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

Date: October 28, 2008

To: Russell Katz, MD, Director
Division of Neurology Products (DNP)

Through: Mark Avigan, MD, CM, Director
and
Cindy Kortepeter, Pharm. D., Team Leader
Division of Pharmacovigilance I (DPV-I)

From: Charlene Flowers, RPh, Safety Evaluator
Office of Surveillance and Epidemiology, DPV-I

Subject: Psychiatric events

Drug Name(s): Apokyn™ (apomorphine)

Application Type/ Number: NDA #21-264 (approval: 4/20/04)

Applicant/sponsor: Vernalis Pharmaceuticals, Inc.

OSE RCM #: 2007-2223

EXECUTIVE SUMMARY

During the New Molecular Entity (NME) review[1] for Apokyn™, "psychiatric disorder" was identified as an area warranting further investigation. This memorandum summarizes AERS cases of various psychiatric disorders reported in association with Apokyn™. Collectively, we reviewed 20 unique cases of apomorphine-associated psychiatric adverse events in patients with Parkinson's disease. Five patients received apomorphine administered by the **intermittent** subcutaneous (SC) route, consistent with the US approved dosing frequency and route of administration; 14 patients were administered apomorphine via **continuous** subcutaneous infusion, which is an unapproved dosing frequency in the

[1] NME review is a high-level systematic postmarketing review of a US approved product that includes a high-level profile of all AERS cases of adverse events since approval.

US. One US case reported giving the drug by the intramuscular (IM)[2] route. It cannot be determined from this review if the dosing frequency (continuous or intermittent) was a factor that impacted on the psychiatric events of interest. Nonetheless, although eight patients were hospitalized, none reported serious self harm such as completed suicides or harm to others. Reported events included acute psychosis, suicide attempt, paranoia, mental confusion, panic attack, aggression, depression, and hallucinations.

Of the eight patients who required hospital admission for the psychiatric events, one patient[3] of unknown age received 2 weeks of apomorphine, experienced acute psychosis and *attempted* suicide. Two other patients[4], 69 and 70 years of age, reported reemergence of antagonistic behavior or visual hallucinations/paranoia when apomorphine was restarted (positive rechallenge) - these rechallenges strengthen the association with apomorphine.

In conclusion, apomorphine is a dopaminergic agonist indicated for the treatment of Parkinson's disease. Because of the drug's safety profile, including warnings of hallucinations, it is plausible that other CNS adverse events can occur (i.e. psychosis, paranoia, etc.). The AERS cases we describe reported potential confounders in the medical histories or with use of concomitant drugs that are known to cause psychiatric events; however, a contribution by apomorphine in the occurrence of the reported psychiatric events cannot be excluded.

(b) (4)

1 BACKGROUND

1.1 INTRODUCTION

During the New Molecular Entity (NME) review for Apokyn™, "psychiatric disorder" was identified as an area warranting further investigation. This memorandum summarizes AERS cases of various psychiatric disorders reported in association with Apokyn™.

1.2 PRODUCT LABELING

The following list of excerpts is not exhaustive.

WARNINGS: Hallucinations: During clinical development, hallucinations were reported by 14% of the patients. Hallucinations resulted in discontinuation of apomorphine in 1% of patients.
WARNINGS: Avoid Intravenous Administration: Serious adverse events (such as intravenous crystallization of apomorphine, leading to thrombus formation and pulmonary embolism) have followed the intravenous administration of apomorphine. Consequently, apomorphine should not be administered intravenously.

PRECAUTIONS: Drug Interactions: Dopamine Antagonists: Since apomorphine is a dopamine agonist, it is possible that dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthenes) or metoclopramide, may diminish the effectiveness of Apokyn. Patients with major psychotic disorders, treated with neuroleptics, should be treated with dopamine agonists only if the potential benefits outweigh the risks.

[2] Intramuscular administration is not a US approved route of apomorphine administration
[3] 5059196
[4] 5200169 and 5337460

Adverse Event Section: The most common adverse events seen in controlled trials were . . . hallucinations . . . confusion, insomnia, depression

DOSAGE AND ADMINISTRATION: The prescribed dose of APOKYN should always be expressed in mL to avoid confusion and doses greater than 0.6 mL (6 mg) are not recommended. APOKYN™ is indicated for subcutaneous administration only.

The dose of Apokyn must be titrated on the basis of effectiveness and tolerance, starting at 0.2 mL (2mg) and up to a maximum recommended dose of 0.6 mL (6mg).

Most patients studied in the apomorphine development program responded to 0.3 mL to 0.6 mL (3 mg to 6 mg). There is no evidence from controlled trials that doses greater than 0.6 mL (6 mg) give an increased effect and these doses are not recommended. The average frequency of dosing was 3 times per day in the development program, and there is limited experience with single doses greater than 0.6 mL (6 mg), dosing more than 5 times per day and with total daily doses greater than 2.0 mL (20 mg).

HOW SUPPLIED: APOKYN (10 mg/mL) containing apomorphine hydrochloride (as apomorphine hydrochloride hemihydrate), USP is supplied as a clear, colorless, sterile, solution in 2 mL glass ampules and 3 mL cartridges.

2 METHODS AND MATERIALS

2.1 AERS SELECTION OF CASES

On August 18, 2008, we conducted a search of the AERS database for cases of psychiatric disorders reported in association with apomorphine. We searched utilizing the drug names apomorphine, Apokyn, apomorphine%, and Apokyn% as well as the following preferred event terms: *ACUTE PSYCHOSIS, AGGRESSION, AGITATION, ANGER, ANXIETY, CONFUSIONAL STATE, PANIC ATTACKS, PARANOIA, and PSYCHOTIC DISORDER.* The results of this search identified 36 unique cases (25 foreign, 11 U.S.) Of these, 16 cases were excluded from further review because of miscoding or overt association of the reported adverse events with a separate cause.

Table 1. AERS reports excluded from final case series (n=16):

Reason for exclusion	Count of excluded cases
Multiple co-suspect drugs including some labeled for Warnings of psych events	2
Mental confusion, paranoia, and hallucination were secondary to steroid use, known to cause psychiatric disorders	1
A constellation of symptoms including anxiety or aggression during abuse with excessive doses of apomorphine	2
Anxiety was a miscoded preferred term in the case	1
Unlikely temporal association, six years, in a patient with psychiatric history	1
Alternative etiology: Patient's mental reaction of anxiety (4), panic (2), and anger (1) that was secondary to -- 'patients' lack of confidence,' post sleep attack, hypertension episode, lack of sleep, a medical adverse event (2), and an unscheduled medication delivery.	7
Of 107 clinical study patients, 3 experienced worsening or new mental confusion without details (three patients represented in one report)	1
Mental confusion was symptom of an anemic blood disorder	1

3 RESULTS

Twenty cases comprise the final case series. Since the US-approved dosing frequency is intermittent, we've characterized the intermittent cases (section 3.1) separately from those administered via continuous infusion (section 3.2).

3.1 Cases of apomorphine administered ***intermittently***

There were six cases of psychiatric disorders with Apokyn™ (apomorphine) administered by intermittent dosing. All were from the U.S.; 5 were given by the subcutaneous route and 1 by the intramuscular route. In Table 2 we provide overall characteristic information for the 6 cases.

Table 2. Characteristics of unique AERS cases received by FDA between 4/20/04 and 8/18/08 of psychiatric disorders associated with Apokyn™ that was administered intermittently (n= 6)

Age (n=5)	Median = 70 years; mean = 69 years; range 60 – 73 years
Gender	Male (3); female (3)
Indication	Parkinson's Disease (6)
Time to onset [days] (n=4)	1 day, 5 days, 14 days, and 60 days
Route/dose[a] **(frequency = intermittent)**	SC: 0.2 ml [2mg] (2); 0.3ml [3mg] (2); Unknown (1); IM: 0.9 mg daily [0.3mg TID] (1)
Dechallenge	Positive (1)[b]
Rechallenge	Positive (1)[c]
Concomitant medications[d] **[none suspect] (n=4)**	Sinemet™, gabapentin, Mirapex™, Stalevo™, Amantadine, Artane™, domperidone, Zoloft™
Psychiatric Medical History (n=3)	Depression – labeled (1); "chronic psychiatric diagnosis" (1); and panic disorder and depression (1)
Adverse psychiatric events (patients experienced one or more events)	Acute psychosis, suicide attempt, paranoia, mental confusion, panic attack, and aggression
Clinical Outcome	Hospitalization (1); other (5) included one emergency room visit
Report year	2006 (4); 2007 (1); 2008 (1)
Report Type/Source	15 day (4); periodic (2)/ United States [US] (6)

[a] dosing frequency varied, but did not exceed four times daily.
[b] adverse event abated with drug discontinuation or dosage decrease
[c] adverse event reemerged when the drug was restarted
[d] Concomitant drug list included dopamine agonists that are known to cause psychiatric disorders

There were six cases reporting psychiatric adverse events with Apokyn™ administered intermittently, including one case reporting reemergence of an event after restarting Apokyn™ (positively rechallenged). The patient[5] received Apokyn™ for three months and was hospitalized twice for "antagonistic" behavior; the patient was given a second course of the drug and the event reemerged (positive rechallenge). The patient's concomitant medications included Seroquel[6] (start date was not reported).

Another patient[7] of unknown age received Apokyn™ at an unknown dose for 2 weeks to treat Parkinsonism. The patient experienced acute psychosis and attempted suicide. It was unknown if

[5] ISR# 5200169
[6] Seroquel™ antagonizes dopamine and Apokyn is a dopamine agonist (labeled: drug-drug interaction) and both products alone may cause some psychiatric disorders
[7] ISR# 5059196

apomorphine therapy was continued. Concomitant medications were not reported. Three[8] patients receiving apomorphine reported either:

- hallucinations (labeled), depression (labeled), and mental confusion
- increased frequency of panic attacks, or
- visual hallucinations (labeled) with paranoia (no prior history of the events in this case)

One other case[9] reported concurrent use of apomorphine (IM administration) and Seroquel[10] and speculate a drug-drug interaction, manifesting as drowsiness, mental confusion, disorientation, delirium, slurred speech, and inability to keep eyes open; no outcome was reported.

3.2 Cases of apomorphine administered ***continuously***

Included are 14 cases representing documented or suspected ***continuous*** subcutaneous administration. All were from foreign sources. In Table 3 we provide overall case characteristic information for the 14 cases.

Table 3. Characteristics of unique AERS cases received by FDA between 4/20/04 to 8/18/08 of psychiatric disorders associated with Apokyn™ that was administered continuously (n= 14)

Age (years) (n=10)	Average (69); Median (70); Range: 54 - 75	
Gender (n=13)	Male (9); Female (4)	
Indication	Parkinson's Disease (12), Not reported (2)	
Time to onset[a] [days] (n=10)	Median (9) Mean - (10) Range: "hours," 1 day – 5 months	
Route of administration	subcutaneous infusion (11); not reported (3)	
Frequency of administration	Continuous infusion (11)	Suspected continuous infusion(3)[b]
Dechallenge	Positive (8)[c]	
Rechallenge	Positive (1)[d]	
Concomitant medications[e] [none suspect] (n=9)	levodopa, pramipexole, Modapar™, rasagiline, ropinirole, Sinemet™, amantadine, Seroquel™, domperidone, Stalevo™, and tramadol.	
Psychiatric Medical history (n= 5)	"little prior history of psychiatric illness + depression without drug management" (1); hallucination (1); mental confusion + cabergoline related psychosis (1); dopamine agonist related hallucination + paranoia (1); schizophrenia and depression (1)	
Adverse Psychiatric events (patients experienced one or more events)	Hallucination (labeled), agitation, aggression, mental confusion, paranoia, "thought disorder," "psychosis"	
Clinical Outcome	Hospitalized – 8[f]; other – 6	
Report year	2005 – 2, 2006 -1, 2007 – 9, 2008 - 2	
Report type/Source	15 day – 14/ Foreign - 14	

[a] Time-to-onset: median and mean values do not include outlier of 5 months.

[b] Apomorphine continuous SC infusion is suspected in these cases because it is an acceptable drug frequency in non-US countries, and in our case series similar non-US countries reported continuous SC infusion. Mixed infusion, continuous and intermittent SC may also occur.

[8] ISR# 5538327, 5210632, and 5210606

[9] ISR# 4732422

[10] Seroquel™ antagonizes dopamine and Apokyn is a dopamine agonist (labeled: drug-drug interaction) and both products alone may cause some psychiatric disorders

[c] adverse event abated with drug discontinuation or dosage decrease
[d] adverse event reemerged when the drug was restarted
[e] Concomitant medications include dopamine agonists known to cause psychiatric disorders
[f] One hospitalization admission was for a non-psychiatric related event - (abdominal pain and granuloma management).

We reviewed 14 cases of psychiatric events associated with apomorphine administered by the continuous subcutaneous route. There were seven hospital admissions pertaining to psychiatric events and one hospitalization associated with a non-psychiatric event. Although some patients were hospitalized to initiate drug administration with continuous SC infusion, their admission was prolonged for the following reasons:

- Psychosis manifested as aggression
- Paranoid/visual and auditory hallucinations/suicide attempt
- Hallucination/mental confusion
- Visual hallucination/"psychosis with jealous mania"
- Visual hallucination/paranoia
- Psychosis manifested as mental confusion/hallucination/paranoia
- "Psychosis"

Two patients admitted for psychiatric events required management with clozapine and quetiapine.

Of the 14 cases, 5 reported a past psychiatric history that included one of the following:
- "little prior history of psychiatric illness: depression with drug management"
- hallucination, mental confusion and cabergoline associated psychosis
- dopamine agonist related hallucination and paranoia
- schizophrenia
- depression.

Nine patients reported use of one or more of the following concomitant drugs that are known to be associated with psychiatric events: Levodopa, pramipexole, Modapar™, rasagiline, ropinirole, Sinemet™, amantadine, domperidone, Limptar™ (quinine), Seroquel™, quetiapine, Stalevo™, and Tramadol™.

Eight cases reported patients who either decreased their dose (2) or discontinued (6) apomorphine and recovered or improved. One compelling case with a positive rechallenge follows:

ISR# 5337460/Italy/2007
A 70 year old female with "little history of psychiatric illness and depressive thoughts that did not require medical intervention" received apomorphine via continuous SC infusion for the treatment of Parkinson's disease. She experienced the following events over a course of five months: she became paranoid and was convinced that her caregiver wanted to kill her, believed her food was poisoned and refused to eat, became agitated, and heard strange voices and felt threatening presences in her bedroom. After admission to a psychiatric hospital, she attempted to jump from a window because she thought the people in the house were going to kill her. She was treated with increased clozapine and decreased apomorphine doses. Apomorphine was subsequently discontinued. The visual and auditory hallucinations improved, but the paranoia persisted. The patient was restarted on apomorphine and one month later, her hallucinations returned (positive rechallenge). Apomorphine and clozapine therapy

continued, and she continued to experience occasional visual hallucinations and paranoia, however, her overall psychiatric condition was stable at the time of the report.

All cases are summarized in a line listing in Table 4 in the appendix.

4 DISCUSSION

Collectively, we reviewed 20 unique cases of apomorphine associated psychiatric adverse events in patients with Parkinson's disease. Five patients received apomorphine administered by the **intermittent** subcutaneous (SC) route, consistent with the US approved dosing frequency and route of administration; 14 patients were administered apomorphine via **continuous** subcutaneous infusion, which is an unapproved method of dosing in the US. One US case reported giving the drug by the intramuscular (IM)[11] route. It cannot be determined from this review if the infusion frequency (continuous or intermittent) was a factor that impacted on the psychiatric events of interest. Nonetheless, although eight patients were hospitalized, none reported serious self harm such as completed suicides or harm to others.

Of the eight patients who required hospital admission for the psychiatric events, one patient[12] of unknown age received a 2 week course of apomorphine and experienced acute psychosis and attempted suicide; two other patients,[13] 69 and 70 years of age, reported reemergence of antagonistic behavior or visual hallucinations/paranoia when apomorphine was restarted (positive rechallenge). These rechallenges strengthen the association with apomorphine.

These were adult patients who received apomorphine primarily via the subcutaneous route of administration for the treatment of Parkinson's disease. The cases reported patients with a medical history positive for psychiatric disorders 40% (8 of 20 patients) or with concomitant drug use known to be associated with psychiatric events 65% (13 of 20 patients), including often co-prescribed dopaminergic agonist (i.e. Levodopa, which is labeled for psychiatric events); however, an involvement of apomorphine in the occurrence of the reported psychiatric events including a possible additive effect with concomitant dopaminergic drug use cannot be excluded.

5 CONCLUSION/RECOMMENDATIONS

Apomorphine is a dopaminergic agonist indicated for the treatment of Parkinson's disease. We reviewed 20 unique cases of psychiatric disorders associated with apomorphine use, including cases with a positive rechallenge. Because of the drug's safety profile, including warnings of hallucinations, it is plausible that other CNS adverse events can occur (i.e. psychosis, paranoia, . . .).

(b) (4)

[11] Intramuscular administration is not a US approved route of apomorphine administration
[12] 5059196
[13] 5200169 and 5337460

Appendix I. Line listing of all cases of apomorphine associated psychiatric events

Table 4. AERS cases of apomorphine associated psychiatric events (n = 20)

ISR#	Age	Sex	Origin	Narrative
4732422	60	M	US	The patient was being treated with Seroquel (quetiapine fumarate) 400 mg oral and Apokyn (apomorphine) 0.3 mg **IM** three times daily, but not in the evening, for Parkinson's disease. The patient has been taking Seroquel and Apokyn since prior to 2002. The patient experienced drowsiness, severe confusion and disorientation, delirium, slurred speech, and could not keep his eyes open after he combined Seroquel and Apokyn. The patient has been switched to Seroquel 400 mg in the evening, and Apokyn 0.3 mg TID, but not in the evening.
5059196	NR$^{\infty}$	M	US	A physician reported that a Hispanic male (age unknown) received subcutaneous apomorphine hydrochloride (Apokyn), dose, frequency, and indication not reported. Approximately two weeks after apomorphine hydrochloride was initiated, the patient experienced acute psychosis and a potential suicide attempt. According to the reporter, the patient was admitted to a psychiatric emergency room. It was unknown if therapy with apomorphine hydrochloride continued. At the time of this report, the outcome was unknown.
5200169	69	M	US	A 69 year old male initiated therapy with apomorphine hydrochloride in Nov-2005. At the end of 2005, the patient began to be "antagonistic" toward the reporter where the patient would hit the reporter. Therapy with apomorphine hydrochloride was discontinued. According to the reporter, the patient was hospitalized for the antagonistic behavior in (b) (6) and at the end of (b) (6) On 03-Nov-2006, the patient was re-started on apomorphine hydrochloride (0.2 ml approximately twice a day) and he again exhibited antagonistic behavior.
5210606	71	M	US	A 71 year old male initiated apomorphine and experienced insomnia, depression, hallucination, and confusion. The patient shot his wheelchair because he thought that it was another person in his house.
5210632	73	F	US	After five days of apomorphine therapy, the patient reported an increased frequency of panic attacks.
5538327	69	F	US	A 69 year old female who did not have a history of hallucinations or paranoia received apomorphine (date not reported), and experienced sleepiness, visual hallucinations, and paranoia. The patient's husband indicated that his wife experienced the same side effects no matter what dose of apomorphine hydrochloride was administered. Apomorphine was discontinued and all the events resolved.
5337460	70	F	Italy	A 70 year old female with "little history of psychiatric illness and depressive thoughts that did not require medical intervention" received apomorphine continuous SC infusion for the treatment of Parkinson's disease. She experienced over a course of five months the following events: she became paranoid and was convinced that her caregiver wanted to kill her, believed her food was poisoned and refused to eat, became agitated, heard strange voices and felt threatening presences in her bedroom. After admission to a psychiatric hospital, she attempted to jump from a window because she thought the people in the house were going to kill her. She was treated with increased clozapine doses and decreased apomorphine doses, then apomorphine was discontinued. The visual and auditory hallucinations improved, but the paranoia persisted. The patient was restarted on apomorphine and one month later, her hallucinations returned (positive rechallenge). Apomorphine and clozapine therapy continued and she continued to experience occasional visual hallucinations and paranoia, however, her overall psychiatric condition was stable at the time of the report.
4665061	67	M	GB	Medical history included previous hallucinations and some obsessive behavior on ropinirole, which resolved after discontinuation. The patient was restless, confused, experienced nocturnal hallucinations, sexual hallucinations, and exhibited paranoid behavior subsequent to apomorphine continuous subcutaneous infusion.. The events required inpatient hospitalization. Apomorphine was discontinued and quetiapine was administered.
5174405	NR$^{\infty}$	M	DE	Less than one day after initiation, the patient developed psychotic symptoms (including aggressiveness and confusion); the patient was then admitted to a psychiatric hospital. At the time of this report, the outcome was unknown and the status of apomorphine hydrochloride therapy was not specified.

ISR#	Age	Sex	Origin	Narrative
5269644	54	M	DE	A 54 year old male patient with a history of schizophrenia and depression received subcutaneous infusion apomorphine hydrochloride (APO-go) [drug details and indication for use not reported]. The physician indicated that in addition to the apomorphine hydrochloride infusion, the patient may have been misusing apomorphine hydrochloride. In (b) (6), the patient was admitted to the hospital for an infected granuloma. In the same month, the patient also experienced hallucinations, paranoid symptoms, and decreased hemoglobin. Treatment during the patient's hospitalization included antibiotics and extirpation of one necrotic granuloma. On an unknown date in January 2007, therapy with apomorphine hydrochloride was discontinued and the dose of levodopa was increased. Subsequently, the hallucinations and paranoid behavior completely resolved. The date of resolution was reported as January, 2007. On (b) (6), the patient was discharged from the hospital. According to the reporter, the events were probably related to apomorphine hydrochloride use.
5397274	70	M	DE	A 70 year old patient with a history of a mental disorder, including an aggravation of psychotic symptoms during treatment with cabergoline (dates unspecified was hospitalized for apomorphine initiation. The dose was subsequently increased to an unknown level on an unknown date in May. On (b) (6) the patient experienced hallucinatory symptoms and "thought disorders" in which he "believed that his money would be stolen". The physician confirmed that these events prolonged the patient's existing hospitalization. On the same day, the patient's apomorphine hydrochloride dosage was decreased to 4.5 mg/hour. The patient's quetiapine dosage was also increased to 25 mg, three times daily on (b) (6) Or (b) (6) the patient prematurely discharged himself from the hospital. According to the physician, the events were probably related to apomorphine hydrochloride therapy. At the time of this report, the events were ongoing.
5551070	NR∞	NR∞	DE	Therapy with apomorphine hydrochloride was initiated on an unspecified date. Subsequently (time to onset unknown), the patient developed psychosis and was admitted to the hospital. Therapy with apomorphine hydrochloride was discontinued on the same day. It was not indicated whether the patient had been discharged from the hospital.
4750055	75	M	GB	A 75 year old male patient with Parkinson's disease was receiving apomorphine 5 mg/hour as a subcutaneous infusion and developed aggressive and hypersexual behaviour on 03/16/05. The reaction abated on 04/20/05 after stopping the drug and the outcome was described as 'improved' at the time of reporting.
5223290	73	M	GB	A 73 year old male patient received subcutaneous infusion of apomorphine hydrochloride (APO-go) (30 mg/12 hours) for the treatment of Parkinson's disease. One day after apomorphine hydrochloride was initiated, the drug was discontinued after the patient exhibited psychotic behavior manifested as confusion, agitation, unsettling behavior, and aggression towards the staff. The patient was treated with 12.5 mg of quetiapine and was allowed to return home. The reporter considered the patient's psychotic behavior to be possibly related to apomorphine hydrochloride therapy.
5223296	66	M	GB	A 66 year old male initiated therapy with apomorphine hydrochloride in November 2006 for the treatment of long standing Parkinson's disease. On approximately 07-Nov-2006, the patient developed "major psychiatric problems especially at night." Symptoms included confusion, hallucinations, and paranoia. Blood tests and a computed tomography (CT) scan of the head showed normal results (measurements not provided). Therapy with apomorphine hydrochloride was discontinued in December, 2006. According to the neurologist, the event was probably due to therapy with apomorphine hydrochloride. At the time of this report, the event was reported as improved.
5313505	67	F	GB	A 67 year old female patient, with a history of hallucinations and constipation, received subcutaneous infusion of apomorphine hydrochloride (APO-go), 1 mg/hr, for the treatment of Parkinson's disease. Concomitantly, the patient received Sinemet Plus, amantadine, domperidone, quetiapine, co-amilofruse, and docusate sodium. Therapy with apomorphine hydrochloride was initiated on 20-Feb-2007. That day (time to onset not reported), the patient experienced psychotic symptoms. According to the reporter, the patient was "lashing out at people with her walking stick". The reporter also stated that the event resulted in a prolongation of the patient's hospitalization. Therapy with apomorphine hydrochloride was discontinued on 21-Feb-2007. On unknown dates, the dose of amantadine was gradually reduced and then discontinued. The patient was also started on rivastigmine, 1.5 mg daily (start date not reported). The psychotic symptoms resolved on 02-Mar-2007. According to a psychiatrist who evaluated the patient, the event was caused by apomorphine hydrochloride. The reporter noted that on an unknown date the patient had scored a 24.5 on a recent Mini Mental State Examination. The reporter also indicated that a long period of hospitalization had been planned for this patient.

ISR#	Age	Sex	Origin	Narrative
5320895	NR∞	M	GB	A male patient (age unknown) received subcutaneous infusion of apomorphine hydrochloride (APO-go), 5 mg/hr, for the treatment of Parkinson's disease. Concurrently, the patient received "lots of other medications for Parkinson's disease". Therapy with apomorphine hydrochloride was initiated on an unknown date. According to the reporter, the patient had been taking apomorphine hydrochloride, at the original dose of 1.5 mg/hr, "for a long time". At an unspecified time in 2006, a previous consultant had increased the dose of apomorphine hydrochloride from 1.5 mg/hr to 5 mg/hr. Subsequently, the patient experienced hallucinations, became very agitated, and was "shouting and screaming". On one occasion, according to the reporter, when the patient's wife tried to place a tablet in his mouth, he "almost bit it off completely". The onset date of these events was not stated. On an unknown date, the events worsened. In October 2006, the patient changed consultants. This consultant, the reporter, considered the patient to be "overdosed by 30%". Therapy with apomorphine hydrochloride was discontinued in October 2006 and the events resolved. The stop date for the events was not reported. At the time of this report, no additional information was available.
5339884	NR∞	F	GB	Therapy with apomorphine hydrochloride was initiated on an unknown date. The reporter indicated that the dose of apomorphine hydrochloride has not significantly changed over the past six months. On an unspecified date, two hours after starting an apomorphine hydrochloride infusion, the patient experienced "extreme paranoia and aggressiveness". According to the reporter, it was not uncommon for the patient to experience these events; however, the symptoms were more severe than usual. It was unknown if therapy with apomorphine hydrochloride continued.
5819685	76	M	GB	A 76 year old elderly male consumer, with a history of hypercholesterolemia and unspecified pain, received subcutaneous apomorphine infusions, 4 mg per hour, for the treatment of Parkinson's disease. Concurrently, the patient received salicylic acid, candesartan, domperidone, paracetamol, ibuprofen, ropinirole, simvastatin, Sinemet, tramadol, and verapamil. Therapy with apomorphine was initiated on 09-Jun-2008 at a dose of 3 mg per hour (total daily dose not specified). On 16-Jun-2008, the patient's dose of apomorphine was increased to 4 mg per hour (total daily dose not specified). Subsequently, on 19-Jun-2008, the patient developed confusion, drowsiness, hypotension (blood pressure readings not provided), a rash, and swollen ankles. Therapy with apomorphine was discontinued on 21-Jun-2008. The reporter considered the events to be medically significant since "the patient was at risk from falls due to drowsiness and confusion overnight." At the time of this report, the events were resolving.
5603249	70	F	GB	A 70 year old female consumer received subcutaneous apomorphine hydrochloride (APO-go), 2 mg (frequency unknown), for the treatment of on-off periods with Parkinson's disease. Concurrently, the patient received Cilroton (domperidone). On an unspecified date, therapy with apomorphine hydrochloride was initiated. In October 2007 (exact date not reported), the patient developed agitation, aggression, and hallucinations, "during titration." Therapy with apomorphine hydrochloride was subsequently discontinued on an unspecified date in October 2007. After apomorphine hydrochloride therapy cessation, the patient's adverse events resolved on an unknown date in October, 2007.

∞ NR = Not reported

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

/s/

Charlene Flowers
10/29/2008 02:14:51 PM
DRUG SAFETY OFFICE REVIEWER

Cindy Kortepeter
10/29/2008 02:17:56 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
10/29/2008 06:52:46 PM
DRUG SAFETY OFFICE REVIEWER