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APPLICATION NUMBER:

20-866

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	March 25, 2009
From	Hylton V. Joffe, M.D., M.M.Sc.
Subject	Cross-Discipline Team Leader Review
NDA #	20-866
Applicant	VeroScience, LLC
Date of Submission	13-April-2008
PDUFA Goal Date	15-October-2008
Proprietary Name / Established (USAN) names	Cycloset (bromocriptine mesylate)
Dosage forms / Strength	0.8 mg tablets
Proposed Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Recommended:	<i>APPROVAL, pending agreement on labeling</i>

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1. Introduction

On August 18, 1997, ErgoScience submitted a new drug application (NDA) for bromocriptine mesylate (previously proposed tradename Ergoset; currently proposed tradename Cycloset) to obtain an indication for the treatment of type 2 diabetes. This NDA was discussed at a meeting of the Metabolic and Endocrinologic Drugs Advisory Committee on May 14, 1998 where panel members unanimously recommended that the NDA not be approved. A summary of the reasons put forth by the panel members for why this NDA should not be approved is included in Dr. Robert Misbin's clinical review and in Section 9 of this memorandum.

On November 20, 1998, the Division issued a Not Approvable (NA) letter to the sponsor. The deficiencies listed in that letter related to the small treatment effect seen in the phase 3 clinical trials and a safety concern for cardiac events based on an imbalance in the incidence of myocardial infarction reported in the Ergoset diabetes trials (3 cases with Ergoset vs. 1 case with placebo) in light of historical events (the voluntary withdrawal of the postpartum breast engorgement indication for Parlodel, another bromocriptine formulation, due to reports of myocardial infarction, strokes, and seizures in postpartum women). The NA letter did not suggest a remedy for these deficiencies.

On April 15, 1999, the company submitted a formal appeal of the NA letter. Senior CDER officials determined that the sponsor had demonstrated sufficient glycemic efficacy for Ergoset. However, it was determined that the sponsor would need to conduct a placebo-controlled, clinical trial to address the potential cardiovascular signal before Ergoset could be approved, particularly in light of its modest efficacy.

Dr. John Jenkins, then Director of Office of Drug Evaluation II, wrote a memorandum, dated October 15, 1999 summarizing the complex administrative history of the NDA, a review of the Sponsor's Complete Response to the NA letter, and the basis for subsequently changing the NA action to an Approvable action. Dr. Jenkins stated that the sponsor will not be required to conduct any additional efficacy studies prior to approval and that the NDA can be approved if the remaining question regarding cardiovascular safety can be adequately addressed.

Subsequently, the Division issued an Approvable letter on October 15, 1999 requesting that the company conduct a new, placebo-controlled trial of Cycloset in patients with type 2 diabetes that is powered to evaluate the potential for a significant increase in the risk of serious cardiac adverse events. The Approvable letter included deficiencies related to development of _____ and a scored 0.8 mg tablet but these deficiencies are no longer applicable because the sponsor is no longer proposing the _____ A pharmacology/toxicology deficiency related to qualification of _____ impurities has also been deemed to be no longer applicable because of bromocriptine's extensive marketing experience (see the Pharmacology/Toxicology section of this memorandum).

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The Approvable letter requested that the pregnancy class be C. The letter also stated that the proposed tradename, Ergoset, was unacceptable because of potential for confusion with sound-alike names, Ergostat and Percocet. The sponsor has subsequently proposed the tradename Cycloset, which the Division of Medication Errors and Prevention (DMEPA) has found to be acceptable.

The focus of the current memorandum is to review the Complete Response to the October 15, 1999 Approvable letter. Please see the original reviews for further details.

2. Background

In pre-submission regulatory meetings, the Division stated that the safety trial should consist of a minimum of 2,000 Cycloset-treated patients and 1,000 placebo-treated patients treated for 6 months to 1 year. The Division requested that patients in the safety trial be representative of the broad type 2 diabetes population who will use Cycloset, if approved. The Division also recommended that the sponsor consider conducting a phase 4 trial to study the addition of Cycloset to metformin because the original Ergoset trials were conducted before metformin was approved in the United States.

On February 2, 2007, the Division met with VeroScience, the new sponsor for Cycloset. At that meeting, several outstanding issues were discussed including:

- Valvulopathy as a new potential safety signal. The Division recommended that the sponsor include data on valvulopathy in the Complete Response to the 1999 Approvable letter.
- The sponsor proposed a subgroup analysis of patients treated with metformin and sulfonylurea in the safety trial to provide information on the efficacy and safety of Cycloset in patients concomitantly treated with metformin. The Division stated that the adequacy of such an approach will be a review issue.
- There are 3 different versions of the drug product – one used for the original clinical trials (conducted by ErgoScience, the original sponsor for the Ergoset NDA), another used in the safety trial that is the focus of this memorandum (conducted by Pliva, the subsequent sponsor for the Cycloset NDA), and a third, which is the to-be-marketed formulation (developed by VeroScience, the current sponsor of the Cycloset NDA). The sponsor agreed to conduct a bioequivalence study comparing the drug product from the safety trial with the to-be-marketed formulation. Because the drug product used for the original NDA is no longer being manufactured, the Division recommended a clinical efficacy bridge between the data from the original NDA and the data in the safety trial. However, the medical and statistical reviewers expressed concern that the confounding effects of background therapy or study design will not permit a reliable estimate of efficacy. The Division stated that the adequacy of a clinical efficacy bridge using the safety trial will be a review issue. Alternatively, the sponsor was given the option of conducting an efficacy study of Cycloset in combination with metformin.

3. CMC

The chemistry reviewers recommend approval of the NDA. Please see Dr. Xavier Ysern's chemistry review for details. Relevant chemistry findings are summarized below.

As discussed above, the Cycloset IND and NDA have transferred ownership 3 times. In May 2006, the IND and NDA were transferred to VeroScience, LLC, which is the current sponsor of the Cycloset NDA. With transfer, Pathoen Pharmaceuticals will be the manufacturer of the to-be-marketed Cycloset tablets. Per Dr. Ysern, Pathoen's manufacturing process does not differ appreciably from the manufacturing processes used by the prior 2 sponsors. The office of Compliance has issued an acceptable recommendation for the manufacturing facilities.

Cycloset is manufactured as an immediate-release tablet. The Cycloset tablet from all 3 of the above-mentioned manufacturers is identical.

Per Dr. Ysern, the Cycloset specifications comply with the USP monograph for bromocriptine mesylate tablets except for bromocriptinine, which is the main degradation product of bromocriptine. The specification for bromocriptinine in Cycloset is not more than (NMT) _____ compared to NMT 3.0% for approved bromocriptine products. However, the level of this impurity is acceptable per pharmacology-toxicology (see below).

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4. Nonclinical Pharmacology/Toxicology

The pharmacology-toxicology review of the original NDA was based on published studies and determined to be adequate. The Complete Response does not contain new non-clinical studies. The pharmacology-toxicology reviewers recommend approval of the NDA. Please see Dr. Kuijpers' review for details. Relevant pharmacology-toxicology findings are summarized below.

Bromocriptine is a dopamine receptor D2 agonist and a D1 receptor antagonist. The mechanism by which bromocriptine improves glycemic control has been postulated to be mediated by activation of central dopaminergic pathways, but has not been definitively elucidated.

There was no evidence of tumorigenicity in the 74-week mouse carcinogenicity study. In the 100-week rat carcinogenicity study, there was an increase in malignant endometrial and myometrial tumors in the mid- and high-dose groups. The pharmacology-toxicology reviewers have attributed this finding to suppression of prolactin-stimulated progesterone secretion in the aging rat, resulting in endometrial stimulation. Because prolactin does not play a role in human progesterone production, this finding is unlikely to be clinically relevant, but will be labeled.

The pharmacology-toxicology reviewers initially requested that the Pregnancy Category be listed as C (because of fetal and pup death in a male rat fertility study). However, the reviewers have subsequently determined that Pregnancy Category B is acceptable based on very low risk to the fetus from animal data (no-observed-adverse-event-levels are multiples of

the clinical dose), reassuring data from human observational studies, and the Pregnancy Category B classification for Parlodel (another formulation of bromocriptine mesylate that relies on the same animal fertility and pregnancy studies referenced for Cycloset).

As mentioned above, the specification for bromocriptinine, the main degradation product of bromocriptine in Cycloset is NMT _____ compared to NMT _____ or the approved bromocriptine mesylate products. The pharmacology-toxicology reviewers have determined that this level of bromocriptinine impurity in Cycloset is acceptable because approved bromocriptine products (which have the NMT _____ specification) are dosed at 5-20 times the proposed dose of Cycloset and have extensive clinical experience.

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5. Clinical Pharmacology/Biopharmaceutics

As explained above, there have been 3 manufacturers of Cycloset tablets. The drug product used in the major clinical trials in the original NDA is no longer available. Therefore, the sponsor has been required to provide an efficacy bridge between that drug product and the drug product used in the 52-week safety trial. Please see the clinical and statistical sections of this memorandum for further details.

In addition, the sponsor performed a pivotal bioequivalence study to bridge the drug product from the 52-week safety trial with the to-be-marketed formulation. The clinical pharmacology reviewers recommend approval of the NDA based on the results from this study and the accompanying favorable inspection by the Division of Scientific Investigations (see Dr. Gopa Biswas' review). Relevant findings from this bioequivalence study are summarized below.

The sponsor performed a single center, randomized, single-dose crossover study in 63 healthy subjects under fed conditions comparing 4.8 mg of the drug product from the 52-week safety trial to 4.8 mg of the to-be-marketed formulation. There was a washout period of at least 7 days between treatments. Dr. Jayabharathi Vaidyanathan, the clinical pharmacology reviewer, concurs with the sponsor that these products are bioequivalent because the 90% confidence intervals were within 80-125% for the ratio of log-transformed area under the time-concentration curve (AUC) and C_{max} (Table 1). The median T_{max} was 1.5 hours for both formulations. Please see Dr. Vaidyanathan's review for further details.

Table 1. Comparison of pharmacokinetic parameters for the drug product used in the 52-week safety trial and the to-be-marketed formulation (adapted from Dr. Vaidyanathan's review)	
Parameter	Geometric LS Means
	Ratio (90% confidence interval)
Cmax (pg/mL)	95.6 (86.6-105.4)
AUC _{0-t} (pg*h/mL)	99.1 (92.7-105.9)
AUC _{0-inf} (pg*h/mL)	96.9 (90.2-104.0)

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

This section will focus on the 52-week safety trial submitted as a Complete Response to the 1999 Approvable letter.

Study Design: This was a double-blind, placebo-controlled, 52-week trial. Patients 30-80 years old with type 2 diabetes and HbA1c $\leq 10\%$ were randomized 2:1 to Cycloset or placebo. Randomization was stratified by study site. To be eligible for the trial, patients were required to be on a stable (≥ 4 weeks) anti-diabetic regimen consisting of diet, up to 2 oral anti-diabetic medications, or insulin with up to 1 oral anti-diabetic medication. Investigators were instructed to not add new anti-diabetic medications during the first 3 months of the trial. During the course of the trial, including the first 3 months, investigators were permitted to adjust dosages of concomitant anti-diabetic agents to avoid hypoglycemia and to achieve the glycemic targets defined by the 2004 American Diabetes Association clinical practice guidelines.

During the first 6-weeks of the trial, the study drug was uptitrated, as tolerated, from an initial daily dose of 0.8 mg of Cycloset or placebo to a maximum dose of 4.8 mg, taken at 8 a.m. with breakfast. Dose increments of 0.8 mg occurred on a weekly basis. Patients who did not tolerate dose escalation to 4.8 mg were permitted to continue in the trial on a lower dose, provided that the tolerated daily dose was at least 1.6 mg.

Exclusion Criteria included:

1. Sympathomimetic drugs within 7 days prior to screening or ≥ 10 days during the trial
2. Ergot derivatives or triptans for migraines
3. Pregnant or lactating women
4. Women of childbearing potential not using adequate contraception
5. Stroke or acute coronary syndrome within the preceding 6 months
6. New York Heart Association (NYHA) class III or IV heart failure
7. Seizure disorder

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8. Orthostatic hypotension
9. Renal impairment for metformin-treated patients; serum creatinine >1.6 mg/dL for patients not on metformin
10. Serum transaminases >3x the upper limit of normal (ULN)

Primary Endpoint: Time-to-first serious adverse event

For this primary endpoint, the sponsor used the standard regulatory definition for serious adverse events. Therefore, an adverse event was classified as serious if it resulted in death, was considered life-threatening or medically important, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability, or was a congenital anomaly.

Serious adverse events were required to be reported through the last follow-up visit or 30 days after the last administration of study drug, whichever came later.

Secondary Endpoints:

1. Composite of serious cardiovascular adverse events (myocardial infarction, stroke, inpatient hospitalization for heart failure or angina, and revascularization surgery)
2. Serious adverse event rates for the individual components of the above-described composite.

Adverse events were coded using MedDRA version 7.0. An independent Event Adjudication Committee (2 cardiologists and 1 endocrinologist) blindly adjudicated all serious adverse events. Consensus was obtained when 2 of the 3 adjudicators agreed.

An independent Data Safety Monitoring Board established prior to study initiation monitored the serious adverse events and performed interim and futility analyses to provide recommendations regarding study continuance.

Efficacy Endpoints: The purpose of the efficacy analysis in this safety trial was to help bridge efficacy between the no longer available bromocriptine formulation used in the original clinical trials and the to-be-marketed formulation. The primary efficacy endpoint was the placebo-subtracted change in HbA1c from baseline to Week 24 among pre-specified subgroups (see below). Although post-hoc subgroup analyses are considered hypothesis-generating, the statistical reviewers accepted the proposed subgroup analyses for the goal of bridging efficacy because these analyses were specified prior to unblinding and agreed upon by FDA.

Although this was a 52-week trial, the sponsor pre-specified that these efficacy analyses would be conducted at Week 24 because of the likelihood that background anti-diabetic medications would change due to the progressive nature of type 2 diabetes. This is a typical timepoint for efficacy analyses of trials evaluating the effectiveness of therapies for type 2 diabetes.

The pre-specified subgroups for the efficacy bridging analyses were:

1. Patients taking metformin + sulfonylurea with baseline HbA1c $\geq 7.5\%$

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2. Patients taking at least one oral anti-diabetic agent with baseline HbA1c $\geq 7.5\%$
3. Patients taking metformin alone or in combination with other oral anti-diabetic agents with baseline HbA1c $\geq 7.5\%$
4. Patients taking sulfonylurea alone or in combination with other oral anti-diabetic agents with baseline HbA1c $\geq 7.5\%$

The first subgroup listed above was pre-specified as the primary population for the bridging efficacy analysis. As discussed by Dr. Lee Pian, the statistical reviewer, the other subgroups listed above have overlapping patients (e.g., a patient on metformin + sulfonylurea would be counted in all 4 of the above listed subgroups). Therefore, in addition to these analyses, Dr. Pian also conducted analyses of disjoint subgroups. Please see Dr. Pian's statistical review for further details.

The primary population for the safety endpoints was the intent-to-treat dataset, consisting of all patients who received at least 1 dose of study medication.

The primary and secondary safety endpoints were tested using a non-inferiority hypothesis with a pre-specified non-inferiority margin of 1.5. The scientific basis for this non-inferiority margin is unclear. The statistical test used a Cox regression model with treatment and center effects and reported a one-sided 96.1% confidence interval for the hazard ratio comparing Cycloset to placebo. The wider-than-usual confidence interval took into account one interim analysis, which was conducted after the last enrolled patient had completed 6 months of study treatment and tested whether the non-inferiority hypothesis for the primary endpoint had been met. To control the type 1 error rate, the interim analysis was tested at an alpha of 0.04068 and the final analysis was tested at an alpha of 0.03938.

For the bridging efficacy analyses, the sponsor used an ANCOVA model adjusting for baseline HbA1c and center effect. The last-observation-carried-forward method was used for missing data due to premature discontinuation from the trial.

For the primary safety endpoint, the sponsor estimated that a sample size of 2,991 patients will provide 90% power at the one-sided alpha = 0.05 level with a non-inferiority margin of 1.5, assuming a placebo event rate of 8%.

For the composite cardiovascular endpoint, a sample size of 3,000 patients would provide 62% power at the one-sided alpha = 0.05 level with a non-inferiority margin of 1.5, assuming an event rate of 3.43%.

RESULTS

This section will focus on the efficacy findings. The primary and secondary safety endpoints are discussed in the Safety section of this memorandum.

Patient Disposition: A total of 2,067 patients were randomized to Cycloset and 1,028 patients were randomized to placebo. Although the intent-to-treat population comprised >99% of these patients, only 53% of the Cycloset-treated patients and 68% of the placebo-treated patients

completed the trial. The difference in completion rates between the treatment groups was driven by withdrawals due to adverse events, which was the most common reason for premature discontinuation from the trial, accounting for 24% of discontinuations in the Cycloset arm and 11% of discontinuations in the placebo arm (please see the safety section of this memorandum for further details).

The average daily dose for Cycloset was 4.4 tablets. Based on tablet counting, >94% of patients were at least 80% compliant with treatment.

Baseline demographics: The intent-to-treat population had a slight male predominance (57%). Two-thirds of the population was Caucasian, and the remaining one-third was black or Hispanic. The mean age was approximately 60 years and the mean body mass index was approximately 32 kg/m². Most patients had been diagnosed with diabetes \geq 1 year prior to study start, and more than one-fourth of patients had diabetes for longer than 10 years. Three-fourths of the population was treated with one or two oral anti-diabetic drugs, approximately 15% were using insulin, approximately 20% were using thiazolidinediones, and approximately 12% were treated with diet alone.

Two-thirds of the population had hypertension, two-thirds had hyperlipidemia, one-half were current or past smokers, and one-third had a family history of cardiovascular disease. The mean baseline LDL-cholesterol was approximately 100 mg/dL (approximately 60% of patients were using statin therapy).

HbA1c: As mentioned above, patients in the primary bridging efficacy population were treated with background metformin + sulfonylurea therapy, had a baseline HbA1c \geq 7.5%, and received at least 1 dose of study medication. This subgroup consisted of 177 Cycloset-treated patients (8.6% of the patients randomized to Cycloset) and 90 placebo-treated patients (8.9% of the patients randomized to placebo). Approximately two-thirds of the patients in this subset were men and the mean HbA1c (\pm SD) was 8.3 \pm 0.7%. As shown in Table 2, the least-squares (LS) mean change from baseline in HbA1c at Week 24 was -0.5% with Cycloset and -0.1% with placebo (LS mean difference -0.4; 95% CI -0.7 to -0.2; $p < 0.01$). Similar findings were noted in the subset of patients on 1-2 oral anti-diabetic medications with baseline HbA1c \geq 7.5% ($n=560$), although approximately one-half of this subset was comprised of patients from the metformin + sulfonylurea subset.

The LS mean difference in HbA1c with Cycloset relative to placebo was slightly larger in the 24-week completers population (-0.7% for the metformin + sulfonylurea subset and -0.5% for the 1-2 oral anti-diabetic medication subset).

For the metformin + sulfonylurea bridging efficacy subset, background anti-diabetic therapy was intensified in 16% of Cycloset-treated patients and 22% of placebo-treated patients. In addition, there was a reduction in the intensity of background anti-diabetic therapy in 6% of Cycloset-treated patients and 3% of placebo-treated patients. Therefore, as Dr. Misbin notes, the observed treatment effect with Cycloset in this bridging efficacy subset is likely an underestimate of the true effect.

There was a small (0.2%) mean reduction in HbA1c from baseline to Week 24 when the entire intent-to-treat population was analyzed (Table 2). Although not a pre-specified efficacy endpoint, this analysis is of interest because it incorporates all randomized patients who had a baseline and at least 1 post-baseline HbA1c measurement. This small treatment effect is most likely due to the low baseline HbA1c values in the overall trial (mean 7% in both treatment groups). Nonetheless, this finding raises the question of utility of Cycloset in patients with mild type 2 diabetes, and should be labeled.

Table 2. HbA1c (%) change from baseline to Week 24 (adapted from Dr. Lee Pian's statistical review)		
	Cycloset N=2054	Placebo N=1016
INTENT-TO-TREAT POPULATION (LAST-OBSERVATION-CARRIED-FORWARD)		
Metformin+sulfonylurea with baseline HbA1c ≥7.5%*	N=177	N=90
Baseline, mean±SD	8.3±0.7	8.3±0.8
Change, LSM±SE	-0.5±0.1	-0.1±0.1
LSM difference: Cycloset-placebo (95% CI); p-value	-0.4 (-0.7, -0.2); p<0.01	
1-2 oral anti-diabetic medications with baseline HbA1c ≥7.5%	N=376	N=183
Baseline, mean±SD	8.3±0.7	8.4±0.8
Change, LSM±SE	-0.4±0.1	0.1±0.1
LSM difference: Cycloset-placebo (95% CI); p-value	-0.4 (-0.6, -0.2); p<0.01	
All randomized patients (regardless of baseline HbA1c)	N=2049	N=1015
Baseline, mean±SD	7.0±1.1	7.0±1.1
Change, LSM±SE	0.0±0.0	0.2±0.0
LSM difference: Cycloset-placebo (95% CI)	-0.2 (-0.3, -0.2)	
24-WEEK COMPLETERS		
Metformin+sulfonylurea with baseline HbA1c ≥7.5%	N=121	N=71
Baseline, mean±SD	8.3±0.7	8.3±0.8
Change, LSM	-0.7	0.0
LSM difference: Cycloset-placebo (95% CI)	-0.7 (-1.0, -0.4)	
1-2 oral anti-diabetic medications with baseline HbA1c ≥7.5%	N=261	N=151
Baseline, mean±SD	8.3±0.7	8.4±0.8
Change, LSM	-0.5	0.1
LSM difference: Cycloset-placebo (95% CI)	-0.6 (-0.8, -0.4)	
LSM = least-squares mean		
*primary statistical population for bridging efficacy		

Dr. Pian summarized descriptive statistics for change from baseline in HbA1c at Week 24 according to other background anti-diabetic therapies in patients with baseline HbA1c ≥7.5% (Table 3). Results for patients treated with background thiazolidinedione therapy were similar to those for non-thiazolidinedione-treated patients, although there were only 41 Cycloset-treated patients with baseline HbA1c ≥7.5% treated with background thiazolidinedione therapy, which limits conclusions. Cycloset appeared to have minimal effects in the subgroup of patients with baseline HbA1c ≥7.5% treated with insulin. Minimal, if any, treatment effects

were also seen in the diet-only subgroup, but the small sample sizes (n=37 for Cycloset; n=13 for placebo) limit conclusions and emphasis should rather be placed on the results from the dedicated monotherapy trial conducted for the original Ergoset NDA, which showed results for monotherapy consistent with the primary bridging efficacy subgroup analysis (see below).

Table 3. Descriptive statistics (mean±SD) for HbA1c (%) change from baseline to Week 24 Intent-to-treat population with last-observation-carried-forward All patients with baseline HbA1c ≥7.5% (adapted from Dr. Lee Pian's statistical review)		
Baseline HbA1c ≥7.5%	Cycloset N=2054	Placebo N=1016
Thiazolidinediones	N=41	N=30
Baseline	8.2±0.7	8.3±0.6
Change	-0.3±1.2	0.1±1.3
No thiazolidinediones	N=536	N=257
Baseline	8.4±0.7	8.5±0.8
Change	-0.3±1.0	0.0±1.1
Diet only	N=37	N=13
Baseline	8.3±0.8	8.3±1.0
Change	-0.1±1.4	-0.3±2.1
Insulin	N=166	N=91
Baseline	8.5±0.7	8.6±0.8
Change	-0.1±1.2	-0.1±0.9
One oral anti-diabetic medication	N=142	N=64
Baseline	8.3±0.7	8.4±0.8
Change	-0.3±0.9	0.1±1.3
Two oral anti-diabetic medications	N=232	N=119
Baseline	8.3±0.7	8.4±0.8
Change	-0.5±0.9	0.0±1.1

Efficacy in the original Ergoset clinical trials: The original NDA contained data from 3 pivotal, multicenter, double-blind, placebo-controlled trials, which compared bromocriptine to placebo as monotherapy (Study M) or as add-on to stable sulfonylurea therapy (Studies K and L) in patients with type 2 diabetes. All three trials used the same dosing regimen of bromocriptine as described for the current safety trial. Each trial had a 2-week run-in period and a 24-week treatment period. The primary efficacy analysis for all 3 trials was the change in HbA1c from baseline to endpoint, performed on the intent-to-treat population using the last-observation-carried forward for missing values.

The HbA1c findings from the bridging efficacy analyses in the 52-week safety trial are consistent with the findings from the original Ergoset pivotal clinical trials (Table 4). Noteworthy findings include the higher mean baseline HbA1c in the original clinical trials (8.8-9.5%) compared to the bridging efficacy subset of the safety trial (8.3%), treatment effects in Studies K and M predominantly due to worsening of HbA1c in the placebo group, and borderline statistical significance in Study M, which had the smallest sample sizes.

Please see Dr. Misbin's clinical review for a summary of other data from the original clinical trials.

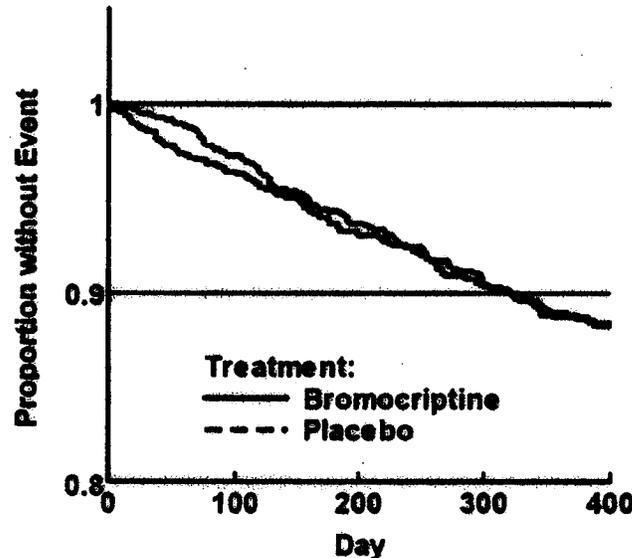
Table 4. HbA1c (%) change from baseline in the original Ergoset clinical trials (intent-to-treat population; last-observation-carried-forward) (adapted from Dr. Lee Pian's 1998 statistical review)		
	Ergoset	Placebo
Study K (add-on to sulfonylurea)	N=114	N=122
Baseline, mean±SE	9.3±0.1	9.4±0.1
Change, LSM±SE	0.0±0.1	0.5±0.1
LSM difference: Ergoset-placebo; p-value*	-0.5; p=0.001	
Study L (add-on to sulfonylurea)	N=114	N=123
Baseline, mean±SE	9.3±0.1	9.5±0.1
Change, LSM±SE	-0.4±0.1	0.2±0.1
LSM difference: Ergoset-placebo; p-value*	-0.6; p<0.001	
Study M (monotherapy)	N=74	N=74
Baseline, mean±SE	9.0±0.2	8.8±0.2
Change, LSM±SE	0.0±0.2	0.4±0.2
LSM difference: Ergoset-placebo; p-value*	-0.4; p=0.052	
LSM = least-squares mean		
*95% confidence interval for the treatment effect was not reported in the 1998 statistical review		

8. Safety

Primary Endpoint: The primary endpoint of the 52-week safety trial was the time-to-first serious adverse event with Cycloset relative to placebo. A total of 176 Cycloset-treated patients (8.6%) and 98 placebo-treated patients (9.6%) experienced a serious adverse event. As discussed by Dr. Pian, the hazard ratio (with one-sided 96% confidence interval) for the primary endpoint was 1.02 (0.82-1.27) using the intent-to-treat population and 1.10 (0.84-1.50) using the per-protocol population. The upper bound of the 95% confidence interval was below the pre-specified non-inferiority margin of 1.50 for the intent-to-treat population and was equal to the non-inferiority margin for the per-protocol population.

Over the first part of the treatment period, there was a slight separation of Kaplan-Meier curves for time-to-first serious adverse event, with findings favoring placebo. However, over the latter part of the trial, the Kaplan-Meier curves for Cycloset and placebo were superimposable (Figure 1). The sponsor did not analyze the time course of different types of non-cardiac serious adverse events. However, as discussed below, the syncopal serious adverse events associated with Cycloset therapy typically occurred shortly after treatment initiation or dose escalation.

Figure 1. Kaplan-Meier curves for time-to-first serious adverse event: intent-to-treat population (from Dr. Lee Pian's statistical review)



Secondary Endpoints:

Table 5 and Figure 2, adapted from Dr. Pian's review, summarize the results for the secondary cardiovascular endpoints. A total of 31 Cycloset-treated patients (1.5%) and 30 placebo-treated patients (3.0%) experienced the pre-specified composite cardiovascular endpoint. The hazard ratio (with 95% two-sided confidence interval) for this composite comparing Cycloset to placebo was 0.58 (0.35-0.96). The hazard ratios for each of the individual components of the composite were below 1.0 although these components had wide confidence intervals (reflecting the small number of events) with all upper bounds exceeding 1.0.

The high differential dropout rate (47% in the Cycloset group and 31% in the placebo group) limits the ability to estimate without bias the true hazard ratios for these cardiovascular endpoints. In addition, cardiovascular outcomes were pre-specified as secondary, not primary endpoints. Therefore, I agree with Dr. Pian that the sponsor's proposed _____ should not be included labeling.

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Of note, the upper bound of the two-sided 95% confidence interval for the hazard ratio for the composite cardiovascular endpoint is less than 1.3 with a reassuring point estimate. Therefore, no additional assessment of cardiovascular safety is needed based on the recommendations in the final guidance issued in December 2008 entitled *Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*. According to the biostatistics review team, this conclusion is valid despite the high differential dropout rates.

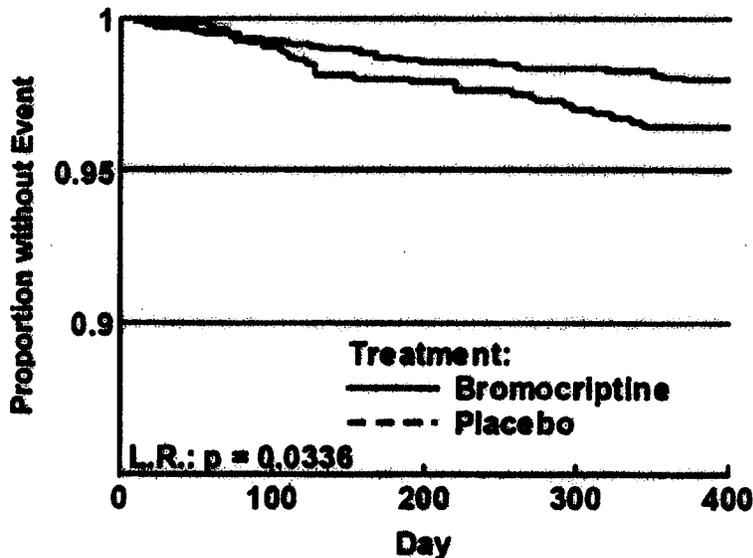
The guidance states that trials longer than 3-6 months will typically be needed to assess cardiovascular safety. Although the guidance provides an example of a minimum 2-year

duration for such trials, I view the completed 1-year safety trial to be sufficient for several reasons. Firstly, the initial concern of cardiovascular safety with bromocriptine emerged from a relatively healthy, younger patient population (postpartum women) compared to the patients with diabetes enrolled in the safety trial (diabetes is considered a coronary artery disease equivalent). Secondly, the 1-year duration of treatment in the safety trial is longer than the expected treatment duration for the (now withdrawn) postpartum indication. Finally, the upper bound of the two-sided 95% confidence interval for the hazard ratio for the composite cardiovascular endpoint was not close to 1.3 (in fact, it was <1.0) with Kaplan-Meier curves that continued to diverge over the course of the trial, providing further reassurance.

Table 5. Secondary endpoint (adapted from Dr. Pian's review)

	Cycloset n (%)	Placebo n (%)	Hazard Ratio (95% confidence interval)
Cardiovascular composite	31 (1.5)	30 (3.0)	0.58 (0.35-0.96)
Individual components of the composite			
Myocardial infarction	6 (0.3)	8 (0.8)	0.44 (0.15-1.26)
Stroke	4 (0.2)	6 (0.6)	0.37 (0.10-1.32)
Inpatient hospitalization for angina	9 (0.4)	9 (0.9)	0.55 (0.22-1.38)
Inpatient hospitalization for heart failure	7 (0.3)	5 (0.5)	0.81 (0.26-2.57)
Revascularization surgery	9 (0.4)	6 (0.6)	0.85 (0.30-2.40)

Figure 2. Time-to-first serious composite cardiovascular adverse event (from Dr. Pian's review)



Deaths: There were 12 reported deaths during the course of the trial (9 Cycloset; 3 placebo). Six of these deaths occurred more than 30 days after stopping study medication (5 Cycloset; 1 placebo) and were not considered treatment-emergent. Of the remaining 6 deaths, 4 occurred

with Cycloset and 2 occurred with placebo, which is consistent with the 2:1 randomization scheme.

The 4 treatment-emergent deaths in the Cycloset group were due to:

- Completed suicide on Day 192 (no history of depression but spouse had died 1 year prior and the patient reportedly had financial and health problems)
- Fatal car accident on Day 121 (also treated with glyburide; cause of accident unknown)
- Found dead (history of stroke)
- Cardiopulmonary arrest

Both treatment-emergent deaths in the placebo group were determined to be cardiac-related by the adjudication committee.

The non-treatment-emergent deaths (i.e., deaths occurring >30 days after the last dose of study medication) in the Cycloset group were due to hepatocellular carcinoma, glioblastoma, lung cancer, septicemia from endocarditis, and one unknown cause of death that occurred 209 days after stopping Cycloset. The 1 non-treatment-emergent death in the placebo group was due to pancreatic cancer.

Serious adverse events: As discussed above, serious adverse events were reported in 176 Cycloset-treated patients (8.6%) and in 98 placebo-treated patients (9.6%). Table 6 summarizes the serious adverse events occurring in more than 1 Cycloset-treated patient and occurring more frequently with Cycloset than with placebo. Of note, none of these serious adverse events occurred more than 0.2 percentage points higher with Cycloset compared to placebo.

Serious adverse events of interest are those potentially related to the centrally-acting effects of Cycloset, specifically syncope and psychiatric events. In addition, serious adverse events related to cardiac arrhythmia are discussed below because of the apparent imbalance favoring placebo.

1. Syncopal/hypotensive serious adverse events: Syncope as a serious adverse event was reported in 13 (0.6%) Cycloset-treated patients and 2 (0.2%) placebo-treated patients (Table 6). For one of the 13 Cycloset cases, syncope was reported in the narrative but was not coded to a preferred term. This patient experienced syncope 5 days after uptitrating to 3 Cycloset tablets daily. Cardiopulmonary resuscitation was performed. The narrative notes that the patient developed electromechanical dissociation. Myocardial infarction and pulmonary embolism were excluded. The patient survived but had mental impairment at the time he was transferred to a long-term care facility.

Ten of these 13 Cycloset cases occurred within 7 days after starting a new dose of Cycloset and 6 occurred within 1 day of the new dose. In contrast, the placebo cases occurred more than 100 days into the treatment period. Twelve of the 13 Cycloset patients were taking concomitant anti-hypertensive medication(s). Two of the Cycloset cases specifically state the syncopal episode occurred in the setting of postural changes and 2 cases had documented hypotension around the time of the event. Some of the Cycloset cases were confounded. For

example, 1 patient had undergone cardiac stenting earlier the same day, 1 patient subsequently had a pacemaker placed, 1 patient was diagnosed with metastatic lung cancer 14 days later, and 1 patient reported several months of vomiting.

The 2 reports of hypotension in Table 6 were (a) attributed to overdiuresis in one patient and (b) described as orthostatic symptoms in a second patient when blood pressure declined from 104/42 mmHg on sitting to 90/40 mmHg on standing at the Week 36 clinic visit.

Based on these findings, I agree with the sponsor's proposal to add language to the Warnings and Precautions section of the label to inform healthcare providers about the risk of orthostatic hypotension and syncope, particularly when Cycloset is initiated or if there is dose escalation.

2. Psychiatric serious adverse events: The report of completed suicide in the Cycloset group is described above in the section on deaths. One of the 2 reports coded as depression with bromocriptine was actually a suicide attempt. This patient had a history of depression (no prior suicide attempts) and was taking Prozac, Effexor, and Ultram. Approximately 10 months after starting bromocriptine, the patient wrote a suicide note and started a car in her closed garage. Neighbors heard the loud engine and called the police who found the patient with a Glasgow Coma Score of 3. Her carboxyhemoglobin was elevated and a toxicology screen was positive for benzodiazepines and oxycodone. Study medication was discontinued.

In total, the Cycloset group had 1 report of completed suicide, 1 report of attempted suicide, 1 report of depression in a patient with no history of depression, and 1 report of bipolar disorder in a patient with a history of anxiety and depression. In the placebo group, there was 1 report of worsening depression and repeated suicidal ideation in a patient with a history of depression. The 2 suicide-related serious adverse events with Cycloset and the 1 suicide-related serious adverse event with placebo are consistent with the 2:1 randomization scheme (of note, there was a second suicide attempt in the placebo group that was not reported as a serious adverse event – see below).

3. Arrhythmia serious adverse events: As shown in Table 6, the sponsor calculated that the Cycloset group had 4 serious reports of atrial fibrillation and 2 serious reports each of atrioventricular block, bradycardia, and supraventricular tachycardia. The placebo group had 1 report of atrial fibrillation.

However, I have reviewed the narratives for serious adverse events and have identified a total of 6 patients in the Cycloset group and 3 patients in the placebo group who developed treatment-emergent atrial fibrillation (2 narratives for Cycloset and 2 narratives for placebo reported atrial fibrillation, but this event was not coded to a preferred term). This corrected count for atrial fibrillation is consistent with the randomization scheme of 2:1.

Review of the narratives for serious adverse events identified 3 Cycloset-treated patients and 2 placebo-treated patients with atrioventricular block, which is consistent with the randomization scheme of 2:1. All 5 patients were appropriately coded to atrioventricular block. Therefore, it is unclear why some of these patients were not included in the tally in the table below.

In summary, the available data on serious adverse events do not support an arrhythmia safety signal.

Table 6. Serious adverse events occurring in more than 1 Cycloset-treated patient and occurring more frequently with Cycloset than with placebo (safety population)		
	Cycloset N=2054 n (%)	Placebo N=1016 n (%)
At least 1 serious adverse event	176 (8.6)	98 (9.6)
Cardiac disorders	51 (2.5)	37 (3.6)
Atrial fibrillation	4 (0.2)	1 (0.1)
Syncope	4 (0.2)	0
Atrioventricular block	2 (0.1)	0
Bradycardia	2 (0.1)	0
Supraventricular tachycardia	2 (0.1)	0
Infections and infestations	27 (1.3)	13 (1.3)
Pneumonia	9 (0.4)	3 (0.3)
Urinary tract infection	2 (0.1)	0
Nervous system disorders	26 (1.3)	14 (1.4)
Syncope	8 (0.4)	2 (0.2)
Syncope vasovagal	1 (<0.1)	0
Loss of consciousness	3 (0.1)	1 (0.1)
Vascular disorders	10 (0.5)	8 (0.8)
Carotid artery occlusion	2 (0.1)	0
Hypotension	2 (0.1)	0
Respiratory, thoracic and mediastinal disorders	13 (0.6)	3 (0.3)
Chronic obstructive airways disease exacerbated	5 (0.2)	1 (0.1)
Chronic obstructive airways disease	2 (0.1)	0
Injury, poisoning and procedural complications	12 (0.6)	3 (0.3)
Multiple fractures	2 (0.1)	0
Accidental overdose* (accidentally injected Humalog instead of Lantus)	1 (<0.1)	0
Musculoskeletal and connective tissue disorders	11 (0.5)	4 (0.4)
Localized osteoarthritis	2 (0.1)	0
Metabolism and nutrition disorders	7 (0.3)	2 (0.2)
Dehydration	5 (0.2)	2 (0.2)
Psychiatric disorders	4 (0.2)	1 (0.1)
Depression	2 (0.1)	0
Bipolar I disorder*	1 (<0.1)	0
Completed suicide*	1 (<0.1)	0
Suicide attempt*	0	1 (0.1)
Reproductive system and breast disorders	4 (0.2)	0
Benign prostatic hyperplasia	2 (0.1)	0

*These events of special interest are included in the table (even though they occur in only 0-1 Cycloset-treated patient) because Cycloset is a centrally-acting medication.

Withdrawals due to adverse events: Approximately 30% of Cycloset-treated patients and 12% of placebo-treated patients reported an adverse event leading to premature treatment discontinuation (Table 7). This difference between treatment groups is driven predominantly by gastrointestinal and nervous system events, particularly nausea (8.7% vs. 1.0%), vomiting (2.1% vs. 0.4%), dizziness (3.4% vs. 0.8%), and headache (2.5% vs. 0.6%). A majority of these events were classified as mild or moderate by the study investigators.

Table 7 also summarizes less frequent, but potentially important adverse events leading to treatment discontinuation.

- Syncope and hypotension causing premature discontinuation from the trial were more frequent with Cycloset than with placebo, consistent with the findings described above for serious adverse events.
- Three Cycloset-treated patients and 1 placebo-treated patient discontinued due to “liver function test abnormal”: One of these Cycloset-treated patients had an increase in alanine aminotransferase (ALT) from 54 U/L at screening to 80 U/L at Week 6, prompting discontinuation of Cycloset. Subsequent ALT measurements (all off Cycloset) from Weeks 12-36 ranged from 97-189 U/L. The second Cycloset-treated patient was reported to have an elevated ALT at the time of hospitalization for dehydration. However, ALT values reported from this hospitalization and all ALT measurements obtained during the study were normal. The third Cycloset-treated patient had a normal ALT at baseline and elevated ALT of 310 U/L at Week 6 that was attributed to a two-week course of clindamycin for a tooth abscess. Cycloset was discontinued on Day 44. Repeat ALT measurements were 600 U/L approximately 1 week later and 303 U/L at Week 12. The placebo-treated patient with “liver function test abnormal” had normal baseline liver tests but ALT of 155 U/L and total bilirubin 2.3 mg/dL on Day 256 (during a hospitalization for chest pain) attributed to fluvastatin. Two Cycloset-treated patients discontinued due to “alanine aminotransferase increased”. One of these patients had an ALT of 106 U/L at Week 12; however, the screening value was 93 U/L. The second patient was erroneously reported to have an elevated ALT of 90 U/L, but his actual ALT was normal. Severe liver toxicity is not a known adverse effect of bromocriptine therapy although the currently approved Parlodel label mentions the possibility of transaminase elevations that are usually transient and not clinically significant. Despite millions of prescriptions for bromocriptine products over decades of use, there is only one crude count of hepatic failure and one crude count of hepatitis fulminant in the Adverse Event Reporting System (AERS).
- Two Cycloset-treated patients were discontinued due to blood creatinine increased. One of these patients terminated at Week 6 for a serum creatinine of 1.4 mg/dL; however, the patient’s screening serum creatinine was also 1.4 mg/dL. The second patient had an increase in serum creatinine from 1.4 mg/dL to 1.7 mg/dL after 6 days of treatment associated with nausea, dizziness, and hypotension. The objective laboratory data from the safety trial do not identify a renal safety signal with Cycloset (see below).
- The patient with “swelling face” was also treated with an ACE inhibitor (unknown duration) and developed generalized swelling of the face, hands, legs, and feet 2 days after

starting Cycloset. However, the patient continued study medication for 15 more days before withdrawing from the trial and on the day of discontinuation, the symptoms were described as mild. Hypersensitivity reactions have been reported with bromocriptine products, and a history of a severe reaction is listed as a contraindication in the proposed label.

Withdrawals due to psychiatric adverse events occurred in 21 (1.0%) Cycloset-treated patients and 5 (0.5%) placebo-treated patients. Several preferred terms (e.g., nightmare, sleep disorder, stress symptoms, disorientation, communication disorder) were each reported in only 1 Cycloset-treated patient and none of the placebo-treated patients. There were 10 instances of preferred terms consistent with mood disorder (e.g., depression, anxiety, mood swings, bipolar I disorder, crying, mood altered) reported among the Cycloset-treated patients compared to 4 such reports among the placebo-treated patients, which is generally consistent with the 2:1 randomization scheme.

Table 7. Adverse events leading to treatment discontinuation (safety population)		
	Cycloset N=2054 n (%)	Placebo N=1016 n (%)
At least 1 adverse event leading to treatment discontinuation	608 (29.6)	117 (11.5)
Occurring in >1% of Cycloset-treated patients and more frequently with Cycloset than with placebo		
Gastrointestinal disorders	278 (13.5)	28 (2.8)
Nausea	179 (8.7)	10 (1.0)
Vomiting	44 (2.1)	4 (0.4)
Diarrhea	26 (1.3)	6 (0.6)
Nervous system disorders	344 (16.7)	26 (2.6)
Dizziness	70 (3.4)	8 (0.8)
Headache	52 (2.5)	6 (0.6)
General disorders and administration site conditions	124 (6.0)	25 (2.5)
Fatigue	75 (3.7)	10 (1.0)
Less frequent, but potentially important adverse events leading to treatment discontinuation		
Syncope	12 (0.6)	1 (0.1)
Hypotension	9 (0.4)	2 (0.2)
Liver function test abnormal	3 (0.1)	1 (0.1)
Alanine aminotransferase increased	2 (0.1)	0
Blood creatinine increased	2 (0.1)	0
Swelling face	1 (<0.1)	0

Common adverse events: Table 8 summarizes adverse events occurring in >5% of Cycloset-treated patients and occurring more frequently with Cycloset than with placebo. Nausea, a well-known side effect of bromocriptine agonists, occurred much more frequently with Cycloset (32%) than with placebo (8%). Other common adverse events reported more frequently with Cycloset than with placebo included vomiting (8% vs. 3%), dizziness (15% vs. 9% - please see discussion of hypotension below), headache (11% vs. 8%), fatigue (14% vs. 7%), and hypoglycemia (7% vs. 5% - please see discussion of hypoglycemia below).

Table 8. Common adverse events occurring in more than 5% of Cycloset-treated patients and occurring more frequently with Cycloset than with placebo (safety population)		
	Cycloset N=2054 n (%)	Placebo N=1016 n (%)
At least 1 adverse event	1832 (89.2)	840 (82.7)
Gastrointestinal disorders	1048 (51.0)	316 (31.1)
Nausea	661 (32.2)	77 (7.6)
Diarrhea	167 (8.1)	81 (8.0)
Vomiting	167 (8.1)	32 (3.1)
Constipation	119 (5.8)	52 (5.1)
Nervous system disorders	688 (33.5)	258 (25.4)
Dizziness	303 (14.8)	93 (9.2)
Headache	235 (11.4)	84 (8.3)
General disorders and administration site conditions	537 (26.1)	197 (19.4)
Fatigue	285 (13.9)	68 (6.7)
Endocrine disorders	194 (9.4)	97 (9.5)
Hypoglycemia	141 (6.9)	54 (5.3)

Adverse events of special interest:

1. Hypotension: Hypotension was reported as an adverse event by 45 (2.2%) Cycloset-treated patients and 8 (0.8%) placebo-treated patients. Because none of these events were reported as serious, there are limited data (e.g., no blood pressure readings) available at the time of the event. Most of these Cycloset-treated patients did not have hypotension at the clinic visits closest to the reported adverse event of hypotension. Of note, 29/45 (64%) Cycloset-treated patients reported that the hypotensive event occurred within the first 8 weeks of the treatment period compared to 3/8 (38%) placebo-treated patients. Only 1 of these 53 patients (received Cycloset) was not taking antihypertensive medication. Most of the remaining 52 patients were taking 2-3 antihypertensive medications.

2. Psychiatric events: Bromocriptine has central nervous system effects; therefore, it is possible that bromocriptine may affect mood or have unintended psychiatric effects. Although the safety trial was not prospectively designed to assess specific psychiatric events, it is noteworthy that a numerically smaller proportion of Cycloset-treated patients reported psychiatric disorders compared to placebo-treated patients (5.6% vs. 6.0%). The Cycloset group had a similar frequency (or numerically lower frequency) of preferred terms consistent with mood abnormalities compared to the placebo group. Completed suicide occurred in 1 Cycloset-treated patient. Suicide attempt occurred in 1 Cycloset-treated patient and 2 placebo-treated patients.

Other adverse events potentially consistent with self-inflicted injury were also reviewed (Table 9). Narratives for these adverse events were requested and none supported suicidal activity (a description of the events in Cycloset-treated patients is listed next to each preferred term in the

table). One Cycloset-treated patient with the preferred term “injury” was reported to have had a wound to her left arm from scissors requiring treatment in an emergency room. No other details are available, but even if this is related to suicidal activity, the proportion of such events with Cycloset still compares favorably to that with placebo.

Table 9. Selected psychiatric adverse events including potential psychiatric-related events in the Injury/Poisoning/Procedural Complications system-organ-class (safety population)		
	Cycloset N=2054 n (%)	Placebo N=1016 n (%)
Psychiatric disorders	116 (5.6)	61 (6.0)
Insomnia	44 (2.1)	25 (2.5)
Depression (one of these Cycloset-treated patients attempted suicide)	13 (0.6)	12 (1.2)
Anxiety	13 (0.6)	8 (0.8)
Nervousness	7 (0.3)	4 (0.4)
Irritability	6 (0.3)	3 (0.3)
Stress symptoms	6 (0.3)	2 (0.2)
Mood swings	3 (0.1)	1 (0.1)
Abnormal dreams	3 (0.1)	0
Depressed mood	2 (0.1)	1 (0.1)
Emotional distress	2 (0.1)	1 (0.1)
Agitation	1 (<0.1)	1 (0.1)
Suicide attempt	0	2 (0.2)
Bipolar I disorder	1 (<0.1)	0
Completed suicide	1 (<0.1)	0
Injury, poisoning and procedural complications*	146 (7.1)	77 (7.6)
Foreign body trauma – staple to finger; glass in foot; trauma to eyes	3 (0.1)	0
Injury – fall; rib sprain; stab wound to left arm from scissors	3 (0.1)	0
Face injury – assault	1 (<0.1)	1 (0.1)
Road traffic accident - >100 days after stopping drug; knee injury	2 (0.1)	0
Accidental overdose – wrong insulin injected	1 (<0.1)	0
Ergot poisoning – verbatim term was “Ergot intolerance”	1 (<0.1)	0

3. Fibrotic events: There were no cases of valvular fibrosis, retroperitoneal fibrosis, or pleural fibrosis reported in the Cycloset safety trial. One Cycloset-treated patient was diagnosed with pulmonary fibrosis on Day 280. This patient had a chronic productive cough, was a former smoker, and did not have a report of confirmatory chest x-ray. Please see the postmarketing section below for further discussion of fibrotic events associated with bromocriptine therapy.

4. Hypoglycemia: To be classified as a hypoglycemic event, the patient was required to either have classic symptoms of hypoglycemia (if a glucose value was not available, the protocol required prompt resolution with food, glucagon, or intravenous glucose; if a glucose value was available, the protocol required a measurement <60 mg/dL) or a documented glucose <50 mg/dL (with or without symptoms). For hypoglycemia to be classified as severe, the protocol required that the patient be unable to self-treat neurological symptoms consistent with

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hypoglycemia in the setting of a blood glucose <50 mg/dL (or evidence of prompt resolution of symptoms with glucose or glucagon if there was no available glucose measurement).

A greater proportion of Cycloset-treated patients than placebo-treated patients reported hypoglycemia as an adverse event (6.9% vs. 5.3%), although both treatment groups had a similar incidence of serious hypoglycemia (0.2% vs. 0.4%), severe hypoglycemia (0.5% vs. 1.0%), and hypoglycemia leading to treatment discontinuation (0.1% vs. 0.3%).

Laboratory data: Liver tests, serum chemistries, and urinalysis were obtained at Weeks -2, 6, 24, and 52. Hematology labs, fasting lipids, electrocardiograms, and body weight were obtained at Weeks -2, 24, and 52.

There were no clinically meaningful differences between treatment groups with regard to mean changes from baseline or shifts from normal at baseline to abnormal at endpoint for any of the standard hematology, chemistry, or urinalysis parameters.

Alert values included serum transaminases $\geq 3x$ ULN, total bilirubin $\geq 2x$ ULN, and serum creatinine $\geq 2x$ ULN. None of the Cycloset or placebo-treated patients developed a serum creatinine alert value. A total of 3 (0.2%) Cycloset-treated patients and no placebo-treated patients had an ALT alert value at early termination or Week 52. One of these patients had a screening ALT of 158 U/L (2.9x ULN) that was 141 U/L on Week 6 and 210 U/L (3.8x ULN) on Day 150. Of note, this patient had discontinued study drug 58 days prior to the Day 150 measurement. The second patient had transaminitis attributed to clindamycin (see the section above on discontinuations associated with adverse events). The last patient had a screening ALT of 27 U/L, a Week 24 ALT of 29 U/L, and a Week 52 ALT of 215 U/L (3.9x ULN). The sponsor reports that this patient had a repeat ALT measurement of 52 U/L and that the investigator attributed the initial abnormal measurement to laboratory error.

Vital signs: There were no clinically meaningful differences between treatment groups with regard to mean changes from baseline to endpoint for any of the vital signs. The mean increase in body weight from baseline to Week 52 was 1.1 kg with Cycloset and 0.7 kg with placebo.

Postmarketing data: Bromocriptine mesylate (e.g., Parlodel) is approved for the treatment of hyperprolactinemia, acromegaly, and Parkinson's disease (the postpartum breast engorgement indication was withdrawn because of postmarketing reports of stroke, some of which were fatal). Dr. Misbin notes that the sponsor estimates _____ patient-years of worldwide exposure to bromocriptine through 2006.

b(4)

A typical therapeutic daily dose of bromocriptine in adults for hyperprolactinemia is 2.5-15 mg but daily doses up to 100 mg can be used in patients with acromegaly and Parkinson's disease. Therefore, findings from the postmarketing database may not necessarily apply to the lower doses developed for the diabetes indication (0.8-4.8 mg).

Using data mining techniques, Dr. Joslyn Swann (Office of Surveillance and Epidemiology) identified postmarketing reports associated with bromocriptine based on the commonly used "EB05 ≥ 2 " criterion (Appendix 1). An event meeting the EB05 ≥ 2 criterion occurs at least

twice the expected rate (with 95% confidence) when considering other drugs and events in the AERS database. This analysis identifies potential associations and signals for further investigation but cannot be used to assess causality or conclude that the event occurs with an increased relative risk.

Table 10 summarizes potentially relevant postmarketing reports with bromocriptine based on the $EB05 \geq 2$ criterion. Of note, all of these events are already included in the label for Parlodel (another bromocriptine mesylate formulation), with the exception of pathological gambling (which is included in the Cabergoline label). Most of these events (except pathological gambling, neuroleptic malignant syndrome upon abrupt withdrawal, pericardial effusion, and delusion) are included in the proposed label for Cycloset. During labeling discussions, the sponsor will be asked to add these other 4 events to the Cycloset label or provide a rationale for why these should not be included.

Preferred term	N	EB05
Retroperitoneal fibrosis	34	43.2
Pericarditis constrictive	6	42.5
Pathological gambling	11	36.9
Pleural fibrosis	7	21.2
Neuroleptic malignant syndrome	45	14.0
Pleural effusion	75	10.2
Pericarditis	24	8.8
Pulmonary fibrosis	32	6.7
Delusion	24	5.4
Hallucination	107	5.1
Psychotic disorder	50	4.2
Orthostatic hypotension	21	2.6
Pericardial effusion	12	2.3
Syncope	74	2.3
Paranoia	16	2.0

Cycloset is an ergot-derived bromocriptine agonist like Pergolide, Cabergoline, and Parlodel. In 2007, articles in the *New England Journal of Medicine* reported an association of valvular heart disease with Pergolide and Cabergoline, the only 2 dopamine agonists that are potent agonists of serotonin receptor $5-HT_{2B}$, like other drugs associated with valvulopathy ($5-HT_{2B}$ receptors are plentiful in human cardiac valves and are thought to be essential for normal cardiac development).¹ Subsequently, Pergolide (used to treat Parkinson's disease) was voluntarily withdrawn. Cabergoline is approved for hyperprolactinemia (but not for Parkinson's disease) and remains on the market because there appears to be little possibility of valvulopathy at the lower doses typically used to treat hyperprolactinemia. Parlodel (a

¹ Roth BL. Drugs and valvular heart disease. *NEJM*. 2007; 356: 6-9.

Schade R, et al. Dopamine agonists and the risk of cardiac-valve regurgitation. *NEJM*. 2007; 356: 29-38.

Zanettini R, et al. Valvular heart disease and the use of dopamine agonists for Parkinson's disease. *NEJM*. 2007; 356: 39-46.

formulation of bromocriptine mesylate, like Cycloset) is not labeled for valvulopathy (there was no association between Parlodel and valvulopathy and Parlodel does not have 5-HT_{2B} activity).

Of note, there are very few postmarketing reports in AERS of valvular disease associated with bromocriptine (4 cases of aortic valve incompetence, 2 cases of aortic valve sclerosis, 2 cases of cardiac valve disease, 1 case of heart valve incompetence, 1 case of heart valve stenosis, 2 cases of mitral valve disease, 4 cases of mitral valve incompetence, 1 case of mitral valve sclerosis, 1 cases of mitral valve stenosis, 1 case of pulmonary valve incompetence, 1 case of tricuspid valve disease, and 3 cases of tricuspid valve incompetence) (Appendix 2).

Based on the findings above, Cycloset is not likely to have an association with valvulopathy. The proposed label for Cycloset states the following (which is acceptable): "Among several studies investigating a possible relation between bromocriptine exposure and cardiac valvulopathy, some events of cardiac valvulopathy have been reported, but no definitive association between bromocriptine use and clinically significant (moderate to severe) cardiac valvulopathy could be concluded."

9. Advisory Committee Meeting

This complete response was not taken to advisory committee meeting because the sponsor has definitively addressed the deficiencies identified in the 1999 Approvable letter. As mentioned previously, the original NDA was discussed at an advisory committee meeting in 1998. Please see Dr. Misbin's clinical review for further details. Briefly, the committee voted unanimously against approval. Reasons cited included:

- **Modest efficacy.** The committee noted that bromocriptine prevented the rise in HbA1c seen with placebo but did not lower HbA1c relative to baseline values, raising questions about whether bromocriptine would treat hyperglycemia. However, in randomized clinical trials, efficacy should be judged based on placebo-corrected treatment effects rather than within-group treatment effects because the placebo effect represents what would have happened had the treatment group not received study drug.
- **Possible imbalance in the risk of myocardial infarction in the Ergoset trials in light of the voluntary withdrawal in 1994 of the indication to suppress postpartum lactation due to reports of myocardial infarction and stroke in otherwise healthy young women.** The complete response has resolved this concern for the diabetes indication.
- **Lack of long-term data and no data on durability of effect.** The complete response has provided reassuring, controlled, safety data to 1-year in a reasonable number of patients. Although durability of treatment effect has not been rigorously assessed beyond Month 6, this meets current approval standards for drugs developed for the treatment of diabetes. It is well known that diabetes is a progressive disorder and most patients will require additional therapies over time.

10. Pediatrics

The Pediatric Review Committee (PeRC) agrees with a waiver for children <10 years of age and a deferral for children and adolescents ≥10 years of age, which is consistent with our approach to other oral treatments for type 2 diabetes.

The sponsor's pediatric plan was presented to PeRC on January 28, 2009. The sponsor is proposing to first perform a clinical pharmacology trial to evaluate safety, tolerability, and standard pharmacokinetic parameters of a single 4.8 mg dose of Cycloset in children with type 2 diabetes aged 10-16 years old. Next, the sponsor proposes conducting a 16-week, randomized, feasibility trial comparing Cycloset (titrated to 3.2 mg) to placebo in 80 children and adolescents aged 10-16 years old treated with diet alone or background metformin therapy. Based on the results from these trials, the sponsor will design a randomized, double-blind, placebo-controlled efficacy and safety trial of at least 6 months duration testing Cycloset vs. placebo in children and adolescents with type 2 diabetes. Because of the centrally-acting effects of Cycloset and the potential vulnerability of this younger population to psychiatric events, the sponsor plans to administer psychiatric questionnaires in the multiple-dose studies described above.

PeRC agreed with the overall approach but recommended that the sponsor incorporate dose-finding in the feasibility trial. PeRC also recommended a head-to-head comparison with metformin (the only recommended oral antidiabetic therapy for children and adolescents) if the sponsor asks for a Written Request.

The sponsor is proposing the following timelines for protocol submission, study initiation, and submission of study reports (Table 11). These timelines are relative to the approval date of the NDA. I recommend that the pediatric timelines be revised for the approval letter. For example, under the current proposal, the feasibility trial protocol would be submitted around the time when the clinical pharmacology trial will be initiated, which is not ideal because results from the first trial could substantially impact on the design of the feasibility trial. Table 11 includes my suggestions for the revised timelines.

Table 11. Timelines for the pediatric studies relative to the approval date of the NDA			
	Protocol submission	Initiation of study	Submission of study report
Clinical pharmacology trial	_____	_____	_____
Feasibility study	*17 months	*20 months	*40 months
Clinical efficacy and safety trial	*40 months	*52 months	*75 months †85 months
*revised timelines proposed by this reviewer			
†Time line if there is a 6-month extension trial to the core clinical efficacy and safety trial			

b(4)

11. Other Relevant Regulatory Issues

The Division of Medication Errors and Prevention (DMEPA) reviewed the tradename "Cycloset" within 90 days of the anticipated approval date and found it to be acceptable.

The Division of Scientific Investigations (DSI) investigated 3 study sites that were selected on the basis of enrollment of large numbers of patients (total of 369 of the 3,070 randomized patients or 12%). DSI concluded that the data generated from these clinical sites were acceptable. One patient was dispensed placebo in error rather than study drug but findings from this patient would not affect conclusions of this ~3,000 patient trial.

Dr. Misbin has reviewed the application for potential conflicts of interest and did not identify anything of concern.

12. Labeling

Please see the labeling attached to the approval letter for the final version agreed upon by the Division and sponsor. The label is formatted according to the Physician Labeling Rule. Relevant safety findings from Parlodel (another formulation of bromocriptine mesylate) and safety concerns identified in the safety section of this memorandum have been adequately incorporated into the Cycloset label.

The Division of Risk Management reviewed and revised the proposed patient package insert (PPI). Please see Ms. Nancy Carothers' review for further details.

The sponsor adequately revised the container labels as requested by DMEPA (please see Melina Griffis' review for further details).

The Division's safety reviewer, Dr. Amy Egan, reviewed the potential safety concerns associated with Cycloset and determined that these concerns are adequately conveyed in the package insert and PPI without the need for a Medication Guide. Please see Dr. Egan's review for further details. Dr. Egan is recommending that the potential for neuropsychiatric adverse events be addressed by asking the sponsor to submit all such adverse events as 15-day reports and to review these adverse events in the quarterly Periodic Safety Update Reports (PSURs). However, my review has not identified a specific psychiatric safety concern. Therefore, I do not recommend 15-day reports for psychiatric adverse events, particularly because individual cases will be difficult to interpret in isolation. Because of the centrally-acting effects of Cycloset, it is reasonable to ask for a summary of psychiatric effects in the PSURs, as recommended by Dr. Egan. We could begin requesting 15-day reports for select events if a potential psychiatric safety signal emerges based on the PSUR data. I have discussed this approach with Dr. Egan who concurs.

Dr. Bruce Schneider, now in the Center for Biologics Evaluation and Research (CBER), reviewed a small euglycemic hyperinsulinemic clamp study at the time of the original NDA submission

b(4)

b(4)

Specific labeling comments based on my review of the data should include:

- The sponsor has limited data supporting efficacy of Cycloset as add-on to background thiazolidinedione therapy. None of the original pivotal clinical trials tested Cycloset in this setting and only 41 Cycloset-treated patients with baseline HbA1c $\geq 7.5\%$ were treated with a thiazolidinedione in the safety trial. In addition, there is no evidence of efficacy in combination with insulin therapy as demonstrated by the mean 0.1% reduction in HbA1c in both the Cycloset and placebo subgroup of patients treated with background insulin therapy (this was a descriptive analysis that was not prespecified). Therefore, I recommend including these findings under Important Limitations of Use and recommend as a postmarketing commitment that the sponsor study Cycloset in these 2 settings.
- In the safety trial, Cycloset had limited efficacy in the overall trial with baseline HbA1c $\geq 7\%$. This finding raises the question of utility of Cycloset in patients with mild type 2 diabetes, and should be noted in labeling.
- The sponsor proposes not to include information on drug interactions with sympathomimetic drugs in the label based on an analysis of patients taking anilides in the safety trial. However, there are limited data on sympathomimetic drugs in the safety trial because patients taking sympathomimetic drugs within 7 days prior to screening or for ≥ 10 days during the trial were excluded. Therefore, the information on drug interactions with sympathomimetic drugs should remain in the label.
- Some postmarketing events in the Parlodel label, (e.g. neuroleptic malignant syndrome upon abrupt withdrawal, pericardial effusion, and delusion) are not included in the Cycloset label. In addition, pathological gambling has been identified in the AERS database as a possible association with bromocriptine based on data mining techniques. The sponsor will be asked to add these events to the Cycloset label or to provide a rationale for why these events should not be included.

13. Recommendations/Risk Benefit Assessment

I recommend APPROVAL of the Cycloset NDA for treatment of type 2 diabetes pending agreement on labeling.

- Risk Benefit Assessment

Cycloset has modest glycemic efficacy (approximately 0.5% relative to placebo) similar to the efficacy seen with WelChol, another recently approved oral antidiabetic medication.

Concerns about cardiovascular safety have been adequately addressed with the 52-week trial included in the complete response.

b(4)

_____ do not support a
_____ claim.

b(4)

Bromocriptine agonists have been widely used over decades for the treatment of other conditions and adverse effects (including rare events such as fibrotic complications) are well known and adequately labeled.

- Recommendation for Postmarketing Risk Management Activities

As discussed above, there is no need for additional risk management activities other than standard labeling, which includes a package insert and patient package insert. Because of the centrally-acting effects of Cycloset, it is reasonable to ask for a summary of psychiatric effects in the PSURs, as recommended by Dr. Egan.

- Recommendation for other Postmarketing Study Commitments

Dr. Misbin, Dr. Egan, and I have not identified any safety concerns that require further study as a postmarketing requirement under the FDA Amendments Act. The upper bound of the 95% confidence interval for the hazard ratio for major cardiovascular events was less than the 1.3 criterion discussed in the recently published diabetes cardiovascular guidance. Therefore, no additional assessment of cardiovascular safety is needed.

I agree with the pediatric deferral (≥ 10 years) and waiver (< 10 years) as requested by the sponsor. Please see Section 10 for recommendations regarding the pediatric study plans and revisions to the pediatric study timelines.

As discussed above under the labeling section, I recommend postmarketing commitments for the study of Cycloset as add-on to thiazolidinedione therapy and as add-on to insulin therapy.

Of note, the sponsor plans to conduct a claims database study focusing on hypotension and syncope, fibrotic complications (e.g., retroperitoneal fibrosis), and liver and renal impairment. Dr. Misbin recommends that the sponsor add valvular heart disease and psychiatric diagnoses to this study and that pharmacovigilance include disorientation/confusion (confusion is already included in the proposed Cycloset label) and schizophrenia. Dr. Misbin's recommendation for monitoring schizophrenia is based on a case report of a 53-year old man without prior history of psychosis who developed schizophrenia 4 days after starting low-dose bromocriptine for a macroprolactinoma. Please see Dr. Misbin's review for details. Based on review of the available data, I do not see a reason for FDA to require the claims database study. However, there is no reason to discourage the sponsor from conducting such a study either. Pharmacovigilance for disorientation/confusion and schizophrenia can be evaluated in the summary of psychiatric events included in PSURs.

Dr. Misbin also recommends (but does not require) that the sponsor consider a postmarketing cardiovascular outcomes trial (for benefit) comparing Cycloset to placebo in patients with HbA1c $\leq 7\%$ because the greatest cardiovascular protection appeared to occur in this subset.

Cross Discipline Team Leader Review

Such a finding is hypothesis-generating, but I agree with Dr. Misbin that further study should not be required.

- **Recommended Comments to Applicant**

None (besides labeling discussions).

APPENDIX 1

ADVERSE EVENT REPORTING SYSTEM

DATA MINING

(Prepared by Joslyn Swann)

Bromocriptine	Visual pathway disorder	Nerv	6	41.5	87.4	166.9
Bromocriptine	Neuroleptic malignant syndrome	Nerv	45	14.0	18.1	23.0
Bromocriptine	Haemorrhagic stroke	Nerv	38	5.3	7.0	9.4
Bromocriptine	Dyskinesia	Nerv	30	4.7	6.6	9.1
Bromocriptine	Hemiplegia	Nerv	30	4.6	6.3	8.7
Bromocriptine	Convulsion	Nerv	186	4.1	4.6	5.2
Bromocriptine	Haemorrhage intracranial	Nerv	21	4.0	5.8	8.5
Bromocriptine	Brain oedema	Nerv	17	3.4	5.1	7.6
Bromocriptine	Cerebrovascular disorder	Nerv	13	3.4	5.5	9.3
Bromocriptine	Grand mal convulsion	Nerv	56	3.2	4.0	4.9
Bromocriptine	Cerebral infarction	Nerv	19	3.1	4.6	6.7
Bromocriptine	Visual field defect	Nerv	18	3.1	4.6	6.7
Bromocriptine	Parkinsonism	Nerv	7	3.0	8.2	25.0
Bromocriptine	Cerebrovascular accident	Nerv	60	3.0	3.7	4.5
Bromocriptine	Headache	Nerv	278	2.7	3.0	3.3
Bromocriptine	Parkinson's disease	Nerv	7	2.6	5.8	17.3
Bromocriptine	Motor dysfunction	Nerv	7	2.6	5.8	17.2
Bromocriptine	Ataxia	Nerv	7	2.6	5.7	16.6
Bromocriptine	Depressed level of consciousness	Nerv	22	2.5	3.6	5.1
Bromocriptine	Syncope	Nerv	74	2.3	2.8	3.4
Bromocriptine	Aphasia	Nerv	13	2.0	3.2	4.9
Bromocriptine	Serotonin syndrome	Nerv	7	1.9	3.7	6.5
Bromocriptine	Subarachnoid haemorrhage	Nerv	8	1.9	3.4	5.9
Bromocriptine	Dysstasia	Nerv	6	1.8	3.6	6.7
Bromocriptine	Cerebral atrophy	Nerv	5	1.8	4.0	9.8
Bromocriptine	Meniere's	Nerv	4	1.8	6.4	37.7
Bromocriptine	Hyperreflexia	Nerv	6	1.7	3.4	6.4
Bromocriptine	Cerebral haemorrhage	Nerv	7	1.7	3.2	5.7
Bromocriptine	Extrapyramidal disorder	Nerv	18	1.7	2.5	3.6
Bromocriptine	Loss of consciousness	Nerv	21	1.6	2.3	3.3
Bromocriptine	Migraine	Nerv	23	1.6	2.2	3.1
Bromocriptine	Hypertonia	Nerv	29	1.6	2.1	2.8
Bromocriptine	Coma	Nerv	36	1.5	2.0	2.6
Bromocriptine	Speech disorder	Nerv	22	1.5	2.1	3.0
Bromocriptine	Dystonia	Nerv	13	1.4	2.3	3.5
Bromocriptine	Facial palsy	Nerv	8	1.4	2.5	4.3
Bromocriptine	Brain injury	Nerv	4	1.4	3.2	7.1
Bromocriptine	Paralysis	Nerv	12	1.4	2.2	3.5
Bromocriptine	Cerebral ischaemia	Nerv	8	1.3	2.4	4.1
Bromocriptine	Dizziness	Nerv	120	1.3	1.5	1.8
Bromocriptine	Somnolence	Nerv	15	1.3	2.0	2.9
Bromocriptine	Encephalopathy	Nerv	9	1.2	2.2	3.6

Bromocriptine	Movement disorder	Nerv	Bromocriptine	Mkt	ment	2.2	3.7
Bromocriptine	Intracranial aneurysm	Nerv	4	1.2	2.8	5.7	
Bromocriptine	Vasculitis cerebral	Nerv	3	1.2	3.6	22.9	
Bromocriptine	Chorea	Nerv	3	1.1	3.4	18.4	
Bromocriptine	Dysarthria	Nerv	9	1.1	2.0	3.3	
Bromocriptine	Apallic syndrome	Nerv	3	1.1	3.2	13.2	
Bromocriptine	Convulsion neonatal	Nerv	3	1.1	3.2	12.7	
Bromocriptine	Hypokinesia	Nerv	6	1.1	2.3	4.6	
Bromocriptine	Choreoathetosis	Nerv	4	1.1	2.5	5.1	
Bromocriptine	Epilepsy	Nerv	5	1.1	2.3	4.3	
Bromocriptine	Dementia	Nerv	7	1.1	2.0	3.5	
Bromocriptine	Hypoxic encephalopathy	Nerv	3	1.1	2.8	6.7	
Bromocriptine	Anoxic encephalopathy	Nerv	3	1.0	2.7	6.3	
Bromocriptine	Stupor	Nerv	12	1.0	1.7	2.6	
Bromocriptine	Hemiparesis	Nerv	5	1.0	2.1	4.1	
Bromocriptine	Pleocytosis	Nerv	3	1.0	2.5	5.8	
Bromocriptine	Psychomotor hyperactivity	Nerv	4	1.0	2.2	4.4	
Bromocriptine	Clonic convulsion	Nerv	7	0.9	1.8	3.1	
Bromocriptine	Tremor	Nerv	36	0.9	1.2	1.6	
Bromocriptine	Myasthenus	Nerv	5	0.9	1.9	3.7	
Bromocriptine	Muscle contractions involuntary	Nerv	3	0.9	2.3	5.2	
Bromocriptine	Hypotonia	Nerv	5	0.8	1.8	3.4	
Bromocriptine	Neuropathy peripheral	Nerv	16	0.8	1.3	1.8	
Bromocriptine	Sedation	Nerv	36	0.8	1.1	1.4	
Bromocriptine	Cerebrospinal fluid rhinorrhea	Nerv	2	0.8	3.6	64.6	
Bromocriptine	Cerebral artery thrombosis	Nerv	3	0.8	2.0	4.4	
Bromocriptine	Status epilepticus	Nerv	3	0.8	2.0	4.4	
Bromocriptine	On and off phenomenon	Nerv	2	0.8	3.0	41.4	
Bromocriptine	Hydrocephalus	Nerv	3	0.8	1.9	4.3	
Bromocriptine	Meningocele	Nerv	2	0.7	2.7	26.9	
Bromocriptine	Locked-in syndrome	Nerv	2	0.7	2.6	18.6	
Bromocriptine	Paresthesia	Nerv	39	0.7	0.9	1.2	
Bromocriptine	Sudden onset of sleep	Nerv	2	0.7	2.3	6.6	
Bromocriptine	Mental impairment	Nerv	4	0.7	1.6	3.2	
Bromocriptine	Coordination abnormal	Nerv	14	0.7	1.1	1.6	
Bromocriptine	Reflexes abnormal	Nerv	2	0.7	2.1	5.6	
Bromocriptine	Hypertensive encephalopathy	Nerv	2	0.7	2.1	5.4	
Bromocriptine	Tonic convulsion	Nerv	2	0.7	2.1	5.4	
Bromocriptine	Nerve compression	Nerv	2	0.6	1.9	4.9	
Bromocriptine	Simple partial seizures	Nerv	2	0.6	1.9	4.9	
Bromocriptine	Dysphasia	Nerv	2	0.6	1.9	4.8	
Bromocriptine	Lacunar infarction	Nerv	2	0.6	1.9	4.8	
Bromocriptine	Masked facies	Nerv	2	0.6	1.9	4.8	

C. Bromocriptine RCM 2008-1575 (2).xls

Bromocriptine	Extensor plantar response	Nerv	2	0.6	1.8	4.6
Bromocriptine	Neurological symptom	Nerv	2	0.6	1.7	4.3
Bromocriptine	Anaesthesia	Nerv	13	0.5	0.8	1.3
Bromocriptine	Myoclonus	Nerv	2	0.5	1.6	4.0
Bromocriptine	Meningem	Nerv	2	0.5	1.6	4.0
Bromocriptine	Balance disorder	Nerv	4	0.5	1.2	2.4
Bromocriptine	Hypoaesthesia	Nerv	11	0.5	0.8	1.3
Bromocriptine	Nervous system disorder	Nerv	4	0.5	1.1	2.2
Bromocriptine	Neuritis	Nerv	2	0.5	1.4	3.6
Bromocriptine	Memory impairment	Nerv	4	0.5	1.0	2.1
Bromocriptine	Paraplegia	Nerv	2	0.4	1.4	3.4
Bromocriptine	Sensory disturbance	Nerv	2	0.4	1.2	3.1
Bromocriptine	Myasthenic syndrome	Nerv	6	0.4	0.8	1.4
Bromocriptine	Lethargy	Nerv	4	0.4	0.9	1.8
Bromocriptine	Akathisia	Nerv	3	0.4	0.9	2.1
Bromocriptine	Cognitive disorder	Nerv	2	0.4	1.1	2.8
Bromocriptine	Neuralgia	Nerv	2	0.3	1.0	2.6
Bromocriptine	Burning sensation	Nerv	3	0.3	0.8	1.8
Bromocriptine	SUNCT syndrome	Nerv	1	0.3	1.4	4.5
Bromocriptine	Cerebral arteritis	Nerv	1	0.3	1.4	4.4
Bromocriptine	Gertmann's syndrome	Nerv	1	0.3	1.4	4.4
Bromocriptine	Wid nerve paresis	Nerv	1	0.3	1.4	4.4
Bromocriptine	Olfactory nerve disorder	Nerv	1	0.3	1.4	4.3
Bromocriptine	Nerve root compression	Nerv	1	0.3	1.4	4.3
Bromocriptine	Upper motor neurone lesion	Nerv	1	0.3	1.3	4.2
Bromocriptine	Multiple sclerosis	Nerv	3	0.3	0.8	1.7
Bromocriptine	Brain mass	Nerv	1	0.3	1.3	4.1
Bromocriptine	Gilets	Nerv	1	0.3	1.3	4.1
Bromocriptine	Intracranial hypotension	Nerv	1	0.3	1.3	4.1
Bromocriptine	Cerebrovascular spasm	Nerv	1	0.3	1.3	4.1
Bromocriptine	Bradycinesis	Nerv	1	0.3	1.3	4.0
Bromocriptine	Cerebellar atrophy	Nerv	1	0.3	1.3	4.0
Bromocriptine	Spastic paralysis	Nerv	1	0.3	1.3	4.0
Bromocriptine	Cerebral haematoma	Nerv	1	0.3	1.3	4.0
Bromocriptine	Hemianopia homonymous	Nerv	1	0.3	1.3	3.9
Bromocriptine	Diplopia	Nerv	1	0.3	1.3	3.9
Bromocriptine	Apraxia	Nerv	1	0.3	1.3	3.9
Bromocriptine	Clonus	Nerv	1	0.3	1.3	3.9
Bromocriptine	Head discomfort	Nerv	1	0.3	1.2	3.9
Bromocriptine	Judgement impaired	Nerv	1	0.3	1.2	3.9
Bromocriptine	Carotid artery thrombosis	Nerv	1	0.3	1.2	3.9
Bromocriptine	Autonomic nervous system	Nerv	1	0.3	1.2	3.8
Bromocriptine	Cerebellar infarction	Nerv	1	0.3	1.2	3.8

Bromocriptine	Cerebral venous thrombosis	Nerv	1	0.3	1.2	3.8
Bromocriptine	Dysgraphia	Nerv	1	0.3	1.2	3.6
Bromocriptine	Menoparesis	Nerv	1	0.3	1.2	3.6
Bromocriptine	Araloxia	Nerv	1	0.3	1.1	3.5
Bromocriptine	Transient ischaemic attack	Nerv	2	0.3	0.8	2.0
Bromocriptine	Paresis	Nerv	1	0.3	1.1	3.3
Bromocriptine	Sciatica	Nerv	1	0.3	1.1	3.3
Bromocriptine	Brooding	Nerv	1	0.3	1.1	3.3
Bromocriptine	Dizziness postural	Nerv	1	0.2	1.0	3.2
Bromocriptine	Petit mal epilepsy	Nerv	1	0.2	1.0	3.2
Bromocriptine	Unresponsive to stimuli	Nerv	1	0.2	1.0	3.1
Bromocriptine	Myelitis	Nerv	1	0.2	1.0	3.1
Bromocriptine	Ischaemic stroke	Nerv	1	0.2	1.0	3.0
Bromocriptine	Parosmia	Nerv	2	0.2	0.7	1.7
Bromocriptine	Syncope vasovagal	Nerv	1	0.2	0.9	2.9
Bromocriptine	Carotid artery stenosis	Nerv	1	0.2	0.9	2.8
Bromocriptine	Quadriplegia	Nerv	1	0.2	0.9	2.7
Bromocriptine	Disturbance in attention	Nerv	2	0.2	0.6	1.6
Bromocriptine	Cerebellar syndrome	Nerv	1	0.2	0.9	2.7
Bromocriptine	Peroneal nerve palsy	Nerv	1	0.2	0.9	2.7
Bromocriptine	Mental retardation	Nerv	1	0.2	0.9	2.6
Bromocriptine	Polymyopathy	Nerv	1	0.2	0.8	2.5
Bromocriptine	Hypersomnia	Nerv	1	0.2	0.8	2.5
Bromocriptine	Hepatic encephalopathy	Nerv	1	0.2	0.7	2.2
Bromocriptine	Intracranial pressure increased	Nerv	1	0.1	0.5	1.4
Bromocriptine	Optic neuritis	Nerv	1	0.1	0.5	1.4
Bromocriptine	Dysgeusia	Nerv	3	0.1	0.2	0.5

APPENDIX 2

ADVERSE EVENT REPORTING SYSTEM

CRUDE COUNTS

(Prepared by Joslyn Swann)



Standard Report

Cases by Primary SOC and PT

Run by: JOSLYN SWANN Date - Time: 01/27/2009 - 12:56 pm

Search Criteria:

- Product Name(s): BROMOCRIPTINE (A)
- BROMOCRIPTINE (V)
- BROMOCRIPTINE MESYLATE (A)
- PARLODEL (T)
- PARLODEL (V)

Manufacturer Type: Sender of ISR

Search Type: CASE

Search for reactions listed: ANY

FDA Revd. Date: From:

Reporter Domestic:

Reporter First Name:

Null Values for Country:

Female:

Age Range: From:

MedWatch Source Study:

MedWatch Source Health Professional:

Expedited (15-Day) ISR:

RA Summary ISR:

Include Deactivated ISRs:

Non-Serious Outcome:

Event End Date:

OTC Products Only:

Include Concomitant Products:

ISR/Case #: FDA Revd. Date: To: 01/26/2009
 Reporter Foreign: Reporter City:
 Patient ID: Gender Unknown:
 Age Range: To: MedWatch Source Literature:
 Direct ISR: 10 Day ISR:
 Initial: Processed ISRs/Cases Only: YES
 ISRs with No Outcome Reported:
 DeC:

Include Combination Products:

Mfr. Control #: Sort in Descending Order:
 Reporter Last Name: Reporter State:
 Male: Null Gender Values:
 Age Range: YEAR: MedWatch Source Consumer:
 Periodic ISR: 5 Day ISR:
 Follow-up: Serious Outcome:
 Event Start Date: ReC:

Non-Excluded Product(s) for Selected Active Ingredient(s):

BROMOCRIPTINE MESYLATE (T)	PARLODEL (T)	BROMOCRIPTINE (BROMOCRIPTINE,) (V)
BROMERGON (V)	BROMERGON (NGX) (V)	BROMERGON (NGX)(BROMOCRIPTINE)
BROMO CRIPTIN (V)	BROMO CRYPTINE 2.5MG CAREMARK/LEX PHARMA (V)	TABLET (V)
BROMOCRIPTIN (V)	BROMOCRIPTIN (PRAVIDEL) (V)	BROMO CRYPTINE 2.5MG CAREMARK/LEX PHARMA (V)
		BROMOCRIPTINA DOROM (BROMOCRIPTINE MESILATE, BROMOCRIPTINE MESILATE,



SOC	FT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Blood And Lymphatic System Disorders	Anemia	27	25	3	16	5	3	0	7
	Anemia Hemolytic Autoimmune	1	1	0	0	0	0	0	0
	Anemia Megaloblastic	1	0	0	0	0	0	0	0
	Aplastic Anemia	2	1	0	1	1	0	0	0
	Blood Disorder	1	1	0	0	0	1	0	0
	Bone Marrow Failure	1	0	0	0	0	0	0	0
	Congulopathy	6	6	1	4	2	1	0	0
	Disseminated Intravascular Coagulation	7	7	1	6	1	1	0	1
	Eosinophilia	3	3	2	2	0	0	0	1
	Hemolysis	2	0	0	0	0	0	0	0
	Hemolytic Anemia	4	1	0	1	0	0	0	0
	Hypocoagulation	1	1	0	1	1	1	0	0
	Hyperparaneoplastic anemia	2	2	0	1	0	0	0	1
	Idiopathic Thrombocytopenic Purpura	3	2	0	2	1	0	0	1
	Iron Deficiency Anemia	4	1	1	0	0	0	0	0
	Leukocytosis	6	4	1	3	0	0	0	3
	Leukopenia	13	7	2	4	1	0	0	2
	Lymphadenopathy	2	2	0	0	0	1	0	1
	Lymphopenia	1	1	0	1	1	0	0	0
	Microcytic Anemia	1	1	0	1	1	0	0	0
	Pancytopenia	6	3	1	2	2	0	0	1
	Polychromasia	1	1	0	1	0	1	0	0
	Polycythemia	1	1	0	1	0	0	0	0
	Splenic Infarction	1	1	0	1	1	0	0	0
	Splenoomegaly	2	1	0	1	0	0	0	0
	Thrombocytopenia	2	2	0	1	0	0	0	0



SOC	FT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Blood And Lymphatic System Disorders	Thrombocytopenia	16	11	4	6	3	1	0	3
	Thrombotic Thrombocytopenic Disorders	1	1	0	0	1	0	0	0
	Purpura	5	5	1	3	5	2	0	0
Cardiac Disorders	Acute Myocardial Infarction	15	11	1	4	2	4	0	3
	Angina Pectoris	4	4	1	3	1	0	0	0
	Aortic Valve Incompetence	2	2	0	1	0	0	0	0
	Aortic Valve Sclerosis	18	15	7	6	4	1	0	6
	Atrial Fibrillation	1	0	0	1	0	0	0	0
	Supraventricular Arrhythmias	1	1	0	1	1	1	0	0
	Atherosclerosis Coronary Artery	21	18	1	13	1	1	0	3
	Atrioventricular Block	3	1	0	1	0	0	0	0
	Atrioventricular Block Complete	1	1	0	1	0	0	0	0
	Atrioventricular Block First Degree	1	1	0	1	0	0	0	0
	Atrioventricular Block Second Degree	36	23	2	18	2	1	0	4
	Bradycardia	1	1	0	1	1	0	0	0
	Brugada Syndrome	1	1	0	1	1	0	0	0
	Bundle Branch Block Left	1	1	0	1	0	0	0	0
	Bundle Branch Block Right	1	1	0	1	0	0	0	0
Cardiac Arrest	29	28	16	19	9	6	1	11	
Cardiac Discomfort	1	1	0	1	0	0	0	0	
Cardiac Disorder	4	4	1	1	0	0	0	1	
Cardiac Failure	22	22	10	12	2	1	0	7	

Search Criteria Name: SWANN Search submitted on: 01-27-2009 12:41:11
 Product/Group Name: BROMOCriptine_ALL-US-01-09
 Reaction/Group Name:

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Note: Each case may have multiple FTs

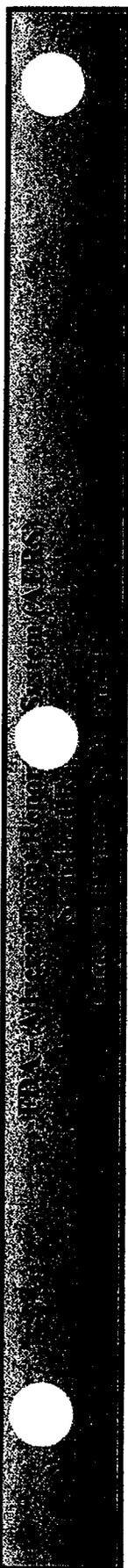
DAVIDSON'S PHARMACEUTICALS

SOC	FT	Total CaseCount	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Cardiac Disorders	Cardiac Failure Congestive	11	10	5	6	2	2	0	1
	Cardiac Flutter	1	1	0	0	0	0	0	0
	Cardiac Hypertrophy	1	1	0	1	1	0	0	0
	Cardiac Tamponade	1	1	1	0	0	0	0	0
	Cardiac Valve Disease	2	2	1	1	0	0	0	0
	Cardio-Respiratory Arrest	3	3	3	2	1	0	0	0
	Cardiomegaly	11	11	2	9	3	1	0	1
	Cardiomyopathy	20	20	10	10	1	6	0	4
	Cardiovascular Disorder	10	8	1	4	0	4	0	3
	Congestive Cardiomyopathy	4	4	0	3	2	0	0	0
	Cor Pulmonale	1	1	1	0	0	0	0	0
	Coronary Artery Disease	3	3	1	1	0	0	0	2
	Coronary Artery Occlusion	6	6	2	4	1	2	0	1
	Coronary Artery Stenosis	1	1	0	0	0	0	0	0
	Cyanosis	10	8	1	5	2	0	0	2
	Diabetic Dysfunction	1	1	0	0	1	0	0	0
	Dilatation Atrial	3	3	1	3	0	0	0	0
	Dilatation Ventricular	1	1	0	0	1	0	0	0
	Extrasystoles	2	2	0	2	0	2	0	0
	Heart Valve Incompetence	1	1	0	0	0	0	0	0
	Heart Valve Stenosis	1	1	0	0	0	0	0	0
	Hepatjugular Reflex	1	1	0	1	1	0	0	0
	Hypertrophic Cardiomyopathy	1	1	1	1	0	0	0	0

Search Criteria Name: SWANNJ Search submitted on: 01-27-2009 12:41:11
 Product/Group Name: INDOMOMETHELINE_ALL-IS-01-09
 Reaction/Group Name:
 Search Case Count: 2589

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Note: Each case may have multiple FTs.



SOC	FT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Cardiac Disorders	Ischemic: Thrombus	1	1	0	1	1	0	0	0
	Left Ventricular Dysfunction	2	2	0	1	0	0	0	0
	Left Ventricular Failure	3	3	0	1	1	2	0	2
	Mitral Valve Disease	2	2	0	0	0	0	0	0
	Mitral Valve Incompetence	4	4	1	2	0	0	0	0
	Mitral Valve Prolapse	2	2	0	2	1	1	0	0
	Mitral Valve Sclerosis	1	1	0	1	0	0	0	0
	Mitral Valve Stenosis	1	1	0	1	0	0	0	0
	Myocardial Infarction	64	58	20	30	10	13	0	11
	Myocardial Ischemia	1	1	0	1	0	0	0	0
	Myocarditis	1	1	1	1	0	0	0	1
	Normal Rhythm	1	1	0	1	0	0	0	0
	Palpitations	19	15	2	9	1	1	0	3
	Pericardial Calcification	1	1	0	1	0	0	0	0
	Pericardial Disease	2	2	0	2	0	0	0	2
	Pericardial Effusion	12	11	2	8	3	1	0	2
	Pericarditis	24	24	2	18	0	0	0	9
	Pericarditis Constrictive	6	6	1	4	1	0	0	1
	Pleuropericarditis	2	2	0	2	1	0	0	0
	Pulmonary Valve Incompetence	1	1	1	1	0	0	0	0
	Right Ventricular Failure	4	4	0	4	1	0	0	1
	Stasis Arrhythmia	5	5	0	5	1	1	0	0
	Stasis Bradycardia	8	7	0	6	1	2	0	0
	Stasis Tachycardia	2	2	0	2	1	1	0	0

Search Criteria Name: SWANNI Search submitted on: 01-27-2009 12:41:11
 Product/Group Name: BROMOCRIPTINE_ALL-JS-01-09
 Research/Group Name:
 Search Case Count: 2589
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 Note: Each case may have multiple FT

SOC	FT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Cardiac Disorders	Supraventricular Extrasystoles	2	2	0	2	1	1	0	0
	Supraventricular Tachycardia	4	4	0	3	0	0	0	2
	Tachycardia	31	20	0	15	2	3	0	6
	Tachycardia Paroxysmal	1	1	0	0	0	0	0	0
	Tricuspid Valve Disease	1	1	0	1	0	0	0	0
	Tricuspid Valve Incompetence	3	3	0	3	0	0	0	0
	Ventricular Arrhythmia	1	1	1	0	0	0	0	0
	Ventricular Dysfunction	2	2	0	2	2	2	0	0
	Ventricular Extrasystoles	3	1	0	1	0	0	0	0
	Ventricular Fibrillation	12	12	3	8	5	6	1	3
	Ventricular Hypertrophy	1	1	0	1	0	0	0	0
	Ventricular Hypokinetic Defect Acquired	4	4	1	3	1	0	0	0
	Ventricular Tachycardia	2	0	0	0	0	0	0	0
	Ventricular Tachycardia	11	11	1	11	2	2	0	3
	Anal Atresia	3	3	0	0	0	0	0	0
	Anomophaly	1	1	0	0	0	0	0	0
	Arteriovenous Malformation	1	1	0	1	0	1	0	0
	Cleft Lip	1	0	0	0	0	0	0	0
	Cleft Palate	1	0	0	0	0	0	0	0
	Colour Blindness	1	1	0	1	0	0	0	0
Congenital Anomaly	41	14	2	3	0	3	7	0	
Congenital Bladder Anomaly	1	1	0	0	0	0	1	0	

Search Criteria Name: SWANNJ Search submitted on: 01-27-2009 12:41:11
Product/Group Name: BROMOCRIPTINE_ALL-IS-01-09
Revised/Group Name:
Search Case Count: 2519

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Note: Each case may have multiple FTs.

SOC	FT	Total Cases/ret	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Congenital, Familial And Genetic Disorders		1	0	0	0	0	0	0	0
	Congenital Central Nervous System Anomaly	1	1	0	0	0	0	1	0
	Congenital Diaphragmatic Hernia	1	1	0	0	0	0	0	0
	Congenital Hand Malformation	1	1	0	0	0	0	0	0
	Congenital Hypothyroidism	1	1	0	0	0	0	0	0
	Congenital Ureteric Anomaly	1	1	0	0	0	0	1	0
	Congenital Vitreous Anomaly	1	1	0	0	0	0	1	0
	Cytogenetic Abnormality	1	0	0	0	0	0	0	0
	Exencephalus	2	2	0	0	0	0	2	0
	Factor V Leiden Mutation	1	1	0	1	0	0	0	0
	Fallopian Tube Torsion	1	0	0	0	0	0	0	0
	Galactosemia	1	1	0	0	0	0	0	0
	Heart Disease Congenital	2	2	2	0	0	0	0	0
	Kidney Malformation	1	1	0	0	0	0	1	0
	Limb Reduction Defect	1	0	0	0	0	0	0	0
	Multiple Congenital Abnormalities	1	1	0	0	0	0	1	0
	Osteopetrosis	1	1	0	1	0	0	0	0
	Pseudohermaphroditism	1	1	0	0	0	0	1	0
	Pulmonary Hypoplasia	1	1	0	0	0	0	1	0
	Pulmonary Valve Stenosis Congenital	1	1	0	0	0	0	1	0
	Renal Agenesis	2	2	0	0	0	0	2	0
	Spina Bifida Occulta	2	2	0	0	0	0	2	0

Search Criteria Name: SWANNU Search submitted on: 01-27-2009 12:41:11

Product/Group Name: BROMOCRIPTINE_ALL-JS-01-09

Research/Group Name:

Search Case Count: 258

Note: Each Case may have multiple FTs

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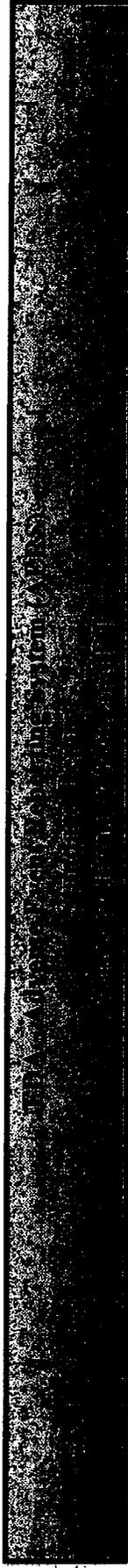
SOC	FT	Total Case/Event	Series	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Congenital, Familial And Genetic Disorders	Transposition Of The Great Vessels	1	1	1	0	0	0	0	0
	Tuberous Sclerosis	2	2	1	0	0	0	0	0
	Umbilical Artery Hypoplasia	1	1	0	0	0	0	1	0
	Vascular Anomaly	1	1	1	1	0	0	0	0
	Ventricular Septal Defect	1	1	0	0	0	0	1	0
	Deafness	3	1	0	1	0	1	0	0
	Ear Pain	1	1	0	1	0	1	0	0
	Hypacusis	1	0	0	0	0	0	0	0
	Otosclerosis	1	1	0	0	0	0	0	0
	Tinnitus	1	6	0	2	0	1	0	0
Ear And Labyrinth Disorders	Vertigo	1	7	0	1	1	0	0	0
	Acromegaly	2	1	0	0	0	0	0	1
	Adrenocortical Insufficiency Acute	1	1	0	1	0	0	0	0
	Adenoma	2	2	0	0	0	0	0	0
	Thyroiditis	4	4	1	3	1	0	0	1
	Diabetes Insipidus	9	9	0	2	0	0	0	0
	Empty Sella Syndrome	1	0	0	0	0	0	0	0
	Endocrine Disorder	1	1	0	1	0	1	0	0
	Goitre	5	5	0	1	0	0	0	0
	Hypoparathyroidism	2	2	0	1	0	1	0	0
Endocrine Disorders	Hypoparathyroidism	4	3	0	3	1	0	0	0
	Hypoparathyroidism	1	1	1	0	0	0	0	0
	Hypothyroidism	6	5	0	3	0	0	0	0
	Hyperthyroidism	9	6	0	5	0	0	0	1
	Inappropriate Antidiuretic Hormone Secretion	1	0	0	0	0	0	0	0
	Parathyroid Disorder	6	6	0	4	2	0	0	0
	Pituitary	1	1	0	0	0	0	0	0
	Necrotic	1	1	0	0	0	0	0	0

SOC	PT	Total Case/Event	Serious	Death	Hospitalized	Life-Threatening	Disabled	Congenital Anomaly	Required Intervention
Endocrine Disorders	Pituitary Infarction	1	1	0	1	0	0	0	0
	Secondary Hypothyroidism	1	1	0	1	0	0	0	0
	Thyroid Disorder	1	1	0	1	0	1	0	0
	Thyroiditis Subacute	1	1	0	0	0	0	0	0
	Adrenal Pheochromocytoma	1	1	0	1	1	0	0	0
	Amblyopia	19	3	0	3	0	0	0	0
	Blapharospasm	1	1	0	0	0	0	0	0
	Blindness	21	16	1	12	1	5	0	2
	Blindness Transient	4	4	0	3	1	0	0	0
	Blindness Unilateral	1	1	0	1	1	0	0	0
Eye Disorders	Cataract	3	2	0	1	0	0	0	0
	Conjunctival Hyperemia	1	1	0	1	1	0	0	0
	Corneal Opacity	1	0	0	0	0	0	0	0
	Diplopia	9	6	0	1	2	1	0	0
	Eye Disorder	5	1	0	0	0	0	0	0
	Eye Irritation	2	2	0	0	0	0	0	0
	Eye Movement Disorder	3	3	0	2	1	1	0	1
	Eye Pain	3	3	0	1	0	1	0	0
	Eye Rolling	2	2	0	1	0	0	0	0
	Eye Swelling	2	2	0	0	0	0	0	0
	Eyelid Disorder	1	1	0	1	0	0	0	0
	Eyelid Ptosis	3	2	0	1	0	1	0	0
	Gaze Palsy	1	1	0	1	0	0	0	0
	Glaucoma	3	0	0	0	0	0	0	0
	Keratitis	1	0	0	0	0	0	0	0
	Keratoconjunctivitis Sicca	3	2	0	0	0	0	0	0
	Lacrimal Disorder	3	1	0	1	0	0	0	0
	Miosis	2	2	1	2	0	0	0	0
	Mydriasis	1	0	0	0	0	0	0	0

Search Criteria Name: SWANNJ Search submitted on: 01-27-2009 12:41:11
Product/Group Name: BROMOCRIPTINE_ALL-JS-01-09
Research/Group Name:
Search Case Count: 2189

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Note: Each case may have multiple PTs.



SOC	PT	Total Case/Event	Serious	Death	Hospitalized	Life-Threatening	Disabled	Congenital Anomaly	Required Intervention
Eye Disorders	Myopia	1	1	0	0	1	0	0	0
	Ocular Itch	1	1	0	0	1	0	0	0
	Ocular Pruritus	1	1	0	0	0	0	0	0
	Ocular Stinging	1	0	0	0	0	0	0	0
	Optic Nerve Disorder	3	3	0	1	0	0	0	0
	Papilloedema	2	2	0	1	0	0	0	1
	Photophobia	6	3	0	2	0	0	0	1
	Photopsia	1	1	0	0	1	0	0	0
	Pupil Fixed	1	1	1	0	0	0	0	0
	Pupillary Reflex Impaired	2	2	0	2	0	0	0	1
	Pupils Unequal	1	0	0	0	0	0	0	0
	Retinal Anisocoria	1	1	0	0	0	0	0	0
	Retinal Detachment	3	1	0	1	0	0	0	1
	Retinal Disorder	2	2	0	1	0	0	0	1
	Retinal Haemorrhage	2	0	0	0	0	1	1	1
	Retinal Oedema	3	3	0	1	0	1	1	1
	Retinal Vascular Disorder	1	1	0	1	0	0	0	0
	Retinal Vein Thrombosis	1	0	0	0	0	0	0	0
	Scotoma	2	2	0	2	0	0	0	0
	Vision Blurred	13	12	0	6	1	3	0	1
Visual Acuity Reduced	6	6	0	5	0	1	0	1	
Visual Impairment	54	27	1	18	3	9	0	8	
Gastrointestinal Disorders	Abdominal Discomfort	1	1	0	0	0	0	0	0
	Abdominal Distention	9	8	1	6	2	0	1	0
	Abdominal Pain	29	21	2	13	3	0	0	2
	Abdominal Pain Lower	1	1	0	1	1	0	0	0

Search Criteria Name: SWANNJ Search submitted on: 01-27-2009 12:41:11
 Product/Group Name: BRONCHOPNEUMONIA ALL-91-09
 Reason/Group Name:
 Search Case Count: 2589

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Note: Each case may have multiple PTs.

SOC	FT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Gastrointestinal Disorders	Abdominal Pain Upper	10	10	1	5	3	0	0	1
	Abdominal Rigidity	1	1	0	1	0	0	0	0
	Abdominal Tenderness	2	2	0	2	1	0	0	0
	Anorectal Disorder	1	1	0	1	1	0	0	0
	Acidosis	14	13	1	13	0	0	0	6
	Cardiomegaly	1	0	0	0	0	0	0	0
	Constipation	21	12	0	8	0	0	0	1
	Dental Caries	2	0	0	0	0	0	0	0
	Diarrhoea	20	13	2	9	3	0	0	1
	Diarrhoea Haemorrhagic	1	0	0	0	0	0	0	0
	Diverticulosis	1	1	0	0	0	0	0	0
	Dry Mouth	6	3	0	2	1	0	0	0
	Duodenal Ulcer	2	2	1	1	0	0	0	0
	Dyspepsia	9	0	0	0	0	0	0	0
	Dysphagia	16	13	4	12	1	2	0	3
	Enteritis	1	1	0	1	0	0	0	0
	Enterocolitis	1	1	0	1	0	0	0	0
	Eruetation	1	0	0	0	0	0	0	0
	Faecal Incontinence	3	3	0	2	0	1	0	0
	Faeces Discoloured	1	1	0	1	0	0	0	1
	Flatulence	6	1	0	1	1	0	0	0
	Gastric Dilatation	1	1	1	1	0	0	0	0
	Gastric Disorder	1	1	0	0	1	0	0	1
	Gastric Ulcer	3	1	0	0	1	0	0	0
	Gastric Ulcer Haemorrhage	2	2	0	1	1	1	0	1
	Gastric Ulcer Perforation	1	0	0	0	0	0	0	0
	Gastritis	5	4	0	1	0	0	0	0
	Gastritis Erosive	2	2	0	1	1	0	0	1

Search Criteria Name: SWANU Search submitted on: 01-27-2009 12:41:11

Product/Group Name: BROMOCRIPTINE_ALL-JS-01-09

Search Case Count: 2389

Search Case Count: 2389 Note: Each case may have multiple FT.

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SOC	FT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Gastrointestinal Disorders		11	6	3	2	0	0	0	0
	Gastrointestinal Disorder								
	Gastrointestinal Hemorrhage	10	4	1	2	0	0	0	1
	Gastrointestinal Necrosis	2	2	0	2	0	0	0	0
	Gastrointestinal Odema	2	2	0	2	0	0	0	0
	Gingival Bleeding	2	1	0	0	0	0	0	0
	Gingival Hypertrophy	1	0	0	0	0	0	0	0
	Gingivitis	1	0	0	0	0	0	0	0
	Glossitis	1	0	0	0	0	0	0	0
	Haematemesis	7	7	2	4	1	0	0	4
	Haematochezia	1	1	0	1	0	0	0	0
	Haemorrhoids	1	1	0	1	0	0	0	0
	Hibbs Hernia	2	2	0	1	1	0	0	1
	Intus Parasitic	5	5	0	5	0	0	0	1
	Intestinal Infarction	2	2	0	2	0	0	0	0
	Intestinal Ischemia	1	1	0	1	1	0	0	0
	Intestinal Obstruction	1	1	0	1	0	0	0	1
	Melena	2	2	0	1	1	0	0	1
	Mesenteric Occlusion	1	1	0	1	0	0	0	1
	Nausea	153	70	3	33	9	5	0	7
	Oesophageal Disorder	1	1	0	1	0	0	0	0
	Oesophageal Hemorrhage	1	0	0	0	0	0	0	0
	Oesophagitis	2	2	1	0	1	0	0	1
	Oral Dyscomfort	1	1	0	0	1	0	0	0
	Pancreatitis	3	2	0	2	0	0	0	0
	Pancreatitis Acute	1	1	0	0	0	0	0	0
	Parosubstia Oral	1	1	0	0	0	0	0	0

Search Criteria Name: SWANNU Search submitted on: 01-27-2009 12:41:11
 Product/Group Name: BROMOCRIFRINE_ALL-JS-01-09
 Recipient/Group Name:
 Search Case Count: 2589
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Note: Each case may have multiple FTs.



SOC	PT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Completed Assembly	Required Intervention
General Disorders And Administration Site Conditions	Condition Aggravated	54	39	8	28	3	2	0	9
	Cyst	4	3	1	3	0	0	0	0
	Death	17	17	17	0	0	0	0	0
	Developmental Delay	1	1	0	0	0	0	0	0
	Discomfort	1	1	0	0	0	0	0	0
	Disease Progression	4	4	1	2	0	0	0	0
	Disease Recurrence	3	3	0	2	0	0	0	0
	Drug Effect Decreased	9	9	1	1	0	0	0	0
	Drug Effect Increased	1	0	0	0	0	0	0	0
	Drug Ineffective	52	19	0	14	2	2	0	2
	Drug Interaction	47	34	0	21	0	2	0	4
	Drug Intolerance	3	3	0	1	0	0	0	0
	Drug Resistance	1	1	0	0	0	0	0	0
	Drug Tolerance Increased	2	1	0	1	0	0	0	0
	Drug Withdrawal Syndrome	20	11	1	7	1	0	0	4
	Effusion	1	1	1	1	0	0	0	0
	Face Oedema	8	0	0	0	0	0	0	1
	Fatigue	29	29	0	11	0	2	0	2
	Feeling Abnormal	10	10	0	4	2	0	0	0
	Feeling Cold	3	3	1	0	0	0	0	0
	Feeling Hot	3	3	0	0	0	0	0	0
	Feeling Itchy	1	1	0	0	0	0	0	0
	Feeling Of Body Temperature Change	1	1	0	0	0	1	0	0
	Fibrosis	3	3	0	1	0	0	0	0
	Foaming At Mouth	1	1	0	1	0	0	0	0
	Food Intolerance	2	2	0	2	0	0	0	0
	Gait Disturbance	23	20	4	11	3	1	0	2

Search Criteria Name: SWANNU Search submitted on: 01-27-2009 12:41:11
 Product/Group Name: BROMOCRIPTINE_ALL-IS-01-09
 Reaction/Group Name:
 Search Case Count: 2599

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Note: Each case may have multiple PTs.

SOC	FT	Total Cases/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
General Disorders And Administration Site Conditions		7	7	0	4	1	0	0	0
General Physical Health Determination		3	3	0	2	0	0	0	0
Generalized Oedema		4	3	0	0	0	0	0	0
Hernia		1	1	0	1	0	0	0	0
Hypertension		1	1	0	0	0	0	0	0
Hypertrophy		6	5	1	4	0	0	0	2
Hypothermia		1	1	0	0	0	0	0	0
Impaired Healing		1	1	0	0	0	0	0	0
Implant Site Reaction		1	1	0	0	0	0	0	0
Inflammation		10	10	0	9	0	0	0	2
Influenza Like Illness		7	3	0	3	0	1	0	1
Irritability		4	4	1	1	0	0	0	0
Lipogranuloma		1	1	0	0	0	0	0	0
Melasma		43	35	5	18	2	1	0	3
Mass		1	1	0	1	0	0	0	0
Mechanical Complication Of Implant		1	1	0	0	0	0	0	0
Microblepharia		1	1	0	0	0	0	0	0
Mucosal Discoloration		1	1	0	0	1	0	0	0
Multi-Organ Failure		2	2	2	2	0	0	0	1
Necrosis		1	1	0	1	1	0	0	0
No Therapeutic Response		1	1	0	0	0	0	0	0
Non-specific Reaction		1	1	0	1	0	0	0	0
Oedema		20	8	1	8	0	0	0	3
Oedema Peripheral		54	25	2	22	3	2	0	6
Pain		28	14	0	9	0	4	0	3
Peripheral Coldness		4	4	0	1	1	0	0	0
Pitting Oedema		1	1	0	1	0	0	0	0

Search Criteria Name: SWANNU Search submitted on: 01-27-2009 12:41:11
Product/Group Name: BROMOCRIPTINE_ALL-IS-01-09
Reactions/Group Name:
Search Count Count: 2588

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Note: Reactions may have multiple FTs



SOC	FT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention	
General Disorders And Administrative Site Conditions	Polycystic	2	2	0	2	0	0	0	0	
	Pyrexia	88	78	13	60	13	4	0	23	
	Sense Of Oppression	1	1	0	1	0	0	0	0	
	Sudden Cardiac Death	1	1	0	1	1	1	0	0	
	Sudden Death	1	1	1	0	0	0	0	0	
	Swelling	3	3	0	1	0	0	0	0	
	Systemic Inflammatory Response Syndrome	1	1	0	1	1	0	0	0	
	Therapeutic Response Decreased	1	1	0	0	0	0	0	0	
	Therapeutic Response	1	1	1	0	0	0	0	1	
	Unexpected	1	0	0	0	0	0	0	0	
	Thirst	1	0	0	0	0	0	0	0	
	Unreliable Event	7	3	0	3	1	3	0	0	
	Hepatobiliary Disorders	Cholangitis	1	1	0	1	0	0	0	0
		Cholecystitis	1	1	0	0	0	0	0	0
		Cholelithiasis	3	3	0	2	0	0	0	0
		Cholestasis	2	2	0	1	0	0	0	0
		Chronic Hepatitis	1	1	0	1	0	0	0	0
		Cytolytic Hepatitis	3	3	2	2	1	0	0	0
		Gallbladder Disorder	1	1	0	0	1	0	0	0
		Hepatic Cirrhosis	3	1	0	1	0	0	0	0
Hepatic Cyst		1	1	0	1	0	0	0	0	
Hepatic Failure		4	4	2	2	1	0	0	0	
Hepatic Function Abnormal		23	7	2	5	0	1	0	1	
Hepatic Pain		2	2	0	1	1	0	0	0	
Hepatic Steatosis		2	1	1	0	0	0	0	1	
Hepatitis		7	5	1	5	1	1	0	2	
Hepatitis Fulminant		1	1	0	0	1	0	0	0	
Hepatocellular Injury	3	3	1	1	0	0	0	0		

Search Criteria Name: SWANNJ Search submitted on: 01-27-2009 12:41:11
 Product/Group Name: ENCOMOCRIPTINE_ALL-JS-01-09
 Reaction/Group Name:
 Search Case Count: 2509

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Note: Each case may have multiple FTs.



SGC	FT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Hematological Disorders	Hematemesis	7	4	0	4	0	0	0	2
	Hypertibrinemia	3	3	1	3	1	0	0	1
	Icteric	6	3	0	1	1	1	0	0
	Icteric Cholestatic	3	2	0	2	0	0	0	0
	Liver Disorder	5	5	1	4	0	1	0	1
Immune System Disorders	Anaphylactic Shock	1	0	0	0	0	0	0	0
	Anaphylactoid Reaction	4	2	0	0	1	0	0	1
	Drug Hypersensitivity	2	2	0	0	1	0	0	0
	Hypersensitivity	15	6	0	5	0	0	0	2
	Serum Sickness	1	1	0	0	0	0	0	0
Infectious And Infections	Abscess	1	1	0	1	0	0	0	0
	Acinetobacter Infection	1	1	1	1	0	0	0	0
	Acute Tenositis	1	1	0	0	0	0	0	0
	Breast Abscess	1	0	0	0	0	0	0	0
	Bronchitis	2	2	0	2	0	0	0	1
	Bronchopneumonia	4	4	3	2	0	1	0	1
	Chlamydial Infection	1	1	1	1	0	0	0	0
	Device Related Infection	1	1	0	1	0	1	0	0
	Diarrhea Infections	1	1	0	0	0	0	0	1
	Escherichia Infection	1	1	0	1	0	0	0	0
	Escherichia Urinary Tract Infection	1	1	0	1	0	0	0	0
	Gangrene	5	1	0	1	0	0	0	0
	Gastroenteritis	4	3	0	3	0	2	0	2
	Gastroenteritis Salmonella	1	1	0	1	0	0	0	0
	Gastrointestinal Tract Infection	1	1	0	0	1	0	0	0
Infection	2	2	2	2	1	0	0	0	
Influenza	1	1	0	0	0	0	0	0	

Search Criteria Name: SWANNJ Search submitted on: 01-27-2009 12:41:11
 Product/Group Name: BRGMOCLIFINE_ALL-FS-01-09
 Search Case Count: 2589

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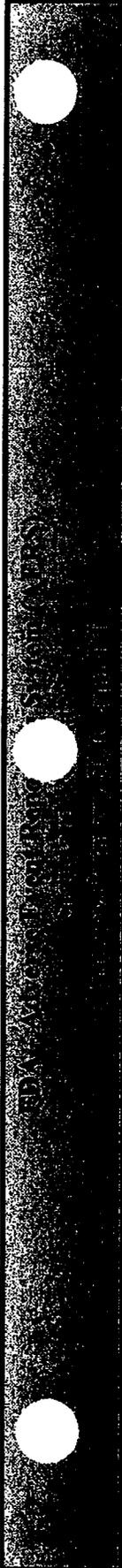
Note: Each case may have multiple FT's

SDC	FT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Interventions
Infectious And Infections									
	Labyrinthitis	1	1	0	0	0	0	0	0
	Mastitis	2	1	0	0	0	0	0	0
	Meningitis	8	8	4	6	1	0	0	4
	Meningitis Neonatal	1	1	0	1	0	0	0	0
	Nasopharyngitis	3	3	0	3	2	1	0	2
	Otitis Media	1	1	0	1	0	0	0	0
	Otitis Media	1	1	0	1	0	1	0	0
	Pharyngitis	1	1	0	1	0	1	0	0
	Pleural Infection	12	12	2	10	0	0	0	6
	Pneumonia	33	31	15	21	5	2	0	8
	Pneumonia Bacterial	1	1	0	1	0	0	0	1
	Pneumonia Viral	1	1	0	1	0	1	0	0
	Proctus Infection	1	1	0	1	0	0	0	1
	Purulent Discharge	1	1	0	1	0	0	0	0
	Pyelonephritis Chronic	1	1	0	1	0	0	0	1
	Rhinitis	47	7	1	5	0	0	0	2
	Salpingitis	1	0	0	0	0	0	0	0
	Septic	9	8	2	7	1	1	0	3
	Septic Shock	1	1	0	1	0	1	0	0
	Stomatitis	1	1	0	1	1	0	0	0
	Sinusitis	2	0	0	0	0	0	0	0
	Staphylococcal Infection	2	2	1	2	0	0	0	0
	Tenonitis Infection	1	1	1	1	0	0	0	0
	Upper Respiratory Tract Infection	2	2	0	2	1	1	0	2
	Urinary Tract Infection	6	6	0	4	1	1	0	1
	Urethritis	1	1	1	1	0	0	0	0
	Vaginal Infection	1	0	0	0	0	0	0	0
	Viral Infection	2	2	0	1	0	0	0	0
	Accident	8	6	0	6	2	1	0	1

Search Criteria Name: SWANNU Search submitted on: 01-27-2009 12:41:11
Product/Group Name: BRGMOCREPTINE_ALL-IS-01-09
Reaction/Group Name:
Search Caus Code: 3189

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Note: Each case may have multiple FTs.



SOC	FT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Injury, Poisoning And Procedural Complications									
	Accidental Drug Intake By Child	2	2	0	2	0	0	0	0
	Accidental Exposure	2	2	0	2	0	0	0	0
	Accidental Overdose	13	4	1	3	1	0	0	0
	Ankle Fracture	1	1	0	0	0	0	0	0
	Antitropeal Bite	1	1	0	1	0	0	0	0
	Arthritis	1	1	0	1	0	0	0	0
	Brain Hemorrhage	1	1	0	0	0	0	0	0
	Cutlidge Injury	1	1	0	0	0	0	0	0
	Concussion	1	1	0	0	1	0	0	0
	Ceasation	1	1	0	1	0	0	0	0
	Drug Exposure During Pregnancy	47	47	2	11	2	0	3	0
	Drug Exposure Via Breast Milk	3	3	0	1	0	0	0	0
	Drug Toxicity	3	3	1	3	1	0	0	0
	Face Injury	2	2	0	0	0	0	0	0
	Facial Bones Fracture	1	1	0	0	0	0	0	0
	Fall	27	27	3	16	4	4	0	3
	Fallopian Tube Perforation	1	1	0	1	0	0	0	0
	Flail Chest	1	1	1	1	0	0	0	0
	Head Injury	1	1	0	1	0	0	0	0
	Injury	5	4	0	3	0	2	0	0
	Intentional Overdose	6	6	1	5	0	0	0	0
	Joint Sprain	1	1	0	1	0	1	0	0
	Laceration	1	0	0	0	0	0	0	0
	Limb Injury	1	1	0	1	0	0	0	0
	Maternal Drugs Affecting Fetus	28	28	1	9	6	2	9	0
	Medication Error	15	10	0	5	1	0	0	0
	Meningeal Lesion	1	1	0	0	0	0	0	0

Search Criteria Name: SWANNU Search submitted on: 01-27-2009 12:41:11
Product/Group Name: BROMOCRIPTINE_ALL-IS-01-09
Reaction/Group Name:
Search Case Count: 2599
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Note: Each case may have multiple FTs



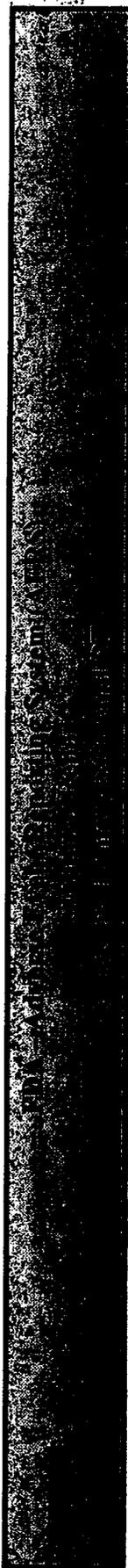
SOC	FT	Total Case/Event	Series	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Injury, Poisoning And Fracture Complications	Multiple Drug Overdose Intentional	1	1	1	0	0	0	0	0
	Multiple Injuries	3	3	0	3	0	1	0	0
	Operative Hemorrhage	1	1	0	0	0	0	0	0
	Optic Nerve Injury	2	2	0	0	0	0	0	0
	Overdose	11	10	1	6	0	0	0	2
	Poor Quality Drug Administered	1	0	0	0	0	0	0	0
	Foot Lumber Fracture Syndrome	1	1	0	1	0	0	0	0
	Procedural Complication	1	1	1	0	0	0	0	0
	Road Traffic Accident	6	6	2	1	1	1	0	0
	Scratch	1	1	0	1	0	0	0	0
	Skateboard Injury	1	1	0	0	0	0	0	0
	Spinal Cord Injury Thoracic	1	1	0	1	1	0	0	0
	Spinal Fracture	1	1	0	0	0	0	0	0
	Subdural Hematomas	1	0	0	0	0	0	0	0
	Subdural Hemorrhage	1	1	1	0	0	0	0	0
	Thermal Burn	1	1	0	1	0	0	0	0
	Tooth Injury	3	3	0	0	0	0	0	0
Investigations	Alanine Aminotransferase Increased	17	13	2	6	3	1	0	1
	Angiogram Central Abnormal	2	2	0	2	0	0	0	0
	Anti-Thyroid Antibody	1	1	0	0	0	0	0	0
	Antinuclear Antibody Positive	3	1	0	1	0	0	0	1
	Antiphospholipid Antibodies Positive	1	1	0	1	1	0	0	0

SOC	FT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Investigations	Agar Score Low	3	3	1	1	0	0	0	0
	Aspartate Aminotransferase Increased	20	15	2	9	4	1	0	1
	Biopsy	1	1	0	0	0	0	0	0
	Biopsy Kidney Abnormal	1	1	0	0	0	0	0	0
	Biopsy Lung Abnormal	1	1	0	1	0	0	0	0
	Biopsy Skin Abnormal	1	1	0	1	0	0	0	0
	Biopsy Stomach Abnormal	1	1	0	0	0	0	0	0
	Blood Albumin Decreased	2	2	0	1	0	0	0	1
	Blood Alkaline Phosphatase Decreased	1	1	1	0	0	0	0	0
	Blood Alkaline Phosphatase Increased	9	7	0	5	1	0	0	1
	Blood Amylase Increased	1	0	0	0	0	0	0	0
	Blood Bilirubin Increased	3	3	0	0	0	1	0	0
	Blood Calcium Decreased	2	2	0	2	0	0	0	1
	Blood Cholesterol Increased	2	2	0	2	0	0	0	0
	Blood Cholinesterase Increased	1	1	1	1	0	0	0	1
	Blood Creatine	1	1	0	1	1	1	0	1
	Blood Creatine Increased	3	3	1	3	1	1	0	3
	Blood Creatine Phosphokinase Increased	43	38	1	30	6	3	0	11
	Blood Creatine Phosphokinase Mb	1	1	0	1	0	0	0	0

Search Criteria Name: SWANNU Search submitted on: 01-27-2009 12:41:11
Product/Group Name: BROMOCRIPTINE_ALL-JS-01-09
Reaction/Group Name:
Search Case Count: 2189

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Note: Each case may have multiple FT.



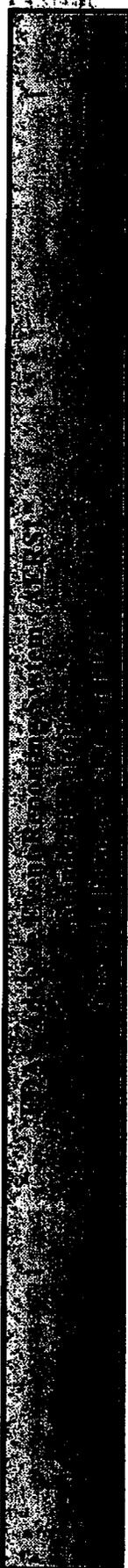
SOC	FT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Investigations									
	Blood Creatinine Increased	12	8	1	6	3	1	0	4
	Blood Fibrinogen Increased	2	2	0	2	1	0	0	0
	Blood Folic Acid Stimulating Hormone Increased	1	1	0	0	0	0	0	0
	Blood Glucose	1	1	0	1	1	1	0	0
	Blood Glucose Decreased	1	1	0	0	0	0	0	0
	Blood Glucose Increased	2	2	0	0	1	0	0	0
	Blood Growth Hormone Decreased	1	1	0	1	1	0	0	0
	Blood Growth Hormone Increased	1	1	0	0	0	0	0	0
	Blood Human Chorionic Gonadotropin Decreased	1	1	0	1	1	0	0	0
	Blood Lactate Dehydrogenase Increased	10	9	0	7	3	0	0	0
	Blood Luteinizing Hormone Decreased	1	1	0	0	0	0	0	0
	Blood Potassium Increased	1	1	0	0	0	0	0	0
	Blood Pressure	1	1	0	1	1	1	0	0
	Blood Pressure Excreted	15	15	0	5	4	0	0	2
	Blood Pressure Inmeasurable	1	1	0	0	1	0	0	0
	Blood Pressure Increased	12	12	1	7	1	2	0	0
	Blood Pressure Systolic Decreased	1	1	0	1	0	0	0	0
	Blood Pressure Systolic Increased	1	1	0	1	0	0	0	0
	Blood Protein Abnormal	1	1	0	0	0	0	0	0

SOC	FT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Investigations	Blood Prolactin Decreased	2	2	0	1	1	0	0	0
	Blood Prolactin Increased	36	28	1	11	1	0	0	2
	Blood Sodium Increased	1	1	0	1	0	0	0	0
	Blood Testosterone Increased	1	1	0	0	0	0	0	0
	Blood Thyroid Stimulating Hormone Decreased	2	2	0	1	1	0	0	0
	Blood Thyroid Stimulating Hormone Increased	2	2	0	1	0	0	0	0
	Blood Uric Acid Increased	3	3	0	2	1	0	0	1
	Blood Urea Increased	10	7	0	6	2	1	0	3
	Blood Viscosity Increased	1	1	0	1	1	0	0	0
	Body Temperature Decreased	1	1	0	0	0	0	0	0
	Body Temperature Increased	3	3	2	2	1	0	0	0
	Bone Scan Abnormal	1	1	0	1	0	0	0	0
	Brain Metabolic Peptide Increased	2	2	1	2	0	0	0	0
	Brain Scan Abnormal	2	2	0	2	0	0	0	1
	Brain Scan Normal	1	1	0	1	1	1	0	0
	C-Reactive Protein Decreased	1	1	0	1	1	0	0	0
	C-Reactive Protein Increased	14	14	2	12	1	1	0	6
	Cardiac Enzymes Increased	1	1	0	1	1	1	0	0

Search Criteria Name: SWANNI Search submitted on: 01-27-2009 12:41:11
Product/Group Name: BROMOCRIPTINE_ALL-IS-01-09
Reaction/Group Name:

Search Case Count: 2589

Note: Each case may have multiple FT



SOC	FT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Investigations	Cardiac Mermur	1	1	0	1	0	0	0	0
	Cardiac Stress Test Abnormal	1	1	0	1	1	1	0	0
	Central Venous Pressure Decreased	1	1	0	1	0	0	0	0
	Chest X-Ray Abnormal	3	3	1	3	0	0	0	1
	Coagulation Factor V Level Decreased	1	1	0	1	1	0	0	0
	Coomb's Direct Test Positive	1	0	0	0	0	0	0	0
	Corneal Reflex Decreased	1	1	1	0	0	0	0	0
	Creatinine Renal Clearance Decreased	4	4	0	3	0	0	0	0
	Caf Myelin Basic Protein Increased	1	1	0	1	1	0	0	0
	Caf Pressure Increased	1	1	0	1	0	0	0	1
	Caf Protein Increased	1	1	0	1	1	0	0	0
	Caf Test Abnormal	13	10	2	9	0	1	0	3
	Culture Urine Positive	1	1	0	1	0	0	0	1
	Cytomegalovirus Antibody Positive	1	1	1	1	1	0	0	0
	Drug Level Below Therapeutic	3	2	0	2	0	0	0	0
	Drug Screen Positive	1	1	0	1	0	0	0	0
	Echocardiogram Abnormal	3	3	1	2	0	0	0	0
	Ejection Fraction Abnormal	1	1	0	1	0	0	0	0
	Ejection Fraction Decreased	4	4	1	3	2	1	0	0
	Electrocardiogram Abnormal	13	12	0	11	2	1	1	2
	Electrocardiogram Peer R-Wave Progression	1	1	0	1	1	1	0	0

Search Criteria Name: SWANNJ Search submitted on: 01-27-2009 12:41:11
 Product/Group Name: BROMOCRIPTINE_ALL-JS-01-09
 Reaction/Group Name:
 Search Case Count: 2159

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Note: Each case may have multiple FTs.



SOC	PT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Investigations	Electrocardiogram Q Waves	1	1	0	1	1	1	0	0
	Electrocardiogram Q: Prolonged	2	2	1	1	0	0	0	0
	Electrocardiogram ST Segment Depressive	1	1	0	0	0	0	0	1
	Electrocardiogram ST Segment Elevation	4	4	0	4	2	1	0	1
	Electrocardiogram ST-T Change	2	2	1	1	0	0	0	0
	Electrocardiogram T Wave Abnormal	1	1	0	1	0	0	0	0
	Electrocardiogram T Wave Inversion	4	4	0	4	2	1	0	0
	Electroencephalogram Abnormal	15	15	1	14	0	5	0	3
	Fibrin D Dimer Increased	1	1	0	1	1	0	0	0
	Fetal Heart Rate Abnormal	3	3	0	2	1	0	0	0
	Gamma-Glutamyltransferase Increased	8	6	1	2	1	1	0	0
	General Physical Condition Abnormal	1	1	0	1	0	0	0	0
	Glasgow Coma Scale Abnormal	1	1	0	1	0	0	0	0
	Hematecrit Decreased	5	5	1	3	2	0	0	0
	Hemoglobin Abnormal	1	1	0	1	0	0	0	0
	Hemoglobin Decreased	11	11	4	10	5	0	0	2
	Heart Rate Increased	4	4	0	1	2	0	0	2
	Heart Rate Decreased	8	8	0	5	0	1	0	0
	Heart Sounds Abnormal	2	2	0	2	0	0	0	0

Search Criteria Name: SWANBU Search submitted on: 01-27-2009 12:41:11
 Product/Group Name: BROMOCRIPTINE_ALL-NS-01-09
 Section/Group Name:
 Search Case Count: 2589
 Date - Time: 01/27/2009 - 12:56 pm
 Run by: SWANBU
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Note: Each case may have multiple PT.

SOC	PT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Investigations	Hepatic Enzyme Increased	2	2	0	2	0	0	0	1
	High Density Lipoprotein Decreased	1	1	0	0	0	0	0	0
	Hormone Level Abnormal	6	0	0	0	0	0	0	0
	Immunoglobulins Abnormal	1	1	0	1	0	0	0	1
	International Normalized Ratio Increased	1	1	0	1	0	0	0	0
	Laboratory Test Abnormal	11	7	1	2	0	2	0	1
	Lipids Abnormal	1	1	0	1	0	0	0	1
	Liver Function Test Abnormal	6	6	0	6	1	1	0	2
	Lymphocyte Count Decreased	1	1	0	0	1	0	0	0
	Lymphocyte Count Increased	1	1	1	1	0	0	0	0
	Mammogram Abnormal	1	1	0	0	0	0	0	0
	Mean Cell Volume Abnormal	1	1	1	1	0	0	0	0
	Monocyte Count Decreased	1	1	1	1	0	0	0	0
	Myeloblast Count Increased	1	1	1	1	0	0	0	0
	Myelocyte Count Decreased	1	1	1	1	0	0	0	0
	Myoglobin Blood Increased	4	4	0	4	1	0	0	2
	Neurological Examination Abnormal	1	1	0	1	0	0	0	1
	Neurotransmitter Level Altered	1	1	0	0	0	0	0	0
	Neutrophil Count Decreased	1	1	0	1	0	0	0	0

Search Criteria Name: SWANNJ Search submitted on: 01-27-2009 12:41:11
Product/Group Name: BRONOCOPRIFENE_ALL-IS-01-09
Reaction/Group Name:
Search Case Count: 2589

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Note: Each case may have multiple PTs.



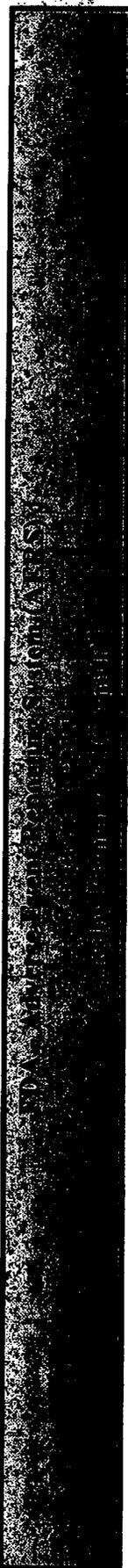
SOC	FT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Cognitive Anomaly	Required Intervention
Investigations	Nuclear Magnetic Resonance Imaging Abnormal	5	5	0	4	0	0	0	0
	Nuclear Magnetic Resonance Imaging Brain Abnormal	3	3	0	3	0	0	0	1
	Genital/Anal Increased	1	1	0	0	0	0	0	0
	Platelet Count Decreased	5	5	1	2	1	1	0	0
	Platelet Count Increased	1	1	0	1	0	0	0	0
	Po2 Decreased	2	2	1	2	0	0	0	1
	Prostatic Specific Antigen Increased	1	1	0	0	0	0	0	0
	Protein S Decreased	1	1	0	1	1	0	0	0
	Prothrombin Level Abnormal	1	1	0	1	1	0	0	0
	Prothrombin Level Decreased	1	0	0	0	0	0	0	0
	Prothrombin Time Prolonged	1	1	0	0	1	0	0	0
	Prothrombin Time Ratio Decreased	1	1	0	1	0	0	0	0
	Pulmonary Function Test Decreased	1	1	0	0	0	0	0	0
	Pulse Abnormal	1	1	1	1	1	0	0	0
	Red Blood Cell Count Decreased	3	3	1	2	1	0	0	0
	Red Blood Cell Sedimentation Rate Abnormal	1	1	0	1	0	0	0	1
	Red Blood Cell Sedimentation Rate Increased	18	16	3	13	0	0	0	4
	Respiratory Rate Increased	4	4	0	3	1	1	0	1
	Scan Abnormal	1	1	0	1	0	0	0	0

Search Criteria Name: SWANNU Search submitted on: 01-27-2009 12:41:11
 Product/Group Name: BROMOCRIPTINE_ALL-IS-01-09
 Reaction/Group Name:
 Search Case Count: 259

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Note: Each case may have multiple FT





SOC	FT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Interventions	
Investigations	Sugar Cervix Abnormal	1	1	0	0	0	0	0	0	
	Thyroid Function Test Abnormal	1	1	0	0	0	0	0	0	
	Thyroxine	1	1	0	0	0	0	0	0	
	Thyroxine Decreased	1	1	0	0	0	0	0	0	
	Thyroxine Free Increased	1	1	0	1	0	0	0	0	
	Thyroxine Increased	1	1	0	0	0	0	0	0	
	Tri-Iodothyronine Increased	2	2	0	1	0	0	0	0	
	Tropoin Increased	1	1	0	1	1	0	0	0	
	Ultrasound Antenatal Screen Abnormal	1	1	0	1	1	0	0	0	
	Ultrasound Scan Abnormal	1	1	0	1	1	0	0	0	
	Ultrasound Skull Abnormal	1	1	0	1	0	0	0	0	
	Urine Output Decreased	1	1	0	0	1	0	0	0	
	Weight Decreased	27	22	1	16	0	1	0	3	
	Weight Increased	17	16	0	3	0	0	0	1	
	White Blood Cell Count Decreased	1	1	1	1	0	0	0	0	
	White Blood Cell Count Increased	11	11	3	8	1	1	0	2	
	White Blood Cells Urine Positive	1	1	0	1	0	0	0	0	
	Metabolism And Nutrition Disorders	Acidosis	2	1	0	1	0	0	0	0
		Anorexia	12	10	4	8	2	0	0	0
		Cachexia	4	4	2	3	0	0	0	2
Decreased Appetite		2	2	0	0	0	0	0	0	
Dehydration		11	10	1	9	0	1	0	0	
Diabetes Mellitus		3	2	2	0	0	0	0	1	
Diabetes Mellitus Insidious Onset		1	1	0	1	0	0	0	1	

EPIDEMIOLOGICAL SURVEILLANCE SYSTEM (ERS)

SOC	FT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Metabolism And Nutrition Disorders	Electrolyte Imbalance	4	4	1	4	0	0	0	1
	Fluid Retention	1	1	0	0	0	1	0	0
	Hypercalcemia	2	0	0	0	0	0	0	0
	Hypercholesterolemia	6	5	2	2	0	0	0	1
	Hypoglycemia	7	5	1	3	0	1	0	1
	Hypertalemia	4	3	3	3	1	0	0	2
	Hypodipicemia	5	2	1	1	0	0	0	0
	Hypophagia	1	1	0	1	0	0	0	0
	Hypocalcemia	1	1	0	1	0	0	0	1
	Hypochloremia	1	1	0	1	0	0	0	0
	Hypoglycemia	9	6	1	4	0	1	0	2
	Hypoglycemia Neonatal	1	1	0	0	0	0	0	0
	Hypotalemia	15	12	3	10	1	2	0	4
	Hyponatremia	8	8	0	8	1	0	0	0
	Hypophagia	2	2	1	2	0	0	0	1
Musculoskeletal And Connective Tissue Disorders	Hypoproteinemia	1	1	1	0	0	0	0	0
	Increased Appetite	3	1	0	1	0	0	0	0
	Lactic Acidosis	1	1	1	0	0	0	0	0
	Malnutrition	2	2	0	2	0	0	0	1
	Obesity	1	0	0	0	0	0	0	0
	Polydipsia	2	2	0	0	2	0	0	0
	Tetany	2	2	0	2	0	1	0	0
	Arthralgia	16	7	0	3	0	1	0	1
	Arthritis	3	2	0	2	0	0	0	1
	Arthropathy	2	1	0	1	0	0	0	0
	Back Pain	11	8	2	8	2	1	0	2
	Bone Erosion	1	1	0	1	0	0	0	0
	Bone Pain	1	1	0	0	0	0	0	0
	Collagen Disorder	1	1	0	1	0	1	0	0

Search Criteria Name: SWANNJ Search submitted on: 01-27-2009 12:41:11

Product/Group Name: BROMOCRIPTINE_ALL-IS-01-09

Reaction/Group Name:

Search Case Count: 259

Note: Each case may have multiple FTs

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SOC	PT	Total Case/Event	Series	Death	Hospitalized	Life-Threatening	Disabled	Congenital Anomaly	Required Intervention
Musculoskeletal And Connective Tissue Disorders	Fibromyalgia	1	1	0	0	0	0	0	0
	Growth Retardation	1	1	0	0	0	0	0	0
	Intervertebral Disc Protrusion	1	1	1	1	1	0	0	0
	Joint Ankylosis	1	1	0	1	0	0	0	0
	Joint Stiffness	4	4	1	3	1	0	0	1
	Mobility Decreased	1	1	0	1	0	0	0	0
	Marploes	1	1	0	0	0	0	0	0
	Muscle Atrophy	4	2	0	2	0	0	0	0
	Muscle Contracture	1	1	0	1	1	1	0	0
	Muscle Rigidity	21	21	0	18	5	2	0	8
	Muscle Spasms	7	4	0	5	1	1	0	0
	Muscle Twitching	6	3	1	1	0	0	0	0
	Muscular Weakness	5	5	0	4	1	2	0	0
	Musculoskeletal Stiffness	7	7	1	3	0	2	0	0
	Myalgia	31	8	0	7	1	2	0	1
	Myopathy	2	1	0	1	0	0	0	0
	Myositis	4	2	0	2	0	0	0	1
	Neck Pain	31	10	2	7	0	2	0	0
	Osteoarthritis	1	1	0	2	0	0	0	0
	Osteolysis	1	1	0	1	0	0	0	0
	Osteoporosis	4	2	0	0	0	0	0	0
	Pain In Extremity	7	7	1	6	2	0	0	1
	Pain In Jaw	1	1	0	0	0	0	0	0
	Pathological Fracture	4	2	0	2	0	0	0	0
	Scleroderma	1	0	0	0	0	0	0	0
	Sjogren'S Syndrome	1	1	0	1	1	0	0	0
	Spinal Disorder	1	1	0	0	0	0	0	0
	Systemic Lupus Erythematosus	1	0	0	0	0	0	0	0
	Tendinous Contracture	4	1	1	0	0	0	0	0

Search Criteria Name: SWANNJ Search submitted on: 01-27-2009 12:41:11
Product/Group Name: BROMOCRIPTINE_ALL-IS-01-09
Reaction/Group Name:
Search Case Count: 2589

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Note: Each case may have multiple PTs.

Pharmacia Biotech Inc. System/ERS

SOC	PT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Musculoskeletal And Connective Tissue Disorders	Tendon Disorder	1	0	0	0	0	0	0	0
	Torticollis	3	3	0	3	0	0	0	0
	Trismus	2	2	0	2	0	0	0	0
Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps)	Acute Myeloid Leukaemia	1	1	1	1	0	0	0	0
	Adenoma Benign	2	2	0	1	0	0	0	0
	B-Cell Lymphoma	1	1	0	0	0	0	0	0
	B-Cell Lymphoma Recurrent	1	1	0	0	0	0	0	0
	Benign Breast Neoplasm	2	2	0	2	0	0	0	0
	Benign Pancreatic Neoplasm	1	1	0	0	0	0	0	0
	Brain Neoplasm	1	1	0	0	0	0	0	0
	Breast Cancer	1	1	1	0	0	0	0	0
	Breast Cancer Female	2	1	0	1	0	1	0	1
	Breast Cancer Metastatic	1	1	0	0	1	0	0	0
	Breast Neoplasm	3	2	0	2	0	0	0	0
	Central Nervous System Neoplasm	1	1	0	1	1	1	0	1
	Cervix Carcinoma	1	1	0	1	0	0	0	0
	Endometrial Cancer	2	1	0	0	0	0	0	0
	Gastric Cancer	1	1	1	1	0	0	0	0
	Gastrointestinal Carcinoma	2	2	2	0	0	0	0	0
	Haemangioma Of Liver	2	2	0	2	0	0	0	0
	Hepatic Neoplasm Malignant	1	1	1	0	0	0	0	0
	Leukaemia	4	4	0	4	0	0	0	0
	Lipoma	1	1	0	0	0	0	0	0
	Lymphoma	2	2	0	2	0	0	0	0
	Malignant Neoplasm Progression	1	1	0	0	0	0	0	0

Search Criteria Name: SWANNJ Search submitted on: 01-27-2009 12:41:11
 Product/Group Name: BROMOCRIPTINE_ALL-JS-01-09
 Reaction/Group Name:

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Note: Each case may have multiple PT's

FDA Adverse Event Reporting System (AERS)

SOC	PT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Neoplasms Benign, Malignant And Unspecified (incl Cyst And Polyp)	Metastases To Liver	1	1	0	1	0	0	0	0
	Metastases To Meninges	1	1	1	1	1	0	0	0
	Myeloproliferative Disorder	2	0	0	0	1	0	0	0
	Neoplasm	8	6	1	3	1	1	0	1
	Neoplasm Malignant	3	3	1	2	0	0	0	1
	Neoplasm Progression	3	3	0	1	0	1	0	1
	Neurinoma Benign	1	1	0	1	0	0	0	0
	Ovarian Cancer Metastatic	1	1	0	0	1	0	0	0
	Pancreatic Carcinoma	1	1	1	0	0	0	0	0
	Pituitary Cancer Metastatic	1	1	1	1	1	0	0	0
	Pituitary Tumour	4	4	1	1	0	2	0	1
	Pituitary Tumour Benign	7	7	0	5	1	0	0	1
	Pituitary Tumour Recurrent	1	1	0	0	0	0	0	0
	Polycythaemia Vera	1	1	0	0	0	0	0	0
	Protactinoma	4	4	0	1	0	0	0	0
	Prostate Cancer	1	1	0	0	0	0	0	0
	Pseudolymphoma	2	1	0	1	0	0	0	0
	Secretory Adenoma Of Pituitary	1	1	0	0	0	0	0	0
	Small Cell Lung Cancer Stage Unspecified	1	1	0	0	0	0	0	0
	Tumour Haemorrhage	2	2	0	2	0	0	0	0
Nervous System Disorders	Ataxia	3	2	0	2	0	0	0	0
	Akinetia	7	6	0	6	0	0	0	0
	Amnesia	13	10	0	7	3	3	0	3

SOC	FT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Nervous System Disorders	Anoxic Encephalopathy	3	3	1	3	3	2	0	0
	Apraxia	3	3	0	3	2	3	0	0
	Apraxia	14	10	1	8	4	7	0	5
	Apraxia	1	1	0	1	0	1	0	0
	Areflexia	1	1	0	1	0	0	0	0
	Autonomic Nervous System Imbalance	1	1	0	1	0	0	0	0
	Balance Disorder	5	5	0	0	1	1	0	0
	Bradykinesia	1	1	0	1	0	0	0	1
	Brain Injury	4	4	0	4	2	2	0	1
	Brain Mass	1	1	1	1	1	0	0	0
	Brain Oedema	17	17	5	11	2	7	0	5
	Burning Sensation	2	2	0	1	0	0	0	0
	Carotid Artery Stenosis	2	2	1	1	0	0	0	1
	Carotid Artery Thrombosis	1	1	0	1	1	0	0	0
	Cerebellar Atrophy	1	1	0	1	0	0	0	0
	Cerebellar Infarction	1	1	0	1	0	0	0	0
	Cerebellar Syndrome	1	1	0	1	0	1	0	0
	Cerebral Arteritis	1	1	0	1	0	0	0	0
	Cerebral Artery Thrombosis	3	3	0	3	0	0	0	0
	Cerebral Atrophy	6	6	0	5	1	1	0	1
	Cerebral Haematoma	1	1	0	1	0	1	0	0
	Cerebral Haemorrhage	7	7	3	5	2	2	0	0
	Cerebral Infarction	19	15	4	11	3	7	0	5
	Cerebral Ischaemia	8	5	0	4	0	1	0	1
	Cerebral Venous Thrombosis	1	1	0	1	0	0	0	1
Cerebral Ventricle Dilatation	1	1	1	1	0	0	0	0	

Search Criteria Name: SWANNU Search submitted on: 01-27-2009 12:41:11
 Product/Group Name: BROMOCRIPTINE_ALL-JS-01-09
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Note: Each case may have multiple PTs

FD-302 (Rev. 05-08-2002) - Report of an Incident (Form 3750)
 Incident Number: 01-27-2009-12:41:11

SOC	FT	Total Case/Event	Serious	Death	Hospitalized	Life-Threatening	Disabled	Congenital Anomaly	Required Intervention
Nervous System Disorders	Cerebrospinal Fluid Rhinorrhea	2	2	0	2	0	0	0	2
	Cerebrovascular Accident	61	47	5	42	7	24	0	16
	Cerebrovascular Disorder	14	11	3	12	0	1	0	5
	Cerebrovascular Spasm	1	1	0	1	0	0	0	1
	Chorea	3	3	1	1	0	0	0	0
	Chorea/athetosis	5	2	0	2	0	0	0	1
	Clastic Convulsion	7	4	0	2	1	1	0	1
	Cloacas	1	1	0	0	1	0	0	0
	Cognitive Disorder	2	2	0	2	1	2	0	0
	Coma	39	34	8	32	10	12	0	10
	Convulsion	206	139	19	111	21	25	0	34
	Convulsion Neonatal	3	3	0	2	0	0	0	0
	Coordination Abnormal	15	10	1	8	1	1	0	1
	Dementia	7	4	2	2	0	1	0	1
	Depressed Level Of Consciousness	26	26	3	20	4	0	0	7
	Diplegia	1	1	0	1	1	1	1	0
	Disturbance In Attention	2	2	0	1	0	0	0	1
	Dizziness	124	47	3	25	2	2	0	5
	Dizziness Postural	1	1	0	1	0	0	0	1
	Drooling	1	1	1	1	0	0	0	1
Dysarthria	9	9	0	7	2	4	0	1	
Dysgeusia	3	0	0	0	0	0	0	0	
Dysgraphia	1	1	0	1	0	0	0	0	
Dyskinesia	34	27	4	18	3	2	0	5	
Dysphasia	2	2	0	2	0	1	0	0	
Dysstasia	6	6	0	2	0	1	0	0	
Dystonia	13	10	0	9	1	1	0	2	

Search Criteria Name: SWANNJ Search submitted on: 01-27-2009 12:41:11
 Product/Group Name: BROMOCRIPTINE_ALL-IS-01-09
 Rescuer/Group Name:
 Search Case Count: 2589

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Note: Each case may have multiple FTs.

SOC	FT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Nervous System Disorders	Encephalopathy	9	9	1	6	3	7	0	6
	Epilepsy	5	5	0	4	0	0	0	0
	Extensor Plantar Response	2	2	1	2	1	0	0	1
	Extrapyramidal Disorder	20	8	1	6	1	1	0	1
	Facial Palsy	8	7	1	4	1	2	0	1
	Gerstmann'S Syndrome	1	1	0	1	0	1	0	0
	Gliosis	1	1	0	1	0	0	0	0
	Grand Mal Convulsions	60	49	0	45	4	8	0	8
	Haemorrhage Intracranial	21	20	5	15	2	9	0	5
	Haemorrhagic Stroke	40	37	10	23	4	17	0	13
	Head Discomfort	1	1	0	0	0	1	0	0
	Headache	289	179	12	133	23	31	0	31
	Hemianopia	4	4	0	4	0	0	0	0
	Hemianopsia	1	1	0	1	0	0	0	0
	Hemiparesis	5	5	0	4	1	1	0	0
	Hemiplegia	32	26	2	21	2	18	0	9
	Hepatic Encephalopathy	1	1	0	0	1	0	0	0
	Hydrocephalus	5	5	4	4	0	1	0	4
	Hypertension	6	4	1	3	1	0	0	0
	Hypersonnia	1	1	0	0	0	0	0	0
	Hypertensive Encephalopathy	2	2	0	2	0	0	0	0
	Hypertonia	30	13	1	10	2	1	0	4
	Hypoesthesia	11	9	0	5	2	2	0	0
	Hypokinesia	5	3	0	3	0	0	0	0
	Hypotonia	5	3	0	2	0	1	0	0
	Hypoxic Encephalopathy	3	3	0	3	3	3	0	0

Search Criteria Name: SWANNJ Search submitted on: 01-27-2009 12:41:11
 Product/Group Name: BROMOCRIPTINE_ALL-JS-01-09

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Note: Each case may have multiple FT's

MDY - Critical Incident Response System (CIRS) - 11/11/09

SOC	FT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Nervous System Disorders	Iliad Nerve Punctis	1	1	0	1	0	0	0	0
	Intracranial Aneurysm	4	3	2	2	0	0	0	0
	Intracranial Hypotension	1	1	0	1	0	0	0	0
	Intracranial Pressure Increased	2	2	0	1	0	0	0	1
	Ischaemic Stroke	1	1	0	1	0	1	0	0
	Judgement Impaired	1	1	0	0	0	0	0	0
	Lacunar Infarction	2	2	0	2	1	1	0	0
	Lethargy	4	4	0	2	0	0	0	0
	Locked-In Syndrome	2	2	0	2	0	0	0	0
	Loss Of Consciousness	22	21	2	12	3	2	0	2
	Masked Faces	2	2	0	2	0	0	0	0
	Memory Impairment	4	4	0	1	0	2	0	0
	Meningism	2	2	0	2	0	0	0	1
	Meningorrhagia	2	2	0	2	0	0	0	0
	Mental Impairment	4	4	0	2	1	2	0	1
	Mental Retardation	1	0	0	0	0	0	0	0
	Migraine	24	16	0	13	0	4	0	2
	Monoparesis	1	1	0	1	0	0	0	0
	Motor Dysfunction	7	7	1	4	0	1	0	0
	Movement Disorder	8	6	0	5	0	0	0	2
	Multiple Sclerosis	3	3	0	1	1	1	0	0
	Muscle Contractions Involuntary	3	3	0	2	0	0	0	2
	Myasthenic Syndrome	6	4	0	3	0	3	0	2
	Myelitis	1	0	0	0	0	0	0	0
	Myoclonus	2	2	1	2	1	0	0	0
Nerve Compression	2	2	0	2	0	0	0	0	
Nerve Root Compression	1	1	0	1	0	0	0	0	

Search Criteria Name: SWANNJ Search submitted on: 01-27-2009 12:41:11
 Product/Group Name: BRONOCRIPTINE_ALL-JS-01-09
 Reaction/Group Name:
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Note: Each case may have multiple FTs.

FDAS - Active System Reports - System (AERS)

SOC	FT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Nervous System Disorders		5	5	1	4	2	3	0	1
	Nervous System Disorder	2	1	0	1	0	0	0	0
	Neuralgia	2	1	0	1	0	0	0	0
	Neuritis	51	49	4	39	8	1	0	16
	Neurologic Malignant Syndrome	2	2	0	1	1	0	0	0
	Symptom	16	8	0	5	1	4	0	0
	Neuropathy Peripheral	5	5	0	4	0	1	0	2
	Nystagmus	1	1	0	0	0	0	0	0
	Olfactory Nerve Disorder	2	2	0	0	0	0	0	0
	On And Off Phenomenon	1	1	0	1	0	1	0	0
	Optic Neuritis	39	10	0	6	0	1	0	1
	Paresthesia	12	11	0	8	3	8	0	6
	Paralysis	2	0	0	2	0	2	0	1
	Paraplegia	2	2	2	1	0	0	0	1
	Paresis	8	8	0	6	0	0	0	1
	Parkinson'S Disease	6	6	0	6	1	0	0	0
	Parkinsonian	2	1	0	0	0	0	0	0
	Parosmia	1	1	0	1	0	0	0	0
	Peroneal Nerve Palsy	1	1	0	1	0	0	0	0
	Petit Mal Epilepsy	3	2	0	2	1	0	0	0
	Pleocytosis	1	1	0	0	0	1	0	1
	Polyneuropathy	4	4	0	3	0	0	0	1
	Psychomotor Hyperactivity	1	1	0	1	0	0	0	1
	Quadruplegia	2	2	0	2	1	0	0	0
	Reflexes Abnormal	1	1	0	1	0	0	0	0
	Sciatica	37	17	2	11	3	0	0	7
	Sedation	2	2	0	2	0	1	0	0
	Sensory Disturbance								

Search Criteria Name: SWANNJ Search submitted on: 01-27-2009 12:41:11
 Product/Group Name: BBROMOCRIPTINE_ALL-IS-01-09
 Reaction/Group Name:

Date - Time: 01/27/2009 - 12:56 pm
 Run by: SWANNJ
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Note: Each case may have multiple FT's

FD-302 (Rev. 10-6-95) Reporting System (ERS)

SOC	FT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Nervous System Disorders	Serotonin Syndrome	8	8	0	7	1	1	0	2
	Simple Partial Seizures	2	2	0	2	1	1	0	0
	Somnolence	16	16	2	6	2	1	0	1
	Spastic Paralysis	1	1	0	1	0	1	0	1
	Speech Disorder	23	20	1	12	1	6	0	5
	Status Epilepticus	4	4	0	2	2	0	0	1
	Stupor	13	8	1	7	0	0	0	2
	Subarachnoid Haemorrhage	8	6	1	6	0	1	0	2
	Sudden Onset Of Sleep	2	2	0	1	0	0	0	0
	Suicidal Syndrome	1	1	0	1	0	0	0	0
	Syncope	78	41	4	21	4	2	1	4
	Syncope Vasovagal	2	2	2	0	1	0	0	0
	Tonic Convulsion	2	2	0	2	0	0	0	0
	Transient Ischaemic Attack	2	2	0	2	1	0	0	0
	Tremor	37	24	2	13	2	2	0	4
	Unresponsive To Stimuli	2	2	1	2	1	0	0	0
	Upper Motor Neurone Lesion	1	1	0	1	0	0	0	1
	Vasculitis Cerebral	3	3	0	2	1	0	0	1
	Visual Field Defect	18	16	0	9	1	2	0	0
	Visual Pathway Disorder	6	6	0	1	0	0	0	0
Pregnancy, Puerperium And Perinatal Conditions	Abortion	36	17	0	13	0	0	2	1
	Abortion Incomplete	1	1	0	1	0	0	0	0
	Abortion Of Ectopic Pregnancy	1	1	0	1	1	0	0	0
	Abortion Spontaneous	10	10	1	0	0	0	0	0
	Azotemia	1	1	0	0	0	0	0	0
	Haemorrhage	1	1	0	0	0	0	0	0

Search Criteria Name: SW/ANNJ Search submitted on: 01-27-2009 12:41:11
 Product/Group Name: BROMOCRIPTINE_ALL-IS-01-09
 Reaction/Group Name:
 Search Case Count: 2589

Date - Time: 01/27/2009 - 12:56 pm
 Run by: SW/ANNJ
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Note: Each case may have multiple FTs.



SOC	FT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Pregnancy, Peripartum And Perinatal Conditions	Blighted Ovum	1	1	0	0	0	0	0	0
	Breech Presentation	2	2	0	1	0	0	0	0
	Cervical Incompetence	1	1	0	1	0	0	0	0
	Complication Of Pregnancy	3	1	0	1	0	0	0	0
	Delivery	1	1	0	0	0	0	0	0
	Eclampsia	5	4	0	4	1	0	0	0
	Ectopic Pregnancy	2	2	0	2	1	0	0	0
	Foetal Disorder	2	2	1	0	0	0	0	0
	Foetal Growth Retardation	1	1	0	0	0	0	0	0
	Heterotopic Pregnancy	1	1	0	1	0	0	0	0
	Induced Labour	1	1	0	1	1	0	0	0
	Intra-Uterine Death	3	3	1	1	0	0	1	0
	Jaundice Neonatal	1	1	0	0	0	0	0	0
	Labour Pains	1	1	0	1	0	0	0	0
	Multiple Pregnancy	1	1	1	0	0	0	0	0
	Neonatal Disorder	2	0	0	0	0	0	0	0
	Normal Newborn	8	8	0	3	0	0	0	0
	Postpartum Disorder	1	1	0	0	0	1	0	0
	Postpartum Haemorrhage	10	0	0	0	0	0	0	0
	Pregnancy	14	14	1	7	2	1	1	0
	Premature Baby	6	6	1	1	1	0	0	0
	Premature Labour	3	3	1	1	0	0	0	0
	Small For Dates Baby	2	2	2	0	0	0	0	0
	Stillbirth	3	3	1	1	0	0	0	0
	Twin Pregnancy	2	2	0	1	1	0	0	0
	Umbilical Cord Abnormality	1	1	0	0	0	0	0	0
	Uterine Contractions During Pregnancy	2	2	0	0	0	0	0	0

Search Criteria Name: SWANNU Search submitted on: 01-27-2009 12:41:11
 Product/Group Name: BROMOCRIPTINE_ALL-JS-01-09
 Recalls/Group Name:
 Search Case Count: 259
 Date - Time: 01/27/2009 - 12:56 pm
 Run by: SWANNU
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 Note: Each case may have multiple PTs

SWANNJ Search Criteria
Product/Group Name: BROMOCRIPTINE_ALL-IS-01-09
Search Case Count: 2589

SOC	PT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Psychiatric Disorders	Delusional Disorder, Persecutory Type	1	1	0	1	0	0	0	0
	Delusional Disorder, Unspecified Type	1	1	0	0	0	0	0	0
	Dependence	1	1	0	0	0	0	0	0
	Depersonalisation	4	2	0	0	0	0	0	0
	Depressed Mood	3	3	0	1	0	0	0	0
	Depression	61	30	3	18	0	4	0	3
	Disinhibition	3	3	0	3	0	0	0	1
	Disorientation	9	9	0	8	2	3	0	2
	Disturbance In Social Behaviour	1	1	0	1	0	0	0	0
	Drug Dependence	4	4	0	3	0	0	0	0
	Early Morning Awakening	1	1	0	0	0	0	0	0
	Eating Disorder	1	1	0	0	0	0	0	0
	Emotional Disorder	11	5	0	2	0	0	0	1
	Emotional Distress	3	3	0	3	0	0	0	0
	Euphoric Mood	4	4	0	4	0	0	0	1
	Fear	1	1	0	1	0	0	0	0
	Fetishism	1	1	0	0	0	0	0	0
	Flight Of Ideas	2	2	0	2	0	0	0	0
	Grandiosity	1	1	0	0	0	0	0	0
	Hallucination	111	56	2	51	4	2	0	9
	Hallucination, Auditory	3	3	0	2	0	0	0	0
	Hallucination, Visual	12	12	1	9	1	0	0	1
	Hallucinations, Mixed	1	1	0	1	0	0	0	0
	Hostility	9	7	0	7	0	0	0	1
	Hyponomania	3	3	0	1	0	0	0	1
	Illusion	1	1	0	1	0	0	0	0
	Impulsive Behaviour	2	2	0	1	0	1	0	0
	Inappropriate Affect	2	2	0	2	0	0	0	0

Note: Each case may have multiple PTs.

SOC	PT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Psychiatric Disorders	Insomnia	38	31	1	21	2	2	0	3
	Intentional Drug Misuse	1	1	0	1	0	0	0	0
	Intentional Self-Injury	2	1	0	1	0	0	0	0
	Libido Decreased	2	1	0	1	0	0	0	0
	Libido Increased	11	6	0	2	0	0	0	0
	Logorrhoia	2	2	0	2	0	0	0	2
	Major Depression	7	5	0	5	1	1	0	0
	Male Orgasmic Disorder	1	1	0	0	0	0	0	0
	Mania	14	12	0	10	0	1	0	2
	Mental Disorder	6	6	0	2	0	0	0	0
	Mood Altered	3	3	0	1	0	0	0	0
	Mood Disorder Due To A General Medical Condition	1	1	0	1	0	0	0	0
	Mood Swings	1	1	0	0	0	0	0	0
	Nervousness	9	5	1	4	0	0	0	1
	Neurosis	2	1	0	0	0	0	0	1
	Obsessive-Compulsive Disorder	1	1	0	1	0	0	0	0
	Pedophilia	2	2	0	0	0	0	0	0
	Panic Attack	5	5	0	0	0	0	0	1
	Panic Disorder	1	1	0	0	0	0	0	0
	Panic Reaction	1	1	0	1	0	0	0	1
	Paranoia	17	9	0	6	0	0	0	1
	Paraphilia	3	3	0	1	0	0	0	0
	Pathological Gambling	13	13	0	7	0	0	0	0
	Persecutory Delusion	6	6	0	5	0	0	0	0
	Personality Change	3	3	0	3	0	0	0	0
	Personality Disorder	32	10	0	9	0	1	0	2
	Phobia	1	1	0	1	0	0	0	0

Search Criteria Name: SWANNJ Search submitted on: 01-27-2009 12:41:11
Product/Group Name: BROMOCRIPTINE_ALL-IS-01-09
Reaction/Group Name:
Search Case Count: 2589

Date - Time: 01/27/2009 - 12:56 pm
Run by: SWANNJ
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Note: Each case may have multiple PTs.



SOC	FT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Psychiatric Disorders									
Photological Disorder	1	1	1	0	1	0	0	0	0
Photophobia	1	1	1	0	1	0	0	0	0
Postpartum Stress Disorder	1	1	1	0	1	0	0	0	0
Posturing	1	1	1	0	1	1	1	0	0
Psychomotor Retardation	1	1	1	0	1	0	0	0	0
Psychotic Disorder	50	35	28	0	28	2	4	0	3
Restlessness	2	2	2	1	2	1	0	0	1
Schizophrenia	3	3	3	0	3	0	0	1	0
Schizophreniform Disorder	3	0	0	0	0	0	0	0	0
Screaming	1	1	1	0	1	0	0	0	0
Self Injurious Behaviour	1	1	1	0	1	0	0	0	0
Sexual Inhibition	1	1	1	0	0	0	0	0	0
Sleep Attacks	3	3	0	0	0	0	0	0	0
Sleep Disorder	5	4	2	1	2	0	0	0	2
Soliloquy	2	2	2	0	2	0	0	0	0
Somatic Delusion	1	1	1	0	1	0	0	0	0
Somatic Hallucination	1	1	1	0	1	0	0	0	0
Stereotypy	1	1	1	1	1	0	0	0	0
Stress	4	4	3	0	3	0	1	0	0
Suicidal Ideation	5	5	3	0	3	1	1	0	0
Suicide Attempt	12	9	6	2	6	1	0	0	2
Tachypnea	1	1	1	0	1	0	0	0	0
Thinking Abnormal	15	6	5	0	5	0	1	0	1
Transient Psychosis	1	1	1	0	1	0	0	0	0
Renal And Urinary Disorders									
Albuminuria	5	2	1	1	1	0	0	0	1
Anuria	5	4	3	1	3	0	0	0	0
Bladder Disorder	1	1	1	0	1	1	0	0	0
Bladder Prolapse	1	1	0	0	0	0	0	0	0

Search Criteria Name: SWANU Search submitted on: 01-27-2009 12:41:11
 Product/Group Name: BROMOCRIPTINE_ALL-IS-01-09
 Renal/Group Name:
 Search Case Count: 2189
 Date - Time: 01/27/2009 - 12:56 pm
 Run by: SWANU
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Note: Each case may have multiple FTs

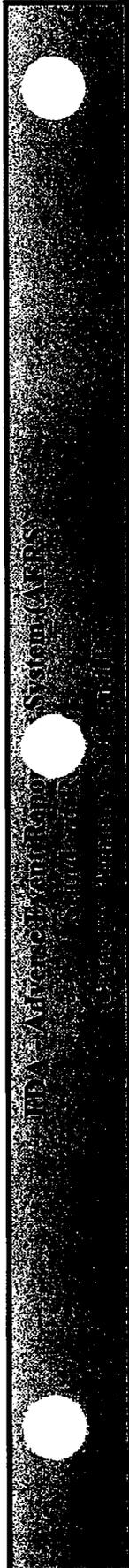
EBM - Adverse Events/PTs - System/ERS

SOC	FT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Renal And Urinary Disorders	Bladder Stenosis	1	0	0	0	0	0	0	0
	Chromaturia	1	1	0	0	0	0	0	0
	Crystalluria	1	0	0	0	0	0	0	0
	Cystitis	2	2	2	0	0	0	0	0
	Haemorrhagic								
	Diabetic	1	1	1	0	0	0	0	1
	Nephropathy								
	Dysuria	4	2	2	0	0	0	0	0
	Glomerulonephritis Membranous	1	1	0	1	0	0	0	1
	Haematuria	1	0	0	0	0	0	0	0
	Hydrocephalus	12	12	0	10	0	1	2	0
	Hydronephrosis	2	2	0	0	0	0	2	0
	Incontinence	1	1	0	1	1	1	0	0
	Lupus Nephritis	1	1	0	1	0	0	0	0
	Micturition Urgency	2	2	0	1	0	0	0	1
	Myoglobinuria	3	3	0	1	0	0	0	1
	Nephrotic Syndrome	3	2	0	1	0	0	0	1
	Nocturia	2	1	0	1	0	0	0	0
	Oliguria	5	2	0	2	0	0	0	0
	Pelkaturia	4	1	0	1	0	0	0	0
	Polyuria	4	4	0	1	2	0	0	1
	Proteinuria	3	3	0	3	0	0	0	1
	Renal Colic	3	1	0	0	0	0	0	0
	Renal Disorder	1	1	0	0	0	0	0	0
	Renal Failure	16	10	1	9	3	2	0	2
	Renal Failure Acute	15	12	4	10	4	0	0	5
	Renal Impairment	10	9	3	7	0	0	0	2
	Renal Infarct	2	2	0	2	1	0	0	0
	Renal Pain	1	1	0	0	0	0	0	0
	Urethral Obstruction	2	2	0	0	0	0	2	0
	Urethral Pain	1	1	0	0	0	0	0	0

Search Criteria Name: SWANNJ Search submitted on: 01-27-2009 12:41:11
 Product/Group Name: BROMOCRIPTINE_ALL-JS-01-99
 Reaction/Group Name:
 Search Case Count: 2589

Date - Time: 01/27/2009 - 12:56 pm
 Run by: SWANNJ
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Note: Each case may have multiple PTs.



SOC	FT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Renal And Urinary Disorders	Urinary Incontinence	12	8	1	3	1	2	0	0
	Urinary Retention	8	8	0	8	0	0	0	4
	Urinary Tract Disorder	2	1	0	1	0	0	0	0
	Urine Abnormality	1	0	0	0	0	0	0	0
Reproductive System And Breast Disorders	Amenorrhoea	8	5	0	4	0	0	0	1
	Breast Atrophy	3	1	0	1	0	1	0	0
	Breast Enlargement	11	1	0	1	0	0	0	0
	Breast Enlargement	7	1	0	0	0	0	0	1
	Breast Involusion	1	1	0	0	0	0	0	0
	Breast Pain	11	3	0	1	0	0	0	0
	Cervix Disorder	1	1	0	1	0	0	0	0
	Dysmenorrhoea	1	0	0	0	0	0	0	0
	Dyspareunia	1	1	0	0	0	0	0	0
	Ejaculation Disorder	2	0	0	0	0	0	0	0
	Erectile Dysfunction	5	2	0	0	0	0	0	0
	Fibrocystic Breast Disease	1	1	0	1	0	0	0	0
	Galactorrhoea	16	2	0	1	0	0	0	1
	Genital Haemorrhage	1	1	0	0	0	0	0	0
Genital Leukoplakia	2	0	0	0	0	0	0	0	
Gynaecomastia	3	0	0	0	0	0	0	1	
Hypomenorrhoea	1	1	0	0	0	0	0	0	
Infertility Female	1	1	0	0	0	0	1	0	
Menometrorrhagia	6	3	1	2	0	0	0	0	
Menorrhagia	6	1	0	0	0	0	0	0	
Menstrual Disorder	4	3	0	1	0	0	1	0	
Metrorrhagia	1	1	0	0	0	0	0	0	
Oedema Genital	1	0	0	0	0	0	0	0	
Oligomenorrhoea	1	1	0	0	0	0	0	0	
Ovarian Disorder	2	2	0	2	0	0	0	0	

Search Criteria Name: SWANNU Search submitted on: 01-27-2009 12:41:11
 Product/Group Name: BROMOCRIPTINE_ALL-IS-01-09
 Search Case Count: 2589
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 Run by: SWANNU
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Note: Each case may have multiple FTs

Pharmacoepidemiology and Therapeutics Institute (PETI) - University of New Hampshire (UNH)

SOC	FT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Reproductive System And Breast Disorders	Ovarian Hyperstimulation Syndrome	2	2	0	0	1	0	0	0
	Pelvic Pain	2	1	0	1	0	0	0	0
	Penis Disorder	2	1	0	0	0	1	0	0
	Polycystic Ovaries	2	2	0	0	1	0	0	0
	Premature Menopause	1	1	0	0	0	0	0	0
	Priapism	1	0	0	0	0	0	0	0
	Prostatic Disorder	3	2	1	1	0	0	0	0
	Scrotal Oedema	1	0	0	0	0	0	0	0
	Suppressed Lactation	1	1	0	0	0	0	0	0
	Testicular Disorder	2	2	0	2	0	0	0	0
	Uterine Cervical Pain	1	1	0	1	0	0	0	0
	Uterine Disorder	2	1	0	1	0	0	0	0
	Uterine Haemorrhage	2	0	0	0	0	0	0	0
	Uterine Pain	1	1	0	0	0	0	0	0
	Vaginal Disorder	1	1	0	0	0	0	0	0
	Vaginal Haemorrhage	7	3	0	3	1	1	0	0
	Vulval Oedema	1	1	1	1	1	0	0	0
Respiratory, Thoracic And Mediastinal Disorders	Acute Respiratory Distress Syndrome	5	5	2	5	2	2	0	2
	Acute Respiratory Failure	1	1	1	1	0	0	0	0
	Allergic Granulomatous Angitis	1	1	1	0	0	0	0	1
	Apropos	9	7	5	5	1	2	0	4
	Asthma	9	1	0	1	0	0	0	0
	Atelectasis	5	5	0	5	1	3	0	2
	Bronchial Hyperreactivity	1	1	0	0	0	0	0	0

Search Criteria Name: SWANNJ Search submitted on: 01-27-2009 12:41:11
 Product/Group Name: BROMOCRIPTINE_ALL-IS-01-09
 Reaction/Group Name:
 Search Case Count: 2489

Date - Time: 01/27/2009 - 12:56 pm
 Run by: SWANNJ
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Note: Each case may have multiple FTs.



SOC	FI	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Respiratory, Thoracic And Mediastinal Disorders	Bronchitis Chronic	1	1	0	1	0	1	0	0
	Bronchospasm	2	2	0	1	1	0	0	1
	Choking	1	1	0	1	0	0	0	0
	Cough	15	14	2	10	2	1	0	2
	Diaphragmatic Disorder	1	1	0	1	0	0	0	0
	Dysphonia	7	2	0	2	0	0	0	1
	Dyspnoea	104	85	3	62	7	10	0	16
	Dyspnoea Exertional	3	3	0	2	0	1	0	1
	Dyspnoea	1	1	0	0	1	0	0	0
	Paroxysmal Nocturnal								
	Epistaxis	6	2	0	2	1	0	0	1
	Hiccnotherax	2	2	0	2	0	0	0	1
	Hyperventilation	4	1	0	1	0	0	0	0
	Hypocapnia	1	1	0	1	0	0	0	1
	Hypoventilation	1	1	0	1	0	0	0	0
	Hypoxia	5	5	1	2	2	3	0	1
	Interstitial Lung Disease	6	6	1	3	2	1	0	0
	Laryngeal Disorder	1	1	0	1	1	0	0	0
	Laryngeal Oedema	2	2	1	0	0	0	0	0
	Laryngospasm	1	1	0	1	0	0	0	0
	Lung Disorder	15	12	3	8	0	1	0	2
	Lung Infiltration	3	3	0	2	0	0	0	0
	Mediastinal Fibrosis	3	2	1	2	0	0	0	0
	Nasal Disorder	1	1	0	1	0	0	0	0
	Neonatal	1	1	0	1	0	0	0	0
	Tachypnoea								
	Orthopnoea	2	2	0	1	1	0	0	0
	Pharyngeal Oedema	2	2	0	0	0	0	0	0
	Pleural Disorder	22	20	4	11	0	2	0	4
	Pleural Effusion	77	64	5	52	4	4	0	20

Search Criteria Name: SWANNJ Search submitted on: 01-27-2009 12:41:11
 Product/Group Name: BROMOCRIPTINE_ALL-IS-01-09
 Reaction/Group Name:

Date - Time: 01/27/2009 - 12:56 pm
 Run by: SWANNJ

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Note: Each case may have multiple FI's

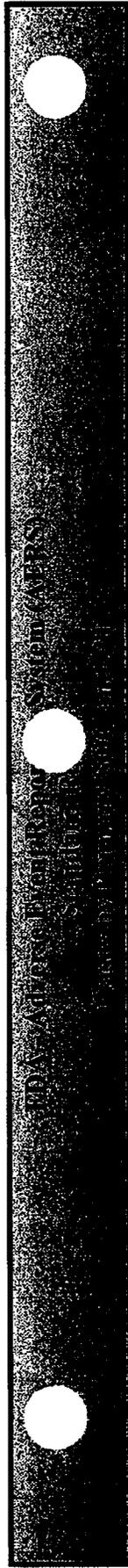
IBPA - Agency of Ryan Reporting System (ARPS)

SOC	PT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Respiratory, Thoracic And Mediastinal Disorders	Respiratory	8	8	3	6	0	0	0	2
	Pleural Hemorrhage	2	2	1	2	1	0	0	0
	Pleurisy	1	1	0	1	1	0	0	0
	Pneumonia Aspiration	11	10	5	8	3	0	0	1
	Pneumonia	1	1	0	1	0	0	0	0
	Pneumothorax	4	4	3	4	1	0	0	0
	Productive Cough	1	1	1	0	0	0	0	0
	Pulmonary Artery Thrombosis	1	1	0	1	0	0	0	1
	Pulmonary Congestion	3	3	2	1	0	1	0	0
	Pulmonary Embolism	19	18	11	11	4	1	0	4
	Pulmonary Fibrosis	32	26	8	10	1	4	0	4
	Pulmonary Hemorrhage	1	1	0	0	0	0	0	0
	Pulmonary Hypertension	3	3	1	2	0	0	0	1
	Pulmonary Infarction	1	1	0	1	0	0	0	1
	Pulmonary Oedema	22	21	4	15	6	3	0	8
	Pulmonary Vasculitis	1	1	0	0	0	0	0	0
	Rales	3	3	0	3	0	0	0	0
	Respiratory Alkalosis	1	1	0	0	0	1	0	0
	Respiratory Arrest	3	2	2	1	1	0	0	0
	Respiratory Depression	2	2	0	2	0	1	0	0
	Respiratory Disorder	20	16	7	9	1	3	0	7
	Respiratory Distress	3	3	0	2	1	0	0	1
	Respiratory Failure	8	8	4	7	2	2	0	1
	Restrictive Pulmonary Disease	1	1	0	1	0	0	0	0
	Rhinorrhoea	2	2	1	1	0	0	0	1
	Sinus Congestion	1	1	0	1	0	0	0	1

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Note: Each case may have multiple PTs.

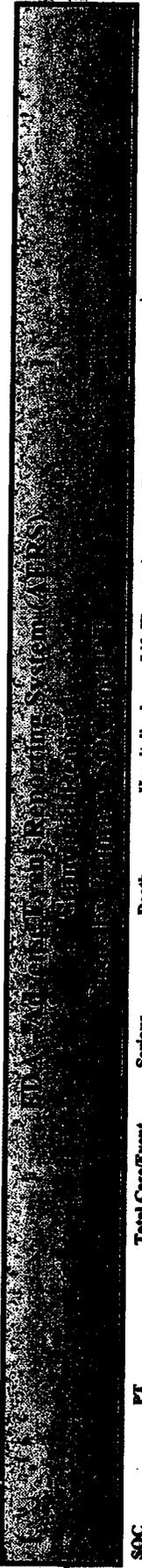


SOC	FT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Respiratory, Thoracic And Mediastinal Disorders	Stridor	1	1	0	1	1	0	0	0
	Tachypnoea	5	5	1	5	0	1	0	0
	Upper Respiratory Tract Congestion	1	1	0	1	0	0	0	0
	Wheezing	2	2	0	0	0	0	0	0
	Yawning	1	1	0	1	0	0	0	0
Skin And Subcutaneous Tissue Disorders	Acne	7	2	0	0	1	0	0	0
	Alopecia	27	5	0	2	1	2	0	0
	Angioedema	5	3	0	2	0	0	0	0
	Cold Sweat	5	5	0	1	2	0	0	1
	Cutaneous Lupus Erythematosus	1	0	0	0	0	0	0	0
	Cutaneous Vasculitis	1	1	0	1	0	0	0	1
	Dermatitis	43	7	2	4	1	0	0	1
	Dermatitis Allergic	1	1	0	0	0	1	0	0
	Dermatitis Bullous	5	3	0	3	0	0	0	1
	Dermatitis Exfoliative	1	1	1	0	0	0	0	0
	Drug Eruption	2	2	1	1	1	0	0	0
	Echymosis	2	0	0	0	0	0	0	0
	Eczema	4	3	0	3	0	0	0	1
	Erythema	2	2	0	1	0	0	0	0
	Erythema Multiforme	3	2	1	1	0	0	0	0
	Haemorrhage Subcutaneous	1	1	0	0	0	0	0	0
	Hair Disorder	2	0	0	0	0	0	0	0
	Hirsutism	1	0	0	0	0	0	0	0
	Hyperhidrosis	34	21	0	14	2	1	0	5
	Lichen Planus	1	0	0	0	0	0	0	0
	Nail Disorder	2	0	0	0	0	0	0	0
	Pemphigoid	1	1	1	0	0	0	0	0
	Petechiae	6	1	0	1	0	0	0	1

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Note: Each case may have multiple FT



SOC	PT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention	
Skin And Subcutaneous Tissue Disorders	Photosensitivity Reaction	3	3	0	3	0	0	0	1	
	Pruritus	22	6	0	3	0	0	0	2	
	Pruritus Generalised	2	2	0	0	0	1	0	0	
	Purpura	4	3	0	3	1	0	0	2	
	Rash	5	5	0	2	1	1	0	0	
	Rash Erythematous	2	2	0	2	0	0	0	2	
	Rash Generalised	1	1	1	1	1	0	0	0	
	Rash Maculo-Papular	9	2	0	0	0	0	0	0	
	Rash Papular	1	1	0	1	0	0	0	0	
	Scar	3	3	0	1	0	0	0	0	
	Scleroderma	1	1	0	1	0	0	0	0	
	Skin Burning Sensation	1	1	0	0	0	0	0	0	
	Skin Discolouration	8	1	1	0	0	0	0	0	
	Skin Disorder	1	1	1	0	0	0	0	0	
	Skin Exfoliation	1	1	1	1	0	0	0	0	
	Skin Lesion	1	1	0	0	0	0	0	0	
	Skin Necrosis	2	2	0	2	0	0	0	0	
	Swelling Face	4	4	0	2	0	1	0	0	
	Toxic Epidermal Necrolysis	1	1	1	0	0	0	0	0	
	Toxic Skin Eruption	1	1	0	1	0	0	0	0	
	Urticaria	23	4	0	4	0	0	0	0	
	Social Circumstances	Activities Of Daily Living Impaired	3	3	0	2	0	0	0	0
		Breast Feeding	1	1	0	0	0	0	0	0
Drug Abuser		3	3	0	2	0	0	0	0	
Gambling		1	1	0	0	0	0	0	0	
Imprisonment		1	1	0	0	0	0	0	0	
Legal Problem		1	1	0	0	0	0	0	0	
Pharmaceutical Product Complaint		3	2	0	0	0	0	0	0	

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SOC	PT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Interventions
Social Circumstances	Pharmaceutical Product Counterfeit	2	0	0	0	0	0	0	0
	Refusal Of Treatment By Patient	1	1	0	1	0	0	0	0
	Sexual Abuse	1	1	0	0	0	0	0	0
	Sexual Activity Increased	1	1	0	0	0	0	0	0
	Sexual Relationship Change	1	1	0	0	0	0	0	0
	Treatment Noncompliance	6	6	0	4	0	0	0	0
Surgical And Medical Procedures	Abortion Induced	5	5	0	0	0	0	3	0
	Adhesiolysis	1	1	0	1	1	0	0	0
	Benign Tumour Excision	1	1	0	0	0	0	0	0
	Bone Marrow Transplant	1	1	0	1	0	0	0	0
	Breast Lump Removal	1	1	0	1	0	0	0	0
	Breecb Extraction	1	1	1	0	0	0	0	0
	Cacarean Section	12	12	0	4	2	1	0	0
	Catheterisation Cardiac	1	1	0	1	0	0	0	0
	Colectomy	1	1	0	1	1	0	0	0
	Continuous Haemofiltration	1	1	0	1	0	0	0	0
	Cranioctomy	1	1	0	0	0	0	0	0
	Craniotomy	1	1	0	1	1	1	0	0
	Deep Brain Stimulation	1	1	0	0	0	0	0	0
	Dialysis	2	2	0	1	1	1	0	1
	Endotracheal Intubation	2	2	0	1	0	0	0	0
	Epistomy	1	1	1	1	1	0	0	0
	Gastric Operation	1	1	0	1	0	0	0	0

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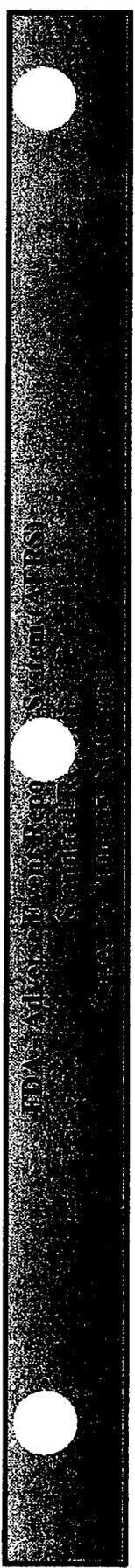
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BAYLOR COLLEGE OF MEDICINE
 DEPARTMENT OF PEDIATRICS
 CHILDREN'S HOSPITAL OF TEXAS
 6625 FORTH STREET, DALLAS, TEXAS 75235
 TEL: 214.756.3000 FAX: 214.756.3001
 WWW.CHILDRENSBAYLOR.COM

SOC	FT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Surgical And Medical Procedures	Gastrointestinal Tube Insertion	1	1	0	1	0	0	0	0
	Haemodialysis	2	2	2	2	1	0	0	0
	Hypophysectomy	2	2	0	1	0	0	0	0
	Implantable Defibrillator Insertion	1	1	0	1	1	0	0	0
	Intestinal Resection	2	2	0	2	0	0	0	0
	Intracerebral Hematoma Evacuation	1	1	0	1	1	1	0	0
	Laparotomy	2	2	0	2	1	0	0	0
	Life Support	1	1	0	1	0	0	0	0
	Pancreatotomy	1	1	0	0	0	0	0	0
	Pericardiectomy	1	1	0	1	0	0	0	0
	Pituitary Tumour Removal	5	5	0	4	0	0	0	0
	Resuscitation	1	1	0	1	1	1	0	0
	Salpingectomy	2	2	0	2	1	0	0	0
	Spinal Decompression	1	1	1	1	1	0	0	0
	Spinal Operation	1	1	0	0	0	0	0	0
	Splenectomy	1	1	0	0	0	0	0	0
	Surgery	8	8	0	5	1	0	0	1
	Toe Amputation	2	2	1	2	1	1	0	0
	Tracheostomy	1	1	0	1	1	0	0	0
	Transfusion	1	1	0	0	0	0	0	0
	Tumour Excision	1	1	0	1	0	0	0	0
	Uterine Dilatation And Curettage	2	2	0	1	0	0	0	0
	Uterine Dilatation And Evacuation	1	1	0	1	0	0	0	0
	Ventriculo-Peritoneal Shunt	1	1	0	1	0	0	0	1
Vascular Disorders	Aneurysm	1	1	1	0	0	0	0	0



SOC	FT	Total Case/Event	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
Vascular Disorders	Angiopathy	7	7	1	4	1	1	0	1
	Arterial Rupture	1	1	1	0	0	0	0	0
	Arterial Spasm	1	1	0	1	0	0	0	0
	Arterial Stenosis	1	1	0	0	0	0	0	0
	Arterial Thrombosis	2	1	1	0	0	0	0	0
	Arterial Thrombosis Limb	2	2	0	2	1	0	0	1
	Arteriosclerosis	3	3	2	1	0	0	0	1
	Ateritis	1	1	0	1	0	0	0	0
	Blood Pressure Fluctuation	3	3	1	0	1	0	0	1
	Circulatory Collapse	5	5	0	4	0	1	0	0
	Deep Vein Thrombosis	10	7	2	5	2	2	0	1
	Embolism	3	3	2	1	1	1	0	1
	Essential Hypertension	1	1	0	1	1	1	0	0
	Flushing	5	5	0	2	0	1	0	0
	Haematoma	2	2	0	2	0	0	0	1
	Haemorrhage	11	6	2	2	2	0	0	0
	Hypertension	214	138	15	111	12	25	0	26
	Hypertensive Crisis	2	2	0	2	0	0	0	0
	Hypotension	88	38	9	25	5	1	0	8
	Infarction	2	2	0	2	1	0	0	0
	Intermittent Claudication	2	2	0	2	1	0	0	0
	Ischaemia	1	1	0	0	0	0	0	0
	Jugular Vein Distension	2	2	0	2	1	0	0	0
	Jugular Vein Thrombosis	1	1	0	1	0	0	0	1
	Lymphoedema	1	1	0	1	0	0	0	0
	Necrosis Ischaemic	1	1	0	1	0	1	0	0
	Orthostatic Hypotension	21	12	2	11	0	1	0	1

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SOC	Total Case/Event
Blood And Lymphatic System Disorders	104
Cardiac Disorders	336
Congenital, Familial And Genetic Disorders	64
Ear And Labyrinth Disorders	28
Endocrine Disorders	52
Eye Disorders	158
Gastrointestinal Disorders	422
General Disorders And Administration Site Conditions	584
HepatoBiliary Disorders	63
Immune System Disorders	23
Infections And Infestations	145
Injury, Poisoning And Procedural Complications	177
Investigations	323
Metabolism And Nutrition Disorders	99
Musculoskeletal And Connective Tissue Disorders	127
Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps)	70
Nervous System Disorders	1075
Pregnancy, Puerperium And Perinatal Conditions	162
Psychiatric Disorders	447
Renal And Urinary Disorders	104
Reproductive System And Breast Disorders	110
Respiratory, Thoracic And Mediastinal Disorders	310
Skin And Subcutaneous Tissue Disorders	193
Social Circumstances	22
Surgical And Medical Procedures	60
Vascular Disorders	445

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/s/

Hylton Joffe
3/25/2009 04:55:03 PM
MEDICAL OFFICER

Mary Parks
3/25/2009 05:07:41 PM
MEDICAL OFFICER