

One Year Post Exclusivity Adverse Event Review CONCERTA[®]

**Pediatric Advisory Committee Meeting
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Overview

- Background
- Clinical Trials for Initial Approval (6-12 years of age)
- Clinical Trial for Exclusivity (Adolescents)
- Methylphenidate Use Information
- Adverse Event Reports for Concerta[®] (12/4/03-1/4/05)

Background Drug Information



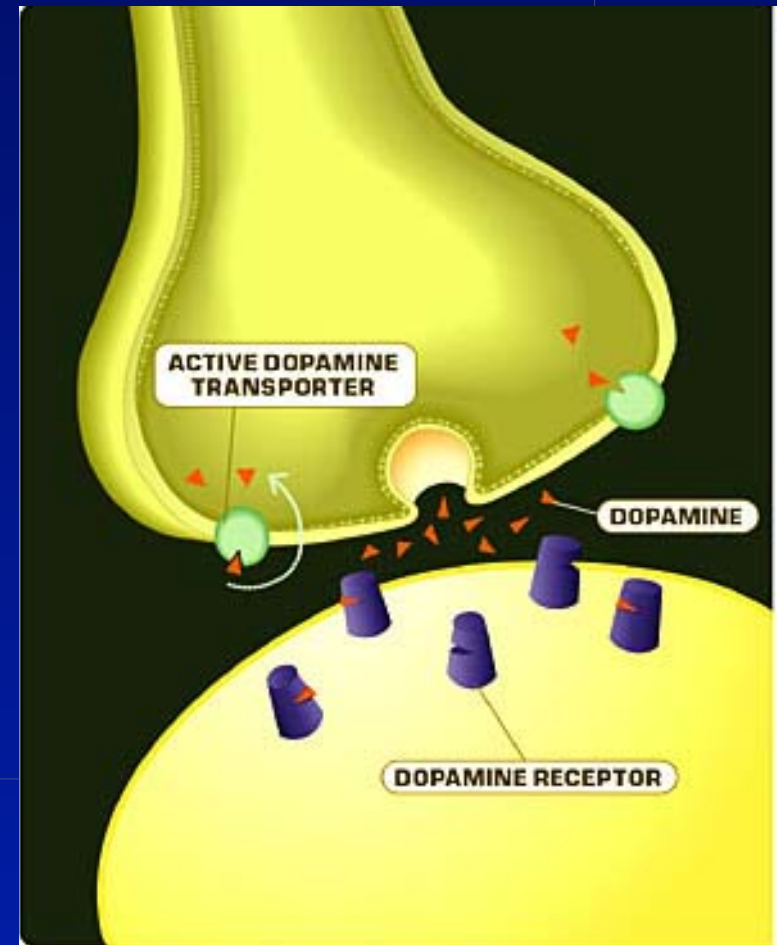
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- **Drug:** Concerta[®] (Methylphenidate HCl Extended Release Tablets)
- **Therapeutic Category:** Central nervous system stimulant
- **Sponsor:** Alza Corporation
- **Indication:** Treatment of Attention Deficit Hyperactivity Disorder (ADHD)
- **Original Market Approval:** August 1, 2000
- **Pediatric Exclusivity Granted:** December 4, 2003

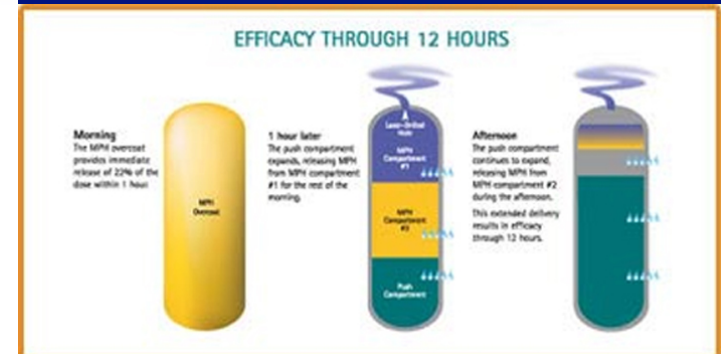
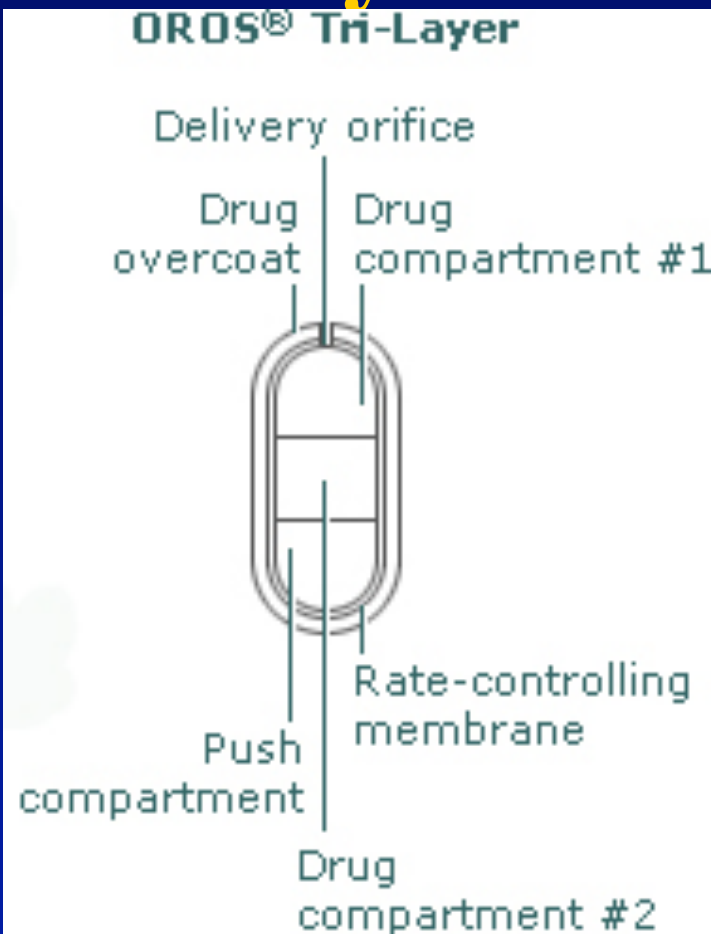
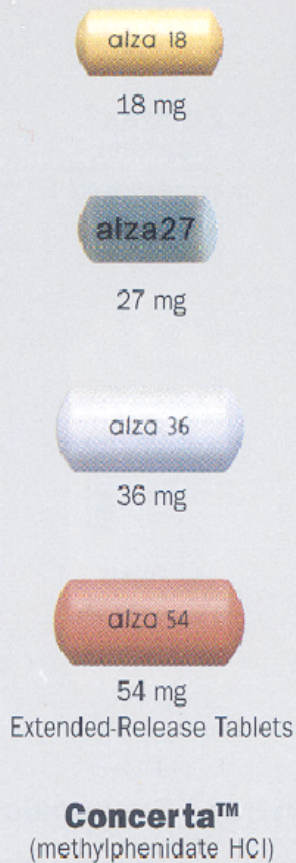
Background Drug Information

Mechanism of action

Therapeutic action of methylphenidate in ADHD is unknown. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.



Concerta[®] Drug Delivery System



Drugs to Treat ADHD

From the Clinical Practice Guidelines

Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement. 2001. Clinical Practice Guideline: Treatment of the school-aged child with attention-deficit/hyperactivity disorder. Pediatrics 108:1033-1044.

Stimulants

(First-Line Treatment)

Methylphenidate

- Short acting
 - Ritalin[®], Methylin[®]
- Intermediate acting
 - Ritalin SR[®], Metadate ER[®], Methylin ER[®]
- Long acting
 - Concerta[®], Metadate CD[®], Ritalin LA[®]

Amphetamine

- Short acting
 - Dexedrine[®], Dextrostat[®]
- Intermediate acting
 - Adderall[®], Dexedrine spansule[®]
- Long acting
 - Adderall XR[®]

Pemoline

- Cylert[®] discontinued by Abbott

Non-Stimulants

- Atomoxetine
 - Strattera[®]

Antidepressants* (Second-Line Treatment)

- Tricyclic antidepressants
 - Imipramine, Desipramine
- Bupropion
 - Wellbutrin[®], Wellbutrin SR[®]

*** Not FDA approved for
ADHD treatment**

Table 4. Recommended Medications for ADHD.

Medication*	Initial Dose	Usual Dose	Doses per Day	Side Effects	Contraindications
<i>mg</i>					
Methylphenidate†					
Ritalin, Methylin	5–10	10–20	2–3	Appetite suppression, stomachaches, headaches, irritability, weight loss, deceleration in rate of growth, exacerbation of psychosis, exacerbation of tics, mild increase in blood pressure and pulse	Marked anxiety, tension, agitation, glaucoma, use of monoamine oxidase inhibitors, seizures, tics
Concerta	18–27	27–54	1		
Metadate ER, Metadate CD, Methylin ER	10	10–20	1		
Ritalin LA	20	20–40	1		
Focalin‡	2.5–5	2.5–10	2–3		
MethyPatch§					
Dextroamphetamine (sulfate alone and in combination with amphetamine salts)†					
Dexedrine	5	5–20	2–3	Appetite suppression, weight loss, stomachaches, headaches, irritability, possible growth inhibition, exacerbation of psychosis, exacerbation of tics, mild increase in blood pressure and pulse	Cardiovascular disease, hypertension, hyperthyroidism, glaucoma, drug dependence, use of monoamine oxidase inhibitors
Dexedrine Spansule	5–10	5–15	1–2		
Adderall	5–10	5–30	1–2		
Adderall XR	5–10	10–30	1		
Atomoxetine¶					
Strattera	10–25	18–60	1	Appetite suppression, nausea, vomiting, fatigue, weight loss, deceleration in rate of growth, mild increase in blood pressure and pulse	Jaundice or other clinical or laboratory evidence of liver injury, use of monoamine oxidase inhibitors, narrow-angle glaucoma
Bupropion					
Wellbutrin SR	100–150	150	1–2	Weight loss, insomnia, agitation, anxiety, dry mouth, seizures, others	Seizures, bulimia, anorexia nervosa, abrupt discontinuation of alcohol or benzodiazepines, use of monoamine oxidase inhibitors or other bupropion products (e.g., Zyban)
Wellbutrin XL	150	150–300	1		

From: Rappley, MD, 2005, Attention deficit-hyperactivity disorder, N. Engl. J. Med. 352:165-173

Initial Studies For Concerta[®] Approval

(Original Market Approval 8/1/00)

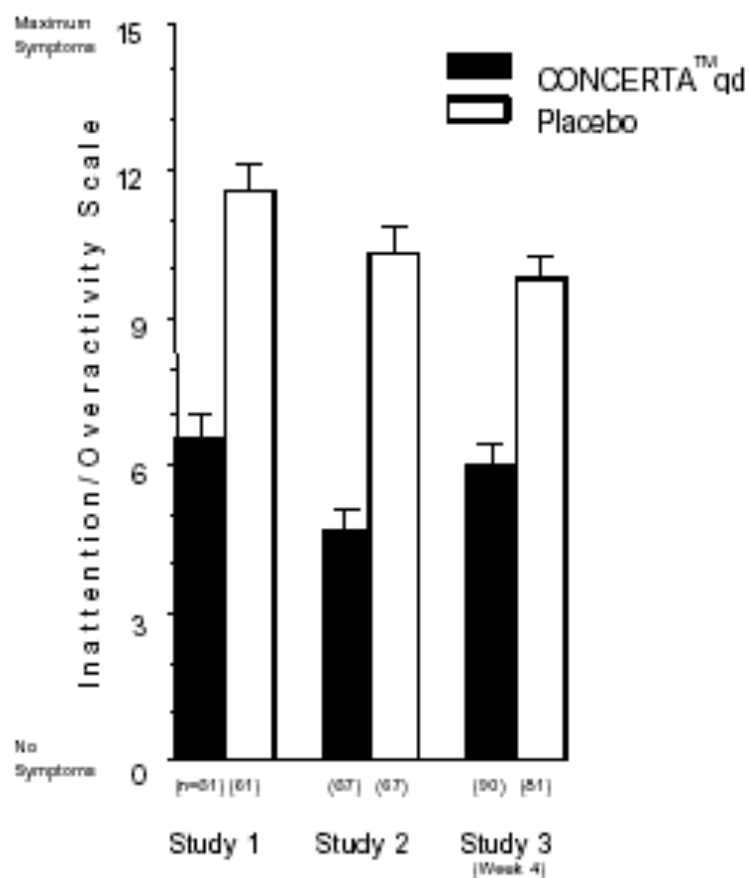
Clinical Trials

- 3 double blind, active and placebo controlled studies in 416 patients 6-12 years of age
- Compared Concerta[®] once daily (18, 36, or 54 mg) to methylphenidate given three times daily over 12 hours (15, 30 or 45 mg total daily dose) and placebo
- Studies 1 and 2 were single-center 3 week crossover studies
- Study 3 was a multi-center 4 week parallel-group comparison
- Primary comparison of interest in all trials was Concerta[®] vs placebo

Initial Studies For Concerta[®]

Results of Clinical Trials (Efficacy)

FIGURE 2
Mean (SEM) Community School Teacher IOWA Conners
Inattention/Overactivity Scores



Initial Studies For Concerta®

Results of Clinical Trials (Adverse Events)

Discontinuation of Treatment

- Study 3
 - Sadness (0.9%)
 - Increase in tics (1%) (Placebo patient)
- Two Open Label Long-Term Safety Trials (24 months and 9 months)
 - Overall rate (6.7%)
 - Insomnia (1.5%)
 - Twitching (1%)
 - Nervousness (0.7%)
 - Emotional lability (0.7%)
 - Abdominal pain (0.7%)
 - Anorexia (0.7%)

Initial Studies For Concerta®

Results of Clinical Trials (Adverse Events From Study 3)

TABLE 4
**Incidence of Treatment-Emergent Events¹ in a 4-Week
Placebo-Controlled Clinical Trial of CONCERTA® In Children**

Body System	Preferred Term	CONCERTA® (n=106)	Placebo (n= 99)
General	Headache	14 %	10 %
	Abdominal pain (stomachache)	7 %	1 %
Digestive	Vomiting	4 %	3 %
	Anorexia (loss of appetite)	4 %	0 %
Nervous	Dizziness	2 %	0 %
	Insomnia	4 %	1 %
Respiratory	Upper Respiratory Tract Infection	8 %	5 %
	Cough Increased	4 %	2 %
	Pharyngitis	4 %	3 %
	Sinusitis	3 %	0 %

¹Events, regardless of causality, for which the incidence for patients treated with CONCERTA® was at least 1% and greater than the incidence among placebo-treated patients. Incidence has been rounded to the nearest whole number.

Initial Studies For Concerta®

Approved Labeling Following the Initial Clinical Trials

- **Contraindications**
 - Agitation (ie. marked anxiety, tension and agitation since the drug may aggravate these symptoms)
 - Hypersensitivity to methylphenidate
 - Glaucoma
 - Tics or a family history or diagnosis of Tourette's
 - MAO inhibitors
- **Warnings**
 - Long-term suppression of growth
 - May exacerbate behavior disturbance and thought disorder in psychotic patients
 - Seizures
 - Potential for gastrointestinal obstruction
 - Hypertension and other cardiovascular conditions
 - Visual disturbance
 - Use in children under 6 years of age
 - **Drug dependence (tolerance, psychological dependence, psychotic episodes and severe depression) (Boxed Warning)**

Initial Studies For Concerta®

Approved Labeling Following the Initial Clinical Trials

Adverse Events with Other Methylphenidate Products

- Nervousness
- Insomnia
- Hypersensitivity (skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with necrotizing vasculitis, and thrombocytopenic purpura)
- Anorexia
- Nausea
- Dizziness
- Palpitations
- Headache
- Dyskinesia
- Drowsiness
- **Blood pressure and pulse changes both up and down**
- **Tachycardia**
- **Angina**
- **Cardiac arrhythmia**
- Abdominal pain
- Weight loss with prolonged therapy
- **Tourette's**
- **Toxic psychosis**
- Abnormal liver function (transaminase elevation to hepatic coma)
- **Cerebral arteritis and/or occlusion**
- Leukopenia and/or anemia
- **Transient depressed mood**
- Scalp hair loss
- Neuroleptic malignant syndrome

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia and tachycardia may occur more frequently

Initial Studies For Concerta®

Approved Labeling Following the Initial Clinical Trials

Overdosage

- Vomiting
- Agitation
- Tremors,
- Hyperreflexia
- Muscle twitching
- Convulsions (may be followed by coma)
- Euphoria
- Confusion
- Hallucinations
- Delirium
- Sweating
- Flushing
- Headache
- Hyperpyrexia
- Tachycardia
- Palpitations
- Cardiac arrhythmias
- Hypertension
- Mydriasis
- Dryness of mucous membranes

Exclusivity Study For Concerta®

(Granted 12/4/03)

Clinical Trial for Adolescents

- A randomized, double blind, multi-center, placebo controlled study of 177 patients 13-18 years of age
- Of 220 patients who entered an open 4-week titration phase, 177 were titrated to an individualized dose (maximum of 72 mg/d) based on meeting specific improvement criteria on the ADHD Rating Scale and the Global Assessment of Effectiveness
- Patients who met the criteria were randomized to receive their individual dose (18-72 mg/d, n=87) or placebo (n=90) during a 2 week double blind phase
- Mean scores for the investigator rating on the ADHD Rating Scale demonstrated that Concerta® was significantly superior to placebo

Exclusivity Study For Concerta[®]

Results of the Clinical Trial for Adolescents (Adverse Events)

Discontinuation of Treatment (Adolescent Trial)

- No Concerta[®] patients discontinued treatment
- One placebo patient discontinued due to increased mood irritability

Exclusivity Study For Concerta®

Results of the Clinical Trial for Adolescents (Adverse Events)

Table 5
Incidence of Treatment-Emergent Events¹ in a 2-Week
Placebo-Controlled Clinical Trial of CONCERTA®
in Adolescents

Body System	Preferred Term	CONCERTA (n=87)	Placebo (n=90)
General	Accidental injury	6 %	3 %
	Fever	3 %	0 %
	Headache	9 %	8 %
Digestive	Anorexia	2 %	0 %
	Diarrhea	2 %	0 %
	Vomiting	3 %	0 %
Nervous	Insomnia	5 %	0 %
Respiratory	Pharyngitis	2 %	1 %
	Rhinitis	3 %	2 %
Urogenital	Dysmenorrhea	2 %	0 %

¹: Events, regardless of causality, for which the incidence for patients treated with CONCERTA® was at least 2% and greater than the incidence among placebo-treated patients. Incidence has been rounded to the nearest whole number.

Current Approved Indications for Concerta® Following the Initial Studies and the Study for Exclusivity

INDICATION AND USAGE

Attention Deficit Hyperactivity Disorder (ADHD)

CONCERTA® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The efficacy of CONCERTA® in the treatment of ADHD was established in three controlled trials of children aged 6-12 and in one controlled trial in adolescents aged 13-17. All patients met DSM-IV criteria for ADHD (see CLINICAL PHARMACOLOGY).

Drug Use Trends:

Methylphenidate (2002-2004)

- Overall increase from 25 million prescriptions (2002) to over 29 million (2004) for single ingredient and combination psychostimulant products¹
- Methylphenidate products accounted for approximately half of all stimulant prescriptions in the past 3 years¹
- Concerta[®] retained approximately half of the market share for methylphenidate products during all 3 years¹

¹IMS Health, National Prescription Audit *Plus*[™], Years 2002 - 2004, Data extracted Jan 2005

Drug Use Trends: Concerta®

- Most frequent prescribers¹
 - Pediatrics (37.1%)
 - Psychiatry (31%)
 - Family practice (11.7%)
- Prescription Claim Characteristics – Patient Demographics²
 - 80% of claims for pediatric patients (age 1-16 years)
 - 75% of all pediatric claims to males
- Indication associated with use³ in pediatric patients
 - Attention deficit disorder (> 96% of mentions during office-based physician visits)

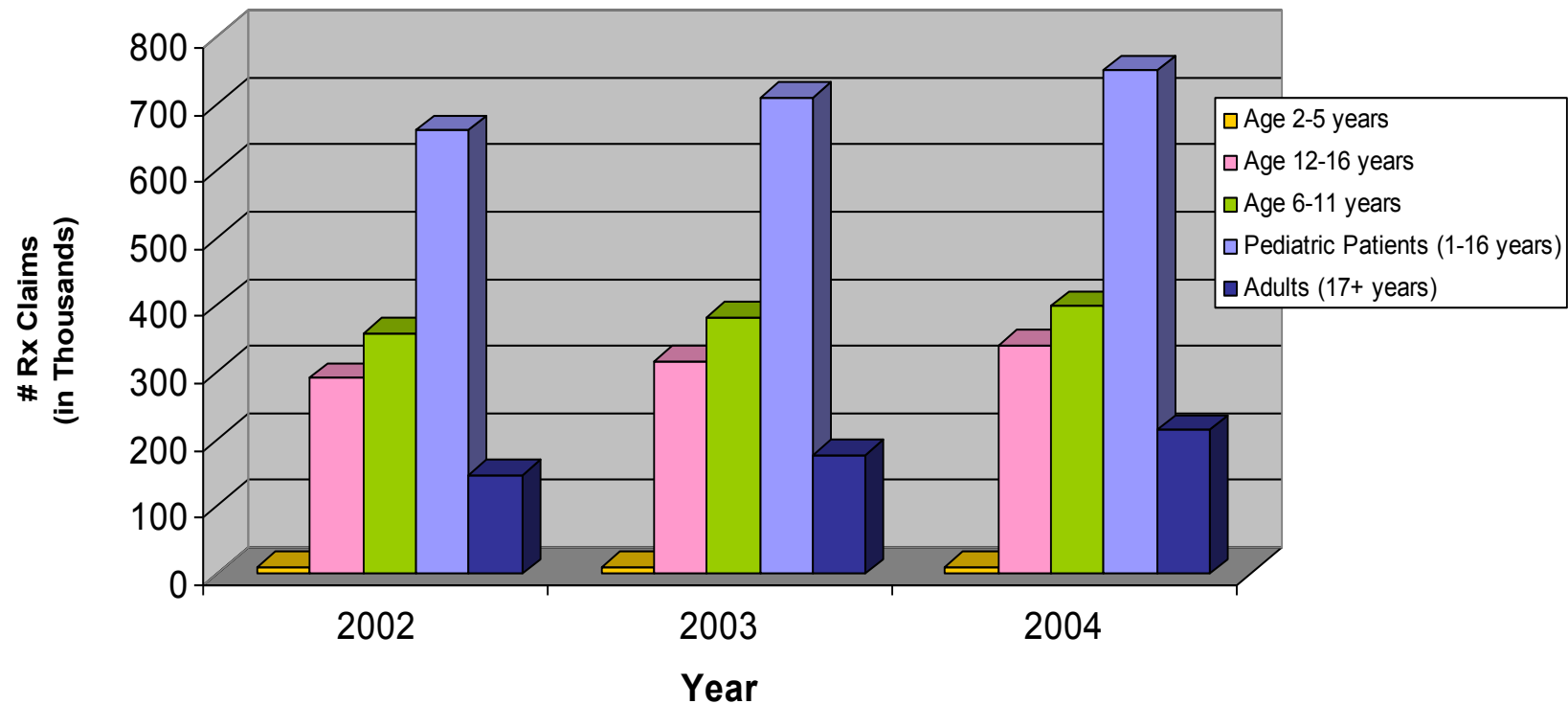
¹IMS Health, National Prescription Audit *Plus*™, Year 2004, Data extracted Jan 2005

²Caremark Dimension Rx™, Years 2002 - 2004, Data extracted Feb 2005

³IMS Health, National Disease and Therapeutic Index™, Years 2002 - 2004, Data extracted Feb 2005

Concerta[®] Prescription Claims By Age, 2002-2004

Number of Prescription Claims for Concerta by Patient Age from the
Caremark Pharmacy Benefit Manager, Years 2002 - 2004



Caremark Dimension Rx™, Years 2002 - 2004, Data extracted Feb 2005

Review of AERS Data Submitted to the FDA Prior to January 4, 2005

- Comparison of Methylphenidate Products
 - Brief comparison of adverse event reports for Concerta[®] and all other methylphenidate products (short and long acting) in children 0-16 years during the one year post exclusivity period
- Discussion of Concerta[®] Adverse Event Reports
 - Raw counts of adverse events for Concerta[®] following exclusivity
 - In depth review of unduplicated reports for Concerta[®] in children 0-16 years of age during the one year post exclusivity period
 - Raw counts of adverse events for Concerta[®] following market approval

Adverse Event Reports for the Methylphenidate Products

December 4, 2003 – January 4, 2005

Characteristic		Concerta [®]	Other Methylphenidate
Total		135	96
Origin	Foreign	77	49
	U.S.	58	47
Gender	Female	26	17
	Male	108	77
	Unknown	1	2
Age	0-1 year	0	1
	2-5 years	1	9
	6-11 years	82	50
	12-16 years	52	36

Adverse Event Reports for the Methylphenidate Products

December 4, 2003 – January 4, 2005

Characteristic		Concerta [®] (N=135)	Other Methylphenidate Products (N=96)
Outcome box checked on MedWatch form (multiple boxes may be checked on one report)	Death	1*	1
	Hospitalization	39	15
	Life-threatening	5	2
	Disability	5	4
	Required intervention	1	9
	Other/Medically important	95	65
	None selected	7	8

* One case in a 16 year old male who had been off Concerta[®] for 7 days who had cardiac arrest and was found with cocaine powder

Deaths in Pediatric Patients Taking Methylphenidate Products

December 4, 2003 – January 4, 2005

- 16-year-old male received Concerta[®] for bipolar disorder for 2 days. Concerta[®] was replaced with Adderall[®]. Seven days after discontinuing Concerta[®], the patient was found in cardiac arrest with cocaine powder in his lap and was pronounced brain dead.

Deaths in Pediatric Patients Taking Methylphenidate Products

December 4, 2003 – January 4, 2005

- 12-year-old male received Ritalin SR[®] from May 2002, which was changed to Ritalin LA[®] in July 2003. He also received medications for asthma. He collapsed on the playground in August 2003 and could not be resuscitated. No acute history of asthma exacerbation was reported. Autopsy showed mild lung inflammation and cerebral edema but was inconclusive regarding cause of death.

Non-fatal Cardiac Arrest in a Pediatric Patient Taking Methylphenidate Products

December 4, 2003 – January 4, 2005

- 13-year-old male with coarctation of the aorta and two mitral valve replacements who was on the heart transplant list because of long-standing dilated cardiomyopathy with a history of sick sinus syndrome and ventricular fibrillation who received Concerta[®] for an “extended duration”. The patient experienced a cardiac arrest, was resuscitated, and had a pacemaker defibrillator inserted. Concerta[®] was continued for 2 more weeks.

Categories of Adverse Events Reported for 28

Methylphenidate Products

December 4, 2003 – January 4, 2005

AE Category	Concerta®	Other Methylphenidate Products
Total	135	96
Psychiatric	36	16
Cardiovascular	20	4
Neurological	16	18
Gastrointestinal	11	5
Hematological	10	4
Miscellaneous	7	8
Special Senses	7	2
Cerebrovascular	2	4
Overdose/abuse	3	2
Lack of effect	3	13
Skin	0	4
Thyroid	1	4
Respiratory	0	5
Significant Confounding Variables	19	7

**Pediatric Adverse Event Reports
for Concerta[®]
December 4, 2003 – January 4, 2005**

Raw Counts of Adverse Event Reports for Concerta[®]#

December 4, 2003 – January 4, 2005

Age	All Reports (U.S.)	Serious (U.S.)	Death (U.S.)
All Ages (Includes age not specified)	265 (144)	243 (123)	13 (13)
Adults (>17 years)	56 (46)	51 (41)	10 (10)
Pediatric (0-16 years)	164 (77)	149 (63)	3 (3)*

* Two deaths occurred in adults (17 year olds), and one death attributable to cocaine use

Includes duplicate reports

Pediatric Adverse Event Reports for Concerta®

December 4, 2003 – January 4, 2005

- 164 Total Reports
 - 2 involved adults
 - 5 are duplicate reports
 - 14 involve non-Concerta® methylphenidate products
- 143 Unduplicated Reports
 - 8 cases where no adverse event was reported
- Leaving 135 Reports

Pediatric Adverse Event Reports for Concerta[®]

December 4, 2003 – January 4, 2005
Confounding Variables in 19 Cases

- Adverse event started before Concerta[®] (1)
- Adverse event started after Concerta[®] discontinued (2)
- Adverse event consistent with pre-existing or familial illness (4)
- Adverse event temporal to use of another drug for which the event is a known effect (7)
- Adverse event resolved during ongoing Concerta[®] use (5)

Characteristics of Pediatric Adverse Event Report Outcomes and Indications for Concerta[®]

December 4, 2003 – January 4, 2005

N=135 Unduplicated Reports

Characteristic		Number of Reports
Origin	Foreign	77
	U.S.	58
Gender	Female	26
	Male	108
	Unknown	1
Age	0 - <1 month	0
	1 month - < 2 years	0
	2-5 years	1
	6-11 years	82
	12-16 years	52

Characteristics of the Pediatric Adverse Event Reports for Concerta[®]

December 4, 2003 – January 4, 2005
N=135 Reports

	Characteristic	Number of Reports
Outcome box checked on MedWatch form (multiple boxes may be checked on one report)	Death	1
	Hospitalization	39
	Life Threatening	5
	Required Intervention	1
	Medically Important/Other	95
	Disability	5
	No Outcome Selected	7
Indication for methylphenidate use	ADHD/Hyperactivity/ADD	108
	Disturbance in attention; Learning disability; Oppositional defiant; Developmental disorder; Tourette's	6
	Unknown	21

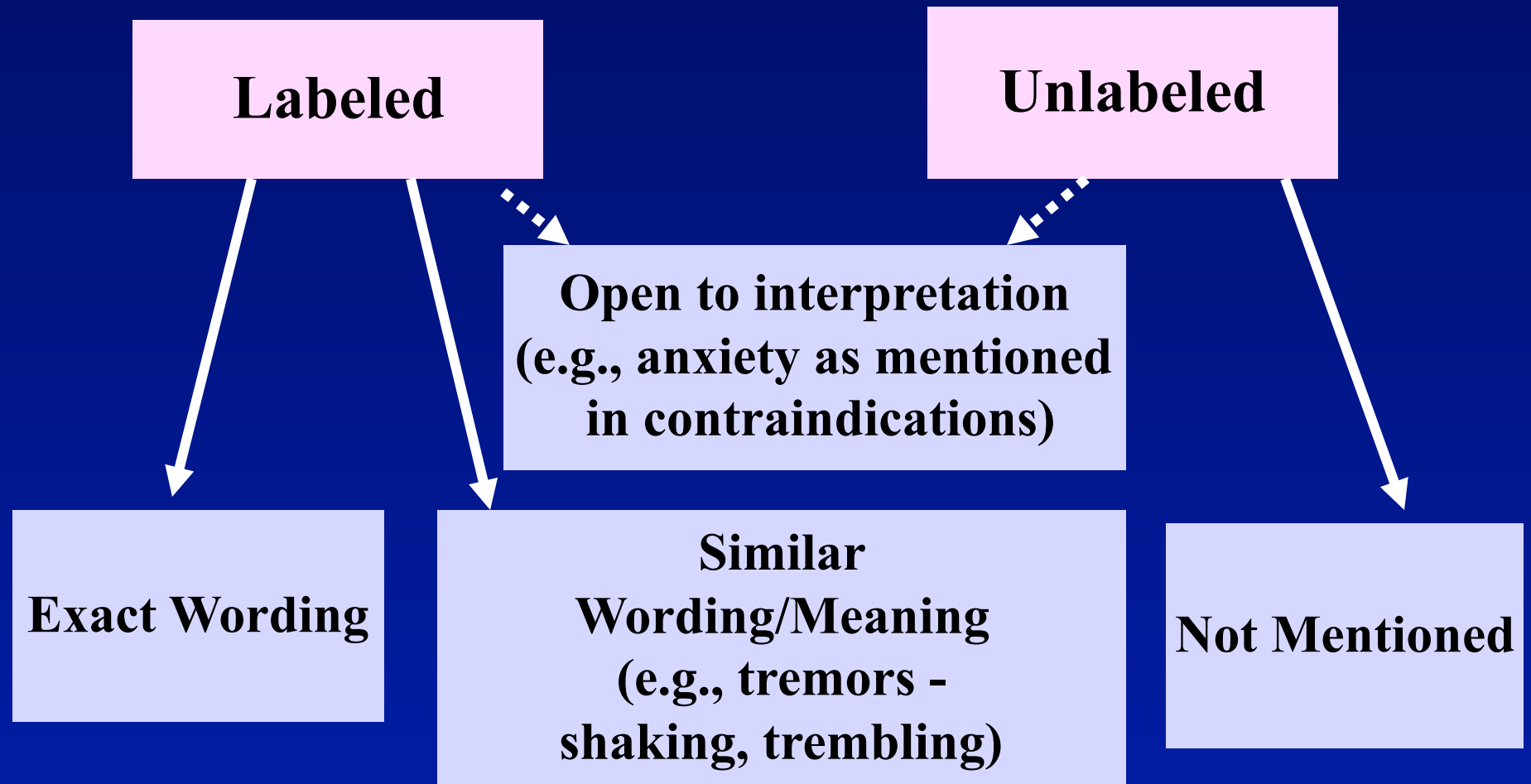
Categories of Adverse Event Reports for Concerta®

December 4, 2003 – January 4, 2005

N=135 Reports

Adverse Event Category	Number of Reports
Psychiatric adverse events	36
Cardiovascular adverse events	20
Neurological adverse events	16
Gastrointestinal adverse events	11
Hematologic adverse events	10
Miscellaneous adverse events	8
Special senses adverse events	7
Cerebrovascular adverse events	2
Overdose/abuse	3
Lack of effect	3
Significant Confounding Variables	19

Reported Concerta[®] Adverse Event Signs/ Symptoms Compared to Labeling



Psychiatric Adverse Events Reported with Concerta[®] December 4, 2003 – January 4, 2005 (N=36 cases)

- **Agitation/behavior disturbance (15)**
 - ✓ Resolved/improved when d/c Concerta[®] (9)
 - ✓ Improved when d/c Concerta[®] & alternative therapy (1)
- **Psychosis/hallucination/visual hallucination (12)**
 - ✓ Resolved/improved when d/c Concerta[®] (8)
- **Suicidal ideation / suicide attempt (11)**
 - ✓ Resolved when d/c Concerta[®] (5)
 - ✓ Improved when d/c Concerta[®] & alternative therapy (1)
- **Anxiety (8)**
 - ✓ Resolved/improved when d/c Concerta[®] (6)
 - ✓ Resolved when d/c Concerta[®] & alternative therapy (1)
 - ✓ Resolved when Concerta[®] dose decreased (1)

NOTE: A case may report more than one adverse event

Psychiatric Adverse Events Reported with Concerta[®]

**December 4, 2003 – January 4, 2005
(N=36 cases) (Cont.)**

- **Sleep disturbance (6)**
 - ✓ Resolved/improved when d/c Concerta[®] (3)
 - ✓ Resolved when d/c Concerta[®] & alternative therapy (1)
- **Obsessive/Compulsive reaction (4)**
 - ✓ Resolved/improved when d/c Concerta[®] (3)
- ✓ **Mania (1)**
 - ✓ Resolved when d/c Concerta[®] (1)
- **Euphoria (2)**
 - ✓ Resolved when d/c Concerta[®] (1)
- **Depression (2)**
 - ✓ Resolved when d/c Concerta[®] (2)

NOTE: A case may report more than one adverse event

Psychiatric Adverse Events Reported with Concerta[®]

December 4, 2003 – January 4, 2005

N=36 Cases

- Reported events
 - Anxiety (fearfulness, phobia, panic attack)
 - Agitation/Behavioral Disturbance (violent behavior, aggression, self-injurious behavior, crying, disinhibition, abnormal behavior, change in behavior, irritability, and social withdrawal)
 - Psychotic behavior, and abnormal thinking
- Contraindications in Concerta[®] Label
 - Concerta[®] is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms
- Warnings in Concerta[®] Label
 - Clinical experience suggests that in psychotic patients, administration of methylphenidate may exacerbate symptoms of behavior disturbance and thought disorder

Psychiatric Adverse Events Reported with Concerta[®]

December 4, 2003 – January 4, 2005

N=36 Cases

- Events Labeled Under Adverse Reactions:
 - Sadness, insomnia, anorexia, increased waking, decreased appetite, sleep disorder, and headache
- Events Labeled Under Other Methylphenidate Products:
 - Choreoathetoid movements
 - Transient depressed mood (depression)
 - Toxic psychosis (hallucinations, visual hallucinations)
- Events Labeled Under Overdosage:
 - Euphoria,
 - Hallucinations (visual hallucinations)
 - Tremor (trembling, shaking)
- Events Labeled Under Information for Patients:
 - Psychosis (abnormal thinking or hallucinations)

Psychiatric Adverse Events Reported with Concerta[®]

December 4, 2003 – January 4, 2005

N=36 Cases

- Unlabeled Events:
 - Suicidal ideation, suicide attempt,
 - Obsessive compulsive reaction (trichotillomania,
pica, rumination),
 - Bad dreams,
 - Listlessness,
 - Psychomotor slowdown,
 - Mania

Underlined = Not labeled

Cardiovascular Adverse Events Reported with Concerta[®] December 4, 2003 – January 4, 2005 (N=20 cases)

- Hypertension / increased blood pressure (5)
 - ✓ Resolved when d/c Concerta[®] (4)
- Tachycardia (5)
 - ✓ Resolved when d/c Concerta[®] (2)
- Syncope (2)
 - ✓ Resolved when d/c Concerta[®] (1)
- Chest pain (7)
 - ✓ Resolved when d/c Concerta[®] (4)

NOTE: A case may report more than one adverse event

Cardiovascular Adverse Events

Reported with Concerta[®]

December 4, 2003 – January 4, 2005

(N=20 cases) (Cont.)

- Left atrial enlargement per EKG (1)
- Dizziness (2)
- Headache (3)
- Dyspnea / dyspnea on exertion (4)
- Vomiting (1)
- Sweating (1)
- Abnormal EKG (1)
- Increased QT interval (2)
- Supraventricular extrasystoles per EKG (1)
- Peripheral vasoconstriction / obstruction (2)

NOTE: A case may report more than one adverse event

Cardiovascular Adverse Events Reported with Concerta[®]

December 4, 2003 – January 4, 2005
N=20 Cases

- Events Labeled Under Warnings:
 - Hypertension, and tachycardia
- Events Labeled Under Adverse Reactions:
 - Dizziness
- Events Labeled Under Other Methylphenidate Products:
 - Chest pain, supraventricular extrasystoles, cardiac arrhythmia, and AV block

Cardiovascular Adverse Events Reported with Concerta[®]

December 4, 2003 – January 4, 2005

N=20 Cases

- Unlabeled Events:
 - Increased QT interval
 - Syncope
 - Left atrial enlargement on EKG
 - Dyspnea, exertional dyspnea
 - Peripheral vascular obstruction with cyanosis in toes, peripheral vasoconstriction

Underlined = Not labeled

Neurological Adverse Events Reported with Concerta[®]

December 4, 2003 – January 4, 2005
N=16 Cases

- Events Labeled Under Warnings:
 - Seizures, epilepsy, focal epilepsy, and absence seizures
- Events Labeled Under Adverse Reactions:
 - Visual disturbance, dystonia, tics, sleep disorder, dyskinesia, restlessness, and headache
- Events Labeled Under Overdosage:
 - Disorientation, tremor (shaking), and confusion

Neurological Adverse Events Reported with Concerta[®] December 4, 2003 – January 4, 2005 N=16 Cases

- Unlabeled Events:
 - Aching extremities, leg numbness, asthenia, retrograde amnesia, sleep walking, eye pain, decreased consciousness, and brain tumor and cyst

Underlined = Not labeled

Special Senses Adverse Events Reported with Concerta[®]

December 4, 2003 – January 4, 2005

N=7 Cases

- Reported event
 - Increased intraocular pressure
- Contraindications in Concerta[®] Label
 - Concerta[®] is contraindicated in patients with glaucoma

Special Senses Adverse Events Reported with Concerta[®]

December 4, 2003 – January 4, 2005

N=7 Cases

- Events Labeled Under Warnings:
 - Visual disturbance (transient blindness, loss of color vision)
 - Diplopia (strabismus)

Special Senses Adverse Events Reported with Concerta[®]

December 4, 2003 – January 4, 2005

N=7 Cases

- Unlabeled Events:
 - Abnormal eye movements
 - Retinopathy
 - Nystagmus and vertigo

Underlined = Not labeled

Cerebrovascular Adverse Events
Reported with Concerta[®]
December 4, 2003 – January 4, 2005
(N=2 cases)

One case each:

- Cerebral aneurysm
- Unspecified cerebrovascular disorder with hallucinations

Cerebrovascular Adverse Events
Reported with Concerta[®]
December 4, 2003 – January 4, 2005
N=2 Cases

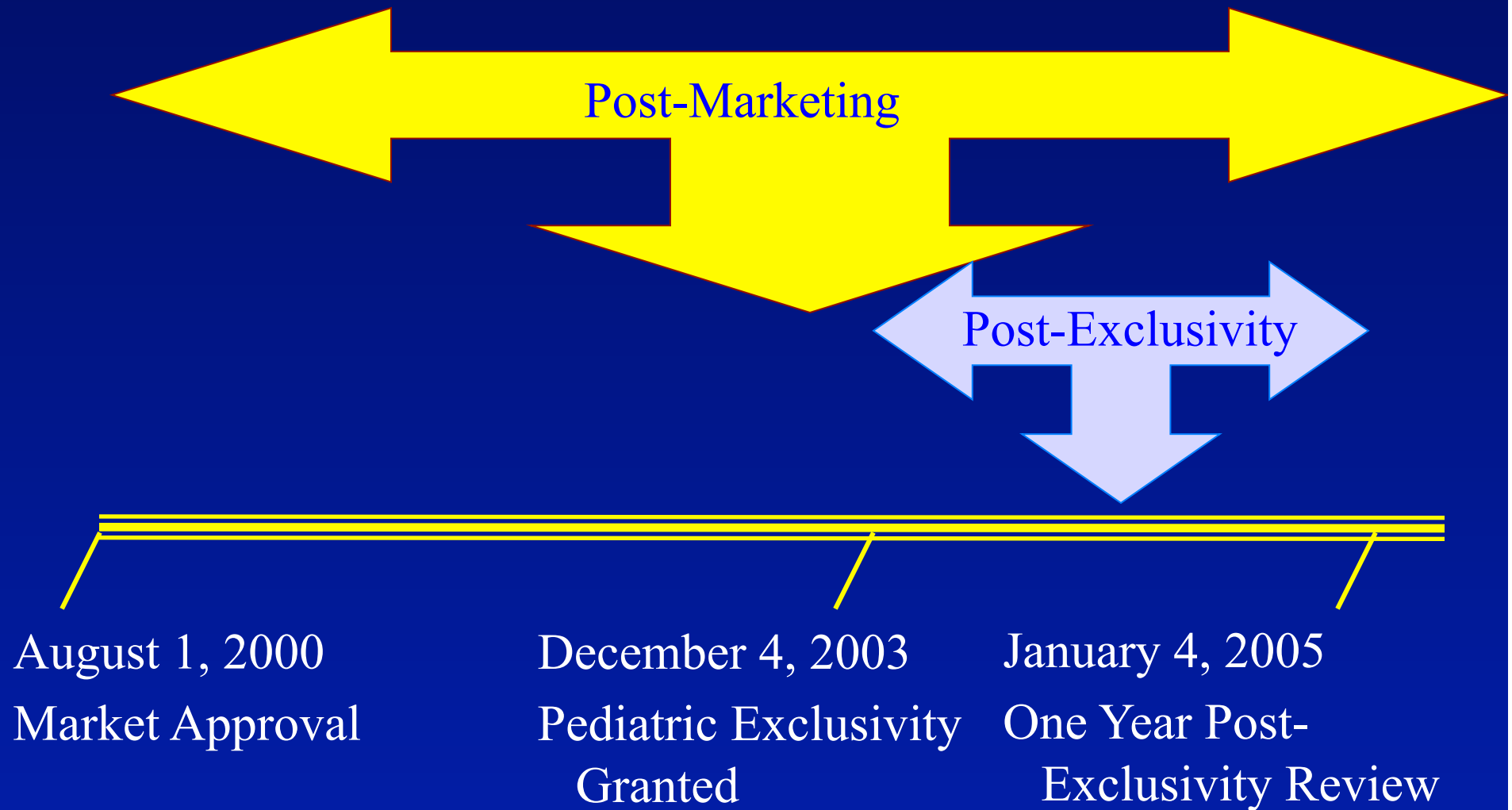
- Events Labeled Under Other Methylphenidate Products:
 - Cerebrovascular disorder

Cerebrovascular Adverse Events
Reported with Concerta[®]
December 4, 2003 – January 4, 2005
N=2 Cases

- Unlabeled Events:
 - Cerebral aneurysm

Underlined = Not labeled

Concerta[®] Timeline



Raw Counts of Adverse Event Reports for Concerta[®]#

August 1, 2000 – January 4, 2005

Age	All Reports (U.S.)	Serious (U.S.)	Death (U.S.)
All Ages (Includes age not specified)	936 (711)	862 (639)	52 (47)
Adults (>17 years)	162 (136)	152 (126)	35 (32)
Pediatric (0-16 years)	642 (479)	599 (438)	16 (14)

Includes duplicate reports

Deaths in Pediatric Patients Taking Concerta[®] Following Market Approval August 1, 2000 (N=7)

- Suicide/Overdose (3)
 - 14 y.o. on Zoloft[®] and Concerta[®] committed suicide
 - 13 y.o. on Wellbutrin[®] and Concerta[®] died of methylphenidate overdose
 - 15 y.o. with Tourette's and autism on Concerta[®] committed suicide by hanging
- Cardiovascular (2)
 - 13 y.o. on Zyrtec[®] and Concerta[®] died in sleep (cardiac arrhythmia)
 - 13 y.o. on Concerta[®] with a history of syncope died a sudden cardiac death with polymorphic ventricular tachycardia
- Other (2)
 - 9 y.o. with a history of asthma on Claritin[®], Flovent[®] and Concerta[®] had viral symptoms with vomiting and coughing. Arrested after increased respiratory distress. Methylphenidate level 156ng/mL (therapeutic 3.7-6.8ng/mL)
 - 16 y.o. off Concerta[®] for 7 days found dead with cocaine powder

Summary:

Concerta[®] Adverse Event Report Profile December 4, 2003 – January 4, 2005

- 135 unduplicated pediatric reports
- Majority of use and adverse events seen in the 6-11 year old population

Summary:

Concerta[®] Adverse Event Report Profile December 4, 2003 – January 4, 2005 (Cont.)

- Psychiatric adverse events
 - Anxiety and agitation
 - Contraindications section states contraindicated in patients with marked anxiety, tension, and agitation since the drug may aggravate these symptoms
 - Thought and behavior disturbance, psychosis, visual hallucination and visual disturbance
 - Warnings section states methylphenidate may exacerbate symptoms of behavior disturbance and thought disorder
 - Warnings section states visual disturbances have been rarely encountered
 - Toxic psychosis, transient depressed mood
 - Adverse Events With Other Methylphenidate Products section
 - Psychosis (abnormal thinking or hallucinations)
 - Information for Patients Taking Concerta[®] section
 - Suicidal ideation is unlabeled

Summary:

Concerta[®] Adverse Event Report Profile December 4, 2003 – January 4, 2005 (Cont.)

- Cardiovascular adverse events
 - Increase in pulse and blood pressure
 - Warnings section
 - Blood pressure and pulse changes (both up and down), angina, and cardiac arrhythmia
 - Adverse Events With Other Methylphenidate Products section
 - Tachycardia, palpitations, cardiac arrhythmias, and hypertension
 - Overdosage section
 - Prolonged QT interval and syncope are unlabeled

Summary:
Concerta[®] Adverse Event Report Profile
December 4, 2003 – January 4, 2005
(Cont.)

- Need to examine adverse event reports in other stimulant products with respect to the psychiatric adverse events
- Need to characterize the cardiovascular risks for all stimulant drug products
- Plan to revise the label to ensure clarity so that all prescribers and patients are appropriately informed

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Additional Slides

Hematologic Adverse Events Reported with Concerta®

December 4, 2003 – January 4, 2005

N=10 Cases

- Events Labeled Under Other Methylphenidate Products:
 - Iron deficiency anemia
 - Neutropenia, and granulocytopenia
 - Hypersensitivity (Henoch-Schonlein purpura, thrombocytopenia, petechiae, eosinophilia)

Hematologic Adverse Events Reported with Concerta[®]

December 4, 2003 – January 4, 2005

N=10 Cases

- Unlabeled Events:
 - Hematoma
 - Lymphocytosis
 - Leukocytosis

Underlined = Not labeled

Gastrointestinal Adverse Events Reported with Concerta[®]

December 4, 2003 – January 4, 2005

N=11 Cases

- Events Labeled Under Other Methylphenidate Products:
 - Increased liver function tests, hepatitis, and lack of weight gain
- Events Labeled Under Adverse Reactions:
 - Anorexia, stomachache (esophagitis), and diarrhea

Gastrointestinal Adverse Events Reported with Concerta[®] December 4, 2003 – January 4, 2005 N=11 Cases

- Unlabeled Events:
 - Gallstones
 - Acute cholecystitis
 - Appendicitis

Underlined = Not labeled

Miscellaneous Adverse Events Reported with Concerta® December 4, 2003 – January 4, 2005 N=8 Cases

- Events Labeled Under Warnings:
 - Growth retardation
- Events Labeled Under Other Methylphenidate Products:
 - Erythematous rash, peripheral swelling and fever
- Unlabeled Events:
 - Acute pulmonary edema, and bradycardia (after intranasal phenylephrine)
 - Acute renal failure
 - Hyperthyroidism
 - Hypoglycemia
 - Pregnancy and spontaneous abortion
 - Increased incidence of herpetic eye infections

Underlined = Not labeled

Adverse Findings in Clinical Trials With Concerta[®]

Adverse Findings in Clinical Trials with CONCERTA[®]

Adverse Events Associated with Discontinuation of Treatment

In the 4-week placebo-controlled, parallel-group trial in children (study 3) one CONCERTA[®]-treated patient (0.9%; 1/106) and one placebo-treated patient (1.0%; 1/99) discontinued due to an adverse event (sadness and increase in tics, respectively).

In the 2-week placebo-controlled phase of a trial in adolescents (Study 4), no CONCERTA[®]-treated patients (0%; 0/87) and 1 placebo-treated patient (1.1%; 1/90) discontinued due to an adverse event (increased mood irritability).

In the two open-label, long-term safety trials (Studies 5 and 6: one 24-month study in children aged 6 to 13 and one 9-month study in child, adolescent and adult patients treated with CONCERTA[®]) 6.7% (101/1514) of patients discontinued due to adverse events. These events with an incidence of >0.5% included: insomnia (1.5%), twitching (1.0%), nervousness (0.7%), emotional lability (0.7%), abdominal pain (0.7%), and anorexia (0.7%).

Treatment-Emergent Adverse Events Among CONCERTA[®]-Treated Patients

Table 4 enumerates, for a 4-week placebo-controlled, parallel-group trial (Study 3) in children with ADHD at CONCERTA[®] doses of 18, 36, or 54 mg/day, the incidence of treatment-emergent adverse events. The table includes only those events that occurred in 1% or more of patients treated with CONCERTA[®] where the incidence in patients treated with CONCERTA[®] was greater than the incidence in placebo-treated patients.

Contraindications in Concerta® Label

CONTRAINDICATIONS

Agitation

CONCERTA® is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

Hypersensitivity to Methylphenidate

CONCERTA® is contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product.

Glaucoma

CONCERTA® is contraindicated in patients with glaucoma.

Tics

CONCERTA® is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome (see ADVERSE REACTIONS).

Monoamine Oxidase Inhibitors

CONCERTA® is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of a monoamine oxidase inhibitor (hypertensive crises may result).

Warnings in Concerta[®] Label

WARNINGS

Depression

CONCERTA[®] should not be used to treat severe depression.

Fatigue

CONCERTA[®] should not be used for the prevention or treatment of normal fatigue states.

Long-Term Suppression of Growth

Data are inadequate to determine whether chronic use of stimulants in children, including amphetamine, may cause suppression of growth. Therefore, growth should be monitored during treatment, and patients who are not growing or gaining weight as expected should have their treatment interrupted.

Psychosis

Clinical experience suggests that in psychotic patients, administration of methylphenidate may exacerbate symptoms of behavior disturbance and thought disorder.

Seizures

There is some clinical evidence that methylphenidate may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in absence of history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

Warnings in Concerta[®] Label

Potential for Gastrointestinal Obstruction

Because the CONCERTA[®] tablet is nondeformable and does not appreciably change in shape in the GI tract, CONCERTA[®] should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic, for example: esophageal motility disorders, small bowel inflammatory disease, "short gut" syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudoobstruction, or Meckel's diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in nondeformable controlled-release formulations. Due to the controlled-release design of the tablet, CONCERTA[®] should only be used in patients who are able to swallow the tablet whole (see PRECAUTIONS: Information for Patients).

Warnings in Concerta[®] Label

Hypertension and other Cardiovascular Conditions

Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, eg, those with preexisting hypertension, heart failure, recent myocardial infarction, or hyperthyroidism. Blood pressure should be monitored at appropriate intervals in patients taking CONCERTA[®], especially patients with hypertension.

In the laboratory classroom clinical trials in children (Studies 1 and 2), both CONCERTA[®] qd and methylphenidate tid increased resting pulse by an average of 2-6 bpm and produced average increases of systolic and diastolic blood pressure of roughly 1-4 mm Hg during the day, relative to placebo.

In the placebo-controlled adolescent trial (Study 4), mean increases from baseline in resting pulse rate were observed with CONCERTA[®] and placebo at the end of the double-blind phase (5 and 3 beats/minute, respectively). Mean increases from baseline in blood pressure at the end of the double-blind phase for CONCERTA[®] and placebo-treated patients were 0.7 and 0.7 mm Hg (systolic) and 2.6 and 1.4 mm Hg (diastolic), respectively.

Visual Disturbance

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

Use in Children Under Six Years of Age

CONCERTA[®] should not be used in children under six years, since safety and efficacy in this age group have not been established.

Warnings in Concerta[®] Label

DRUG DEPENDENCE

CONCERTA[®] should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

Concerta[®] Label for Adverse Events with Other Methylphenidate Products

Adverse Events with Other Methylphenidate HCl Products

Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy. There have been rare reports of Tourette's syndrome. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: instances of abnormal liver function, ranging from transaminase elevation to hepatic coma; isolated cases of cerebral arteritis and/or occlusion; leukopenia and/or anemia; transient depressed mood; a few instances of scalp hair loss. Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten year old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

Overdosage in Concerta[®] Label

OVERDOSAGE

Signs and Symptoms

Signs and symptoms of acute methylphenidate overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

Pediatric Adverse Event Reports for Concerta[®]

December 4, 2003 – January 4, 2005

Re-challenge Information

- Psychiatric adverse events
 - 15 year old psychiatric and non-psychiatric adverse events reported. Unspecified symptoms recurred on restarting Concerta[®]
 - 10 year old with hallucination, diplopia and headache with Concerta[®], events resolved off Concerta[®], re-challenge with one dose resulted in chest pain and back pain, events resolved off Concerta[®]
- Cardiovascular adverse events
 - 11 year old with hypertension, dizziness, chest pain, left atrial enlargement after 4-5 months of Concerta[®], events resolved off Concerta[®], no recurrence at 9 days after re-challenge
 - 14 year old with cardiac arrhythmia, AV block, and increased QT interval after more than a year of Concerta[®], no recurrence on re-challenge after the addition of a beta-blocker