

CLINICAL REVIEW

Clinical Review Section

As of 12/31/02, there were 233 patients continuing in APO401. Most tables included in the ISS and SU1 were updated and presented in SU2.

Exposure

This current Safety Update (SU2) summarizes the safety experience of 550 patients. On average, these patients were 65 years of age, had Parkinson's disease for 11 years, and had "Off" episodes for a significant portion of their hours awake. SU2 provides data for 535 patient-years of treatment with APM in the Bertek clinical development program, representing data from 14 new patients enrolled in APO401 since SU1 and a total increase of 116 patient-years of exposure to APM (28 % increase above SU1 APM exposure).

Patient Disposition

There have now been 522 patients (a 3% increase over SU1) enrolled in APO401. Compared to SU1, the percentage of patients discontinuing APO401 increased from 49% to 55%. This increase in discontinued patients was not attributed to any specific adverse events, and the distribution across categories (e.g. adverse events, lack of effects, lost to follow-up, etc.) remained largely unchanged from that observed for SU1.

After a protocol amendment requiring in-office dosing and observation to determine the initial outpatient prescribed dose, approximately half of the patients was observed during single or multiple in-office dosing. Most patients received their initial APM dose at ~ 2 mg and no patients were known to exceed 4 mg APM dose as the initial dose ever received. The initial prescribed outpatient dose of APM for the 525 patients treated in an outpatient setting was ≤ 2 mg (~ 43 %), $> 2 - 4$ mg (35 %), $> 4 - 6$ mg (~ 15 %), and > 6 mg (~ 6 %). Doses > 4 mg would have been prescribed after observing the patient during in-office dosing. There were no apparent differences in the distribution of initial outpatient prescribed dose by age or gender. Over 12 months, the average APM dose used to treat episodic "Off" episodes increased by less than 1 mg.

Deaths

During the Bertek APM clinical development through 06/30/03, 27 of 550 patients (5%) were reported to have died. Ten deaths were presented in the ISS and 4 more were reported in SU1. Of the 27 deaths, 13 patients were reported to have died during the time period covered by SU2 (6/1/02 - 6/30/03). Of 13 deaths included in SU2, 2 were not appropriate to be counted in SU2 because they occurred > 30 days after the last APM treatment. One of these deaths (APO401/39/001) was subsequently removed from the safety database because there were no other adverse events associated with this patient. Thus, the appropriate number of deaths for inclusion in the safety database (up through 12/31/02) appears to be 25. The investigator and sponsor did not consider that any of these deaths were likely related to APM use.

CLINICAL REVIEW

Clinical Review Section

Although none of the deaths were reported as sudden deaths, the sponsor acknowledged in SU2, that the following 2 deaths reported up to the time of SU1 might be considered as sudden death Patient APO401 1/007's death was attributed to a probable cardiac arrhythmia occurring 4 hours after his last APM dose Patient APO401/36/008's death at 12 hours after her last APM dose was not witnessed

In my original Safety Review (6/20/03), I had noted that there were seven cases (e.g. 1 cardiac arrest, 1 feet fractures leading to death, 4 pneumonias, 1 meat aspiration) for which there were insufficient details about the timing of APM dosing and a lack of other important details and pertinent negatives to exclude the possibility that APM play a role in an event that ultimately led to a patient's death. I did not have good reasons to suspect that APM contributed to death and I tended to agree with the sponsor that APM was not a likely contributor to a patient's death. In SU2, I was not able to exclude APM's potential role in several cases when I take a conservative approach because of limited or missing information about APM dosing related to the event of death or leading to death.

In reviewing 11 deaths for SU2, I do not suspect that there was reasonable expectation or suggestion that APM had caused or contributed to any of these deaths. Nevertheless, as previously, if one takes a most conservative perspective, there are 7 cases for which I am not able to exclude APM as a contributory factor to a patient's death because of insufficient details about the timing of APM dosing relative to an event and/or a lack of other important details and pertinent negatives. I have provided narrative summaries of examples of some of these cases. Of these 11 deaths in SU2, it is of interest that 5 were associated with pneumonia. Altogether, pneumonia was associated with 9 (36 %) of the 25 total deaths.

- APO401/01/001*APO202A This 73-year-old male patient, who was enrolled in APO401 started APM therapy at a dose of 4 mg (0.4ml) on 8/16/99. He was using APM at a dose of 6 mg three times per day prior to the event. Following radiation treatment for multiple myeloma that was first diagnosed on 1/15/99, the patient died on 1/25/99 after sustaining a head injury from a fall after getting out of bed. The death certificate indicated death due to cardiopulmonary arrest and multiple myeloma.

Comment I am unable to exclude a contributory role of APM directly or indirectly (e.g. an event eventually leading to a patient's death) toward this patient's death because of a lack of details.

- APO401/21/007 The 72-year-old male patient was enrolled in APO401 and started 2 mg apomorphine as needed on 10/6/00. At the time of the event the patient was on 4 mg apomorphine as needed for "Off" episodes. The patient's medical history is significant for Parkinson's disease, peripheral neuropathy, and status post right pallidotomy (1997). On 1/15/01 the patient's wife called and stated the patient continued to be severely frozen. The patient was sent to the emergency department and admitted to the hospital. He was given Ativan in an attempt to break excessive muscle rigidity and then rechallenged with immediate-acting levodopa. On 1/16/01 the patient was doing better and rehabilitation treatment was

CLINICAL REVIEW

Clinical Review Section

recommended On — the site coordinator called to report the patient had died of sepsis due to pneumonia

Comment I am unable to exclude a contributory role of APM directly or indirectly (e.g. an event eventually leading to a patient's death) toward this patient's death because of a lack of details

• APO401/35/004 This 75-year-old male patient was admitted to the hospital complaining of abdominal pain related to constipation - the exact date of admission is unknown. While in the hospital, the patient's blood pressure dropped. The date of death was given as —, the exact cause of death is pending. The date of last dose of APM was reported to have been on 1/29/03. This event was considered as unlikely related to APM administration.

Comment Because of a lack of details, it is not clear if the blood pressure dropped around the last time of APM treatment and what was the patient's course after the decrease in blood pressure and what exactly led to the death.

Treatment-Emergent Adverse Events (AEs) Classified as Serious (SAEs)

Of the 550 patients, 124 (23%) experienced at least one SAE through 12/31/02. Based upon Table 47.3, the sponsor noted that SAEs with an incidence of $\geq 1\%$ were "fall" (N = 23 or 4%), "death NOS" (N = 18 or 3%), "pneumonia" (N = 17 or 3%), "dehydration" (N = 11 or 2%), "urinary tract infection" (N = 10 or 2%), "myocardial infarction" (N = 8 or 1%), and "hip fracture" (N = 8 or 1%). However, the sponsor has counted the preferred AE term pneumonia NOS as pneumonia. When I review the incidence of cases of various types of preferred terms for pneumonia that I would count as pneumonia (including pneumonia NOS, aspiration pneumonia, pneumonia bacterial NOS, bronchopneumonia, lobar pneumonia NOS), there were 29 events of pneumonia in 26 patients (5%). Considering this same type of analysis, there had been 24 events of pneumonia in 23 patients (4%) at the time of SU1.

In Table 47.3, the sponsor compared the frequency and incidence of SAEs presented in SU1 and the current safety update. I focused my review on looking for new, remarkable SAEs that had not been reported previously, or SAEs where the incidence increased by $\geq 2\%$. The only SAE of note was for SAE coded as "fall" and this event increased from 2% of patients in SU1 to 4% of the study population in SU2. The sponsor also noted this change. **With the exception of SAEs coded specifically as fall, I agree with the sponsor, that there was little change in the overall SAE profile presented in SU1 as compared to SU2 based upon the tabulations in the safety database.**

SAEs including deaths were updated manually through 6/30/03 using the Pharmacovigilance SAE database and narrative summaries were provided. Thirty-seven patients reported additional SAEs from 01/01/03 to 06/30/03 and these were not yet entered into the tabulations of the safety database. The sponsor noted that SAEs reported after 12/31/02 by more than 1 person were "death NOS" (8 patients), "pneumonia NOS" (7 patients), "fall" (3 patients), and "confusion",

CLINICAL REVIEW

Clinical Review Section

“dyspnea NOS”, “hypoxia”, “prostate cancer NOS”, “sepsis NOS” and “squamous cell carcinoma” by 2 patients each

During my review of these narrative summaries, I found 8 patients for whom the narrative mentioned pneumonia and 3 others that mentioned aspiration pneumonia. Thus, there were 11 patients (30 %) with pneumonia out of 37 patients experiencing TE-SAEs between 1/1/03 and 6/30/03. If I add these 11 cases of pneumonia to the 26 other cases of pneumonia entered into the safety database as of 12/31/02, there were 37 patients with pneumonia as an SAE. These numbers translate to a 7 % incidence of pneumonia as an SAE. Considering the frequency of pneumonia as an SAE, the frequent association (36 %) of pneumonia with death, and the relatively common incidence (8 %) of any type of pneumonia coded as a TEAE (SAE or non-SAE), I think that the occurrence of pneumonia should clearly be described in the label. I recognize that the patients who were studied in this development program represent a relatively older population of patients who are at a significant risk for developing pneumonia. Nevertheless, it is not possible to know whether APM treatment increases the incidence of pneumonia because of the **very limited study of patients under randomized, double-blinded, placebo-controlled conditions**. For example, 120 patients received APM for 732 patient-days of treatment and 103 patients received placebo for 375 patient-days of treatment. Significant APM exposure compared to placebo treatment over an extended period of time (e.g. months) might be expected to demonstrate a greater incidence of pneumonia during APM treatment (vs placebo), if APM treatment was associated with pneumonia. In the absence of such information, I consider it reasonable to note the incidence of pneumonia during the open-label treatment.

The sponsor also reviewed SAEs of special interest that had occurred during the time of the SU2 (6/1/02 – 6/30/03). The SAEs of special interest included falls, cardiovascular events (atrial fibrillation, cardiac arrest, myocardial infarction), psychiatric events (confusion, psychosis), syncope and/or orthostatic hypotension, and other SAEs (cerebrovascular accident, pneumonia, dehydration). For most of these SAEs, a narrative summary (summaries were also provided in volume 10 for all new SAEs including deaths and all previously reported SAEs including deaths) was presented in this section along with a categorization of whether the SAE was considered possibly related to APM treatment, unlikely/not-related to APM treatment, or an uncertain relationship to APM use. In most instances, the SAE was not considered related to APM treatment.

I have presented some selected SAEs of interest because the sponsor thought that APM's causality or contributory role was possible or uncertain or because I considered the narrative to be of interest for presentation.

- APO401/43/003 A 45-year-old male patient was enrolled in APO401 and started APM therapy 2 to 5 times daily at 2 mg on 05/08/01. The patient's medical history is significant for allergies to aspirin and penicillin, chronic sinusitis, GERD, chronic bronchitis, sleep apnea, lumbar degenerative disk disease, erectile dysfunction, neurogenic bladder, orthostatic hypotension (1999), and several hernias. The study drug was interrupted from — to — due to a SAE (delirium and fever on —). The patient restarted APM 2 to 5 times daily at 4 mg on 10/12/01. On 3/25/02, the APM dose was increased to 5 mg, 2 to 5 times daily.

CLINICAL REVIEW

Clinical Review Section

The patient previously experienced three other SAEs (pneumonia on — fever and confusion on — and hyperthermia on — His APM therapy was interrupted from — due to the AEs of fever, confusion and hyperthermia The patient resumed APM 5 mg per injection on 6/20/02 On — the patient presented to the ER and was admitted to the hospital with **acute onset of confusion and disorientation and elevated temperature up to 104 for the past 24 hours** His ex-wife had concerns that the patient had not been compliant totally with his medications and that the patient probably had overdosed his medications including taking more doses of APM and less doses of Sinemet than allotted Upon admission, the patient was prescribed 5 mg APM QID, his Sinemet had been held for two days On — the patient was transferred to a referral hospital due to the acute confusion with unexplained fevers Upon admission, the patient was found to be confused and agitated The patient admitted he was having visual and auditory hallucinations for the past several days, but the hallucinations disappeared and had not occurred after admission Vital signs revealed a temperature 102.2, blood pressure 143/71, pulse 107, and oxygen saturation 94% on room air CBC, urinalysis, and biochemical panels were unremarkable His chest x-ray revealed small bilateral pleural effusion Blood cultures were negative for growth The patient was re-started with Sinemet Intravenous fluids, Ativan, and continuous positive airway pressure were initiated APM was limited to nurses only giving it to him and he was only allowed APM QID His other antiparkinsonian medications were maintained as Sinemet CR 25/100 mg TID, Sinemet 25/100 mg QID, Permax 1.5 mg TID after admission The patient had no acute confusion and maintained afebrile after the first day of admission Due to his acute improvement in his mental status and clarification of his medication, the patient was discharged on — with a diagnosis of polypharmacy and acute mental status changes The treating physician attributed the cause of the acute confusion and fever to polypharmacy

Comment Although the etiology of this event was not clearly established, I question whether this patient's event may have represented a neuroleptic malignant syndrome, possibly related to poor compliance of taking his other dopaminergic medications (e.g. Sinemet and/or pergolide)

• APO401/64/004 The patient is a 63-year-old male with a medical history significant for myocardial infarction (1974), hypertension (1974), peripheral edema, and abnormal electrocardiograms The patient enrolled in APO401 and started APM on 7/8/02, and was taking 6-8 mg as needed for "Off" episodes at the time of the event On — the site was notified that the patient was taken to the emergency room for shortness of breath, diaphoresis and confusion on — The patient was admitted that day and denied nausea, or chest pain In-patient evaluations did not suggest myocardial infarction, pulmonary embolism or cerebrovascular accident The patient was discharged on — good condition to follow-up with his primary care physician The date and time of the last APM dose before the event was unknown

Comment The sponsor noted that the relationship between this patient's confusion and APM was questionable I agree with the assessment because there are insufficient details about APM dosing relative to the event

CLINICAL REVIEW

Clinical Review Section

• APO401/27/001(APO302)P A 75-year-old female patient was enrolled in APO401 and started 2 mg apomorphine on 7/15/00. On 8/14/02, her dose was adjusted to 4 mg APM 8 to 9 injections per day due to worsening neuropsychiatric symptoms. Since May 2002, the patient had gradual worsening of neuropsychiatric symptoms related to her late-stage Parkinson's disease. The patient complained of leg pain and her family noted her increased agitation and increasingly psychotic behavior including paranoid delusions. Symptoms became unmanageable and she was admitted to the hospital on [redacted] with a diagnosis of psychosis. Her medical history was significant for Parkinson's disease, anxiety, sleep disturbance and psoriasis. All Parkinson's medications, including APM, were discontinued at admission as the investigator believed that they were contributing to her psychosis. After hospital admission, Sinemet was resumed followed by Trazodone and Paxil. Seroquel was resumed at a decreased dosage. The patient responded well and was transferred to a rehabilitation hospital on [redacted].

Comment The sponsor commented that this appeared to be an episode of drug-induced psychosis that was likely related to APM, in conjunction with her other Parkinson's disease medication. I agree that this assessment seems reasonable.

• APO401/23/028(APO303) A 64-year-old male patient with a medical history significant for heart murmur, headache, left knee replacement surgery, and hiatal hernia, was enrolled in APO401, and began apomorphine therapy at a dose of 5 mg twice a day on 08/13/01. On [redacted] the patient was at church and stated he felt very dizzy. The patient went outside to his car to administered one injection of 5 mg APM, hoping to feel better. Fifteen minutes after dosing, the patient experienced an episode of syncope. He was brought to the emergency room, and released to home on the same date after he recovered.

Comment The sponsor commented that this syncopal event for was likely to be related to APM therapy. I agree with this assessment.

• APO401/61/004 The 64-year-old male patient was enrolled in APO401 and started to use apomorphine 4 mg 6 times a day on 8/22/01. The patient's medical history is significant for Parkinson's disease and frequent kidney stones. On [redacted] the patient was brought to the ER with a sudden onset of slurred speech for 8 hours. His latest APM injection was 3 hours prior to the onset of the slurred speech. Physical examination revealed weakness on the right side. A CT of the head was negative for bleed. He was subsequently admitted and underwent a MRI of the brain on [redacted] which revealed a lacunar infarct in the left thalamus region. Intravenous fluids and aspirin 325 mg every day were initiated. The patient's symptoms stabilized and slightly improved during the hospital stay. On [redacted] he was discharged home in stable condition with some residual weakness on the right side and some speech problems partially due to his Parkinson's disease. Following discharge, the patient reportedly improved every day.

Comment The sponsor noted that this event had a questionable relationship to APM therapy. I agree with this assessment.

My review of these SAEs of special interest as well as all SAEs did not suggest a change in my assessment of the safety profile of APM outlined in my original Safety Review (6/20/03).

CLINICAL REVIEW

Clinical Review Section

TEAEs Associated with Dropout

From 6/1/02 through 12/31/02, 20 of 550 patients had 40 TEAEs associated with study discontinuation. Those events reported by $\geq 2\%$ of patients were injection site reactions (5%), death (3%), nausea (3%), vomiting (2%), dyskinesias (2%), dizziness not vertigo (2%), and somnolence (2%). These data represented a cumulative incidence of 25 % (140/550) of patients who had discontinued from study because of one or more TEAEs. The sponsor presented a table showing the frequency of TEAEs occurring during this period and also a cumulative table (Table 47.3) comparing the frequency and incidence of SAEs presented in SU1 and SU2. I focused my review on looking for new, remarkable TEAEs that had not been reported previously, or TEAEs where the incidence increased by $\geq 2\%$. I did not find any new, remarkable TEAEs causing study dropout that had not been reported previously, nor any TEAEs where the incidence increased by $\geq 2\%$. The sponsor noted that the overall incidence of TEAEs associated with study discontinuation increased from 22 % to 25 %, reviewed some of the frequency figures from various perspectives, and presented selected brief narrative summaries from some patients. The sponsor did not provide much interpretive analyses of these data. Nevertheless, I did not find any new information that changed my perspective and assessment about TEAEs prompting study dropout that had been outlined in my Safety Review (6/20/03).

AEs Suggestive of Fall

Falls are not uncommon in patients with Parkinson's disease, and therefore may go unreported by the patient during clinical trials. It is likely, however, that injuries sustained in falling are reported as adverse events, however, they may not always be linked to "falls" during MedDRA mapping.

Although special efforts had been undertaken during the Bertek clinical development program to capture all instances of falls, the DNDP requested a re-analysis of TEAEs suggestive of falls so that a more accurate picture of the number of patients who may have experienced an AE related to a fall could be presented. A new search strategy with terms suggested by the Agency was conducted including the following MedDRA preferred terms considered to be suggestive of fall: Fall, Laceration, Abrasion, Fracture, Hematoma, Ecchymosis, Joint Sprain, Head Injury, and Limb Injury NOS. One term, Crush Injury, suggested by the Agency was not included in the search strategy because of an alternate etiology (motor vehicle accident, Patient APO401/01/001, SAE No. APO401.006). **Following the re-analysis of TEAEs possibly suggestive of a fall using the additional terms suggested by the DNDP, the sponsor noted that 167 out of 550 patients (30%) reported TEAEs suggestive of fall, including 141 (26%) patients with TEAEs that were actually coded to Fall. Non-serious TEAEs that were suggestive of falls were reported by 28% of the patient population (152 patients), and included 127 patients (23%) with non-serious TEAEs actually coded to Fall (Table 93.6). SAEs suggestive of falls were reported by 26 (5%) patients, and included the 23 (4%) patients with SAEs coded to Fall.** Previously, the sponsor's analysis (using the sponsor's proposed AE terms) of AEs possibly suggestive of falls had shown that 128 patients (24 %) had experienced an TEAE that could be related to a fall, and 25 patients (5 %) had experienced an SAE possibly suggestive of a fall.

CLINICAL REVIEW

Clinical Review Section

Thus, the DNDP's recommended re-analysis illustrated 25 % more TEAEs that could be possibly construed as related to a fall but the incidence of SAEs possibly suggestive of a fall did not change

The sponsor commented, that although not always clear from the AE report, the terms Ecchymosis and Hematoma were often related to injection site reactions. Thus, Bertek conducted an additional search strategy that included the following MedDRA preferred terms considered to be suggestive of fall: Fall, Fracture, Abrasion, Laceration, Head Injury, Joint Sprain, Or Limb Injury NOS. Based upon this analysis, 158 of 550 patients (29%) reported TEAEs suggestive of fall, including 141 (26%) patients with TEAEs actually coded to Fall. Non-serious TEAEs suggestive of falls were reported by 144 patients (26%), and included 127 patients (23%) with non-serious TEAEs actually coded to Fall. SAEs suggestive of falls were reported by 25 (5%) patients, and included the 23 (4%) patients with SAEs coded to Fall. The sponsor's new analysis that it proposed was very similar to the results obtained in the re-analysis requested by the DNDP.

The re-mapping procedure had identified 11 additional patients that had "fall" as part of the narrative that should have been coded to Fall as a Preferred MedDRA Term, no SAEs associated with the fall were discovered. The sponsor noted that all these results indicated that falls (especially falls that were serious) had been adequately captured in the ISS.

All TEAEs

The sponsor summarized the most common ($\geq 5\%$) preferred term TEAEs by organ system and noted that Table 76.4 compared the frequency and incidence of TEAEs presented in SU1 and now in SU2. As of 12/31/02, 488 of 550 patients (89%) had experienced at least one TEAE. The sponsor further noted that the incidence of TEAEs was not influenced by age, sex, concurrent use of COMT inhibitors or vasodilator, or by dose or frequency of APM. Since the data lock date of SU1, 200 of the 257 patients (78%) continuing in APO401 had at least one TEAE. The most common TEAEs (occurring $> 5\%$ of patients) in descending order were fall (17%), urinary tract infection (7%), hallucinations (7%), nausea (6%) and somnolence (5%). The sponsor did not provide any additional, substantive interpretation of the data reviewed.

I focused my review on looking for new, remarkable TEAEs that had not been reported previously, or TEAEs where the incidence increased by $\geq 2\%$. I did not find any new, remarkable TEAEs causing study dropout that had not been reported previously, nor any TEAEs where the incidence increased by $\geq 2\%$.

The safety profile of TEAEs did not appear to change in SU2 based upon a similar presentation of the incidence of TEAEs categorized according to high level group term or preferred terms of MEDRA analyses as had been made in the ISS and SU1. However, I would like to point out that occasionally the sponsor seemed to focus on the incidence of preferred AE terms that often reflected a similar clinical event. In SU1, the sponsor had previously analyzed a variety of AE terms of special interest that may have been suggestive of fall, suggestive of orthostatic

CLINICAL REVIEW

Clinical Review Section

hypotension, and suggestive of postural dizziness I have already reviewed this information on events suggestive of fall. These previous analyses indicated that there were 53 patients (out of 536) with 70 events possibly suggestive of orthostatic hypotension representing an incidence of 10 %, and that there were 125 patients (out of 536) with 203 events possibly suggestive of postural dizziness representing an incidence of 23 %. The sponsor did not include such analyses of the new information contained in SU2. However, I conducted my own analyses of the incidence of TEAEs for pneumonia (including TEAEs for pneumonia NOS, aspiration pneumonia, pneumonia bacterial NOS, bronchopneumonia, lobar pneumonia NOS), for a “significant” decrease of blood pressure (including TEAEs for hypotension, postural hypotension, decreased blood pressure), and for dizziness irrespective of positional changes (including TEAEs for dizziness, postural dizziness). My analyses of data in SU2 showed that the incidence of pneumonia (8 %), “significant” decrease of blood pressure (11 %), and dizziness irrespective of positional changes (21 %), was substantial. My analyses of data in SU2 showed similar results as those possibly suggestive of orthostatic hypotension and postural dizziness presented in SU1. This analysis of pneumonia is new and was not presented previously by the sponsor or me. My interpretation of these data is that the occurrence of these events is quite substantial and such information should be presented in the label.

In summary, my overall assessment of TEAEs contained in SU2 was that the safety profile of APM based upon TEAEs occurring during APM did not significantly change from my assessment presented in my original Safety Review.

Vital Signs

The sponsor presented analyses of orthostatic vital signs (VS) as had been conducted and presented previously in SU1. These various analyses at baseline and post-treatment assessed the frequency of various VS changes such as a decrease of systolic blood pressure by ≥ 20 mm Hg, ≥ 40 mm Hg, or by ≥ 30 mmHg or more to a value of ≤ 90 mm Hg, a decrease of diastolic blood pressure by ≥ 10 mm Hg, ≥ 20 mm Hg, or by ≥ 20 mmHg or more to a value of ≤ 50 mm Hg, or an increase or decrease of pulse by ≥ 15 beats per minute (bpm) while supine, sitting, and/or standing. Some VS measurements were obtained during observation after in-office APM dosing (although the post-treatment time for collecting data was not standardized) and other measurements were obtained randomly at a visit at which APM was not administered (i.e. no in-office APM dosing).

The sponsor noted that the data contained in the analyses of SU2 were consistent with results presented previously. More specifically, the sponsor commented that there were results showing similar shifts in blood pressure observed after direct observation of APM exposure, and that blood pressure changes were more prominent after patients went from supine to standing positions. The shift to more patients having orthostasis (i.e. orthostatic hypotension) post-baseline after treatment with APM was unchanged and the sponsor interpreted that these orthostatic blood pressure changes were likely due to the patients' underlying Parkinson's disease and/or other diseases rather than to APM administration.

CLINICAL REVIEW

Clinical Review Section

I reviewed these analyses and compared them to analyses conducted and presented in SU1. My original Safety Review presented a substantive discussion of the effects of APM on VS and orthostatic VS. **My assessment of the new data (that was relatively small in extent compared to what had been presented earlier from patient visits) in SU2 was that my assessment outlined in my Safety Review did not change.** The open-label nature of the much of the new and cumulative data analyzed here from outpatient visits does not permit one to draw an unequivocal conclusion that decreased blood pressure measurements associated with APM treatment are clearly due to APM rather than to the patient's age, Parkinson's Disease, and/or concomitant medications. **Nevertheless, I believe that when considering everything known about APM and its effects on blood pressure (including some safety information collected by the sponsor and the published literature), one cannot escape the reasonable conclusion that APM has the potential for producing significant blood pressure lowering effects irrespective of position and that these potent cardiovascular effects may be associated with AEs such as postural dizziness/light-headedness and/or syncope.**

I conclude that there is no substantive change in the safety profile of APM from SU2 compared to the safety profile that I had assessed in the ISS and SU1.

Post-Marketing Experience in Europe

Attachment 9 contained the Britannia Pharmaceuticals Periodic Safety Update Report covering the period 31 March 2002 to 31 March 2003.

APM hydrochloride injection is available in Europe as the Apo Go Pen, a 3-mL multidose pen containing 10 mg/mL of APM hydrochloride, which is used for intermittent injections only and Apo Go ampoules, 2-mL and 5-mL ampoules, each containing 10 mg/mL of APM hydrochloride, which are used for both intermittent injections and continuous subcutaneous infusion of APM. The Marketing Authorization Holder (MAH) for Britaject Injection and Pen in the UK is Britannia Pharmaceuticals, the distributor of Forum Products. New licenses were granted to Forum Products for this identical product on the basis of new scientific data. These formed the basis of a Mutual Recognition Procedure. During the review period, APM hydrochloride injection has also been marketed by Forum Products via its distributor, Britannia Pharmaceuticals, on a limited compassionate basis, in the following countries: Czech Republic, Iceland, Canada, Norway, Slovenia and Hong Kong. In some territories, APM is marketed under the tradename Britaject, which has an identical formulation as Apo Go. According to Bertek, marketing of APM as the Apo Go Pen has been launched in Austria, Germany, Spain, Greece, Ireland, and Portugal. Bertek also noted that as of 31 March 2003, that Britannia Pharmaceuticals estimated that 900 patients were receiving APM treatment in the UK and an additional 250 patients are receiving APM in territories outside of the UK. Regarding this use, there was no specification of the percentage of patient exposure to either formulation nor to the method of administration such as intermittent injections or continuous subcutaneous infusion. **Neither I did find any description of the exposure (i.e. extent of patient use) for any formulation of APM in countries outside the UK.**

CLINICAL REVIEW

Clinical Review Section

It is pertinent to note that the Apo Go Pen formulation of APM used in Europe does not contain any benzyl alcohol. This observation further underscores the virtual absence of any human information (let alone patient information) about the safety of an injectable APM formulation containing 0.5% benzyl alcohol and additionally supports the need for reviewing an actual safety experience of the APM pen formulation (containing 0.5% benzyl alcohol) that the sponsor wants to market in the U.S.

The post-marketing section noted that on the 28th February 2002, the European CPMP issued a position statement on dopaminergic substances (which included APM) and sudden sleep onset following a review of available data from clinical studies, spontaneous reports and published literature. The new wording (see below) was implemented for Apo Go ampoules during the Mutual Recognition Procedure. A variation was submitted in the UK and other Member States to amend the Apo Go Pen Summary of Product Characteristics (SmPC) and patient leaflet in November.

New wording: Apomorphine has been associated with somnolence, and other dopamine agonists can be associated with sudden sleep onset episodes, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with apomorphine. Patients who have experienced somnolence must refrain from driving or operating machines. Furthermore, a reduction of dosage or termination of therapy may be considered.

Since the last SU1, there have been two serious spontaneous adverse reactions reported to Britannia Pharmaceuticals (sleep attack in a 55 year old male patient, and shortness of breath, hypotension, seizure and respiratory failure in a 75 year old male patient). Both were unexpected adverse reactions and concerned patients who had received APM by subcutaneous infusion.

Based on data reviewed in the post-marketing section, the sponsor noted that there were no new findings that would impact the current safety profile of APM subcutaneous injections as presented by Bertek in the Integrated Summary of Safety section of the NDA.

I conclude that there is no substantive change in the safety profile of APM related to the foreign post-marketing experience of APM presented in SU2 compared to the safety profile that I had assessed in the ISS and SU1 based upon the reported foreign post-marketing experience of APM.

5. LABELING ISSUES

In this section, I will comment on the sponsor's response to comments from DNDP about revising the label and other significant revisions that the sponsor has made to the label

Issues Related to Disagreement Between Data Contained in the DNDP Label Provided in the Approvable Letter and the Revised Label Submitted by the Sponsor

Warnings

- The sponsor modified the frequency of falls from — and the frequency of falls characterized as serious from 5% — Based upon the reanalyses of falls requested by DNDP, these figures are incorrect. The frequency of TEAEs that were possibly suggestive of falls is 30 % and the frequency of serious ones remains at 5 % I discussed this discrepancy with the sponsor and discovered that the sponsor was incorporating incidence figures based upon specific preferred term coding of “fall” rather than using incidence figures derived from analyses of events possibly suggestive of falls as had been included in the label provided by the DNDP in the approvable letter. The sponsor has agreed that the correct figures for this section are 30% for events possibly suggestive of falls and 5 % for analagous events characerized as serious
- I differ with the sponsor's — incidence figure for coronary events. My review of Table 76.0 for TEAEs showed 6 patients with angina (e.g. angina pectoris or unstable angina), 8 patients with myocardia infarction, 3 patients with cardiac arrest, 3 patients with cardiorespiratory arrest (that I would also include in this section), and 1 patient with myocardial ischemia that was not counted in the incidence figure here for coronary events. Thus, these cases add up to 21 patients (21/550 or 4 %) If the 2 cases (at least acknowledged by the sponsor in SU2) of “sudden death” were described here, the 4 % incidence would not change, but the term sudden death would be restored.

I have asked the sponsor to clarify the incidence figure based upon what I described above and have also asked the sponsor to respond about the total number of cases that it could consider as possible “sudden death.” The sponsor has not yet responded as of 3/25/04

Pharmacokinetics

- The sponsor changed the range of C_{max} from 10 to 60 minutes to — The 60 minute end of the range for C_{max} had been provided by the biopharmaceutical reviewer, Dr John Duan. The sponsor noted that results from a study of patients (Study APO-073) showed a C_{max} range up to — minutes and that this figure was more reflective of patient data. I believe that the 60 minute figure should remain because it reflects a more robust experience based upon the study of volunteers who were healthy or had various degrees of renal or hepatic impairment and patients. The experience from the study APO073 is relatively small and only represents ~ 10 % of the the total C_{max} dataset collected from a much larger group of human subjects. Considering that only 6 Parkinson's Disease patients were included in

CLINICAL REVIEW

Clinical Review Section

Study APO-073 involving 3 cross-over doses of APM, this experience is not likely to represent the variability for Camx that would be observed in a larger population of subjects

New Labeling Issues Related to Additions of the Sponsor or Issues Not Specifically Addressed in the Label Provided by the DNDP in the Approvable Letter

Clinical Studies

- The sponsor added information that _____ This information should be deleted because this is a secondary efficacy endpoint that was studied and there were no adjustments of criteria for statistical significance related to multiple comparisons of this endpoint or others (i.e. multiplicity) Secondary efficacy endpoint results are not normally presented in the label. In addition, these results were based upon objective motor testing and it is not clear how well patients can reliably perceive when they experience improved motor function relative to the demonstration of improved motor function by some objective testing.
- The sponsor added a paragraph _____ DNDP had noted that it was not impressed with results from this study because of much greater between-group treatment difference in the second period vs the first period and thought that results of this study should not be included in the label. The sponsor did not specifically address DNDP's concerns about the period effect. I continue to believe that results of this study do not need to be included in the label.
- The DNDP had asked the sponsor to conduct additional analyses of efficacy data to determine the effects of APM for treating spontaneous "Off" and "end of dose wearing off" and had commented "that this section will need revision based on those analyses." The sponsor noted that its analyses showed that APM was effective for treating both types of "Off" episodes, a detailed discussion was provided in the response to DNDP Clinical Comment # 1 but it did not propose any changes in this section of the label. I disagree with this perspective and think that the label should include some comment that both types of "Off" episodes respond to APM treatment. It may be appropriate to note also in the label that this information was obtained by retrospective, post-hoc analyses.
- The sponsor addressed a question of DNDP why the randomization of patients to placebo in Study APO302 resulted in more patients randomized to placebo than originally planned according to the randomization plan. The sponsor noted that some centers did not fill the randomization blocks completely and that because of this, inclusion of these patients in the study resulted in more patients randomized to placebo (44 %) than originally planned for placebo (33 %).

CLINICAL REVIEW

Clinical Review Section

Contraindications

On 3/31/04, the sponsor contacted DNDP to ask if the Agency still has "concerns about the use of ondansetron with apomorphine that should be provided in the labeling" This topic had arisen after an internal review of Bertek's development program for APM In 1997, Mylan Pharmaceuticals (Bertek) was informed that it could not conduct studies to compare the ability of ondansetron to prevent APM-induced nausea and vomiting with the ability of trimethobenzamide to do the same because the Agency was aware of a serious problem when APM and ondansetron were used in combination Mylan was not informed of the nature of the serious adverse reaction There is no information to indicate that Mylan investigated this drug interaction animal studies nor that is attempted to see if this issue could be addressed in humans

On 3/13/97, DNDP received reports that 3 healthy volunteers had experienced serious adverse reactions consisting of severe hypotension, syncope/loss of consciousness, and bradycardia and one subject experienced seizure activity These adverse reactions occurred within a half hour of administration of 10 mg Zydys apomorphine after 3 days of oral ondansetron 8 mg every day (including administration 30 minutes prior to Zydys APM) This experience was observed under IND — () and occurred in 3 of 12 subjects studied and prompted a CLINICAL HOLD for studying additional humans with Zydys APM and ondansetron All 3 subjects recovered (additional details regarding this experience are described in my review of Labeling Issues)

The following DNDP clinical review of these cases was abstracted from the review of Dr Bob Rappaport

The sponsor has submitted ten-day safety reports for three healthy subjects exposed to study drug in IND protocol

1) 49 yo male received ondansetron 8 mg po qd for 3 days, last dose 08 34 followed by single dose Zydys Apomorphine 10 mg P0 at 09 04 Thirty-four minutes later subject pallid and diaphoretic, unresponsive to verbal stimulus Subject experienced seizure activity lasting several seconds At 09 39 BP = 70 systolic and subject unresponsive to pain With Narcan 0 4 mg IV subject was slightly responsive to verbal stimulus At 09 46 systolic BP still in 70's and normal saline infusion begun By 10 48 all adverse events resolved

2) 51 yo female received ondansetron 8 mg p0 qd for 3 days, last dose 08 41 followed by single dose Zydys Apomorphine 10 mg P0 at 0911 Eighteen minutes later subject complained of chest heaviness and was pallid and diaphoretic She lost consciousness at 0930 and was unresponsive to verbal stimulus BP and pulse not palpable After Narcan 04 mg IV the subject became responsive to verbal stimulus At 09 34 BP =80 systolic and subject required constant stimulation to stay awake Subject complained of nausea and vomited IV normal saline infusion started Subject vomited again and IV ondansetron 4 mg was administered At 1000 subject placed on cardiac monitor and had sinus bradycardia at 42-52 bpm 500 cc normal saline infused All adverse events resolved by 11 00 Narcan 0 4 mg had been administered twice

CLINICAL REVIEW

Clinical Review Section

3) 53 yo female received ondansetron 8 mg po qd for 3 days, last dose 0842 followed by single dose Zydys Apomorphine 10 mg PO at 09 12 Twenty-four minutes later subject was pallid, weak and became unresponsive for about 30 seconds When roused she was disoriented BP = 74/50 and HR = 52 After Narcan 0 4 mg IV subject's BP = 100/58 She was noted to have generalized trembling By 10 00 all adverse events had resolved

Conclusions

All three subjects experienced hypotension, diaphoresis, pallor and loss of consciousness following administration of a single dose of Zydys Apomorphine 10 mg PO Previous experience with this formulation at doses up to 30 mg resulted in no significant adverse events Therefore, these events must be due either to an interaction between the apomorphine preparation and ondansetron (which has not previously been administered with apomorphine to our knowledge), or to a CMC problem with the Zydys preparation

Recommendations

This study has been discontinued and placed on hold and should remain so until an adequate explanation for the serious AE's noted above has been delineated, and plans to avoid this and similar life threatening AE's in the future have been defined

Caution should be advised to all other investigator's using the Zydys Apomorphine formulation or combination treatments with apomorphine (in any formulation) and ondansetron

These most serious adverse reactions were suspected as being related to a drug interaction between ondansetron and APM because similar reactions did not occur with the use of ondansetron Neither did such dramatic adverse reactions appear to occur in subjects administered single doses of Zydys APM at 10 mg or higher (up to 30 mg) in the absence of ondansetron Nevertheless, the nature of the suspected drug interaction was never characterized IND \sim was subsequently withdrawn

This suspected drug interaction between ondansetron and APM is most serious, of great concern, and should be described in the APOKYN label by making ondansetron a contraindication and cross-referencing this information in the Drug Interactions section I question whether this suspected drug interaction might even occur with other 5HT₃ antagonist so that this adverse reaction could potentially be a result of a drug interaction between APM and the class of other similar drugs that act as 5HT₃ antagonists (e g granisetron, dolasetron, alosetron)

I have serious concerns that serious reactions, potentially life-threatening, could occur if patients used APM in conjunction with ondansetron, and possibly even of 5HT₃ antagonists Such potential drug interaction use with ondansetron and APOKYN would likely be associated with much higher plasma levels of both drugs The C_{max} for 10 mg Zydys APM is \sim 3 ng/ml, much lower than the mean C_{max} expected with use of the lowest dose (2 mg) of APOKYN recommended for use in the label It is important to recall that the mean C_{max} for the highest recommended dose (6 mg) of APOKYN would be \sim 30 ng/ml and that patients could potentially

CLINICAL REVIEW

Clinical Review Section

use a higher than recommended dose (e.g. 10 mg) off-label that would have a mean C_{max} of ~50 ng/ml. In addition, the normal daily use of ondansetron is 8 mg BID or TID. Thus, it seems clear that if such drug interactions occurred after approval of APOKYN, these drug interactions would likely be accompanied by much higher levels of both drugs and one would expect even more severe adverse reactions than those previously observed.

I also believe that there is a reasonable possibility that some patients might use APOKYN in combination with ondansetron or other similar 5HT₃ antagonists. First, some physicians might opt for the off-label chronic use of ondansetron or a related drug to prevent or minimize nausea and vomiting instead of the recommended anti-emetic, trimethobenzamide that is also being used in an off-label indication. Second, some patients might be treated with these 5HT₃ antagonists to prevent nausea and vomiting for chemotherapy or radiation therapy if some patients also require treatment for a cancer. Some could also receive these drugs for the prevention of post-operative nausea and vomiting. Finally, a search of the literature reveals publications describing the use of ondansetron for the treatment of hallucinations in Parkinson's Disease or drug-induced psychosis in Parkinson's Disease. Thus, there seems to be a reasonable possibility that patients could use APOKYN and ondansetron or one of the other 5HT₃ antagonists.

Given the potential for this serious drug interaction between APOKYN and ondansetron or other 5HT₃ antagonists, I consider it critical that such information must be contained in the APOKYN label.

If this information cannot be included in the APOKYN label, then NDA 21264 should receive another approvable letter.

Warnings

- The sponsor added some specific information about the experience with using Tigan and APM and filled in the blanks for specific numbers requested by DNDP. The sponsor's edits seem appropriate and adequate.
- Regarding injection site reactions, the DNDP had asked the sponsor to address why the experience involving the occurrence of induration and nodules in "most" patients with panniculitis that was described in the foreign label was not reflected in the safety experience of Bertek. The sponsor speculated with 3 potential reasons for this difference. The foreign experience supposedly included a predominant use of continuous APM infusion and a reference was made to a publication about this issue. The sponsor also noted that patients in Europe have been advised to inject APM through clothes and this method of administration could potentially introduce minute quantities of foreign particulate and chemical matter under that skin that might cause irritation. I consider the sponsor's response on this issue to be satisfactory.

CLINICAL REVIEW

Clinical Review Section

- Regarding injection site reactions, the sponsor was also asked to justify the use of the benzyl alcohol formulation of APM for which there was no human experience with the exception of a minimal experience derived from administering a low dose to a small number of healthy volunteers. The sponsor addressed this issue in a response to Clinical Comment # 8 and I reviewed my assessment of the sponsor's response earlier in this review.
- Regarding the injection site reactions section of the label in the Warning section, DNDP noted that injection site sarcomas were observed in — carcinogenicity studies and commented that this important information should be included in the label [

only has access to publicly available information. This remains a significant problem. I believe that we must explore every potential way to get this information in the label.

- The sponsor has added incidence information based upon the safety update describing the frequency of injection site reactions in general and the most common reactions. This information is reasonable and satisfactory for inclusion. The sponsor has also added [

I do not believe that this statement should be specified here because the experience conducted under randomized, double-blinded, placebo-controlled conditions was very limited and a different experience might have been observed with a more extensive experience under such conditions. In addition, the specific experience in some randomized, double-blinded, placebo-controlled trials will be described in the adverse event section.

- DNDP asked the sponsor to review its database for any potential allergic reactions and consider describing this experience. The sponsor has added a sentence noting that less than 1 % of patients treated with APM each of the following reactions: face edema, tongue edema, urticaria, allergic dermatitis, or drug hypersensitivity. This addition seems reasonable.

- In the Warning about Falling Asleep during Activities of Daily Living, the sponsor has added a sentence noting [

This sentence is not appropriate here nor anywhere in the label for reasons outlined earlier when the sponsor proposed adding this to the Clinical Trials section of the label.

- In the Warning on Symptomatic Hypotension, the sponsor added a sentence summarizing mean decrements in systolic and diastolic blood pressure after single doses — compared to placebo results. While I think that a comment describing the magnitude of these blood pressure decrements is reasonably appropriate, I disagree with the magnitude of the changes described based upon orthostatic vital sign data contained in my Safety Review (6/20/03) and derived from the sponsor's analyses.

CLINICAL REVIEW

Clinical Review Section

Furthermore, I see no reason why the changes should be noted when these hypotensive changes were progressively dose-dependent and observed throughout the whole range of dosing (e.g. 2 – 10 mg). Instead of the sponsor's language, I propose language such as "single dose-dependent mean decrements in SBP/DBP ranging from 5/3 mm Hg after 2 mg apomorphine to 16/8 mm Hg after 10 mg".

The sponsor also proposed describing the occurrence of "severe" systolic hypotension in a small number of patients as "moderate" systolic hypotension. I see no good rationale for this change and think that the language should remain as "severe".

Previous drug-drug interactions studies with sublingual APM and alcohol, and nitrates showed clearly increased safety risks associated with increased hypotension and other events (e.g. syncope) related to hypotension.

The memo (6/7/00) of the Deputy Division Director (Marianne Mann, M.D.) for the DRUDP (HFD-580) noted that the "available data do not support an acceptable risk/benefit" and this conclusion was primarily based upon the unacceptable incidence of hypotension and hypotensive-related adverse events including syncope occurring with the use of both with and without other interacting agents (e.g. alcohol, nitrates). A 4 mg dose of sublingual apomorphine would produce a similar bioavailability as ~0.7 mg injectable APM (APOKYN).

I believe that it is also relevant to note that the foreign label draws attention to the prescriber about a potential drug-drug interaction concern for APM and antihypertensive or cardiac active drugs. Under the general section of the label called Interaction with other medicinal products and other forms of interaction, there is a subheading called Antihypertensive and Cardiac Active Medicinal Products. This paragraph notes "Even when co-administered with domperidone, apomorphine may potentiate the antihypertensive effects of these medicinal products. See section 4.4 special warnings and precautions for use above." This section 4.4 then notes "Since apomorphine may produce hypotension. Even when given with domperidone treatment, care should be exercised in patients with pre-existing cardiac diseases or in patients taking vasoactive medicinal products such as antihypertensives, and especially, in patients with pre-existing postural hypotension." The foreign label for APM also advises caution with drugs with narrow therapeutic margin because effect of APM on other such drugs unknown because not studied.

CLINICAL REVIEW

Clinical Review Section

Pharmacodynamic interactions between sublingual APM (5 mg) and non-nitrate antihypertensive drug groups (ACE inhibitors, beta blockers, diuretics, calcium channel blockers, alpha₁ blocker) were shown in a placebo-controlled study (Fagan T C et al, *Amer J Cardiol*, 88 760-766, 2001),

This publication showed that blood pressure decrements (in supine and/or standing positions) were often lower when APM was administered with these various groups of antihypertensive drugs than when blood pressure was measured only after the antihypertensive drug and placebo These results suggested that, at the least, that there were some additive effects of both drugs on lowering blood pressure However, it is critical to recall that there is limited bioavailability (~ 18 %) with sublingual APM and that there is essentially complete bioavailability (~ 100 %) with subcutaneously injected APM Thus, 5 mg of sublingual APM would be equivalent to < 1 mg injection of APM Considering that doses of injectable APM (i e APOKYN) to be used would likely range from 2-6 mg per injection (and patients could potentially use up to 10 mg APM off-label), the interaction studies between non-nitrate antihypertensive drugs (and sublingual APM) are of limited relevance to the greater concerns about the risk of hypotension and hypotension-related adverse events from pharmacodynamic interactions between APOKYN and many anti-hypertensive drugs **Thus, it would be important to indicate these concerns clearly in the label and Patient Package Insert and for Bertek to study the effects of APM and other interacting agents including alcohol, nitrates (short-acting and long-acting), and various categories of anti-hypertensive drugs as a phase 4 requirement**

Altogether, these various observations support the addition of statements advising caution regarding the concomitant use of vasodilating drugs or antihypertensive drugs with APM and a potential safety concern for an increased risk of hypotension and hypotensive-related adverse events I believe that it is possible to justify the use of such statements without necessarily relying on data from clinical experience and because the results of the drug-drug interaction study of effects on blood pressure has been published

Furthermore, I think that it would be desirable to add stronger statement to the label in several locations advising caution against the concomitant use of APM and alcohol within a "short" interval (? 2 hours or perhaps even somewhat longer) particularly because of concerns for hypotension and hypotensive-related adverse events I think that this caution about concomitant alcohol should be noted in the Warning section on symptomatic hypotension, and in the Drug-Drug interaction part, and the Patient Information part of the Precautions section Presently, the sponsor's proposed Information for Patients section notes that "Alcohol and vasodilating medications may potentiate the hypotensive effect of apomorphine" In contrast, the patient package insert contains stronger language regarding the concomitant use of APM and alcohol Under the section, "What should I avoid while taking APOKYN?", the sponsor has proposed **"Do not drink alcohol while you are taking APOKYN Alcohol used with APOKYN can cause worse side effects"** I see no reason why the cautionary warning in the label for Prescribers should not be similar to what the sponsor has proposed for patients in the Patient Package Insert

CLINICAL REVIEW

Clinical Review Section

alcohol — sublingual APM) and that the results of studying the hypotensive effects APM with alcohol that prompted this contraindication involved a lower exposure to APM than would be expected from using injectable APM (APOKYN)

Language to consider in the Warning section on Symptomatic Hypotension might be

1

- In the Warning section on Coronary Events, the sponsor notes that "approximately — of patients treated with apomorphine experienced angina, myocardial infarction, and cardiac arrest" DNDP had asked the sponsor to provide the appropriate % and had also included the term sudden death that the sponsor has deleted. The sponsor did not provide a specific justification for deleting the term sudden death but merely referenced Table 76.0 that shows the incidence of all TEAEs according to organ systems, high level group terms, and preferred terms. When I reviewed these terms, there were no patients who were categorized as having sudden death as a preferred term. However, the sponsor acknowledged (see my review of Safety Update 2) that there were at least 2 cases that could be construed as sudden death despite the fact that they had not been coded as such. I think that these 2 cases should be counted as sudden death for inclusion in the label and added to the patients contributing to the % if they are not already included.

I had asked the sponsor to clarify the total number of cases in the NDA that it considers as possible "sudden death." The sponsor has responded that there are 3 cases (APO401/54/006, APO401/ — 007, APO401/36/008) that might be considered as sudden death despite the fact that these none of these 3 cases had been coded as "sudden death" as a preferred term. I agree with this number of 3 cases for which each patient's death was unexpected and there was no clear cause of death. Thus, there were 22 patients (out of 550 total) who had experienced angina (any type), myocardial infarction, myocardial ischemia, cardiac arrest (including cardiorespiratory arrest), and/or sudden death. **Thus, the incidence of these coronary events should be 4 % and the term sudden death should be restored.**

- The sponsor deleted the language on QT Prolongation from the Warning section and added language regarding QT prolongation in the Precautions section. **I disagree with the sponsor's proposal to describe the experience with QT prolongation in the Precautions section and recommend in the strongest terms that this potential risk be retained in the Warning section as DNDP originally proposed for the reasons outlined in my review of Clinical Comment # 3.**

CLINICAL REVIEW

Clinical Review Section

I think that the most important points that should be made include 1) a comment that QTc prolongation was observed in the randomized, double-blinded, placebo-controlled study APO302 in which patients were randomized to a range of doses (2-10 mg) over that of placebo, 2) an open label study (i.e. APO303) showed that doses of 8 and 10 mg APM were associated with QTc prolongation (5 - 9 msec) above that of patients treated with placebo during a double-blind part of the study, 3) there were 2 patients (both at 6 mg) who experienced markedly abnormal QTc increments (i.e. > 60 msec) from pre-dose QTc to QTc intervals > 500 msec acutely after dosing, 4) a description of the potential significance of QTc prolongation as a surrogate for the risk Torsades de pointes (e.g. ventricular polymorphic tachycardia) should be clearly spelled, along with the clinical manifestations of Torsades de pointes (e.g. palpitation, syncope, cardiac arrest, sudden death), 5) a description of the factors that can increase the risk for Torsades de pointes in the setting of QTc prolongation (e.g. female gender, hypokalemia, bradycardia, left ventricular dysfunction/heart failure, hypomagnesemia, and digitalis therapy), and 6) a caution that using other drugs that prolong QTc could potentially result in greater QTc prolongation and therefore greater risk for Torsades de pointes

- **Serious Adverse Events Related to Drug Interaction Between APM and Ondansetron**

On 3/31/04, the sponsor contacted DNDP to ask if the Agency still has "concerns about the use of ondansetron with apomorphine that should be provided in the labeling" This topic had arisen after an internal review of Bertek's development program for APM. In 1997, Mylan Pharmaceuticals (Bertek) was informed that it could not conduct studies to compare the ability of ondansetron to prevent APM-induced nausea and vomiting with the ability of trimethobenzamide to do the same because the Agency was aware of a serious problem when APM and ondansetron were used in combination. Mylan was not informed of the nature of the serious adverse reaction. There is no information to indicate that Mylan investigated this drug interaction animal studies nor that it attempted to see if this issue could be addressed in humans.

On 3/13/97, DNDP received reports that 3 healthy volunteers had experienced serious adverse reactions consisting of severe hypotension, syncope/loss of consciousness, and bradycardia and one subject experienced seizure activity. These adverse reactions occurred within a half hour of administration of 10 mg Zydys apomorphine after 3 days of oral ondansetron 8 mg every day (including administration 30 minutes prior to Zydys APM). This experience was observed under IND _____ and occurred in 3 of 12 subjects studied and prompted a CLINICAL HOLD for studying additional humans with Zydys APM and ondansetron. All 3 subjects recovered (additional details regarding this experience are described in my review of Labeling Issues). These most serious adverse reactions were suspected as being related to a drug interaction between ondansetron and APM because similar reactions did not occur with the use of ondansetron. Neither did such dramatic adverse reactions appear to occur in subjects administered single doses of Zydys APM at 10 mg or higher (up to 30 mg) in the absence of ondansetron. Nevertheless, the

CLINICAL REVIEW

Clinical Review Section

nature of the suspected drug interaction was never characterized IND — was subsequently withdrawn

This suspected drug interaction between ondansetron and APM is most serious, of great concern, and should be described in the APOKYN label by making ondansetron a contraindication and cross-referencing this information in the Drug Interactions section. I question whether this suspected drug interaction might even occur with other 5HT₃ antagonist so that this adverse reaction could potentially be a result of a drug interaction between APM and the class of other similar drugs that act as 5HT₃ antagonists (e.g. granisetron, dolasetron, alosetron)

I have serious concerns that serious reactions, potentially life-threatening, could occur if patients used APM in conjunction with ondansetron, and possibly even of 5HT₃ antagonists. Such potential drug interaction use with ondansetron and APOKYN would likely be associated with much higher plasma levels of both drugs. The C_{max} for 10 mg Zydys APM is ~ 3 ng/ml, much lower than the mean C_{max} expected with use of the lowest dose (2 mg) of APOKYN recommended for use in the label. It is important to recall that the mean C_{max} for the highest recommended dose (6 mg) of APOKYN would be ~ 30 ng/ml and that patients could potentially use a higher than recommended dose (e.g. 10 mg) off-label that would have a mean C_{max} of ~ 50 ng/ml. In addition, the normal daily use of ondansetron is 8 mg BID or TID. Thus, it seems clear that if such drug interactions occurred after approval of APOKYN, these drug interactions would likely be accompanied by much higher levels of both drugs and one would expect even more severe adverse reactions than those previously observed.

I also believe that there is a reasonable possibility that some patients might use APOKYN in combination with ondansetron or other similar 5HT₃ antagonists. First, some physicians might opt for the off-label chronic use of ondansetron or a related drug to prevent or minimize nausea and vomiting instead of the recommended anti-emetic, trimethobenzamide that is also being used in an off-label indication. Second, some patients might be treated with these 5HT₃ antagonists to prevent nausea and vomiting for chemotherapy or radiation therapy if some patients also require treatment for a cancer. Some could also receive these drugs for the prevention of post-operative nausea and vomiting. Finally, a search of the literature reveals publications describing the use of ondansetron for the treatment of hallucinations in Parkinson's Disease or drug-induced psychosis in Parkinson's Disease. Thus, there seems to be a reasonable possibility that patients could use APOKYN and ondansetron or one of the other 5HT₃ antagonists.

Given the potential for this serious drug interaction between APOKYN and ondansetron or other 5HT₃ antagonists, I consider it critical that such information must be contained in the APOKYN label.

CLINICAL REVIEW

Clinical Review Section

[**information cannot be included in the APOKYN label, then NDA 21264 should receive another approvable letter**] **If this**

- Under Information for Patients in the Precautions section, the sponsor has noted that “Alcohol and vasodilating medications may potentiate the hypotensive effect of apomorphine” In contrast, the patient package insert contains stronger language regarding the concomitant use of APM and alcohol **I have noted previously (in my labeling issues discussion under the Symptomatic Hypotension part of the Warnings section) my concerns about the fact that the caution about using alcohol in the Information for Patients section is understated compared to the stronger language proposed by the sponsor to avoid alcohol while taking APOKYN in the Patient Package Insert**

Language to consider in this section might be

“Alcohol should be avoided because of concerns about the occurrence of increased hypotension compared to the hypotension that might occur from apomorphine administration without concomitant alcohol Caution should also be exercised regarding the potential for increased hypotension that might occur when apomorphine is administered with concomitant vasodilator drugs, especially short-acting or long-acting nitrates, or antihypertensive drugs that lower blood pressure Cross-reference should also be made to other sections such as Symptomatic Hypotension in the Warning section and Drug-Drug Interactions in the Precautions section”

- Under Drug Interaction in the Precautions section, the sponsor updated the incidence of TEAEs such as fall and bone and joint injuries The paragraph is labeled as referring to “Vasodilators” Although I do not disagree with this term, the term “antihypertensive drug” should also be added to inform about concerns regarding the concomitant use of vasodilator drugs (including short-acting or long-acting nitrates) and antihypertensive drugs Although a pharmacological mechanism of many of these drugs involves vasodilatation, many of these drugs (verapamil, doxazosin, amlodipine, nifedipine) associated with a high frequency of certain TEAEs are also considered anti-hypertensives used for the indication of hypertension

There is an increased frequency of hypotension/decreased blood pressure associated with APM use and antihypertensive medication regardless of pharmacological mechanism of action will lower blood pressure Thus, the blood pressure lowering effect of APM could be additive or synergistic to that of any vasodilator or anti-hypertensive medication or alcohol and lead to increased lowering of blood pressure or significant hypotension **Consequently, I think that it is important to specify the terms antihypertensive drugs to draw the prescriber’s attention to the possibility that any antihypertensive drugs might promote a pharmacodynamic interaction resulting in a higher frequency of certain TEAE such as serious falls** Despite the fact that the sponsor did not include all types of antihypertensives in the search for TEAEs associated with vasodilating drugs, I see no reason

CLINICAL REVIEW

Clinical Review Section

not to use the terms, antihypertensive drugs. Because the pharmacodynamic effect that these “vasodilator” drugs share with all anti-hypertensive medications is lowering of blood pressure, it is likely that the increased association described here could be observed with any antihypertensive medication. The investigation of sublingual apomorphine with various types of antihypertensive drugs often showed that blood pressure decrements (in supine and/or standing positions) were lower when APM was administered with these various groups of antihypertensive drugs than when blood pressure was measured only after the antihypertensive drug and placebo. It is important to recall that the exposure to APM (e.g. 5 mg sublingual APM equivalent to ~ 0.9 mg APOKYN) would be lower than that from the lowest dose of APOKYN (2 mg). Thus, there is a significant concern that drug-drug interaction studies investigating potential pharmacodynamic interactions (on lowering blood pressure) between injectable APM and vasodilator drugs (especially short-acting and long-acting nitrates), APM and antihypertensive drugs, and APM and alcohol will show significant pharmacodynamic interactions manifested by greater hypotension and possibly an increased incidence of hypotensive-related adverse events.

During my review of SU2, I noted that the frequency of serious myocardial infarction was higher (3%) in patients using vasodilating drugs than the incidence (e.g. 1%) in those not using them. In addition, the incidence of serious pneumonia was 5% in patients using vasodilating drugs and 3% in those without these drugs. The incidence of all types of TE-pneumonia preferred terms without regard to serious categorization was also higher (7% vs 4%) when vasodilating drugs were used.

In addition, there was a higher incidence of hypotension (10% vs 4%) and lethargy (4% vs 1%) associated with the use of vasodilating medications.

I believe that these additional findings should be described in this section. The higher frequency of myocardial infarction is particularly noteworthy as is the higher frequency of pneumonia, especially considering that so many deaths were also associated with pneumonia. **Considering the well recognized hypotensive effects of APM and the hypotensive effects of many of these vasodilating medications, I think that it is quite reasonable to expect that an increased occurrence of many, if not perhaps all these events, might be related to increased hypotension associated with the concomitant use of these vasodilating medications and APM.**

I have noted previously (in my labeling issues discussion under the Symptomatic Hypotension part of the Warnings section) my concerns about the potential safety risks for increased hypotension when APM is used with vasodilator drugs, antihypertensive drugs, or alcohol and the various reasons and lines of evidence for my concerns for increased risk of hypotension and hypotensive-related adverse events.

Language to consider in the Drug-Drug Interactions part of the Precautions section might be

Vasodilator and Antihypertensive Drugs There was a higher incidence of certain types of serious adverse events and adverse events not necessarily categorized as serious associated

CLINICAL REVIEW

Clinical Review Section

with the concomitant use of vasodilator drugs including short-acting or long-acting nitrates and antihypertensive drugs. Compared to the incidence of serious adverse events observed in patients who were not using these concomitant drugs, there was a higher incidence of falls (5 % vs 2 %), bone and joint injuries (6 % vs 2 %), pneumonia (5 % vs 3 %), and myocardial infarction (3 % vs 1 %) associated with the use of these concomitant drugs. Compared to the incidence of adverse events that were not categorized as serious and were observed in patients who were not using these concomitant drugs, there was a higher incidence of hypotension (10 % vs 4 %), pneumonia (7 % vs 4 %), and lethargy (4 % vs 1 %) associated with the use of these concomitant drugs. Although the pathophysiological mechanism underlying the higher incidence of these adverse events associated with the concomitant use of vasodilator and antihypertensive drugs has not clearly been established, increased hypotension may be responsible.

- Under Carcinogenicity in the Precautions section,

The sponsor noted that
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Currently, Bertek only
has access to the publicly available information

It is not clear from the specific language in the sponsor's response

I view the inclusion of this information of injection site sarcomas in rodents in the label as a critically important issue

CLINICAL REVIEW

Clinical Review Section

Because it was not clear from the sponsor's response

DNDP asked the sponsor

the sponsor was unable to provide any information, said that it would look into the matter and respond to DNDP. As of 4/7/04, DNDP has not yet received a response to DNDP's request.

I consider that it is important to include information in the APOKYN label about a potential risk for injection site cancer following chronic, intermittent APOKYN use. I would consider it unethical not to inform (in the label) users about this potential risk of which we are aware. I consider this to be a similar issue as informed consent in terms of informing human subjects about potential safety risks when they enroll in experimental studies. **If the carcinogenicity findings cannot be described in the APOKYN label now, then I would conclude that an approvable action would be appropriate for APOKYN at this time.** The sponsor must consider conducting its own carcinogenicity studies and these studies should be initiated as soon as possible.

- Under the Geriatric Use section of Precautions, the sponsor should add respiratory events to the other types (e.g. falls/bone and joint injuries, cardiovascular, and gastrointestinal) of SAEs that occurred in geriatric patients (i.e. ≥ 65 years old). The incidence of respiratory, thoracic, and mediastinal disorders occurring as an SAE was _____ in younger patients) in these older patients.

The incidence of hypotensive-related adverse events (i.e. hypotension NOS, hypotension postural aggravated, and postural hypotension) was relatively similar in patients ≥ 65 years old (10.0%) and in patients < 65 years old. Nevertheless, it may be desirable to caution about a theoretical concern for increased risk of hypotension resulting from apomorphine treatment in geriatric patients who not infrequently exhibit an increased susceptibility to postural/orthostatic hypotension.

- Under the Precaution section, I would note that 3 patients experienced TEAEs that were characterized with priapism. Considering that APM has been developed as treatment for impotence, and priapism rarely occurs with APM, this information should be mentioned in the label. Although none of the cases of priapism in the APOKYN NDA were characterized as SAEs, priapism can present as an urgent and potentially serious problem requiring urgent attention, possibly a visit to an emergency room.
- Under the section of Adverse Events in Controlled Clinical Trials, the sponsor has added language noting that virtually all patients (i.e. 547 out of 550 patients) were taking dopamine agonists (predominantly L-Dopa) along with their other Parkinson's Disease medications. I would delete the wording noting dopamine agonists because I do not consider L-Dopa to be a

CLINICAL REVIEW

Clinical Review Section

dopamine agonist as compared to other standard dopamine agonists (e.g. pramipexole, ropinirole, pergolide, bromocriptine) L-Dopa is a precursor for the production of dopamine

The sponsor deleted a sentence

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There is no explanation nor rationale provided as to why the sponsor has done this. I believe that the sentence should remain because this gives perspective that a relatively small percentage (32 %) of patients participated in controlled clinical trials

- The DNDP had asked that the sponsor not combine TEAEs from studies of fundamentally different designs and instead requested that the sponsor draft paragraphs describing TEAEs occurring in > 2 % of APM-treated patients. This specific request is shown below in italics

Agency Label Request We should not combine ADRs from studies of fundamentally different designs. Please draft a paragraph presenting the adverse events that occurred in greater than 2% of apomorphine-treated patients in descending order for 2 studies: Study 202 (treatment naive patients treated for one month) and Study 302 (chronically treated patients dosed once)

The sponsor did not incorporate such paragraphs in the proposed label submitted but instead provided paragraphs for DNDP to consider for studies 202 and 302 in a separate response section and also proposed a paragraph

The following (in italics) represents the sponsor's specifically proposed language for consideration by DNDP

[

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• APO302

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Reviewer's Comments

If the sponsor wants to have for a paragraph noting that 1 patient represents 5 % and 3 % of patients in studies 202 and 302, respectively, the sponsor should also note that 1 patient represents 2 % of patients in study 303 if safety data from this study are also presented. It may also be helpful to specify the number of patients in each study. Thus, the frequency cut-off for APM-treated patients would be 5 %, 3 %, and 2 %, respectively for studies 202, 302, and 303. I believe that the lowest % available for each study should be presented.

I do not see a reason to describe the TEAEs occurring in study 202 in a paragraph format if the same information is presented in a table (still retained in the proposed label) showing this same information plus corresponding results for placebo and total number of patients treated with APM or placebo.

The sponsor did not provide a specific source from which it obtained the frequency of the TEAEs described for study 302 (nor study 303) so that this reviewer can confirm the data summarized. I believe that it can be clarified better to indicate that in study 302 that two of the four randomized groups received the usual APM dose or its placebo equivalent volume plus 2 mg apomorphine or plus 0.2 ml placebo, if randomized to placebo plus 0.2 ml group.

CLINICAL REVIEW

Clinical Review Section

Finally, it is not possible to assess the accuracy of the statement

because the sponsor did not identify the data source for the statement

The DNDP did not want to present efficacy results of study 303 (cross-over study) in the controlled clinical trials section because DNDP did not consider this to be a positive pivotal study due to a period effect such that the results of period 2 were mainly responsible for the statistical significance of primary efficacy endpoint for the whole study. However, it would not be unreasonable to present safety results from the controlled portion of this study. This study was somewhat similar to study 202 in that the study enrolled patients who were naive to APM treatment. Whereas study 202 used a parallel group design (APM or placebo) in which patients were treated with a dose of APM that was therapeutically equivalent (based upon change in UPDRS motor score at ~ 20 minutes) to the levodopa dose, study 303 enrolled patients who were naive to APM and involved a cross-over design. In this cross-over design, patients received a single injection treatment of either 4 mg APM and then placebo, or placebo and then 4 mg APM, on different days after having been treated with a single dose of 2 mg APM on a previous day. Other major differences between these studies were the number of patients (20 APM and 9 placebo in study 202 and 51 APM and placebo in study 303) treated and the duration of treatment. Study 202 captured the safety experience over a longer period up to 1 month but study 303 reflected a much more limited safety experience derived from a single treatment with APM and placebo. Of interest, the incidence of study 202's most frequent APM treatment associated TEAEs (e.g. yawning, dyskinesias, nausea, somnolence, dizziness, rhinorrhea) was fairly different in magnitude compared to the safety experience described for study 303. In addition, other APM treatment associated TEAEs (e.g. hallucinations, edema, chest pain/pressure) occurring in 10 % of patients in study 202 were not described for study 303 based upon an incidence cut-off of $\geq 5\%$. Thus, these studies appear to reflect a somewhat different safety experience. Although study 303 reflects a safety experience from a much larger number of patients, the experience is very restricted in the extent/duration of treatment. **I am not convinced that there is much value in presenting the controlled experience from study 303, particularly because the incidence of most TEAEs that are common to both studies is significantly lower than the experience described in study 202 and this description might lead prescribers toward underestimating the risk of many TEAEs of significance. However, if the controlled experience from study 303 is described in the label, important differences compared to study 202 and the limited extent/duration of treatment for study 303 should be clearly emphasized or at least noted.**

- Under the section Other Adverse Events Observed during All Phase 2/3 Clinical Trials, the sponsor has moved the order of some TEAEs based upon changes noted in SU2, and added other TEAEs (hypotension including postural hypotension, and dehydration). **If this information on TEAEs is presented in a paragraph in order of descending frequency, I believe that the order of some of these TEAEs should be adjusted based upon combining similar TEAEs that had been described with a lower incidence because different preferred terms were used to describe the event. The sponsor has taken a "splitter" approach and split coded similar TEAEs as distinct TEAEs with different**