CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-031/S-052

Trade Name: Paxil

Generic Name: paroxetine hydrochloride

Sponsor: GlaxoSmithKline

Approval Date: February 6, 2006

Indication: Major Depressive Disorder, Obsessive Compulsive Disorder, Panic Disorder, Social Anxiety Disorder, Generalized Anxiety Disorder, Posttraumatic Stress Disorder.

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APPLICATION NUMBER:

NDA 20-031/S-052

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APPLICATION NUMBER:

NDA 20-031/S-052

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-031/S-048/051/052
NDA 20-936/S-022/026/027
NDA 20-710/S-015/016

GlaxoSmithKline
Attention: James Murray
Director Regulatory Affairs
One Franklin Plaza
PO Box 7929
Philadelphia, PA 19101-7929

Dear Mr. Murray:

We acknowledge receipt of your supplemental new drug applications dated June 16, 2005 (NDAs 20-031/S-048, 20-936/S-022), October 7, 2005 (NDA 20-936/S-026), October 21, 2005 (NDAs 20-031/S-051 and 20-710/S-015) and December 5, 2005 (NDAs 20-031/S-052, 20-936/S-027, and 20-710/S-016) submitted under section 505(b) of the Federal Food Drug and Cosmetic Act for Paxil (paroxetine hydrochloride) tablets (NDA 20-031), Paxil (paroxetine hydrochloride) CR tablets (NDA 20-936), and Paxil (paroxetine hydrochloride) suspension (NDA 20-710).

These supplemental applications provide for the following revisions to product labeling:

20-031/S-048
20-936/S-022

- Under CONTRAINDICATIONS - to include a statement that concomitant use of paroxetine in patients taking pimozide is contraindicated.

- Under PRECAUTIONS – the addition of a new subsection entitled "Pimozide" under the PRECAUTIONS-Drug Interactions section.

20-031/S-051
20-936/S-026
20-710/S-015

The supplement informs the Agency of GSK's submitted change to the packaging (carton & container) by including a black box warning and a Medication Guide in all of the paroxetine products' labeling to describe the potential for increased risk of suicidal ideation in children and adolescents who take antidepressants, and to distribute each product presentation in unit-of-use packaging to ensue every patient receives the MedGuide.

20-031/S-052
20-936/S-027
20-710/S-016

This supplement provides for revisions to the WARNINGS and PRECAUTIONS-Pregnancy section to include information on the study of major congenital malformation among infants born to women dispensed paroxetine in the first trimester. The Pregnancy category also changed from a "C" to a "D" category.

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in your labeling submitted on December 5, 2005. Accordingly, these supplemental applications are approved effective on the date of this letter.

[(b4)]

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Renmeet Gujral, Pharm. D., Regulatory Project Manager, at (301) 796-1080.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
2/6/2006 09:10:49 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-031/S-052

SUMMARY REVIEW

REGULATORY PROJECT MANAGER
LABELING REVIEW

Date: January 4, 2006
NDA: 20-031 (Tablets), 20-710 (Oral Suspension), & 20-936 (CR)
DRUG: Paxil (paroxetine HCl) Tablets, Oral Suspension, & CR
Sponsor: GlaxoSmithKline (GSK)
Indication: MDD/OCD/SAD/GAD/PTSD

NDA	Supplement	Dated	Action
Paxil (paroxetine hydrochloride) tablets (NDA 20-031)			
20-031	SLR-042	3-16-04	Approved 7-13-05
20-031	SLR-046	11-30-04	Open
20-031	SLR-048	6-16-05	Open
20-031	SLR-049	8-30-05	Open
20-031	SLR-050	9-6-05	Open
20-031	SLR-051	10-21-05	Open
20-031	SLR-052	12-5-05	Open
Paxil (paroxetine hydrochloride) CR tablets (NDA 20-936)			
20-936	SLR-018	3-16-04	Approved 7-13-05
20-936	SLR-021	11-30-04	Open
20-936	SLR-022	6-16-05	Open
20-936	SLR-023	8-30-05	Open
20-936	SLR-025	9-6-05	Open
20-936	SLR-026	10-7-05	Open
20-936	SLR-027	12-5-05	Open
Paxil (paroxetine hydrochloride) suspension (NDA 20-710)			
20-710	SLR-009	10-3-00	Approved 2-15-01
20-710	SLR-015	10-21-05	Open
20-710	SLR-016	12-5-05	Open

Notes of Interest

1. The Paxil and Paxil suspension products share the same labeling. The Paxil CR labeling is a stand alone document.
2. There were no corresponding supplements submitted to the Paxil suspension NDA in previous labeling changes since GSK was unaware that they not only needed to update the Paxil tablets NDA but also the suspension NDA whenever labeling changes are enacted. They rectified this error for the last 2 open Paxil supplements.
3. At this point, the Division is unable to act on four open labeling supplements dated 11-30-04 and 8-30-05, submitted as CBE applications (NDAs 20-031/SLR-046/049 and 20-936/SLR-021/023). These supplements provide for revisions to the Precautions section to add new statements about akathesia, tinnitus, a new drug interaction statement for Fosamprenavir/ritonavir, serotonin syndrome, & serotonigic drugs. A statement has also been added under "Adverse Reactions" for Hallucinations. They also (b) (4)

(b) (4)

.

REVIEW

20-031/SLR-048
20-936/SLR-022
Dated: 6-16-05
CBE: Yes
Label Code: PX:L35
Reviewed by Medical Officer and OCPB: yes, acceptable

The agency requested the sponsor (GSK) to conduct an in vivo study to examine risk of an interaction between paroxetine and pimozide in an Agency letter dated 12-4-02. GSK conducted the study and provided the agency with this CBE as a result from the study. OCPB was consulted on this CBE. Both the medical reviewer as well as OCPB recommend these supplements to be approved.

These supplements provide for revisions to the package insert in the following sections:

- under CONTRAINDICATIONS, to include a statement that concomitant use of paroxetine in patients taking pimozide is contraindicated.
- under PRECAUTIONS, to include information from study 29060/877 under "Drug Interactions" under a new subheading "Pimozide"

20-031/SLR-049
20-936/SLR-023
Dated: 8-30-05
CBE: Yes
Label Code: PC:L17
Reviewed by OCPB: Currently under review
Medical Reviewer: Currently under review

The sponsor has added the following language to the Warnings to Physician section of labeling which is taken from the APA guidelines. This is an augmentation to the class labeling language for suicidality:

- A statement has been added under WARNINGS section, Clinical Worsening and Suicide Risk subsection:

  "In addition, patients with a history of suicidal behavior or thoughts, those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at an increased risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment".[American Psychiatric Association, Practice Guideline for the Assessment and Treatment of Patients with Suicidal Behaviors, 2003] [Brown, 2000]

The sponsor had added the following language under the PRECAUTIONS section, "Discontinuation of Treatment with Paxil" subsection as underlined:

- Dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations and tinnitus), anxiety, confusion headache lethargy, emotional lability, insomnia, and hypomania.

A drug interaction statement has been added under the PRECAUTIONS section, under a new heading " Fosamprenavir/Ritonavir"

- **Fosamprenavir/ritonavir:** Co-administration of fosamprenavir/ritonavir with paroxetine significantly decreased plasma levels of paroxetine. Any dose adjustment should be guided by clinical effect (tolerability and efficacy)."

A statement has been added under "ADVERSE REACTIONS"

- **"Hallucination:** In pooled clinical trials of immediate-release paroxetine hydrochloride, hallucinations were observed in 22 of 9089 receiving drug and 4 of 3187 patients receiving placebo."

20-031/SLR-050
20-936/SLR-025
Dated: 9-06-05
CBE: Yes
Label Code: PA:L18
Reviewed by Safety Team: yes

The supplement provides for the following revision:

- Revisions to the **PRECAUTIONS-Pregnancy** section based upon preliminary results of the Ingenix pregnancy data.

Notes: The Agency became aware of another database in which there was confirmatory evidence of a casual association between paroxetine exposure during the first trimester of pregnancy and congenital malformations. This resulted in several meetings with GSK in which they agreed to change the pregnancy from C to D. These changes were submitted in a separate supplement.

20-031/SLR-051
20-936/SLR-026
20-710/SLR-015
Dated: 10-21-05 & 10-7-05
CBE: Yes
Label Code: N/A
Reviewed by Medical Officer: No
Reviewed by Chemist: No

The supplement informs the Agency of their submitted change to the packaging (carton & container) by including a black box warning and a Medication Guide in all of the paroxetine products' labeling to describe the potential for increased risk of suicidal ideation in children and adolescents who take antidepressants, and to distribute each product presentation in unit-of-use packaging to ensue every patient receives the MedGuide.

Notes: GSK submitted this supplement to make the Agency aware they will be including a Medication Guide with all of the containers and unit dose packaging of paroxetine. The standard practice is to distribute Medication Guides to each patient receiving an antidepressant.

20-031/SLR-052
20-936/SLR-027
20-710/SLR-016
Dated: 12-5-05
CBE: Yes
Label Code: PA: L19
Reviewed by Medical Officer: Yes

This supplement includes information on the study of major congenital malformation among infants born to women in the first trimester. Preliminary data was included from the Ingenix database from January 2003- September 2004 as well as the Swedish Medical Birth Registry from July 1995- December 2003. Also, the sponsor thoroughly discussed the matter with the agency and came to a conclusion to change the Warnings and Precautions section of the prescribing information for Paxil. The Pregnancy category also changed from a "C" to a "D". Furthermore, a Dear Healthcare Professional letter was sent out as well as posted on the sponsor's website.

CONCLUSIONS

1. The above labeling supplements only provide for those revisions as stated above for these open supplements and were compared to the last approved labeling(7-13-05).

2. I recommend an acknowledgement and retain letter issue for 20-031/SLR-050 & 20-936/SLR-025 since these changes were superseded by the agreed upon revisions to the Warnings and Precautions-Pregnancy section submitted in supplements 20-031/SLR-052, 20-936/SLR-027, and 20-710/SLR-015.

3. I recommend that an approval letter issue for open supplemental applications 20-031/SLR-048/051/052, 20-936/SLR-022/026/027, and 20-710/SLR-015/016.

4. Since the Division cannot take an action on 4 CBE applications, NDAs 20-031/SLR-046/049 and 20-936/SLR-021/023 (see review above), I recommend that our approval letter state that we acknowledge that these supplements, submitted as CBE, are still under review.

Renmeet Gujral, Pharm.D.
Regulatory Project Manager

Paul David, RPh.
Supervisory Consumer Safety Officer

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Renmeet Gujral
2/3/2006 03:30:26 PM
CSO

Paul David
2/6/2006 08:26:19 AM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-031/S-052

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data

NDA: 20-936; 20-031
Drug: paroxetine
Route: oral
Indication: major depressive disorder; generalized anxiety disorder; panic disorder; social anxiety disorder; (b) (4) obsessive-compulsive disorder; post-traumatic stress disorder
Materials reviewed: August 22, 2005, September 6, 2005, November 4, 2005, and December 5, 2005 submissions from GSK; articles and abstracts referenced within review
Sponsor: GlaxoSmithKline
Reviewer: Alice T.D. Hughes, MD

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1 Executive summary

Published evidence to date regarding the teratogenic risk of selective serotonin reuptake inhibitors (SSRIs) has not suggested an increased risk for major congenital malformations following maternal exposure to these drugs in the first trimester of pregnancy. However, the published studies have not included enough cases with paroxetine exposure to contribute to the understanding of paroxetine risk specifically.

New studies indicate that paroxetine is associated with an increased risk for congenital malformations, particularly cardiovascular malformations. Evidence of an increased risk for birth defects with paroxetine first emerged from preliminary analyses of a GSK-sponsored retrospective cohort study using a managed care database. This study was conducted as a part of GSK's investigation of a possible association between bupropion and congenital malformations. Preliminary analyses of this study indicated that maternal exposure to paroxetine in the first trimester of pregnancy was associated with a statistically significant increased risk for overall and cardiovascular malformations compared to exposure to other antidepressants in the first trimester. The majority of the cardiovascular malformations associated with paroxetine were ventricular septal defects.

In September, 2005, GSK revised their prescribing information for paroxetine in response to these results. They submitted a Changes Being Effected (CBE) labeling supplement to the FDA and posted revised labeling and a statement on their website on September 6, 2005. On September 9, 2005, they initiated mailing of "Dear Healthcare Professional" letters to prescribers in the United States.

Following the submission of GSK's September, 2005 CBE labeling supplement, the Division obtained results from a study based on Swedish national registry data that

supported the findings of the managed care database cohort study. In this study by Kallen et al., infants exposed to paroxetine in early pregnancy had an approximately two-fold increased risk for cardiac defects compared to the entire Swedish national registry population, although their risk for congenital malformations overall was not elevated. Most of the cardiovascular malformations were atrial and ventricular septal defects. The increased risk for cardiovascular malformations was not observed for any of the other selective serotonin reuptake inhibitors (SSRIs) in this Swedish registry study.

Updated analyses from the managed care database cohort study using a larger dataset were submitted to the Division in November, 2005. Although the relevant odds ratios for paroxetine compared to all other antidepressants were slightly lower in these analyses, and the odds ratio for cardiovascular malformations was no longer statistically significant, an increased risk of overall congenital malformations (OR 1.8; 95% confidence interval [CI] 1.2—2.8) and cardiovascular malformations (OR 1.5; 95% CI 0.8—2.9) following first trimester exposure to paroxetine compared to first trimester exposure to other antidepressants remained evident.

Based on the November, 2005 cohort study analyses and the Swedish national registry study, the FDA requested that paroxetine's pregnancy category be changed from C to D[1] and that paroxetine's labeling be revised accordingly. GSK submitted a CBE labeling supplement on December 5, 2005 in response to the FDA request. In this supplement, they changed the pregnancy category to D and added the most recent data pertaining to paroxetine's teratogenicity to the *Warnings* section,

This memorandum will summarize all available evidence pertaining to paroxetine-associated congenital malformation risk and will summarize the actions that the Division and GSK have taken and plan to take based on this evidence.

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[1] Pregnancy category A indicates that adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters). Pregnancy category B indicates that animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women ***or*** that animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters). Pregnancy category C indicates that animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans and the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks ***or*** that there are no animal reproduction studies and no adequate and well-controlled studies in humans. Pregnancy category D indicates that there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective). Pregnancy category X indicates that studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available).

1.1 Background—assessment of risk for birth defects with bupropion

In September, 2003, the Division received the *Bupropion Pregnancy Registry Interim Report*. This report described outcomes for 322 pregnancies prospectively registered between September 1, 1997 and February 28, 2003 with earliest exposure to bupropion in the first trimester. The prospectively collected data from the registry indicated a higher than expected number of cardiovascular malformations associated with exposure to bupropion (7/271; 2.7%). The majority of the cardiovascular anomalies were ventricular outflow tract defects. The risk of *all* congenital cardiac defects is estimated to be approximately 9/1000 live births, based on population-based studies in the US.[2] The risk of *serious* structural congenital heart defects in the general population is estimated by the California Birth Defects Monitoring Program to be approximately 1 in 400 (or 2.5/1000) live births.[3]

The total number of all birth defects (10/271; 3.7%) evident in the bupropion pregnancy registry was consistent with the expected background rate of all birth defects in the United States.[4] Data from the *Bupropion Pregnancy Registry Interim Report* are described in more detail in my memorandum dated November 26, 2003.

To further investigate the possibility of an association between bupropion exposure during pregnancy and congenital cardiovascular malformations, GlaxoSmithKline (GSK) initiated a claims-based, retrospective cohort study conducted by Ingenix using managed care insurance claims data. This study was already underway at the time that the Division received and reviewed the *Bupropion Pregnancy Registry Interim Report.*

The preliminary report of the retrospective cohort study (*Bupropion in Pregnancy and the Occurrence of Cardiovascular and Major Congenital Malformations: A Preliminary Report*) was submitted to the bupropion NDA on February 7, 2005. Results of additional analyses requested by the Division of Neuropharmacological Drug Products[5] were submitted on June 14, July 19, and August 22, 2005.

In the original study, GSK compared the risk for all congenital malformations and cardiovascular malformations in women exposed to bupropion[6] in the first trimester with the risk in two other cohorts—women exposed to antidepressants other than bupropion in

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[2] Botto LD, Correa A, Erickson JD. Racial and temporal variations in the prevalence of heart defects. *Pediatrics.* 2001;107

[3] California Birth Defects Monitoring Program website. http://www.cbdmp.org/bd_heart.htm. Accessed 2005 October 11.

[4] The CDC estimates that approximately 3% of infants born in the United States each year have birth defects (Centers for Disease Control and Prevention website. http://www.cdc.gov/ncbddd/bd/faq1 htm#chanceofBD. Accessed 2005 September 6)

[5] The Division of Neuropharmacological Drug Products was divided into the Division of Neurology Products and the Division of Psychiatry Products in July 2005; references to the "Division" in this review subsequent to the split refer to the Division of Psychiatry Products.

[6] Women exposed to bupropion in the first trimester included those on bupropion monotherapy and those who took bupropion as part of antidepressant polytherapy.

the first trimester and women exposed to bupropion outside of the first trimester. There was no comparator group without any antidepressant exposure during pregnancy.

Although GSK's original analysis used two mutually exclusive Ingenix databases (the Lab Rx and Research Databases), the subsequent analyses that gave rise to the paroxetine signal used only the Ingenix Research Database. In the Research Database analyses, a more sensitive congenital malformation case definition was used and all cases of congenital malformation were verified by review of medical records, which was not possible in the LabRx database. I will thus restrict my discussion in this review to the analyses using the Ingenix Research Database.

The investigators identified women who had been dispensed an antidepressant between January 1, 1994 and December 31, 2002 and had at least one live birth between January 1, 1995 and December 31, 2002. ICD-9 and CPT-4 codes were used to identify births. They identified three cohorts—deliveries with dispensing of bupropion during the first trimester, regardless of the dispensing of other antidepressants that occurred during or outside of the first trimester (the first trimester was defined as occurring from the earliest possible conception date through 12 weeks following the latest possible conception date; the conception date was estimated by examining the sequences of procedures and diagnoses in the medical claims data); deliveries with dispensing of antidepressants other than bupropion in the first trimester (a cohort sampling method was used because this group was much larger than the other groups); and deliveries with dispensing of bupropion before the first trimester (between one and 18 months prior to the earliest possible conception date) or after the first trimester but before delivery, regardless of the dispensing of other antidepressants that occurred during or outside of the first trimester.

The investigators identified congenital malformations using ICD-9 codes by searching the medical claims of both mothers and infants and confirming all identified cases by medical record review. Minor malformations (e.g., mild hypospadias, congenital cataract, hip click, mild pulmonic stenosis, and anal stricture) were excluded. Cases of patent ductus arteriosus and ostium secundum type atrial septal defects were excluded because these were considered to be associated with prematurity. Claims were searched from nine months before to nine months after delivery.

The investigators conducted analyses comparing the three cohorts with respect to congenital malformations in general and cardiovascular malformations specifically.

The tables below summarizes the results of the retrospective cohort analysis with cases of chromosomal anomalies removed (these results are from GSK's June 14, 2005 submission; the original analyses submitted in February, 2005 included chromosomal anomalies as cases, and I will not report those results in this review).

Odds Ratios for congenital and cardiovascular malformations
Bupropion first trimester vs. other antidepressants first trimester
Ingenix Research Database

Congenital Malformations	Cases	Total no. infants	Prevalence/ 1000 live births	OR; 95% CI	Adjusted OR; 95% CI*
Bupropion—first trimester (BFT)	15	463	32.4	1.3; 0.8—2.3	1.2; 0.7—2.2
Other antidepressants—first trimester (OAFT)**	80	3241	24.7		
Cardiovascular Malformations					
Bupropion—first trimester	8	463	17.3	1.6; 0.7—3.5	1.6; 0.7—3.5
Other antidepressants—first trimester**	35	3241	10.8		

*Adjusted for age, calendar year of delivery, dispensing of lithium, dispensing of carbamazepine, diagnosis of pre-eclampsia or eclampsia, and infant sex
**4,782 women (who had 5,034 infants) were initially identified who had been dispensed antidepressants other than bupropion in the first trimester. After the application of the cohort sampling method, 3,142 women (who had 3,241 infants) were in the final cohort.

Odds Ratios for congenital and cardiovascular malformations
Bupropion first trimester vs. bupropion outside first trimester
Ingenix Research Database

Congenital Malformations	Cases	Total no. infants	Prevalence/ 1000 live births	OR; 95% CI	Adjusted OR; 95% CI**
Bupropion—first trimester (BFT)	15	463	32.4	2.1; 0.9—5.1	2.0; 0.8—4.7
Bupropion—outside first trimester (BOFT)	8	519	15.4		
Cardiovascular Malformations					
Bupropion—first trimester	8	463	17.3	2.3; 0.7—7.6	2.3; 0.7—7.9
Bupropion—outside first trimester	4	519	7.7		

The majority of the cardiovascular defects associated with bupropion were ventricular septal defects. The pattern of ventricular outflow tract defects observed in the bupropion pregnancy registry was not replicated. Ventricular septal defects also accounted for the majority of the cardiovascular malformations identified in the comparator cohorts.

GSK conducted two additional analyses that I will not discuss in detail here to explore the effect of possible confounding variables—an analysis of cardiovascular

malformations stratified by first trimester exposure to drugs known or suspected to affect the developing cardiovascular system and a nested case-control study using data abstracted by chart review to examine the possibility of confounding by indication. The results of the stratified analysis were equivocal, but suggested that concomitant teratogen dispensings could be contributing to the elevated risk for congenital malformations observed in women dispensed bupropion in the first trimester. In the nested case-control study, the odds ratios for all congenital malformations and cardiovascular malformations specifically did not change substantially after adjustment for depression or anxiety during pregnancy and smoking before or during pregnancy.

Based on the results of the bupropion analyses from the Ingenix Research Database, which were equivocal with respect to the association between bupropion and overall and cardiovascular congenital malformations, the Division requested that GSK conduct similar analyses in the Ingenix Research Database for all individual antidepressants other than bupropion to which women were exposed during the same study period (capturing live births between 1995 and 2002). This analysis had two primary purposes:

- To explore whether any risk associated with bupropion for congenital malformations was an antidepressant class effect
- To more accurately assess the risk associated with individual antidepressants. As noted above, the original analyses done by GSK included patients exposed to bupropion in the first trimester who may also have been exposed to additional antidepressants in the first trimester. In the subsequent analyses requested by the Division, GSK was to consider birth defect risk in women exposed to bupropion alone (i.e., as the only antidepressant) in the first trimester, and perform the same analyses for all of the antidepressants to which women in the study's managed care database were exposed in the first trimester.

2 Results of August, 2005 preliminary analyses examining birth defect risks following first trimester exposure to paroxetine and other antidepressants

GSK compared the risk for congenital malformations (both overall and cardiovascular malformations specifically) following first trimester exposure to individual antidepressants in the Ingenix Research Database with the risk following first trimester exposure to all other antidepressants as a group. In assessing the risk for congenital malformations associated with individual antidepressants other than bupropion, GSK used the group of women that had been identified using the cohort sampling method; they did not perform analyses based on outcomes for all women dispensed individual antidepressants during the relevant time period.

The methods for their analysis of the risk associated with individual antidepressants other than bupropion were similar to the methods described above for the bupropion analyses using the Ingenix Research Database with four key exceptions:

1. GSK used only one comparison group for each antidepressant studied, comparing the risk for malformations following first trimester exposure to each individual antidepressant with the risk associated with first trimester exposure to all other antidepressants; a comparison group composed of infants with exposure to the relevant antidepressant outside of the first trimester was not used as it had been in the bupropion study.
2. GSK examined overall and cardiovascular malformation risk using two approaches based on whether or not women had been dispensed more than one antidepressant in the first trimester:
    - In the first approach, they examined the risk for overall and cardiovascular malformations following first trimester exposure to individual antidepressants as the *only* antidepressant exposure in the first trimester and
    - In the second approach, they examined the risk for overall and cardiovascular malformations following first trimester exposure to the antidepressant being assessed in women who may also have had additional exposures to other antidepressants in the first trimester
3. GSK did separate analyses based on first trimester dispensing of suspected teratogens for both overall and cardiovascular malformations:
    - In one set of analyses women who had been exposed to suspected teratogens in the first trimester were excluded
        - A different set of teratogens was used for the overall malformation analyses and the cardiovascular malformation analyses
            - The following drugs were considered to be teratogens for the purposes of the overall congenital malformation analyses: aminoglycoside antibiotics, ACE inhibitors, androgens, anticholinergic drugs, busulfan, carbamazepine, cyclophosphamide, danazol, diethylstilbestrol, etretinate, fluconazole, indomethacin, isotretinoin, lithium, methimazole, methotrexate, misoprostol, oral corticosteroids, paramethadione, penicillamine, phenytoin, propylthiouracil, tetracycline, thalidomide, trimethadoin, valproic acid, warfarin
            - The following drugs were considered to be teratogens for the purposes of the cardiovascular congenital malformation analyses: busulfan, carbamazepine, cyclophosphamide, etretinate, isotretinoin, lithium, methotrexate, paramethadione, phenytoin, thalidomide, trimethadoin, valproic acid
    - In the second set of analyses, all women were included regardless of concomitant teratogen dispensings in the first trimester
4. In assessing the risk for congenital malformations associated with individual antidepressants other than bupropion, GSK included women in the comparator group who were dispensed the antidepressant in question as part of antidepressant polytherapy. For example, in assessing the risk for congenital malformations (both overall and cardiovascular) associated with paroxetine, the comparator

group included women dispensed paroxetine as part of a multidrug antidepressant regimen.

GSK repeated the analyses for bupropion using the revised analysis methodology in addition to conducting analyses for each antidepressant other than bupropion to which women were exposed in the first trimester in the Ingenix Research Database. These antidepressants included amitriptyline, amitriptyline/chlordiazepoxide, citalopram, clomipramine, desipramine, doxepin, fluoxetine, fluvoxamine, imipramine, mirtazipine, nefazadone, nortriptyline, paroxetine, protriptyline, sertraline, trazadone, and venlafaxine.

In this review, I will discuss only the analyses examining risk for malformations (overall and cardiovascular) following first trimester exposure to individual antidepressants in women who were not also exposed to another antidepressant or one of the known or suspected teratogens listed above in the first trimester. These analyses permit the least confounded assessment of the risk for congenital malformations associated with individual antidepressants.

Below, I summarize the results of these analyses for bupropion, citalopram, and paroxetine. Exposure to these antidepressants in the first trimester was associated with the highest odds ratios for overall and cardiovascular malformations compared to women exposed to all other antidepressants in the first trimester (and not dispensed known teratogens). Only in the case of paroxetine did the 95% confidence intervals for overall and cardiovascular malformations exceed and not include one. None of the other antidepressants had odds ratios for congenital or cardiovascular malformations following first trimester exposure that were significantly elevated compared to the overall group of antidepressants. In Appendix 9.1, I have attached the results of the salient analyses for all antidepressants.

Odds ratios for congenital and cardiovascular malformations for mutually exclusive categories of specific antidepressants dispensed during the first trimester compared to all other antidepressants dispensed during the first trimester (excluding women with teratogenic drug dispensings); Ingenix Research Database (live births 1995—2002)

Congenital Malformations	Cases	Total no. infants	Prevalence/ 1000 live births	OR; 95% CI	Adjusted OR; 95% CI*
Paroxetine	23	527	43.6	2.0; 1.2—3.4	2.2; 1.3—3.6
Bupropion	6	248	24.2	0.9; 0.4—2.2	1.0; 0.4—2.3
Citalopram	7	188	37.2	1.53; 0.70—3.37	1.4; 0.6—3.1
Cardiovascular Malformations					
Paroxetine	11	589	18.7	2.0; 1.0—4.0	2.1; 1.0—4.2
Bupropion	2	282	7.1	0.6;	0.6;

				0.1—2.6	0.1—2.7
Citalopram	5	217	23.0	2.3; 0.9—5.9	2.2; 0.8—5.9

*Odds ratios adjusted for age, calendar year of delivery, diagnosis of pre-eclampsia or eclampsia, and infant sex.

The majority of the cardiovascular defects that occurred following first trimester exposure to paroxetine were ventricular septal defects (VSDs). Eight of the eleven defects associated with exposure to paroxetine alone were VSDs; 10 of the 14 cardiovascular defects associated with any exposure to paroxetine in the first trimester were VSDs. Two of the 14 cases of paroxetine-associated VSDs were also associated with atrial septal defects. The remaining cardiac defects in infants exposed to paroxetine in the first trimester were as follows: small-moderate patent ductus arteriosus and restrictive patent foramen ovale with left ventricular volume overload; atrial septal defect with bilateral pulmonary branch stenosis; transposition of the great arteries (congenitally corrected) with mild-moderate pulmonary stenosis; and coarctation of the aorta.

No unexpected defect or pattern predominated among the non-cardiac malformations associated with any first trimester use of paroxetine.[7] There were no cases of omphalocele and no cases of craniosynostosis.

3 Brief review of published studies and abstracts through September, 2005 CBE submission

The Ingenix analysis is one of four recent studies that have demonstrated an increased risk for major congenital malformations following exposure to paroxetine or any other SSRI during pregnancy. No studies published prior to 2005 had demonstrated an increased risk for major congenital malformations associated with exposure to SSRIs (considered as a group or individually), although one study (Chambers et al.[8]) did demonstrate an increased risk for minor structural anomalies associated with fluoxetine exposure compared to a control group. A table summarizing the available evidence pertaining to SSRI-associated birth defect risk following first trimester exposure is included in Appendix 9.3.

In the remainder of this section, I will briefly summarize the evidence pertaining to paroxetine-associated birth defect risk that was available at the time that GSK submitted their CBE labeling supplement in September, 2005. I will not discuss data from the

[7] The non-cardiac defects reported following first trimester exposure to paroxetine were: pyloric stenosis (2); congenital left hip subluxation; congenital microcephaly; first degree hypospadias; cleft palate and hypospadias; imperforate anus with perineal fistula, right renal agenesis and left-sided grade II hydronephrosis; bilateral hip dysplasia; left unilateral complete cleft lip and cleft palate; agenesis of corpus callosum with left cerebellar hypoplasia; imperforate anus and posterior forchette fistula, arthrogryposis mutiplex congenita (the baby was premature and died); lipomyelomeningocele

[8] Chambers CD, Johnson KA, Dick LM, et al. Birth outcomes in pregnant women taking fluoxetine. N Engl J Med1996;14:1010-1015.

published studies of SSRI-associated birth defect risk[9,10,11] that did not include any exposures to paroxetine, although these studies are summarized in Appendix 9.3.

3.1 Studies without evidence for risk

Kulin et al.[12] examined birth outcomes following first trimester exposure to SSRIs in a prospective multi-center cohort study from the Teratology Information Service Centers. Participants for the study were selected from the population of callers to the Teratology Information Service. Exposure information was obtained by interviews conducted prior to birth outcome. Birth outcomes for 267 women exposed to SSRIs in the first trimester were compared to outcomes for a control group exposed to agents not considered to be teratogenic (e.g. dental x-rays, acetaminophen). 97 of the SSRI-exposed women were exposed to paroxetine. The relative risk for major malformations among SSRI-exposed neonates was 1.06 (95% CI 0.43—2.62). There were nine major malformations each in the SSRI-exposed group and the control group. Two of these were cardiovascular malformations in the SSRI group whereas four were cardiovascular in the control group. Kulin et al. do not report outcomes following exposure to individual antidepressants.

Studies by Simon et al.,[13] Hendrick et al.,[14] and Diav-Citrin et al.[15] assessed birth outcomes following exposure to SSRIs in early pregnancy. The number of women with exposure to SSRIs in each of these studies ranged from 138 to 185; exposure to paroxetine in each of these studies was 19, 28, and 89. There was no control group in the study by Hendrick et al. Although these studies did not demonstrate an increased risk for congenital malformations associated with SSRIs, they had too few SSRI-exposed women to adequately assess whether exposure to SSRIs either as a group or individually is associated with an increased risk for congenital malformations.

A study by Ericson et al.[16] published in 1999 used prospectively collected Swedish registry data (data from the Swedish Medical Birth Register supplemented with data from the Swedish Hospital Discharge Register and the Register of Congenital Malformations) to study the association between SSRI exposure in early pregnancy and the risk for birth defects. The Swedish Medical Birth Registry, which was established in 1973, contains

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[9] Pastuszak A, Schick-Boschetto B, Zuber C, et al. Pregnancy outcome following first-trimester exposure to fluoxetine (Prozac). JAMA 1993;17:2246-2248

[10] Nulman I, Rovet J, Stewart DE, et al. Neurodevelopment of children exposed in utero to antidepressant drugs. N Engl J Med 1997;4:258-262.

[11] Chambers CD, Johnson KA, Dick LM, et al. Birth outcomes in pregnant women taking fluoxetine. N Engl J Med1996;14:1010-1015.

[12] Kulin NA, Pastuszak A, Sage S, et al. Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors - A prospective controlled multicenter study. JAMA 1998; 279:609-610.

[13] Simon GE, Cunningham ML, Davis RL. Outcomes of prenatal antidepressant exposure. Am J Psychiatry 2002;12:2055-2061.

[14] Hendrick V, Smith LM, Suri R, et al. Birth outcomes after prenatal exposure to antidepressant medication. Am J of Obstet Gynecol 2003; 188: 812-815.

[15] Diav-Citrin O, Shechtman S, Weinbaum D, et al. Pregnancy outcome after gestational exposure to paroxetine: a prospective controlled study [abstract]. Teratology 65(6):298, 2002.

[16] Ericson A, Kallen B, Wilholm BE. Delivery outcome after the use of antidepressants in early pregnancy. Eur J Clin Pharmacol 1999;55:503-508.

data regarding approximately 98.6% of Swedish infants and mothers. Data regarding maternal drug exposures are obtained at the first prenatal visit, which is most frequently at 10 weeks of pregnancy. Ericson's study, which was based on outcomes following 531 SSRI exposures (including 118 exposures to paroxetine specifically), demonstrated no increased risk for congenital malformations associated with SSRI exposure in early pregnancy compared to the expected background rate in the Swedish population. 21 congenital malformations were observed following SSRI exposure in early pregnancy; five of these were cardiovascular malformations.[17] The expected number of malformations overall was 18.7. The investigators did not assess risk associated with individual SSRIs. Moreover, they did not report analyses of risk for specific malformations, although they did report that there were no unusual types or clusters of major congenital malformations following SSRI exposure.

A review article by Hallberg et al.[18] published in 2005 reported more recent data from the Swedish Medical Birth Registry, without any supplementary data from the other two relevant Swedish registries—the Register of Congenital malformations and the Hospital Discharge Register. According to Hallberg et al., information on 4291 infants born to women exposed to SSRIs in early pregnancy was available through September, 2003. 708 of these SSRI exposures were to paroxetine. Hallberg reported that 3.4% of these infants exposed to paroxetine in early pregnancy were reported to have congenital malformations, which is in line with the expected background rate. Hallberg et al. did not state how many of these malformations were cardiovascular, although they reported that no particular type of malformation was overrepresented following SSRI exposure in early pregnancy. They also did not report the percentage of overall congenital malformations or cardiovascular malformation for the entire Swedish Medical Birth Register through 2003.

3.1.1 Reviewer comment

A Research Report from the Centre for Epidemiology (National Board of Health and Welfare) that is available on the Swedish Medical Birth Registry's website[19] indicated that data on both maternal exposures and infant diagnoses are incomplete in the Swedish Medical Birth Register. When infants are transferred to neonatal units, discharge diagnoses are not always reported to the Medical Birth Register.

In a study of the accuracy of Register data conducted in 2001, medical records were compared with Register data for 582 of the deliveries that were recorded in the Register in 1998. This nonrandom subgroup was oversampled for cases of infant death and premature birth. In the study, a congenital malformation diagnosis was not recorded in

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[17] One VSD, 2 unspecified cardiac defects, 1 patent ductus arteriosus, and 1 hypoplastic left heart syndrome (this infant also had hypospadias).

[18] Hallberg P, Sjoblom V. The use of selective serotonin reuptake inhibitors during pregnancy and breast-feeding: a review and clinical aspects. Journal of Clinical Psychopharmacology 2005; 25: 59-73.

[19] The Swedish Medical Birth Register: A Summary of Content and Quality. Swedish Medical Birth Registry website. http://www.sos.se/epc/english/Medical%20Birth%20Registry htm. Accessed 2005 October 31.

the Register for 29 infants with congenital malformations according to the medical record. 28 cases of congenital malformations were accurately captured in the Register for the sample.

The authors of the Research Report stated that data from Hospital Discharge Register and Register of Congenital Malformations can supplement the Swedish Medical Register data and increase the ascertainment of congenital malformations. The authors recommended "such a procedure…for final epidemiological analyses of congenital malformations."

Because information in the Swedish Medical Birth Register on infant diagnoses is incomplete, the data from the Swedish Medical Birth Registry that was reported in Hallberg's review article may not accurately reflect the true number of infants with congenital malformations born following exposure to paroxetine.

3.2 Studies indicating risk (through September, 2005)

At the time of GSK's September, 2005 CBE labeling supplement submission, three studies in addition to the Ingenix Research Database cohort study had indicated a risk for congenital malformations associated with either paroxetine or SSRIs in general.

Alwan et al. conducted a case-control study using data from the National Birth Defects Prevention Study (NBDPS), an ongoing multi-center case-control study of birth defect risk factors. In the NBDPS, cases are ascertained through birth defects surveillance systems in eight US states and maternal exposures during pregnancy are collected by interview after delivery (after the birth outcomes are known). Alwan et al. identified 5357 infants delivered between 1997 to 2001 with selected major birth defects and 3366 normal controls. Adjusted analyses showed that women who took any SSRI in the first trimester were more likely than those who were not exposed to have an infant with omphalocele (n= 161; OR 3.0, 95% CI 1.4—6.1). The strongest association was found with paroxetine (OR 6.3, 95% C1: 2.0-19.6), which accounted for 36% of all SSRI exposures. The investigators also found an association between exposure to any SSRI and having an infant with craniosynostosis (n= 372; OR 1.8, 95% CI 1.0-3.2). No association was observed with SSRIs for other classes of major malformations.

Wogelius et al. conducted a population-based cohort study in four Danish counties. They identified (using population-based prescription databases) 1054 women with first trimester exposure to SSRIs and 150,908 women without first trimester exposure to SSRIs. They determined outcomes using regional hospital discharge registries. They extracted data regarding potential confounders from the National Birth Registry. Odds ratios (adjusted for maternal age, smoking, and parity) for congenital malformations overall and cardiovascular malformations were calculated for women who redeemed SSRI prescriptions during early pregnancy compared to women without first trimester SSRI exposure. Adjusted odds ratios were 1.4 (95% CI: 1.1–1.9) for congenital malformations overall and 1.6 (95% CI: 1.0 – 2.6) for congenital cardiac malformations. The majority of these defects were ventricular septal defects. Outcomes following exposure to specific antidepressants were not analyzed.

A small cohort study by Unfred et al.[20] used prospectively gathered exposure data from the California Teratogen Information Service to compare risk for major malformations in 96 infants exposed to paroxetine in the first trimester with risk in a control group not exposed to any known teratogens. 4.2% (4/96) of paroxetine-exposed infants had major malformations compared to 0.5% (1/195) of control infants; p=0.04 for difference. The investigators noted that there was no pattern of defects evident in paroxetine-exposed infants, and that the percentage of malformations in the control group was "considerably less than expected."

4 Paroxetine September 6, 2005 CBE Labeling Supplement

In response to the preliminary analyses from their managed care database cohort study, GSK submitted a "Changes Being Effected" labeling supplement pertaining to paroxetine and the risk for birth defects on September 6, 2005. GSK's labeling changes are reproduced below (additions are underlined and in red text; deletions are crossed out):

(b) (4)

In their September 6, 2005 document entitled "Regulatory Supporting Documentation," GSK cited the Ingenix study, the Alwan study, and the Wogelius study as supporting evidence that paroxetine may be associated with an increased risk for congenital

[20] Unfred C, Chambers C, Felix R. et al. Birth outcomes among pregnant women taking paroxetine (Paxil) [abstract], Organization of Teratology Information Services, 14th Annual Meeting Program, 2001.

malformations. They also cited and discussed other studies that have provided contravening evidence and have not supported that paroxetine or other SSRIs are associated with an increased risk for major congenital malformations—the publications and abstracts by Kulin, Ericson, Hallberg, Unfred, Diav-Citrin, and Hendrick (discussed above).

5 Additional unpublished data from Wogelius study, Swedish registries study, and Ingenix cohort study

Because of the conflicting evidence pertaining to paroxetine and the risk for birth defects, in addition to concerns regarding the completeness of the Swedish registry data cited by Hallberg et al., the Division sought additional data following the submission of GSK's September, 2--5 CBE labeling supplement. The Division contacted Dr. Wogelius to obtain information pertaining to birth defects following first trimester exposure to paroxetine specifically in the Danish cohort study. The Division also contacted Dr. Bengt Kallen of Lund University in Sweden to obtain additional Swedish registry data pertaining to paroxetine and the risk for birth defects, particularly cardiovascular congenital malformations.

Subsequent to obtaining additional data from these sources, the Division received the preliminary results of updated analyses from the Ingenix Research Database from GSK. These updated analyses of the congenital malformation risk associated with individual antidepressants expanded the study database to include maternal exposures and outcomes for live births from January 2003 through Sept 2004.

In the remainder of this section, I will discuss the data from these three sources—the Danish cohort study, the Swedish registries study, and the updated Ingenix Research Database cohort study.

5.1 Wogelius study

The Division received data pertaining to paroxetine from Dr. Wogelius (by e-mail) on October 31, 2005. Of the 1054 SSRI-exposed women in the study, 220 were exposed to paroxetine in the first trimester. 11 of these children exposed to paroxetine were diagnosed with congenital malformations (11/220; 5.0%). One of these malformations was a cardiac defect (defectus septi atrioventriculorum cordis). There were no cases of omphalocele or craniosynostosis.

5.2 Swedish registry study (Kallen et al.)

In response to the Division's inquiries regarding Swedish national registry data pertaining to paroxetine and birth defect risk, the Division received by e-mail a study report based on Swedish national registry data from Dr. Kallen and Dr. Olausson on October 25, 2005. In this study, infants exposed to paroxetine in early pregnancy had an increased risk for congenital cardiac defects compared to the entire Swedish national registry population.

Dr. Kallen's study differed from the information presented in the review article by Hallberg in that the birth defect ascertainment was improved by supplementing the Swedish Medical Birth Register data with data from the Swedish Hospital Discharge and Congenital Malformation Registries. Kallen et al compared risk for overall congenital and cardiac malformations in children of women exposed to antidepressants (n=6,896) in early pregnancy to the risk for these outcomes in the registry population as a whole for the period July 1, 1995 through 2003. Cases of malformations due to chromosomal anomalies were excluded. Antidepressants were assessed for risk individually as well as in groups (any antidepressant, tri/tetracyclics, SSRIs, others). Neonatal outcomes were identified from three sources—diagnoses given by the neonatologist attending to the newborn to the Swedish Medical Birth Register, reports to the Swedish Register of Congenital Malformations, and diagnoses reported to the Hospital Discharge Register. Exposures were assessed by midwife interview at the first prenatal visit. The study included 815 women who received paroxetine and 5123 women who received other SSRIs in early pregnancy. 51 women were exposed to more than one antidepressant in early pregnancy.

Women exposed to antidepressants in early pregnancy were more likely than other pregnant women to also be exposed to one or more of the following drugs in early pregnancy: drugs for peptic ulcer, thyroid drugs, opiates, migraine drugs, anticonvulsants, neuroleptics, sedatives, and hypnotics. 61 antidepressant-exposed women were exposed to concomitant anticonvulsants in early pregnancy. One of the infants exposed to an anticonvulsant and an antidepressant (type not reported) was diagnosed with a VSD.

The following table summarizes the chief results of the original analysis (received on October 25, 2005):

	Any malformation			Any cardiac defect		
Exposure category	N	OR*	95% CI	N	OR*	95% CI
Population	35, 394	1.00	reference	7249	1.00	reference
Any antidepressant	296	0.93	0.83—1.05	77	1.21	0.96—1.51
Tri/tetracyclic drug	70	1.14	0.89—1.45	19	1.57	0.99—2.49
Clomipramine	62	1.27	0.98—1.64	18	1.87	1.16—2.99
SSRI	202	0.87	0.76—1.01	55	1.17	0.90—1.53
Citalopram	91	0.89	0.60—1.29	18	0.76	0.47—1.25
Sertraline	46	0.77	0.58—1.04	12	1.00	0.87—1.78
Paroxetine	36	0.97	0.70—1.36	17	2.22	1.39—3.55
Fluoxetine	24	0.88	0.60—1.29	8	0.71	0.23—2.20
Other antidepressant	18	0.65	0.41—1.04	2	0.38	0.10—1.44

* Odds ratios adjusted for year of birth, maternal age, parity, and smoking

None of the SSRIs as a group or individually were associated with an increased risk for congenital malformations overall. As the table above indicates, paroxetine and clomipramine were associated with a statistically significant increased risk for cardiac defects. The strongest effect was on the risk for ventricular and atrial septal defects. The

OR for paroxetine (vs. registry population) for septal defects was 2.29 (95% CI 1.28—4.09).

After learning of these study results and after obtaining permission from Dr. Kallen, the Division notified GSK of the findings. Subsequent to that teleconference, GSK requested that Dr. Kallen conduct additional analyses of the data including more recently collected exposures and outcomes. The Division received updated analyses on November 17, 2005 from GSK after GSK received the analyses from Dr. Kallen. The updated analyses continued to demonstrate that paroxetine was associated with an increased risk for cardiovascular malformations, although the risk was slightly diminished with the addition of 12 months of outcome data.

Dr. Kallen's original study has been accepted by the medical journal *Reproductive Toxicology* and is currently in press.

Additional analyses
In the additional analyses received on November 17, 2005, the investigators included updated outcome data through 2004 from the Hospital Discharge Register for births that occurred between July 1, 1995 and December, 2003. For the preliminary analyses, only data from this Register through 2003 had been available to the investigators. In 2004, additional cases of malformations were reported among infants born during the preceding period of study; these cases were included in the investigators' subsequent analyses. The additional year of follow-up data also led to the removal of cases of malformations that occurred in some infants with Down's syndrome.

In these additional analyses, the OR for paroxetine (vs. the entire register population) for any cardiac defect was 1.78; 95% CI 1.12—2.75. 13 of the 19 cardiac defects that occurred following early pregnancy exposure to paroxetine were atrial or ventricular septal defects. The OR for paroxetine (vs. the entire registry population) for atrial and ventricular septal defects was 1.92; 95% CI 1.12—3.10. There were three serious cardiac defects following early pregnancy paroxetine exposure—two cases of endocardial cushion defects (one with pulmonary artery stenosis) and one case of tetralogy of Fallot.

Paroxetine was not associated with an increased risk for congenital malformations overall, as was the case in the preliminary analyses. Paroxetine was also not associated with an increased risk for any specific malformations other than cardiac defects.

SSRIs as a class were not associated with an increased risk for cardiac defects, any other specific defects, or congenital malformations overall. The investigators did not report the risk for congenital malformations associated with specific antidepressants other than paroxetine in these additional analyses.

5.3 Updated Ingenix Research Database analyses

On November 4, 2005, GSK submitted updated analyses for their managed care database retrospective cohort study, including additional maternal exposures and birth outcomes from January, 2003 through September, 2004. The updated analyses thus included live births from January, 1995 through September, 2004.

All of their analyses assessing risk for congenital and cardiovascular malformations associated with individual antidepressants dispensed during the first trimester (compared to all other antidepressants) were repeated with the larger cohorts. The most relevant updated analyses assessed the risk associated with individual antidepressants in women dispensed those antidepressants as the only antidepressant in the first trimester in the absence of concomitant teratogen dispensings. The drugs that were considered teratogens in the updated analyses were the same as the drugs that had been considered teratogens in the earlier analyses based on data through 2003. As was the case with these earlier analyses, different lists of teratogens were used in the overall congenital malformation analyses and the cardiovascular malformation analyses. Odds ratios were calculated and adjusted for maternal age, geographic region, infant sex, bipolar disorder, eclampsia, and dispensings of lithium, phenytoin, and fluconazole.

The adjusted odds ratio for all congenital malformations for paroxetine compared to all other antidepressants dispensed in the first trimester was 1.8 (95% CI 1.2—2.8). There were 27 cases of congenital malformations among 717 infants in the paroxetine cohort; the prevalence of all congenital malformations was 37.7 per 1,000 births. Newly identified cases of congenital malformations in 2003 and 2004 were the following: hydronephrosis (1); uteropelvic junction obstruction (1); partially cleft lip (1); and pyloric stenosis (1).

The adjusted odds ratio for cardiovascular malformations for paroxetine dispensed in the first trimester compared to all other antidepressants dispensed in the first trimester was 1.5 (95% CI 0.8—2.9). The prevalence of cardiovascular malformations in the updated paroxetine cohort was 14.7 per 1,000 births. There was one new cardiovascular malformation case identified between January, 2003 and September, 2004. This was a case of VSD, which was described as a small, atypical, muscular VSD.

None of the other antidepressants had odds ratios for congenital or cardiovascular malformations following first trimester exposure that were statistically significantly elevated compared to the overall group of antidepressants. In Appendix 9.2, I have attached the results of the salient analyses for all antidepressants.

GSK plans to finalize the results of their analyses of the risk for all congenital malformations and cardiovascular malformations associated with paroxetine and submit this final analysis to the Division in January, 2006. The following additional refinements and additional data are expected:

- Comparison group refinements. Specifically, women dispensed paroxetine as part of antidepressant polytherapy will be excluded from the comparison group.

- Covariate adjustments will be done that are specific to paroxetine; currently, the odds ratios are adjusted for variables that were identified in the bupropion analyses

6 Reviewer comments regarding data received through November, 2005

GSK's analyses using the Ingenix Research Database and Kallen's analyses using Swedish registry data suggest that paroxetine exposure in the first trimester is associated with an increased risk for cardiovascular malformations following first trimester exposure. In both of these studies, the increased risk for cardiovascular defects appeared to be primarily for atrial and ventricular septal defects. The increased risk for cardiovascular congenital malformations that was evident in the Ingenix and Kallen analyses was not evident for the other SSRIs. The Ingenix study also indicated that paroxetine was associated with an increased risk for congenital malformations overall compared to exposure to other antidepressants in the first trimester.

Although the odds ratios for congenital and cardiovascular malformations for paroxetine compared to all other antidepressants dispensed in the first trimester decreased in the updated Ingenix analyses based on a larger dataset, a statistically significant increase in the risk for all malformations was still evident. The odds ratio for cardiovascular malformations was no longer statistically significant but was still elevated for paroxetine compared to all other antidepressants as a group. The pattern of cardiovascular malformations in the updated analyses was consistent with the pattern observed in the earlier analyses.

The odds ratios for cardiac defects for paroxetine compared to the entire registry population also decreased in the updated Swedish registry analyses that were based on additional outcomes for the same study period. A statistically significant increase in the risk for cardiac malformations was still evident, however, and the pattern of defects was consistent both with the preliminary analyses and with the pattern observed in the Ingenix study.

The strengths of the Ingenix study include the large number of patients exposed to paroxetine (and the other SSRIs individually) and the study design. Because it is a claims-based study, timing of exposures could be reliably established and recall bias was eliminated. The use of a control group of women exposed to other antidepressants in the first trimester is both a strength and a weakness. The benefit is that indication (psychiatric disease) is eliminated as a confounder. However, the drawback is that a class effect can not be detected because there was no comparison group that lacked exposure to antidepressants in the first trimester.

Another key weakness of the Ingenix analyses received to date is that the comparison group included women prescribed paroxetine polytherapy. Because inclusion of paroxetine-exposed women in the comparison group biases toward the null hypothesis,

exclusion of these women in the final analyses is likely to increase the odds ratio for paroxetine.

A final important limitation of the Ingenix analyses assessing the risk associated with individual antidepressants other than bupropion is that the analyses are based on a randomly sampled subcohort. Outcomes associated with all paroxetine dispensings during the study period have thus not been captured. This is unlikely to affect the odds ratios, however, if the subcohort is a truly random sample.

The strengths of the Kallen study include a large number of exposures to paroxetine, the use of data from three registries to ascertain congenital malformations as thoroughly as possible, and the comprehensive nature of Swedish registry data. The Swedish Medical Birth Register contains data obtained prospectively regarding exposures and fetal outcomes for over 98% of the Swedish population and thus allows comparison of risk for birth defects associated with exposure to particular drugs to the risk for these defects in the general population. This type of comparative analysis is not possible in conventional registries (such as the bupropion pregnancy registry) that track outcomes in infants following exposure to particular drugs, because unexposed women and infants are not included. Other inherent limitations of registry data do apply, however, to Kallen's study. Outcome and exposure data may not have been complete. Given that outcome data were obtained from three sources, outcome data are likely to be more accurate than exposure data. Because exposure data were obtained by interview, exposures may have been reported that did not occur, not all exposures may have been reported, and the precise timing of exposures may have been inaccurate. These limitations, however, are likely to bias results towards the null hypothesis. The evidence for risk in the Kallen analyses, therefore, should not be dismissed due to the limitations inherent in registry data.

The data from the Ingenix and Kallen studies are complemented by the results of the study by Wogelius et al., which indicated that SSRIs were associated with an increased risk for cardiac malformations compared to no antidepressant exposure. The number of exposures to individual SSRIs in this study was too small, however, to assess cardiovascular malformation risk for each SSRI.

Although the preliminary results of the study by Alwan et al. do not appear to support an increased risk for cardiovascular malformations following first trimester exposure to paroxetine, they do provide support for an association between paroxetine and omphalocele. Omphaloceles are another defect that would be likely to arise in the first trimester of gestation; it is thus biologically plausible that paroxetine exposure in the first trimester could be associated with an increased risk for both of these defects. Additional information regarding the design and results of both of the Alwan and Wogelius studies are needed before any definitive conclusions about them can be made.

Prior studies that did not demonstrate an association between paroxetine or other SSRIs and birth defects had methodological flaws and/or too few relevant exposures to adequately assess paroxetine-associated birth defect risk.

In my view, although the available data pertaining to paroxetine-associated congenital malformation risk are not definitive, the results of the Kallen and Ingenix studies are compelling and do warrant labeling changes. Data from the Alwan study pertaining to an increased risk for omphalocele following first trimester exposure to paroxetine may ultimately need to be placed in labeling, but we do not currently have enough information regarding the methodology or results of the Alwan study to take this action now.

The results of the Kallen study render (b) (4) [redacted] Swedish registry data provide further support for an association between paroxetine and an increased risk for cardiovascular malformations.

In my view, the complementary data from the Ingenix and Kallen studies constitute sufficient evidence on which to base a change of paroxetine's pregnancy category from C to D. We now have evidence from two epidemiological studies using separate data sources demonstrating positive evidence of human fetal risk that does not appear to be shared by the other SSRIs. Because the defects in these studies were primarily atrial and ventricular septal defects, which are not the most serious cardiac defects, and because the magnitude of risk elevation is relatively low, use of paroxetine in pregnant women may still be deemed to be acceptable by patients and their physicians in some cases despite the evident risk for congenital malformations.

In addition to changing the pregnancy category, I recommend that the sections of paroxetine's prescribing information pertaining to the use of paroxetine in pregnancy be revised to describe the risks associated with first trimester exposure to paroxetine that were demonstrated in the Kallen and Ingenix studies. (b) (4) [redacted].

To further assess paroxetine-associated risk for all congenital malformations, GSK should conduct another study using a complementary data source. Particular attention should be paid to whether any risk identified is a class effect. The designs of the Ingenix and Kallen studies did not allow optimal assessment of the presence of an antidepressant class effect.

The Division has discussed this with GSK and they plan to conduct a study using data from the Slone Epidemiology unit's case-control database. They expect that this study will be completed in January, 2006.

7 Regulatory Briefing

The Division held a Regulatory Briefing on November 18, 2005 to seek input regarding whether the available data support a change in paroxetine's pregnancy category from C to D. The consensus was that the data, although rapidly evolving, do support this change.

The group's consensus was that women who are planning to become pregnant or who may become pregnant should generally not be started on paroxetine therapy given the other treatment options available. For women already receiving paroxetine who are in their first trimester of pregnancy, consideration should be given to stopping paroxetine and switching to another antidepressant. The group felt that the apparent nature and magnitude of paroxetine-associated birth defect risk was such that women who discover that they are pregnant and are taking paroxetine should not be unnecessarily alarmed. For individual women receiving paroxetine, the potential risk may be justified by the benefit to the mother. The group felt that the nature and attributable risk of birth defects associated with paroxetine should be carefully detailed in labeling and in information sheets for patients and healthcare providers.

The group consensus was that the Ingenix analyses should be repeated using data pertaining to outcomes following first trimester exposure to paroxetine for *all* women with first trimester exposure to paroxetine in the Ingenix Research Database during the relevant study period, not just a random sample of women with first trimester paroxetine exposure.

8 Action to be taken by Division and GSK

Since receiving Kallen's Swedish registry study and the updated analyses from the Ingenix cohort study, the Division has had multiple discussions with GSK regarding further labeling changes pertaining to paroxetine-associated birth defects risk. GSK agreed to change paroxetine's pregnancy category from C to D and to submit another CBE labeling supplement that includes this change, the appropriate accompanying recommendations, and the new data from the Ingenix study and the Kallen study. This labeling supplement, which was submitted on December 5, 2005, is discussed further in section 8.1 below.

Coincident with the December, 2005 labeling changes, the Division wrote a Public Health Advisory and updated the paroxetine Patient and Healthcare Provider Information Sheets with information regarding the apparent risk for congenital malformations following first trimester exposure to paroxetine. These documents were posted on the FDA's website on December 7 and 8, 2005.

The following additional steps in the Divison's analysis of the association between paroxetine and birth defects are planned:

- Obtain more information regarding the design and results of the Alwan study
- Await the final Ingenix Research Database analyses expected in early 2006

- Await additional analyses based on additional years of exposure from the Swedish registries
    - GSK soon expects to obtain updated Swedish registry study analyses incorporating data through 2005 from Dr. Kallen. They expect that the subsequent data obtained from Dr. Kallen will include data regarding additional maternal exposures and birth outcomes, as well as adjustment for additional confounding variables including previous miscarriages, maternal body mass index, maternal education, and nationality.
- Await the results of the case-control study using Slone Epidemiology Unit data expected in early 2006

The final results of the Ingenix analyses, additional data from the Alwan study, updated data from the Swedish registries study, and the results of the case-control study using data from the Slone Epidemiology Unit may necessitate additional labeling changes pertaining to paroxetine-associated birth defect risk.

8.1 December 5, 2005 CBE labeling supplement

On December 5, 2005, GSK submitted a CBE labeling supplement. In this supplement, they changed paroxetine's pregnancy category to D and added a subsection entitled "Usage in Pregnancy" to the *Warnings* section. This section, which is reproduced below in its entirety (although only the language in the *Teratogenic Effects* section has been revised), contains revisions to the language previously contained in the *Precautions* Pregnancy subsection. The new *Precautions* Pregnancy section now contains the following statement: "Pregnancy Category D. See WARNINGS—Usage in Pregnancy: Teratogenic and Nonteratogenic Effects."

> **Usage in Pregnancy: *Teratogenic Effects:*** Epidemiological studies have shown that infants born to women who had first trimester paroxetine exposure had an increased risk of cardiovascular malformations, primarily ventricular and atrial septal defects (VSDs and ASDs). In general, septal defects range from those that are symptomatic and may require surgery to those that are asymptomatic and may resolve spontaneously. If a patient becomes pregnant while taking paroxetine, she should be advised of the potential harm to the fetus. Unless the benefits of paroxetine to the mother justify continuing treatment, consideration should be given to either discontinuing paroxetine therapy or switching to another antidepressant (see PRECAUTIONS—Discontinuation of Treatment with PAXIL**)**. For women who intend to become pregnant or are in their first trimester of pregnancy, paroxetine should only be initiated after consideration of the other available treatment options.
>
> A study based on Swedish national registry data evaluated infants of 6,896 women exposed to antidepressants in early pregnancy (5,123 women exposed to SSRIs; including 815 for paroxetine). Infants exposed to paroxetine in early pregnancy had an increased risk of cardiovascular malformations (primarily VSDs and ASDs) compared to the entire registry population (OR 1.8; 95% confidence interval 1.1-2.8). The rate of cardiovascular malformations following early pregnancy paroxetine exposure was 2% vs. 1% in the entire registry population. Among the same paroxetine exposed infants, an examination of the data showed no increase in the overall risk for congenital malformations.
>
> A separate retrospective cohort study using US United Healthcare data evaluated 5,956 infants of mothers dispensed paroxetine or other antidepressants during the first trimester (n = 815 for paroxetine). This study showed a trend towards an increased risk for cardiovascular malformations

for paroxetine compared to other antidepressants (OR 1.5; 95% confidence interval 0.8-2.9). The prevalence of cardiovascular malformations following first trimester dispensing was 1.5% for paroxetine vs. 1% for other antidepressants. Nine out of 12 infants with cardiovascular malformations whose mothers were dispensed paroxetine in the first trimester had VSDs. This study also suggested an increased risk of overall major congenital malformations (inclusive of the cardiovascular defects) for paroxetine compared to other antidepressants (OR 1.8; 95% confidence interval 1.2-2.8). The prevalence of all congenital malformations following first trimester exposure was 4% for paroxetine vs. 2% for other antidepressants.

Animal Findings: Reproduction studies were performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately 8 (rat) and 2 (rabbit) times the MRHD on an mg/m^2 basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at a dose of 1 mg/kg/day or approximately one-sixth of the MRHD on an mg/m^2 basis. The no-effect dose for rat pup mortality was not determined. The cause of these deaths is not known.

Nonteratogenic Effects: Neonates exposed to PAXIL and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS—Potential for Interaction With Monoamine Oxidase Inhibitors).

There have also been postmarketing reports of premature births in pregnant women exposed to paroxetine or other SSRIs.

When treating a pregnant woman with paroxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION).

8.1.1 Reviewer comment

The sponsor's December 5, 2005 CBE is consistent with our discussions with GSK and is acceptable.

9 Appendices

9.1 Ingenix analyses for all antidepressants; 1995--2002

9.1.1 All Congenital Malformations

Table 5 Odds ratios for congenital malformation according to mutually exclusive categories of specific antidepressants dispensed during the first trimester, excluding women with teratogenic drug dispensings*, cohort analysis, Ingenix Research Database (1995-2002)

Antidepressant	Cases**	No. of Infants	Prevalence†	Odds Ratio‡ Crude	95% CI	Adjusted§	95% CI
Amitriptyline	1	146	6.8	0.26	0.04 - 1.85	0.27	0.04 - 1.96
Amitriptyline / Chlordiazepoxide	0	3	0	0		0	
Bupropion	6	248	24.2	0.95	0.41 - 2.20	0.99	0.42 - 2.30
Citalopram	7	188	37.2	1.53	0.70 - 3.37	1.39	0.62 - 3.11
Clomipramine	0	3	0	0		0	
Desipramine	0	5	0	0		0	
Doxepin	0	14	0	0		0	
Fluoxetine	18	820	22.0	0.82	0.48 - 1.40	0.82	0.48 - 1.39
Fluvoxamine	0	13	0.0	0		0	
Imipramine	0	24	0	0		0	
Mirtazapine	0	5	0	0		0	
Nefazodone	1	41	24.4	0.96	0.13 - 7.07	0.94	0.13 - 6.96
Nortriptyline	0	62	0	0		0	
Paroxetine	23	527	43.6	2.05	1.25 - 3.36	2.20	1.34 - 3.63
Protriptyline	0	3	0	0		0	
Sertraline	7	507	13.8	0.49	0.23 - 1.08	0.48	0.22 - 1.05
Trazodone	2	49	40.8	1.65	0.39 - 6.92	1.98	0.47 - 8.39
Venlafaxine	2	129	15.5	0.60	0.15 - 2.45	0.59	0.14 - 2.42
More than one type of antidepressant	14	406	34.5	1.45	0.81 - 2.60	1.42	0.79 - 2.55

*Maternal dispensing of a teratogenic drug within three months before pregnancy (up to one year before delivery) through the end of the first trimester.
**Infants with chromosomal defects were not counted as cases of malformation in this analysis.
†Prevalence per 1,000 live born infants.
‡Reference group for odds ratio calculations is all other antidepressants.
§Adjusted for age, calendar year of delivery, diagnosis of pre-eclampsia or eclampsia, and infant sex.

From GSK Table 5, August 22 submission

9.1.2 Cardiovascular Malformations

Table 7 Odds ratios for cardiovascular malformation according to mutually exclusive categories of specific antidepressants dispensed during the first trimester, excluding women with dispensings of teratogenic drugs affecting the cardiovascular system*, cohort analysis, Ingenix Research Database (1995-2002)

Antidepressant	Cases**	No. of Infants	Prevalence†	Odds Ratio‡ Crude	95% CI	Adjusted§	95% CI
Amitriptyline	1	171	5.8	0.52	0.07 - 3.82	0.56	0.08 - 4.16
Amitriptyline / Chlordiazepoxide	0	3	0	0		0	
Bupropion	2	282	7.1	0.63	0.15 - 2.62	0.64	0.15 - 2.66
Citalopram	5	217	23.0	2.30	0.89 - 5.94	2.22	0.83 - 5.95
Clomipramine	0	3	0	0		0	
Desipramine	0	5	0	0		0	
Doxepin	0	19	0	0		0	
Fluoxetine	12	955	12.6	1.22	0.62 - 2.41	1.23	0.62 - 2.44
Fluvoxamine	0	17	0	0		0	
Imipramine	0	29	0	0		0	
Mirtazapine	0	8	0	0		0	
Nefazodone	0	50	0	0		0	
Nortriptyline	0	69	0	0		0	
Paroxetine	11	589	18.7	2.00	0.99 - 4.03	2.08	1.03 - 4.23
Protriptyline	0	4	0	0		0	
Sertraline	0	563	0	0		0	
Trazodone	1	58	17.2	1.61	0.22 - 11.90	1.66	0.22 - 12.43
Venlafaxine	2	150	13.3	1.24	0.30 - 5.18	1.22	0.29 - 5.15
More than one type of antidepressant	6	476	12.6	1.19	0.50 - 2.84	1.19	0.49 - 2.86

From GSK Table 7, August 22 submission

9.2 Updated Ingenix analyses; 1995—2004

9.2.1 All congenital malformations

Table 5 updated: Odds ratios for all congenital malformations according to mutually exclusive categories of specific antidepressants dispensed during the first trimester, excluding women with teratogenic drug dispensings, Ingenix Research Database (1995-Sept 2004)

Antidepressant	Cases	No. of Infants	Prevalence per 1,000	Crude Odds Ratio*	95% CI	Adjusted Odds Ratio*	95% CI
Amitriptyline	3	175	17.1	0.71	0.22-2.27	0.74	0.23-2.35
Amitriptyline / Chlordiazepoxide	0	4					
Amitriptyline / Perphenazine	0	0					
Bupropion	12	624	19.2	0.79	0.43-1.44	0.75	0.41-1.38
Citalopram	7	302	23.2	0.98	0.45-2.12	1.05	0.48-2.28
Clomipramine	0	6					
Desipramine	0	8					
Doxepin	0	16					
Escitalopram	3	72	41.7	1.84	0.58-5.83	1.69	0.52-5.48
Fluoxetine	23	1118	20.6	0.84	0.53-1.33	0.84	0.53-1.33
Fluvoxamine	0	17					
Imipramine	0	27					
Mirtazapine	0	6					
Nefazodone	1	47	21.3	0.90	0.12-6.58	0.92	0.13-6.74
Nortriptyline	0	72					
Paroxetine	27	717	37.7	1.81	1.17-2.79	1.82	1.17-2.82
Protriptyline	0	4					
Sertraline	16	843	19.0	0.77	0.45-1.31	0.78	0.46-1.34
Trazodone	2	57	35.1	1.51	0.36-6.28	1.69	0.41-7.07
Trimpramine	0	0					
Venlafaxine	3	204	14.7	0.61	0.19-1.93	0.59	0.19-1.88
More than one type of antidepressant	23	773	29.8	1.33	0.84-2.12	1.33	0.84-2.11

*Reference group for the odds ratio calculation of each antidepressant category consists all of the other antidepressants shown in the table.

From GSK Table 5, November 4, 2005 submission

Cardiovascular malformations

Table 7 updated: Odds ratios for cardiovascular malformations according to mutually exclusive categories of specific antidepressants dispensed during the first trimester, excluding women with dispensings of teratogenic drugs affecting the cardiovascular system, Ingenix Research Database (1995-Sept 2004)

Antidepressant	Cases	No. of Infants	Prevalence per 1,000	Crude Odds Ratio*	95% CI	Adjusted Odds Ratio*	95% CI
Amitriptyline	3	214	14.0	1.38	0.43-4.44	1.47	0.46-4.77
Amitriptyline / Chlordiazepoxide	0	4					
Amitriptyline / Perphenazine	0	0					
Bupropion	4	714	5.6	0.51	0.18-1.40	0.48	0.17-1.32
Citalopram	5	362	13.8	1.37	0.55-3.44	1.42	0.56-3.59
Clomipramine	0	6					
Desipramine	0	8					
Doxepin	0	22					
Escitalopram	2	83	24.1	2.44	0.60-9.98	2.12	0.50-8.91
Fluoxetine	15	1292	11.6	1.16	0.65-2.09	1.22	0.68-2.20
Fluvoxamine	0	22					
Imipramine	0	36					
Mirtazapine	0	11					
Nefazodone	0	56					
Nortriptyline	0	82					
Paroxetine	12	814	14.7	1.54	0.82-2.91	1.54	0.81-2.92
Protriptyline	0	5					
Sertraline	5	937	5.3	0.47	0.19-1.18	0.47	0.19-1.17
Trazodone	1	67	14.9	1.46	0.20-10.70	1.39	0.19-10.20
Trimpramine	0	0					
Venlafaxine	3	244	12.3	1.20	0.37-3.86	1.14	0.35-3.68
More than one type of antidepressant	11	929	11.8	1.18	0.61-2.28	1.21	0.63-2.34

*Reference group for the odds ratio calculation of each antidepressant category consists all of the other antidepressants shown in the table.

From GSK Table 7, November 4, 2005 submission

9.3 Summary of existing evidence (for paroxetine and other SSRIs)

Evidence *for* risk					
Source	Design	N (paroxetine)	N (other SSRIs)	Key results	Comments
Ingenix (for GSK); data 1995--2003	Cohort	704 (527 exposures to paroxetine as only AD)	3581 (all ADs)	1. Adjusted OR for paroxetine (alone) for all congenital malformations: 2.20; 95% CI 1.34—3.63 (vs. all other ADs) 2. Adjusted OR for paroxetine for cardiovascular malformations: 2.08; 95% CI 1.03—4.23 3. No convincing risk with any other AD	1. No comparison group without antidepressant exposure; 2. Most of the CV malformations were VSDs
Ingenix (for GSK); expanded dataset 1995—September 2004	Cohort	1020 (815 exposures to paroxetine as only AD)	5956 (all ADs)	1. Adjusted OR for paroxetine (alone) for all congenital malformations: 1.82; 95% CI 1.17—2.82 (vs. all other ADs) 2. Adjusted OR for paroxetine for cardiovascular malformations: 1.54; 95% CI 0.81—2.92	
Alwan et al. 2005 (abstract)	Case-control (NBDPS)	36% of all SSRI exposures (number not specified)	5357 cases; 3366 control	1. increased risk for omphalocele with paroxetine vs. no AD: OR 6.3 (95% CI 2.0—19.6) 2. first trimester exposure to any SSRI (vs. no antidepressant exposure) assoc. with increased risk for both omphalocele (n=161; OR 3.0;	1.Exposure data collected by interview after outcomes known 2. Additional info re methodology and results expected 11/05 (confidential)

				95% CI 1.4—6.1) and craniosynostosis (n=372; OR 1.8; 95% CI 1.0—3.2) but not any other major malformations	
Wogelius et al. 2005 (abstract)	Population-based cohort study (4 counties in Denmark)	220	1054	1. Adjusted OR for all congenital malformations: 1.4 (95% CI 1.1—1.9); [SSRI exposure in first trimester vs. no exposure] 2. Adjusted OR for congenital cardiovascular malformations: 1.6 (95% CI 1.0—2.6)	1.exposure data from prescription databases; outcome data from Danish National Birth Registry 2. No analyses done for individual SSRIs 3. 11 infants exposed to paroxetine in utero had congenital malformations (1 septal defect)
Unfred et al. 2001(abstract)	cohort study (California Teratogen Information Service)	96		1.Major malformations in paroxetine-exposed (first trimester) infants vs. control infants: 4.2% (4/96) vs. 0.5% (1/195); p=0.04 for difference 2. no pattern of defects evident, per authors	GSK used this in their Dear HCP letter as support for absence of risk (given that malformation rate in line with expected background rate)
Kallen and Olausson; 1995--2003 (additional analyses using Hospital Discharge Register outcome data through 2004)	Swedish registry study (SMBR data supplemented by Register of Congenital Malformations and Hospital Discharge Register data)	815	6896 (all ADs) 5123 (all SSRIs)	1. OR for CV defects for paroxetine: 1.78; 95% CI 1.12—2.75 (vs. registry pop.) 3. OR for all congenital malformations with paroxetine 1.03; 95% CI 0.75—1.41 (vs. registry pop.) 4. No increased risk for CV or overall	1. Exposure data assessed prospectively 2. Majority of cardiac defects associated with paroxetine exposure were atrial and ventricular septal defects

				malformations for SSRIs as a group	
Equivocal results					
Chambers et al. 1996 (NEJM)	prospective cohort study (California Teratogen Information Service)	0	164 (fluoxetine)	1. 5.5% (9/164) of infants with first trimester fluoxetine exposure had major structural anomalies vs. 4.0% (9/226) controls; p=0.63 for difference 2. Fluoxetine-exposed infants had an increased percentage of infants with at least 2 *minor* structural anomalies	1. Risk for birth outcomes with first trimester fluoxetine exposure compared with risk in control group (women who called to ask about nonteratogenic exposures)
***No* evidence of risk**					
Kulin et al. 1998 (JAMA)	prospective cohort study (9 Teratology Information Service Centers)	97	267 (all SSRIs: paroxetine, sertraline, fluvoxamine)	1. RR 1.06 (95% CI 0.43—2.62) for major malformations among (first trimester SSRI-exposed infants vs. controls 2. 9 malformations in each group (2 CV in SSRI grp and 4 CV in control grp)	1. Outcomes following exposure to individual antidepressants not reported
Ericson et al. 1999 (Eur J Clin Pharm)	Swedish Registry study (SMBR data supplemented Hospital Discharge Register and Register of Congenital Malformations)	118	531 (all SSRIs)	1. Congenital malformations not more frequent than expected following first trimester SSRI exposure--Obs: 21 total (5 CV) Expected: 18.7 2. no unusual types or clustering of any major congenital malformations	1. Analysis for individual SSRIs not done/reported
Simon et al. 2002 (Am J Psych)	population-based cohort study (Group Health Cooperative)	28	185 (all SSRIs)	1. OR for major malformations (for SSRI exposure vs. no exposure): 1.36 (95% CI 0.56—3.30) [12 vs. 9]	1. No assessment of risk by trimester 2. Exposure ascertained through pharmacy

				2. OR for minor malformations (for SSRI exposure vs. no exposure): 1.14 (95% CI 0.56—2.31)	records; outcomes prosp. ascertained 4. Matching of exposed and controls for psychiatric history (reduces possibility of confounding by indication)
Hendrick et al. 2003 (AJOG)	prospective uncontrolled study	19	138 (all SSRIs)	1.4% (2/138) SSRI-exposed infants had major congenital malformations; authors concluded that this is consistent with background rate	1. Tiny 2. Uncontrolled 3. No assessment by trimester of exposure
Diav-Citrin et al. 2002 (abstract)	Controlled cohort study (Israeli Teratogen Information Service)	89 (paroxetine first trimester)	96 (fluoxetine first trimester)	Rate of congenital anomalies following first trimester exposure similar in 3 groups: paroxetine 4.1% (3/73); fluoxetine 3/71 (4.2%); controls 2.1% (12/580); p=.351 for difference	
Nulman et al. 1997 (NEJM)	Controlled cohort study; (Motherisk)	0	55 fluoxetine	Incidence of major malformations among 3 groups similar (3 in TCA group[VSD, hypospadias, pyloric stenosis]; 2 in fluoxetine group [VSD, PDA]; 2 in control group [VSD, cyanotic heart disease])	
Pastuszak et al. 1993 (JAMA)	Controlled cohort study (Motherisk)	0	128 (fluoxetine first trimester)	risk for major malformations in infants exposed to fluoxetine in the first trimester was comparable to risk observed in infants exposed to TCAs and non-teratogens	

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