

- Bertek expects to completely reply to the approvable letter in late September 2003 if the Division agrees that the mass balance studies data can be provided at a later date
- Previously, Bertek believed that, based on old and faulty techniques, auto-oxidation is the major metabolic elimination path, but currently Bertek no longer believes that auto-oxidation is the major metabolic pathway

Use of Proposed Algorithm for Characterizing Treatment of "Off" Relative to Dosing Interval

- The Division had questions about proposed algorithm
- There was some discussion about defining end of dose "off" relative to the length of the dosing interval and not just in terms of absolute time (i.e., one hour pre next dose)

Cut-off Date Changes to Safety Update and Serious Adverse Event

- The Division accepts the change in the cut-off date for the safety update from May 31, 2002 to December 31, 2002, and accepts the new Serious Adverse Event report cut-off date June 30, 2003

ACTION ITEMS

- 1 Bertek will provide as much information as available regarding plasma metabolite data, and an argument explaining why auto-oxidation is incorrect and why the studies represented in the posters are accurate
- 2 Since a mass balance study will take almost a year to conduct, it may be acceptable to accept these data post approval Bertek should provide a time line for completion of this study
- 3 The Division will present this concern to the Office Director, Dr Temple

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Teresa Wheelous
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CSO

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MEDICAL OFFICER

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**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I**

FACSIMILE TRANSMITTAL SHEET

DATE: July 2, 2003

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Subject NDA 21-264 Apomorphine HCl Injection Approvable Letter

Total no of pages including cover 37

Frank,

The following is a copy of the approvable letter for Apomorphine that was signed today

Document to be mailed YES

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MEMORANDUM

DATE June 27, 2003

FROM Director
Division of Neuropharmacological Drug Products/HFD-120

TO File, NDA 21-264

SUBJECT Recommendation for Action on NDA 21-264, for the use of
Apomorphine Hydrochloride subcutaneous injection \square
 \square Parkinson's Disease

NDA 21-264, for the use of Apomorphine Hydrochloride subcutaneous injection \square \square Parkinson's Disease (PD), was submitted by Bertek Laboratories on 4/17/00. The Division refused to file the application because of pre-clinical and clinical deficiencies (the latter related to inadequate safety data). The Division had multiple meetings with the sponsor subsequent to this action, and the application was re-submitted on 12/31/02. The application was granted Fast Track status, on the basis of the fact that it is the first treatment proposed for the acute treatment of "Off" periods (episodes of often complete immobility in advanced PD patients, occurring either at the end of a Sinemet dosing interval or at random times) in this population.

The application consists of data from four randomized controlled trials, safety experience in 536 unique individuals, CMC, pre-clinical, and pharmacokinetic data. The application has been reviewed by Dr. Len Kapcala, medical reviewer (reviews dated 6/20/03 and 6/27/03), Dr. Sharon Yan, statistician (review dated 6/16/03), Dr. Thomas Broadbent, chemist (review dated 6/13/03), Dr. John Duan, Office of Clinical Pharmacology and Biopharmaceutics (review dated 6/25/03), Dr. Paul Roney, pharmacologist (review dated 6/17/03), Dr. Lois Freed, supervisory pharmacologist (memo dated 6/27/03), Dr. Stephen E. Langille, microbiologist (reviews dated 6/12/00, 4/9/03, and 5/14/03), and Dr. John Feeney, Neurology Team Leader. The review team (with the exception of Dr. Roney) recommends that the application be considered approvable, although they have many comments.

I will briefly review the pertinent data, and offer the division's recommendation for action on this NDA.

EFFICACY

As noted above, the sponsor has submitted the results of four controlled trials: Studies 202, 301, 302, and 303.

Study 202

This was a randomized, placebo controlled, parallel group study in PD patients with "Off" periods presumably optimally treated with available oral anti-PD medications. The primary analysis was to be performed on the results of a single dose with either treatment, although patients were to be continued on their randomized treatment for a total of 4 weeks. A total of 30 patients were to complete the study, with a 2:1 randomization to drug and placebo.

Patients were to come to the site the night before the study was to begin, and their regular AM dose of Sinemet was withheld. At the onset of an "Off" period, assessment of motor function was done, followed by administration of their standard dose of Sinemet. Within 60-120 minutes, or the onset of an "On" period, motor function was assessed again. If a patient experienced a 30% improvement in motor function (as assessed by the UPDRS motor score) after Sinemet dosing compared to their motor function during the "Off" period, they were considered Dopamine Responsive, and returned for the controlled trial.

The controlled trial followed the above phase. In this phase, an "Off" period was precipitated as described above, and the patient's motor function was assessed. Patients were randomized to receive either apomorphine or placebo at this point, and treated with an initial dose of 2 mg (or placebo). If the patient did not obtain a response that was at least 90% of the response seen with their regular Sinemet dose in the earlier phase, the dose was escalated to 4 mg or corresponding placebo (given no earlier than 2 hours after the first dose). If a therapeutic effect was not achieved, the study drug was increased by 2 mg increments until a response as defined above was achieved, or a maximum single dose of 10 mg (or corresponding placebo) was administered. The various doses could have been administered on different days.

The primary analysis was the ratio of the percent change in UPDRS Motor Scale following study drug to the percent change following the Sinemet dose. Secondary variables included a hand-tapping test and a test of timed walking.

A total of 29 patients (20 on apomorphine, 9 on placebo) were included in the intent-to-treat dataset.

Of the 20 patients randomized to apomorphine, 18 achieved a Therapeutic Equivalent Dose, while no placebo patient did. The following table displays the distribution of these doses.

Dose	N
2 mg	3
4 mg	7
6 mg	5
8 mg	3

The results of the primary analysis was as follows

	Apomorphine	Placebo	P-value
UPDRS	0.96	0.0	<0.0001
Hand-tapping	0.84	-0.04	<0.0001
Timed walking	1.0	-0.04	<0.0001

Study 301

This was a randomized, placebo controlled, cross-over study in patients receiving sc apomorphine for at least 3 months. In this trial, patients received their typical dose of apomorphine (or placebo) given as a single dose to treat an "Off" period that occurred at least one hour after AM dosing of their routine anti-PD medications, they were then crossed over to the other treatment on the next day. In this study, patients continued to take their routine standard treatment of Sinemet and other anti-PD drugs (that is, an "Off" period was not induced). The primary outcome was the change in UPDRS Motor Score from pre-dose to 20 minutes post-dosing with study medication. Patients were also assessed at other time points for 60 minutes post-study drug administration, and the time to first perception of significant relief of immobility.

A total of 17 patients were randomized, with 16 patients having data for both treatment periods. Most patients received single doses of 5 mg or less (9 patients received a dose of 3 mg); one patient each received a dose of 8 or 10 mg. The following table presents the pertinent results.

Time	Sequence	Pd 1 Median	Pd 2 Median	P-value
10 min	A-P	-14.5	2	0.004
	P-A	-3	-13.5	
20 min	A-P	-23.5	1.5	0.002
	P-A	-3.5	-22.5	
60 min	A-P	-17.5	2.5	0.005
	P-A	-1	-5.5	

A test for period effect yielded a p-value of 0.67, but the power of this test is quite small. There was a numerical improvement in placebo treated patients in Period 1, but not in Period 2, but the median improvement in Period 1 for Apo was -23.5 and for Placebo, -3.5, still a large between-treatment difference.

Study 303

This was a randomized, placebo controlled cross-over study in patients comparing the effects of a 4 mg dose of apomorphine to placebo

This study was a "forced" titration study, designed primarily to assess tolerability and safety in patients experiencing spontaneous "Off" periods. Patients first received a single, open-label dose of 2 mg of apomorphine. On their next visit, they were randomized to receive either apomorphine 4 mg or placebo. On the next visit, they received the opposite treatment. In subsequent visits, they were to receive open-label doses of 6 mg, 8 mg, and 10 mg. Dose titration was discontinued at any point that the patient experienced intolerable adverse effects. After the dose escalation, they were to receive their selected dose for 6 months open-label treatment.

The primary analysis was on the change in UPDRS Motor Score from pre-dose to 20 minutes after dosing (4 mg vs placebo). Change in UPDRS from pre-dose to 40 and 90 minutes post-dose and AUC for UPDRS out to 90 minutes post-dose were also assessed.

A total of 50 patients had data for both treatment periods. The following table presents the relevant results for the mean change from pre-dose UPDRS to the described time point.

Time	Placebo	Apomorphine	P-value
20 min	-2.8	-11.2	0.0002
40 min	-3.0	-13.5	<0.0001
90 min	-1.6	-5.0	0.02

While these results were obviously significant, a significant period effect was detected ($p=0.004$) for the 20 minute time point (see the table below). Therefore, an analysis of the first period data was performed, the p-value for this contrast was 0.17. The following table presents the results by period.

Period	Measure	Apomorphine	Placebo
1	Mean	-9.5	-4.6
	Median	-7	-1
2	Mean	-13.0	-0.6
	Median	-12	-1

The sponsor believed that the data were not normally distributed and performed a non-parametric analysis of the data which yielded significant results at all 3 time points. Dr. Yan concluded that the data were normally distributed and therefore performed an ANOVA with the results shown above.

Study 302

This was a randomized, double-blind, placebo controlled, parallel group study in patients being treated with sc apomorphine for "Off" periods for at least 3 months. In this study, patients were randomized to one of 4 single-dose treatments in a 2:1:2:1 ratio: 1) their routine dose of apomorphine, 2) placebo "routine" dose, 3) routine apomorphine + 2 mg, or 4) placebo "routine" dose + 2 mg (0.2 mL). Patients were to treat an "Off" period that occurred at least one hour after their AM dose of their routine oral anti-PD medications. The primary outcome was the change in UPDRS Motor Score from pre-dose to 20 minutes after dose in the pooled drug vs pooled placebo groups. If this comparison was significant, comparisons of the individual groups were to be performed. Responses at 10 and 90 minutes, timed walking, time to patient declared relief, AUC for up to 90 minutes, and percent change in UPDRS Motor Score were also assessed.

A total of 60 patients were to be randomized: 40 to apomorphine, 20 to placebo. Ultimately, 35 patients were randomized to drug, and 27 to placebo. The following table presents the pertinent results for the comparisons for the individual apomorphine doses on Mean Change from pre-dose in UPDRS Motor Score (the primary pooled analysis revealed highly significant between-treatment differences at 10 and 20 minutes, but not at 90 minutes).

Time	Routine APO Dose	Pbo	P-value
10 min	-16.5	-5.6	0.0003
20 min	-23.7	-7.4	<0.0001
90 min	-4.8	-4.9	0.96

(the results for the APO + 2 mg vs placebo contrasts essentially mirrored these)

Analyses of AUC were strongly significant (p-values all equal to or less than 0.0005), and analyses of timed-walking revealed significant p-values from 7.5 minutes post-dose to 40 minutes post-dose (last time tested). Analyses of the time to onset of relief did not detect significant between-treatment contrasts (see Dr. Yan's review, page 39-42).

SAFETY

The NDA contains reports of safety experience in 536 unique individuals. Unlike most typical NDAs, there is very little controlled trial data, and the controlled trial subjects received only single doses in controlled settings (although several of the controlled trials enrolled patients who had been treated with apomorphine for at least 3 months, this extended treatment occurred prior to enrollment in the trials, and this pre-randomization experience was not systematically collected)

Most of the extended safety data were obtained in Study 401 (N=444), an open-label extension study in which patients were followed for 6 months or more. Complicating the interpretation of the safety data is the fact that there is little controlled trial safety data, there was no randomization to fixed doses, patients treated themselves chronically with a variable number of doses per day, and the population is elderly with multiple medical problems in whom background rates of serious medical events are unknown quantitatively, but the rates are clearly substantial.

There were a total of 5217 days in which dosing data were recorded in patient diaries (this represents a small percentage of total days in which patients received treatment, but should be representative of the complete experience). In these 5217 recorded days of dosing, 94% (4908) of the single doses utilized by patients were between 2 mg and 7 mg. In approximately 75% of these days, patients self-administered 4 or fewer injections. A total of about 78% of the daily doses recorded were 20 mg or below.

A total of 311 patients received treatment for between 6-12 months, and 171 patients received treatment for at least 1 year. Approximately 84% of the experience in patients who received treatment for 6-12 months was obtained with individual doses of 6 mg or less (mean about 4 mg), and approximately 89% of the experience greater than 1 year was obtained at individual doses of 6 mg or less.

Overall, approximately 75% of patients received fewer than 4 injections per day (mean of 3).

DEATHS

There were a total of 14 deaths reported in the database, all of which occurred in Study 401. Dr. Kapcala has examined the records for these deaths, while there are no deaths that clearly appear to be drug related, there are a number of cases for which we do not have sufficient information to completely rule out a contribution of the drug. As Dr. Kapcala notes, it is at least possible that patients experienced vomiting or hypotension that could have contributed to events that led to a patient's death (e.g., aspiration leading to pneumonia, hypotension).

leading to falls, etc) We have no way of knowing if drug contributed in these cases, nor do we have a reliable estimate of the background mortality in this population, so it is difficult to assess whether or not the experience here represents increased mortality compared to the background rate Both Drs Kapcala and Feeney consider 2 hours post-dose to be the period of risk for potentially drug-related adverse events I am inclined not to restrict our examination to this period, it seems quite possible that an event (e g , hypotension) could occur beyond 2 hours post-dose, or, even if it was restricted to the 2 hour period, a clinical sequelae could occur at a later time (hypotension at, say, 1 hour post-dose causing an MI several hours later) It should be noted, however, that we have no affirmative evidence that any of these deaths were drug related

Serious Adverse Events (SAEs)

There were no SAEs reported in apomorphine treated patients in the controlled trials Dr Kapcala's Table 15 (page 61 of his review) lists the SAEs reported in the total safety database

The most common SAEs as reported by the sponsor were pneumonia (3%), followed by fall (2%), with many events occurring at 1% (3-4 patients each)

Dr Kapcala re-grouped a number of terms that appeared to describe reasonably similar events, when he did this, he re-calculated rates for pneumonia (4.3%), fall (4.8%), and cardiovascular events, including arrhythmia, heart failure, coronary artery disorder events, syncope and hypotension (3%)

He examined narratives for these events, he concluded that while there seemed to be no obvious connection to treatment, for most cases there was insufficient evidence presented to definitively rule out a contribution of the drug While he considers a number of these cases "possibly" related to treatment, I am not as convinced that we can conclude anything about drug-relatedness of these cases

Of particular note, Dr Kapcala determined that there was a greater incidence of SAE falls (5% vs 2%) and bone and joint injuries (6% vs 1%) in patients taking vasodilators compared to those who were not

Further, he noted that the hazard for the occurrence of SAEs remained constant throughout the duration of treatment at about 0.2 events/patient-year for any interval (see his Table 16, page 66)

Discontinuations

There were 3 discontinuations from apomorphine in the controlled trials, all from Study 202, the longest controlled trial, 1 due to chest pain, one due to nausea and vomiting, and one due to a schedule conflict

A total of 120 patients (22.4%) discontinued treatment due to an adverse event. The most common adverse event responsible for treatment discontinuation was nausea in 3% of patients, followed by dyskinesia and vomiting (each 2.1%), and dizziness (not vertigo) and death (each 1.7%), somnolence (1.5%), hallucinations (1.1%), and back pain and hypotension (each 0.9%).

Interestingly, as Dr. Kapcala also notes, the rate of patient discontinuation due to an adverse event is about 4 patients/patient-year within the first week of treatment initiation, drops to 0.8 patients/patient-year in the next 3 weeks, then drops to between 0.1-0.3 patients/patient-year for remaining treatment duration intervals (see his Table 21, page 79). As he further notes, it appears that the high rate of discontinuation due to an adverse event shortly after treatment discontinuation is also related to the initial dose, being greatest at initial doses of 6 mg or more, but not necessarily related to the number of injections/day.

Adverse Events

As pointed out earlier, there is little controlled trial data in which to evaluate the relative incidence of adverse events attributable to apomorphine. Further, most of the controlled data were derived in studies in which only single doses were given in controlled settings.

However, in Study 202, patients were in a randomized setting for up to 4 weeks. In this study, the following rates of ADRs were reported (taken from Dr. Kapcala's Table 22, page 81):

Event	Apomorphine (%) N=20	Placebo (%) N=9
Yawning	8 (40%)	0
Dyskinesia	7 (35%)	1 (11%)
Somnolence	7 (35%)	0
Nausea/ Vomiting	6 (30%)	1 (11%)
Dizziness	4 (20%)	0
Rhinorrhea	4 (20%)	0
Chest Pain	3 (15%)	1 (11%)
Hallucination/ Confusion	2 (10%)	0
Edema	2 (10%)	0

Adverse events in the other controlled trials essentially mirrored this experience, although it should be noted that in two of the studies, patients had already been on the drug for greater than 3 months in uncontrolled (and undocumented)

settings, it is difficult to know how to interpret ADRs seen in the single dose controlled setting in these cases (i.e., the rates seen may be underestimates, given that these patients were presumably a selected subset who could reasonably well tolerate the drug)

Dr Kapcala's Table 28 (page 87) describes the most common ADRs in the entire database. The most common events in descending order were nausea (30%), fall (22%), dyskinesia (21%), dizziness (17%), somnolence (18%), yawning (15%), injection site bruising (15%), hallucinations (12%), and vomiting (10%)

As with SAEs, the sponsor and Dr Kapcala further examined certain events that could reasonably be combined, these events included ADRs suggestive of falls, orthostatic hypotension, and postural dizziness. A total of 128 patients (24%) experienced 323 events reasonably considered falls. A total of 53 patients (10%) had events reasonably considered suggestive of orthostatic hypotension (hypotension, postural hypotension, decreased blood pressure, syncope), and 125 patients (23%) had events suggestive of postural dizziness. I cannot tell from the analyses presented how many unique patients are included in these analyses, and all of the suggested events (falls, hypotension, and orthostatic hypotension) could reasonably be considered to represent similar events (that is, they could all be manifestations of hypotension, orthostatic or not)

As with SAEs and ADRs related to discontinuation, Dr Kapcala examined the time course of ADRs (Table 29, page 91). The rate of ADRs was greatest in the first week (27 patients/pt-yr), decreasing to about 8 patients/pt-yr for the remainder of the first month, dropping to about 2 patients/pt-yr from the 1st to the 6th month, with decreasing rates beyond that.

Again, there is very little data in the NDA that can speak directly to dose response. Recall that in Study 303, patients were to receive increasing doses in a "forced" paradigm, that is, they were to receive doses up to 10 mg, if tolerated. While the numbers of patients dropped dramatically as the doses were increased (56 patients received 2 mg, 51 received 4 mg, 44 received 6 mg, 25 received 8 mg, and 14 received 10 mg), it does appear that at least certain ADRs were dose related, not unexpectedly (see Dr Kapcala's Figure 2, page 94). Of course, again, these data may present an underestimate of the true rate of ADRs at increasing doses, given that only patients who can tolerate the drug receive the higher doses.

Laboratory Findings

There were infrequent laboratory values that were increased over baseline and few that were persistently abnormal or persistently reached criteria for being clinically meaningful. Dr Kapcala notes that, in his view, were apparent persistent increase in the percentage of eosinophils in a small number of patients. However, I have discussed this with him and it appears that only 1

patient had a persistent slight increase in the percentage of peripheral eosinophils

Orthostatic Hypotension

Dr Kapcala examined in detail the capacity of apomorphine to cause orthostatic hypotension. Much of the work focussed on the data from Study 303, in which, again, patients received increasing doses of drug over hours to days. These analyses are summarized in Tables 35-44, pages 107-111 of his review.

Tables 40 and 41, page 110, present the change from placebo in the change from pre-dose systolic and diastolic blood pressure in the sitting and standing positions (the sponsor did not systematically evaluate change from supine to standing). Mean drops in systolic pressure compared to placebo appeared to peak at about 20 minutes after dosing, although changes persisted out to 90 minutes post-dosing. Decreases compared to placebo ranged from about 10 mm Hg at 4 mg to 15 mm Hg at 8 mg. Similar, but slightly smaller changes were seen in the sitting position.

Changes on the order of 4-6 mm Hg in diastolic pressure were seen at most doses in the standing position. There seemed to be no change in orthostatic blood pressure changes with increasing dose.

The percentage of patients who met criteria for orthostatic hypotension in Study 303 are presented in Dr Kapcala's Table 48, page 113 of his review. The greatest difference from placebo occurred in the 4-8 mg groups, from 20 to 90 minutes post-dose.

Similar mean results were seen in Study 302 in which patients treated for at least 3 months were randomized to single doses equal to their usual dose or their usual dose plus 2 mg, or placebo. The largest mean changes were seen in the higher dose group (mean dose 5.8 mg) at 20 minutes, but effects persisted out until 90 minutes.

Data from the open-label experience also suggests that apomorphine can cause orthostatic hypotension, but without a concurrent control, the data are difficult to interpret.

Of considerable interest is the finding of hypotension detected in the controlled trial 302, in which patients had been treated with apomorphine for at least 3 months. This finding suggests that, at least in some patients, hypotension can persist after considerable durations of treatment.

EKG

The sponsor collected Holter monitor data (leads V2, V4, and V6) in patients in Study 303 and 073 (the latter was a sub-study of Study 401 in 6 PD patients who received their own maintenance dose, then doses plus and minus 2 mg compared to their maintenance dose, and then their maintenance dose every 90 minutes for 3 doses)

Dr Kapcala presents the relevant results on QTc intervals in Study 303 in Tables 55-63, pages 131-139 of his review

Table 56 presents particularly relevant data, in my view. This table presents the change from placebo in the change from pre-dose for the various doses at various post-dose times. As Dr Kapcala notes, mean differences of between about 5-9 msec were seen in the 8 mg dose group

Table 63 (page 139) presents outlier data, while there are no obvious dose-related patterns, it is worth noting that 2 patients (2 mg, 6 mg) experienced a QTc interval of >500 msec. There was one additional patient who experienced a QTc interval of >500 msec at a 4 mg dose in Study 302 (in which none of the placebo patients did)

Standard 12 lead EKGs were performed in Study 302, in which patients had previously received treatment for at least 3 months, and then received their routine dose, their routine dose + 2 mg, or placebo. Table 66 (page 142 of Dr Kapcala's review) shows the mean change from placebo in the change from pre-dose in the 2 dose groups. This table reveals an increase in mean difference in QTc of about 4-8 msec, although there are some anomalous findings (a 7 msec decrease in the higher dose group at 20 minute post-dose measurement)

No apparent important changes from baseline were noted in Study 401, in which EKG was not timed to dosing

Table 68 (page 143 of Dr Kapcala's review) presents the results of the Holter data in Study 73 after 3 maintenance doses given every 90 minutes. While Dr Kapcala concludes that there were no important changes compared to pre-dose, the increases seen from 90-270 minutes post-dose (using the Fridericia correction) range from about 5 to about 10 msec (the peak was seen at 180 minutes post-dose)

Other Issues

Abuse

As Drs Kapcala and Feeney note, there have been rare reports of patients severely abusing apomorphine, presumably due to its effect on increasing libido, to the point of injecting frequent doses that may be associated with significant dyskinesias and hallucinations. Apomorphine has been consulted to the Controlled Substances Staff [

1] Apparently, CSS determined that the abuse potential would be low due to the view that doses that would be reinforcing would be unlikely to be taken secondary to the high rate of nausea expected at those doses. However, given the drug's pharmacology, the reports of abuse, and the fact that PD patients may not experience nausea to the degree that patients with erectile dysfunction might, we have recently asked CSS to re-evaluate the abuse potential of sc apomorphine in patients with PD.

Pre-clinical

The sponsor has submitted limited pre-clinical data. They have submitted 13 and 16 week studies in rats, 13 week levodopa/carbidopa/apomorphine combination studies in rat, 13 week and 39 week studies in cynomolgous monkeys, in vitro and in vivo genetic toxicity studies, and limited PK and ADME data. They have performed no reproductive or carcinogenicity studies, and have requested waivers of the requirements to perform these latter studies.

The request for waiver of the carcinogenicity requirement is based on the advanced age of the population, the presumed short duration of treatment, the lack of positive findings on the in vivo genetic toxicity studies, and the fact that there exist multiple carcinogenicity studies already performed with apomorphine.

While in vivo genetic toxicity studies are negative, there are positive findings in numerous in vitro studies.

In a 6 month p53 study, there was an increase in subcutaneous sarcomas at the injection site compared to the saline control, but the increased incidence was seen with the vehicle control group as well as in the drug groups. However, in a 24 month study in female Sprague-Dawley rats (dosing in male rats had to be interrupted), there was a significant increase in subcutaneous sarcomas in the high dose group given 2 mg/kg/day. According to the review of that study

the concentration of the drug used in this study was 1 mg/ml, whereas the concentration in the product in our NDA is 10 mg/ml

The sponsor's rationale for requesting a waiver of the requirement to perform reproduction studies is based again on the age of the population to be treated, a Segment I study in the literature, and the negative findings in the in vivo genotoxicity studies

In addition, the sponsor has not completely determined the metabolic profile of apomorphine in animals

In addition, there are apparently 2 degradants identified in the drug product that appear above the level of qualification. Dr. Roney recommends that, if the sponsor cannot lower the specification to below the level of qualification, these degradants will need to be qualified.

CMC

Numerous deficiencies in the CMC portion of the application have been identified by Dr. Broadbent, relating both to the drug substance and drug product.

Pharmacokinetics and Biopharmaceutics

The ADME of apomorphine have not been completely characterized. Multiple metabolic pathways have been proposed, but the major circulating chemical species are not known.

Tigan

It appears that many, if not most, patients in Study 401 (and several of the controlled trials) were receiving concomitant Tigan, the protocol called for patients to begin treatment with Tigan 250 mg TID prior to initiation of treatment with apomorphine, and to continue for at least 6 weeks. The actual use (duration, pattern of use, number of patients using Tigan, etc.) is not well described in the NDA. Beside the numerous questions (for example, for labeling) that this fact raises, as Dr. Feeney points out, the 250 mg dosage strength is no longer available in the US, it was replaced by a 300 mg strength recently in partial fulfillment of the sponsor's DESI obligation.

Comments

The sponsor has submitted the results of 4 randomized controlled trials purporting to establish the effectiveness of subcutaneous apomorphine as an acute treatment for "Off" episodes in patients with late stage PD. These studies

all examine the effects of single doses of apomorphine under controlled conditions, although Study 202 had a 4 week phase that was not considered by the sponsor to be the primary basis for establishing effectiveness (Dr Feeney describes pertinent results of this phase) Two of the studies (Studies 301 and 302) examined the effects (under controlled conditions) of single doses in patients previously treated with apomorphine for at least 3 months, and so address the question of effectiveness beyond a single dose

In my view, these studies taken together establish the effectiveness of sc apomorphine in the acute treatment of "Off" episodes As previously noted, there appeared to be a period effect in Study 303, and analysis of the first period data did not yield a statistically significant between-treatment difference However, even in this study, the treatment effect was numerically large Therefore, at least 3 of the 4 studies submitted contribute to a finding of substantial evidence of effectiveness

I am not convinced that the sponsor has presented evidence that this product provides an important clinical advantage over existing oral treatments, albeit it is the only product to be used for the acute treatment of "Off" periods

Specifically, several of the approved oral anti-PD drugs have been shown to decrease overall daily waking "Off" time We have no evidence that the total daily decrease in "Off" time achieved with the acute treatment of episodes with apomorphine is any greater than that achieved with chronic oral therapy (patients cannot treat an unlimited number of episodes each day and the effect of any injection does not persist indefinitely) If we had assurance that the patients enrolled into the apomorphine trials were truly refractory to treatment with available oral medications, we might be in a position to come to a different conclusion However, the sponsor has not presented evidence that the patients enrolled into these trials were fundamentally different from the advanced PD patients typically enrolled into studies of chronically administered oral therapies However, of course, this does not alter the conclusion that apomorphine is effective as administered

No study utilized a multiple fixed dose design, and so it is impossible to draw definitive conclusions about specific effective doses Study 202 examined the effects of a range of doses from 2 mg-10mg, Study 301 permitted patients to use their routine dose (2-10 mg), Study 303 examined the effects of a 4 mg dose, and Study 302 examined the effects of the patient's routine dose (mean dose of about 4 mg) or a 2 mg higher dose (mean dose of 5.8 mg)

In the three studies in which the dose was flexible, most patients utilized doses of between 4-6 mg Few patients received doses lower than 4, and fewer received doses greater than 6 mg

While the controlled trials only examined the effects of single doses, of course patients treated themselves in open-label studies with multiple injections each day. In the safety data base, the vast majority of patients received 4 or fewer injections, and the vast majority of these patients used individual doses of 6 mg or less, the total daily dose in about 80% of patients was 20 mg or less.

As Dr. Feeney points out, interpretation of the effectiveness (and safety) of sc apomorphine is somewhat complicated by the fact that it appears that many patients received concomitant Tigan, and at doses no longer available. It is difficult to imagine that Tigan contributed to the effectiveness of the product, and I do not believe that the sponsor would need to address the effect of Tigan on effectiveness. Whether or not the apparent widespread use of Tigan in these patients will need to be addressed in labeling for safety purposes will be addressed below.

As Dr. Feeney points out, the sponsor wishes to obtain a claim for the treatment of both spontaneous "Off" periods as well as end of dose "Off" periods. It is reasonable to consider these 2 types of episodes as having different characteristics, and possibly different responses to a given treatment. I agree with Dr. Feeney that studies in which an "Off" period was artificially induced by withholding oral medications most closely resembles an end of dose event, and the sponsor has demonstrated that the treatment is effective against these

Other studies permitted the treatment of a "naturally" occurring "Off" period that occurred at least one hour after treatment with oral medications. I agree with Dr. Feeney that we do not know if these episodes represented random "Off" episodes, or were, in fact, end of dose episodes, obviously, we cannot know this without information on the timing of the episodes in comparison to the dosing intervals for the oral medications. We should ask the sponsor for this information.

We have little information about the appropriate timing of injections within an episode, that is, if an injection does not provide a satisfactory response, do additional injections provide a benefit, and, if they do, how many can be given within what time frame for a single episode? These questions cannot be answered with the data before us. We should ask the sponsor to provide data on these questions, but I recognize that any data they have on this issue will be useful only as safety data (they do not have controlled data on this question as far as I know).

Regarding safety, the sponsor has submitted data in 536 patients, the vast majority of which was obtained in uncontrolled settings, making interpretation of the data difficult. Further complicating the interpretation is that serious adverse events occur spontaneously in this population, so that judging drug-relatedness even for serious events is problematic, at best.

Nonetheless, certain conclusions seem clear

Subcutaneous apomorphine is capable of decreasing blood pressure, and producing dyskinesias, nausea/vomiting, yawning, somnolence, and dizziness. Most adverse events occur early in treatment, and it is difficult to judge whether these events are dose related, although it seems reasonable to presume that at least some of them are.

A relatively large number of patients in the database (24%) experienced falls. Whether this is related to episodes of hypotension is impossible to know, but an equal percentage of patients (23%) experienced events reasonably considered postural dizziness. Whether these events are also related to changes in blood pressure is unknown, but it is reasonable to conclude that at least some proportion are. While it has been difficult to document significant orthostatic changes, methodologic problems in the studies may have had an effect on detecting any such events (patients were not assessed for changes from lying to standing, and there are no studies that examine blood pressure effects in patients randomized to fixed doses).

As noted above, there is little experience with individual doses greater than 6 mg, or more than 4-5 injections per day, or total daily doses greater than 20 mg. At least some adverse events appear dose related, and it seems reasonable to restrict dosing recommendations to these individual and total doses. While the sponsor has submitted data that appears to document that many patients received an initial dose of 6 mg, there are questions about whether or not this is accurate, we have asked the sponsor to address this, but it seems reasonable to, in the absence of further clarification on this point, limit the initial dose to 2-4 mg and to not increase the individual doses until these lower doses have been demonstrated to be tolerable.

The data submitted to date suggest that at individual doses of 8-10 mg, there may be potentially significant prolongation of the QTc interval. Indeed, there are 3 patients (one each at 2, 4, and 6 mg) who developed a QTc interval > 500 msec.

Treatment-naive patients were monitored with a Holter monitor in Study 303, while patients who had received previous treatment were monitored with 12 lead EKGs (6 patients who had received previous treatment also were monitored with Holter). Serious questions have been raised about the adequacy of Holter monitoring to reliably evaluate the QT interval. I believe that the data generated to date at least suggest that sc apomorphine is capable of prolonging the QT interval, and, because we do not have sufficient data from well-designed studies to adequately examine the effects of the drug on the QTc interval, I would recommend that the sponsor perform a formal dose response study to evaluate this question further. This study can be performed in Phase 4.

The apparent almost ubiquitous use of Tigan in the apomorphine treated patients poses a thorny problem, although I do not believe that we have sufficient information to definitively decide how to dispose of this issue. If it were true that essentially all patients in the safety database received pre- and concomitant treatment with Tigan, it would be impossible to determine the tolerability of the apomorphine alone, and either labeling would need to recommend concomitant treatment with Tigan (which is approved only to treat post-operative and gastroenteritis related nausea and/or vomiting) or we would have to require the sponsor to generate data in non-Tigan treated patients to determine the intrinsic tolerability of sc apomorphine. However, I believe that at this time we should ask the sponsor to address this problem, as part of our request, we should ask for a detailed accounting of actual Tigan use in the NDA population, including numbers of patients who used Tigan, what doses, and for what duration (in particular, whether it was used as pre-treatment, concomitant treatment, or both). It would also be important to ask for a description of Tigan use in the period of time prior to randomization in those patients enrolled in the controlled trials in which prior use was required. While I suspect that that prior use data was not systematically collected, it might still be useful to know whether or not Tigan was used in these patients. Obviously, any other data sources available to the sponsor that might be able to address this issue should be requested, and submitted.

An important general issue that needs to be discussed, of course, is the issue of causality of adverse events. Much of the (chronic) safety data in a typical NDA is generated in open-label, uncontrolled studies, but typically there exists a relatively robust (size, duration) experience in controlled trials that provides a basis for comparing ADR rates between drug and control. In this NDA, the controlled experience is extremely small and brief. There are many events in the open-label experience that are potentially important (falls, cardiovascular events, pneumonia, etc.) that both happen commonly in this population and could reasonably (in some cases) be the result of treatment with apomorphine. For the vast majority of these events, we do not know, and cannot tell, whether or not the drug was responsible. Dr. Kapcala suggests that we ask the sponsor for additional data (in particular, he would like to see pertinent negatives included in narratives, descriptions, etc.) to attempt to clarify any potential relationship to drug. Further, as described above, Dr. Feeney uses an estimate of period of risk to attempt to determine if certain ADRs may be drug-related.

I have reservations about these efforts. I do not believe that the sponsor has much more data of the sort we would like for the cases described by Dr. Kapcala, and, as I discussed earlier, I am not sure that restricting our examination to only those events that occur within 2 hours of a dose of apomorphine is necessarily adequate. I believe, instead, that labeling should note and describe appropriately the panoply of important events that did occur, sections of labeling can be drafted to describe the events and present, fairly, the difficulties involved in their interpretation.

There are, as described earlier, pre-clinical concerns

Primarily, these concerns relate to the sponsor's request to waive the requirements for carcinogenicity and reproduction studies

I believe that the reproduction studies are needed, but that they can be deferred into Phase 4. While I acknowledge that there will be some patients eligible for this treatment who are of childbearing potential, I believe that they will constitute a very small percentage of the potential population.

In general, I agree with the review team that the carcinogenicity studies can also be deferred into Phase 4.

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There is, as well, the issue of potential degradants that may be present above the level of qualification. If this persists, they will need to be qualified.

There is an additional issue related to the 2 formulations proposed for marketing.

The sponsor proposes an ampoule and a cartridge. The ampoule is used with a regular syringe, the patient drawing up the appropriate dose into multiple syringes to have ready.

The cartridge is to be placed into an injection device on which the specific dose can be set via a dial that controls the volume injected. The drug product in the cartridge contains benzyl alcohol, and the sponsor has obtained essentially all clinical exposure with the ampoule formulation. Therefore, the sponsor has no experience with the use of the product that contains the benzyl alcohol. This raises questions about both safety and efficacy. For example, we know nothing about the potential for this product to produce local irritation (although there

apparently are products approved for injection that contain benzyl alcohol, we have no information about the tolerability of apomorphine combined with benzyl alcohol) For these reasons, I believe we should ask the sponsor to address this question, if they cannot provide an adequate answer, we should consider not approving this formulation

Finally, as a number of reviewers have noted, we do not have detailed information about the metabolic fate of the drug in humans or animals This is critical information, and the sponsor must obtain it, again, in Phase 4

Recommendations

I believe the sponsor has demonstrated that sc apomorphine is effective in the treatment of acute "Off" periods in patients with advanced PD I further believe that, with the additional information requested, the drug can be administered acceptably safely, given adequate labeling

For these reasons, then, I recommend that the Agency issue the attached Approvable letter, with attached labeling

/s/

Russell Katz, M D

Associated Neurologists, P C
69 Sandpit Road, Suite 300
Danbury, Connecticut 06810

6/26/03

Dear Dr Murphy

Between May 29, 2003 and June 2, 2003, Mr Edward J Janik and Ms Rebecca C Brown, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol # APO303 entitled "Study of Orthostatic Changes Upon Apomorphine Dose Initiation in Late Stage Parkinson's Disease Patients A Dose Escalation Study with a Double-Blind Placebo-Controlled Efficacy Determination at 4 mg") of the investigational drug (apomorphine) Injection, performed for Bertek Pharmaceuticals Inc This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations We are aware that at the conclusion of the inspection, Mr Janik and Ms Brown presented and discussed with you Form FDA 483, Inspectional Observations We wish to emphasize the following

You did not maintain adequate and accurate records [21 CFR 312.62(b)] in that the patient outcome rankings of several adverse events for subject 012 were changed, six months after the initial assessment was made, without noting the reason(s) for the changes In addition, there were two sets of adverse event experience forms completed for subject 013 at the 5/7/01 visit One set noted chest pressure signed and dated 3/14/02 while the other set noted chest pressure, sedation, and yawning not initialed or signed

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies

Page 2 – John M Murphy, M D

We appreciate the cooperation shown Investigators Janik and Brown during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,



Antoine El-Hage, Ph D
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI 3004016716

Field Classification VAI

Headquarters Classification

1)NAI

2)VAI- no response required

3)VAI- response requested

4)OAI

Deficiencies noted

X_madequate and inaccurate records (06)

cc

HFA-224

HFD-120 Doc Rm NDA#21-264

HFD-120 Review Div Dir Katz

HFD-120 MO Kapcala

HFD-120 PM Wheelous

HFD-46/47c/r/s/ GCP File #10931

HFD-47 NK/BRF

HFR-NE250 DIB Kravchuk

HFR-NE250 Bimo Monitor Madigan

HFR-NE2530 Field Investigators Janik/Brown

GCF-1 Seth Ray

r/d BRF 6/24/03

reviewed AEH 6/26/03

revised BRF 6/26/03

f/t ml 6/26/03

o \BRF\Investigator VAI\Murphy 6 03

Reviewer Note to Rev Div M O

- At this clinical site, 10 subjects were enrolled and 5 subjects completed the protocol
- An audit of all 10 subjects' records was conducted All subjects signed and dated the consent form
- Inspectional findings 1) The patient outcomes for six adverse events of subject 012 at 4/3/01 and 4/5/01 visits were changed from 1 to 3, six months after the initial assessment, without noting the reason(s) for the changes 2) For subject 013, there were two sets of adverse event experience sheets for 5/7/01 visit One set, signed and dated 3/14/02, noted chest pressure while the other set, not initialed or signed, noted chest pressure, yawning, and sedation
- Overall, data appear acceptable

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE June 23, 2003

TO Russell Katz, M D , Director
Division of Neuropharmacological Drug Products
HFD-120

VIA Teresa Wheelous, Regulatory Project Manager
Division of Neuropharmacological Drug Products
HFD-120

FROM Jeanine Best, M S N , R N , P N P
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH Tom Piazza-Hepp, Pharm D , Acting Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT ODS/DSRCS Review of Directions for Use for apomorphine HCL
ampule and pen, NDA 21-264

Executive Summary

_____ submitted *Direction for Use* for Pen Directions and Ampule/Syringe for use with apomorphine hydrochloride, USP for the rescue treatment of "off episodes" associated with Parkinson's Disease

Comments

- No Patient Package Insert (PPI) was submitted for use with the *Directions of Use*. We recommend that a PPI, formatted like a Medication Guide, be available for patient use. The product has important risk and side effect information that should be available for a patient or caregiver's reference.
- The *Directions for Use* are written at too high of a reading comprehension level. Simplify the vocabulary and sentence structure for low literacy readers. A 6-8th grade reading comprehension level is optimal for patient materials.

- Ensure that all accompanying diagrams are well labeled and clearly illustrated
- Enlarge the font size to 10 point to aid in the ease of readability Older adults in particular have difficulty reading a smaller font size
- For more information about writing device instructions for patients, refer the April 19, 2001, CDRH Guidance Document *Guidance on Medical Device Labeling, Final Guidance for Industry and FDA Reviewers*

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Jeanine Best
6/23/03 09 32 14 AM
CSO

Leslie Wheelock
6/23/03 09 35 57 AM
UNKNOWN
Signing for Toni Piazza-Hepp, Pharm D

MEMORANDUM

NDA 21-264 Apomorphine Hydrochloride Injection

FROM. John Feeney, M D
Neurology Team Leader

SUBJECT Injectable Dopamine Agonist for the Acute Treatment of "Off" Periods in Patients With Advanced Parkinson's Disease

DATE June 13, 2003

Apomorphine is a dopamine agonist, developed by the sponsor for the treatment of Off periods in advanced Parkinson's Disease (PD) The motor complications which develop in PD after years of levodopa treatment include "end-of-dose wearing off" (timed to dosing) and unpredictable "on-off periods" (not timed to dosing) The sponsor believes their development program supports the efficacy and safety of apomorphine in the treatment of both types of Off periods

The primary support for this application comes from 4 randomized, double-blind, placebo-controlled trials, APO202, APO301, APO302, and APO303 APO202 and APO303 were designed to demonstrate the efficacy of a single dose of apomorphine in patients naive to apomorphine prior to the study APO301 and APO302 were designed to demonstrate the continued efficacy of apomorphine after longterm use (at least 3 months)

Study APO401 was an open-label, uncontrolled study designed to collect longterm safety experience APO401 provided almost all of the safety experience in the NDA

Dr Leonard Kapcala performed the clinical efficacy and safety reviews
Dr Sharon Yan performed the statistical review Dr Duan performed the biopharmaceutics review Dr Paul Roney was the pharmacology/toxicology reviewer
Dr Broadbent was the chemistry reviewer

Nomenclature

Three proposed names, _____ have been reviewed by DMETS (Division of Medication Errors and Technical Support, the nomenclature group) and found unacceptable The sponsor has not yet proposed an alternative name

Chemistry

Dr Broadbent believes an Approvable action is appropriate His review includes enumerates a number of chemistry issues that the sponsor will need to address

Among these issues, the sponsor has set the specification for one degradant at the $\frac{1}{100}$ % level. Unless the specification is set lower ($\frac{1}{1000}$ %), the impurity would need to be qualified through additional toxicology studies (Dr. Roney's pharm/tox review also includes a discussion of this.)

The sponsor will supply apomorphine 1) as a single-use 2 mL ampule, and 2) as a 3 mL cartridge which can be used with a dosing pen. The former is to be broken open on a given day and used to fill an appropriate number of syringes for use on that day only. The latter is fitted into the dosing pen and the size of the individual dose is dialed, multiple doses can then be given. The clinical development program relied almost exclusively on the ampule method of delivery.

A consult from the Center for Devices found the dosing pen acceptable. The pen is apparently a modification of a dosing pen already marketed.

Carton and Container Labeling

Previous marketing experience with multiple dose vials, such as the one to be used with apomorphine, has taught us that dosing errors will inevitably occur unless the **total vial dose** is clearly represented in vial labeling. Therefore, if the vial label read "10mg/mL—2mL," a patient might draw up the entire vial contents and inject it, thinking the entire vial contents represented 10mg.

The sponsor has proposed a label stating both the total vial contents and the concentration, "20mg/2mL (10mg/mL)." Dr. Phillips of DMETS finds this acceptable, but expressed a preference that the 10mg/mL appear underneath 20mg/2mL and not beside it. He also suggested the "20" be larger than currently proposed.

Pharm/Tox

Dr. Roney has reviewed the preclinical studies in support of this application.

Metabolism in animals (and humans) has not been adequately characterized. Dr. Roney believes these studies should be done post-Approval to document the relevance of the chronic tox studies for human dosing.

The sponsor has asked for a waiver of the usual requirement for reproduction studies. They argue that patients with advanced PD are generally beyond the reproductive years, with rare exception. The review team has found references which state that up to 10% of patients with PD are diagnosed by the age of 40 years. While the average time to "end-of-dose wearing off" is 5 years, the onset could be as early as 2 years. Therefore, the review team believes that there will be patients still in their reproductive years for whom apomorphine would be indicated.

The sponsor has not performed carcinogenicity studies despite a fairly strong signal (seemingly stronger than for the two recently-approved oral dopamine agonists, Mirapex

and Requip) of genotoxic potential. Carcinogenicity studies for both Mirapex and Requip were completed pre-Approval. However, apomorphine may address an unmet medical need, possibly justifying completion of carcinogenicity studies post-Approval. Dr. Roney has expressed his concern that even the preliminary dose-finding studies needed to plan carcinogenicity studies have not yet been performed.

There is one finding in the rat carcinogenicity study, which merits attention. In the high-dose, female group, 6/70 rats had sarcomas at injection sites, 1/70 vehicle-controls had the same finding. The same high dose was used in the male rat group, but males did not tolerate the systemic side effects and dosing in that group was stopped prematurely. A mouse carcinogenicity study was not performed. While this signal may not be relevant for apomorphine administered sublingually, the signal seems very relevant for the subcutaneous administration of apomorphine.

Because the evidence for sarcoma formation is not strong, pending further study, Dr. Lois Freed, the pharm/tox team leader, has expressed the opinion that this signal should not prevent product approval if the finding could be described in product labeling.

Histopathologic changes in the retina have been identified with other dopamine agonists (Mirapex and Requip) in carcinogenicity studies.

In the chronic toxicology studies, Dr. Roney noted that testicular size and weight were diminished.

Injection Site Tolerability

The sponsor proposes two formulations of apomorphine for use. The first, to be provided in single-use ampules (used to fill multiple syringes for a given day), does not contain benzyl alcohol. The second, to be provided in multiple-use cartridges, does contain benzyl alcohol. The original acute tissue tolerability studies and the later chronic toxicology studies all used the formulation without benzyl alcohol. These studies showed only occasional inflammatory reactions, fibrosis, and necrosis. Dr. Roney notes that there are other marketed drug products for parenteral administration which contain benzyl alcohol, so that we can potentially rely on that experience to cover the absent benzyl alcohol in the current studies. The clinical development program relied almost exclusively on the ampule method of delivery, absent benzyl alcohol. No patients were

dosed with the dosing pen, while roughly 40 normal volunteers received a 2mg dose with the dosing pen

Efficacy Studies

Study APO202

Both Dr Kapcala and Dr Yan believe that this study supports the short-term efficacy of apomorphine in treatment-naive patients. The study enrolled patients with advanced PD who were still experiencing Off periods despite optimal therapy with carbidopa/levodopa products and an oral dopamine agonist. Patients were required to have at least 2 hours of Off time per day. Allowed, but not required, were COMT inhibitors and selegiline. All patients were pre-treated with trimethobenzamide to prevent nausea.

The study was powered to demonstrate a 17 point difference between drug and placebo on the UPDRS motor scale.

At Visit 1, all patients were hospitalized for further eligibility testing. Medications for PD were withheld after midnight. The next morning baseline motor testing was performed during the induced Off time. The patient's usual morning dose of carbidopa/levodopa was then administered and repeat motor testing was performed when On time was achieved or between 1-2 hours, whichever occurred first. If the patient improved by 30% on the UPDRS motor subscale, the patient was eligible to be randomized.

At Visit 2, eligible patients were again hospitalized. Medications for PD were again withheld after midnight. The next morning patients were randomized in a 2:1 ratio to apomorphine or placebo. Baseline motor testing was performed. Patients were then given 0.2mL (2mg) of test article. Motor testing was repeated when On time was achieved or at 15 minutes, whichever occurred first. If a patient's improvement on the UPDRS motor subscale was 90% of the improvement seen after levodopa at Visit 1, further dose escalation was stopped. If not, 0.4mL (4mg) of test article was given (2 hours post first test dose) and motor testing was repeated. Dose escalation could continue if necessary with 0.6mL (6mg), 0.8mL (8mg), and 1.0mL (10mg). Once a patient achieved the required motor improvement or the 1.0mL dose, dose escalation stopped.

Twenty-nine patients were randomized, 20 apomorphine and 9 placebo. Of the 20 apomorphine patients, 18 achieved the levodopa equivalent response (at least 90% of the UPDRS change seen with levodopa at Visit 1). Of the 9 placebo patients, 0 achieved the levodopa equivalent response. One of the 9 placebo patients did stop titration after the 0.6mL dose because of lack of benefit.

The dose titration results are as follows

	2mg	4mg	6mg	8mg	10mg
Apomorph	3	7	5	3	2
Placebo	0	0	1	0	8

Therefore, Study 202 had the potential to support the efficacy of 4mg and 6mg, but the small numbers of patients at 8mg and 10mg would make conclusions about those doses difficult

For both groups, the Off state UPDRS motor score was 36-39. After dose titration, there was a mean 24 point improvement in the apomorphine group and a mean 0 point improvement in the placebo group

The primary analysis called for a comparison between treatment groups of the ratio, (average % response following study drug / average % response following levodopa). That ratio was 0.96 for the apomorphine arm and 0 for the placebo arm, a difference that was statistically significant, $p < 0.0001$

After the inpatient testing described above, the protocol allowed for 1 month of blinded outpatient treatment. This extension period was not set up as a separate efficacy study (the numbers of patients per group were diminishingly small), the analyses were planned as secondary analyses for the overall study. Nevertheless, diary data were collected for patients and all results trend in favor of apomorphine. Patients and caregivers were allowed to give as many as 5 doses per day as needed, recording results in diaries. Seventeen apomorphine patients and 8 placebo patients completed the outpatient phase.

In both groups, an average of about 2 doses were given per day. For apomorphine, 95% of administered doses were believed to abort the Off period, for placebo, 23% of doses were believed to abort the Off period. Total daily Off time was also collected. The mean change from baseline in average daily Off time was -1.7 hours for the apomorphine group and 0 hours for the placebo group.

Study APO301

This study was designed to demonstrate the longterm efficacy of apomorphine in patients so-treated for at least 3 months. In this study, 17 patients who had advanced PD, treated with levodopa, a dopamine agonist, and apomorphine were randomized in a crossover design to receive active drug or placebo on day 1 to treat an Off period and then the alternative treatment on day 2 to treat an Off period. The dose administered was the usual apomorphine dose for that patient. Prior to randomization, patients were required to have received an average of 2 doses of apomorphine per day for the prior week, with doses of 10mg or less.

Allowed, but not required, were COMT inhibitors and selegiline. Four patients had domperidone listed as a concomitant medication to prevent nausea, the other patients did not receive medication for nausea.

On each study day (day 1 and day 2) patients received their usual morning medications and were then followed until an Off period was identified. The UPDRS motor score was then recorded just prior to dosing, and then again at 10min, 20min, and 60min. Other measures included a dyskinesia rating scale and time-of-onset of significant improvement in immobility. The primary efficacy measure was the change in UPDRS motor score at 20min post dosing.

One patient had no post-treatment efficacy measures and was dropped from all analyses considered in Dr. Yan's review. (The sponsor did perform some analyses including this subject, carrying forward all pre-dose data.) Pre-dose UPDRS motor scores averaged 40 points. An average treatment effect of 21 points at 20minutes was shown for the apomorphine vs 3 points for placebo. Because the normality assumptions were not met, a non-parametric test was performed. The results were statistically significant in favor of apomorphine. The results are shown below.

Mean UPDRS Change by Treatment and Period

	Apomorphine	Placebo
Period 1	-19 mean -23 median	-5.5 mean -3.5 median
Period 2	-23 mean -22 median	-0.9 mean 1.5 median

Dr. Yan performed a test for period effect which was not significant. She does however caution that such tests are not extremely sensitive. Obviously, there was a placebo effect in the first period which was not seen in the second period.

By protocol, if a significant period effect was identified, the results of the first period would be analyzed separately as a parallel design. With the non-parametric analysis of the first period data alone, the p-value was 0.0922 (not significant).

Given the overall result of the trial, along with the consistent, large effect of apomorphine across both periods, I would consider this a positive trial.

The doses used in Study 301 are shown below.

	2mg	3mg	4mg	4.5mg	5mg	8mg	10mg
Apom	2	9	2	1	1	1	1

Therefore, Study 301 may only address the longterm efficacy of doses of 3-4mg.

Study APO303

This was a randomized, double-blind, crossover study in previously apomorphine-naive patients with advanced PD. Eligible patients were seen during office visits which occurred no more than 3 days apart. At titration visit 1 (TV1), patients were all treated with 2mg apomorphine. At titration visit 2 (TV2), patients were randomized to receive 4mg apomorphine or placebo. At titration visit 3 (TV3), patients were crossed over to receive the alternative treatment to TV2. At later visits, all patients received apomorphine in escalating doses up through 10mg or their maximally tolerated doses.

Patients were required to have Off periods, either end-of-dose Off, spontaneous Off, or both. Carbidopa/levodopa was required, with at least one of the following: selegiline, an oral dopamine agonist, or a COMT inhibitor. All patients were pre-treated with trimethobenzamide to prevent nausea.

At each visit (titration visits 2 and 3, in particular), patients received their usual anti-Parkinsonian medications in the morning and then reported to the clinic. At the first Off period that occurred more than 1 hour after dosing, baseline motor testing was performed to include the UPDRS. Then the patient received test medication (4mg apomorphine or placebo), and motor testing was repeated at 20 minutes, 40 minutes, and 90 minutes.

The primary outcome measure was the change in UPDRS motor score from pre-dosing to 20 minutes. The primary analysis was a repeated measures ANCOVA with the terms of sequence, subject within sequence, pre-dose score, treatment, and period. If there was a significant treatment-period interaction as measured by sequence effect, data from titration visit 2 only were to be analyzed as a parallel design, using a one-way ANCOVA with the terms treatment and pre-dose score.

One patient dropped out after TV2. Therefore, there were 51 patients in the ITT analysis, but only 50 patients in the per protocol (PP) subset (completed both crossover visits, TV2 and TV3). Dr. Yan argues in her review that the PP analysis is the more appropriate one, both yield a p-value of 0.0002. There was no significant deviation from the normal assumption. The results are shown below.

Mean UPDRS Change by Treatment and Period

	Apomorphine	Placebo
Period 1	-9.5 mean -8 median	-4.6 mean -2 median
Period 2	-13 mean -12 median	-0.6 mean -1 median

The p-value for the sequence effect is 0.0038 with a larger treatment effect seen in the second period. When the data from TV2 only is analyzed, the p-value is 0.166. [Note: A

non-parametric analysis results in a significant p-value for the first period analysis, but Dr Yan disagrees with the sponsor's assertion that a non-parametric analysis is called for]

Obviously, the magnitude of the change from baseline for the apomorphine group is much smaller than that seen in APO202 and APO301. This, combined with the placebo effect in the first period, contributes to Dr Yan's p-value of 0.166 for the first period.

Therefore, the evidence for a treatment effect is not very robust, given the larger effect size in the second period and the negative result when the first period is analyzed as a parallel design. It is interesting to note that the increasing treatment effect in the second period mirrors the pattern seen in Study 301.

In conclusion, APO303 was only designed to address the efficacy of the 4mg dose of apomorphine. I would not consider this a positive study.

Study APO302

Study 302 is similar to Study 301, except that it was a parallel design instead of a crossover design. It was only recently completed and, in fact, is not discussed in the sponsor's Integrated Summary of Efficacy. Dr Yan reviewed the study. The primary objective of the study was to demonstrate the continued effectiveness of apomorphine in patients exposed for at least 3 months. Patients so-exposed were randomized to 1 of 4 groups in a 2:2:1:1 ratio.

- Apomorphine at the usual dose and volume
- Apomorphine at 2mg (0.2mL) above the usual dose
- Placebo at the same volume as the usual apomorphine dose
- Placebo at 0.2mL above the usual volume of the apomorphine dose

Twelve patients had trimethobenzamide listed as a concomitant medication to prevent nausea, the other patients did not receive medication for nausea.

In all respects, the study mirrored Study 301. The primary analysis compared the combined apomorphine arms to the combined placebo arms.

There were 35 apomorphine patients and 27 placebo patients in the ITT population. Patients in the pooled apomorphine group experienced a mean reduction in the UPDRS motor score of -24.2 at 20 minutes compared to -7.4 points for the pooled placebo group. The treatment difference was statistically significant, $p < 0.0001$.

In Study 302, patients took their usual medications and were followed until an Off period occurred. (The Off was required to occur at least an hour or more after dosing.) If the Off occurred well before the next usual dosing time, it would be a spontaneous Off. If it occurred around the time of the next usual dosing time, it would be an end-of-dose Off.

If it occurred after the next usual dosing time, it would be an induced Off, as studied in Study 202

During this review period, Drs Yan and Kapcala did not identify information on the timing of the Off periods treated in Study 302. This information should be requested from the sponsor (if collected in the CRFs). In contrast to the induced Offs studied in Study 202, the Offs in Study 302 have the potential to address the efficacy of apomorphine for spontaneous Off periods, *if the times to Off are generally shorter than the usual dosing intervals*

The mean dose studied in APO302 (combined apomorphine groups) was 5.1 mg with the following distribution

2mg	3mg	4mg	5mg	6mg	7mg	8mg	9mg	10mg
2	3	10	6	9	1	1	1	2

Therefore, Study 302 may only address the longterm efficacy of doses of 4-6mg

As stated, the randomization in this study was a 2:1 randomization. However, there were 35 patients in the active group and 27 in the placebo group. At my request, Dr Yan investigated the deviation from the planned ratio. She found no obvious explanation. The sponsor should be asked to address this issue.

NIH Study

This study was performed with a different formulation than the one proposed in this NDA. A subset of the data from this trial was presented by the sponsor in the Integrated Summary of Efficacy. It was not reviewed by Drs Yan or Kapcala. As part of this multi-faceted study, patients with spontaneous Off periods and patients with end-of-dose Off periods were separately studied. In both, Off periods were induced by withholding medications and the timecourse of response to apomorphine characterized. While the response and the timecourse of response were similar for the 2 patient populations, the response of spontaneous Off periods were not studied. Therefore, the sponsor's contention that spontaneous Off periods and end-of-dose Off periods respond similarly does not seem to be directly supported by this study.

**APPEARS THIS WAY
ON ORIGINAL**

Dose-Response

There are no fixed-dose, dose-response studies presented in the NDA. Therefore, nothing definitive can be stated about dose response. The following observations can be made from APO202, APO301, APO302, and APO303:

In treatment-naive patients, APO202 supports dosing from 4-6mg, while APO303 suggests minimal if any effect from a 4mg dose.

In chronically-treated patients, APO302 supports dosing from 4-6mg, while APO301 supports dosing from 3-4mg.

There is no strong data that a dose of 2mg is effective. Doses above 6mg have not been adequately assessed.

**APPEARS THIS WAY
ON ORIGINAL**

Safety

The original NDA safety database includes 512 patients, with 300 patient-years of experience. Of the 512, 300 were treated for at least 4 months and 100 were treated for at least a year. The sponsor submitted a safety update which included an additional 20 patients (n=536) and increased the overall exposure to 400 patient-years.

Almost all of the safety experience is derived from APO401, an open-label, uncontrolled study. Amendment 2 to the protocol allowed for the collection of orthostatic blood pressure measurements and information on dosing. There were 226 patients treated in APO401 after this amendment.

With the exception of EKG data, most of the safety experience is summarized in the original Integrated Summary of Safety (ISS). Subsequent to the ISS, the APO302 study report was submitted which included detailed EKG data collected in patients previously treated with apomorphine for 3 months or more. Additional EKG data was also collected in treatment-naive patients in APO303, along with 3-lead holter data. As discussed by Dr. Kapcala, this 3-lead holter data may be of uncertain value for measuring EKG interval data.

Of note, in APO303, patients were put through a forced titration to a maximum tolerated dose, up to 10mg. Therefore, safety data was collected at doses that may not be routinely needed in general use. During APO303, in addition to holter monitoring, detailed blood pressure readings timed to dosing were recorded in roughly 50 patients during the forced titration. In APO302, patients chronically treated with apomorphine were randomized to continue the same dose or to increase to dose 2mg higher than their maintenance dose. Again, safety data was collected at doses slightly higher than may be routinely needed in general use.

Across the entire safety database, only 34 patients received at least one dose > 8mg. While 122 patients received an average dose > 4mg for 6 months or more, only 41 received an average dose > 6mg for 6 months or more. Only 11 patients received an average dose > 8mg for 6 months or more.

[

]

Subcutaneous apomorphine for PD is available in Europe through a different sponsor, Britannia. Postmarketing data for that product has been submitted in the current NDA.

Demographics

Of the 516 patients described in the ISS, 57% were 65 years of age or older. The average duration of PD was 11 years with an average age of onset of 54 years. At study

entry, 97% of patients were taking an oral dopamine agonist and 41% were taking a COMT inhibitor. In APO401, only 10/488 patients initiated apomorphine without using trimethobenzamide.

Deaths

There were 10 deaths described in the ISS and another 4 described in the safety update. While additional data about time of dosing might help better characterize a few of these cases, none of the events appear unusual for an older age group with advanced PD. Given the information provided, none of the deaths can be attributed to apomorphine with any certainty.

Among the 14 deaths, I can identify 6 where the death was either attributed to a cardiac cause or might be considered a sudden unexplained death. Four of these occurred more than 12 hours post apomorphine. Of the other two, one occurred 2.5 hours post apomorphine during a peri-operative period associated with blood loss and one was a sudden death 4 hours post apomorphine.

The 6 patient numbers are

- 401/13/005
- 401/54/006
- 401 - 007
- 401/13/011
- 401/28/001
- 401/36/008

Serious AEs

There were a total of 227 SAEs in 103 patients, roughly 20% of treated patients. All of these were reported in open-label, uncontrolled experience. Most were not unexpected, given the older population with advanced PD that was being treated. Pneumonia occurred in 3% of patients and serious falls occurred in 2% of patients. All other events occurred in $\leq 1\%$ of patients. Serious events of particular interest are discussed below.

Serious AEs/Events of Coronary Ischemia

Obviously, cardiovascular events are not unexpected for an older age group with advanced PD. Those described in the ISS are listed below, along with the time from apomorphine.

- 401/05/008 (15 min)
- 401/08/008 (3 episodes, the second 1 hr post apomorphine)
- 401/25/005 (hospital admission 3.5 hrs post apomorphine)
- 401/30/001 (unknown)
- 401/40/010 (2 hrs)

- 401/58/005 (1 hr)
- 401/61/001 (2-3 hrs)

Knowing the potential of apomorphine to induce hypotension (see below), the sponsor reports that none of these events was obviously preceded by a presyncopal feeling. Nevertheless, if lowered blood pressure were the mechanism for a drug-induced coronary effect, the lack of reporting of such symptoms does not rule out the occurrence of hypotension.

If we wanted to invoke lowered blood pressure as a mechanism for drug-induced coronary events, we might expect the similar occurrence of cerebrovascular events. In fact, there was one such event.

- 401/55/004 (1 hr)

Dr. Boehm, a member of DNDP's Safety Group, helped me with the following assessment of the above events.

Among the thirteen ischemic adverse events, cardiac and cerebrovascular, a number of these events occurred in close proximity to the time of last injection. Because there was only a small amount of randomized controlled trial data to examine, we used the uncontrolled safety data to examine the relationship between ischemic events and acute apomorphine exposure. Based on apomorphine's pharmacological properties, we classified the two hours post dosing as acute exposed time and more than 2 hours after dosing as not exposed time. If ischemic adverse events were not related to acute drug exposure, then we expected there to be no cluster of such events during the acute exposed time. We did not have the actual times of injections for each subject but we knew that the average number of injections per patient was 3 per day. Therefore, if we consider the two hours following dosing as exposed time, the subjects were exposed for 6 hours each day on average and not exposed for eighteen hours each day. In other words, in a 24 hour day, Study subjects were exposed for about 25% (6/24) of the time. Assuming no relationship between ischemic events and acute dosing, with a total of 13 ischemic event cases observed we would expect that 25% or 3.25 cases would occur during the exposed time, we observed 5 cases (including the patient admitted 3.5 hrs post dosing).

Using the binomial distribution to explore how unusual a finding this might be led to the following. If one assumes no relationship between occurrence of ischemic events and exposure, given a total of thirteen events, the probability of observing five or more ischemic events during the exposed period is 0.21. This analysis does not provide strong evidence of a relationship between acute apomorphine exposure and increased risk for ischemic events.

In APO202, there were 3 reports of chest pain (not classified as serious AEs). Two occurred with apomorphine and one occurred on placebo.

- 202 — 008 (unknown, dose titration continued without further chest heaviness/not classified as a serious AE)
- 202 — 1/014 (1 hr, note episode of chest pain was not classified as a serious AE, but did result in study discontinuation and further cardiac tests)
- 202 — 013 (unknown, this patient was receiving placebo)

Finally, one other patient (401/27/013) had chest pain 25 minutes after apomorphine during open-label treatment (non-serious AE) The patient continued on apomorphine without further reported problems The patients had a previous history of non-cardiac chest pain

Serious AEs/Falls

There were 25 serious events suggestive of falls Based on the information available, Dr Kapcala did not believe that any could be attributed to apomorphine with any certainty He did believe that lack of information for many cases made it impossible to completely rule out apomorphine as a contributory cause (perhaps by lowering blood pressure excessively in some patients)

Discontinuations Due to Adverse Events

Three patients discontinued from study because of AEs suggestive of falls Eleven patients discontinued because of AEs suggestive of orthostatic hypotension Thirteen patients discontinued because of AEs suggestive of postural dizziness

Common Adverse Events

APO202, as a positive parallel-group study in naive patients (and with a 30-day outpatient treatment period) may best represent the common adverse event profile of apomorphine in patients with PD The sponsor has proposed a table of adverse events from this study for labeling The most common AEs in that study with a greater frequency than placebo were yawning, dyskinesias, drowsiness/somnolence, nausea/vomiting, dizziness, rhinorrhea, chest pain/pressure, hallucinations/confusion, and edema Unfortunately, the treatment groups were small in size with only 20 apomorphine patients and 9 placebo patients

Across the whole safety database, the same common AEs were noted as in APO202

Vital Signs

There are 3 main sources of information about vital signs In APO401, after Amendment 2, supine and standing blood pressure and pulse measurements were recorded at each visit The timing in relation to dosing was left to each investigator's discretion In APO303, sitting and standing measurements were recorded at 20, 40, and 90 minutes post-dosing as naive patients were moved through the forced dose escalation up to their maximum tolerated dose or 10mg In APO302, sitting and standing measurements

were recorded at 20 and 90 minutes post-dosing in chronically treated patients randomized to placebo, the maintenance dose, or the maintenance dose plus 2mg. Dr Kapcala has presented the vital sign data in tables he created using the sponsor's data. He believes APO303 provides the most informative data about vital signs.

In APO303, patients received their usual morning doses of anti-PD drugs and were followed until an Off period occurred. Then, they were dosed with apomorphine. Dr Kapcala makes the point that, because apomorphine is not administered with the anti-PD drugs, the effects on vital signs may be an underestimate of the effect should they all be administered together. This is a point worthy of consideration as we look at the results. During this review cycle, the times of apomorphine dosing in relation to the other anti-PD drugs were not obvious to the review team. I believe this information would be helpful in assessing Dr Kapcala's claim. If enough apomorphine dosing occurred within 1-2 hours of dosing with levodopa, the coincident T_{max} of levodopa and apomorphine might in fact stress the vascular response maximally. This data should be requested. [This data will also help assess the efficacy for spontaneous Off versus end-of-dose Off.]

Dr Kapcala is correct when he points out that sitting-to-standing measurements will underestimate orthostatic effects compared to supine-to-standing. And he is correct that the sequential dosing titration scheme has the potential to underestimate the frequency of blood pressure effects at the higher doses, 8mg and 10mg.

Dr Kapcala's analyses of APO303 demonstrates that apomorphine 2-10mg causes a 5-16mmHg drop in resting sitting systolic BP. It causes a slight 2-4 beat/min decrease in heart rate. At baseline, roughly 5-8% of patients met the criteria for orthostatic hypotension. Roughly 15-18% of patients met the criteria after apomorphine 2-6mg. Lower percentages at 8-10mg doses probably reflect some selection bias since over half the patients drop out prior to dosing at these levels.

After the forced titration period of APO303, patients were treated for 6 months at their optimal dose. Dr Kapcala states that comparable effects on vital signs to those already described continued to be observed during chronic dosing suggesting that adaptation does not occur. Dr Kapcala states that the results in APO302 were similar to the vital sign data from APO303. This, too, would argue that adaptation to these effects does not occur, since patients in APO302 had all been treated for at least 3 months.

In APO401, of the 47 patients dosed in office and studied, several had orthostatic systolic BP drops of 30mmHg or more in conjunction with an absolute systolic BP less than 90mmHg, certainly a combination that could lead to syncope.

EKGs

Dr Kapcala has presented tables, based on the sponsor's data, summarizing the effects of apomorphine on QT interval. Uncorrected QT data are not presented. Because of confusion about which "non-apomorphine" data the sponsor used for

determining the best correction for QT within the safety database, Dr Kapcala presents QTc, corrected using Bazett's and Fredericia's correction factors

Recall from above that apomorphine is associated with a slight mean decrease in heart rate on the order of 2-4 beats/minute. For drugs that cause bradycardia, the uncorrected QT interval will increase. Bazett's method undercorrects the QT at heart rates slower than 60. Fredericia's method is biased in the other direction, but to a smaller degree.

Again, APO302 and APO303 provide the most complete data. Because APO302 used traditional 12-lead EKGs, I will summarize that data first.

EKGs in APO302 were performed at 20 minutes and 90 minutes. For the group randomized to the maintenance dose plus 2mg, there does not appear to be any change in QT at 20 minutes. There is an increase of 4-8msec at 90 minutes. For the group randomized to the maintenance dose, there was one outlier whose results drive the results for the whole group. This outlier received a 4mg dose and showed (at 20 minutes) a 77msec increase in QT with an absolute QT > 500msec.

EKGs in APO303 were performed using a 3-lead holter technology. Results were analyzed at 20, 40, and 90 minutes post-dosing. At 40 minutes, there appears to be an increase in QTc at doses of 8-10mg on the order of 2-8msec. Two patients, one at 2mg and one at 6mg, were clear outliers with > 60msec increases in QT and absolute QTs > 500msec. One patient at 10mg had a 60msec increase in QT but did not exceed an absolute value of 500msec.

Therefore, there were 3 clear outliers on QT (> 500msec) across all apomorphine groups in both studies, while no placebo patients reached this threshold. The sponsor did not identify any new concern for arrhythmias from the holter data in APO303, there is no mention of any cases of torsades in the safety database. Of course, cases of torsades might go unidentified in the absence of concurrent EKG data. Unmonitored syncope has the potential to represent torsades.

Clinical Lab Findings

According to Dr Kapcala, one lab finding that seemed unexpected was the increased percentage of patients with an abnormally high percentage of eosinophils in their differential blood counts. The significance of this finding is unclear. One patient had an increased ALT and AST (both 135), follow-up on this patient is pending.

Drug Abuse and Dependence

Over the years, a number of reports have appeared in the literature about patients who abuse levodopa. Out of proportion to their objective motor deficits, these patients begin to ask for and use larger and more frequent doses of levodopa. Often this use results in

dyskinesias and hallucinations Some patients have developed an organic psychosis, requiring hospitalization

Levodopa has the ability to increase libido and it is this psychosexual stimulation that is believed to underlie these cases of abuse

In the ISS, the sponsor has described a half-dozen similar, but more dramatic cases from postmarketing surveillance for subcutaneous apomorphine in Europe These cases are all characterized by increasingly frequent daily injections in the face of markedly abnormal behavior

Given the rapid onset of action of subcutaneous apomorphine, it follows that it may lend itself more readily to abuse than oral levodopa due to the more immediate gratification Because the need for increased dosing will be at the discretion of patients and not always monitorable by health care practitioners, it will be imperative that practitioners are aware of the possibility for abuse and vigilant for evidence that patients are using apomorphine out of proportion to their motor complaints Therefore, the potential for abuse should eventually be highlighted in the Warnings section of labeling

The abuse potential for apomorphine was previously addressed by the FDA Office of Controlled Substances (OCS) in a consult

In the consult

OCS stated, "Apomorphine does not have high abuse liability because the doses required to produce reinforcing responses will also induce an emetic response This dual action will inherently limit the self-administration of apomorphine for abuse purposes " Rodent studies did show that apomorphine has a profile suggestive of reinforcing effects (it is self-administered, can induce conditioned place preference, and will substitute for amphetamine and other dopaminergic agonists), but OCS noted that rodents do not have emetic centers Thus, OCS believed that the animal data were not relevant given that humans have a prominent emetic response

Given the anecdotal reports of PD patients abusing apomorphine, OCS has been re-consulted In PD patients using antiemetic medication, perhaps the abuse potential of apomorphine is increased The new OCS consult is pending

Literature

The world's literature provided information on almost 3000 patients treated with apomorphine In general that experience mirrors that seen in the NDA There was one report of 2 patients with sudden onset of sleep, as described with other dopaminergic drugs This should be reflected in labeling

Inspections

Inspections of 3 clinical sites have been performed DSI's final report does not raise concerns about the acceptability of the data

Labeling

The sponsor will supply apomorphine as a cartridge (to be used with a dosing pen) and as ampules to be broken open and used to fill syringes. Each calls for a Patient Package Insert. The sponsor's proposed language for these has been forwarded for review by Office of Drug Safety (ODS) and DDMAC.

Tigan (trimethobenzamide)

In APO401, which provided the bulk of experience with apomorphine for PD, essentially all patients began treatment with apomorphine only after pre-treatment with Tigan 250mg po tid for several days. The protocol recommended that Tigan be continued for at least 6 weeks after apomorphine initiation. The protocol stated, "In some patients, antiemetic therapy can be withdrawn gradually, depending on the tolerance to apomorphine."

In the NDA, the overall exposure to Tigan is not well-characterized. Therefore, it is not clear to the review team how much of the apomorphine experience is coincident with Tigan. By scanning the appropriate appendix to the APO401 study report (concomitant medications), it appears that some patients did stop Tigan after 6 weeks, but many appear to have used concomitant Tigan for many months (up to 1 year). From the listing, it is not clear if patients used Tigan continually or on an as needed basis. Therefore, the sponsor should be asked to summarize the experience with Tigan.

Tigan has a long regulatory history. As an old drug, it was a subject of the Drug Efficacy Study Implementation (DESI) program. In 1979, FDA concluded that Tigan was effective for the treatment of postoperative nausea and vomiting and for nausea associated with gastroenteritis. At the same time, FDA concluded that 400mg orally was the effective dose based on relative bioavailability to the intramuscular formulation.

In December, 2002, FDA announced the resolution of issues related to Tigan Capsules. A supplemental NDA for Tigan was approved, 300mg orally was determined to be the effective dose. At the same time, the continued marketing of unapproved trimethobenzamide products was deemed unlawful.

There are 3 issues that follow:

1. The safe use of apomorphine for PD necessitates that patients be treated as they were in the NDA, with Tigan (at least as pre-treatment). Thus, the labeling for apomorphine will convey a new indication to Tigan. At the same time, I am not aware of any direct evidence showing that Tigan is effective for this intended use.
2. The prolonged use of Tigan in the apomorphine development program (many months) has not previously been studied. There may be additional studies (clinical and preclinical) that would be appropriate to support the chronic use of Tigan.

- 3 The dose of Tigan used in the apomorphine development project was 250mg tid. This dose is no longer lawfully marketed in this country, the marketed dose is 300mg. It will be a matter of judgment whether the 50mg increment has the potential to interfere with the efficacy of apomorphine at the approved doses and alter the safety profile seen in the NDA.

Conclusions

- 1 **Indication** The sponsor is seeking a claim for the treatment of two types of Off periods: end-of-dose wearing Off and spontaneous Off. The sponsor has submitted data which supports the efficacy of apomorphine for the acute treatment of "end-of-dose wearing off." In the initial phase of APO202, the sponsor induced Off periods by withholding PD medication overnight. I believe such induced Off periods may well approximate end-of-dose Off periods, but I believe there may be more underlying complexity to the spontaneous Off periods unrelated to time of dosing. In APO301 and APO302, patients received their morning doses of PD medication and were followed until their first Off of the day (at least 1 hour post dosing). Whether the results of APO301 and 302 address the efficacy of apomorphine for spontaneous Off periods depends on the realized distributions of time-to-Off in those studies. If many studied Off periods occurred well before the usual dosing interval, the results may bear on spontaneous Off periods. If the great majority of Off periods occurred well after the usual dosing interval, then the results bear more on end-of-dose off.
- 2 **Clinical Trials** The sponsor believes they have submitted 4 positive controlled trials. As discussed above, the between-group difference in APO303 was smaller than expected, with a larger between-group difference after the crossover. Therefore, I do not consider APO303 a positive study. APO202 was a positive study in treatment-naive patients. APO301 and APO302 were positive studies in chronically-treated patients.
- 3 **Carcinogenicity Studies/Injection Site Sarcomas** The sponsor has not performed their own carcinogenicity studies. ————— there is a signal of injection site sarcomas —————
————— This issue needs further consideration —————
- 4 **Reproduction Studies** These have not been performed. Given that some patients who would use this product will still be in their reproductive years, these studies should be done.
- 5 **Metabolism in Clinical and Preclinical Studies** It is not clear what the predominant circulating species is in humans and what it was in the preclinical toxicity studies. Ideally, this information should be available pre-approval. In light of the considerable previous human experience, I believe the sponsor can be asked to pursue this data post-approval.
- 6 **QT Prolongation** There appears to be an effect of apomorphine on the QT interval, such that doses of 8-10mg are associated with a 2-8msec prolongation. No cases of torsades were identified during the NDA review. There are cases of syncope and

- sudden death, but these might not be unexpected in this patient population. This should be described in labeling.
- 7 **Coronary Ischemia** Cases of angina and myocardial infarction have occurred in close proximity to apomorphine dosing (within 2hrs). However, cases of cardiac arrest and sudden death have occurred in the NDA at times unrelated to dosing, suggesting that these events are background events in this patient population. It does add to our concern that hypotension might provide a mechanistic explanation for coronary ischemia, and that an additional patient had a stroke in close proximity to apomorphine dosing. Stroke, like coronary ischemia, might be induced by excessive hypotension. These events should be described in labeling.
 - 8 **Hypotension** Like other dopamine agonists, apomorphine has the potential to lower resting systolic and diastolic BP. While orthostatic changes were not prominent during BP monitoring, cases of clinical orthostasis occurred. Syncope and presyncope are also described above.
 - 9 **Falling** Patients with PD are at risk of falling due to the underlying motor deficits of PD, concomitant autonomic instability seen in some patients with PD, and from syncope caused by the blood pressure lowering effects of the drugs used to treat PD. Subcutaneous apomorphine has the potential to increase the risk of falling by simultaneously lowering blood pressure and improving mobility.
 - 10 **Dosing/Size of Each Dose** The studies, APO202, APO301, and APO302, support the efficacy of apomorphine at doses of 3-6mg. There is no strong evidence that a dose of 2mg will be effective. Doses higher than 6mg were not systematically studied, there is no evidence that doses > 6mg provide any additional benefit. In the NDA, 110 patients received at least one dose > 6mg, but some of these patients may have only received a single dose >6mg during the forced titration. Therefore, I believe the maximum recommended dose supported by the NDA is 6mg.
 - 11 **Dosing/Dosing Interval** If an initial dose of apomorphine is not effective for end-of-dose wearing off after 20-40minutes, should a patient be re-dosed? There are some descriptions of this practice within the NDA, but the experience is very limited. A pharmacokinetic argument can be made against such re-dosing for end-of-dose wearing off. Presumably, the time of end-of-dose wearing off signals the end of a dosing interval and the approaching need to re-dose with the usual dose of levodopa. Therefore, the first dose of apomorphine would be expected to be almost concurrent with a dose of levodopa. If the apomorphine is ineffective within 20-40minutes and one were to consider re-dosing with apomorphine, the effect of the second dose would be expected 20-40minutes later, *at the time of the T_{max} for levodopa*. The coincidence of the T_{max}'s for levodopa and the second dose of apomorphine suggests potential for excessive dopaminergic stimulation, raising safety concerns. Such safety concerns have certainly not been addressed within the current safety database.
 - 12 **Dosing/Total Number of Doses Per Day (Total Daily Dose)** The average number of doses per day across the NDA was 3. Seventy-five percent of patients in the NDA database had an average of < 4 doses per day. In APO202, the protocol only allowed a maximum of 5 injections per day. Of the roughly 5000 diary days accounted for in APO401, 15% of the days noted 6-10 injections. I believe a

maximum of 5 doses per day should be the recommended frequency at the present time

- 13 Dosing/Dose Escalation In APO202, patients were dosed to effect, beginning with doses of 2mg In that study, the goal was to match the peak effect of the usual levodopa dose for that patient I would propose that all patients be started on single dose of 2mg and they or their caregivers be instructed in administration At weekly or bi-weekly intervals, patients should have follow-up visits to re-evaluate efficacy and safety If indicated, the dose could be escalated, in increments of 1mg to a maximum of 6mg
- 14 There are a number of chemistry issues that need to be addressed If a lower specification cannot be set for one degradant, then that degradant will need to be qualified as per Dr Roney's review
- 15 The use of Tigan in the NDA needs to be better characterized The approval of apomorphine for PD raises 3 issues related to Tigan These are discussed in the preceding section

Recommendations

The sponsor should be sent an Approvable Letter with draft labeling The Approvable Letter should reflect the issues discussed above

**APPEARS THIS WAY
ON ORIGINAL**

Wheelous, Teresa A

From Kapcala, Leonard P
Sent Wednesday, June 04, 2003 5:48 PM
To 'Andrea Miller@mylanlabs.com', 'Frank Sisto@mylanlab.com'
Cc Kapcala, Leonard P, Wheelous, Teresa A
Subject RE: ? About Outpatient Diary CRFs and Specific Analyses of Diary Data for APO202 and Other questions about treating "Off"

Importance High

Hi Andrea,

Thank you for the PDF version of this submission regarding "off" episodes

I have a few new questions

1 Table 63.0 (ISS Safety Update) shows that the number of total treatment-emergent AEs (TEAEs) associated with dropouts is 238 for 120 patients. However, when I look at ISS Safety Update table 69.0 (part 1 and 2) and add up the total # of TEAEs associated with dropouts, I get 238 and the total number of patients with these TEAEs is 133. Thus, there is a difference of 3 TEAEs and 13 patients for the same data in the Safety Update. Would someone please explain this discrepancy? Is one set of numbers correct and is the other set incorrect? If so, what are the correct numbers?

2 Table 71.1 in the ISS Safety Update shows the 3 dose ranges for patients who dropped out for a TEAE. The dose range is for 0 > 0 up to < 4 mg and 4 mg. There does not seem to be a breakdown for doses > or = to 4 mg. Furthermore, there is no Table 72. The next table is 73.0. Where are the data for patients treated with doses = to 4 mg or > 4 mg? Would you please tell me where they are located. If these data are missing, would you please provide them? Is Table 72 missing? If so, would you please tell me what it is supposed to show and then provide it? The table of contents just seems to miss 72.0

Would you please call (301-594-5521) tomorrow and let me know if you can provide a quick answer and at least confirm that someone is checking this now, hopefully, for a quick response. Please call if there are any other questions that anyone has.

Thank you

Len

-----Original Message-----

From: Andrea Miller@mylanlabs.com [mailto:Andrea.Miller@mylanlabs.com]
Sent: Tuesday, June 03, 2003 6:13 PM
To: Kapcala, Leonard P
Cc: 'Frank.Sisto@mylanlabs.com', Wheelous, Teresa A
Subject: Re: ? About Outpatient Diary CRFs and Specific Analyses of Diary Data for APO202 and Other questions about treating "Off"

Dr. Kapcala,

Please find attached a copy of the response to your May 27, 2003 e-mail regarding treating "off" episodes. This response has also been sent in paper via FedEx to the application. Should you have any questions or require any clarifications on this correspondence, please call me.

Have a nice evening,

Andrea

(See attached file 052703 E-MAIL Response pdf)

"Kapcala, Leonard
P"
<Andrea Miller@mylanlabs com>,
<KAPCALAL@cder fd
<Frank Sisto@mylanlabs com>
a gov>
<KAPCALAL@cder fda gov>, "Wheelous, Teresa A"
05/27/2003 11 05
Specific Analyses of Diary Data for APO202
PM

To "'Andrea Miller@mylanlabs com'"
"'Frank Sisto@mylanlabs com'"
cc "Kapcala, Leonard P"
<WHEELOUST@cder fda gov>
Subject ? About Outpatient Diary CRFs and
and Other questions about treating "Off"

Hi Andrea and Frank,

I have some questions about treating "off" episodes

1 I was looking at vol 6 (of 111) for study 202 I was unable to find the CRFs for the outpatient diary data collection Are these CRFs somewhere in the NDA? If not, would you please FAX me a copy of them on Wednesday?

Neither was I able to find the specific analysis plan for these data Pages 61 and 62 of vol 6 (8-5-61,62) briefly summarized an approach for analyzing these data and also noted that some revisions were made in the analytical approach to these data Is there a more detailed description of how outpatient diary data were analyzed in study 202? If so, please tell me where I can find it

3 Based upon the protocol for 202, it did not appear that information was captured in the diary to distinguish specifically whether the patient experienced an "end of dose wearing off" or an unpredictable "on/off" Is this correct? If not, please tell me where I can find this information

4 In all 4 controlled studies (202, 30, 30, 302), it did not appear that specific information was captured as to whether a patient experienced an "end of dose wearing off" or an unpredictable "on/off" that was to be treated during the controlled phase Is this correct? If this is not correct, please specify where I can find information characterizing whether an "off" episode that was treated was an "end of dose wearing off" or an unpredictable "on/off "

5 In studies 301, 303, and 302, I understand that patients were to receive injection of study medication for their first "off" episode that occurred at least 1 hour after the usual morning therapy Is there information contained within the NDA that specifies whether these "off" episodes that were treated had occurred within each patient's dosing interval for levodopa or whether their next scheduled levodopa dose had to be held because an "off" episode (that was to be treated) had not yet occurred and regular medications were to be held until "off" was treated?

Would you please call me tomorrow to try to give me an update tomorrow about which issues/questions can be answered quickly and when answers can be expected for the remaining questions that were not yet able to be answered ?

Thanx

Len

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page(s) of trade secret.

and/or confidential

commercial information

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