Table 26 **Dose-Dependent Effects of Apomorphine Treatment Difference (vs Oral Medication) on Time Course of QTc Changes (vs "Pre-Dose") in Study 303**

Rx Group	Placebo - Oral Medication N = 42		APM 2 mg – Oral Medication N = 50		APM 4 mg – Oral Medication N = 43		APM 6 mg– Oral Medication N = 39		**APM 8 mg– Oral Medication N = 18**		**APM 10 mg – Oral Medication N = 11**	
	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF	**QTcB**	**QTcF**	**QTcB**	**QTcF**
Δ at 20' after Pre-dose	-2 3	-0 5	-3 9	-1 4	-1 7	0	-3 2	0	**-0 4**	**1 6**	**1 0**	**1 1**
Δ at 40' after Pre-dose	-0 1	1 3	-2 3	2 2	0 5	5 0	-2 3	3 6	**3 0**	**6 1**	**5 0**	**8 5**
Δ at 90' after Pre-dose	-1 3	-0 6	0	-0 1	-1 4	0 1	-3 6	0 2	**1 3**	**2 3**	**-7 1**	**-2 8**
Δ Maxi-mal	0 2	-0 1	-0 3	0 8	-0 7	1 7	0	1 8	**2 0**	**1 7**	**-0 6**	**-0 6**

Data Source Sponsor's ISS Safety Update Reanalyzed (5/27/03 submission) Tables 1 4 3XB and 1 4 3XF
Treatment Difference = Treatment Change – Placebo Change
QTcB = Bazett correction QTcF = Fredericia correction
Δ Maximal = Maximal change from pre-dose considering any timepoint (e g 20, 40, or 90 minutes after injection/pre-dose)
Placebo change – oral medication change was no calculated by sponsor but by reviewer using mean differences

Table 27 **Dose-Dependent Effects of Apomorphine Treatment Difference (vs Placebo) on Time Course of QTc Changes (vs "Baseline") in Study 303**

Rx Group	Oral Medication – Placebo N = 47		APM 2 mg – Placebo N = 50		APM 4 mg – Placebo N = 43		APM 6 mg– Placebo N = 39		**APM 8 mg– Placebo N = 18**		**APM 10 mg – Placebo N = 11**	
	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF	**QTcB**	**QTcF**	**QTcB**	**QTcF**
Δ at 20' after Pre-dose	1 3	1 3	2 4	2 9	0	0 2	0 6	1 5	**2 9**	**- 1 7**	**- 1 0**	**- 4 4**
Δ at 40' after Pre-dose	- 1 0	- 0 3	0 1	2 5	- 1 9	2 0	- 1 2	2 9	**1 4**	**5 2**	**5 8**	**2 7**
Δ at 90' after Pre-dose	1 0	0 7	1 1	1 9	- 0 4	0 7	0 9	1 2	**2 8**	**6 3**	**- 3 4**	**- 5 2**
Δ Maxi-mal	0	- 3 0	4 1	3 7	- 0 5	1 1	2 4	2 9	**2 6**	**4 8**	**4 9**	**1 6**

Data Source Sponsor's ISS Safety Update Reanalyzed (5/27/03 submission) Tables 1 4 2XB and 1 4 2XF
Treatment Difference = Mean Active Treatment Change – Mean Placebo Change calculated by reviewer (not calculated by sponsor)
QTcB = Bazett correction QTcF = Fredericia correction
Δ Maximal = Maximal change from baseline QTc considering any timepoint (e g 20, 40, or 90 minutes after injection/pre-dose)

Table 28 **Dose-Dependent Effects of APM Treatment Difference (vs Oral Medication) on Time Course of QTc Changes (vs "Baseline") in Study 303**

Rx Group	Placebo - Oral Medication N = 44		APM 2 mg – Oral Medication N = 50		APM 4 mg – Oral Medication N = 43		APM 6 mg– Oral Medication N = 39		**APM 8 mg– Oral Medication N = 18**		**APM 10 mg – Oral Medication N = 11**	
	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF	**QTcB**	**QTcF**	**QTcB**	**QTcF**
Δ at 20' after Pre-dose	-1 3	-1 3	1 1	1 6	-1 3	-1 1	-0 7	0 2	**1 6**	**-3 0**	**-2 3**	**-5 7**
Δ at 40' after Pre-dose	1 0	0 3	0 2	2 8	-0 9	2 3	-0 2	3 2	**2 4**	**5 5**	**6 8**	**3 0**
Δ at 90' after Pre-dose	-1 0	-1 8	-0 6	-0 4	-1 4	-0 9	-0 1	-0 6	**1 8**	**4 5**	**-4 4**	**-7 0**
Δ Maxi-mal	0	-1 1	3 7	3 0	-0 5	0 4	2 4	1 8	**2 6**	**3 7**	**4 9**	**0 5**

Data Source Sponsor's ISS Safety Update Reanalyzed (5/27/03 submission) Tables 1 4 3XB and 1 4 3XF
Treatment Difference = Mean Treatment Change – Mean Placebo Change calculated by reviewer (not calculated by sponsor)
QTcB = Bazett correction QTcF = Fredericia correction
Δ Maximal = Maximal change from baseline QTc considering any timepoint (e g 20, 40, or 90 minutes after injection/pre-dose)

baseline because of the proximity of QT measurements relative to APM administration Nevertheless, I view the analyses based upon QTc changes from baseline as similarly supportive of a concern that high doses of APM prolong QTc because APM also shows a treatment effect (relative to placebo or oral medication) on prolonging QTc when QTcB and QTcF changes from baseline are assessed

During the investigation of effects of 10 mg APM, there was a suggestion of APM-induced QTc prolongation because the treatment effect relative to placebo (i e APM - placebo) showed a mean increment of 8 msecs (QTcB, Table 14) and of 5 msecs (QTcF, Table 16) at 40 minutes The sponsor had surveyed results of individual patient responses and noted that one patient (40/028) had shown a very large increment at 40 minutes after 10 mg APM (Figure 5) The sponsor then conducted similar analyses as in shown in Table 14 and Table 16 but excluded data from this "outlier" patient for the 10 mg APM group and the placebo group I agree that this approach seems reasonable I also concur with the sponsor that this result from this one patient accounted for the apparent mean QTcB and QTcF increment vs placebo because the QTc increment at 40 minutes disappeared when results of this patitent were excluded In addition, it seems reasonable to suggest that the apparent increment exhibited after the first treatment with 10 mg APM was not real because it was not reproducibly demonstrated on 3 subsequent occasions after administration of 10 mg APM (Figure 5)

When QTc changes from baseline were analyzed for the 10 mg APM treatment, there was no clear suggestion that APM produced a QTc (QTcB or QTcF) increment at any time based upon results of all patients including patient 40/028 (Table 18 and Table 20) After patient 40/028's results were excluded from the analyses of QTc change from baseline in the assessment of APM's treatment effect relative to placebo, mean results at 20, 40, and 90 minutes after APM generally became more negative (Table 19 and Table 21)

Thus, APM's treatment effect for increasing QTcB or QTcF above predose relative to placebo had appeared to have been based upon results of a single "outlier" patient who did not reproducibly exhibit a similar response to 10 mg on 3 repeat occasions I recognize that that there does not appear to be a suggestion of QTc prolongation when one excludes the experience of the first study of patient 40/028 after 10 mg APM in the mean QTcB and QTcF group analyses for change from "predose" or for change from "baseline" relative to placebo treatment **However, I cannot dismiss the observation that APM's 10 mg treatment effect relative to oral medication (another control group) suggested QTc prolongation based upon a 5 msec (QTcB) and 8 msec (QTcF) increment from predose at 40 minutes (Table 14 - Table 17)** Similar analyses of the APM treatment effect relative to oral medication did not suggest QTc prolongation when assessing QTc change from baseline In view of this, I have noted previously that I consider QTc changes from predose to be more relevant for evaluating QTc effect, particularly for a drug administered intermittently as APM **While trying to interpret the potential significance of these various analyses of the 10 mg APM group, it is important to note that these paired results of treatment effects for APM vs placebo or APM vs oral medication had been derived from a very small number of paired comparisons (e g 6 - 8)** This small number of paired comparisons (6 - 8) for the 10

mg APM data (Table 14 - Table 17) was approximately half of the number of paired comparisons (12 - 16) for the 8 mg APM data **Because of the considerable drop-out rate in escalating the APM dose to the 10 mg level, it is possible that there may have been a selection bias in these results representing a selection process based upon tolerability to APM and/or cardiovascular toxicity Such a potential selection bias could obscure or mask a more marked effect of 10 mg APM for prolonging QTc that actually exists because some patients who could exhibit this effect have dropped out of the dose escalation Conceivably, this same phenomenon may have been present and contributed toward underestimating QTc prolongation for 8 mg APM because only approximately half of the patients studied at 6 mg continued to be studied at the next higher dose (i e 8 mg)**

There are other caveats of importance to recall regarding QTc results for study APO303 These QT/QTc data had been collected with Holters, a potentially less sensitive methodology for investigating drug effects on QTc Most of the data (e g oral medication, 2 mg, 6 mg, 8 mg, 10 mg) were collected under open-label conditions Whereas relatively small numbers of patients contributed to the high dose APM data (8 mg, N = 18, 10 mg, N =11), the data collected at other treatments appeared to be more robust because of the larger number of patients studied (e g placebo, N = 44, 2 mg APM, N = 50, 4 mg APM, N = 43, 6 mg APM, N = 39) Furthermore, the number of paired results (8 mg or 10 mg vs placebo and 8 or 10 mg vs oral medication) upon which the treatment effects of APM were analyzed was even smaller

In summary, I believe that these various analyses of APM effects on QTc overall suggest or at the very least raise the question of QTc prolongation at APM doses above 6 mg Given that these results are based upon the use of Holters, that are considered to represent a less sensitive, unvalidated methodology for characterizing drug-induced QTc prolongation, these results suggesting QTc prolongation may be an underestimate of the actual QTc prolongation that can occur from high doses of APM It is also important to note that the sponsor previously provided a publication (Christiansen J L et al , Pace 19 1296-1301, 1996) in which Holter monitor results were compared to standard ECG results **The conclusion of the authors of this publication was "In the assessment of QT interval, potential sources of error of this magnitude could limit the clinical utility of ambulatory monitoring in detecting prolongation of the QT interval for diagnostic purposes "** The best way to address these concerns and deficiencies of APO303 and APO302 would be to conduct a randomized, double-blind, placebo-controlled study in which patients are randomized to a fixed dose of APM and investigated for effects on QTc with 12 lead standard ECGs

- Although the sponsor attempted to argue that there is not a sufficient concern to warrant a warning statement about the potential for APM to produce QTc prolongation, I have a very different view and believe that there are several reasons that support the legitimacy of such a warning in the label Overall, I interpret results of studies APO302 and APO303 as suggesting the possibility of QTc prolongation, especially during high dose APM treatment QTc prolongation is a potentially serious adverse reaction serving as a surrogate for serious

arrhythmia because of the association of QTc prolongation with serious arrhythmia (e g Torsades de pointes) Torsades de pointes, that can be fatal, is not an event that could be tolerated by making a false negative assessment for the risk of this most serious event There were some cases of syncope and sudden death in the NDA and it was not possible to exclude QTc prolongation induced arrhythmia as contributory event for syncope or sudden death Most of the NDA safety experience is derived from open-label study **The NDA safety experience conducted under randomized, double-blind, placebo-controlled conditions was extremely limited, and did not facilitate the opportunity of showing a greater frequency of APM-related adverse reactions (over placebo) that may have been related to QTc prolongation** There was significant inhibition (0 127 μM = IC_{50}) of APM in in vitro studies hERG channel in in vitro studies suggesting a serious potential for QTc prolongation in humans Such relatively, potent inhibition of hERG channels by APM suggests a significant risk for Torsades de pointes (and human QTc prolongation) based upon results presented in Table 22 and Table 23 **In summary, I believe that all of the issues and concerns summarized earlier in this paragraph in concert support the need to describe the potential risk of QTc prolongation in the Warnings section of the label**

The sponsor referenced 21 CFR § 201 57 to note that the **WARNINGS** section of labeling provides language for determining what is included in this section " shall describe serious adverse reactions and potential safety hazards as soon as there is reasonable evidence of an association of a serious hazard with a drug," It is also potentially relevant note that immediately following the sponsor's quotation that the regulations specify "a causal relationship need not have been proved " It is interesting to note that the sponsor did not specify this last portion of **WARNINGS** labeling language Furthermore, this section does not define " as soon as there is reasonable evidence of an association of a serious hazard with a drug " The regulations for IND Safety Reports (21 CFR § 312 32), however, do define "associated with the use of the drug" as meaning "There is a reasonable possibility that the experience may have been caused by the drug " If I make a similar interpretation of the **WARNINGS** section language regarding " association of a serious hazard with a drug" as that for "associated with the use of the drug" defined in the IND section of the regulations, then I believe that it is reasonable to describe QTc Prolongation under the Warning section of the label rather than under the Precautions section as proposed by the sponsor I further point to language [21 CFR § 201 57 (g) (3)] in the **Warnings** section of the label that notes that this section "shall identify any potentially fatal adverse reaction " **I firmly believe that there is sufficient reason to warrant description of QTc prolongation in the Warnings section of the label considering that 1) I interpret the host of observations supporting possible QTc prolongation from APM treatment, 2) the actual spectrum of risk and extent of APM-induced QTc prolongation remains to be characterized, 3) it is unequivocally recognized that QTc prolongation may be associated with Torsades de pointes, a potentially fatal arrhythmia, 4) it is not possible to exclude the possibility, to a reasonable extent, that some cases of sudden death or syncope were related to Torsades de pointes, and 5) CFR language supports the inclusion of a potentially fatal adverse reaction in the WARNINGS section of the label**

- In response to DNDP's comment about "the need to perform a formal, randomized, placebo controlled trial to evaluate the effects of the full dose range of sc apomorphine on the QTc interval" after approval, the sponsor responded that "it is not possible to conduct a randomized study that does not have some degree of selection bias " The sponsor further pointed out that there is no experience in administering large doses of APM without titration to naive patients due to the pronounced nausea and hypotensive effects that could occur and that it was not aware that any patient that received an initial APM dose > 4 mg A comment was made that any randomized study of high APM would have to include a run-in period, and even under such circumstances, there would be a significant loss of patients at higher doses The sponsor made reference to APO303 where doses where titrated to tolerance, only about half of the patients reached 8 mg and about a fourth of patients reached 10 mg Bertek argues that there will be concerns about selection bias irrespective of the study design Consequently, after approval, the sponsor proposes to study patients who are prescribed higher doses by their physician This study would be based upon a large group of investigators who agree to enroll patients who need doses higher than 6 mg Twelve-lead ECG data would be collected at pre-dose and post-dose Patients would remain in the study for 30 days and we would follow their use of doses greater than 6 mg

Based upon the descriptive proposal of what the sponsor would like to conduct, there is no mention of blinding, randomization to dose assignment, nor inclusion of a placebo group for comparison There is insufficient detail presented to envision precisely what the sponsor would do to characterize the risk for QTc prolongation **While I recognize that the study desired by DNDP may be somewhat complex in design and more difficult to conduct than the usual study assessing QTc, I believe that a randomized, double-blinded, placebo-controlled study can be conducted with an aim toward limiting bias** I acknowledge that it would be necessary to have a run-in/titration phase rather than to randomize patients to high (> 6 mg injection) fixed doses for initial administration if APM naive patients were studied I am concerned that it would clearly less than ideal to study only patients who receive high doses of APM from their physician because of their tolerability because these patients could represent a selection bias related to ease of tolerability and/or cardiovascular toxicity

I have summarized (below) the major study design elements that I believe would be important to include in a study desired by DNDP to characterize or exclude a human risk for QTc prolongation related to APM treatment I propose 2 study designs for consideration Proposal 1 includes a more ideal study design that attempts to minimize selection bias but may be associated with more substantial toxicity Proposal 2 includes a less ideal study design with potentially dose selection bias but that is likely to decrease the potential for toxicity

Proposal 1

- Randomization of APM naive patients (ages 40 – 75) to fixed dose, parallel groups of placebo or APM

- Double-blinding

- Use of a positive control (e g oral moxifloxacin) for assay sensitivity of QTc prolongation

- Run-in/titration phase during which patients would increase the APM exposure gradually (e g increase exposure to APM by 2 mg ? every 3 days) until the maximal dose 10 mg is achieved over approximately 2 weeks)

- Provide patients/caregivers with ampoules to be used for each specific day to treat "off" episodes over 2 weeks and provision of ampoules appropriate to the titration to the randomized fixed dose for each patient

- Incorporation of a double dummy treatment design using injection (APM or placebo) and oral administration of positive control (e g oral moxifloxacin) or placebo, oral administration would be performed on a single occasion at the time of QTc study

- Randomization to 1 of 7 treatment groups

  - 1) placebo injection and oral placebo, N = 16,

  - 2) placebo injection and oral moxifloxacin, N = 16,

  - 3) 2 mg APM and oral placebo, N = 16,

  - 4) 4mg APM and oral placebo, N = 16,

  - 5) 6 mg APM and oral placebo, N = 16,

  - 6) 8 mg APM and oral placebo, N = 32, larger numbers of patients should be randomized to the highest dose groups in anticipation of increased drop-out rate related to APM dose

  - 7) 10 mg APM and oral placebo, N = 48, larger numbers of patients should be randomized to the highest dose groups in anticipation of increased drop-out rate related to APM dose

- 12 lead standard ECGs with at least 3 collected at baseline (e g every 30 minutes before administration of treatment injection), and post-treatment ECGs at +20, 40, 60, and 90 minutes

- collection of orthostatic vital signs (supine and standing blood pressure and pulse) at similar times as ECGs are collected **but after** collection of each ECG

Proposal 2

- Randomization of APM treated patients (ages 40 – 75), who are being treated with high dose APM (> 6 mg injections for ? at least 1 or 2 weeks, but ? not total APM treatment for more than ? 4, 6, or 8 weeks to attempt to study patients relatively early in their APM treatment) to injection of placebo or APM

- Double-blinding, cross-over design studying patients on 2 consecutive days with APM abstinence for at least 12 hours, on 1 of 2 days each patient would receive only placebo

- Use of a positive control (e g moxifloxacin) for assay sensitivity of QTc prolongation

- Run-in/titration phase during which patients would increase the APM exposure gradually (e g increase exposure to APM by 2 mg ? every 3 days) until the maximal dose 10 mg is achieved at approximately 2 weeks)

- Incorporation of a double dummy treatment design using injection (APM or placebo) and oral administration of positive control (e g oral moxifloxacin) or placebo, oral administration would be performed on each occasion at time 0 of each ECG/QTc study

- Randomization of 1 of 6 treatment groups

  - 1) placebo injection and oral placebo or oral moxifloxacin, N = 16-20,

  - 2) 2 mg APM and oral placebo or double placebo, N = 16-20,

  - 3) 4mg APM and oral placebo or double placebo, N = 16-20,

  - 4) 6 mg APM and oral placebo or double placebo, N = 16-20,

  - 5) 8 mg APM and oral placebo, N = 16-20,

  - 6) 10 mg APM and oral placebo or double placebo, N = 16-20,

- 12 lead standard ECGs with at least 3 collected at baseline (e g every 30 minutes before administration of treatment injection), and post-treatment ECGs at +20, 40, 60, 90, 120, and 180 minutes

- collection of orthostatic vital signs (supine and standing blood pressure and pulse) at similar times as ECGs are collected **but after** collection of each ECG

I conclude that

1) preclinical in vitro hERG channel results for APM support a serious potential risk of APM for Torsades de pointes and human QTc prolongation,

2) preclinical in vitro Purkinje fiber assay results investigating the effect of APM on action potential duration were not performed appropriately in a most sensitive manner and thus the negative result reported by the sponsor is of indeterminate significance,

3) a description of a potential risk of QT/QTc prolongation from APM and the potential clinical significance of this QTc prolongation is warranted in the WARNINGS section of the label based upon the totality of information available and summarized in my assessment,

4) the sponsor should conduct a randomized, double-blinded, placebo-controlled study to evaluate the effects of the full dose range (up to 10 mg) of subcutaneous APM on the QTc interval

4 Clinical Comment 4

FDA Comment 4

Concomitant Tigan The exposure to Tigan in the NDA needs to be fully characterized prior to approval While we know that essentially all patients received Tigan, we do not know how Tigan was used over time Please provide information bearing on this issue It would be helpful to break down the apomorphine exposure into time with and without Tigan Specifically, determine the number of patients who were able to successfully taper off of Tigan and continue apomorphine Once off Tigan, did patients need to resume Tigan?

Bertek Response

Tigan (trimethobenzamide) exposure information was obtained from our long-term safety study, APO401 APO401 is an ongoing open label study designed 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 On average, patients participating in APO401 had PD for 11 4 years and an age of onset of 53 7 years Based upon responses to question 39 of section IV of the UPDRS at baseline, physicians classified 46% and 34% of the patients as having 1-25% and 26-50% of their waking time spent in an "Off" state, respectively Based on diary card assessment of dosing frequency, patients participating in APO401 averaged 3 apomorphine doses daily As of December 31,

2002, 522 patients had enrolled in APO401, representing 533 patient years of apomorphine therapy

In brief

- 52 6% of the overall apomorphine exposure was without Tigan administration
- 2 3 % (n=12) patients either never took Tigan, or stopped Tigan before beginning apomorphine therapy All other patients began apomorphine therapy with Tigan
- 47 5% (n=248) patients took Tigan throughout the study, while 50 2% (n=262) patients were able to stop Tigan at some point during the study while continuing apomorphine therapy
- Of those patients who were able to initially stop Tigan and continue apomorphine therapy, 95% were able to remain off Tigan for the duration of the study
- Of those patients who were able to initially stop Tigan, 25%, 50% and 75% stopped after 32, 65, and 129 days (or approximately 1, 2 and 4 months) of apomorphine therapy, respectively

As of the data lock point of December 31, 2002, 522 patients had enrolled in APO401 Tigan use was captured on the case report forms Attachment 34 1 lists all patients by site and patient number, along with their days on apomorphine with and without the use of Tigan Overall calculated exposure (last page of Attachment 34 1) indicated that there were 533 37 patient-years (i e , 194683 days / 365 days per year) of apomorphine therapy, and apomorphine was administered 52 6% of the time without concurrent Tigan use

Table 29 and Table 30 summarize the number of days that patients continued in APO401 with and without concurrent Tigan administration The column labeled "Frequency" lists the number of patients in each time period Approximately equal numbers of patients received apomorphine for at least 121 days with (223 patients or 42 72%) and without (212 patients or 40 61%) antiemetic therapy

Table 29 Days on APM with Tigan

cat2	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0 days	12	2 30	12	2 30
1- 30 days	122	23 37	134	25 67
31- 60 days	89	17 05	223	42 72
61- 90 days	40	7 66	263	50 38
91-120 days	42	8 05	305	58 43
>120 days	217	41 57	522	100 00

Table 30 Days on APM without Tigan

cat1	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0 days	223	42 72	223	42.72
1- 30 days	37	7 09	260	49 81
31- 60 days	16	3 07	276	52.87
61- 90 days	25	4 79	301	57 66
91-120 days	9	1 72	310	59 39
>120 days	212	40 61	522	100 00

Table 31 describes the percent of study days that patients continued to receive Tigan As previously noted, the column labeled "Frequency" lists the number of patients for each percentage interval of study participation This frequency table indicates that 12 patients (2 3%) either stopped Tigan before starting apomorphine therapy, or never began Tigan, 44 06% of patients received Tigan for less than 50% of the time during treatment with apomorphine, and 50% of patients received Tigan during at least 75% of the time during apomorphine therapy

Table 31 Frequency of Percent of Days on APM AND Tigan

cat3	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0%	12	2 30	12	2 30
>0 - <25%	142	27 20	154	29 50
25 - <50%	76	14 56	230	44 06
50 - <75%	31	5 94	261	50 00
75 - <100%	38	7 28	299	57 28
100%	223	42 72	522	100 00

Table 32 shows the number and percent of patients who began, continued or discontinued Tigan administration during the study Similar to the data presented in Attachment 34 3, one can discern the 12 patients (approximately 2%) who either stopped Tigan before starting apomorphine therapy, or never began prophylactic Tigan therapy About the same percentage of patients discontinued as those who remained on Tigan during the study (50% [n=262] vs 48% [n=248], respectively)

Table 32 Frequency of Whether Patients Stopped Tigan Early

ntaperoff	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Stopped Tigan before starting APO	5	0 96	5	0 96
Still on Tigan as of last known APO dose	248	47 51	253	48 47
Never took Tigan	7	1 34	260	49 81
Stopped Tigan Early	262	50 19	522	100 00

Of the 262 patient who discontinued Tigan, 249 patients were able to remain off Tigan for the duration of the study, while 13 (4 96%) patients later restarted Tigan (Table 33) On average, these 13 patients received apomorphine for 92 days (range = 1-242 days, median value = 65 days) before discontinuing Tigan, and resumed antiemetic therapy 59 days (range 1-245 days, median value = 32 days) later

Table 33 Patients Who Stopped Tigan Early

stop2	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Stopped - No Restart	249	95 04	249	95 04
Stopped & Restarted	13	4 96	262	100 00

Of the 262 patients who were able to discontinue Tigan, 11 patients discontinued Tigan just prior (< 7 days) to stopping apomorphine therapy Excluding these 11 patients, the median number of days for the remaining 251 patients on APO401 before discontinuing Tigan was 65 days (minimum = 1 day, maximum = 991 days, average = 112 days, Attachment 34 7)

In summary, the 522 patients who participated in APO401 received apomorphine therapy approximately 53% of the time without concurrent Tigan administration Equal numbers of patients were able to administer apomorphine for at least 121 days with (42% of patients) and without (41% of patients) antiemetic therapy Approximately 44% and 50% of patients received Tigan therapy less than 50% and at least 75% of the time, respectively Approximately 2% of the study population never required Tigan during the study to prevent nausea About 50% of the study population was able to discontinue Tigan completely during the course of the study, only 5% of these patients restarted prophylactic antiemetic treatment Patients usually received apomorphine together with antiemetic therapy for about 2 months before Tigan was discontinued, although the range for this central estimate was large

Reviewer's Comments, Discussion, and Conclusions

- Almost all patients (98 %) used Tigan at least for some time along with APM, and approximately half of the patients (48 %) took Tigan throughout the study along with APM The exposure to APM without Tigan administration was 280 patient-years, slightly more than half of the total, overall exposure to APM (533 patient-years) and the exposure to APM and concomitant Tigan was 253 years Although the sponsor presented various tables showing the number of patients taking or not taking Tigan along with APM for various time intervals, there was no presentation of the APM exposure for these various subgroups based upon interval ranges of the concomitant use of both drugs Nevertheless, the sponsor's analyses and presentations indicated that there was considerable safety experience collected both with and without concomitant Tigan administration

- Most (95 %) of the patients (249) who had used APM and Tigan together and who discontinued Tigan were able to remain off Tigan Correspondingly, only approximately 5 %

(13 patients) needed to restart Tigan For those patients who had taken Tigan with APM for part of the study, approximately half used Tigan for < 25 % of the APM treatment time and approximately one quarter of these patients used APM and Tigan for an interval ranging between 25 % to < 50 % of the APM treatment time Thus, the bulk (~ 75 % of patients) of exposure to Tigan for only part of the APM treatment period occurred for less than half of the total APM treatment period

- I have a minor disagreement with one of the sponsor's descriptions of data and difference of opinion about the sponsor's calculation of cumulative frequency and cumulative percent in several tables In referring to Table 29, the sponsor noted that 223 patients (42 72 %) received APM and Tigan for at least 121 days I interpret this respective number of patients to be 217 (41 57 %) In Table 29, Table 30, Table 31, and Table 32, the sponsor includes patients in the group of the first line of each of these tables in the cumulative frequency and cumulative percent calculations but I consider this inappropriate because each of these groups are not relevant to the title of the table For example, Table 29 (Days on APM with Tigan) shows that 12 patients never took Tigan and APM, thus these patients should not be counted in the cumulative calculations Similarly Table 30 (Days without Tigan) shows 223 patients who are counted in the cumulative calculations but this is not appropriate because these patients were always on APM and Tigan and they were never on APM without Tigan

- It was not clear why patients discontinued Tigan Such information was not captured in a manner whereby one could understand why Tigan was discontinued Tigan could have been discontinued for a variety or reasons including desire not to take a medication that was not necessarily needed, because of one or more adverse events, and/or related to tolerability

I conclude that the sponsor has reasonably addressed DNDP's inquiries and presented information that provides a better understanding of how Tigan was used in conjunction with APM

5 Clinical Comment 5

FDA Comment 5

The dose of Tigan used in the apomorphine development project was 250mg tid This dose is no longer marketed in this country, the marketed dose is 300mg It will be a matter of judgment as to whether the 50mg increment could interfere with the efficacy of apomorphine at the approved doses or alter the safety profile seen in the NDA We ask you to explain why you believe a 50mg increment in dosing for Tigan will not significantly alter the experience with apomorphine

Bertek Response

Prior to May 2002, patients were instructed to use trimethobenzamide 250 mg TID (the dosage section of that product labeling indicated that trimethobenzamide can be dosed at 250 mg TID or

QID) In May 2002 the APO401 (Open-label) protocol was modified to allow the use of trimethobenzamide 300 mg (the dosage section of that product labeling indicates that trimethobenzamide can be dosed at 300 mg TID or QID) The first trimethobenzamide 300 mg was dispensed on 05/28/02 The trimethobenzamide 250 mg at the sites was used until it was depleted or expired which ever came first As previously agreed, the database lock for this re-submission was December 31, 2002 There is limited follow-up (due to the 4 month follow-up visit interval) on the few patients that had been transferred to trimethobenzamide 300 mg TID as of this database lock date We have not seen any new adverse events associated with this change There is no change in the frequency of serious adverse events or deaths since the change, however, analysis of the frequency of all adverse events since the change is not possible due to the small number of patients transferred prior to December 31, 2002 Specifically, there were 27 patients that received Tigan 300 mg Seven of these 27 patients had data after 300 mg was started Three of the seven patients were started on 300 mg trimethobenzamide without prior exposure to 250 mg Only four of the seven have data available on 250 mg prior to the transfer to 300 mg and after the transfer

Bertek proposes to analyze the APO401 data to compare the incidence of adverse events and changes in the dose of apomorphine that occurred prior to and after the change to trimethobenzamide 300 mg in our safety update following approval The proposed analysis will evaluate the effects of the change in dose on efficacy (changes in dose) and safety (changes in adverse event frequencies)

The Agency has also proposed that, after approval, Bertek conduct a randomized placebo-controlled trial to investigate the actual necessity for the use of concomitant trimethobenzamide to decrease nausea and vomiting in patients, who initiate and continue treatment with apomorphine We agree to conduct this trial as a post-approval commitment This study could be designed to address the risk / benefits of trimethobenzamide 300 mg Also, as noted in Bertek's response to the FDA's Biopharmaceutics Comment #3, Bertek commits to the conduct of a pharmacokinetic study addressing the differential effects of a 250 mg three times a day (TID) versus 300 mg TID dosing regimens of trimethobenzamide on the pharmacokinetics of apomorphine This pharmacokinetic study will further describe the differences, if any, of the 50 mg of trimethobenzamide

Finally, Bertek's investigations indicate that trimethobenzamide 250 mg continues to be marketed in the United States While the Agency noted in the December 24, 2002 Federal Register (Vol 67, No 247) that the 250 mg product was no longer considered a DESI drug, a petition has been filed on January 23, 2003 to Docket 96N-0227 challenging this decision A trimethobenzamide 250 mg product has remained on the market since that time without the Agency taking regulatory action against that product Therefore, at this time, a 250 mg is still available

Reviewer's Comments, Discussion, and Conclusions

- The sponsor noted that it had not observed any new adverse events associated with this change of a few patients from the tid administration of Tigan 250 mg to the 300 mg formulation Neither was there a change in the frequency of serious adverse events or deaths since the change in Tigan **However, Bertek correctly acknowledged that an analysis was not possible because of the limited data available** Whereas, as few as 27 patients had received the Tigan 300 mg formulation, only 7 of these 27 patients had data after 300 mg was started Three of these patients were started on 300 mg Tigan without prior exposure to 250 mg Tigan and 4 of these patients had data available on 250 mg (prior to the transfer to 300 mg) and after the transfer I agree that such minimal data are not worthy of analysis and the question remains unanswered about whether the use of the 300 mg Tigan formulation is associated with any greater risk than that which occurred when patients used the 250 mg dose formulation

- Bertek had proposed to analyze the APO401 data to compare the incidence of adverse events and changes in the dose of APM that occurred prior to and after the change to 300 mg Tigan following approval The proposed analysis would evaluate the effects of the change in dose on efficacy (changes in dose) and safety (changes in adverse event frequencies) I suspected that the amount of data that would be available for in the near future would be quite limited and the sponsor confirmed my impression during a teleconference in which I made my inquiry about the amount of new safety data available regarding the use of the 300 mg Tigan formulation

  The sponsor commented that it could potentially address the risks/benefits of the 300 mg Tigan dose in the randomized placebo-controlled trial (to investigate the actual necessity for the use of Tigan to decrease nausea and vomiting in patients, who initiate and continue treatment with APM) to which it had agreed I agree that this is a reasonably good way to address the concern under discussion in addition to comparing the frequency of adverse events associated with the use of the 300 mg Tigan (vs 250 mg) when a considerable experience has been collected with this new, 300 mg formulation I do not consider the safety experience to be collected in the planned pharmacokinetic study of the different dose/formulations (250 vs 300 mg) to be likely to yield any insight into the question of whether the new formulation is associated with any new or increased safety risk because the extent of concomitant exposure to each formulation and APM will be minimal

- I am also aware, as the sponsor has indicated, that the use of 250 mg trimethobenzamide formulation (a generic one) may be continuing in the U S , but if so, I believe that this would be illegal I am not aware that the Agency has taken a regulatory action to prevent the continued marketing of the 250 mg formulation against any generic companies marketing 250 mg trimethobenzamide Thus, if APM were approved and became available in the near future, it is possible that patients might have the option of using an illegally marketed 250 mg or the approved proprietary 300 mg formulation of trimethobenzamide (i e Tigan) TID I am not aware that a 300 mg trimethobenzamide has received approval as a generic product formulation

- I am not aware of any rationale why the 300 mg Tigan formulation ought to affect the efficacy or safety profile of APM from a pharmacokinetic perspective or interaction The oral Tigan 300 mg formulation was developed because Tigan is a DESI drug and the 250 mg oral formulation was not considered to be effective Consequently, the proprietary sponsor of Tigan recently obtained an approval of the oral 300 mg Tigan formulation based upon bioequivalence to the approved IM formulation of Tigan Although the 300 mg oral formulation of Tigan can be associated with some CNS adverse events as can APM use, it is unknown whether the concomitant use of the 300 mg formulation of Tigan is associated with a different safety profile than the one characterized in the NDA and based upon the concomitant use of 250 mg Tigan with APM

I conclude that

1) **it remains unknown whether the 300 mg formulation of Tigan is associated with a different efficacy or safety profile than the profiles characterized during the concomitant use of the 250 mg formulation of Tigan because data are not available for analysis of this issue,**

2) **answers regarding safety questions can be derived from future analyses of safety experience resulting from a planned, randomized, double-blind, placebo-controlled study assessing the need to use 300 mg Tigan tid and future analyses from ongoing open-label APO401 study in which patients are being switched to the 300 mg Tigan,**

3) **insight as to whether the 300 mg Tigan formulation might alter the efficacy of APM might be obtained from the planned pharmacokinetic study addressing whether the 300 mg Tigan affects the APM pharmacokinetic profile differently than the 250 mg Tigan,**

6 Clinical Comment 6

FDA Comment 6

After approval, you should conduct a randomized, parallel group, placebo-controlled trial to investigate the actual necessity for the use of concomitant Tigan to decrease nausea and vomiting in patients who initiate and continue treatment with apomorphine While we are describing the concomitant use of Tigan in our version of labeling, we believe that more definitive evidence of the benefit of Tigan should be accrued

Bertek Response

Bertek commits to the post approval conduct of a randomized placebo-controlled trial to investigate the actual necessity for the use of concomitant trimethobenzamide to decrease nausea and vomiting in patients, who initiate and continue treatment with apomorphine

Reviewer's Comments, Discussion, and Conclusions

The sponsor has provided a reasonable response to DNDP's post-approval requirement to conduct a randomized, parallel group, placebo-controlled trial to investigate the actual necessity for the use of concomitant Tigan to decrease nausea and vomiting in patients who initiate and continue treatment with APM Although the sponsor has not provided any specific proposal for this study, I do not think that it is necessary at this point that a protocol or synopsis of protocol be submitted for review or agreed upon at this time I believe that the important issue is to obtain the sponsor's commitment to conduct such a study and to make it a post-approval commitment

I conclude that the sponsor's response to commit to a randomized, parallel group, placebo-controlled trial to investigate the actual necessity for the use of concomitant Tigan to decrease nausea and vomiting in patients who initiate and continue treatment with APM after APM approval is reasonable and adequate at this time

7 Clinical Comment 7

FDA Comment 7

Please address the capability of the intended patient population to self-administer apomorphine by subcutaneous injection We recognize that patients have been supplied with ampules/syringes in your studies to date, but we are interested in knowing whether self-administration or administration by a caregiver was usual Please address the capability of patients with advanced Parkinson's disease to use the dosing pen

Bertek Response

The clinical development program submitted in support of the NDA clearly documents that advanced Parkinson's disease patients and their caregivers are capable of administering subcutaneous apomorphine In the development program, 33% of patients self administered subcutaneous apomorphine all or most of the time An additional 29% of patients self-administered subcutaneous apomorphine at least some of the time Thirty-seven percent of patients received their subcutaneous apomorphine injections via a caregiver all or most of the time This indicates that 62% of the patients self-administered apomorphine at least some of the time

During our Pre-NDA Meeting with the Division of Neuropharmacologic Drug Products on January 10, 2002, Bertek indicated that it planned to market both pens and ampules The

minutes from that meeting are provided in Attachment 37 1 Bertek indicated that we would evaluate and compare the ease and accuracy of using the pen It was Bertek's understanding following this meeting that a clinical trial with the pen would not be required for approval

There are three studies which address capabilities of patients with Parkinson's disease to use the pen system

1 Cartridge/Pen versus Ampule/Syringe Comparison Protocol
2 Pharmacokinetics Study
3 Patient Survey

Cartridge/Pen versus Ampule/Syringe Comparison Study In this study, which was provided in the NDA beginning on page 4-2-254, Volume 2 of the June 14, 2002 submission, participants dispensed repeatedly from cartridges using manual injector pens (pen system) to determine the delivery volumes (mean and relative standard deviation) of the cartridge/pen configuration Similar volumes were dispensed repeatedly from ampules using syringes to determine the mean delivery volume and relative standard deviation of the ampule/syringe configuration For the convenience of the reviewer, a copy of this study report is provided in Attachment 37 2

Two separate groups of five individuals participated in the study of dose dispensing accuracy and repeatability Group A was comprised of laboratory analysts and Group B was comprised of lay persons Each group received written and verbal instructions on the correct steps for operation of the manual injector pen

The results of the Cartridge/Pen versus Ampule/Syringe Comparison study for Groups A and B meet the pre-established acceptance criteria In general, the pen demonstrated superior standard deviations at the lowest dispensed volume At the middle and higher volumes the relative standard deviations were equivalent Based upon these results, Bertek found that the pen and syringe are equally usable by both laboratory analysts and lay persons as demonstrated by the similarity of means, relative standard deviations and comparison values

Pharmacokinetics Study A phase I, open-label, three-way crossover study in healthy volunteers was conducted to compare the pharmacokinetics of apomorphine HCl formulated with benzyl alcohol (BA) versus apomorphine HCl formulated without benzyl alcohol and to compare the pharmacokinetics of apomorphine HCl delivery from a cartridge using a pen device to that from a syringe manually-filled from an ampule or cartridge The study, APOM-02115, was submitted as an amendment to the NDA on April 29, 2003 A synopsis of this study is provided in Attachment 37 3 for the convenience of the reviewer

The objectives of this study were to investigate the following effects, as they relate to the pharmacokinetics of apomorphine, following a single subcutaneous administration of apomorphine HCl injection 2 mg (0 2 mL x 10 mg/mL) in healthy volunteers

i) The overall effect of the apomorphine delivery device plus that of 0 5% (w/v) that benzyl alcohol (Reviewer's note the sponsor in this submission and previous submissions had erroneously specified benzyl alcohol as — % instead of 0 5 %, the correct concentration) in the cartridge formulation (pen/cartridge vs syringe/ampule)

ii) Potential effects of the apomorphine delivery device (pen/cartridge vs syringe/cartridge)
iii) Possible effects of benzyl alcohol (0 5% w/v) used in the cartridge formulation (syringe/cartridge vs syringe/ampule)

Pharmacokinetic parameters were derived from plasma apomorphine concentration-time curves for each formulation/delivery device in thirty-four (34) healthy, non-smoking, male and female subjects To decrease the likelihood of nausea and vomiting associated with apomorphine, all volunteers received 250 mg (1 x 250 mg capsule) of the anti-emetic drug trimethobenzamide three to four times a day starting three days prior to dosing, once on the morning prior to apomorphine administration, and continuing until six (6) hours after apomorphine HCl dose administration for each dosing phase

Apomorphine with BA was administered (1 x 2 mg, Treatment A) using a pen/cartridge injection device as a single subcutaneous injection into the subjects abdominal wall Apomorphine with BA (1 x 2 mg, Treatment B) was injected using a syringe filled from a cartridge Apomorphine without BA (1 x 2 mg, Treatment C) was injected using a syringe filled from an ampule Apomorphine treatments (A, B, or C) were separated by seven (7) days Serial blood samples, 10 mL (1 x 10 mL), were collected prior to dosing (0 hr) and at 10, 20, 30, 40 and 50 minutes, and 1, 1 5, 2, 2 5, 3 and 4 hours after dose administration

Mean apomorphine CPEAK, AUCL, AUCI and Cl/F values for the cartridge formulation (Treatment A) were estimated at 5 5 ng/mL, 5 3 (ng•hr)/mL, 6 2 (ng•hr)/mL and 344 L/hr respectively These values were comparable to the mean values for CPEAK, AUCL, AUCI and Cl/F estimated for subjects receiving an injection of the apomorphine HCl cartridge formulation via syringe (Treatment B, 6 1 ng/mL, 6 1 (ng•hr)/mL, 7 1 (ng•hr)/mL and 298 L/hr, respectively) and for subjects administered an injection of apomorphine HCl ampule formulation (Treatment C, 5 5 ng/mL, 5 8 (ng•hr)/mL, 6 7 (ng•hr)/mL and 307 L/hr, respectively) Based upon estimates of systemic exposure (CPEAK, AUCL and AUCI), the intersubject variability of apomorphine delivery was comparable for Treatment A (pen/cartridge, 30% or less) and Treatment C (syringe/ampule, 27% or less)

The results of this study demonstrate the following for a single 2-mg subcutaneous injection of apomorphine

- The rate and amount of apomorphine delivered by the pen/cartridge system was equivalent to that delivered by the syringe/ampule
- BA had no effect on the rate and amount of apomorphine delivery by either the pen/cartridge system or syringe/ampule
- BA did not increase the incidence of adverse events In particular, the incidence in injection site reactions was similar among all three products tested

Patient Survey Bertek conducted a patient survey entitled "*Apomorphine Hydrochloride Patient and Caregiver Research — An Expanded Study*" in patients with advanced Parkinson's disease (PD) The Survey results are provided in Attachment 37 4 In-person interviews were conducted

with patients who had participated in the apomorphine development program and patients that had not previously used subcutaneous apomorphine In addition to the interview process, patients were shown a video-tape of the apomorphine delivery systems The patients were given the opportunity to use the pen system Specifically, they were permitted to load the cartridge, attach the needle, purge the system, dial in a set amount and inject the contents into a tissue In-person one-hour interviews were conducted with Parkinson's disease patients from six sites Sixty-three patients had no previous experience with apomorphine or the delivery systems The remaining 14 patients had participated in the apomorphine development program and had experience with apomorphine and the ampule/syringe delivery system The majority (13/14) of the apomorphine experienced patients indicated that they preferred the pen delivery system over the syringe delivery system citing ease of use, convenience, and more discreet as reasons for the preference

In summary, Bertek has demonstrated that patients and caregivers have administered subcutaneous apomorphine during the clinical studies by breaking open an ampule, withdrawing a dose from the ampule via a syringe and subsequently injecting the dose subcutaneously Furthermore, Bertek has demonstrated that the cartridge formulation delivered using a pen device (pen system) was bioequivalent to the ampule formulation delivered using a manually-filled syringe (syringe system), the pen system and the syringe system are equally usable by caregivers, and that patients indicated that they preferred the pen system over the syringe system

Reviewer's Comments, Discussion, and Conclusions

- Bertek noted that it indicated at the preNDA meeting its plan to market both pens and ampoules, that it planned to evaluate the ease and accuracy of using the pen, and that it was its understanding that a clinical trial with the pen would not be required However, based upon these meeting minutes, I cannot find any mention that there would be the potentially complicating safety issue that the pen would contain 0 5 % benzyl alcohol, an ingredient not found in the ampoule formulation of APM Furthermore, the meeting minutes specify that "Mylan will evaluate and compare the ease and accuracy of using the pen in patient caretakers, technicians, and patients " I interpret this sentence to mean that patients would receive treatment with the pen by self administration and by caretaker administration I did not interpret this to mean that there would be no safety experience derived from actual use of the pen formulation in patients **The sponsor has not presented any data regarding the safe use of the pen in patients based upon actual administration of the pen formulation of APM to patients** I have been told during a teleconference that some patients are receiving APM treatment with the pen but there is no safety experience that has been accumulated, analyzed, and submitted for our review

- **I strongly believe that it is important to assess the safe use of the pen formulation of APM in patients based upon actual treatment of patients by patients and caregivers using the pen** Considering the toxic potential of overdosing with APM, I believe that it is critical to show that both patients and caregivers can actually accurately administer APM with the pen safely There is also the potential concern about increased adverse event skin

reactions because of the potential irritating effects of the 0 5 % benzyl alcohol that has been added as a preservative This issue is discussed in greater detail in # 8 Comment and Response **However, even if one considers the 0 5 % benzyl alcohol by itself to be tolerable, how can one know or predict that injection of APM with 0 5 % benzyl alcohol will not significantly increase the risk of adverse events in the skin at the injection site?** The most recent Safety Update reports that all types of injection site adverse events were very common occurring with a incidence of 26 % and this incidence does not illustrate the frequency of repeat reactions in the same patients More specifically, the most common of these various local injection site adverse reactions include injection site bruising (16 %), injection site granuloma (4 %), injection site pruritis (2%), and injection site reaction NOS (2 %)

- Based upon the sponsor's response, it appears that a minority of patients (33 %) self-administered APM injection The most common administration (37 %) of APM occurred by a caregiver Although Bertek noted that 29 % of patients self-administered APM at least some of the time, it is not possible to assess how frequently this occurred

- The sponsor commented that 3 studies address the capabilities of patients with Parkinson's disease to use the pen system The first study was a protocol comparing the ability of 2 groups of individuals (i e 5 laboratory analysts and 5 lay persons) to dispense a volume accurately and repeatedly using the pen and syringes The results outlined by the sponsor earlier suggested that the pen can be used similarly by these individuals Although the number of individuals studied was relatively small, this study does not address the accurate dispensing of volumes from the pen and administration of APM to patients using the pen

  The second study was a biopharmaceutical study studying pharmacokinetic (PK) parameters in healthy subjects of the pen and ampoule formulations of APM This crossover study involved 34 healthy volunteers (relatively young , 19-55 yo) who received a single injection (into the abdominal wall) of 2 mg APM from the pen, 2 mg from a syringe filled from an ampoule, and 2 mg from a syringe filled from the pen There were no remarkable injection site adverse events from the pen use relative to the ampoule formulation These data represent the only safety experience submitted using the pen **However, it is important to note that the APM dose was very low (2 mg) and the administration was given by a health care provider Thus, this experience does not address accuracy of pen use by patients or caregivers nor potential local injection site reactions from higher doses (e g up to 6 mg based upon a reasonable safety experience presented in the NDA, and > 6 mg up to potentially 10 mg if the whole pen volume was accidentally administered)**

  A survey was conducted in a total of 77 Parkinson's disease patients Some (N = 14) had received APM in the clinical development program and others (N = 63) had not Patients were shown a videotape, given the opportunity to "use" the pen system (e g loading the cartridge, attaching the needle, purging the system, dialing a set volume, and injecting the contents into "tissue" but not into themselves) Of the 63 patients, who had not previously

received APM and initially enrolled in this survey study, 42 patients indicated that that would be willing to try APM with the pen, and 4 would not try it I did not find any mention of why there were only 46 responses when 77 patients had enrolled Of the 14 patients, who had previously received APM and initially enrolled in this survey study, 13 patients indicated that that would be willing to try APM with the pen, and 1 would not try it **I find these survey results not to be very relevant to the important question at hand How easily and safely can APM with the pen be administered to patients by patients and caregivers based upon actual APM administration of the pen to patients not theoretical administration?**

I conclude that

1) **there are significant concerns that patients with Parkinson's Disease can safely administer APM with the pen delivery system without possibly sustaining needle injuries from recapping the needle, and without possibly overdosing themselves (because this pen device does inform the patient if the cartridge has sufficient volume of APM for a single injection) due to the occasional necessity of administering the desired APM treatment as 2 injections,**

2) **demonstration of the safety of using the APM pen should be based upon the presentation of analyses showing the experience of the pen based upon actual use in patients involving administration both by patients and caregiver and should not be based upon less compelling, indirect or theoretical information,**

3) **a safety experience with the pen can be collected in patients, analyzed in comparison with the safety profile of the ampoule formulation, and these data and analyses can be submitted to support an approval of the pen formulation**

8 Clinical Comment 8

FDA Comment 8

Please justify the use of the benzyl alcohol formulation, you have presented no data about the safety of this formulation other than single 2 mg doses in normal volunteers

Bertek Response

Justification Apomorphine cartridges are designed to be used for multiple injections with an injector pen supplied by Becton Dickinson As described by USP <1> Injections and USP <51> Antimicrobial Preservatives-Effectiveness, benzyl alcohol 0 5% has been added to the

apomorphine cartridges as a preservative to prevent the growth of microorganisms that may be introduced from multiple injections

Evidence to Support Safety Benzyl alcohol and its metabolite, benzoic acid, are approved for use as a food additive, with daily intake levels of up to 5 mg/kg regarded as acceptable Topical applications containing 5% benzyl alcohol (10% for hair dyes) are regarded as safe for use in cosmetic formulations Benzyl alcohol is also widely used in pharmaceutical products as an antimicrobial preservative and as a local anesthetic and antipruritic Concentrations of up to 2 2% can be found in many parenteral products

In humans and animals, benzyl alcohol is readily absorbed after ingestion or topical application Benzyl alcohol rapidly disappears from the injection site following intramuscular injection in rats Following oral or subcutaneous administration to humans and animals, benzyl alcohol was rapidly oxidized to benzoic acid which was conjugated with glycine and excreted as hippuric acid in the urine Doses of benzyl alcohol considered safe for adults was reported to be 4 5 mg/kg

In the Bertek apomorphine clinical development, patients on average administered apomorphine 3 times daily, with few patients receiving more than 5 injections per day or more than 20 mg Relating daily dose to the amount of benzyl alcohol injected subcutaneously, most patients will receive less than 1 mg per injection and less than 3 mg per day Even if a patient administered the entire contents of the cartridge in one injection, the amount of benzyl alcohol received would be 50-70 times less than the adult dose generally regarded as safe Systemic toxicity from benzyl alcohol contained in apomorphine injections is therefore not expected A more detailed justification of the safety of benzyl alcohol is provided in Attachment 38

In the Bertek apomorphine clinical development, the average age of the 550 participants was 65 years (range 38-86 years) The initial outpatient therapeutic dose for the 525 patients treated in an outpatient setting was 2 mg or less in 43 4%, greater than 2 mg up to and including 4 mg in 35%, and over 4 mg up to 6 mg in 15 2% Relatively few patients (6 3%) began with doses greater than 6 mg There were no apparent differences in the distribution of initial outpatient prescribed dose by age or gender In 262 patients treated for 12 months or more, the average apomorphine dose used to treat episodic "Off' episodes increased by less than 1 mg On average, patients in the Bertek clinical development program administered apomorphine 3 times daily,' with few patients receiving more than 5 injections per day or more than 20 mg

Relating daily dose to the amount of benzyl alcohol injected subcutaneously, most patients will receive less than 1 mg per injection and less than 3 mg per day Even if a patient administered the entire contents of the cartridge in one injection (30 mg apomorphine, 4 5 mg benzyl alcohol), the amount of benzyl alcohol received would be 50-70 times less than the adult dose generally regarded as safe Systemic toxicity from benzyl alcohol contained in apomorphine injections is therefore not expected

Benzyl alcohol has, however, produced dermal irritation (but not sensitization, phototoxicity or photosensitivity) in patch studies Thus, it is possible that some patients may experience dermal

reactions to subcutaneous apomorphine administration In clinical trials using a benzyl alcohol-free product, 26% of 550 patients experienced application site reactions associated with apomorphine injections, further described as abscesses, anesthesia and bruising

One Bertek crossover study compared the response to apomorphine with and without benzyl alcohol following a single 2-mg subcutaneous injection in 36 healthy volunteers The only dermal reaction noted was mild pruritus in one subject following apomorphine with benzyl alcohol that resolved with application of a hot pack

In conclusion, 0 5% benzyl alcohol contained in apomorphine cartridges is not expected to produce systemic toxicity in Parkinson's disease patients Application site reactions associated with apomorphine administration can be expected in 25-30% of patients using a benzyl alcohol-free product In the clinical development program the patient (or caregiver) was instructed to massage the injection site after administration This will likely lessen the dermal exposure time to both chemicals In addition, Bertek will monitor the incidence of application site reactions for both the ampule (benzyl alcohol-free) and cartridge

Reviewer's Comments, Discussion, and Conclusions

- In its justification for the safety of administering benzyl alcohol (the most commonly used antimicrobial preservatives in parenteral products), the sponsor has reasonably made a case for the safety of benzyl alcohol relative to systemic toxicity However, this was not as much of a concern to the DNDP as potentially the local toxicity Considering that that local injection site adverse reactions were very common (occurring in ~ 30 % of patients) with the subcutaneous injection of the APM formulation without benzyl alcohol, t he DNDP is particularly concerned with the potential toxicity of an APM formulation also containing benzyl alcohol Conceivably, the addition of benzyl alcohol could increase the frequency and /or severity of local injection site adverse events by its own toxicity or by toxicity of benzyl alcohol interacting locally with APM **Without a safety experience of using the APM formulation containing benzyl alcohol, it is difficult to know whether the toxicity would be worse than the already significant local toxicity already observed with an APM formulation that did not contain any benzyl alcohol**

- The sponsor referred to 4 publications supposedly supporting the safety of benzyl alcohol administration to animals and humans and provided these publications after my request In general, these references mainly seemed to focus on systemic toxicity of benzyl alcohol Thus, I do not find much relevance of these publications to the question of local toxicity of benzyl alcohol administered subcutaneously to humans One reference specifically did note that "In humans, several cases of hypersensitivity reactions, especially to cosmetic products containing benzyl alcohol , have been reported " The publications referenced by the sponsor were submitted after my request ,but these publications do not specifically address the toxicity of BA administered subcutaneously to humans and animals to any significant degree

- The sponsor commented that benzyl alcohol rapidly disappears from injection site of rats after intramuscular injection However, I do not necessarily know how applicable that phenomenon might be to benzyl alcohol administered subcutaneously in rats and particularly in humans Besides the possibility of differential species sensitivity to benzyl alcohol administered subcutaneously, there is also the possibility of different tissue sensitivity (e g subcutaneous tissue vs muscle) of toxicity

- The sponsor had noted that most patients would receive < 1 mg of benzyl alcohol per injection of BA and < 3 mg per day I disagree with this projection because each 1 mg of APM contains 0 5 mg benzyl alcohol and the average APM dose was 4 mg and the average frequency of injection was 3 times daily total Based upon these figures, the average amount of benzyl alcohol administered would be 2 mg /injection and 6 mg/d Although the bulk of APM use for > 4 mg /injection ranged up to 6 mg, nearly 40 % of patients received APM injections > 4 mg and up to 10 mg, and approximately 13 % received APM injections > 6 mg In addition, approximately 25 % of patients used APM with a frequency from 5 - 11 times daily Consequently, some patients could receive as much as 5 mg benzyl alcohol if the whole 1 0 ml was dispensed from a pen However, the label had been written by DNDP to precommend APM dosing up to 6 mg and to note that there is little experience with APM injections > 6 mg

- In referring to benzyl alcohol , the sponsor noted that " Concentrations of up to 2 2% can be found in many parenteral products " The submission had noted that 3 products (ardeparin = Normiflo® , methylprednisolone = Depo-Medrol®, recombinant human growth hormone = Norditropin®) contain ≥ 0 5 % benzyl alcohol However, I cannot find ardeparin in the Physician's Desk Reference (PDR), recombinant human growth hormone (Norditropin®) does not contain benzyl alcohol according to the PDR, and methylprednisolone (Depo-Medrol®) is not a good example to show the absence of local toxicity because the primary pharmacological effect of methylprednisolone is anti-inflammatory and this action could minimize or mask any potential local toxicity from benzyl alcohol

  I had asked the sponsor to what U S products approved for subcutaneous administration was it referring? The sponsor said that it would provide examples of such products and they are shown in Table 34 The concentrations of benzyl alcohol and amount of benzyl alcohol injected subcutaneously in some these products are similar to or greater than benzyl alcohol concentration or amount to be injected with APM Adverse event data of several of these products show injection site reactions more frequently than placebo when studies have been conducted with placebo I believe that it is reasonable to say that there may not be a great risk of administering benzyl alcohol with APM when one considers that benzyl alcohol is commonly administered subcutaneously in approved U S products However, I cannot say whether the common injection site adverse events that were observed when APM was administered without benzyl alcohol would not be observed more frequently nor that more severe local injection site toxicity would not be observed when APM containing benzyl alcohol is administered to patients, especially at the highest doses Not only might benzyl

Table 34 List of Some U.S FDA Approved Products in PDR Containing Benzyl Alcohol (BA) for Subcutaneous Injection

PRODUCT	BA CONTENT	ROUTE
Bacteriostatic water for injection		
Sodium Chloride for injection		
AquaMephyton	0 9%	SC, IV, IM
Enbrel	0 9% BWFI diluent	SC
Epogen	1%	SC, IV
Fragmin	1 4%	SC
Gonal F	0 9% BWFI diluent	SC
Intron A	0 9% BWFI diluent	SC, IV, IM
Leukine	1 1%	SC, IV infusion
Lupron	0 9%	SC
Lovenox	1 5%	SC
Nutropin	0 9% BWFI diluent	SC
Pegasys	1%	SC
Procrit	1%	SC, IV
Roferon A	1%	SC, IM
Saizen	0 9% BWFI diluent	SC, IM

alcohol increase toxicity from injection site reactions by itself, but benzyl alcohol could potentially produce more local toxicity via unknown interactions with APM This concern supports a desire to characterize the safety profile of APM containing benzyl alcohol based upon actual administration of this formulation to patients and collection of the safety experience for comparison with the safety experience of APM without benzyl alcohol

- The sponsor also commented that the patient (or caregiver) had been instructed in the clinical development program to massage the injection site after administration and that this maneuver will likely lessen the dermal exposure time to both chemicals? However, I do not have any idea whether this maneuver will necessarily result in less local injection site toxicity I think that this statement is made upon the basis of speculation because it seems logical

I conclude that

1) there are no actual data that support the safe use of the APM pen formulation containing 0 5 % benzyl alcohol because the sponsor has not presented any use data from patients treated with the benzyl alcohol formulation but has only presented only the minimal experience of single injections of low dose (2 mg with 0 5 % benzyl alcohol) APM given to healthy volunteers,

2) the sponsor has not adequately justified the safe us of the APM formulation containing 0 5 % benzyl alcohol, particularly with respect to DNDP's concern about increased local toxicity at the injection site,

3) actual pen use data of APM containing 0 5 % benzyl alcohol (derived from patients who self -administer APM and who receive it from a caregivers) should be submitted for DNDP review to support the safe use of the APM pen,

4. SAFETY UPDATE 2 (SU2)

Introduction

The sponsor noted in its cover letter that it addressed all of DNDP requests and recommendations for the Safety Update in 8 volumes (#4 – 11)

The current Safety Update (Safety Update 02 – SU2) extends the safety experience based upon CRF data updated through 12/31/02 and compares incidence and frequency of adverse events (AEs) to information presented for SU1 (i e , through 05/31/02) SU2 focuses on serious adverse events (SAEs) from the only ongoing study – APO401 (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) APO401 is an ongoing open-label study, with scheduled visits at month 1, month 4, and 4-month intervals thereafter, through which most of the safety information for apomorphine has been generated, there is no controlled experience with APM contained in SU2 Additional SAEs (including deaths) obtained after the data lock point (12/31/02) through 06/30/03 were presented as narratives Table 35 presents information about cut-off dates for data contained in the ISS and SUs and Table 36 presents a summary of safety information contained in the ISS and SUs

Table 35 Summary of Data Cut-Off Dates for ISS and Safety Updates

	ISS	ISS Safety Update #1 (SU1)	ISS Safety Update #2 (SU2)
Received by FDA	9/17/02	1/2/03	10/20/03
CRF Data Clock Date*	12/31/01	5/31/02	12/31/02
SAE & Death Clock Date Cut-Off	3/31/02	5/31/02	6/30/03**

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

**SAE and Death information were provided as narratives and were not included in summary tabulations, Summary tabulations contain SAE and Death information up to 12/31/02

Table 36 Summary of Safety Information Contained in ISS and Safety Updates

Safety Parameter	ISS	Safety Update #1 (new patients and/or events)	Safety Update #2 (Response to Approvable Letter) (new patients and/or events) **(new information in this update as % of original ISS data)**	Cumulative Total as of Safety Update #2
# APM-Treated Patients	516	20	14 **(3 %)**	550
Deaths	10	4	13 **(130 %)**	27
SAEs # pts	81	22	21 "new" patients" (total 37 pts including "new" pts and "old" pts with previous SAE) **(26 %)**	124
SAEs # events	176	51	102 **(58 %)**	329
Discontinuations for TEAE # pts	100	20	20 **(20 %)**	140
Discontinuations for TEAE # events	193	45	40 **(21 %)**	278
TEAEs # pts	441	30	17 **(4 %)**	488
TEAEs # events	3413	916	839 **(25 %)**	5168
Patient-Years APM Exposure	306	113	116 **(28 %)**	535

New data contained in Safety Update #2 and presented in this table are underestimates of information submitted because tabulated data are based upon a cut-off date for CRFs of 12/31/02 However, death and SAE information were submitted as narratives based upon a 6/30/03 cut-off date and some SAE data appears to be from events occurring after 6/30/03