in the first trimester to be 101.07 mg (n= 36; SD, 122.10) over 2.69 days (n =26; SD,2.27). Limitations for both studies are small sample size and the lack of exact dosage amounts of dextromethorphan taken by the women in the study. The Applicant included the conclusion of the Einarson et al. (2001) paper in the labeling, as it describes the use of dextromethorphan in pregnancy, however, it does not address long term use of dextromethorphan in AXS-05 during pregnancy. Therefore, in general, the use of dextromethorphan appears to be safe in pregnancy, however, these studies are not adequate to draw definitive conclusions of the safety of long-term use of dextromethorphan in pregnancy.*

Pregnancy Registry

One international pregnancy registry study (see Table 1, page 13) for bupropion was completed in 2008.[29] This registry followed 1597 pregnancies involving exposure to bupropion. Of the 1597, a total of 994 pregnancies were followed to an outcome (1005 outcomes). The results of the registry excluded a major teratogenic effect of bupropion and did not detect a signal of a major problem with birth defects in women exposed to bupropion during their pregnancy. However, the registry was not designed to exclude an increase in the risk for specific defects. This registry is described in the current product labeling for bupropion (Wellbutrin 2019).

The National Pregnancy Registry for Antidepressants listed in the Wellbutrin labeling is currently ongoing and data is not yet available.

[27] Heinonen OP, Slone D, Shapiro S: Birth Defects and Drugs in Pregnancy. Littleton, Mass.:John Wright-PSG, 1977, pp 379, 496.
[28] Aselton P, Jick H, Milunsky A, Hunter JR, Stergachis A: First-trimester drug use and congenital disorders. Obstet Gynecol 65:451-455, 1985.
[29] GlaxoSmithKline Bupropion Pregnancy Registry. Final report: 1 September 1997 through 31 March 2008. Registry Report. Wilmington, NC, 2008

Table 1.

Prospective Registry - Bupropion Exposure in Pregnancy by Country of Origin
1 September 1997 – 31 March 2008

Country	Number of Reported Pregnancies[a]
Australia	4
Belgium	8
Canada	50
Czech Republic	1
Estonia	1
France	41
Germany	1
Holland	1
Luxemburg	1
Namibia	1
New Zealand	2
South Africa	3
Spain	4
Sweden	1
United Kingdom	25
United States	850
TOTAL	**994**

[a] Includes only patients with known pregnancy outcomes

LACTATION

Nonclinical Experience

Bupropion and its metabolites are present in animal milk.[10]

Review of Pharmacovigilance Database

There are no reports of AXS-05 exposure during lactation in the clinical trials.

Applicant's Review of Literature

The applicant performed a search of the literature using EMBASE with drug names (AXS-05, bupropion, dextromethorphan, Wellbutrin, etc.) and lactating terminology (refer to page 6 above). The applicant noted that their search did not identify any relevant articles between 2018 to present with their search parameters.

DPMH Review of Literature:

DPMH conducted a search of Thomas Hale's book (Medications and Mothers' Milk), the Drugs and Lactation Database (LactMed)[30], Micromedex, Drugs in Pregnancy and Lactation, and of the published literature in PubMed and Embase using the search terms "bupropion" or "dextromethorphan" and "lactation" or "breastfeeding."

Bupropion hydrochloride

The conclusions/recommendation from the literature review conducted by DPMH in 2018[10] has not changed.

[30] https://www.ncbi.nlm.nih.gov/books/NBK501184/

[10] DPMH Review of WELLBUTRIN (bupropion), WELLBUTRIN SR (bupropion) NDA 18644 and 20358, Catherine Roca, M.D., Medical Officer, April 20, 2018. DARRTS Reference ID# 4251915.

Micromedex states, “Infant risk cannot be ruled out, and reports that the American Academy of Pediatrics rates bupropion as a “Drug for which the effect on nursing infants is unknown but may be of concern.”

Briggs rates bupropion as, “limited human data- potential toxicity.”
In Medications and Mothers’ Milk, bupropion is rated “L3-Limited Data-Probably compatible.” Hale cites the same literature as mentioned above in LactMed. Hale reports the Relative Infant Dose (RID) as ranging from 0.11-1.99%, and the milk/plasma ration as ranging from 2.51-8.58.

Bupropion is referenced in LactMed, which states, “limited information indicates that bupropion doses of up to 300mg daily produce low levels in breastmilk and would not be expected to cause any adverse effects on breastfed infants. However, there is little reported use in breastfed newborn infants and case reports of a possible seizure in two partially breastfed 6- month olds. If bupropion is required by a nursing mother, it is not a reason to discontinue breastfeeding. However, another drug may be preferred, especially while nursing a newborn or preterm infant. Infants exposed to bupropion and an SSRI through breastfeeding should be closely monitored for vomiting, diarrhea, jitteriness, or sedation and possibly measurement of serum levels to rule out toxicity if there is a concern.”

One new reference was included in the LactMed database that was not present in DPMH’s 2018 review. The summary is below:

- Uguz, F[31] presented a new safety scoring system for the use of psychotropic drugs during lactation. Bupropion scored 4.0/10, which translates into a usage recommendation of “possible with caution” (only when necessary).The scoring system is based on the following 6 safety parameters: reported total sample, reported maximum relative infant dose, reported sample size for relative infant dose, infant plasma drug levels, prevalence of reported any adverse effect, and reported serious adverse effects. The total score ranges from 0 to 10. Higher scores represent a good safety profile, where the risks of adverse effects are very low. The scores are based on reported maximum relative infant dose (RID), reported sample size for RID, infant plasma drug levels, prevalence of observed adverse event and reported serious adverse event.

Reprotox summarized the same information that was found in LactMed.

Reviewer’s comment:
There are no new safety signals that were identified during this review. DPMH 2018 review reported on two postmarketing reports of seizures in six- month old infants; one of these infants was exposed to the combination of bupropion and escitalopram, the other had a concurrent respiratory infection. It is not clear from these reports if the seizures were due to exposure to bupropion through breastmilk. Therefore, I agree with the applicant’s findings that there are no new relevant findings between 2018 to present.

[31] Uguz F. A New Safety Scoring System for the Use of Psychotropic Drugs During Lactation. American Journal of Therapeutics. 2021;28(1):e118–e126.

Dextromethorphan hydrobromide
Micromedex states, Infant risk is minimal and Reprotox did not locate studies on possible lactation effects of this agent. In Hale's Medications and Mothers' Milk is rated "L3 - No Data-Probably Compatible"

According to LactMed[32] neither the presence of dextromethorphan in milk nor its effect on breastfed infants have been studied. It is unlikely that with usual maternal doses amounts in breastmilk would harm the nursing infant, especially in infants over 2 months of age. Additionally, although dextromethorphan has not been studied in breast-feeding, two articles published in the U.S. Pharmacist expected concentrations in breast milk would be low and is unlikely to cause harm[33,34]. However, the dosing regimen for dextromethorphan in the combination product of AXS-05 would be used over a longer period of time than the typical dosage requirements found in the OTC labeling of cough suppressants containing dextromethorphan. In addition, there have been several publications that have associated long term use of dextromethorphan with neuropsychiatric consequences in adults, although these symptoms are seen at higher dosages (> 120 mg/day)[35,36]. Therefore, it is important to understand the amount of dextromethorphan that may be present in breast milk.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
Nonclinical Experience
Nonclinical fertility studies from the listed drugs (Wellbutrin and Nuedexta) will be relied upon for AXS-05 product labeling.

There were no effects on male and female fertility when rats were administered oral doses of bupropion up to 300 mg/kg/day in females prior to mating and either through Day 13 of gestation or through lactation, and in males for 60 days prior to and through mating.

When dextromethorphan was co-administered with quinidine orally (0/0, 5/100, 15/100, and 50/100 mg/kg/day) to male and female rats prior to and during mating, and continuing to Day 7 of gestation in females, no effect on fertility was observed up to the highest dose tested.

Review of Literature
The applicant performed a search of the literature using EMBASE with drug names (bupropion, dextromethorphan, Wellbutrin, etc.) and fertility terminology (refer to page 6 above). The applicant noted that their search did not identify any relevant articles between 2018 to present with their search parameters.

[32] https://www.ncbi.nlm.nih.gov/books/NBK501456/
[33] Ledan, Seema H. "OTC Medication Use in Pregnancy and Breastfeeding." U.S. Pharmacist., vol. 44, no. 9, Jobson Pub Corp, 2019, pp. 16–19.
[34] Masters, Kelly P. "Breast-Feeding and OTC Medications." U.S. Pharmacist., vol. 32, no. 7, Jobson Pub Corp, 2007, pp. 8–12.
[35] Hinsberger A, Sharma V, Mazmanian D. Cognitive deterioration from long-term abuse of dextromethorphan: a case report. J Psychiatry Neurosci. 1994;19(5):375-377.
[36] Bernstein, Laura B. PsyD; Albert, David MD; Baguer, Carlos PhD; Popiel, Maryann MD Long-term Dextromethorphan Use and Acute Intoxication Results in an Episode of Mania and Autoenucleation, Journal of Addiction Medicine: July/August 2020 - Volume 14 - Issue 4 - p e133-e135

DPMH conducted a review of Micromedex, ReproTox, TERIS, Embase, and PubMed using the terms, "bupropion", or dextromethorphan, or "Wellbutrin" and "fertility," "oral contraceptives," and "infertility". DPMH 2018 review found one case report related to bupropion HCl and infertility. Tanrikut et al. reported 76% DNA fragmentation in the semen analysis of a male subject while on bupropion[37]. There are no new relevant articles identified from 2018 to present. There were no relevant articles on dextromethorphan hydrobromide and effects on fertility identified from the literature review search.

Reviewer comment:
The applicant's review is adequate, and no publications related to an adverse effect of bupropion or dextromethorphan on fertility or hormonal contraceptives were located.

DISCUSSION AND CONCLUSIONS

Pregnancy

AXS-05

Seven subjects became pregnant while taking AXS-05 during clinical trials. Upon identification of pregnancy, AXS-05 was discontinued. Three pregnancies resulted in full-term deliveries. One pregnancy is still ongoing with no complications to date, while the outcomes of the other three pregnancies are unknown (two lost to follow-up, one withdrawal of consent). Due to the small sample size, it is not possible to draw any substantive conclusions about adverse pregnancy and infant outcomes after exposure to AXS-05 during pregnancy.

In the embryo-toxicity mouse study, treatment with BUP/DM up to the highest doses (150/68 mg/kg) demonstrated no effect on body weights, body weight changes, food consumption, gross pathology findings, uterine data, fetal weights, or fetal examination data. However, toxicity and death was demonstrated in some maternal animals. According to the nonclinical team, the recommended animal model to study the embryo-toxicity effects of AXS-05 is the rabbit model. An additional reproductive toxicity study in rabbits will be requested to further evaluate the combination effect of bupropion and dextromethorphan as fetal malformations.

Bupropion hydrochloride

The recent published literature on bupropion use during pregnancy has been reviewed for potential safety concerns. The previous interim analysis of the NBDPS by Alwan et al., identified a possible association of LVOTO with bupropion use during pregnancy. However, the final analysis conducted by Anderson et al., on the completed data from the NBDPS did not find a significant association of risk of LVOTO with bupropion use during pregnancy. Instead, Anderson et al., identified diaphragmatic hernia after accounting for nonmedication-related factors as having a potential association with bupropion use during pregnancy. The Division of Epidemiology 1 (DEPI)[38] reviewed the available published literature to consider whether the data support the risk association for diaphragmatic hernia in infants whose mothers used bupropion during pregnancy and concluded the published articles do not suggest an elevated risk

[37] Tanrikut C, Schlegel PN. Antidepressant-associated changes in semen parameters. Urology. 2007;69:185.e%-185e7.

[38] DEPI Review of Published Literature to Assess Maternal Use of Specific Antidepressant Medications During Early Pregnancy and the Risk of Selected Birth Defects. NDA 215430, Dinci Pennap, PhD, MS, July 1, 2021. DARRTS Reference ID# 4820739

of diaphragmatic hernia. Furthermore, DEPI stated that they disagree with the authors' interpretation (Anderson et al.) of the observed elevated odds ratio of diaphragmatic hernia comparing fetal exposure in early pregnancy to exposure in months 4 through 9 of pregnancy due to study design flaws, potential unmeasured confounding, selection bias, and exposure misclassification.

Data from published sources have not definitively demonstrated an association of bupropion and major congenital malformations. The applicant included a statement from the Wellbutrin labeling that provides the findings from the NBDPS and the completed pregnancy registry. DPMH recommends leaving the information from the completed registry and updating that for NBDPS. The information (b) (4) (b) (4) will be omitted. However, to improve readability under labeling subsection 8.1 Pregnancy, Data, Human Data, discussion is needed with DP and OSE DEPI for a more concise description of the studies. DP has identified deficiencies for this NDA, therefore, work on the labeling of AXS-05 will be discontinued for this application cycle.

Dextromethorphan hydrobromide
Published epidemiological studies on dextromethorphan use in pregnancy did not reveal an association with dextromethorphan and major congential malformations. However, these studies had several limitations such as small sample size, small amounts of drug taken or lack definitive amounts of dosage, and the time exposure was not specifically analyzed. AXS-05 (BUP/DM) is intended to be prescribed chronically to treat MDD, as such, DPMH recommends not incorporating any information of these dextromethorphan studies in the labeling as there is no information regarding pregnancy outcomes with long-term usage of this drug. Information on the usage of AXS-05 will be collected as part of the pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants. The labeling can be updated in the future with the results from the registry.

Lactation
There is no information regarding the use of AXS-05 in lactating animals or humans. For bupropion, data from published literature has reported the presence of bupropion and its metabolites in human milk. Although seizures have rarely been reported, it is not clear from these reports if the seizures were due to exposure to bupropion through breastmilk. Current bupropion labeling includes information about the seizures in breastfed infants and a lactation study of 10 women who had bupropion and its active metabolites were measured in expressed milk. The average daily infant exposure (assuming 150 mL/kg daily consumption) to bupropion and its active metabolites was 2% of the maternal weight-adjusted dose. DPMH recommends keeping the current bupropion labeling language.

The presence of dextromethorphan in milk nor its effect on breastfed infants have been studied. Due to its chemical properties (60-70% bound to serum albumin and MW 370.33 Da), dextromethorphan may be present in breast milk. However, dextromethorphan has only been previously used for short courses while as part of the combination product of AXS-05, it is now intended to be used chronically. Since we do not have information regarding long-term use of dextromethorphan, DPMH recommends using the standard PLLR risk/benefit statement in subsection 8.2 of AXS-05 labeling and for the Applicant to conduct a postmarketing milk-only

clinical lactation study as there is anticipated use of AXS-05 in females of reproductive potential. Refer to the FDA draft Guidance for Industry "Clinical Lactation Studies: Considerations for Study Design", published May 9, 2019.[39]

Females and Males of Reproductive Potential

There are no data on AXS-05 and its effects of fertility in humans. Limited data in the published literature are insufficient to determine an adverse effect of bupropion on fertility. The current animal data in the labeling for Nuedexta and Wellbutrin do not indicate an adverse effect on fertility. No publications were found indicating an adverse effect of bupropion or dextromethorphan on hormonal contraceptives. Therefore, DPMH recommends that Subsection 8.3 be omitted from labeling.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2, 8.3 and section 17 of labeling for compliance with the PLLR (see below). DPMH labeling recommendations are below but do not reflect Nonclinical input. DP has identified deficiencies for this NDA, and work on the labeling of AXS-05 will be discontinued for this application cycle. Future labeling discussion should consider making subsection 8.1 Pregnancy, under the Data heading more concise and improving readability.

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is an independent pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants, including PROPRIETARY NAME, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Antidepressants at 1-866-961-2388 or online at:

https://womensmentalhealth.org/research/pregnancyregistry/antidepressants/.

Risk Summary

The available data on the use of PROPRIETARY NAME in pregnant women is insufficient to evaluate for a drug-associated risk of major birth malformations, miscarriage, or other adverse maternal or fetal outcomes. However, there are available data on one of the individual components of PROPRIETARY NAME, bupropion.

Data from epidemiological studies of pregnant women exposed to bupropion in the first trimester have not identified an increased risk of congenital malformations overall. *(see Data).* There are risks to the mother associated with untreated depression in pregnancy *(see Clinical Considerations*).

[39] https://www.fda.gov/media/124749/download

When dextromethorphan-bupropion was administered orally to pregnant mice during the period of organogenesis, pregnancy was not affected and no gross pathologic findings or placental or fetal findings were observed at any dose level. When bupropion alone was administered to pregnant rats during organogenesis, there was no evidence of fetal malformations at doses up to approximately 21 times the maximum recommended human dose (MRHD) of 210 mg/day. When given to pregnant rabbits during organogenesis, non-dose–related increases in incidence of fetal malformations, and skeletal variations were observed at doses approximately 2 to 5 times the MRHD and greater. Decreased fetal weights were seen at doses approximately 5 times the MRHD and greater *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

A prospective, longitudinal study followed 201 pregnant women with a history of major depressive disorder who were euthymic and taking antidepressants during pregnancy at the beginning of pregnancy. The women who discontinued antidepressants during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressants. Consider the risks to the mother of untreated depression and potential effects on the fetus when discontinuing or changing treatment with antidepressant medications during pregnancy and postpartum.

Data

Human Data

Bupropion

Data from the international bupropion Pregnancy Registry (675 first trimester exposures) and a retrospective cohort study using the United Healthcare database (1,213 first trimester exposures) did not show an increased risk for malformations overall. The Registry was not designed or powered to evaluate specific defects but suggested a possible increase in cardiac malformations.

No increased risk for cardiovascular malformations overall has been observed after bupropion exposure during the first trimester. The prospectively observed rate of cardiovascular malformations in pregnancies with exposure to bupropion in the first trimester from the international bupropion Pregnancy Registry was 1.3% (9 cardiovascular malformations/675 first trimester maternal bupropion exposures), which is similar to the background rate of cardiovascular malformations (approximately 1%).

Data from the United Healthcare database, which had a limited number of exposed cases with cardiovascular malformations, and a case-control study (11,700 infants with cardiovascular malformations and 20,093 infants with non-cardiovascular malformations) of self-reported antidepressant use, including bupropion (n =728) from the National Birth Defects Prevention Study (NBDPS) did not show an increased risk for cardiovascular malformations overall after bupropion exposure during the first trimester.

Study findings on bupropion exposure during the first trimester and risk for left ventricular outflow tract obstruction (LVOTO) or ventricular septal defect (VSD) are inconsistent and do not allow conclusions regarding a possible association. The United Healthcare database lacked sufficient power to evaluate the LVOTO association. NBDPS found slightly increased risk for LVOTO after partially accounting for underlying maternal conditions (n=14; adjusted odds ratio [OR] = 1.18 (0.58, 2.43)), and the Slone Epidemiology case control study did not find increased risk for LVOTO. The Slone Epidemiology Study found an increased risk for VSD following first trimester maternal bupropion exposure (n = 17; adjusted OR = 2.5; 95% CI: 1.3, 5.0) but did not find increased risk for any other cardiovascular malformations studied (including LVOTO as above). The NBDPS and United Healthcare database study did not find an association between first trimester maternal bupropion exposure and VSD.

For the findings of LVOTO and VSD, the studies were limited by the small number of exposed cases, inconsistent findings among studies, and the potential for chance findings from multiple comparisons in case control studies.

Animal Data

In studies conducted in pregnant mice, dextromethorphan-bupropion was administered orally during the period of organogenesis at doses of 0-0, 26-57, 34-75, and 68-150 mg/kg/day, respectively. Administration of dextromethorphan-bupropion did not affect body weight, weight gain, food consumption, or pregnancy at any dose level and did not produce gross pathologic findings or placental or fetal findings at any dose level. The no-effect level for reproductive organ findings in mice was 68-150 mg/kg in both sexes, which is approximately 3.7/3.5 times the MRHD for PROPRIETARY NAME on a mg/m^2 basis.

When dextromethorphan/quinidine was administered orally (0/0, 5/100, 15/100, and 50/100 mg/kg/day) to pregnant rats during the period of organogenesis, embryo-fetal deaths were observed at the highest dose tested and reduced skeletal ossification was observed at all doses. The lowest dose of dextromethorphan tested (5 mg/kg/day) in combination with quinidine (100 mg/kg/day) is approximately half the MRHD of 90 mg/day on a mg/ m^2 basis. Oral administration to pregnant rabbits during organogenesis in two separate studies (0/0, 5/60, 15/60, and 30/60 mg/kg day; 0/0, 5/100, 15/100, and 50/100 mg/kg/day) resulted in an increased incidence of fetal malformations at all but the lowest dose tested. The no-effect dose of dextromethorphan (5 mg/kg/day) in combination with quinidine (100 mg/kg/day) is similar to the MRHD on a mg/ m^2 basis.

When dextromethorphan/quinidine was orally administered to female rats during pregnancy and lactation in two separate studies (0/0, 5/100, 15/100, and 30/100 mg/kg/day; 0/0, 5/100, 15/100, and 50/100 mg/kg/day), pup survival and pup weight were decreased at all doses, and developmental delay was observed in offspring at the mid and high doses. A no-effect dose for adverse developmental effects was not identified. The lowest dose of dextromethorphan tested (5 mg/kg/day) in combination with quinidine (100 mg/kg/day) is approximately half the MRHD on a mg/ m^2 basis.

When dextromethorphan/quinidine was orally administered (0/0, 5/50, 15/50, 25/50 mg/kg) to male and female rats on postnatal day (PND) 7, the highest dose resulted in neuronal death in brain (thalamus and medulla oblongata). PND 7 in rat corresponds to the third trimester of gestation through the first several months of life but may extend to approximately three years of age in humans.

In studies conducted in pregnant rats and rabbits, bupropion alone was administered orally during the period of organogenesis at doses of up to 450 and 150 mg/kg/day, respectively (approximately 21 and 14 times the MRHD, respectively, on a mg/m^2 basis). There was no evidence of fetal malformations in rats. When given to pregnant rabbits during organogenesis, non-dose–related increases in incidence of fetal malformations and skeletal variations were observed at the lowest dose tested (25 mg/kg/day, approximately 2 times the MRHD on a mg/m^2 basis) and greater. Decreased fetal weights were observed at doses of 50 mg/kg/day (approximately 5 times the MRHD on a mg/m^2 basis) and greater. No maternal toxicity was evident at doses of 50 mg/kg/day or less. In a pre- and postnatal development study, bupropion administered orally to pregnant rats at doses of up to 150 mg/kg/day (approximately 7 times the MRHD on a mg/m^2 basis) from embryonic implantation through lactation had no effect on pup growth or development.

8.2 Lactation

Risk Summary

Data from published literature report the presence of bupropion and its metabolites in human milk *(see Data)*. Limited data from postmarketing reports of buproprion use in lactating patients have not identified a clear association of adverse reactions in the breastfed infant. There are no data on the effects of bupropion or its metabolites on milk production. It is not known whether dextromethorphan is present in human milk. There are no data on the effects of dextromethorphan on the breastfed infant or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PROPRIETARY NAME and any potential adverse effects on the breastfed infant from PROPRIETARY NAME or from the underlying maternal condition.

Data

In a lactation study of 10 women, levels of orally dosed bupropion and its active metabolites were measured in expressed milk. The average daily infant exposure (assuming 150 mL/kg daily consumption) to bupropion and its active metabolites was 2% of the maternal weight-adjusted dose. Postmarketing reports have described seizures in breastfed infants. The relationship of bupropion exposure and these seizures is unclear.

17 PATIENT COUNSELING INFORMATION

Pregnancy

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during therapy with PROPRIETARY NAME. Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to PROPRIETARY NAME during pregnancy *[see Use in Specific Populations (8.1)]*.

Appendix A:

Table 1. Relevant Publications Regarding Bupropion in Pregnant Women∞

Author / Year	Title	Exposed (Bupropion)	Unexposed	Outcome	Results (95% CI)
Turner / 2019	Systematic Review and Meta-Analysis to Assess the Safety of Bupropion and Varenicline in Pregnancy	3376	n/a	Proportion with congenital malformations (4 studies)	1.0% (0.0%–3.0%) p=0.00
		262	n/a	Mean birthweight (5 studies)	3305.9 g (3173.2–3438.7g)
		260	n/a	Mean gestational age (5 studies)	39.2 weeks (38.8–39.6 weeks)
Tran / 2020	Use of smoking cessation pharmacotherapies during pregnancy is not associated with increased risk of adverse pregnancy outcomes: a population-based cohort study	91	912	Any adverse perinatal outcome:	HR=0.93 (0.73-1.19)
		12	192	Preterm birth (< 37 weeks)	HR=0.62 (0.34–1.11)
		37	369	Small for gestational age	HR=0.89 (0.60–1.30)
		32	325	Admission to neonatal special care	HR=0.90 (0.62–1.32)
		15	157	Severe neonatal morbidity complications	HR=0.87 (0.50–1.52)
		34	289	Emergency caesarean section	HR=1.15 (0.78–1.71)
		5	49	Severe maternal morbidity complications	HR=0.95 (0.37–2.43)
DeVries /2021	A Systematic Review and Meta-Analysis Considering the Risk for Congenital Heart Defects and of Antidepressant Classes and Individual Antidepressants	143	6448	Any congenital heart defects	OR=1.23 (1.01, 1.49); p=0.04
Patrick/2021	Development and Validation of a Model to Predict Neonatal Abstinence Syndrome.	907	217,113	Neonatal abstinence syndrome (NAS)	Bupropion exposed mothers: (+) NAS = 2% (n=57) (-) NAS = 0 (n=850) P<0.001

Author / Year	Title	Exposed (Bupropion)	Unexposed	Outcome	Results (95% CI)
	opulation cohort study.				

HR=Hazard ratio; NAS=neonatal abstinence syndrome; OR=odds ratio;
[∞]Applicant's table provided in April 15, 2021 IR response, located in Module 1.11.3

Table 2. Risk of specific birth defects after early pregnancy exposure to Bupropion compared to women who were unexposed 3 months before pregnancy and during pregnancy. [∞]

Author / Year	Title	Exposed (Bupropion)	Unexposed	Outcome	Results aOR* (95% CI)
Anderson / 2020	Maternal Use of Specific Antidepressant Medications During Early Pregnancy and the Risk of Selected Birth Defects Case-control study	57	11046	Any heart defect	1.24 (0.83, 1.84)
		8	2339	Conotruncal defects	0.85 (0.40, 1.81)
		4	1081	Tetralogy of Fallot	0.99 (0.35, 2.76)
		14	2002	LVOTO defects	1.59 (0.87, 2.91)
		5	**585**	**HLHS**	**2.08 (0.82, 5.28)**
		5	1060	Coarctation of the aorta	1.09 (0.43, 2.77)
		4	453	Aortic stenosis	1.73 (0.62, 4.87)
		8	1885	RVOTO defects	1.05 (0.49, 2.24)
		7	1381	Pulmonary valve stenosis	1.19 (0.53, 2.65)
		24	4271	Septal defects	1.33 (0.80, 2.21)
		6	1517	VSD – perimembranous	0.97 (0.41, 2.27)
		12	2189	ASD – secundum	1.25 (0.64, 2.44)
		11	1968	Any neural tube defect	1.45 (0.73, 2.90)
		9	1167	Spina bifida	1.83 (0.86, 3.92)
		17	4323	Any oral cleft	0.94 (0.53, 1.66)
		4	1443	Cleft palate only	0.64 (0.23, 1.78)
		13	2880	Cleft lip with or without cleft palate	1.10 (0.59, 2.05)
		4	**444**	**Intestinal atresia/stenosis**	**2.69 (0.96, 7.59)**
		6	985	Anorectal atresia/stenosis	1.69 (0.72, 3.99)
		15	2346	Hypospadias, 2nd or 3rd degree	1.45 (0.74, 2.83)
		4	1137	Any limb deficiency	0.90 (0.32, 2.50)
		4	664	Transverse limb deficiency	1.57 (0.56, 4.39)
		7	1441	Craniosynostosis	0.98 (0.44, 2.19)

Author / Year	Title	Exposed (Bupropion)	Unexposed	Outcome	Results aOR* (95% CI)
		9	**802**	**Diaphragmatic hernia**	**2.77 (1.34, 5.71)**
		4	1309	Gastroschisis	0.61 (0.18, 2.04)

aOR=adjusted odds ratio[a]; ASD=atrial septal defects; HLHS=hypoplastic left heart syndrome; HR=Hazard ratio; LVOTO=left ventricular outflow tract obstruction; NAS=neonatal abstinence syndrome; OR=odds ratio; VSD=ventricular septal defects.

***** aOR of 2.0 or greater and a lower confidence interval bound of 0.8 or greater were considered as significant findings.

[a] adjusted for maternal race, obesity, smoking, education, and family income— cases and controls with preexisting type 1 or 2 diabetes in the mother were excluded.

LVOTO, left ventricular outflow tract obstruction; HLHS, hypoplastic left heart syndrome; RVOTO, right ventricular outflow tract obstruction; VSD, ventricular septal defect; ASD, atrial septal defect.

[∞]Applicant's table provided in April 15, 2021 IR response, located in Module 1.11.3

Table 3. Risk of specific birth defects after early pregnancy exposure to Bupropion compared to women who were exposed outside of early pregnancy[b, ¥]

Author / Year	Title	Exposed (Bupropion)	Exposed outside of Early pregnancy	Outcome	Results aOR* (95% CI)
Anderson / 2020	Maternal Use of Specific Antidepressant Medications During Early Pregnancy and the Risk of Selected Birth Defects Case-control study	57	149	Any heart defect	1.09 (0.69, 1.73)
		8	28	Conotruncal defects	0.75 (0.31, 1.77)
		4	14	Tetralogy of Fallot	0.74 (0.23, 2.41)
		14	33	LVOTO defects	1.18 (0.58, 2.43)
		5	13	HLHS	1.05 (0.35, 3.16)
		5	11	Coarctation of the aorta	1.23 (0.40, 3.78)
		4	8	Aortic stenosis	1.49 (0.42, 5.34)
		8	30	RVOTO defects	0.85 (0.36, 2.04)
		7	25	Pulmonary valve stenosis	0.92 (0.36, 2.32)
		24	53	Septal defects	1.32 (0.73, 2.41)
		6	23	VSD – perimembranous	0.73 (0.28, 1.92)
		12	27	ASD – secundum	1.34 (0.62, 2.93)
		11	25	Any neural tube defect	1.34 (0.60, 3.00)
		9	18	Spina bifida	1.38 (0.57, 3.34)
		17	49	Any oral cleft	1.08 (0.55, 2.10)
		4	21	Cleft palate only	0.57 (0.18, 1.77)
		13	28	Cleft lip with or without cleft palate	1.48 (0.69, 3.19)

Author / Year	Title	Exposed (Bupropion)	Exposed outside of Early pregnancy	Outcome	Results aOR* (95% CI)
		6	8	Anorectal atresia/stenosis	2.52 (0.78, 8.11)
		15	24	Hypospadias, 2nd or 3rd degree	1.91 (0.84, 4.33)
		4	11	Any limb deficiency	1.06 (0.31, 3.61)
		4	6	Transverse limb deficiency	1.65 (0.43, 6.24)
		7	19	Craniosynostosis	0.99 (0.39, 2.54)
		9	**4**	**Diaphragmatic hernia**	**6.50 (1.85, 22.88)**
		4	21	Gastroschisis	0.72 (0.22, 2.35)

aOR=adjusted odds ratio[a]; ASD=atrial septal defects; HLHS=hypoplastic left heart syndrome; HR=Hazard ratio; LVOTO=left ventricular outflow tract obstruction; NAS=neonatal abstinence syndrome; OR=odds ratio; VSD=ventricular septal defects.

* aOR of 2.0 or greater and a lower confidence interval bound of 0.8 or greater were considered as significant findings.

[a] adjusted for maternal education— cases and controls with preexisting type 1 or 2 diabetes in the mother were excluded.

LVOTO, left ventricular outflow tract obstruction; HLHS, hypoplastic left heart syndrome; RVOTO, right ventricular outflow tract obstruction; VSD, ventricular septal defect; ASD, atrial septal defect.

[e]Exposed to an antidepressant 2–3 months before pregnancy (B3, B2) and/or in the second or third trimesters of pregnancy (P4–P9) only

[¥]Table included by Reviewer, based on information from supplemental eTable 4[40]

[40]Anderson KN, Lind JN, Simeone RM, et al. Maternal Use of Specific Antidepressant Medications During Early Pregnancy and the Risk of Selected Birth Defects [published online ahead of print, 2020 Aug 5]. JAMA Psychiatry. 2020;77(12):1246-1255.

Table 4. Case reports from the Literature Regarding the Use of Bupropion in Pregnant Women[∞]

First Author / Year	Title	Case Report
Maňáková / 2018	Antiepileptic Drugs During Pregnancy. Cztis Experience	A 33-year-old woman suffering from depression was treated with alprazolam, venlafaxine, clonazepam, bupropion, zolpidem and trazodone during pregnancy. She gave birth to a female that was smaller for gestational age with small hemangioma
Brajcich / 2020	Why the Maternal Medication List Matters: Neonatal Toxicity from Combined Serotonergic Exposures Individual Case Report	A 34-week gestation male infant was delivered via caesarian for breech positioning, partial placental abruption, and preeclampsia without severe features. Maternal history was notable for bipolar disorder and posttraumatic stress disorder, for which she was taking venlafaxine 150 mg daily, bupropion hydrochloride 300 mg daily, quetiapine 200 mg daily, and gabapentin 1200 mg 3 times daily. He presented nearly immediately after birth with encephalopathy and abnormal movements. He was discharged from the hospital with a normal neurologic examination at 14 days, and has had appropriate development and normal neurologic examination up to 15 months.

[∞]Applicant's table provided in April 15, 2021 IR response, located in Module 1.11.3

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/s/

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	July 14, 2021
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 215430
Product Name and Strength:	Auvelity (dextromethorphan HBr and bupropion HCl) tablets, 45 mg/105 mg
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Axsome Therapeutics, Inc.
FDA Received Date:	02/22/2021
OSE RCM #:	2021-377
DMEPA Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 REASON FOR REVIEW

As part of the approval process for Auvelity[a] (dextromethorphan HBr and bupropion HCl) tablets, the Division of Psychiatry (DP) requested that we review the proposed Auvelity prescribing information (PI), container label, and Medication Guide (MG) for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

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

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed container label may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for Axsome Therapeutics, Inc.

We reviewed the Division's draft revisions to the proposed Prescribing Information (PI) and we also reviewed the Medication Guide (MG). Our review did not identify areas of vulnerability that may lead to medication errors. Therefore, we have no comments regarding the PI or MG at this time.

[a] The proposed proprietary name "Auvelity" was found conditionally acceptable in the following review: Howard, C. Proprietary Name Review for Auvelity (dextromethorphan-bupropion) NDA 215430. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 Jul 12. RCM No.: 2021-1044723936.

4 RECOMMENDATIONS FOR AXSOME THERAPEUTICS, INC.

Table 2. Identified Issues and Recommendations for Axsome Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label			
1.	The established name statement is presented as follows (b) (4)	The established name statement on the container label is not consistent with the established name statement that has been determined by the Division.	Revise the established name statement to read as follows: "(dextromethorphan HBr and bupropion HCl) tablets"
2.	The Medication Guide (MG) statement is too small.	The MG statement may be difficult to read due to its small size.	Slightly increase the size of the MG statement in order to increase its prominence.
3.	The net quantity statement is too small.	The net quantity statement may be difficult to locate and read due to its small size.	Increase the size of the net quantity statement.
4.	The statement of dosage (b) (4) is not consistent with the Prescribing Information (PI).	The statement is not consistent with the PI (Section 2.1) which states (b) (4)	To ensure consistency with the PI, revise the statement of dosage to read "Recommended Dosage: See package insert."
5.	The statement "For oral use" is not on the label.	The route of administration should be on the label.	Add the statement "For oral use" to the principal display panel.
6.	According to the Dosage and Administration, the tablets should be swallowed whole and not crushed, divided, or chewed.	The label lacks the cautionary statement regarding crushing, dividing, etc.	Consider adding the following statement to the principal display panel (PDP): "Swallow tablets whole. Do not crush, divide, or chew." If space is limited on the PDP, consider adding the cautionary statement to the side panel.
7.	The proposed proprietary name (b) (4) is on the label.	The proposed proprietary name (b) (4) was found unacceptable. The newly	Change the proprietary name presentation to "Auvelity".

Table 2. Identified Issues and Recommendations for Axsome Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		proposed name “Auvelity” was found conditionally acceptable.	

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Auvelity that Axsome Therapeutics, Inc. submitted on 02/21/2021 and the Division's revisions to the draft PI as of 06/25/2021.

Table 3. Relevant Product Information for Auvelity	
Initial Approval Date	N/A
Active Ingredient	dextromethorphan hydrobromide and bupropion hydrochloride
Indication	Treatment of major depressive disorder (MDD) in adults
Route of Administration	Oral
Dosage Form	Tablets
Strength	45 mg/105 mg (45 mg dextromethorphan hydrobromide and 105 mg bupropion hydrochloride)
Dose and Frequency	The recommended starting dosage is one tablet orally once daily for 3 days. After 3 days, increase to the maximum recommended dosage of one tablet twice daily, given at least 8 hours apart.
How Supplied	Bottles of 30 tablets
Storage	Store in original bottle at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
Container Closure	(b) (4)

APPENDIX F. LABEL AND LABELING

F.1 List of Label and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Auvelity container label and Prescribing Information (PI) submitted by Axsome Therapeutics, Inc. on 02/21/2021. We also reviewed the Division's draft revisions to the PI as of 06/24/2021.

- Container label
- Prescribing Information submitted by Axsome Therapeutics (image not shown) available at: \\CDSESUB1\evsprod\nda215430\0001\m1\us\1-14-1-3-draft-label.pdf

F.2 Label Image (not to scale)

Container Label

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

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/s/

LORETTA HOLMES
07/14/2021 03:20:05 PM

SEVAN H KOLEJIAN
07/18/2021 10:12:25 PM

Clinical Inspection Summary

Date	07/15/2021
From	Jenn Sellers, M.D., Ph.D., Medical Officer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Simran K Parihar, Pharm.D. Regulatory Project Manager David Millis M.D., Clinical Reviewer Michael Davis, M.D., Clinical Team Leader Division of Psychiatry Products (DP)
NDA #	215430
Applicant	Axsome Therapeutics, Inc.
Drug	Dextromethorphan-Bupropion
NME	No
Therapeutic Classification	Antidepressant
Proposed Indication	Treatment of Major Depressive Disorder (MDD)
Consultation Request Date	March 12, 2021
Summary Goal Date	July 20, 2021
Action Goal Date	August 20, 2021
PDUFA Date	August 22, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical data from two clinical trials, Protocols AXS-05-MDD-301 and AXS-05-MDD-201, were submitted to the Agency in support of NDA 215430 for dextromethorphan-bupropion for the treatment of major depressive disorders (MDD). The sponsor, Axsome Therapeutics, Inc., and the clinical investigator (CI) sites of Drs. Harper, Hassman, Joyce, and McGill were inspected in support of this application. Based on the results of these inspections, the conduct of the above studies was adequate, and the clinical data generated from the CI sites appear to be reliable in support of this NDA. However, since allegations (Complaint #9790, see below) against Dr. Hassman could not be investigated further during the inspection because the ORA field investigator was not able to reach the complainant as the phone number provided in the complaint was no longer in service. In addition, the field investigator was not able to interview any of the lab technicians who participated in the inspected studies because they had left the institute. Although the review of study documents was not able find any evidence to support the complaint, we would recommend a sensitivity analysis regarding this site in order to assess the robustness of the study results.

Of note, the inspection result for the sponsor Axsome is based on an inspection summary provided by the FDA field investigator via email and is therefore preliminary. If significantly new or different information is contained in the final FDA Establishment Inspection Report, an addendum to this clinical inspection summary will be filed.

II. BACKGROUND

Dextromethorphan is an uncompetitive antagonist of the N-methyl-D-aspartate receptor (an ionotropic glutamate receptor) and a sigma-1 receptor agonist. Bupropion hydrochloride is an antidepressant and was initially approved in US in 1985 for major depressive disorder (MDD). The study drug, AXS-05, is a fixed dose combination of 45 mg dextromethorphan HBr and 105 mg bupropion hydrochloride.

The sponsor, Axsome Therapeutics, Inc., has been developing AXS-05 for the treatment of MDD. The clinical evidence of the efficacy and safety of AXS-05 in the treatment of MDD came from two randomized controlled clinical trials: The Phase 3 GEMINI trial (Study AXS-05-MDD-301) and the Phase 2 ASCEND trial (Study AXS-05-MDD-201). AXS-05 was granted Breakthrough Therapy Designation for the treatment of MDD on 25 March 2019. Clinical investigator and a sponsor inspection were conducted for the following protocols:

Protocol AXS-05-MDD-301 (GEMINI trial)

Title: "A Randomized, Double-Blind, Placebo-Controlled Trial of AXS-05 in Subjects with Major Depressive Disorder (GEMINI)"

Subjects: 327 subjects were randomized

Study Sites: 43 centers in the US

Study Initiation and Completion Dates: 20 Jun 2019 and 05 Dec 2019

The primary study objective was to evaluate the efficacy of AXS-05 as measured by the change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score to Week 6.

This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of AXS-05 in MDD subjects aged 18 to 65 years. The main inclusion criteria included currently meeting DSM-5 criteria for MDD without psychotic features based on the Structured Clinical Interview for DSM-5 Clinical Trial Version (SCID-5-CT), with a current major depressive episode of at least 4 weeks in duration at Visit 1; a MADRS score of ≥25 and Clinical Global Impression – Severity scale (CGI-S) ≥4 at screening (Visit 1) and Baseline (Visit 2). There were three study periods: an up to 4-week Screening period, a 6-week double-blind treatment period, and a safety follow up period.

Eligible subjects were randomly assigned 1:1 to either AXS-05 (45 mg dextromethorphan-105 mg bupropion) or placebo treatment for 6 weeks. The dosing was once daily in the morning from Days 1 to 3 and then twice a day from Days 4 to 42. During the treatment period, subjects recorded their mood daily by completing a daily visual analog mood scale (VAMS). Study visits occurred at screening (Visit 1), baseline (Day 1, Visit 2), and on Day 4 as well as Weeks 1, 2, 3, 4, 6, and 7 (Visits 3 to 9).

Primary efficacy endpoint was the change from baseline in the MADRS total score to Week 6.

Key secondary efficacy endpoints:

- Change in MADRS total score from baseline to Week 2
- Percentage of subjects achieving remission (MADRS total score of ≤10) at Week 2
- Change in MADRS total score from baseline to Week 1
- Percentage of responders (≥ 50% reduction in MADRS total score) at Week 6

Protocol AXS-05-MDD-201 (ASCEND trial)

Title: "A Randomized, Double-Blind, Active-Controlled Trial of AXS-05 Administered Orally to Subjects with Major Depressive Disorder"

Subjects: 97 subjects were randomized

Study Sites: 4 US clinical investigators participated in the study

Study Initiation and Completion Dates: 31 May 2018 and 27 Dec 2018

The primary study objective was to assess the effect of AXS-05 versus bupropion as measured by the MADRS.

This was a Phase 2, randomized, double-blind, active-controlled study to evaluate the efficacy and safety of AXS-05 in MDD subjects (aged 18 to 65 years) compared to bupropion. There were three study periods: an up to 4-week Screening period, a 6-week double-blind treatment period, and a safety follow up period

Eligible subjects were required to have a diagnosis of MDD and a current major depressive episode (MDE) of moderate or greater severity, based on the site investigator's rating of MADRS ≥25 and a Clinical Global Impression (CGI) severity score (CGI-S) of ≥ 4. In addition, a blinded independent assessor was used to confirm the diagnosis of MDD and a current MDE of moderate or greater severity based on a clinical review. The Quick Inventory of Depressive Symptomatology (Self-Report) (QIDS-SR-16) had to be ≥13 at Screening or Baseline. Eligible subjects were randomly assigned 1:1 into either AXS-05 or placebo treatment for 6 weeks. Study visits occurred at Visit 1, Baseline (Day 0, Visit 2), and on Days 3, 7, 14, 21, 28, 42 and 49 (Visits 3 – 9).

Primary efficacy endpoint was the change from baseline in the MADRS total score to Week 6.

Rationale for Site Selection

Sites were generally selected based on enrollment, good efficacy results, complaints, and inspection history.

Site # 201 in Study AXS-05-MDD-201 and Site #807 in Study AXS-05-MDD-301 were selected because according to the sensitivity analysis results provided by the FDA statistician assigned to this NDA, the data from these sites are critical for the overall efficacy analysis. That is, without the data from Site #201, Study AXS-05-MDD-201 would be considered negative; and without the data from Site #807, Study AXS-05-MDD-301 would be considered negative.

Dr. Hassman was selected to be inspected as part of the PDUFA inspections for this application due to a recent complaint (#9790). The complainant alleged that the Hassman Research Institute asked their employees to do unethical things, such as switching subjects' blood and urine samples to make them eligible for a clinical trial. In addition, the complainant alleged that this issue was not related to a specific trial but occurred across the institute.

The inspection of the sponsor was related to Complaint #9454. OSI received this complaint in February 2020 regarding Axsome Therapeutics' conduct as the sponsor of Protocol AXS-05-301 (i.e., not one of the protocols for this NDA but for the same investigational product). The complainant alleged (b) (4)

(b) (4)

A sponsor inspection was issued as a part of the surveillance inspection and to evaluate the above-described allegations.

III. RESULTS

1. Linda Harper, M.D

Site # 201
618 E. South Street, Suite 100
Orlando, FL 32801
Inspection dates: May 12 - 17, 2021

At this site for Protocol AXS-05-MDD-201, 66 subjects were screened, 51 were enrolled, and 39 subjects completed the study. Twelve subjects discontinued the study. The line listings of these 12 discontinuations with their dates and reasons were verifiable.

The inspection reviewed the signed informed consent forms (ICFs) for all 66 screened subjects, the primary endpoint efficacy data for all 51 enrolled subjects and also included a study record audit for 30 of the enrolled subjects. The study records reviewed included, but not limited to, inclusion/exclusion criteria; randomization, blinding, dosing, and study drug administration; the primary efficacy endpoint; adverse event reporting; and protocol deviations. The study

monitoring, screening & enrollment log, SOPs, ethics committee approval and communications, financial disclosures, FDA 1572s, Dr. Harper's CV, study staff background and training, organizational chart, delegation of authority log, investigational product (IP) shipment packing lists, and master IP accountability log were also reviewed during the inspection.

The primary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events.

2. **Howard Hassman, M.D.**
Site # 823
175 Cross Keys Road, Centennial
Center, Suite 107
Berlin, NJ 8009
Inspection dates: April 15 - May 3, 2021

At this site for Protocol AXS-05-MDD-301, 39 subjects were screened, 23 were enrolled, and 17 subjects completed the study. Six subjects were discontinued. One subject withdrew consent and five subjects were lost of follow up.

The inspection reviewed informed consent forms, study eligibility criteria, adverse events, and drug accountability for all 23 enrolled subjects and the primary and the key secondary efficacy endpoint data for 12 of 23 enrolled subjects. Other subject records reviewed included, but were not limited to, medical histories, physical examinations, progress notes, concomitant medications, protocol deviations and other regulatory records such as Independent Review Board (IRB) approvals, training records, delegation of authority logs, FDA Form 1572s, financial disclosures and monitoring repots.

The primary and the key secondary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events.

There was an anonymous complaint against Dr. Hassman alleging switching of subjects' blood and urine samples to make them eligible for a clinical trial (see Complaint #9790 above). The ORA field investigator called the complainant, but the phone number provided in the complaint was no longer in service. In addition, the field investigator was not able to interview any of the lab technicians who participated in the inspected studies because they had left the institute. Therefore, the complaint could not be investigated further.

Reviewer comment: We recommend a sensitivity analysis with regard to the efficacy data from Dr. Hassman's site because of the allegation that could not be investigated.

3. **John Joyce, M.D.**
Site # 807 for Protocol AXS-05-MDD-301
Site # 401 for Protocol AXS-05-MDD-201
5200 Belfort Road, Suite 420
Jacksonville, FL 32256
Inspection dates: May 3 - 7, 2021

At this site for Protocol AXS-05-MDD-301, 53 subjects were screened, 43 were enrolled, and 33 subjects completed the study. Ten subjects discontinued the study. The reasons of the

discontinuations were described below. All the discontinuations and causes were verifiable.

- Four subjects withdrew consent
- Three subjects (all in AXS-05 group) discontinued due to AEs, which had been reported:
  - Subject #(b) (6) due to restlessness
  - Subject #(b) (6) due to diarrhea and anxiety
  - Subject #(b) (6) due to mental fogginess and visual distortion
- Two subjects were lost to follow up
- One subject (#(b) (6) in placebo group) withdrew consent due to lack of efficacy

At this site for Protocol AXS-05-MDD-201, 3 subjects were screened and enrolled, and one subject completed the study. Two subjects were lost to follow up.

The study records of 25 of 43 enrolled subjects in Study AXS-05-MDD-301 and all three subjects in Study AXS-05-MDD-201 were reviewed. The records reviewed included, but were not limited to, informed consent forms, subject medical records and worksheets, the primary and the key secondary efficacy endpoint data, adverse events, protocol deviations, laboratory reports, and concomitant medications. Other documents (in the regulatory files) were also reviewed, including institutional review board approvals, correspondence between the IRB and Dr. Joyce, study training records, delegation logs, FDA 1572s, financial disclosures, drug accountability, correspondence, and site monitoring correspondence between the monitor and Dr. Joyce.

The primary and the key secondary efficacy endpoint data were verifiable for these 25 of 43 enrolled subjects. There was no evidence of underreporting of adverse events.

4. **Lora McGill, M.D.**
   Site # 808
   6401 Poplar Avenue, Suite 420
   Memphis, TN 38119
   Inspection dates: April 26 - 30, 2021

At this site for Protocol AXS-05-MDD-301, 22 subjects were screened, 14 were enrolled, and 12 subjects completed the study. Two subjects discontinued. One subject withdrew consent and the other was lost to follow-up.

Subject records for all 14 enrolled subjects reviewed included, but were not limited to, informed consents, screening, eligibility and enrollment records, case report forms, clinical records, data collection and verification, primary efficacy endpoint data (MADRS score) as well as clinical global impressions improvement and clinical global impressions severity scores, adverse events, laboratory records, Form 1572, financial disclosure, drug accountability, clinical site training, monitoring procedures and protocol compliance.

The primary and the key secondary efficacy endpoint data were verifiable for all 14 enrolled subjects. There was no evidence of underreporting of adverse events.

5. **Axsome Therapeutics, Inc. (sponsor)**
22 Cortlandt, 16th Floor
New York, NY 10007
Inspection dates: June 21 – July 1, 2021

The sponsor was inspected in accordance with the Sponsor/Monitor/Contract Research Organization (CRO) data validation compliance program, CP 7348.810. The inspection reviewed and assessed monitoring, vendors, data management (audit trails and data reconciliation); CI selection and qualifications (curriculum vitae, financial disclosure, and IRB); CV and job description for medical monitors and clinical site monitors; drug accountability; subject enrollment and disposition data; protocol deviations; primary efficacy data, and adverse events/serious adverse events reporting. No areas of concern were found.

The inspection also investigated Complaint #9454 (see above) regarding the sponsor's adverse event reporting for Study AXS-05-301 (i.e., a study not included in this NDA but with the same investigational product). The inspection did not find any evidence (b) (4) as it was alleged. The sponsor did reclassify one serious adverse event to a non-serious adverse event for one subject (# (b) (6)) for Study AXS-05-MDD-201. Specifically, this subject presented to an emergency room at about 4pm because she had experienced tunnel vision, visual hallucinations, hearing voices, and racing thoughts earlier that day. The psychiatric consult found the subject to be lucid, coherent, oriented, and alert, with no psychotic symptoms, and cleared her for discharge at about 6pm the same day. Since the subject's husband was "out of town", the subject was admitted to the hospital at 6:17pm for overnight observation. The subject was discharged the second day at about 11:30am.

Reviewer's comment: This reclassification of a serious adverse event (to non-serious) seems reasonable and was an isolated event.

{See appended electronic signature page}

Jenn W. Sellers, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Phillip Kronstein, M.D.
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cc:
DARRTS: NDA 215430
DP/Project Manager/Simran K Parihar
DP/Division Director/Tiffany Farchione
DP/Medical Officer/David Millis
DP/Clinical Team Leader/Michael Davis
OSI/Office Director/David Burrow
OSI/Deputy Office Director/Laurie Muldowney
OSI/DCCE/Division Director (Acting)/Kassa Ayalew
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Jenn Sellers
OSI/GCP Program Analyst/Yolanda Patague

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JENN W SELLERS
07/15/2021 09:38:45 AM

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KASSA AYALEW
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

A Review of Published Literature

Date:	July 01, 2021
Reviewer:	Dinci Pennap, PhD, MS, MPH Division of Epidemiology I
Team Leader:	Kira Leishear, PhD, MS Division of Epidemiology I
Deputy Director:	CAPT. Sukhminder K. Sandhu, PhD, MS, MPH Division of Epidemiology I
Subject:	A Review of Published Literature to Assess Maternal Use of Specific Antidepressant Medications During Early Pregnancy and the Risk of Selected Birth Defects
Drug Name:	AXS-05 (dextromethorphan hydrobromide and bupropion hydrochloride)
Application Type/Number:	NDA 215430
Applicant/sponsor:	Axsome Therapeutics
OSE RCM #:	2021-1038

TABLE OF CONTENTS

EXECUTIVE SUMMARY

The Division of Psychiatry (DP) consulted the Division of Epidemiology (DEPI) to evaluate the available published literature to consider whether the data support the risk association for diaphragmatic hernia in infants whose mothers used bupropion during pregnancy, and if the potential safety concern should be included in (b) (4) (b) (4) the label.

Bupropion was approved by the FDA for the treatment of major depressive disorder (MDD) and as an aid in smoking cessation on December 23, 1985 and May 14, 1997, respectively. Subsequently, bupropion sustained release (SR) tablet was approved for MDD and bupropion extended release (XL) tablet was approved for the treatment of MDD and prevention of seasonal affective disorder (SAD) on May 27, 2004. On December 23, 2013, the bupropion label was updated to reflect preliminary findings from epidemiological studies that showed no increased risk of overall congenital malformations and no increased risk for cardiovascular malformations after bupropion exposure during the first trimester. In August 2020, Anderson et al. published updated findings from the same data source and reported increased odds of diaphragmatic hernia following early pregnancy exposure to bupropion. This review assesses the design and quality of the Anderson et al. article.

We identified four articles that focused on in-utero exposure to bupropion and the risk of congenital malformations. Except for the Anderson et al. article, the review articles do not suggest an elevated risk of diaphragmatic hernia. Because no diaphragmatic hernia case was reported in the other observational studies, this review primarily assesses the design and quality of the Anderson article. The article suggests an elevated risk of congenital diaphragmatic hernia following early pregnancy in-utero exposure to bupropion. Findings from other observational studies do not support this notion, and we disagree with the authors' interpretation of the observed elevated odds ratio of diaphragmatic hernia comparing fetal exposure in early pregnancy to exposure in months 4 through 9 of pregnancy. Study design flaws, potential unmeasured confounding, selection bias, and exposure misclassification preclude interpretations of findings from the Anderson article. At best, the Anderson article is hypothesis generating and should be interpreted as such.

DEPI recommends no label updates based on the findings in the Anderson et al. article.

1 INTRODUCTION

The Division of Psychiatry (DP) consulted the Division of Epidemiology (DEPI) to evaluate the available published literature to consider whether the data support the risk association for diaphragmatic hernia in infants whose mothers used bupropion during pregnancy, and if the potential safety concern should be included in (b) (4) (b) (4) the label. This review is for AXS-05 (dextromethorphan hydrobromide & bupropion hydrochloride).

To streamline the literature search and focus on high quality studies, this review will assess published literature from 2010 through May 2021. Articles published before 2010 will be reviewed only if their findings are included in pooled analyses that are published in the assessed period.[1] This review will provide information necessary to determine if (b) (4) the labeling (b) (4) should be updated.

In May 2021 Division of Psychiatry (DP) sent DEPI a consult with the following verbatim request:

> *DPMH would like to consult request to DEPI. They would prefer some feedback within the next 20-30 days, given the timeline of this priority review. AXS-05 (45mg dextromethorphan hydrobromide & 105 mg bupropion Hydrochloride) tablet is indicated for the treatment of major depressive disorder (MDD). Review of the literature for bupropion and pregnancy identified a potential congenital malformation. This newly identified congenital malformation was reported by Anderson et al., which provided the final analysis of the National Birth Defects Prevention Study (NBDPS). Anderson et al. found that after accounting for underlying maternal conditions (covariate modeling), bupropion was only associated with diaphragmatic hernia. The interim results of the NBDPS are described in the current bupropion product labeling (section 8.1) (Wellbutrin SR, 2019) and reported on malformations dealing with left ventricular outflow track obstruction (LVOTO) defects (Alwan et al., 2010) among pregnant women using bupropion. The interim results did not report on diaphragmatic hernia. We were unable to find any other publication where diaphragmatic hernia was associated with bupropion in mothers exposed to bupropion in the 1st trimester of pregnancy. Please review the Anderson 2020 paper and its finding of congenital malformation of diaphragmatic hernia after bupropion use while pregnant. We note the cases in this study are small and there may be some confounding factors such as the higher percentage of smokers in the bupropion-treated group compared to the controls. Smoking is a risk factor for congenital diaphragmatic hernia. The author claims that smoking was corrected for in their model, however, we would like your feedback regarding the covariate modeling approach used in this study to determine*

[1] A 2010 cutoff was used because the label was last updated in 2013 based on findings from a 2010 publication. As at 2010, no other study had associated diaphragmatic hernia with bupropion use in pregnancy.

the significance of the diaphragmatic hernia finding. Please also provide your input as to whether this safety concern warrants inclusion in the labeling.

1.1 BACKGROUND

Bupropion (Wellbutrin®) is recommended at a target dose of 300mg/day as 150mg twice daily. With a mean (±SD) elimination half-life of 21 (±9) hours after chronic dosing, it reaches steady-state plasma concentration within 8 days. When bupropion was administered to pregnant rats during organogenesis, there was no evidence of fetal malformations at doses up to approximately 11 times the maximum recommended human dose (MRHD) of 400 mg/day. When given to pregnant rabbits during organogenesis, non-dose-related increases in incidence of fetal malformations, and skeletal variations were observed at doses approximately equal to the MRHD and greater. Decreased fetal weights were seen at doses twice the MRHD and greater.

1.2 REGULATORY HISTORY

Bupropion	NDA	Regulatory Action	Date
Immediate Release Tablet	018644	Approval	December 23, 1985
Sustained Release Tablet	020358	Approval	May 27, 2004
Extended Release Tablet	021515	Approval	May 27, 2004
Zyban	020711	Approval	May 14, 1997
Teratogenic Information in Label Package Insert	Suppl-46		December 23, 2013

Wellbutrin® (bupropion hydrochloride), an antidepressant of the aminoketone class, is chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitor, or other known antidepressant agents. It was approved by the FDA for the treatment of major depressive disorder (MDD) on December 23, 1985. On May 14, 1997, FDA approved Zyban® (bupropion hydrochloride) as an aid in smoking cessation treatment with an indicated starting dose of 150mg per day. Subsequently, bupropion sustained release (SR) tablet was approved for MDD and bupropion extended release (XL) tablet was approved for the treatment of MDD and prevention of seasonal affective disorder (SAD) on May 27, 2004.

On July 16, 2013, DPMH reviewed[2] a case control study by Louik et al. that assessed bupropion exposure in pregnancy and risk of cardiac defects. In collaboration with DEPI, DPMH concluded that the available cumulative data on the risk of congenital malformations overall, based on epidemiological studies of pregnant women exposed to bupropion in the first trimester, are consistent across studies and indicate no increased risk. However, they noted that some of these studies present conflicting results regarding

[2] Leyla Sahin, Melissa S Tassinari, Lynne P Yao. New case control study on bupropion exposure in pregnancy and risk of cardiac defects; Pregnancy Labeling. DARRTS reference ID: 3342043

the risk of specific cardiovascular defects (LVOTO and ventricular septal defect), and an increased risk for specific cardiovascular defects following bupropion exposure during pregnancy could not be determined. Therefore, DPMH concluded that this information should not be included in the 'Risk Summary' but should be included under 'Data'. In concurrence with DP and DEPI, DPMH concluded that available data do not support a reclassification of the pregnancy category from C to D. In addition, they noted that the current regulatory language under Pregnancy, "WELLBUTRIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus" adequately reflects the risk-benefit profile regarding use in pregnancy.

On December 23, 2013, the Wellbutrin® (bupropion) label was updated to reflect findings from epidemiological studies[3,4,5,6] that showed no increased risk of overall congenital malformations and no increased risk for cardiovascular malformations following bupropion exposure during the first trimester. Specifically, the prospectively observed rate of cardiovascular malformations in pregnancies with exposure to bupropion in the first trimester in an international pregnancy registry was 1.3% (9 cardiovascular malformations/675 first-trimester maternal bupropion exposures), which is similar to the background rate of cardiovascular malformations (approximately 1%).[7] The updated label also reflects findings from a case-control study (6,853 infants with cardiovascular malformations and 5,763 with non-cardiovascular malformations) from the National Birth Defects Prevention Study (NBDPS) that showed no increased risk for overall cardiovascular malformations after bupropion exposure during the first trimester (Supplement-46).

On April 20, 2018, DPMH reviewed the Pregnancy and Lactation labeling subsection for Wellbutrin and Wellbutrin SR and made the following conclusion:[8]

> *Data from published sources and the applicant's database have not definitively demonstrated an association of bupropion and major congenital malformations. Current labeling already*

[3] Alwan S, Reefhuis J, Botto LD et al. Maternal use of Bupropion and risk for congenital heart defects. Am J Obstet Gynecol. 2010; 203:52e1-6.

[4] Cole JA, Modell JG, Haight BR, et al. Bupropion in pregnancy and the prevalence of congenital malformations. Pharmacoepidemiol Drug Saf 2007; 16: 474-484.

[5] Chun-Fai-Chan B, Koren G, Fayez I et al. Pregnancy outcome of women exposed to bupropion during pregnancy: A prospective comparative study. American Journal of Obstetrics and Gynecology. 2005; 192:932-6.

[6] Louik C., Kerr S., and Mitchell A.A. First-trimester exposure to bupropion and risk of cardiac malformations. Pharmacoepidemiol Drug Saf. 2014; 23(10):1066-1075

[7] Wellbutrin Label. https://www.accessdata fda.gov/drugsatfda_docs/label/2017/018644s052lbl.pdf reference ID: 4094044

[8] Roca, C., Dinatale, M., Yao, L.P. Pregnancy and Lactation Labeling for Wellbutrin and Wellbutrin SR. DARRTS reference ID: 4251915

addresses issues related to major published epidemiologic studies and results from the completed pregnancy registry. Labeling will be updated to current PLLR formatting with "Data" and "Clinical Considerations" subheadings.

1.3 PRODUCT LABELING

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

Data from epidemiological studies of pregnant women exposed to bupropion in the first trimester indicate no increased risk of congenital malformations overall. All pregnancies, regardless of drug exposure, have a background rate of 2% to 4% for major malformations, and 15% to 20% for pregnancy loss. No clear evidence of teratogenic activity was found in reproductive developmental studies conducted in rats and rabbits; however, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at doses approximately equal to the maximum recommended human dose (MRHD) and greater and decreased fetal weights were seen at doses twice the MRHD and greater. WELLBUTRIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Consider the risks of untreated depression when discontinuing or changing treatment with antidepressant medications during pregnancy and postpartum.

Human Data

Data from the international bupropion Pregnancy Registry (675 first-trimester exposures) and a retrospective cohort study using the United Healthcare database (1,213 first trimester exposures) did not show an increased risk for malformations overall.

No increased risk for cardiovascular malformations overall has been observed after bupropion exposure during the first trimester. The prospectively observed rate of cardiovascular malformations in pregnancies with exposure to bupropion in the first trimester from the international Pregnancy Registry was 1.3% (9 cardiovascular malformations/675 first-trimester maternal bupropion exposures), which is similar to the background rate of cardiovascular malformations (approximately 1%). Data from the United Healthcare database and a case-control study (6,853 infants with cardiovascular malformations and 5,763 with non-cardiovascular malformations) from the National Birth Defects Prevention Study (NBDPS) did not show an increased risk for cardiovascular malformations overall after bupropion exposure during the first trimester.

Study findings on bupropion exposure during the first trimester and risk for left ventricular outflow tract obstruction (LVOTO) are inconsistent and do not allow

conclusions regarding a possible association. The United Healthcare database lacked sufficient power to evaluate this association; the NBDPS found increased risk for LVOTO (n = 10; adjusted OR = 2.6; 95% CI: 1.2, 5.7), and the Slone Epidemiology case control study did not find increased risk for LVOTO.

Study findings on bupropion exposure during the first trimester and risk for ventricular septal defect (VSD) are inconsistent and do not allow conclusions regarding a possible association. The Slone Epidemiology Study found an increased risk for VSD following first trimester maternal bupropion exposure (n = 17; adjusted OR = 2.5; 95% CI: 1.3, 5.0) but did not find increased risk for any other cardiovascular malformations studied (including LVOTO as above). The NBDPS and United Healthcare database study did not find an association between first trimester maternal bupropion exposure and VSD.

For the findings of LVOTO and VSD, the studies were limited by the small number of exposed cases, inconsistent findings among studies, and the potential for chance findings from multiple comparisons in case control studies.

Animal Data

In studies conducted in rats and rabbits, bupropion was administered orally during the period of organogenesis at doses of up to 450 and 150 mg per kg per day, respectively (approximately 11 and 7 times the MRHD, respectively, on a mg per m2 basis). No clear evidence of teratogenic activity was found in either species; however, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at the lowest dose tested (25 mg per kg per day, approximately equal to the MRHD on a mg per m2 basis) and greater. Decreased fetal weights were observed at 50 mg per kg and greater.

When rats were administered bupropion at oral doses of up to 300 mg per kg per day (approximately 7 times the MRHD on a mg per m2 basis) prior to mating and throughout pregnancy and lactation, there were no apparent adverse effects on offspring development.

8.3 Nursing Mothers

Bupropion and its metabolites are present in human milk. In a lactation study of 10 women, levels of orally dosed bupropion and its active metabolites were measured in expressed milk. The average daily infant exposure (assuming 150 mL per kg daily consumption) to bupropion and its active metabolites was 2% of the maternal weight-adjusted dose. Exercise caution when WELLBUTRIN is administered to a nursing woman.

2 REVIEW METHODS AND MATERIALS

This review will focus on published observational studies of in-utero exposure to bupropion and congenital malformations, particularly diaphragmatic hernia, in humans.

DP requested a review of a publication by Anderson et al.[9] In addition, we conducted five PubMed searches beginning January 1, 2010 and ending on May 31, 2021 with the following search terms:

(((bupropion) AND (diaphragmatic hernia)) AND (Humans[MeSH Terms])) AND (("2010/01/01"[Date - Publication] : "2021/05/31"[Date - Publication]))])) (**0 article**)

(((bupropion) AND (birth defects)) AND (Humans[MeSH Terms])) AND (("2010/01/01"[Date - Publication] : "2021/05/31"[Date - Publication])) (**33 articles**)

(((bupropion) AND (congenital malformations)) AND (Humans[MeSH Terms])) AND (("2010/01/01"[Date - Publication] : "2021/05/31"[Date - Publication])) (**23 articles**)

(((bupropion) AND (pregnancy)) AND (Humans[MeSH Terms])) AND (("2010/01/01"[Date - Publication] : "2021/05/31"[Date - Publication])) (**93 articles**)

((antidepressants) AND (diaphragmatic hernia)) AND (("2010/01/01"[Date - Publication]: "2021/05/31"[Date - Publication])) **(5 articles)**

The searches were restricted to English language and human subjects. Studies were selected for review if: 1) authors investigated bupropion use during pregnancy, 2) they had a comparator group, 3) they reported an effect measure, and 4) the outcomes investigated included any major congenital malformations and/or diaphragmatic hernia.

Of the 154 articles retrieved, 38 were duplicate studies, 46 assessed outcomes that are unrelated to congenital malformation/diaphragmatic hernia, 46 were commentaries or letters to the editor, 4 articles were case reports, 8 articles included study populations other than pregnant women (2 animal studies, 5 adult studies, and 1 study of children and adolescents), 1 article did not assess bupropion exposure, 1 study had a small sample size of bupropion users (n=72), 1 article was a meta-analysis of randomized clinical trials, and 5 studies were not pharmacoepidemiologic studies, leaving 4 remaining studies including the Anderson et al article.[1,10,11,12]

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[9] Anderson KN, Lind JN, Simeone RM, et al. Maternal Use of Specific Antidepressant Medications During Early Pregnancy and the Risk of Selected Birth Defects. JAMA Psychiatry. 2020;77(12):1246–1255. doi:10.1001/jamapsychiatry.2020.2453

[10] Turner E, Jones M, Vaz LR, Coleman T. Systematic Review and Meta-Analysis to Assess the Safety of Bupropion and Varenicline in Pregnancy. Nicotine Tob Res. 2019 Jul 17;21(8):1001-1010. doi: 10.1093/ntr/nty055. PMID: 29579233.

[11] Tran DT, Preen DB, Einarsdottir K, Kemp-Casey A, Randall D, Jorm LR, Choi SKY, Havard A. Use of smoking cessation pharmacotherapies during pregnancy is not associated with increased risk of adverse pregnancy outcomes: a population-based cohort study. BMC Med. 2020 Feb 5;18(1):15. doi: 10.1186/s12916-019-1472-9. PMID: 32019533; PMCID: PMC7001233.

[12] Alwan S, Reefhuis J, Botto LD, et al. Maternal use of bupropion and risk for congenital heart defects. American Journal of Obstetrics and Gynecology. 2010 Jul;203(1):52.e1-6. DOI: 10.1016/j.ajog.2010.02.015.

In addition to the above PubMed search, we conducted a web search for bupropion and diaphragmatic hernia and found two reported cases of diaphragmatic hernia in a bupropion pregnancy registry that had a relatively small sample size, lacked an appropriate comparison group, and had a high loss to follow-up rate.[13] Findings from the registry study did not suggest an elevated risk of birth defects and the study was not included in the list of reviewed articles because of their high loss to follow-up rate and because the exposed population was only sufficient to detect major teratogenicity and not specific defects.

3 REVIEW RESULTS

3.1 ANDERSON ET AL., 2020

3.1.1 Study Objective

This study examined associations between individual antidepressants and specific birth defects with and without attempts to partially account for potential confounding by underlying conditions.

3.1.2 Study Methods

3.1.2.1 Design & Setting

This population-based, multicenter case-control National Birth Defects Prevention Study included cases with selected birth defects who were identified from surveillance systems. Controls were randomly sampled live-born infants without major birth defects identified via vital records or hospital birth logs from the same birth months and state- or county-level (depending on the site) geographic catchment area as cases. Mothers participated in a computer-assisted telephone interview 6 weeks to 24 months after the estimated due date (EDD), with a median time to interview of 11 months for case- and 9 months for control mothers (67% case and 65% control mother participation, respectively).

3.1.2.2 Study Type

Case-control study [National Birth Defects Prevention Study (NBDPS)]

3.1.2.3 Population & Time Period

Study sites collected data on females aged 12 through 53 years who had pregnancies ending on or after October 1, 1997, through those with an estimated date of delivery on or before December 31, 2011.

3.1.2.4 Exclusion Criteria

Infants with known single-gene disorders or chromosomal abnormalities were excluded. Mothers were excluded if they had incomplete medication history (797 [1.8%]), pre-

[13] The Bupropion Pregnancy Registry Final Report
https://pregnancyregistry.gsk.com/documents/bup_report_final_2008.pdf

pregnancy type 1 or 2 diabetes (830 [1.9%]), or used a known teratogenic medication during the 3 months before conception or during pregnancy (215 [0.5%]). Mothers were also excluded if they, without prompting, reported having a depressive, bipolar, or anxiety disorder but did not report antidepressant use (79 [0.2%]).

3.1.2.5 Protected Health Information (PHI) Requirements

Institutional review board approval was provided by all sites and mothers gave oral interview informed consent.

3.1.2.6 Outcome & Exposure

Cases with selected birth defects were identified from surveillance systems using standard case definitions and included live births (all sites), stillbirths (all sites but New York before 2000 and New Jersey), and terminations (all sites except Georgia before 1999, Massachusetts before 2011, New York before 2000, and New Jersey). Clinical data were abstracted from medical records and classified by clinician geneticists and other clinicians.

Exposed population. Mothers were asked about the use of citalopram, fluoxetine, paroxetine, sertraline, venlafaxine, and bupropion during the 3 months before conception or during pregnancy. Mothers were asked start and stop dates, duration, and frequency of medication use. Timing before or during pregnancy was calculated using pregnancy months (consecutive 30-day intervals from the estimated conception date to delivery/end of pregnancy). Medications were coded using Boston University's Slone Drug Dictionary which links medication products to corresponding active components. The authors identified antidepressants in the following classes: SSRI, SNRI, tricyclic antidepressants and other norepinephrine reuptake inhibitor, monoamine oxidase inhibitor, and other antidepressants.

Early pregnancy exposure was defined as maternal report of using 1 or more medication product(s) in these classes in any dose, duration, or frequency from the month before conception through the third pregnancy month. Early pregnancy antidepressant use was coded to indicate component (e.g., sertraline only) or class-level (e.g., SSRIs only) monotherapy exposure; when multiple antidepressants were used, women were coded as such.

Unexposed population. Women were considered unexposed if they reported no antidepressant use during the 3 months before conception through their pregnancy's end. Women were considered exposed only outside of early pregnancy if they reported exposure to any antidepressant, but solely during the 2 to 3 months before conception and/or pregnancy months 4 through 9.

Table 1. Birth Defects assessed in the Anderson et al. Article

Any heart defects

- Conotruncal defects
  - Tetralogy of Fallot
  - d'Transposition of the great arteries
  - Double outlet right ventricle, other type
- Atrioventricular septal defects
- Anomalous pulmonary venous return
  - Total anomalous pulmonary venous return
- Left ventricular outflow tract obstruction defects
  - Hypoplastic left heart syndrome
  - Coarctation of the aorta
  - Aortic stenosis
- Right ventricular outflow tract obstruction defects
  - Pulmonary valve stenosis
- Septal defects
  - VSD – peri-membranous
  - VSD – muscular (not simple)
  - ASD – secundum
- Single Ventricle/Complex Heart

Any neural tube defects

- Anencephaly and craniorachischisis
- Spina bifida

Other defects

- Hydrocephaly
- Dandy-Walker malformation
- Cataracts
- Glaucoma/anterior chamber defects
- Anotia/Microtia
- Any oral cleft
  - Cleft palate only
  - Cleft lip with or without cleft palate
- Esophageal atresia
- Intestinal atresia/stenosis
- Duodenal atresia/stenosis
- Anorectal atresia/stenosis
- Hypospadias, second and third degree
- Any limb deficiency
  - Longitudinal limb deficiency
  - Transverse limb deficiency
- Craniosynostosis
- Diaphragmatic hernia
- Omphalocele
- Gastroschisis

3.1.2.7 Covariates

Maternal race/ethnicity (non-Hispanic White, not non-Hispanic White), pre-pregnancy BMI ($\geq$30 kg/m^2), maternal education (>12 years, $\leq$12 years), early pregnancy smoking (yes, no), and early pregnancy alcohol use (yes, no).

3.1.2.8 Sample Size/Power

The NBDPS included 32,200 case and 11,829 control mothers. The Anderson et al. study included 30,630 case mothers of infants with birth defects and 11,478 control mothers. Early pregnancy antidepressant use was reported by 1562 cases (5.1%) and 467 control mothers (4.1%). Of these, 1570 were exposed to selective serotonin reuptake inhibitors, 208 were exposed to serotonin-norepinephrine reuptake inhibitors, 57 were exposed to tricyclic and other norepinephrine reuptake inhibitors, and 341 were exposed to other antidepressants (of those exposed to other antidepressants, 277 were exposed to bupropion in early pregnancy).

3.1.2.9 Statistical Analyses

To identify associations between early pregnancy antidepressant exposure and specific birth defects, Anderson and colleagues used multivariable logistic regression to calculate adjusted odds ratios (aORs) and 95% confidence intervals for NBDPS-eligible birth defects that had 4 or more exposed cases.

They tested 2 model sets:

1) Model 1: Mothers exposed to each antidepressant during early pregnancy compared with mothers unexposed to an antidepressant before or during pregnancy
2) Model 2: Mothers exposed to each antidepressant during early pregnancy compared with mothers only exposed to an antidepressant outside of early pregnancy (to account partially for confounding by the underlying condition)

Model sets 1 of birth defect analyses, which compared early pregnancy antidepressant-exposed women with women unexposed to antidepressants before and during pregnancy, were adjusted for maternal race/ethnicity, pre-pregnancy body mass index, education, and early pregnancy smoking and alcohol use. Covariate selection was different for Models 1 and 2 (only maternal education was included in the model). To assess the potential role of the different covariates in observed differences in the aORs in Models 1 and 2, a sensitivity analysis controlling for the same covariates in the both models was performed.

The authors reported having substantial power to detect small to moderate effect sizes for many associations. Because the power to detect rarer birth defects was limited given smaller control-case ratios, especially for the confounding by underlying condition analyses, they considered effect sizes when interpreting results instead of statistical significance according to the guidelines by the American Statistical Association. They also noted associations as meaningfully elevated if aORs were 2.0 or greater and lower confidence interval bounds were 0.8 or greater.

3.1.3 Study Results

Compared with unexposed control mothers, early pregnancy antidepressant-exposed control mothers were more likely to be older, non-Hispanic white, have higher levels of education, have a higher pre-pregnancy body mass index, report early pregnancy smoking or alcohol use, periconceptional folic acid use, and have a previous live birth. Compared with control mothers only exposed to an antidepressant outside of early pregnancy, early pregnancy antidepressant-exposed control mothers had higher levels of education.

In model 1, they observed elevated aORs for bupropion and 3 defects: 1) Hypoplastic left heart syndrome (HLHS) [aOR 2.08 (95% CI: 0.82-5.28)]; 2) Intestinal atresia/stenosis [aOR 2.69 (95% CI: 0.96-7.59)]; 3) Diaphragmatic hernia [aOR 2.77 (95% CI: 1.34 – 5.71). Only the odds ratio for diaphragmatic hernia was statistically significant. In model 2, after accounting for the underlying condition, the odds ratio for HLHS was attenuated [aOR 1.05 (95% CI: 0.35-3.16)] while they observed an elevated aOR for bupropion and diaphragmatic hernia (aOR, 6.50; 95% CI, 1.85-22.88). The number of exposed cases of intestinal atresia/stenosis was not sufficient to calculate an aOR.

The observed associations between early pregnancy antidepressant use and specific birth defects, after accounting at least partially for the underlying condition, were largely similar in the main analysis and the sensitivity analysis.

Table 2. Bupropion Exposure and Diaphragmatic Hernia

Model 1: Unexposed Comparators				**Model 2**: Exposed Comparators			
	Cases	Controls	Total		Cases	Controls	Total
Bupropion				**Bupropion**			
Yes	9	45	54	Yes	9	45	54
No	802	10,886	11,688	No	4	125	129
Total	811	10,931	11,742		13	170	183

3.1.4 Study Conclusions

Findings suggest varied risks for specific birth defects after early pregnancy use of individual SSRIs, venlafaxine, and bupropion, all of the authors reported as first-line antidepressants. These findings suggest that confounding by underlying conditions should be considered when assessing congenital malformation risks. The authors concluded that for women who require antidepressants during pregnancy, relative differences in the safety of specific medications may be useful to consider in risk-benefit decision-making.

3.2 ALWAN ET. AL 2010

3.2.1 Study Objective

This study aimed to determine if maternal bupropion treatment in early pregnancy is associated with congenital heart defects in the infant.

3.2.2 Study Methods

3.2.2.1 Design & Setting

This study used data from the NBDPS, a multi-site case-control study of environmental and genetic risk factors for >30 selected categories of major birth defects. The authors assessed infants born on or after October 1, 1997, who had an EDD on or before December 31, 2004.

3.2.2.2 Study Type

Case-control study [National Birth Defects Prevention Study (NBDPS)]

3.2.2.3 Population & Time Period

The authors assessed infants born on or after October 1, 1997, who had an EDD on or before December 31, 2004.

3.1.2.4 Exclusion Criteria

Infants with recognized or strongly suspected chromosomal abnormalities or single-gene conditions were excluded from the study. Infants of women with pregestational type 1 or 2 diabetes (304 case and 32 control mothers) were excluded from adjusted analyses

because of the strong association of diabetes with birth defects. Infants with incomplete maternal interviews were excluded (n=276) and mothers who reported having depression but who did not report use of an antidepressant during their pregnancy were excluded (n=6).

Not all types of heart defects were included in the NBDPS; those that were excluded were either heart defects that were not well ascertained in infancy, very rare, often related to preterm delivery (patent ductus arteriosus, patent foramen ovale), vascular defects that are not true malformations of the heart, or heart defects that were associated with chromosomal abnormalities.

3.2.2.4 Protected Health Information (PHI) Requirements,

Institutional review board approval was provided by all participating sites.

3.2.2.5 Outcome & Exposure

Case infants were ascertained by population-based birth defects surveillance systems at 10 study sites (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah). Case infants were either live births, fetal deaths >20 weeks' gestation, or electively terminated pregnancies with reliably ascertained defects (Arkansas, California, Georgia, Iowa, New York [since 2000], North Carolina, Texas, and Utah). Control infants were liveborn with no major birth defects, randomly selected from the same geographical populations using either birth hospital or vital records. Only 1 case or control infant was included from each multifetal pregnancy. Four major categories of heart defects and 6 other categories of birth defects met the inclusion criterion of at least 3 cases exposed to bupropion in the period between 1 month before and 3 months after conception.

Exposed population. Mothers were asked during the interview if they took any medications from a provided list of medications, which included Wellbutrin and Zyban. Exposure was defined as reported use of bupropion anytime between 1 month before and 3 months after conception.

Unexposed population. Women were considered unexposed if they did not use any antidepressant at any time during pregnancy.

3.2.2.6 Covariates

The following potential confounders were evaluated: maternal age (<35, ≥35 years), maternal race (non-Hispanic white, other), maternal education (≤12 years, >12 years), maternal obesity before pregnancy (body mass index <30 kg/m^2, ≥30 kg/m^2), maternal smoking and alcohol use from 1 month before to 3 months after conception, use of a dietary supplement containing folic acid from 1 month before to 1 month after conception, annual family income (<$20,000, ≥$20,000), plurality (singleton, twins and above), and parity (no previous live births, ≥1 live birth).

3.2.2.7 Sample Size/Power

A total of 12,383 case infants (including 6853 diagnosed with at least 1 of the selected heart defects and 5763 diagnosed with at least 1 of the 6 categories of noncardiac defects

studied) and 5869 control infants were analyzed. Among all case and control mothers, 90 (0.5%) reported use of bupropion in the 1 month before to 3 months after conception.

3.2.2.8 Statistical Analyses

Crude analyses were done using Pearson $\chi 2$ tests. Crude and adjusted odds ratios (ORs) and Fisher's exact confidence limits were estimated. Only heart defects or other birth defect categories that had at least 3 cases exposed to bupropion in the period from 1 month before to 3 months after conception were analyzed in the study.

3.2.3 Study Results

A statistically significant association was observed between the occurrence of a left outflow tract heart defect in the infant and maternal bupropion use, based on 10 exposed pregnancies (adjusted OR, 2.6; 95% confidence interval [CI], 1.2–5.7). The main diagnoses assigned to the 10 exposed cases were coarctation of the aorta in 5 cases (1 of which also had features of a hypoplastic left heart variant), hypoplastic left heart syndrome in 3 cases, and aortic stenosis in 2 cases. Out of the 10 exposed cases with left outflow tract defects, 7 were isolated cardiovascular defects, 2 also had multiple noncardiac birth defects, and 1 infant who had coarctation of aorta was suspected to have PHACE syndrome (P, Posterior fossa abnormalities and other structural brain abnormalities; H, Hemangioma(s) of the cervical facial region; A, Arterial cerebrovascular anomalies; C, Cardiac defects, aortic coarctation and other aortic abnormalities; E, Eye Anomalies).

Mothers of all 10 cases reported taking Wellbutrin. None of these 10 mothers reported concomitant use of a medication with known teratogenic effects, although two also reported use of other antidepressants (fluoxetine and paroxetine in 1 case and fluoxetine and sertraline in the other) in the first trimester. Limiting the exposure to the period of 2 months after conception, when cardiac embryogenesis is most likely to be susceptible to a teratogenic effect, reduced the number of cases exposed to 7 but did not affect the point estimate for the OR, and the association remained of borderline statistical significance (adjusted OR, 2.6; 95% CI, 1.0–6.4).

They also tested crude and adjusted associations of any congenital heart defect included in the NBDPS with maternal bupropion use, but exposure prevalence was not significantly different between cases and controls (OR, 1.4; 95% CI, 0.8–2.5; n = 34). Likewise, no significant association with maternal bupropion use was observed with any of the 6 noncardiac defects categories analyzed [neural tube defects, cleft lip with or without palate, cleft palate, hypospadias (second or third degree), limb deficiency, and gastroschisis].

3.2.4 Study Conclusions

The authors concluded that their results are based on exploratory analyses of a case-control study and therefore inconclusive. Further studies are needed to confirm their findings in other datasets and to assess whether the risk extends to other birth defects. Notably, the observed absolute risk for left outflow tract heart defects in this study is small. Nevertheless, risks and benefits of antidepressant medications need to be considered on a case-by-case basis and clearly presented to women who are pregnant or

planning pregnancy so that they can make informed decisions in consultation with their physicians. No case of diaphragmatic hernia was reported in this study.

3.3 TRAN ET. AL 2020

3.3.1 Study Objective

To assess the risk of adverse perinatal outcomes and major congenital anomalies associated with the use of varenicline, bupropion and nicotine replacement therapy (NRT) in pregnancy in Australia.

3.3.2 Study Methods

3.3.2.1 Design & Setting

The Smoking MUMS (Maternal Use of Medications and Safety) is a cohort design based on all pregnancies that resulted in a birth (gestational age ≥ 20 weeks or birthweight ≥ 400 g) in two Australian states, New South Wales (NSW) and Western Australia (WA), between 2003 and 2012. The study used linked records from four data sources including perinatal data (deliveries in 2003–2012), dispensing data for pharmaceuticals subsidized through the Pharmaceutical Benefits Scheme (2003–2013), hospital admissions (2001–2013) and deaths (2003–2014).

3.3.2.2 Study Type: Cohort study

3.3.2.3 Population & Time Period

The authors identified a base cohort of pregnant women (conception between 1 January 2004 and 9 April 2012) who smoked during pregnancy. Conception date was estimated using the equation: date of conception = date of delivery − gestational age at delivery × 7 + 14 days. The beginning and end points of cohort entry ensure that dispensing data were available for at least 1 year prior to conception and deliveries in 2012 did not disproportionately include pregnancies with gestation shorter than 40 weeks.

3.3.2.4 Exclusion Criteria

Exclusion criteria included multiple births, conception within 6 months from the immediate preceding delivery, interstate residents and overseas visitors (likely incomplete capture of hospital admission and dispensing data), use of multiple smoking therapies in the same pregnancy, use of potentially teratogenic medications during pregnancy (category D and X, according to the Australian Therapeutic Goods Administration classification system), likely data errors (birthweight < 1000 g whilst gestational age > 38 weeks, birthweight > 5500 g whilst gestational age < 37 weeks, based on the Australian birthweight chart) and missing data (mostly due to geographical area of residence and Apgar score not being recorded). In the analysis of the major congenital anomaly outcome, pregnancies linked to anomalies due to chromosomal malformations, viral infection (e.g. cytomegalovirus, rubella) and known exogenous causes were also excluded.

3.3.2.5 Protected Health Information (PHI) Requirements,

The study was approved by the Australian Institute of Health and Welfare Ethics Committee, the NSW Population and Health Services Research Ethics Committee, the Department of Health WA Human Research Ethics Committee, the Aboriginal Health and Medical Research Council of NSW Ethics Committee and the Western Australian Aboriginal Health Ethics Committee. The study used routinely collected data that have been anonymized. Waiver of consent to participate was obtained.

3.3.2.6 Outcome & Exposure

The primary outcomes of the study were whether a woman or neonate experienced any adverse perinatal event at birth and whether the neonate had any major congenital anomaly. Any adverse perinatal event was a composite of 10 individual birth outcomes, including preterm birth (< 37 weeks, medically indicated or spontaneous), small for gestational age (SGA, birthweight < 10th percentile sex- and gestational age-specific), Apgar score at 5 min < 7, admission to neonatal special care (NSC), severe neonatal morbidity complications, emergency caesarean section, severe maternal morbidity complications, preterm premature rupture of membranes (PPROM), placental abruption and perinatal death (stillbirth or 28-day neonatal death). These outcome variables were derived from the perinatal record, hospital record relating to the mother's delivery, hospital record relating to the baby's birth and mortality data. Outcomes including SGA, NSC admission, Apgar score and severe neonatal morbidity complications were assessed among live births only.

The second primary outcome was a diagnosis of any major congenital anomaly recorded in hospital admissions occurring within 18 months from birth, among live-born babies in NSW.

Dispensing data included records of all subsidized varenicline, NRT patches and bupropion. Records of these therapies dispensed in the period from 100 days pre-conception to date of delivery were identified; the earliest dispensing in this period was referred to as the index dispensing. Days covered by each dispensing was estimated by dividing the quantity dispensed by recommended daily dosage.

A pregnancy was identified as exposed if there were one or more dispensings of the therapy in the gestation period (i.e. conception to delivery) or pre-conception dispensings were sufficient to last into the gestation period (i.e. date of the index dispensing + days covered by pre-conception dispensings ≥ date of conception). Date of exposure was defined as either (i) date of the index dispensing if dispensed after conception or (ii) date of conception if pre-conception dispensings were sufficient to last into the gestation period or (iii) date of the first post-conception dispensing if pre-conception dispensings were insufficient to last into the gestation period.

3.3.2.7 Covariates

Covariates for propensity scores models included state of birth, year of conception, maternal age at conception, Aboriginal and/or Torres Strait Islander status, country of birth, marital status, quintiles of socio-economic disadvantage scores associated with the residential area, geographical remoteness of the residential area, private health insurance,

parity, previous caesarean section, number of hospital admissions in the year prior to conception and pre-existing maternal morbidities (mental health, chronic airway conditions, diabetes, hypertension, cardiovascular diseases, epilepsy, chronic renal diseases, thyroid disorders, substance and alcohol diagnoses, anemia and coagulation disorders, the use of steroids, non-steroid anti-inflammatory drugs and medications for gastro-esophageal reflux diseases). For the analysis of congenital anomalies, the propensity score model included an additional variable indicating whether the mother had previously had a child with a major congenital anomaly.

3.3.2.8 Sample Size/Power

There were 1,017,731 pregnancies belonging to 686,884 women in NSW and WA. The base cohort included 103,753 women who smoked in 140,913 pregnancies; of those, 13,667 pregnancies were excluded. Following the selection of one pregnancy per woman, data analyses included 233, 1057, and 330 women who were exposed to bupropion, varenicline, and NRT, respectively, and 96,255 unexposed women.

3.3.2.9 Statistical Analyses

For analyses addressing the primary outcome, each exposed pregnancy was matched to ten unexposed pregnancies on propensity score, using a greedy five- to one-digit algorithm. To address the second primary outcome, matching (1:1 ratio) was done using both propensity score and gestational age at exposure. Absolute standardized differences were calculated to assess balance in the characteristics of the comparison groups (balanced if the difference < 0.1). Cox proportional hazard modelling (discrete tier for matched data, gestational week as time scale) was used to estimate hazard ratios (HRs). In the Cox models, exposure was defined as a time-dependent variable, i.e. a pregnancy was considered unexposed until the gestational week at exposure. The window of exposure was the first trimester (gestational week at exposure < 13) when examining congenital anomalies, up to week 37 (gestational week at exposure < 37) for the composite adverse perinatal event and preterm birth, and until delivery for other individual perinatal outcomes.

3.3.3 Study Results

The risk of having any adverse perinatal event was not significantly different between bupropion-exposed and unexposed pregnancies (hazard ratio [HR] 0.93, 95% confidence interval [CI] 0.73 to 1.19) or between NRT-exposed and unexposed pregnancies (HR 1.02, 95% CI 0.84 to 1.23). Compared to unexposed women, there was a lower risk of any adverse perinatal event in those who were exposed to varenicline (HR 0.86, 95% CI 0.77 to 0.97).

3.3.4 Study Conclusions

The authors concluded that there was also no significant increase in the risk of any adverse perinatal event associated with exposure to bupropion and NRT. No case of diaphragmatic hernia was reported in this study.

3.4 TURNER ET. AL 2019

3.4.1 Study Objective

To review evidence for the safety of varenicline and bupropion in pregnancy

3.4.2 Methods

3.4.2.1 Study Selection and Inclusion

The authors searched MEDLINE, EMBASE, CINAHL, and PsychINFO databases and hand-searched reference lists from reviews. They also searched for ongoing and unpublished studies at: www.gsk-clinicalstudyregister.com; clincialtrials.gov; www.who.int/trialsearch; www.controlled-trials.com/isrctn; and www.ukctg.nihr.ac.uk. As bupropion and varenicline were licensed and became available relatively recently, they limited their search to studies published from 1990 until May 25, 2017 with no language restrictions. Search terms relating to pregnancy were developed from those used in a Cochrane review and were combined with qualitative terms relating to smoking, varenicline, or bupropion.

3.4.2.2 Sample Size/Power

The authors identified 772 studies (1053 including duplicates); no ongoing trials were identified from registries and no completed, unpublished studies were identified from pharmaceutical company databases. They identified 30 articles for retrieval in full and 18 were included in this review. Included studies comprised two randomized controlled trials, eleven cohort studies, two case–control studies, and three case reports. Maternal or fetal adverse outcomes were reported in fourteen bupropion and four varenicline studies

3.4.2.3 Statistical Analyses

The authors used a random effects DerSimonian and Laird model to generate pooled means and 95% confidence intervals with heterogeneity quantified by the I^2 statistic.

3.4.3 Study Results

Six studies, four cohort and two case control studies reported congenital malformations. Cohort studies included 3376 pregnancies and from these studies the pooled estimate for the percentage of congenital malformations amongst live-born infants exposed to bupropion at any point during gestation was 1.0% (95% CI = 0.0%–3.0%, I^2 = 80.9%). Pregnancies that ended in stillbirth, miscarriage, intra-uterine fetal death, or termination were excluded from the analysis.

The two case–control studies had conflicting results. Both studies used the National Birth Defects Prevention Study (NBDPS) criteria to classify congenital cardiac defects. Alwan et al. found no evidence that maternal bupropion exposure in pregnancy increased infants' risks of developing congenital cardiac defects (adjusted odds ratio 1.4, 95% CI = 0.8–2.5). However, they report an increased risk of left outflow tract cardiac defects (adjusted odds ratio 2.6, 95% CI = 1.2–5.7) which was not found by Louik et al. (adjusted odds ratio 0.4, 95% CI = 0–2.4). Louik et al. investigated the risk of developing eight different cardiac defects following bupropion exposure but did not attempt to estimate the

overall risk of any cardiac defect and reported an increased risk of ventricular septal defects (adjusted odds ratio 2.9, 95% CI = 1.5–5.5) which was not reported by Alwan et al. (adjusted odds ratio 1.2, 95% CI = 0.5–3.4). Louik et al. found no increased risks for other sub-categories of cardiac defects following bupropion exposure.

3.4.4 Study Conclusions

This review found no conclusive evidence for the safety of gestational use of bupropion or varenicline. Pooling the limited available evidence suggests that bupropion has no major positive or negative impacts on the rates of congenital abnormalities. No case of diaphragmatic hernia was reported in the reviewed studies.

4 DISCUSSION

Our literature search confirms that only a few studies have assessed the safety of fetuses exposed to bupropion during pregnancy since 2010, and some of these studies have produced conflicting findings that preclude the establishment of a safety profile.[14,15,16] Findings from our literature search do not suggest a need to update the conflicting reports of cardiovascular risks that are currently in the Wellbutrin label. Besides the registry report described in Section 2[17] and the Anderson article, we found no publication associating early pregnancy exposure to bupropion and diaphragmatic hernia. Because the registry study is of low design quality and had low statistical power to detect increased risk of specific defects, this review focuses on the quality of the Anderson et al. article and the interpretation of their findings. To assess the design and quality of the Anderson article, the following considerations are worth noting:

Potential confounding. To partially address the complex pathophysiology of perinatal mental health conditions and its association with adverse birth outcomes that could potentially confound estimates of associations between medication treatments and congenital malformations, Anderson et al compared women exposed to bupropion in their early pregnancy to those exposed only in months 4 through 9 of pregnancy. This comparison is based on the assumption that the comparison group may have similar conditions, as well as other factors associated with these conditions, during and around the time of pregnancy but did not take antidepressants during early pregnancy. Specifically, the authors state that ‘one would expect to see elevated adjusted odds ratios for associations between the antidepressant and specific birth defects if the antidepressant

[14] Louik C, Kerr S, Mitchell AA. First-trimester exposure to bupropion and risk of cardiac malformations. Pharmacoepidemiol Drug Saf. 2014 Oct;23(10):1066-75. doi: 10.1002/pds.3661. Epub 2014 Jun 12. PMID: 24920293.

[15] Alwan S, Reefhuis J, Botto LD, Rasmussen SA, Correa A, Friedman JM; National Birth Defects Prevention Study. Maternal use of bupropion and risk for congenital heart defects. Am J Obstet Gynecol. 2010 Jul;203(1):52.e1-6. doi: 10.1016/j.ajog.2010.02.015. Epub 2010 Apr 24. PMID: 20417496.

[16] Anderson KN, Lind JN, Simeone RM, et al. Maternal Use of Specific Antidepressant Medications During Early Pregnancy and the Risk of Selected Birth Defects. JAMA Psychiatry. 2020;77(12):1246–1255. doi:10.1001/jamapsychiatry.2020.2453

[17] The Bupropion Pregnancy Registry Final Report
https://pregnancyregistry.gsk.com/documents/bup_report_final_2008.pdf

was associated with the outcome, as the underlying condition and its corollaries would be taken at least partially into account given the analytic strategy.' However, contrary to the authors' statement, accounting for a potential confounder such as an underlying condition should attenuate the observed effect. Of note, the reported point estimate and confidence interval for diaphragmatic hernia changed from 2.77 (1.34, 5.71) (comparison to unexposed women) to 6.50 (1.85, 22.88) (comparison to women exposed in later months). This is unusual and suggests that the compared groups may be more different than the authors assumed. An appropriate comparator group would be women with confirmed diagnoses during early pregnancy and no record of medication use. Unfortunately, the authors reported excluding such women who self-reported a diagnosis and no medication use without prompting. This suggests that, without asking their survey participants about diagnosis, the authors assumed that all unexposed patients had no diagnosis and vice versa for exposed patients. This assumption is unfounded and could have biased their findings and complicates the comparison of the odds ratios that did or did not partially account for underlying conditions as defined by bupropion exposure.

To further address imbalances in measured covariates such as early pregnancy cigarette smoking that was disproportionately higher among bupropion users, covariates were added to models if they resulted in a 10% or greater change in a point estimate for association between the exposure and any defect. While early pregnancy smoking and alcohol use were not adjusted for in the model that compared women exposed to bupropion early in pregnancy to women exposed later in pregnancy, a sensitivity analysis that included these covariates suggests that the drastic increase in odds ratios from 2.77 (compared to unexposed women) to 6.50 (compared to women exposed to bupropion in later pregnancy) is not driven by these measured confounders (odds ratio for sensitivity analysis = 6.92). Because the adverse effect of smoking, alcohol use, and substance abuse during pregnancy is not limited to early pregnancy, the authors' failure to account for these potential confounders in later trimesters suggests that the effect of unmeasured confounders cannot be ruled out. Further, the unusual increase in the estimated odds ratios after partially adjusting for underlying conditions and adjusting for early pregnancy smoking and alcohol use suggests that the compared groups are different in characteristics other than their exposure status.

Potential recall bias and differential misclassification. Exposure ascertainment was done via a computer-assisted telephone interview 6 weeks to 24 months after delivery and exposure was self-reported. It is expected that mothers of children with anomalies may be more likely to report exposure compared to their counterparts whose children have no birth defects. Such bias could overestimate the odds of observed defects and could explain the observed increase in the odds ratios for diaphragmatic hernia. Furthermore, the median time to interview was, on average, 2 months longer for mothers of cases compared to mothers of controls. This differential exposure reporting may further increase recall bias among mothers of cases.

Exposure Ascertainment and Potential Misclassification. Early pregnancy exposure was defined as maternal report of using 1 or more medication product(s) in any dose, duration, or frequency from the month before conception through the third month of pregnancy. The authors did not account for differential half-lives of antidepressants which could have resulted in exposure misclassification. Such misclassification could be

differential or non-differential with the potential of biasing measured estimates away or toward the null.

Underlying Disease Severity and Clinical Differences. Because antidepressant selection/prescription is not random and is often based on shared clinician-patient decision-making about safety and effectiveness, assessing the impact of differential medication selection on observed findings is crucial. Anderson et al, could not account for potential differences in disease severity, relapse risk, or other clinical differences among women who received specific antidepressants (e.g., bupropion), continued using antidepressants during pregnancy compared with those who discontinued treatment before pregnancy, or those who initiated treatment after the first trimester that could have biased their findings. Having a data source with records of underlying diagnoses could have mitigated these concerns.

Other Studies that have Assessed Bupropion Exposure and Birth Defects. The other articles reported in this review assessed the overall risk of congenital malformation and reported no case of diaphragmatic hernia. While Tran et al. report findings from an Australian cohort that may be substantially different from the population in the Anderson article, Alwan et al. assessed data from the first seven years of the NBDPS (1997 through 2004), the same data source as the Anderson et al article (1997 through 2011). In comparison to the Alwan article (cases =12,383; controls = 5,869) that focused on bupropion exposure and cardiovascular anomalies, Anderson et al. reported more cases (n=30,630) and control (n=11,478), and assessed a wider range of antidepressants and congenital malformations. The difference in the number of enrolled cases and controls suggests that infants' status as a cases or control influences study participation. If antidepressant exposure was also associated with study participation, study findings could have been affected by selection bias. In this case, selection bias would bias findings away from the null, overestimating the observed odds of birth defects.

5 CONCLUSION

The Anderson article suggests an elevated risk of congenital diaphragmatic hernia following early pregnancy in-utero exposure to bupropion. Findings from other observational studies do not support this notion. Study design flaws, potential unmeasured confounding, selection bias, and exposure misclassification preclude interpretations of findings from the Anderson article. At best, the Anderson article is hypothesis generating and should be interpreted as such.

6 RECOMMENDATIONS

DEPI recommends no label updates based on the findings in the Anderson et al. article.

APPENDICES

Table 1 – Design Summary of the Anderson et. al Article.

	Study
1.1 Objectives/Aims/Scope	To examine the associations between individual antidepressants and specific birth defects with and without attempts to partially account for potential confounding by underlying conditions
1.2.1 Design	
1.2.1.1 Type	Case-control
1.2.1.2 Data Source	National Birth Defects Prevention Study
1.2.1.3 Time Period	October 1, 1997 through December 31, 2011
1.2.1.4 Criterion (Selection) Standards	Infants with known single-gene disorders or chromosomal abnormalities were excluded. Mothers were excluded if they had incomplete medication history, pre-pregnancy type 1 or 2 diabetes, or used a known teratogenic medication during the 3 months before conception or during pregnancy. Mothers were also excluded if they, without prompting, reported having a depressive, bipolar, or anxiety disorder but did not report antidepressant use
1.2.1.5 Protected Health Information	Institutional review board approval was provided by all sites and mothers gave oral interview informed consent
1.2.2 Setting	United States: National Birth Defects Prevention Study
1.2.3 Exposure/Intervention	Early pregnancy exposure was defined as maternal report of using 1 or more medication product(s) in these classes in any dose, duration, or frequency from the month before conception through the third pregnancy month
1.2.4 Outcome(s)	Cases with selected birth defects were identified from surveillance systems using standard case definitions and included live births, stillbirths, and terminations
1.2.5 Covariates	Maternal race/ethnicity (non-Hispanic White, not non-Hispanic White), pre-pregnancy BMI (≥30kg/m2), maternal education (>12 years, ≤12 years), early pregnancy smoking (yes, no), and early pregnancy alcohol use (yes, no)

1.2.6 Sample Size	Maternal race/ethnicity (non-Hispanic White, not non-Hispanic White), pre-pregnancy BMI (≥30kg/m2), maternal education (>12 years, ≤12 years), early pregnancy smoking (yes, no), and early pregnancy alcohol use (yes, no)
1.2.7 Statistical Analyses	They used multivariable logistic regression to calculate adjusted odds ratios and 95% confidence intervals for NBDPS-eligible birth defects with 4 or more exposed cases.
1.2.8 Study Results (if relevant)	In model 1, they observed elevated aORs for bupropion and 3 defects: 1) Hypoplastic left heart syndrome [n=5, aOR 2.08 (95% CI: 0.82-5.28)]; 2) Intestinal atresia/stenosis [n=4, aOR 2.69 (95% CI: 0.96-7.59)]; 3) Diaphragmatic hernia [n=9, aOR 2.77 (95% CI: 1.34 – 5.71). In model 2, after accounting for the underlying condition, they observed an elevated aOR for bupropion and diaphragmatic hernia (aOR, 6.50; 95% CI, 1.85-22.88).

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Food and Drug Administration
Center for Drug Evaluation and Research Division of Cardiology and Nephrology

Date: June 9, 2021

From: Division of Cardiology and Nephrology (DCN), CDER

Tzu-Yun McDowell, Clinical Reviewer

Mary Ross Southworth, Deputy Safety Director

Through: Norman Stockbridge, Director, DCN, CDER

To: Simran Parihar, RPM, Division of Psychiatry (DP), CDER

Subject: Clinical meaningfulness of heart rate changes with AXS-05

Background

AXS-05, a fixed-dose combination of 45 mg dextromethorphan hydrobromide and 105 mg bupropion hydrochloride is being developed for the indication of treatment of major depressive disorder (MDD) in adults. NDA 215430 for AXS-05 was submitted in February 2021 and is under a priority review in the Division of Psychiatry (DP).

Dextromethorphan and bupropion each target different receptor systems that are associated with antidepressant activity. Bupropion, an aminoketone antidepressant, was approved for the treatment of MDD. The bupropion in the combination is used both for its neuropharmacological properties as well as for its ability to inhibit the metabolism of dextromethorphan through CYP2D6 thus substantially increase dextromethorphan plasma concentration. Steady state plasma concentrations of dextromethorphan and bupropion when given as a combination product are achieved within 8 days. The elimination half-life of dextromethorphan and bupropion was about 22 hours following 8 days of administration of AXS-05. Administration of dextromethorphan did not appear to affect the PK of bupropion.

The primary clinical data in support of the safety of AXS-05 in patients with MDD includes a pivotal phase 3 placebo-controlled study (6-weeks exposure, GEMINI), a phase 2 active-controlled study (6-weeks exposure, ASCEND) and a long-term, uncontrolled study (up to 12 months exposure, COMET). DP is evaluating a possible safety signal for tachycardia in the vital signs data from the long-term study. DP's initial analysis of the data shows that the mean heart rate (HR) change from baseline at the last visit had a right skew of distribution with a mean change of 3 bpm (see **Appendix**). DP has requested input from the Division of Cariology and Nephrology (DCN) on whether this magnitude of difference is clinically meaningful and sufficiently large to warrant a label warning for tachycardia.

It is noted that tachycardia was listed as an adverse reaction commonly encountered in subjects treated with bupropion (WELLBUTRIN®) in the current PI. The incidence of tachycardia was 10.8% in the bupropion group compared with 8.6% in the placebo group in the placebo-controlled trials. The dose of bupropion in these studies was in the range of 300-600 mg/day which is higher compared to the dose of bupropion in AXS-05 (starting dose dextromethorphan/bupropion: 45/105 mg/day for three days then 90/210 mg/day, given as 45/105 mg twice daily).

DCN Approach to the Consult Review

It is difficult to interpret the safety results from uncontrolled data. To assess the potential safety signal of HR increases and tachycardia, DCN also evaluated the data from the pivotal placebo-controlled study and will discuss the results from the long-term, single arm study in the context.

Materials Reviewed

- Clinical Study AXS-05-MDD-301 (GEMINI): A randomized, double-blind, placebo-controlled trial of AXS-05 in subjects with MDD
  \\cdsesub1\evsprod\NDA215430\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ind1\5351-stud-rep-contr\axs-05-mdd-301\axs-05-mdd-301-csr-body.pdf
- Clinical Study AXS-05-303 (COMET): An open-label study to assess the long-term safety of AXS-05 in subjects with MDD
  \\cdsesub1\evsprod\NDA215430\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ind1\5352-stud-rep-uncontr\axs-05-303\axs-05-303-csr-body.pdf

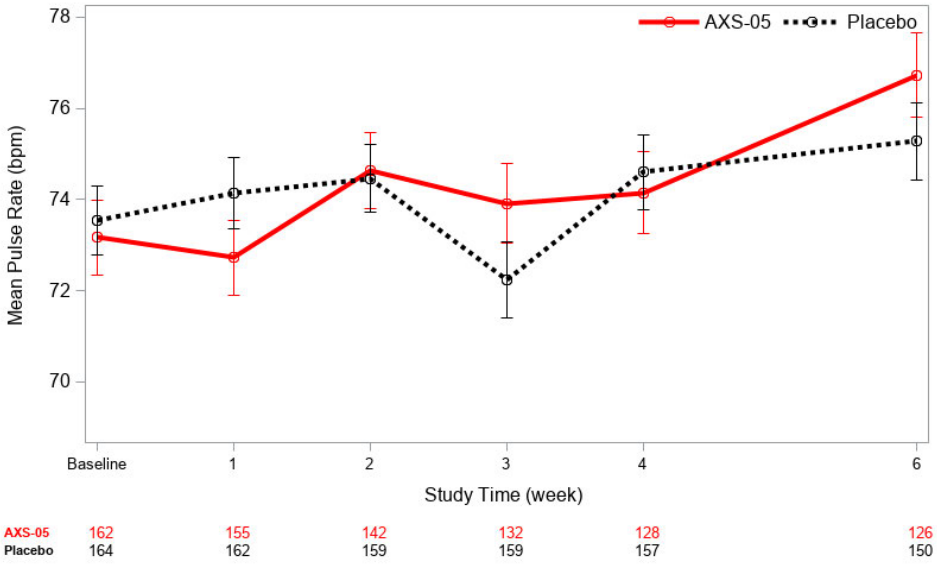
Pivotal Placebo-Controlled study (GEMINI)

This was a Phase 3, multi-center, randomized, double-blind, placebo-controlled study to evaluate efficacy and safety of AXS-05 in subjects with MDD. Eligible subjects were randomly assigned a treatment in a 1:1 ratio, to either AXS-05 or placebo treatment for 6 weeks. Subjects received study treatment once daily for the first 3 days and then received study treatment twice daily from Day 4 to 42. Vital signs were measured at screening, baseline (Day 1) and each study visit weekly from Week 1 to Week 6. Adverse events were assessed at each visit. A total of 326 subjects received at least one study treatment and were included in the safety population.

Heart Rate Results

The time-course of average HR and the difference in the HR changes from baseline between AXS-05 and placebo are shown in Figure 1 and Table 1 below.

Figure 1 Average Heart Rate across Time in GEMINI, Safety Population



Reviewer's Figure Source: GEMINI advs

Table 1 Mean HR across Time and Change from Baseline in GEMINI, Safety Population

	AXS-05			Placebo			Change from Baseline Difference (AXS-05 vs. Placebo)
	N	Mean (SD)	Change from baseline, LS Mean (SE)	N	Mean (SD)	Change from baseline, LS Mean (SE)	LS Mean (95%CI)[a]
Baseline	162	73.2 (10.3)	---	164	71.1 (10.2)	---	---
Week 1	155	72.7 (10.3)	-0.7 (0.7)	162	74.1 (10.1)	0.6 (0.7)	-1.3 (-2.8, 0.3)
Week 2	142	74.6 (9.9)	1.2 (0.7)	159	74.5 (9.4)	0.7 (0.6)	0.5 (-1.0, 2.0)
Week 3	132	73.9 (10.0)	0.7 (0.8)	159	72.2 (10.6)	-1.5 (0.7)	2.2 (0.5, 3.9)
Week 4	128	74.1 (10.1)	0.9 (0.8)	157	74.6 (10.2)	0.9 (0.7)	-0.02 (-1.7, 1.7)
Week 6	126	76.7 (10.4)	3.5 (0.8)	150	75.3 (10.4)	1.7 (0.8)	1.8 (-0.1, 3.6)
Last Visit (LOCF[b])	162	76.2 (10.5)	2.9 (0.7)	164	74.7 (10.5)	1.3 (0.7)	1.7 (0.0, 3.3)

a LS mean for difference between groups for week 1 to week 6 was derived from the mixed model for repeated measures including baseline HR as a covariate. LS mean for difference between groups at last visit was derived from ANOCVA including baseline HR as a covariate
b Last observation carried forward (LOCF)
Reviewer's Table Source: GEMINI advs

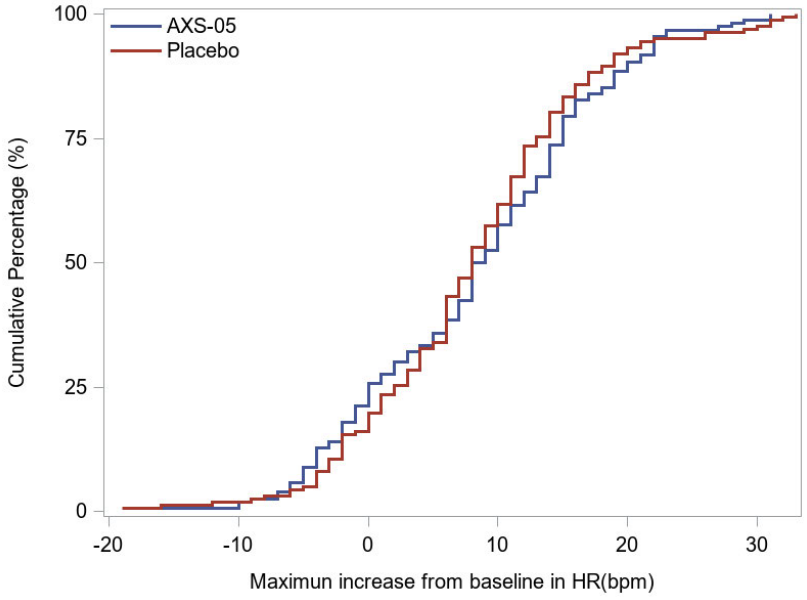
The largest difference between groups was observed in Week 3 with ΔΔHR of 2 bpm. The HR increase in the AXS-05 group over placebo was not consistently observed across time. Table 2 lists the categorical analysis results for the selected criteria. These results indicate that a higher percent of subjects in the AXS-05 treatment group met the selected criteria for HR increases; though the difference was modest (<5%) between groups. There were very few subjects in either group with an extreme HR (i.e., HR> 100 bpm). The cumulative distribution plot for the maximum HR increase from baseline shows similar results (Figure 2).

Table 2 Categorical Analysis for HR in GEMINI, Safety Population

	AXS-05		Placebo	
Criteria	**Subject[a]**	**Observation[b]**	**Subject[a]**	**Observation[b]**
≥ 10 bpm increase	74/156 (47.4%)	127/684 (18.6%)	69/162 (42.6%)	122/790 (15.4%)
≥ 20 bpm increase	18/156 (11.5%)	25/684 (3.7%)	13/162 (8.0%)	16/790 (2.0%)
≥ 30 bpm increase	2/156 (1.3%)	2/684 (0.3%)	5/162 (3.1%)	5/790 (0.6%)
HR > 100 bpm	1/156 (0.6%)	1/684 (0.1%)	2/162 (1.2%)	2/790 (0.3%)

a Number of subjects with baseline and at least one post-baseline measure
b Number of post-baseline measures among subjects with a baseline measure
Reviewer's Table Source: GEMINI advs

Figure 2 Cumulative Distribution of Maximum Heart Rate Increases in GEMINI, Safety Population



Reviewer's Figure Source: GEMINI advs

Reviewer's Comment: *The magnitude of HR increases seen in the pivotal placebo-controlled study does not indicate a safety concern in particular considering that there were no corresponding clinical findings in the study (e.g., no reported AE of tachycardia in either group).*

Open-Label, Long-Term Safety Study (COMET)

This was a multi-center, open-label study designed to evaluate the long-term safety and efficacy of AXS-05 in the treatment of MDD. Eligible subjects must have completed a prior study with AXS-05 (GEMINI or AXS-05-301, an active-controlled study in patients with treatment resistant depression, TRD) or must have met the Diagnostic and Statistical Manual Of Mental Disorder, 5th Edition (DSM-5) criteria for MDD without psychotic features. Subjects received AXS-05 once daily for the first 3 days and then received AXS-05 twice daily up to 12 months. Vital signs were measured every week for 2 weeks, then every 2 weeks for the first 2 months, then monthly thereafter. The study was concluded after 100 subjects had been exposed to AXS-05 for 12 months. A total of 876 subjects received at least one dose of AXS-05, including 611 (70%) AXS-05 naïve subjects who have not participated a prior study with AXS-05, 126 subjects (14%) who had previously received AXS-05 in the prior studies and 139 subjects (16%) who received either placebo or active control (bupropion) in the prior studies (non-AXS-05).

Adverse Events related to Tachycardia

Table 3 lists the reported AEs related tachycardia. There were a total of 8 AEs (8/876, 0.9%) related to HR increased and tachycardia; none were serious. It is noted that all but one event occurred soon after the initiation of AXS-05 (within 8 days of study treatment). One event resulted in discontinuation of study drug (Case #7) and for the rest of the cases, AXS-05 dose remained unchanged. All subjects who reported tachycardia related AEs had not been treated with AXS-05 previously and majority of them had not participated in prior clinical studies with AXS-05 (treatment Naïve).

Table 3 Listing of Subjects with Reported Adverse Events related to Tachycardia, Safety Population, COMET

Case#	Prior Treatment	Age / Sex / Race	AE	Severity	Start Day of AE[a]	Causality[b]
1	Naive	29 / F / BLACK OR AFRICAN AMERICAN	Tachycardia	MILD	5	POSSIBLY
2	Naive	33 / M / WHITE	Tachycardia	MODERATE	2	POSSIBLY
3	Naive	55 / F / BLACK OR AFRICAN AMERICAN	Heart rate irregular	MILD	7	PROBABLY
4	Naive	38 / F / WHITE	Tachycardia	MODERATE	2	POSSIBLY
5	Naive	20 / F / WHITE	Tachycardia	MILD	7	PROBABLY
6	Naive	55 / F / WHITE	Tachycardia	MILD	8	PROBABLY
7	Non-AXS-05	52 / F / WHITE	Heart rate increased	MILD	2	DEFINITELY
8	Non-AXS-05	26 / F / WHITE	Ventricular extrasystoles	MILD	48	POSSIBLY

a Start day of AEs relative to the start day of AXS-05 b. Causality of AE was assessed by the investigators

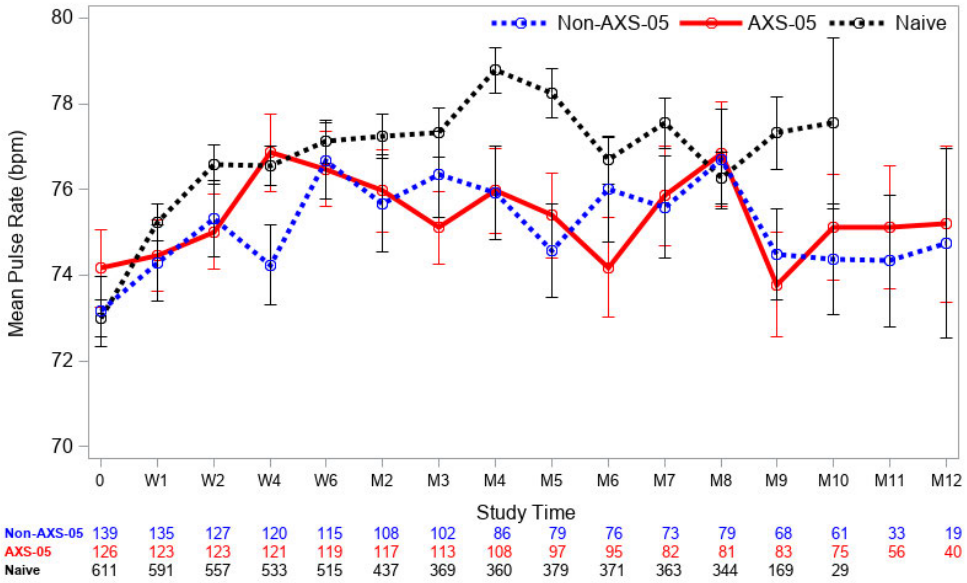
Reviewer's Table Source: COMET adsl and adae

Reviewer's Comment: *Although there is a temporal relationship between drug initiation and these events, without a control group, it is difficult attribute causality to the drug. The bottom line is the incidence was very low (<1%) and the events were mostly mild and did not result in any change of study treatment.*

Heart Rate Results

The time-course of average HR and the difference in the HR changes from baseline at the last visit among treatment groups (prior treatment) are shown in Figure 3 and Table 4. The average HR changes from baseline in all AXS-05 treated subjects remain small (~3 mmHg). This magnitude of change is not that different compared to the results in the placebo-controlled study (Table 1). However, it is noted that AXS-05 naïve subjects appeared to have a greater increase in HR compared to subjects who had previously participated in AXS-05 studies.

Figure 3 Average Heart Rate across Time in COMET, Safety Population



Reviewer's Figure Source COMET advs

Table 4 Mean Heart Rate: Baseline, Last Visit and Change from Baseline, Safety Population, COMET

	Naïve[a] (N=611)	**Non-AXS-05[a] (N=139)**	**AXS-05[a] (N=126)**	**All (N = 876)**
Baseline Mean (SD)	73.0 (10.5)	73.2 (9.8)	74.2 (10.2)	73.2 (10.4)
Last Visit (LOCF[b]) Mean (SD)	76.5 (11.3)	75.4 (11.0)	75.4 (11.0)	76.2 (11.2)
Change from Baseline LS Mean (95% CI)	3.5 (2.9, 4.2)	2.3 (0.9, 3.7)	1.8 (0.4, 3.3)	3.1 (2.5, 3.6)
Comparisons	**Naïve vs. AXS-05**	**Non-AXS-05 vs. AXS-05**		---
Change from Baseline Difference LS Mean (95% CI)	1.7 (0.1, 3.3)	0.5 (-1.5, 2.5)		

a Treatment group was based on prior treatment received in the AXS-05 studies
b Last observation carried forward (LOCF)

Reviewer's Table Source: COMET asvs

The results of the categorical analysis for HR also indicates that a higher percent of subjects met the selected criteria in the AXS-05 naïve group compared with others (Table 5). Event rate was calculated for the categorical analysis in both placebo-controlled study and long-term study for a comparison (Table 6). Overall, the results seen in the long-term study do not deviate much from the placebo-controlled study and did not clearly indicate an increased risk of elevated heart rate in patients chronically treated with AXS-05.

Table 5 Categorical Analysis for HR in COMET, Safety Population

	Naive		***Non-AXS-05***		***AXS-05***		***All***	
	Subject	**Observation**	**Subject**	**Observation**	**Subject**	**Observation**	**Subject**	**Observation**
≥ 10 bpm increase[a]	398/595 (66.9%)	1405/5043 (27.9%)	69/137 (50.4%)	280/1287 (21.8%)	74/124 (59.7%)	304/1437 (21.2%)	541/856 (63.2%)	1989/7767 (25.6%)
≥ 20 bpm increase[a]	180/595 (30.3%)	388/5043 (7.7%)	36/137 (26.3%)	74/1287 (5.7%)	29/124 (23.4%)	70/1437 (4.9%)	245/856 (28.6%)	532/7767 (6.8%)
≥ 30 bpm increase[a]	41/595 (6.9%)	68/5043 (1.3%)	9/137 (6.6%)	16/1287 (1.2%)	10/124 (8.1%)	15/1437 (1.0%)	60/856 (7.0%)	99/7767 (1.3%)
HR > 100 bpm	55/595 (9.2%)	110/5043 (2.2%)	10/137 (7.3%)	14/1287 (1.1%)	6/124 (4.8%)	10/1437 (0.7%)	71/856 (8.3%)	134/7767 (1.7%)

[a] Heart rate increases from baseline
Reviewer's Table Source: COMET asvs

Table 6 Event Rate for Categorical Analysis for HR in GEMINI and COMET[a], Safety Population

	Long-Term Extension Study (COMET)				**6-week Placebo-Controlled (GEMINI)**	
	Non-AXS-05	**Naive**	**AXS-05**	**All**	**AXS-05**	**Placebo**
	Event Rate (per 100 pt-yrs)[b]				**Event Rate (per 100 pt-yrs)[b]**	
≥ 10 bpm increase[c]	151.1	304.1	163.7	244.0	589.0	478.9
≥ 20 bpm increase[c]	53.9	76.2	36.8	64.2	120.0	72.6
≥30 bpm increase[c]	11.4	14.0	11.2	13.0	12.8	27.3
HR > 100 bpm	12.8	19.1	6.6	15.5	6.4	10.9

a Cross-study comparisons should be interpreted in caution
b Number of case/total patient-year exposure. The calculation was based on the first occurrence of the event within each criterion
c Heart rate increases from baseline
Reviewer's Table Source: COMET asvs

Reviewer's Comment: *The greater increases in HR observed among AXS-05 naïve subjects (newly treated) compared to others were of interest. There were no major differences among groups in terms of main demographics and baseline characteristics. However, it is noted that AXS-05 naïve subjects had a higher baseline Montgomery-Asberg Depression Rating Scale (MADRS) score (a median of 32) compared to that in rollover subjects (a median of 20 in AXS-05 group; a median of 23 in Non-AXS-05 group), which indicates that AXS-05 naïve subjects were on average more severely depressed at baseline. Whether or not this observed difference contributed to the HR results is unknown. However, the magnitude of HR changes in the long-term study was generally in line with the results in the placebo-controlled study and did not raise a major safety concern regarding drug-induced tachycardia.*

Consult Question:

" DP is evaluating a possible safety signal for tachycardia in the vital signs of data for Study AXS-05-303, a one-year, open-label safety study of AXS-05 in patients with MDD. Our initial analysis of the data shows that the percentages of patients with increases or decreases in diastolic blood pressure of 10 mmHg or greater are 13.5% and 13.2% respectively, suggesting that increases and decreases are distributed evenly throughout the population" (see Appendix table generated by the clinical reviewer). "However, we do not see a similar balance between patients demonstrating increases or decreases in heart rate. 25.4% of patients had an increase in heart rate of 10 bpm or greater, and 11.3% of patients had a decrease in heart rate of 10 bpm or greater. DP is requesting an opinion from DCN on whether this magnitude of difference is clinically meaningful and sufficiently large to warrant a label warning for tachycardia, despite the low value for mean change in heart rate, which was 3 bpm. DP also requests guidance and assistance with additional analyses regarding changes in heart rate to help clarify the nature and clinical meaningfulness of the potential safety signal."

DCN Response:

The magnitude of HR increase observed in the placebo-controlled study as well as in the long-term study does not indicate a major safety concern. It is noted that the HR increases appeared to be slightly greater among AXS-05 naïve subjects compared to rollover subjects in the long-term study, but there was no evidence for a hyper-responder group driving the trivial mean changes of HR. Overall, the AXS-05 clinical program suggests a small HR effect of AXS-05 and there was no strong and serious corresponding clinical events of these HR changes. Although tachycardia was listed as an adverse reaction in the section 6 of the PI for bupropion (WELLBUTRIN®), the daily dose of bupropion was higher in those studies compared to AXS-05 studies. DCN does not recommend including a warning for tachycardia in the labeling for AXS-05.

Appendix

Table 1. AXS-05 (Dextromethorphan HBr 45 mg + Bupropion HCl 105 mg): Changes in Systolic Blood Pressure, Diastolic Blood Pressure, and Heart Rate from Baseline to Last Study Visit, Study AXS-05-303 (1-Year Open-Label Safety Study)

Change Category	Systolic BP (n=856)	Diastolic BP (n=856)	Heart Rate (n=856)
Mean Change from Baseline	0.83 mmHg	0.11 mmHg	3.09 bpm
Increase from Baseline: >0 to <5	18.2%	26.6%	19.0%
Increase from Baseline: 5 to <10	12.9%	15.3%	17.6%
Increase from Baseline: 10 to <15	9.1%	7.5%	11.1%
Increase from Baseline: 15 to <20	6.3%	4.2%	6.8%
Increase from Baseline: 20 to <25	4.6%	1.2%	4.2%
Increase from Baseline: 25 to <30	1.6%	0.5%	2.1%
Increase from Baseline: >=30	1.2%	0.1%	1.2%
Decrease from Baseline: >0 to <5	14.4%	16.2%	15.5%
Decrease from Baseline: 5 to <10	12.7%	15.2%	11.1%
Decrease from Baseline: 10 to <15	9.1%	7.8%	6.4%
Decrease from Baseline: 15 to <20	4.7%	3.2%	2.8%
Decrease from Baseline: 20 to <25	2.7%	1.8%	1.3%
Decrease from Baseline: 25 to <30	1.5%	0.2%	0.7%
Decrease from Baseline: >=30	1.1%	0.2%	0.1%

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/s/

TZU-YUN C MCDOWELL
06/10/2021 08:56:00 AM

MARY R SOUTHWORTH
06/10/2021 09:11:24 AM

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06/10/2021 09:14:37 AM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 215430
Submission Number	001
Submission Date	2/22/2021
Date Consult Received	3/5/2021
Drug Name	AXS-05 (Dextromethorphan hydrobromide and Bupropion hydrochloride)
Indication	Major Depressive Disorder
Therapeutic dose	AXS-05 (45 mg dextromethorphan HBr and 105 mg bupropion HCl) is once daily for the initial 3 days of therapy then increased to twice daily.
Clinical Division	DP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult dated 3/5/2021 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review under IND-124813 dated 06/15/2020 in DARRTS;
- Previous IRT review under IND-124813 dated 10/14/2020 in DARRTS;
- Sponsor's Clinical Study Report for QT study AXS-05-109 (SN0001; link);
- Highlights of Clinical Pharmacology and Cardiac Safety (SN0004; link);
- Investigator's Brochure (SN0004; link); and
- Sponsor's proposed product label (SN0001; link)

1 SUMMARY

No significant QTc prolongation effect of AXS-05 (a fixed-dose combination product of 45 mg dextromethorphan and 105 mg bupropion) was detected in this QT assessment.

The effect of AXS-05 was evaluated in a randomized, double-blind, placebo- and positive-controlled, multiple-dose, 3-period, 6-way crossover study in healthy subjects (Study # AXS-05-109). The proposed therapeutic dose of AXS-05 (45 mg dextromethorphan and 105 mg bupropion) is once daily for the initial 3 days of therapy followed by twice daily administration. The highest dose evaluated was 90 mg dextromethorphan and 210 mg bupropion (two morning doses; administered simultaneously on Day 7) which covers the therapeutic exposures at steady state (Section 3.1). However, the marginally lower peak concentrations of dextromethorphan (~119 ng/mL vs. ~95 ng/mL) and bupropion (~139 ng/mL vs. ~121 ng/mL) compared to those observed in subjects with hepatic impairment were achieved at the supra-therapeutic dose in the QT study (Section 1.2).

Assay sensitivity was established by the moxifloxacin arm. The data were analyzed using by-timepoint analysis as the primary analysis (see Table 1). The analyses showed that the combination product AXS-05 is not associated with significant increases in the QTc interval. The findings of this analysis are further supported by the available exposure-response analysis (Section 4.5) and categorical analysis (Section 4.4).

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

Treatment	DAY	Time (hour)	N	ΔΔQTcF (msec)	90% CI (msec)
AXS-05 Therapeutic dose	6	3	39	4.7	(1.7, 7.8)
AXS-05 Supratherapeutic dose	7	6	39	6.6	(3.3, 9.8)
Moxifloxacin 400 mg*	7	3	38	10.7	(7.6, 13.8)

**Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 3 time points was 6.2 msec.*

For further details on the FDA analysis, please see Section 4.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

The sponsor describes that the expected high clinical exposure scenario is represented by patients with moderate hepatic impairment (Study # AXS-05-105). Based on a dedicated hepatic impairment study, there was ~1.3-fold increase in the peak concentration of dextromethorphan and ~1.7-fold increase in the peak concentration of bupropion compared to those observed in the matched controls. No dose adjustment is proposed in this population.

Based on the cross-study comparison (HI *vs*. QT studies), the marginally lower peak concentrations of dextromethorphan (~119 ng/mL vs. ~95 ng/mL) and bupropion (~139 ng/mL vs. ~121 ng/mL) were achieved at the supra-therapeutic dose in the QT study. However, these peak concentrations of bupropion are lower than those associated with 300 mg once daily dose of Wellbutrin XL tablet (Cmax,ss: ~167 ng/mL; Tmax: 5 h). Although a dedicated QT study was not conducted for bupropion alone, no significant QTc prolongation effect of was detected in our previous assessment for a combination product containing bupropion and naltrexone (Contrave; 16 mg naltrexone and 180 mg bupropion) in a dedicated thorough QT study (link).

Considering the observations that- 1) these are cross-study comparisons of exposures, 2) this is a negative study with the primary by-time analyses suggesting that the product is not associated with significant increases in the QTc interval, and 3) there is a shallow relationship between ΔQTcF and plasma concentration of both components, the IRT has no significant concerns with the marginally lower exposures of dextromethorphan achieved at the supra-therapeutic dose in the QT study.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SN0001 (link) from the IRT. Our changes are highlighted (*addition*, *deletion*). Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

At the recommended therapeutic dose, <Tradename> does not prolong the QT interval to any clinically relevant extent.

We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Axsome Therapeutics, Inc. is developing a fixed dose combination of dextromethorphan and bupropion (AXS-05) for the treatment of major depressive disorder (MDD) in adults. Dextromethorphan (hydrobromide salt, MW: 370.33) is a noncompetitive antagonist of the NMDA receptor, an ionotropic glutamate receptor, and sigma-1 receptor agonist. It is approved for the treatment of cough and it is available as suspension (30 mg/5 mL) and extended-release tablet formulations for the over-the-counter use (Delsym, NDA- 018658, Oct-1982; 21 CFR 241.74; Generally Recognized as Safe and Effective). Similarly, bupropion (racemic, hydrochloride salt, MW: 276.2) is an aminoketone (also a CYP2D6 inhibitor) which is approved for the treatment of treatment of major depressive disorder and it is available as extended-release tablet (100, 150, 200 mg) formulations (Wellbutrin tablet, NDA 018644, discontinued; Wellbutrin ER and XL tablet, NDA 020358 & NDA 021515, by GSK, Oct- 1996). The recommended starting dose is 150 mg per day which can be titrated to the maximum daily dose of 400 mg (to be administered as twice daily). The maximum dose for Wellbutrin XL tablet formulation is 300 mg once daily. The peak concentrations of ~167 ng/mL (Tmax: 5 h) were observed for bupropion at steady state with 300 mg once daily dose of Wellbutrin XL tablet (Study # 2543; ClinPham Review;

link). Dose (or dosing frequency) reduction is recommended in subjects with hepatic impairment or renal impairment.

The sponsor highlights that the clinical utility of dextromethorphan (as monotherapy) is limited as it is rapidly and extensively metabolized (through CYP2D6) resulting in low systemic exposures even with high and repeated doses. Dextromethorphan is metabolized by hepatic O-demethylation primarily by CYP2D6 to one active metabolite, dextrorphan, and by CYP3A4 and N demethylation to 3-methoxymorphinan. Bupropion and its metabolites (erythron-hydro-bupropion, threo-hydro- bupropion, hydroxy-bupropion) are CYP2D6 inhibitors. In this fixed dose combination product, bupropion is expected to inhibit the metabolism of dextromethorphan resulting in increased plasma concentrations of dextromethorphan into a potentially therapeutic range. In addition, bupropion exerts its pharmacological activity by inhibiting dopamine and norepinephrine reuptake. Thus, the sponsor claims unique pharmacological profile with a dual pharmacodynamic and pharmacokinetic synergy for this fixed dose combination. The sponsor also highlights that concomitant administration of dextromethorphan does not affect the pharmacokinetics of bupropion.

The product is formulated as a bi-layer tablet formulation containing 45 mg dextromethorphan hydrobromide (immediate release) and 105 mg bupropion hydrochloride (sustained release) for oral administration. The proposed therapeutic dose of AXS-05 (45 mg dextromethorphan HBr & 105 mg bupropion HCl) is once daily for the initial 3 days of therapy then increased to twice daily. Thus, the maximum proposed therapeutic dose for the present indication is 45 mg dextromethorphan hydrobromide and 105 mg bupropion hydrochloride twice daily (90 mg dextromethorphan and 210 mg bupropion per day; Study # AXS-05-MDD-201). Following administration of maximum therapeutic dose, the steady-state peak concentrations of ~77 ng/mL (Tmax: ~3 h; half-life ~22 h) and ~88 ng/mL (Tmax: ~2 h; half-life ~20 h) are expected for dextromethorphan and bupropion, respectively. Due to the inhibition of CYP2D6 by bupropion, significant accumulation is expected for dextromethorphan at steady state with the proposed maximum therapeutic dose (Cmax Racc: ~21). However, minimal accumulation is expected for bupropion at steady state with the proposed maximum therapeutic dose (Cmax Racc: ~1.5). The maximum tolerated dose is not established, and the maximum studied dose is 60 mg dextromethorphan hydrobromide and 150 mg bupropion hydrochloride twice daily.

Bupropion is extensively metabolized (mainly by CYP2B6) forming three major and active metabolites (hydroxy-bupropion by CYP2B6, and threo-hydro-bupropion and erythro-hydro-bupropion by carbonyl reductase). Similarly, dextromethorphan is extensively metabolized by CYP2D6 to dextrorphan, its primary metabolite, which is further metabolized to glucuronide conjugate and is rapidly eliminated by the kidneys.

The sponsor conducted a dedicated renal impairment study (Study # AXS-05-104) assessing the impact of renal function (moderate renal impairment) on the pharmacokinetics of both components. Subjects received open-label AXS-05 (45 mg dextromethorphan HBr & 105 mg bupropion HCl) for 8 days. Increased exposures of dextromethorphan (Cmax: ~119 ng/mL; Day 8) and bupropion (Cmax: ~92 ng/mL; Day 8) were observed in subjects with moderate renal impairment relative to matched healthy controls. However, the pharmacokinetics was not assessed in subjects with severe renal impairment and the dosing of AXS-05 in subjects with severe renal impairment is not

recommended. Similarly, the sponsor conducted a dedicated hepatic impairment study (Study # AXS-05-105) assessing the impact of hepatic function (moderate hepatic impairment) on the pharmacokinetics of both components. Subjects received open-label AXS-05 (45 mg dextromethorphan HBr & 105 mg bupropion HCl) for 8 days. Increased exposures of dextromethorphan (Cmax: ~119 ng/mL; Day 8) and bupropion (Cmax: ~139 ng/mL; Day 8) were observed in subjects with moderate hepatic impairment relative to matched healthy controls. No dose adjustment is proposed by the sponsor in this population. However, the pharmacokinetics was no assessed in subjects with severe hepatic impairment and the dosing of in subjects with severe hepatic impairment is not recommended.

The sponsor proposed dose modification to once daily administration (instead of twice daily administration) in subjects with renal impairment, in poor metabolizers of CYP2D6, and during concomitant administration of AXS-05 with inhibitors of CYP2D6. However, there is no dose modification proposed in subjects with hepatic impairment.

3.1.2 Nonclinical Safety Pharmacology Assessments

The sponsor did not include non-clinical assessment under the highlights of clinical pharmacology and clinical safety.

3.2 SPONSOR'S RESULTS BY TIME ANALYSIS

AXS-05 excluded the 10 msec threshold at the therapeutic and supratherapeutic dose levels for ΔΔQTcF.

Reviewer's comment: The reviewer's independent by-time point analysis results are similar to the sponsor's results. Please see Section 4.3 for details.

3.2.1.1 Assay Sensitivity

Assay sensitivity was established by the moxifloxacin arm in the sponsor's by-time analysis.

Reviewer's comment: The reviewer's independent analysis results are consistent with the sponsor's results, i.e., assay sensitivity was demonstrated in the study. Please see Section 4.3.1.1 for details.

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTcF (i.e., >500 msec or >60 msec over baseline, HR (<45 or >100 beats/min), PR (>220 msec and 25% over baseline) and QRS (>120 msec and 25% over baseline).

Reviewer's comment: The reviewer's categorial analysis results are similar of the sponsor's results. Please see Section 4.4 for details.

3.2.3 Exposure-Response Analysis

The sponsor explored the PK/PD relationship between the change from baseline in QTc interval (ΔQTcF) and the plasma concentration of bupropion and dextromethorphan using linear mixed effects model (Garnett et al. 2018). The sponsor's analysis shows that there was a slight positive slope of 0.000039 msec/pg/mL for the relationship between ΔΔQTcF and plasma concentration of dextromethorphan. However, the analysis did not indicate a significant relationship between ΔΔQTcF and plasma concentration of bupropion (slope: –0.002842 msec/ng/mL). Based on the linear model the predicted ΔΔQTcF was 3.4 msec (upper 90% CI 4.1 msec) at the mean Cmax of 66.9 ng/mL for dextromethorphan and the mean Cmax of 74.0 ng/mL for bupropion at therapeutic dose and 4.1 msec (upper 90% CI 5.2 msec) at the mean Cmax of 88.8 ng/mL for dextromethorphan and the mean Cmax of 115.5 ng/mL for bupropion at supratherapeutic dose. The results of the sponsor's analysis suggest an absence of significant QTc prolongation at the highest anticipated therapeutic dose.

Reviewer's comment: The conclusion of the reviewer's analysis agreed with the sponsor's analysis. Please see Section 4.5 for details.

3.2.4 Safety Analysis

All subjects received at least one dose of the study drug (therapeutic and supratherapeutic doses of AXS-05, moxifloxacin, or placebo) and comprised the safety population (N=42).

No deaths, serious, or severe TEAEs were reported during the study. One subject was early discontinued due to the TEAE of "Anxiety" which was graded as moderate in severity. Three (3) TEAEs related to vital signs (heart rate increased, body temperature increased, and blood pressure increased) were experienced by 4 subjects who received AXS-05. All these TEAEs were judged as mild in severity except blood pressure increased which was judged as moderate in severity.

Reviewer's comment: None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., syncope, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no large increases or decreases in heart rate (i.e. |mean| < 10 beats/min) were observed (see Section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY TIME ANALYSIS

The analysis population used for by time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer used linear mixed model to analyze the drug effect by time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The default model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects and baseline as a covariate. The default model also includes subject as a random effect and an unstructured covariance matrix to explain the associated between repeated measures within period.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups. The maximum ΔΔQTcF values by treatment are shown in Table 2.

Figure 1: Mean and 90% CI of QTcF Timecourse (unadjusted CIs).

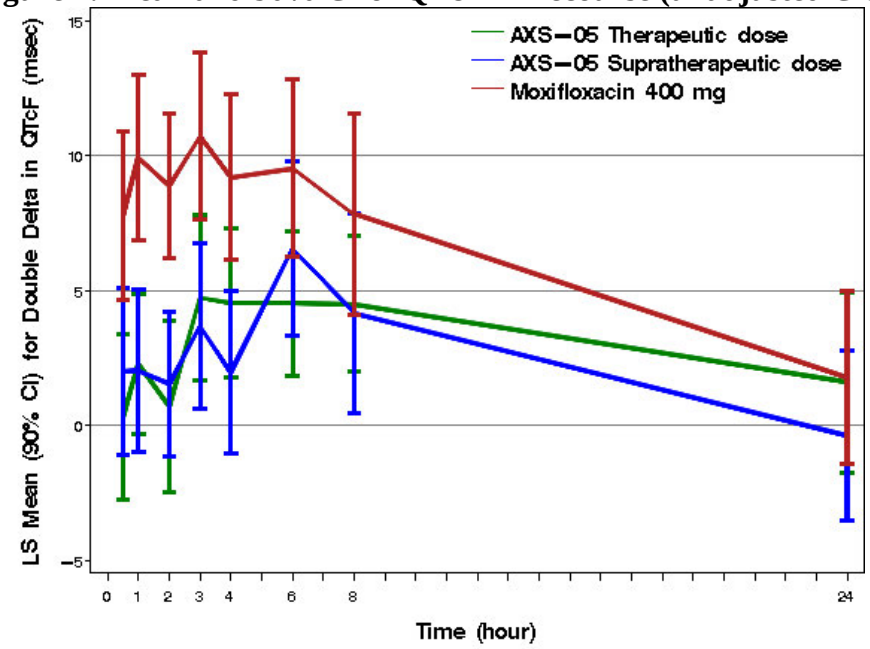


Table 2: The Point Estimates and the 90% CIs for QTcF

	AXS-05 Therapeutic dose (N=39, Day6)			AXS-05 Supratherapeutic dose (N=39, Day7)		
	ΔQTcF (msec)		ΔΔQTcF (msec)	ΔQTcF (msec)		ΔΔQTcF (msec)
Time (hour)	LSmean	LSmean Placebo	LSmean (90% CI)	LSmean	LSmean Placebo	LSmean (90% CI)
0.5	-6.0	-6.4	0.3 (-2.7, 3.4)	-4.2	-6.2	2.0 (-1.1, 5.1)
1	-2.7	-5.0	2.3 (-0.3, 4.9)	-1.6	-3.6	2.0 (-1.0, 5.1)
2	-3.2	-4.0	0.7 (-2.5, 3.9)	-1.7	-3.2	1.5 (-1.1, 4.2)
3	0.8	-4.0	4.7 (1.7, 7.8)	0.3	-3.4	3.7 (0.6, 6.7)

	AXS-05 Therapeutic dose (N=39, Day6)			AXS-05 Supratherapeutic dose (N=39, Day7)		
	ΔQTcF (msec)		ΔΔQTcF (msec)	ΔQTcF (msec)		ΔΔQTcF (msec)
Time (hour)	LSmean	LSmean Placebo	LSmean (90% CI)	LSmean	LSmean Placebo	LSmean (90% CI)
4	0.8	-3.7	4.5 (1.8, 7.3)	1.4	-0.5	2.0 (-1.0, 5.0)
6	-3.5	-8.0	4.5 (1.8, 7.2)	-0.9	-7.4	6.6 (3.3, 9.8)
8	-5.6	-10.1	4.5 (2.0, 7.0)	-4.1	-8.3	4.2 (0.5, 7.9)
24	-3.3	-4.8	1.6 (-1.7, 4.9)	-4.4	-4.0	-0.4 (-3.5, 2.8)

4.3.1.1 Assay sensitivity

The time-course of changes in ΔΔQTcF is shown in Figure 1 and shows the expected time-profile with a mean effect of >5 msec after Bonferroni adjustment for 3 time points (Table 3).

Table 3: The Point Estimates and the 90% CIs for QTcF

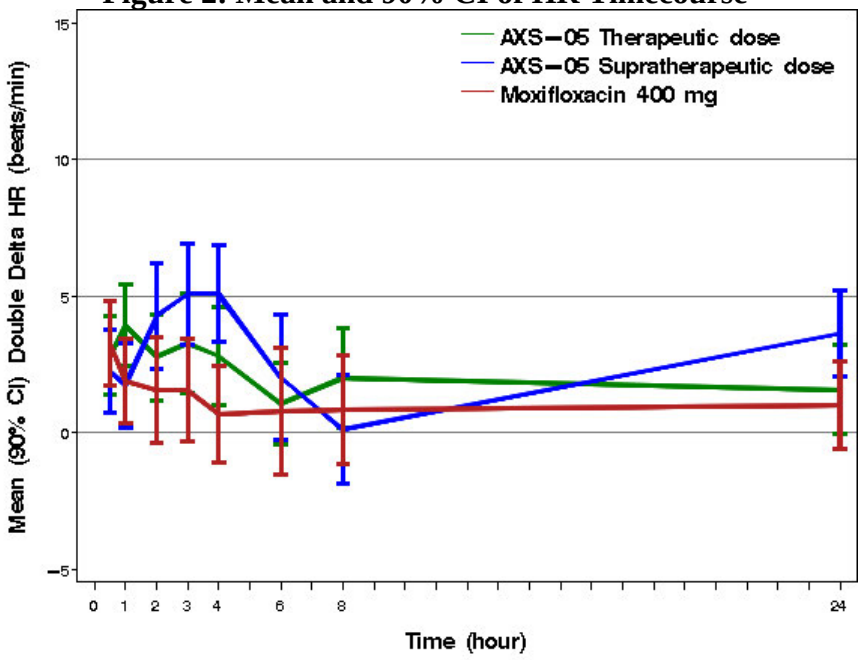
		ΔQTcF (msec) Moxifloxacin 400 mg (N=38)	ΔQTcF (msec) Placebo (N=39)	ΔΔQTcF (msec) Moxifloxacin 400 mg		
Day	Time (hour)	LSmean	LSmean	LSmean	90% CI	Adjust 90% CI*
7	0.5	1.6	-6.2	7.8	(4.6, 10.9)	(3.1, 12.4)
	1	6.3	-3.6	9.9	(6.8, 13.0)	(5.4, 14.4)
	2	5.7	-3.2	8.9	(6.2, 11.6)	(4.9, 12.9)
	3	7.3	-3.4	10.7	(7.6, 13.8)	(6.2, 15.3)
	4	8.7	-0.5	9.2	(6.2, 12.2)	(4.7, 13.7)
	6	2.1	-7.4	9.5	(6.3, 12.8)	(4.7, 14.4)
	8	-0.5	-8.3	7.8	(4.1, 11.6)	(2.4, 13.3)
	24	-2.3	-4.0	1.8	(-1.4, 5.0)	(-2.9, 6.5)

* Bonferroni method was applied to all time points to adjust for multiple endpoint evaluation at 3 time points around moxifloxacin C_{max}.

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups.

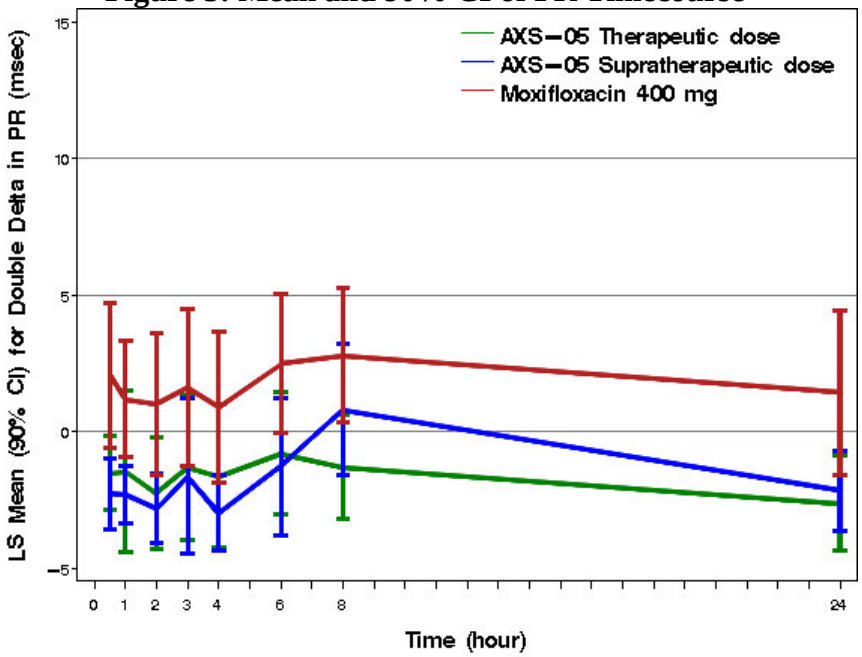
Figure 2: Mean and 90% CI of HR Timecourse



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups.

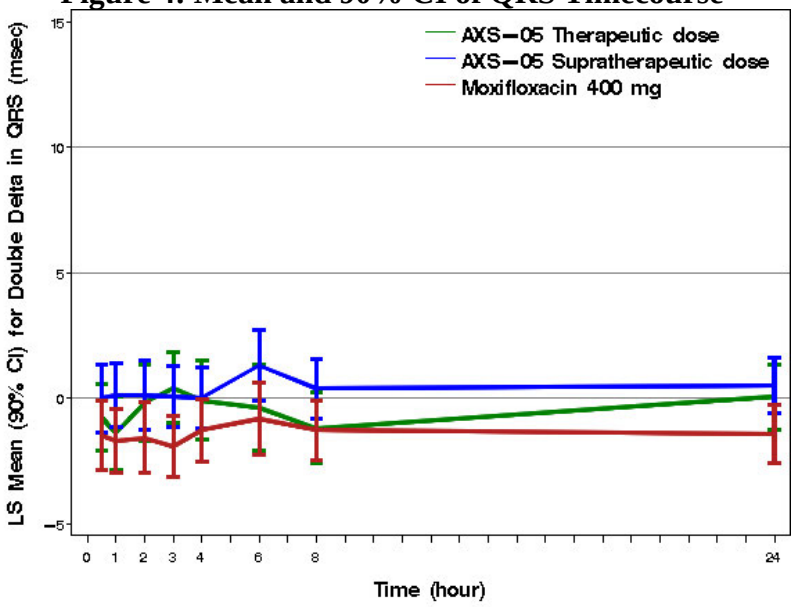
Figure 3: Mean and 90% CI of PR Timecourse



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups.

Figure 4: Mean and 90% CI of QRS Timecourse



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and includes both scheduled and unscheduled ECGs.

4.4.1 QTc

Except one subject in the moxifloxacin group, no subject experienced QTcF >450 msec in the study. No subject had change from baseline in QTcF >60 msec in the study.

4.4.2 HR

Except one subject in the placebo group experienced HR <=45 beats/min at 3 time points, no subject had HR >100 beats/min or <=45 beats/min in the study.

4.4.3 PR

No subject had PR >220 msec in the study.

4.4.4 QRS

No subject had QRS >120 msec in the study.

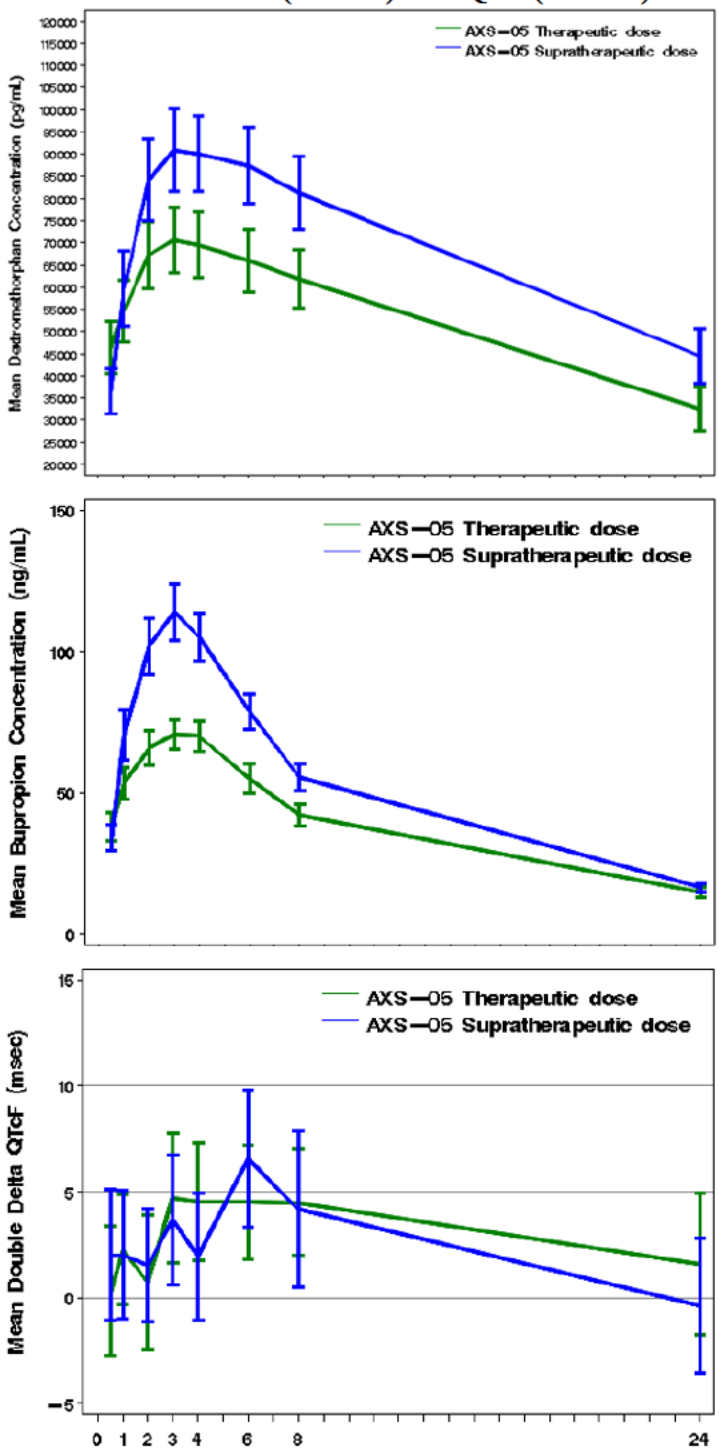
4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis was to assess the relationship between plasma concentration of bupropion (and dextromethorphan) and ΔQTcF. Exposure response analysis was conducted using all subjects with baseline and at a least one postbaseline ECG with time-matched PK.

Prior to evaluating the relationship between bupropion (and dextromethorphan) concentration and QTc using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more

than a 10 bpm increase or decrease in mean HR); 2) delay between bupropion concentration and ΔQTc and 3) presence of non-linear relationship.

Figure 5: Time course of dextromethorphan concentration (top), bupropion concentration (middle) and QTc (bottom)



An evaluation of the time-course of bupropion concentration and changes in ΔΔQTcF is shown in Figure 5. There was no apparent correlation between the time at maximum effect

on ΔΔQTcF and peak concentrations of bupropion (or dextromethorphan) indicating no significant hysteresis.

Figure 6: Assessment of linearity of bupropion concentration-QTc relationship

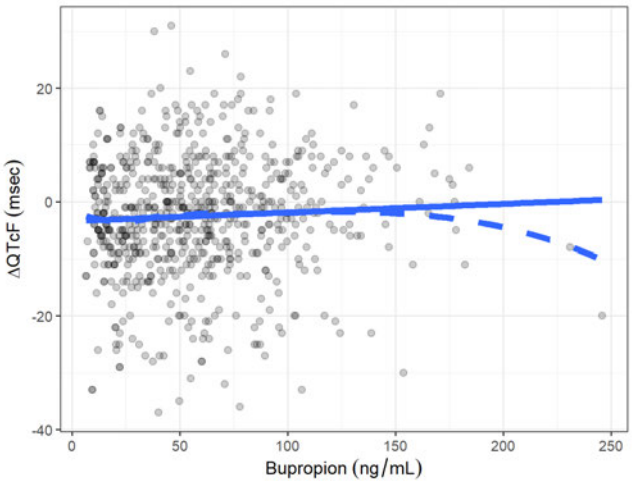
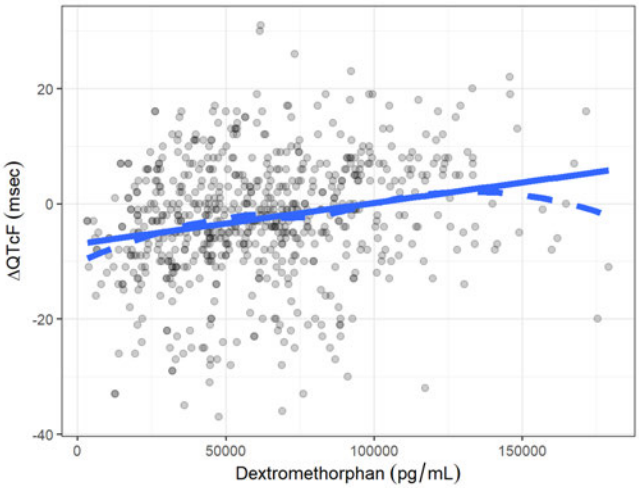


Figure 7: Assessment of linearity of dextromethorphan concentration-QTc relationship



Although the sponsor did not perform non-clinical assessment evaluating the relative contributions of two components, assessment of linearly indicates a slight positive slope for the relationship between ΔQTcF and plasma concentration of dextromethorphan (Figure 7). Thus, the observed effects might be attributed to dextromethorphan as no significant relationship was observed between ΔQTcF and plasma concentration of bupropion (Figure 6). Since the by-time analyses did not suggest that the combination product of dextromethorphan and bupropion is associated with significant increases in the QTc interval, no further concentration-QT assessment using multivariate analysis was performed (Section 7). Assay sensitivity was also established using by time analysis. Please see Section 4.3.1.1 for additional details.

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/s/

JANELL E CHEN
05/06/2021 08:06:50 AM

DALONG HUANG
05/06/2021 09:24:56 AM

DEVI KOZELI on behalf of RAMAN K BAWEJA
05/06/2021 10:19:03 AM
Signing on behalf of Ray as he is out of the office

GIRISH K BENDE
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