

pooled APM group was + 3 msec. The most outstanding finding in the categorical analyses was that one patient who received 6 mg showed a 76 msec QTc increment up to maximal value of 514 msec at 20 minutes and a 54 msec increment at 90 minutes.

Overall, I conclude that these results support a concern about potentially significant QTc prolongation and that these results may underestimate the QTc prolongation that actually occurs when assessing QTc with more sensitive methods such as using standard ECGs, and assessing QTc at 40 minutes after treatment with various doses up to 10 mg. The risk of QTc prolongation may be greatest at high doses (e.g. 8 or 10 mg). However, individuals receiving ≤ 6 mg, but who have decreased renal and/or hepatic clearance of APM, could potentially generate increased plasma levels similar to those from patients with normal clearance who receive high doses of APM.

Preclinical Concerns

I believe that the sponsor should conduct preclinical carcinogenicity, reproductive toxicity and metabolic studies. However, considering that this is a fast track product for an unmet need and that the overwhelming population of patients who should use this product appropriately is relatively elderly and has advanced Parkinson's disease, I am not convinced that reproductive toxicity studies need to be conducted prior to approval. Neither am I absolutely convinced that carcinogenicity studies need to be conducted prior to approval. However, I am less convinced that these studies should not be conducted prior to approval because the sarcomas observed at injection sites (in only female rats that were able to tolerate high dose subcutaneous APM, males did not tolerate highest doses) occurred during APM exposures that are relatively similar to those expected in Parkinson's disease patients using intermittent subcutaneous APM. Animal metabolic studies can be completed in parallel with human studies conducted to characterize metabolism and metabolic pathways.

Conclusions

- 1 I consider this application to have shown efficacy of APM in treating "off" episodes in 3 pivotal trials.
- 2 Although there is significant toxicity associated with the use of APM, I consider this application to show sufficient safety considering the risk-benefit ratio to support an approvable action.
- 3 The sponsor needs to address several issues before an approval for APM can be granted.

Recommendations

Action Recommendation

I recommend an approvable action.

The following issues need to be addressed prior to approval

- 1 Characterize the magnitude of QTc prolongation in a randomized, double-blinded, placebo controlled parallel group fixed dose study in which patients are slowly titrated to their randomized doses of APM ranging between 2 to 10 mg. This study should be performed with standard 12 lead ECGs that should be read centrally under blinded conditions. ECGs should be collected at several times (e.g. ≥ 3) before dosing and at various post-treatment timepoints including 20, 40, 60, 90, and 120 minutes. Orthostatic (supine and standing) VS should also be collected in such a study at similar timepoints after ECG collection.
- 2 Analyze results of pivotal trials (APO 301, 302, 303) separately to show whether the "Off" that was treated was an end of dose "wearing off" or an "on/off" "Off" occurring at least 1 hour after morning antiparkinsonian medications was treated in these pivotal studies and antiparkinsonian medications were held until an "off" had been treated. This study design would allow treatment withheld induced "off" if patients were treated beyond their normal dosing interval with levodopa/dopa decarboxylase inhibitor. You should propose a definition for end of dose "wearing off" and "on"/"off" and obtain agreement from DNDP regarding your analysis plan for addressing this issue.
- 3 Characterize the local reaction profile to administration of a range of higher doses (i.e. > 2 mg, up to 10 mg single doses) containing benzyl alcohol. You only studied single injections of 2 mg with benzyl alcohol. There could be an increased incidence of local injection site reactions to much higher doses containing larger amounts of alcohol.
- 4 Collect a safety experience of patients using the cartridge device for injecting APM and show that the toxicity profile is not dissimilar than the one demonstrated for using APM from ampoules. There could be a higher error rate involving APM administration via the pen device and potentially a more toxic safety profile. The sponsor might randomize patients to both APM formulations and observe and compare the safety profile of each formulation after treatment for some prolonged period.
- 5 Analyze and present the results of Holter data (from study APO303) for cardiac rhythm abnormalities if Holter data were collected for a prolonged period during different treatment exposures in Study APO303.
- 6 Analyze and present laboratory results of study APO303 (patients naive to APM) and show shift tables at various times such as after the forced titration period and at the end of the trial (e.g. after 6 months after forced dose titration or last treatment the study).
- 7 Address the issues of abnormal laboratory shifts results from normal to high for serum cholesterol, triglycerides, glucose, alkaline phosphatase, ALT, AST, BUN, creatinine, and percentage of eosinophils. Although these findings were observed most commonly in the open-label experience in study APO401, some similar abnormal shifts were also observed in

other studies. The sponsor should also provide a shift analysis for all APM treated patients for the total eosinophil count from baseline to any time and also to the end of the study or last treatment.

- 8 Analyze and present shift tables for laboratory abnormalities in subjects in the clinical pharmacology studies separately (for studies in which this has not been done). The sponsor should also integrate these findings across similar clinical pharmacology studies.
- 9 Provide an analysis and description of how patients used the ampoule formulation of APM. This analysis could include such information as indicating: 1) the frequency APM was administered by the patient vs a caregiver, 2) the frequency APM was drawn into a syringe to treat an acute episode vs used from a pre-filled syringe, 3) the frequency of the setting (home/residence vs outside home/residence) in which APM was administered, and 4) the frequency a patient or caregiver was unable to administer APM and when unable, the reason for this. You should also indicate storage information (e.g. temperature kept, how long, etc.) when APM was pre-filled into a syringe for the next use.
- 10 Address the labeling changes shown in DNDP edits, questions, and recommendations.

The following issues can be addressed after approval.

- 11 Conduct drug-drug interaction studies assessing the interactions of APM with alcohol and APM with vasodilating drugs (especially both short and long acting nitrates) particularly for hypotension, orthostatic hypotension, and syncope.
- 12 Conduct studies to show the PK of APM in patients with all severities of renal and hepatic dysfunction.
- 13 Characterize the metabolism of APM in humans and animals.
- 14 Initiate carcinogenicity studies as soon as possible.
- 15 Initiate reproductive toxicity studies as soon as possible.

2 INTRODUCTION AND BACKGROUND

2.1 Background and Rationale for Clinical Development of Apomorphine (APM)

Parkinson's disease (PD) is a neurodegenerative disorder of uncertain etiology. Hallmark characteristics include clinical symptoms of tremor, rigidity, and bradykinesia, and pathological evidence of degeneration of the dopaminergic nigrostriatal pathway, marked striatal dopamine deficiency, and the presence of laminated inclusions (Lewy bodies) in the neurons of the substantia nigra. Although incompletely understood, the pathophysiology of Parkinson's disease involves basal ganglia dysfunction. In Parkinson's disease, a decrease in dopaminergic stimulation of the striatum unbalances the complex electromechanics of motor function.

Pharmacological treatment of Parkinson's disease has been primarily directed towards striatal dopamine replacement. The oral administration of the dopamine precursor, levodopa (LD), remains the foundation for the current symptomatic treatment of Parkinson's disease. Early clinical results, especially in patients with advanced disease, were impressive, and at times dramatic. However, long-term use of LD has been associated with decreasing effectiveness and increase in adverse events.

Combined use of a peripheral dopa decarboxylase (e.g. carbidopa - CD) with LD provides additional therapeutic benefit by decreasing the peripheral degradation of LD. This pharmacological effect of CD results in increased plasma levels of LD and a longer half-life of plasma LD that ultimately increases the central delivery of LD to the brain and central dopamine levels. Levodopa/carbidopa (i.e. LD/CD) remains the mainstay of treatment for Parkinson's disease. However, approximately 10 percent of all subjects treated with LD will develop motor fluctuations per treatment year, so that approximately 50 percent are affected after five years of LD therapy. Although the pathophysiology of these "Off" episodes is not completely understood, it has been proposed that these episodes of hypomobility are the result of the pharmacokinetic and pharmacodynamic properties of LD. As the disease progresses and dopaminergic nerve terminals are lost, the buffering capacity of the striatum is lost because of the short plasma half-life of LD. The "efficacy half-life" becomes shorter and shorter. In the advanced stages of Parkinson's disease, the short duration of action of LD is thought to have secondary pharmacodynamic consequences resulting in complex patterns of drug response.

Apomorphine (APM) is a non-selective dopaminergic agonist with potent D₁ and D₂ pharmacological actions. There is a significant preclinical and clinical literature base demonstrating antiparkinsonian effects of APM. APM is the oldest and one of the most potent dopaminergic agonists. APM HCl is identified chemically as 4*H*-Dibenzo[de,g]quinoline-10,11-diol, 5,6,6a,7-tetrahydro-6-methyl-, hydrochloride, hemihydrate, and 6αβ-Aporphine 10,11-diol hydrochloride hemihydrate. APM HCl is manufactured as a sterile solution (10 mg/mL) in 2-mL ampoules and 3-mL cartridges (for manual injector pens) for subcutaneous injection using the following inactive ingredients: sodium metabisulphite, sodium hydroxide, hydrochloric acid, and water for injection. Hydrochloric acid and sodium hydroxide are used

to adjust the pH of the final product between _____ Sodium metabisulphite is added to the product _____ Benzyl alcohol is added to the cartridge as a preservative To further _____ the ampoule headspace is filled _____

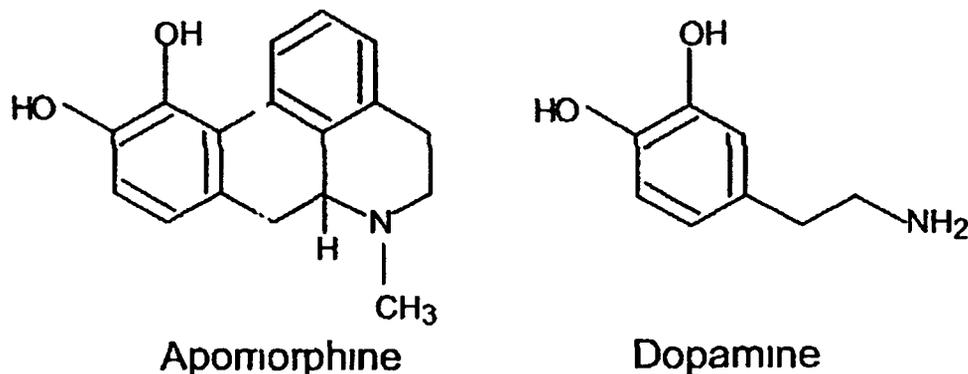


Figure 1 Chemical Structure of Apomorphine and Dopamine

Although known for decades to possess potential antiparkinsonian effects, APM has not been the subject of complete clinical development because subcutaneous injection of APM was inconvenient and because peripheral dopaminergic agonist activity, expressed as nausea/vomiting and hypotension (especially orthostatic), was considered to be inconsistent with practical clinical development. The successful development of newer oral dopamine agonists has demonstrated that peripheral dopamine agonist activity does not represent a significant limitation to practical therapy, possibly because of reduced sensitivity of peripheral dopamine receptors in patients receiving long-term dopaminergic therapy. Although new oral dopamine agonists might delay the onset of late stage motor fluctuations, it is estimated that approximately 50,000 U.S. patients suffer "Off" events despite administration of optimized regimens of available oral antiparkinson drugs. Under these circumstances, interest in APM was renewed specifically to take advantage of the rapid therapeutic response following subcutaneous administration.

2.2 "Off" in Parkinson's disease

A brief discussion of the nature of these motor fluctuations is helpful to understand the risk / benefit and efficacy of a medication such as APM for the treatment of Parkinson's disease. Two areas of particular concern are noted. The first is the characterization of the types of hypomobility states ("Off" episodes). The second is the clinical importance of these "Off" episodes.

Motor fluctuations, periods of hypomobility or immobility, can be divided into two major categories. The first category is termed "Wearing Off" or end of dose "Off" episodes. "Wearing Off" episodes are usually the first "Off" episodes encountered by Parkinson's disease in the course of their disease. These predictable fluctuations, as the name suggests, occur in association with the end of LD dosing intervals. They usually occur approximately three to five hours after each dose of LD. Initially these episodes can be treated by shortening the dosing interval and to

some extent by adding controlled release LD. The second category of motor fluctuations, random on-off fluctuations are not predictable based on the LD dosing schedule. These "Off" episodes can occur abruptly and without warning and are also known as "On"/"Off".

Having discussed the types of "Off" episodes experienced by Parkinson's disease PD, it is important to consider the clinical significance of these events. The disability associated with these events can be characterized as direct and indirect. The direct impact depends on the degree of hypomobility associated with the individual "Off" episodes. The less severe episodes may be associated with the inability to perform basic hygiene, eat, or perform other activities of daily living. Symptoms associated with these "Off" periods can include sensory (pain) symptoms, autonomic symptoms and psychiatric symptoms. Some of these "Off" episodes are so pronounced as to result in complete immobility, which has resulted in the terms "Off" and "frozen" or "freezing" being used to describe these events. These episodes can be accompanied by fixed and painful dystonic posturing, profuse sweating, tachycardia, and panic. Perhaps equally debilitating are the indirect effects of "Off" episodes. Patients can become fearful of having an "Off" episode while away from home that they no longer leave their houses.

Recognizing that Parkinson's disease is that it is a progressive neurodegenerative disease, the quantity and quality of the episodes of hypomobility or immobility (e.g. "Off") typically increase as the disease progresses. Despite treatment with LD/CD and the more recently approved prophylactic treatments consisting of dopaminergic agonists, selegiline, and catechol-ortho-methyl transferase (COMT) inhibitors, and amantadine, which often reduce the amount of "Off" time per day, patients with Parkinson's disease, especially those with later stages of disease, often continue to experience "Off" episodes.

There currently is no approved medication to treat (i.e. abort) the symptoms of established "Off" episodes acutely. Such a treatment could possibly improve the quality of life for patients with late stage Parkinson's disease suffering debilitating "Off" episodes. The FDA has granted this application Fast Track status, a rolling submission and a 6 month priority review because APM was deemed potentially capable of providing a new treatment (i.e. acute treatment to reverse "Off").

APM by either intermittent subcutaneous injection or by continuous subcutaneous infusion is approved in the United Kingdom, France, and the Netherlands to control motor fluctuations. The current NDA focuses on the use of intermittent subcutaneous injections of APM as acute ("rescue") treatment of "Off" events in patients with more advanced Parkinson's Disease.

2.3 Pharmacokinetic and Pharmacodynamic Considerations

To appreciate the potential benefit of APM treatment it is helpful to understand some important pharmacokinetic (PK) and pharmacodynamic (PD) considerations. Absorption of APM after subcutaneous administration is relatively rapid and virtually complete with bioavailability approaching 100%. Based upon many studies in the literature and the sponsor's own PK studies, T_{max} reflecting C_{max} shows considerable variability and ranges in most patients from approximately 15 to 45 minutes with perhaps most patients showing T_{max} near 30 minutes.

Recognizing that that the PD effect of APM is relatively immediate and mindful of its Tmax, it is not surprising that significant PD effects are observed beginning at a few minutes after administration and peaking between 15 and 45 minutes in many patients. Thus, the PK/PD relationships support that potential for rapid onset of therapeutic benefit and somewhat sustained actions of APM after subcutaneous administration.

2.4 Intended Indication

The sponsor notes that this NDA presents data in support of the effectiveness of subcutaneous injections of APM for the following indication

[_____]

2.5 Regulatory History

Mylan Pharmaceuticals Inc (Mylan), (a wholly-owned subsidiary of Mylan Laboratories Inc , the Sponsor) currently holds IND #52,844 that details the investigation of APM HCl injection in the acute symptomatic (rescue) treatment of "Off" episodes in patients with "On/Off" or "Wearing-Off" effects associated with late stage Parkinson Disease. Bertek Pharmaceuticals (another wholly-owned subsidiary of Mylan Laboratories) is Mylan's marketing division for branded products and would be the sponsor's marketing organization for the product in this NDA should the application be approved. This NDA is being re-submitted by Bertek Pharmaceuticals after it was initially submitted by Mylan in 2000 but it was not accepted for filing (i.e. Refuse to File). Mylan and Bertek are used interchangeably throughout the application in referring to the sponsor.

In April 1993, _____ received Orphan Designation for the use of APM in the above indication. This designation was subsequently transferred to Mylan. In a January 1999 meeting with the Agency, the Sponsor presented its plans for NDA submission after the completion of study APO202 demonstrated the significant treatment effects of APM to reverse induced "Off" episodes under medically observed conditions and those occurring in patients during one month of _____ use (i.e. outpatient conditions). During a discussion with Dr. Robert Temple (ODE 1 Office Director), Mylan learned that the NDA could not be approved without evidence of effectiveness after continual use (defined as at least 3 months in duration), which could be conducted in patients already receiving APM. Although the sponsor understood that additional toxicology and safety data would be required prior to approval, the sponsor originally believed that this information could be provided as amendments to the NDA. Thus in April 2000, Mylan Pharmaceuticals Inc submitted an NDA (assigned NDA #21-264 to the DNDP) for Apomorphine Hydrochloride Injection, 10 mg/mL. However, the FDA notified the sponsor that it refused to file NDA #21-264 on grounds of inadequate pharmacology/toxicology, and clinical safety information.

DNDP held several meetings (face to face or teleconferences) subsequently to help the sponsor address shortcomings identified in the 2000 NDA submission. DNDP gave the sponsor

significant feedback particularly about collecting safety data desired by DNDP prospectively. In addition, DNDP recommended collecting particularly adequate safety data assessing the effects of APM on orthostatic hypotension and potential adverse events related to APM's potent effects on the cardiovascular and central nervous system. More specifically, DNDP recommended studying patients who were naive to APM from immediately prior to APM administration up until at least 1 hour later and to assess the effect of administration of APM initially, after a relatively short repeated treatment period (e.g. weeks), and after more prolonged treatment (months). DNDP also recommended that the sponsor collect 12 lead ECG data to exclude or at least characterize potential QTc prolongation, at various times shortly after dosing.

On 1/10/02 DNDP held a pre-NDA meeting with the sponsor to plan for the NDA resubmission. During subsequent discussions that outlined the requirements for NDA filing the FDA offered the option of a rolling submission. Bertek formally accepted the offer of a rolling submission in December 2001. The FDA also granted NDA #21-264 Fast Track status on June 27, 2001.

2.6 Identification of Studies Supporting Effectiveness

This NDA submitted 4 pivotal studies to show efficacy of APM but Table 1 only shows summaries of 3 pivotal studies. Studies APO202 and APO301 are two prospective multi-center randomized placebo-controlled pivotal trials that the sponsor proposes documents the efficacy of APM to reverse the hypomobility associated with "Off" episodes in APM-naive patients (APO202) and in patients receiving APM for at least 3 months (APO301). APO401 was designed as the main safety study to increase the U.S. experience in the long term use of APM and to assess the safety of outpatient self-administration of APM on a prospective basis. Patients enrolled in APO401 could also enroll in three companion sub-studies. Patients, naive to APM, were initially enrolled in APO303 (a substudy of APO401) and were studied under double-blinded, placebo controlled conditions using a cross-over design (4 mg vs placebo) to assess the efficacy of APM on reversing "Off". APO303 is also considered to be a pivotal study showing efficacy of APM. Patients enrolled in APO303 underwent a more controlled forced dose titration/escalation regimen than patients in APO401 in order to document orthostatic vital sign changes and potential electrocardiographic changes due to APM and to identify dose escalation methods that might acutely minimize adverse cardiovascular effects of APM. Patients enrolling in APOM-0073 participated in open-label pharmacokinetic and pharmacodynamic assessments to identify pharmacokinetic and pharmacodynamic relationships in APM's actions.

Results of pivotal study APO302 conducted by the sponsor were submitted with the Safety Update. Patients enrolling in APO302 (parallel group design), another substudy of APO401, participated in efficacy assessments in a randomized, double-blinded, placebo-controlled study to demonstrate the continued ability of APM to reverse "Off" events after at least three months' use of APM. In APO302 there was also collection of safety information, especially orthostatic vital sign changes and potential electrocardiographic changes timed to dosing. APO302 is not described in the tabular summary of trials (Table 1).

3 TABULAR SUMMARY DESCRIPTION OF CLINICAL STUDIES

Studies APO202, APO301, and APO303 are pivotal studies conducted by the sponsor and shown in the Table 1. Another pivotal study APO302 that was not submitted in the original submission of clinical data is not shown in this tabular summary. APO302 results were submitted with the ISS Safety Update. APO401 was the main safety study (including long-term treatment) conducted by the sponsor. APO073 is a substudy of APO401 that was conducted by the sponsor and investigated acute pharmacokinetic and pharmacodynamic relationships of APM in a few patients with Parkinson's disease. APO073 is listed as a supportive study. APONIH and APO101 are considered supportive studies and were not conducted by the sponsor. APO161 is a retrospective review of a safety experience of APM treatment in the United Kingdom.

Table 1 Overview of Clinical Studies Conducted with Apomorphine HCl Injection

Study Type	Study No (Ref No)	Study Title	Study Design	Drugs Dosage and Duration of Exposure	N A/P	Age Range (yr)	% M/F	Results
<p>Abbreviations Used (S)AE = (serious) adverse event, A/P= active to placebo ratio, APO = apomorphine, BID = twice daily, BP = blood pressure, DB = double-blind, IP = inpatient, IV = intravenous infusion, LD = levodopa, MD = Maintenance Dose, MPI = Maximum % Improvement, NA = Data not available, NS = Not Statistically Significant, OP = outpatient, P = placebo, PC = placebo controlled, PD = Parkinson's Disease, PG = parallel groups, PK/PD = pharmacokinetic-pharmacodynamic, R = randomized, SC = subcutaneous, TV = Treatment Visit, UPDRS (MS) = Unified Parkinson's Disease Rating Scale (Motor Scores), XO = crossover</p>								
PIVOTAL EFFICACY STUDIES								
Phase II Efficacy and Safety US Study 4 Sites	APO202	A Prospective Randomized Double-Blind Placebo-Controlled Parallel Groups Study Of The Safety And Efficacy Of Subcutaneous Injections Of Apomorphine In The Treatment Of "Off" Episodes In Patients With "On-Off" Or "Wearing-Off" Effects Associated With Late Stage Parkinson's Disease	DB R PC PG	SC individualized based on LD response Avg Apo Dose = 5.4 mg Inpatient dose based on response to LD Outpatient DB R PC treatment duration was one month	29 20/9	45-80	69/31	Inpatient mean post injection UPDRS scores were reduced by 23.9 v 0.1 points by APO v PL respectively (p < 0.0001). Dyskinesia was significant 20 minutes after dosing and was of a magnitude equal to that after oral LD. During the 1 month outpatient phase the mean % injections resulting in successful OFF was 95% and 23% for APO and PL (p = 0.0001). The outpatient response to APO is an independent substantiation of APO's efficacy. AEs recorded in 85% of APO patients included injection site reactions, yawning, drowsiness, dyskinesia, nausea, vomiting, dizziness, rhinorrhea, hallucinations or confusion and chest pain.
<p>Abbreviations Used (S)AE = (serious) adverse event, A/P= active to placebo ratio, APO = apomorphine, BID = twice daily, BP = blood pressure, DB = double-blind, IP = inpatient, IV = intravenous infusion, LD = levodopa, MD = Maintenance Dose, MPI = Maximum % Improvement, NA = Data not available, NS = Not Statistically Significant, OP = outpatient, P = placebo, PC = placebo controlled, PD = Parkinson's Disease, PG = parallel groups, PK/PD = pharmacokinetic-pharmacodynamic, R = randomized, SC = subcutaneous, TV = Treatment Visit, UPDRS (MS) = Unified Parkinson's Disease Rating Scale (Motor Scores), XO = crossover</p>								
PIVOTAL EFFICACY STUDIES								
Phase III Efficacy and Safety Foreign Study 2 UK Sites	APO301 (APOS-001)	A Prospective Randomized Placebo-Controlled Crossover Study of the Safety and Effectiveness of Subcutaneous Injections of Apomorphine in the Treatment of "Off" Episodes in Patients With "On/Off" or "Wearing-Off" Effects Associated With Late Stage Parkinson's Disease	DB R PC XO	SC individualized based on past history (at least 3 months) of APO Avg Apo Dose = 3.9 mg over the 2 dosing days	17 8 A/P 9 P/A	48-72	71/29	At the average dose of 3.91 mg, mean post injection UPDRS scores at 20 minutes were reduced by 20.0 and 3.00 points by APO and P respectively (p < 0.0001). These results were corroborated by non-parametric analyses using the exact Wilcoxon Rank Sum Test (p = 0.0005 for treatment effect, p = 0.6058 for sequence effect). At 10 minutes and 60 minutes APO versus P changes in UPDRS motor scales were also significant (10 minutes 15.4 v 2.70 p = 0.0086, 60 minutes 12.6 v 0.4 p = 0.0009). AEs occurred in 3 of 17 (17.6%) patients during placebo testing, 0 of 16 patients during APO testing, and in 2 of 17 patients on non-treatment days. There were no deaths or SAEs.

CLINICAL REVIEW

Study Type	Study No. (Ref No)	Study Title	Study Design	Drugs, Dosage and Duration of Exposure	N	Age Range (yr)	% M/F	Results
Abbreviations Used (S)AE = (serious) adverse event, A/P = active to placebo ratio, APO = apomorphine, BID = twice daily, BP = blood pressure, DB = double-blind, IP = inpatient, IV = intravenous infusion, LD = levodopa, MD = Maintenance Dose, MPI = Maximum % Improvement, NA = Data not available, NS = Not Statistically Significant, OP = outpatient, P = placebo, PC = placebo controlled, PD = Parkinson's Disease, PG = parallel groups, PK/PD = pharmacokinetic-pharmacodynamic, R = randomized, SC = subcutaneous, TV = Treatment Visit, UPDRS (MS) = Unified Parkinson's Disease Rating Scale (Motor Scores), XO = crossover								
PIVOTAL EFFICACY STUDIES								
Phase III Primarily Safety Efficacy Component US Study 22 US Sites	APO303 (sub-study of APO401)	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	IP Forced Titration Dose Initiation DB R, PC XO component at 4 mg 6 month OP Phase	SC IP forced titration dose introduction from 2 10 mg at 2 mg increments DB R, PC XO at the 4-mg dose introduction level 6-month open OP treatment at optimal dose Ongoing Study (Data through January 2002, SAEs updated through March 2002)	56	45-82	59/42	56 patients enrolled, 51 patients participated in the IP efficacy assessment. The mean change in pre-dose UPDRS-MS was significantly greater after 4 mg APO v P at 20 (-11 v -3), 40 (-14 v -3) and 90 minutes (-5 v -2). Results were confirmed by non-parametric methods. As of January 2002, 8 subjects completed and 27 subjects continue OP therapy. 96% patients had at least 1 AE. 15 patients discontinued due to AEs. Common AEs included yawning, dizziness, nausea, rhinorrhea, sedation, BP reduction and headache. The incidence of AEs and orthostatic was related to dose. One of 3 SAEs (sinus arrest, syncope) was drug related. One death was not considered drug related.

Study Type	Study No. (Ref No)	Study Title	Study Design	Drugs, Dosage and Duration of Exposure	N	Age Range (yr)	% M/F	Results
Abbreviations Used (S)AE = (serious) adverse event, A/P = active to placebo ratio, APO = apomorphine, BID = twice daily, BP = blood pressure, DB = double-blind, IP = inpatient, IV = intravenous infusion, LD = levodopa, MD = Maintenance Dose, MPI = Maximum % Improvement, NA = Data not available, NS = Not Statistically Significant, OP = outpatient, P = placebo, PC = placebo controlled, PD = Parkinson's Disease, PG = parallel groups, PK/PD = pharmacokinetic-pharmacodynamic, R = randomized, SC = subcutaneous, TV = Treatment Visit, UPDRS (MS) = Unified Parkinson's Disease Rating Scale (Motor Scores), XO = crossover								
KEY SAFETY STUDY								
Phase III Long Term Safety US Study 61 Sites	APO401 (parent study for APO303 and APOM-0073)	An Open Label Study to Evaluate the Long-Term Safety and Effectiveness of Subcutaneous Injections of Apomorphine in the Treatment of "Off" Episodes in Patients With "On-Off" or "Wearing-Off" Effects Associated With Late-Stage Parkinson's Disease	Open Titration to optimal dose	SC Titration to optimal dose Treatment for 1 year with optional extension Ongoing Study (Data through December 2002, SAEs updated through March 2002)	488	38-99	66/34	488 patients received APO, 278 are active, 129 on APO for at least 12 months. Most patients withdrew because of AEs. The average single dose for patients receiving APO for at least 12 months was 3.91 mg. Ten deaths were reported—none attributed to APO. Most AEs were mild to moderate and included dizziness, nausea, dyskinesia and orthostatic hypotension. No clinically significant laboratory trends were observed. Seven SAEs occurred that involved orthostasis or syncopal type episodes. Two of these events occurred within 30 minutes of injection and within 60 minutes. The remaining events occurred greater than 2 hours after the last apomorphine dose.

CLINICAL REVIEW

Study Type	Study No (Ref No)	Study Title	Study Design	Drugs Dosage and Duration of Exposure	N A/P	Age Range (Yr)	% M/F	Results
Abbreviations Used (S)AE = (serious) adverse event A/P= active to placebo ratio APO = apomorphine BID = twice daily BP = blood pressure DB = double-blind IP = inpatient, IV = intravenous infusion LD = levodopa MD = Maintenance Dose MPI = Maximum % Improvement NA = Data not available NS = Not Statistically Significant, OP = outpatient P = placebo PC = placebo controlled PD = Parkinson's Disease PG = parallel groups PK PD = pharmacokinetic-pharmacodynamic R = randomized SC = subcutaneous, TV = Treatment Visit, UPDRS-(MS) = Unified Parkinson's Disease Rating Scale (Motor Scores) XO = crossover								
SUPPORTIVE STUDIES								
Phase II Supportive Efficacy Clinical Pharmacology PK PD US Study 3 Sites	APOM-0073 (sub-study of APO401)	A Multiple Center Phase I Open-Label Pharmacokinetic (PK) and Pharmacodynamic (PD) Study Following Subcutaneous Administration of Apomorphine HCl to Patients with Idiopathic Parkinson's Disease	Open 4 Treatment Visits All PD patients on stable APO dose	TV1 MD TV2/TV3 R between MD-2 mg and MD+2 mg TV4 MD every 90 min x 3 doses	6	57-73	67/33	The mean peak APO concentration occurred at 13.6 minutes after the SQ injection and declined with a half life of 43 minutes and with an elimination rate that appeared to obey first-order one-compartment kinetics Indices of both efficacy (UPDRS-MS and Webster step second scores) and safety (BP and DRS) correlated with APO plasma concentrations The correlation of plasma APO concentrations with parameters describing pharmacological outcome (both efficacy and safety) provides independent substantiation of drug effectiveness

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SUPPORTIVE STUDIES								
Phase II Academic - Government Basic Science Study Retrospective Analysis of Efficacy and Safety Parameters US study 1 Site	APONIH	A Double-Blind Placebo-Controlled Dose-Response Study Of Apomorphine In The Treatment Of "Off" Episodes In Parkinson's Disease Patients Grouped By Response to Levodopa / Carbidopa (based on data from a study conducted by the Experimental Therapeutics Branch National Institute of Neurological Disorders and Stroke National Institutes of Health) Apomorphine Responses In Parkinson's Disease And The Pathogenesis Of Motor Complications (Neurology 1997 48:369-372)	DB PC XO	SC individualized by titration on basis of Columbia Rating Scale Range 0 to 6mg Treatment duration was 2 weeks	34	32-74	68/32	Max % improvement in modified Columbia Rating Score produced by APO were 35, 40, 77 and 73% respectively (paired difference p<0.001 v PL) in each of four subgroups (LD naive, stable, wearing off, on/off). Responses of patients classified as "wearing-off" or "on-off" subsets were not significantly different from each other, but were different from responses in patients at earlier stages of disease severity

Study Type	Study No (Ref No)	Study Title	Study Design	Drugs Dosage and Duration of Exposure	N A/P	Age Range (Yr)	% M/F	Results
Abbreviations Used (S)AE = (serious) adverse event A/P= active to placebo ratio APO = apomorphine BID = twice daily BP = blood pressure DB = double-blind IP = inpatient, IV = intravenous infusion LD = levodopa MD = Maintenance Dose MPI = Maximum % Improvement NA = Data not available NS = Not Statistically Significant, OP = outpatient P = placebo PC = placebo controlled PD = Parkinson's Disease PG = parallel groups PK-PD = pharmacokinetic pharmacodynamic R = randomized SC = subcutaneous, TV = Treatment Visit, UPDRS (MS) = Unified Parkinson's Disease Rating Scale (Motor Scores) XO = crossover								
SUPPORTIVE STUDIES								
Supportive Phase II Efficacy and Safety Foreign Study	AP0101	A Double-Blind Placebo Controlled Study With Apomorphine In A Pen Given To Parkinson's Patients With On-Off Phenomena Pen Injected Apomorphine Against Off Phenomena In Late Parkinson's Disease A Double Blind Placebo Controlled Study (J Neurol Neurosurg Psychiatry 1995 58 681-687)	DB PC XO	SC individualized by titration on basis of Columbia Rating Scale	22 XO	44-72	45/55	14 subjects completed the study 8 patients discontinued due to hypotension (3) unsatisfactory effect (2) exanthema (1) unclear "Off" periods (1) and lack of motivation (1). APO produced a statistically significant reduction in the mean daily duration and severity of "Off" periods. Efficacy and safety was demonstrated for two months under outpatient conditions

CLINICAL REVIEW

Study Type	Study No (Ref No)	Study Title	Study Design	Drugs, Dosage and Duration of Exposure	N A/P	Age Range (yr)	% M/F	Results
Abbreviations Used (S)AE = (serious) adverse event A/P = active to placebo ratio APO = apomorphine BID = twice daily BP = blood pressure DB = double-blind IP = inpatient, IV = intravenous infusion LD = levodopa MD = Maintenance Dose MPI = Maximum % Improvement, NA = Data not available NS = Not Statistically Significant, OP = outpatient, P = placebo PC = placebo controlled PD = Parkinson's Disease PG = parallel groups PK PD = pharmacokinetic-pharmacodynamic, R = randomized SC = subcutaneous, TV = Treatment Visit, UPDRS(MS) = Unified Parkinson's Disease Rating Scale (Motor Scores) XO = crossover								
SUPPORTIVE STUDIES								
Supportive Phase IV Safety Foreign Study	APO161 (APOD-401)	A Retrospective Safety Review of Subjects Treated with Apomorphine for Parkinson's Disease at One Centre Over a 13 Year Period (1986 to 1999) Middlesex Study	Retrospective Safety Review	Individualized dose SC intermittent, SC continuous nasal IV and rectal	188	26-76	62/38	188 patients were reviewed with 159 summarized with complete CRF 60 deaths were documented with a mean of almost 6 years between APO introduction Time of death and cause of death was similar to that expected of late stage Parkinson's disease The most serious adverse events related to development of skin lesions and neuropsychiatric reactions that can require treatment discontinuation. Adverse events lack of effect, and complexity of dosing contributed to discontinuation of therapy by 20% of patients within 1 year Overall population median treatment duration is currently 70 months

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4 FOREIGN MARKETING HISTORY

Bertek Pharmaceuticals, the sponsor of this NDA, has not yet marketed the product under review. However, Britannia has marketed APM that is administered subcutaneously. I will review the foreign marketing history of Britannia's product briefly.

Overview of Worldwide Experience with Apomorphine

European Experience with Apomorphine

Britannia has distributed APM in the UK since 1991, initially as compassionate use for treatment of the "Off" events associated with Parkinson's disease. In 1993, the 2 mL ampoules (10 mg/mL) were approved, followed by approval of the 5 mL ampoule in 1994. A prefilled syringe was approved in 1996. The 5 mL ampoule is primarily used for subcutaneous continuous infusion. Britannia has now received EU mutual recognition for APM. APM has also been licensed for use in Parkinson's disease patients in France, Argentina, Australia, Italy, and Lebanon. It is also used on a compassionate use basis in Canada, Ireland, Spain, Denmark, Norway, Poland, and the Czech Republic.

In the UK, APM is used to treat "Off" phenomena. The daily dose of APM is typically between 3 mg and 30 mg per day in divided doses. Injection frequency ranges from 1 to 10 injections per day. The total recommended daily dose of apomorphine should not exceed 100 mg and an individual injection should not exceed 10 mg.

Britannia used a "named" patient program to track patient distribution prior to its approval in the UK. After approval, it has continued to use the same distribution program since approval of the 2 mL ampoule that captures a significant percentage of the users in the UK. As of July 30, 1999, — patients had been included in this program.

The post-marketing experience as maintained by Britannia is reviewed later (see Post-Marketing Experience).

Apomorphine (Britaject™) has been distributed in the UK, as ampoules for subcutaneous injection, by Britannia Pharmaceuticals Ltd, since July 1991, initially on a compassionate basis. A marketing authorization for the 2 mL ampoules (10 mg/mL) was granted in August 1993. Five mL ampoules (10 mg/mL) were introduced in 1994 and a 3 mL (10 mg/mL) multidose, prefilled pen (Britaject Pen™) has been available since October 1996.

Apo Go Pen is a 3 mL multidose pen containing 10 mg/mL of apomorphine hydrochloride. In the UK, APM hydrochloride is also available as 2 mL and 5 mL ampoules, each containing 10 mg/mL of apomorphine hydrochloride. Apo Go Pen was authorized through the Mutual Recognition Procedure. It should be noted that the last national Marketing Authorization for Apo Go Pen was not granted until 2001. Following this, a type II variation concerning a minor change

to the pen design was submitted and has recently been approved (November 2001) Furthermore, reimbursement negotiations are still ongoing in some countries Hence, distribution of the licensed product has not commenced in any of the concerned Member States, with the exception of the UK A letter was issued by Forum Products on 23 October 2001 notifying all the concerned Member States of the above, in explanation for the delay in the submission of the first PSUR Although the licensed product has still not been introduced in any of the Member States, beyond the UK, it has been available in Ireland, Sweden, Spain, Portugal, Germany and more recently Denmark on a limited compassionate basis It is estimated that ~ patients receive APM in territories outside of the UK The safety data included in this review is, therefore, largely from the UK and territories where the product is established (the Netherlands, Taiwan) It should be noted that many patients in the UK receive APM by subcutaneous infusions and the majority of safety data contained within this review relates to that route of administration, which is unlicensed in the other European countries

APM has been licensed for use in patients with Parkinson's disease by Laboratoire Aguettant in France and Argentina and by Chiesi in Italy It has been estimated that currently there are — patients receiving treatment in these countries

There has been no pertinent safety information received from those territories There have been no Marketing Authorization withdrawals or suspensions in any country or restrictions on distribution Likewise there have been no clinical trial suspensions, dosage modifications, formulation changes or changes in target population or indications

In summary, Britannia Pharmaceuticals has distributed APM for the treatment of the late stage symptoms of Parkinson's disease in the UK since 1991 and more recently in other countries outside the UK During this time there have been relatively very few adverse events and those reported have generally been related to the pharmacology of the drug and consistent with those observed in clinical trials Only two serious unexpected reports have been received, which were both associated with the off label intravenous administration of APM in patients with young onset, long standing Parkinson's disease

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5 PRECLINICAL SUMMARY

I have provided a brief summary of preclinical data to support this NDA. For greater details, see the review of the Pharmacologist/Toxicologist (Dr P Roney)

The sponsor has submitted repeat toxicology studies (including chronic studies in rats and monkeys), genotoxicity studies, limited pharmacokinetic studies and local irritation studies. The sponsor did not submit any studies on pharmacology, safety pharmacology, carcinogenicity or reproductive toxicity. To address some of these data gaps, the sponsor submitted papers from the scientific literature to provide data on pharmacology, safety pharmacology, pharmacokinetics and reproductive toxicity. The data from the literature are of limited utility in assessing the potential effects of apomorphine because it is not possible to conduct a detailed examination of the data. In addition, there are substantive issues that have not been addressed in the literature. In particular, there is a lack of data on the potential effects of APM on reproductive function and on the heart conduction system (e.g. QTc).

The primary toxicity observed in APM treated animals (rats, monkeys) are related to clinical signs associated with excessive stimulation of dopamine receptors. Weight loss has been observed in treated animals, but no consistent effects on hematology or clinical chemistry parameters were observed. One potential concern is male reproductive tract toxicity. Decreased testes weight and altered testes histology were observed in rats and monkeys at doses comparable to what would be used clinically. The potential effects on male reproduction have not been examined in segment I reproductive toxicity studies. The sponsor also submitted a study examining the potential effects of levodopa/carbidopa on APM toxicity in rats, but the levodopa/carbidopa doses were too low to permit meaningful comparisons. This study should be repeated.

APM is genotoxic in multiple in vitro systems. It induced frameshift mutations in Ames assay, especially in TA1537. It was also positive in the mouse lymphoma assay causing an increase in both large colonies (indicative of mutations) and small colonies (indicative of clastogenic events). APM induced chromosomal aberrations in cultured human lymphocytes. APM was negative in the in vivo mouse micronucleus test. However, this test only used once daily dosing. Because APM will be used multiple times during the day, it is desirable that the in vivo micronucleus test be conducted using a multiple dose per day regimen.

The sponsor cites ICH guidelines in requesting a waiver to conduct carcinogenicity studies post approval. This is permitted when the drug is meant for the treatment of a serious debilitating disease. However, the pharmacology/toxicology reviewer (Dr Roney) does not believe that the sponsor has taken steps to initiate these studies (e.g., at least starting to conduct dose range finding studies in mice and submitting a carcinogenicity study protocol to Executive Carcinogenicity Assessment Committee).

The sponsor has also requested a waiver from conducting reproductive toxicity studies.

Dr Roney does not consider the sponsor's arguments to be persuasive, especially considering that its own clinical studies included patients with reproductive potential. There are also reports in the scientific literature of pregnant patients with Parkinson's disease who experience worsening of "Off", the indication that the sponsor intends to treat with this drug. It seems that the sponsor's arguments do not adequately support the waiver of reproductive toxicity studies for the pharmacology/toxicology reviewer, Dr Roney. This is a major data gap in the preclinical database.

The chemistry section of the application sets specification of — for a pair of degradation products in the drug product. This is above the threshold for qualification — at the proposed clinical dose levels. Dr Roney believes that the sponsor needs to either lower the specification for these impurities or conduct a qualification study (a four to 13 week study in a single species) to assess the potential for the degradation product to affect the safety of the drug product. Dr Roney does not consider it necessary to conduct genotoxicity studies to qualify the degradation products because APM is strongly genotoxic in its own right.

Recently we learned that carcinogenicity studies at the highest dose in females resulted in sarcomas at injection sites using a p-53 animal model.

APM — Males were not able to tolerate the highest dose. These sarcomas occurred at an exposure similar to that planned for humans. This issue is of potentially significant concern for sublingual.

The sponsor has not conducted preclinical studies on metabolism. Neither is the metabolism of APM in humans clearly understood. There appears to be a need for studies to clarify metabolic pathways in both animals and humans. Both species should be studied. Despite the fact that human metabolic data would be of paramount interest, collecting information on metabolism in animals would also be important to show that metabolism is relatively similar and therefore preclinical studies conducted in animals have potential relevance to humans. There could be a concern if humans generated a unique metabolite not generated in animal toxicology studies or if humans generated much higher amounts of one or more metabolites than are generated in animals species upon which toxicology conclusions rest. If either of these possibilities is the case, then additional toxicology studies would be needed in a species that mimics human metabolism to show that toxicological results from that species are relevant to humans.

In summary, preclinical studies suggest that the dose limiting toxicity associated with APM are central nervous system signs associated with excessive pharmacological stimulation of dopamine receptors. The studies also suggest that there is potential for effects on the male reproductive system, but definitive reproductive toxicity studies have not been conducted in male or female animals. Carcinogenicity studies have not been conducted, but the sponsor has requested permission to conduct these studies post approval, which is acceptable. The sponsor should also conduct dose range finding studies for carcinogenicity studies in mice prior to approval. Studies that can be conducted as phase IV commitments include the carcinogenicity studies, in vivo micronucleus test, and the combination study. Preclinical metabolism studies are also needed.

6 FINANCIAL DISCLOSURE

All principal investigators in the pivotal efficacy studies (i.e. Studies APO- 202, 301, 302, 303) completed financial disclosure forms certifying that there were no financial conflicts. Considering the individuals who had completed the forms, there did not appear to be any instances involving a financial conflict.

7 DATA SOURCE DESCRIPTION

The source of data for this NDA review was contained in the original rolling NDA submission that began in 5/02. The Clinical section (#8) was submitted in September 2002. In addition, the sponsor has made numerous document submissions in response to my questions and requests for additional data, data presentations, and/or data analyses. The sponsor also submitted a ISS Safety Update that was received on 1/2/03 and started the review clock because critically desired ECG data and analyses were not submitted until then.

8 FDA BIORESEARCH MONITORING PROGRAM INSPECTIONS

Inspections of 3 sites (Study 202, Investigator-Hutton, 14 patients, Study 303 Investigator-Trosch, 8 patients, Study 303, Investigator-Murphy, 10 patients) involved in pivotal trials were conducted by the Division of Scientific Investigation (DSI) in May and early June 2003. Reports have not been written and provided yet. I have been told by Dr. Ni Khin inn DSI that there were no 483 regulatory violations with Investigator sites Hutton and Trosch. There were three minor 483 items related to adverse event reporting in the study subject files.

9 HUMAN PHARMACOKINETICS and PHARMACODYNAMICS

APM is a potent, short-acting, dopamine agonist. Its mechanism of action is believed to involve primarily the stimulation of dopamine receptors in the corpus striatum, which leads to anti-parkinsonian activity.

The literature showed that for subcutaneous (SC) administration, APM is rapidly absorbed with complete absorption. The plasma to whole blood concentration ratio was equal to one. Plasma protein binding of APM was estimated at greater than 99.9% over a range of 1257 ng/mL to 3112 ng/mL. T_{max} ranges from approximately 10 to 60 minutes with most subjects achieving maximal plasma concentrations between 20 to 40 minutes. APM is distributed into CSF with peak concentrations of less than 10% of the peak plasma concentration and occurring 10 to 20 minutes after those in the plasma.

APM is rapidly cleared from plasma. Renal elimination of unchanged or conjugated R-apomorphine is not a major route of elimination in humans. The catechol-O-methyl transferase (COMT) metabolite is undetectable. In vitro study showed that APM is subject to photo degradation and autooxidation. Following SC administration to the abdomen, APM pharmacokinetics are most commonly described as biphasic. The $t_{1/2\alpha}$ was 14.2 ± 6.8 minutes and $t_{1/2\beta}$ was 69.7 ± 26 minutes. Although the $T_{1/2}$ elimination for subcutaneous apomorphine based upon literature and Bertek's PK program is considered to be approximately 1 hour, the $t_{1/2}$ elimination for sublingual APM

was approximately 2-3 hours. The influences of age, gender, weight, duration of Parkinson's disease, L-dopa dose and duration of therapy, and clinical state were not significant for APM clearance in humans. Possible pharmacokinetic (PK) as well as pharmacodynamic (PD) interactions between levodopa and APM have been reported.

A strong correlation between the CSF concentration of APM and its effect have been demonstrated. The pharmacokinetics and pharmacodynamics have been described as "quantal" with a threshold concentration below which no therapeutic response is seen. Increasing concentrations above the threshold may prolong the duration of therapeutic response, but do not elicit a greater magnitude of response.

Although literature studies provide a general understanding of the clinical pharmacology of apomorphine, there are several issues of concern. It is not clear what the major route of elimination is and what proportion each route accounts for elimination of APM. Neither is the precise quantitative role that autooxidation plays in the clearance of APM clear. The impact of renal and hepatic impairment on the pharmacokinetics of APM had not been previously clarified.

The applicant conducted 3 in vitro metabolism studies and 6 human pharmacokinetic studies. The in vitro studies explored the metabolic routes, induction and inhibition potential of APM. These results suggested that it is unlikely that there would be metabolism-based drug-drug interactions between APM and other drugs via CYP enzyme metabolic transformations. The pharmacokinetic parameters for APM HCl obtained in these studies were similar to those reported in the literature. The results indicated pharmacokinetic dose proportionality over the dosage range (2 mg to 8 mg) in idiopathic Parkinson's disease patients. APM did not have a tendency to accumulate in patients with idiopathic Parkinson's disease. A PK/PD analysis in patients with Parkinson's Disease showed that the improvement in motor function following subcutaneous APM administration occurred within 10 minutes (peak effect occurred around 40 minutes after dosing) and persisted for approximately 90 minutes. The EC_{50} in patients with Parkinson's disease is 10.7 ng/mL and 5.3 ng/mL for the UPDRS motor scores and the modified Webster step second test scores, respectively. A simulation based on this model showed that doses more than 6 mg did not produce significant extra improvement of UPDRS scores compared to lower doses whereas dose-dependent decreases were shown for blood pressures (systolic and diastolic) and pulse. Based upon results of this simulation, it might also be desirable to increase dose by 0.5 mg instead of 1 mg.

The apparent clearance of 280 L/h, which is higher than hepatic blood flow, supports the existence of autooxidation of APM as an elimination route. However, the *in vivo* evidence of autooxidation was not provided. Furthermore, autooxidation could not account for most of the APM eliminated. The major route of elimination is not clear. In addition, C

A mass balance study is recommended to clarify this issue. Neither is the metabolism of APM clearly understood in animals.

The patients with moderate hepatic impairment had 24% higher C_{max} and 9% higher AUC compared to the normal subjects. The patients with moderate renal impairment had 50% higher C_{max} and 15% higher AUC compared to the normal subjects. In patients with moderate renal impairment, the starting dose is recommended to be 1 mg (reduced from the proposed starting dose 2 mg) by the Biopharmaceutical reviewer, Dr Duan. A cartridge (3-mL) was developed for use in a multiple use pen with benzyl alcohol as preservative, while the 2-mL ampoule was used in all the clinical trials conducted by the applicant. In an amendment, two bioequivalence studies were submitted. Based on the study results, and considering that benzyl alcohol is not expected to interfere with the pharmacokinetics of apomorphine, the cartridge formulation is considered to be bioequivalent to the clinical formulation (ampoule formulation).

There did not appear to be a significant problem with adverse events related to local injection of the APM formulation (2 mg) containing benzyl alcohol. I asked the chemistry reviewer and pharmacology/toxicology review what is the maximal amount of benzyl alcohol that is permitted in other approved products containing benzyl alcohol. I would like to compare this with the amount to be injected with a high dose of APM such as 10 mg. I have not received an answer. It would be desirable for the sponsor to characterize the local reaction profile to administration of a range of higher doses (i.e. > 2mg, up to 10 mg single doses) containing the preservative benzyl alcohol. Considering that the sponsor only studied single injections of 2 mg with benzyl alcohol, it is possible that there might be an increased incidence of local injection site reactions to much higher APM doses containing larger amounts of benzyl alcohol.

A more detailed review of PK/PD information and issues can be found in the review of the Biopharmaceutical reviewer, Dr John Duan.

10 EXPOSURE AND DOSING FOR APOMORPHINE

A total of 536 unique patients (as of Safety Update) were treated in the trials conducted by the sponsor. Table 2 shows the breakdown of the various numbers of patients who were treated in the controlled trials and/or in the open-label safety trial (APO401). Most patients (i.e. 508) were treated in the safety study based upon initial treatment in that study or initial treatment in a controlled study followed by subsequent treatment in this open-label extension, safety study. There were 33 patients who were initially treated in a randomized, controlled study who did not subsequently enroll in study APO 401. Table 2 further indicates that 121 patients received APM, 104 patients received placebo, and 66 patients received both study medications in the randomized, controlled studies.

Table 2 Exposure of Number of Patients to APM and / or Placebo in Controlled Studies and/or Open-Label Safety Study

Treated in Any Sponsor Study	Controlled Study			Treated with APM in Open-Label Safety Study APO401	Not Treated with APM in Open-Label Extension Safety Study After Treatment in Controlled Study
	Any Rx APM, Placebo or Both	APM	Placebo		
APO 202 ^a (controlled)	29	20	9	13 (8 ^e -APM, 5 ^e -Placebo)	16 (12 ^e -APM, 4-Placebo)
APO 301 ^b (controlled)	17	16 ^e	17	0	17
APO 303 ^c (controlled)	51	50	51	51 ^e	0
APO 302 ^d (controlled)	62 (not counted in total because counted as part of study APO401)	35 (not counted in total because counted as part of study APO401)	27 (not counted in total because counted as part of study APO401)	51 ^e (not counted in total because counted as part of study APO401)	0
APO 401 (open-label safety)				444 ^e	
Total	159	121	104	508	33

^a Parallel group study design of patients who were naive to APM

^b Cross-over study design of patients who had been treated with APM for ≥ 3 months

^c Cross-over study design of patients who were naive to APM (except for single dose exposure to 2 mg) APO303 was substudy of APO401 Patients were simultaneously enrolled in studies APO303 and 401 and were subsequently treated in APO401 at the completion of APO303

^d Parallel group study design of patients who had been treated with APM for ≥ 3 months in study APO401 APO302 was a substudy of APO401 and patients were simultaneously enrolled in both studies Patients enrolled in study APO302 came from Study APO401 and were subsequently returned to Study APO401 at the completion of treatment in APO302

^e Counted as 1 of 536 unique patients treated with APM in development program (25-APO202, 51-APO303, 16-APO301, 62-APO302, 444 directly treated in APO401) This exposure includes 20 new patients who entered APO401 between data cut-off dates for the ISS and Safety Update

The safety information contained in the ISS and Safety Update is derived from 5 phase 2/3 studies conducted by the sponsor. A total of 536 unique patients participated in all studies as of the Safety Update. Based upon the cut-off dates used for the ISS Safety Update, the sponsor presented data and analyses for 536 unique patients and provided a prospective safety experience of approximately 419 patient years of APM treatment consisting of 311 patients treated for ≥ 6 months and 171 patients treated for ≥ 12 months. The Safety Update provided updated safety experience on 20 new patients who enrolled in study APO401 between data cut-off dates for the ISS and Safety Update and on the 278 patients who had continued in study APO401. The vast majority of patients (i.e. 508 as of 5/31/02) had participated in the main safety study (APO401). The ISS submitted had provided data on 306 patient years.

The sponsor makes a point in the ISS that its patient exposure estimates are based upon completed CRFs. Considering this, the sponsor noted that not every patient in APO401 had a 6 month visit after the scheduled 4 months visit but that the next visit was at 8 months. Thus, CRF data would slightly underestimate the experience in patients treated up to 6 months but whose exposure was not captured on CRFs.

I created tables showing patient exposure by gender at ≥ 6 months and ≥ 12 months based upon ISS tables using CRF data presented in the Safety Update. Table 3, Table 4, and Table 5 show the tabulation of cumulative long-term APM exposure of patients by the average prescribed APM dose using various dose cut-off thresholds (e.g. 4, 6, or 8 mg). These tabulations also indicate a further breakdown by gender and the cumulative exposure time (e.g. ≥ 181 days and ≥ 366 days). When the 6 mg dose cut-off is applied (Table 4), it is apparent that a relatively small number of patients (e.g. 41) and percentage of patients (e.g. 13 %) were exposed to APM for 6 months or longer considering an average single injection dose of > 6 mg. When this same dose cut-off is applied for exposure to APM for 1 year or later, not surprisingly, the number of patients (e.g. 19) and percentage of patients (e.g. 11 %) become smaller. When the next cut-off of 8 mg is applied (Table 5), it is clearly apparent that there is minimal exposure to an average single injection dose above 8 mg. For example, only 11 patients (4 %) were treated with an average single injection dose above 8 mg for 6 months or longer and only 2 patients (1 %) were treated with an average single injection dose above 8 mg for 1 year or longer. Based upon these data analyses, it would seem that there is significant long-term exposure safety data to support 6 mg as the maximal single injection dose. Considering data in Table 4 and Table 5, it appears that the number of patients who were treated with a single injection dose that was greater than 6 mg but did not exceed 8 mg was 30 patients for 6 months or longer and 17 patients for 1 year or longer. Thus, a relatively small experience of long-term exposure safety data has also been collected at the average single dose range of $> 6 - 8$ mg. In view of all these data, I believe that there is substantial long-term safety experience to support a single dose of APM up to 6 mg and limited data to support consideration of 8 mg as the maximal single dose.

Table 3 Tabulation of Cumulative Apomorphine Exposure data by Average a Prescribed Apomorphine Injection Dose and Gender Using a Cut-Off of 4 mg

Average Prescribed Apo-morphine Injection Dose	Cumulative Apomorphine Exposure ≥ 181 days (6 months) (311 total Parkinson's disease patients)			Cumulative Apomorphine Exposure ≥ 366 days (12 months) (171 total Parkinson's disease patients)		
	Males	Females	Total	Males	Females	Total
≤ 4 mg	121	6	189 (61 %)	70	37	107 (63 %)
> 4 mg	88	34	122 (39 %)	47	17	64 (37 %)

Table 4 Tabulation of Cumulative Apomorphine Exposure data by Average Prescribed Apomorphine Injection Dose and Gender Using a Cut-Off of 6 mg

Average Prescribed Apo-morphine Injection Dose	Cumulative Apomorphine Exposure ≥ 181 days (6 months) (311 total Parkinson's disease patients)			Cumulative Apomorphine Exposure ≥ 366 days (12 months) (171 total Parkinson's disease patients)		
	Males	Females	Total	Males	Females	Total
≤ 6 mg	181	89	270 (87 %)	105	47	152 (89 %)
> 6 mg	28	13	41 (13 %)	12	7	19 (11 %)

Table 5 Tabulation of Cumulative Apomorphine Exposure data by Average Prescribed Apomorphine Injection Dose and Gender Using a Cut-Off of 8 mg

Average Prescribed Apo-morphine Injection Dose	Cumulative Apomorphine Exposure ≥ 181 days (6 months) (311 total Parkinson's disease patients)			Cumulative Apomorphine Exposure ≥ 366 days (12 months) (171 total Parkinson's disease patients)		
	Males	Females	Total	Males	Females	Total
≤ 8 mg	203	97	300 (96 %)	116	53	169 (99 %)
> 8 mg	6	5	11 (4 %)	1	1	2 (1 %)

Dose and Frequency of Use of APM

Table 3, Table 4, and Table 5 provide information on the average prescribed APM dose for long-term exposure for all patients and also according to gender. Considering all 536 patients treated with APM for any time, 19 % used an average dose of ≤ 2 mg, 45 % used an average dose of > 2 mg up to 4 mg, 24 % used an average dose of > 4 up to 6 mg, 9 % used an average dose of > 6 mg up to 8 mg, and 4 % used an average dose of > 8 mg up to 10 mg. The most common dose range used was > 2 mg up to 4 mg and the vast majority (~ 87 %) of patients used an average injection dose of ≤ 6 mg. Thus, a total of 69 patients had received an average dose of > 6 mg for any duration and 22 patients had received an average dose of > 8 mg for any duration. There were 110 patients who received at least a single dose > 6 mg and only 34 patients received at least a single dose > 8 mg for any duration. Overall, the extent of experience with doses above 6 mg is relatively limited.

Although study APO202 (maximum number daily injections permitted = 5) collected diary data about the frequency of APM use, the bulk of this experience about use comes from study APO401 (maximum number daily injections permitted = 10). Diary data were collected by 436 out of 508 patients in study APO401 and provided information about the frequency of dosing. Most patients (73 %) administered an average of 1- 4 injections daily. Some patients used a higher range of daily injections such as > 4 up to 7 (20 %) and > 7 (4 %). Few patients (3 %) used APM relatively rarely such as on an average basis of less than 1 injection daily. The average daily injection frequency of all patients was 3.0 with a range of 0 to 9.3.

Patients in studies APO202 and APO401 (including substudy APO303) were allowed the option to repeat an injection of APM if a patient had not experienced an adequate therapeutic response by at least 20 minutes after injection. Considering that the mean T_{max} in many subjects is around 20 minutes and that T_{max} usually occurs in most subjects between 20 – 40 minutes after injection, it seems that repeating an injection as early as 20 minutes after APM could be unnecessarily premature in many patients. Although study of patients showed statistically significant benefit/improvement in UPDRS motor score at 20 minutes, this may be a relatively early time to repeat an injection in significant numbers of patients based upon pharmacokinetic and pharmacodynamic considerations and the variation of individual responses. Furthermore, study APO303 showed that changes in UPDRS motor scores from baseline were greater at 40 minutes than those at 20 minutes and the mean T_{max} in some of the sponsor's PK studies was approximately near 40 minutes. Repeating injections at too frequent intervals could result in significant plasma accumulation of plasma APM levels and also increased and possibly unnecessary toxicity. Study 073 that investigated PK and efficacy effects of repeat dosing in a few patients (e.g. 6) repeated dosing at 90 minute intervals. Thus, it is not clear how "safe" it is to repeat an injection at short intervals and what the minimal dosing interval should be.

The sponsor presented limited information about repeat APM dosing at short intervals because of inadequate therapeutic response. The sponsor's Listing 29.0 in the ISS Tables showed diary information (e.g. timing data for 133 injections) about repeat dosing within 30 minutes of a previous injection in 59 patients. The majority (71 injections or 53 %) of these repeat injections

appeared to be a protocol violation because they occurred before 20 minutes after the previous injection. There were many instances (21 injections in 15 different patients) in which a repeat injection occurred within 5 minutes and 3 instances in 3 different patients in which the repeat injection was recorded to have occurred at 1 minute!

It was difficult to understand how commonly shortly repeated injections occurred overall, the distribution of when it occurred within a 2 hour dosing interval and what was the outcome in terms of efficacy and safety. Consequently, I asked the sponsor the following questions to try to understand what was the experience for repeating an injection "shortly" after one injection of APM. I consider this to be important information that needs to be considered relative to describing an appropriate dosing interval in the label.

1 How many different patients (in all studies) took a repeat injection of APM a "short" time later if they did not experience a response within a "short time" after their injection?

2 Do you know the total number of times that a repeat injection was administered (in all studies) because of no response or an inadequate response "shortly" after the injection of APM?

3 Do you know the average number of times this occurred on a per patient basis for each patient who ever did this?

4 Do you know the average time interval between the original injection and the repeat injection?

5 Do you know the range (minimum and maximum times) for the time interval between the original injection and the repeat injection?

6 Do you know the frequency distribution of repeat injections relative to the time interval between the original injection and the repeat injection? For example, you might show that 20 patients administered repeat injections between 20 to 30 minutes, 50 patients administered repeat injections between 31 to 60 minutes, and 30 patients administered repeat injections between 61 to 120 minutes after the "failed" injection.

7 Do you have any information on the efficacy and safety of repeat injections such as how frequently a repeat injection was successful for reversing "Off" and the frequency of developing adverse reactions (if so, what were they by type and number?) associated with the repeat injections?

As of 6/3/03 I had not yet received a response.

The sponsor has not yet conducted studies showing the experience of patients and caregivers for using the cartridge injection device for APM. It would be desirable to see an experience of patients and caregivers using the cartridge device for injecting APM and to show that the toxicity profile is not dissimilar than the one demonstrated for using APM from ampoules. Conceivably,

there could be a higher error rate involving APM administration via the cartridge device and potentially a more toxic safety profile

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11 INTEGRATED SUMMARY OF SAFETY (ISS) AND SAFETY UPDATE

11.1 Reviewer’s Approach to Reviewing the Safety Data Presented and Analyzed in the ISS and Safety Update

The Clinical section of NDA 21264 containing the ISS was submitted to the Agency by the sponsor on 9/17/02. However, ECG data that DNDP considered to be a critical part of the safety data desired were not included in that submission. NDA 21264 was being submitted as a rolling submission (beginning in 5/02) of various components over time but the review clock was not supposed to start until DNDP considered that all important data for all disciplines including all significant safety had been submitted. Thus, DNDP told the sponsor that it would not consider “starting the review clock” by filing the NDA until critically desired ECG data were also submitted. By the time that the sponsor was ready to submit these ECG data, the sponsor was also ready to submit the Safety Update. Thus, the sponsor submitted the Safety Update along with the ECG data presentations and analyses and this submission was received by the Agency on 1/2/03. Initially, DNDP had concerns that the sponsor had not submitted ECG data presentations/analyses adequately according to recommendations and requirements outlined in the minutes of the pre-NDA. However, after discussions between the DNDP and the sponsor, DNDP eventually decided toward the latter part of February 2003 to file the NDA as of the 1/2/03 submission date.

When I began safety reviewing of this NDA, I already had the Safety Update. The sponsor had incorporated data from the additional Safety Update period into the data contained in the original ISS tables. Thus, the ISS tables submitted when the review clock began (1/2/03) contained all safety data including information from the Safety Update. Consequently, when I review safety data, my review will evaluate information that integrates the ISS safety data from the Safety Update with safety data submitted in the original ISS. I will focus on all the combined ISS data and will not usually make a distinction between safety data from the original ISS with data from the ISS Safety Update. Table 6 shows the sponsor’s cut-off dates used for presenting and analyzing safety data.

Table 6 ISS Safety Data Cut-Off Dates

	ISS	ISS Safety Update
Received by FDA	9/17/02	1/2/03
CRF Data Clock Date ^a	12/31/01	5/31/02
SAE & Death Clock Date Cut-Off	3/31/02	5/31/02

^a Study APO303 used a CRF data clock of 1/31/03

11.2 Reviewer's Overview of Data Sources for ISS and Safety Update

The safety information contained in the ISS is derived from 5 phase 2/3 studies conducted by the sponsor. All studies except APO301 (conducted in the U K) were conducted in the U S . A total of 536 unique patients participated in all studies as of the Safety Update. Based upon the cut-off dates shown in Table 6, the ISS Safety Update presented data and analyses for 536 unique patients and provided a prospective safety experience of 419 patient years of APM treatment consisting of 311 patients treated for ≥ 6 months and 171 patients treated for ≥ 12 months. The Safety Update provided new safety experience on 20 new patients who had enrolled in study APO401 between the original data cut-off date and the new data cut-off date and updated safety experience on the 278 patients who had continued in study APO401. The vast majority of patients (i.e. 508 as of 5/31/02) had participated in the main safety study (APO401). Table 2 (in Exposure to Apomorphine section) shows the number of patients participating in the various studies. There were two, stand-alone, controlled, efficacy studies (APO202 and APO301) that were not substudies of the main safety study (APO401).

Study APO202 was a double-blind, placebo-controlled parallel group study of 29 patients (naive to APM) who were studied as inpatients over approximately 1 week followed by an outpatient phase over 4 weeks. Patients from this study were allowed to enter an open-label, extension phase (Study APO401) to collect additional safety experience.

Study APO301 was a double-blind, placebo-controlled cross-over study of 17 patients who were treated with a single injection of APM or placebo on 2 separate days. Prior to study enrollment, these patients had been treated chronically with intermittent injections of APM for a period of at least 3 months. These patients, who were studied in the U K , did not have the opportunity of participating in Study APO401 to collect additional safety experience.

Study APO401 was an open-label trial designed to collect safety experience in newly enrolled patients or patients who had participated in a controlled, efficacy study. This trial was the main basis upon which the sponsor collected safety data prospectively. Two other trials (Study 303 and 302) were substudies of APO401. The schedule of events for APO401 is shown in Table 7.

Study APO303 was a substudy of APO401 designed mainly to collect orthostatic vital sign (VS) and electrocardiographic (via Holter) data with respect to dosing in patients who were naive to APM. Patients received increasing single doses of APM (starting at 2 mg and escalating at 2 mg increments up to 10 mg, e.g. 2, 4, 6, 8, 10 mg) over several days as tolerated under open-label conditions except at the 4 mg level. The sponsor also incorporated a controlled, cross-over efficacy design evaluation in this trial by having patients receive either 4 mg APM or placebo on separate days under double-blinded conditions when patients were escalated to the 4 mg level. After collecting safety data at the 10 mg or highest tolerated level, patients (51) were then followed for a period up to 6 months to collect safety data before offered the opportunity of continuing to be followed in APO401 to collect additional safety experience. Patients were simultaneously enrolled in Study APO303 and APO401 and were followed in APO401 after completing APO303.