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# APPROVAL PACKAGE FOR:

# APPLICATION NUMBER

# 21-264

# Clinical Pharmacology and Biopharmaceutics Review

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW**

| | | | |
|---|---|---|---|
| **NDA** | 21-264 | **SUBMISSION DATES** | October 17, 2003 |
| **DRUG NAME** | Apokyn (Apomorphine hydrochloride) | | |
| **DOSAGE STRENGTH** | Injection 10 mg/mL | | |
| **SPONSOR** | BERTEK Pharmaceuticals Inc<br>Morgantown, WV25504 | | |
| **REVIEWER** | John Duan, Ph D | | |
| **TEAM LEADER** | Ramana Uppoor, Ph D | | |
| **TYPE OF SUBMISSION** | Response to Approvable Letter | | |

## I Executive Summary

Apomorphine is a potent, short-acting, dopamine agonist Its mechanism of action involves the stimulation of dopamine receptors in the corpus striatum, which leads to anti-parkinsonian activity In the NDA submitted on January 7, 2003, the sponsor was seeking approval for subcutaneous injection formulation of Apomorphine indicated for the rescue treatment of "off episodes" associated with Parkinson's disease The Agency issued an approvable letter on July 2, 2003 in which several issues regarding Clinical Pharmacology and Biopharmaceutics were raised including elimination route of apomorphine, protein binding and potential drug interactions The current submission provides the information regarding the elimination route of apomorphine based on a mass balance study on sublingual formulation of apomorphine (from posters of a professional meeting) and proposes to amend the original view in the NDA submission to reference the new information Primarily, the sponsor wishes to conduct the required mass balance study post-approval (not pre-approval as requested in the approvable letter) with subcutaneous apomorphine to confirm the new metabolic information from these meeting posters The sponsor will remove the current statements regarding protein binding from the labeling until a study is completed as a post approval commitment They do not think the drug interaction study between apomorphine and alcohol and between apomorphine and vasodilators are necessary and made several arguments in this regard In addition, the protocol synopses for mass balance and protein binding and for drug interaction between apomorphine and trimethobenzamide are provided The sponsor should take the previous available information especially the bioavailability difference between subcutaneous and sublingual formulation into consideration when designing and conducting the mass balance study An explanation should also be provided for the fact that the apparent clearance (280 L/h) is higher than hepatic blood flow With the safety concern regarding the possible significant adverse effects posed by pharmacodynamic interaction, the drug interaction studies between apomorphine and alcohol and between apomorphine and nitrates should be conducted

## COMMENTS TO THE MEDICAL OFFICER (NOT TO BE SENT TO THE SPONSOR)

1 In this submission, the view regarding the elimination of apomorphine is changed completely from previous submission (original NDA) This may not be appropriate considering the following facts

- It is noted that the bioavailability of apomorphine from sublingual tablets, relative to a subcutaneous injection was 16-18% [redacted] whereas that of subcutaneous formulation is almost 100% This is consistent with the literature collected in the original submission (where it was stated that a the bioavailability of sublingual apomorphine ranged from 10 to 22% of a parenteral apomorphine dose b there was a similarity in $C_{max}$ and AUC of a 3-mg SC dose versus 30-mg SL dose)

- The fact that the apparent clearance of 280 L/h is higher than hepatic blood flow has to be explained

- The so-called "state-of-the-art" technology is an LC-MS-MS, which can not overthrow all the previous work published in the literature, which provide certain valuable information

Therefore, when planning and conducting the study, these factors should be taken into consideration

2 The mass balance study should be conducted in a timely fashion and submitted for review The study should have extra subjects to enroll in order to replace for dropouts if necessary

3 Based on the finding [redacted] there is a significant dose related pharmacodynamic interaction between apomorphine and alcohol Coadministration [redacted] at 4 mg or higher doses and alcohol (at 0 3 g/kg and 0 6 g/kg) is associated with greater drop in systolic and diastolic blood pressure compared to either [redacted] alone or alcohol alone administration The incidences of related adverse events are also significantly higher when [redacted] coadministered with alcohol Although coadministration of 3 mg [redacted] (the maximum proposed dose) with 0 6g/kg alcohol did not result in significant changes in blood pressure compared to [redacted] alone or alcohol alone, the incidence of drug related adverse events including dizziness and nausea was higher with the combination group Coadministration of 6 mg [redacted] and the lower alcohol dose of 0 15 g/kg did not result in significant changes in blood pressure [redacted] discussed by the Urologic Subcommittee of the Reproductive Health Drugs Advisory Committee [redacted] AC members expressed serious concerns regarding the cardiovascular side effects of this drug and its pharmacodynamic interaction with alcohol [redacted] Therefore, a drug interaction study is necessary based on the following considerations, although the sponsor made several arguments in the response to oppose it

- The pharmacodynamic interaction between apomorphine and alcohol is dose dependent Considering the bioavailability difference between sublingual and subcutaneous administration (16% vs 100%), the subcutaneous formulation results in much higher amount bioavailable, which may increase the magnitude of the interaction
- One of the major safety concerns for apomorphine is cardiovascular side effects (hypotension) and the interaction with alcohol may increase the risk

4 Similarly, the drug interactions between apomorphine and nitrates from a pharmacodynamic point of view are of concern The Advisory Committee also recommended contraindication for nitrates use

5 There are controversy statements regarding the metabolic pathway of apomorphine On page 17 of the responses, the proposed chart indicated that the apomorphine sulfate has not been detected in monkeys However, on page 15 of the same document, it was stated that apomorphine sulfate was detected in the urine of cynomolgus monkey

6 This submission made several corrections regarding the number of the pharmacokinetic parameters, which are reasonable There are no further comments to the labeling on the Clinical Pharmacology and Biopharmaceutics related statements

## COMMENTS TO THE SPONSOR

1 The mass balance study should be conducted in a timely fashion and submitted for review The study should have extra subjects to enroll in order to replace for dropouts if necessary

2 Although a drug interaction is unlikely from pharmacokinetic point of view, the pharmacodynamic drug interactions between apomorphine and alcohol or nitrates may raise the safety concerns To address these concerns, the drug interaction studies should be conducted

3 Please check the proposed metabolic pathway of apomorphine On page 17 of the responses, the proposed chart indicated that the apomorphine sulfate has not been detected in monkeys However, on page 15 of the same document, it was stated that apomorphine sulfate was detected in the urine of cynomolgus monkey

## RECOMMENDATIONS

Although we are not completely convinced about the dramatically changed views of the metabolic pathway, in line with the agreement reached between the Division and the sponsor, the sponsor can conduct the mass balance study post approval provided the relevant comments are taken into consideration in the studies to be conducted Please convey the comments to the sponsor as appropriate

/S/

John Duan, Ph D
Reviewer
Division of Pharmaceutical Evaluation I

Date

/S/

Ramana Uppoor, Ph D
Team Leader
Division of Pharmaceutical Evaluation I

Date

cc Orig 21,264
HFD-120 Division File
HFD-860 MMehta, CSahajwalla, RUppoor, JDuan
CDR

## II The comments made by the Agency and the responses from the sponsor

The sponsor's responses to the Clinical Pharmacology and Biopharmaceutics comments in the Approvable Letter dated July 2, 2003 are presented in the Appendix

## III The Issues Identified by Previous Review

The review for the original NDA identified several issues related to Clinical Pharmacology and Biopharmaceutics that are listed below

1 The elimination route of apomorphine

In the original NDA, the statements regarding the elimination of apomorphine are based on the literature After IV infusion, total renal excretion of apomorphine, apomorphine sulfate, and apomorphine glucuronide in humans were 0 3 ± 0 4%, 3 8 ± 1 0% and 6 0 ± 2 2% of an administered dose, respectively The sponsor concluded in original NDA submission that renal elimination of unchanged or conjugated R-apomorphine is not a major route of elimination for apomorphine in humans On the other hand, based on an in vitro study reported in the literature (Van der Geest R et al 1998), autooxidation could account for 30% of apomorphine clearance Using the same logic, the sponsor speculated that autooxidation could account for 30-70% of apomorphine clearance The previous review raised several concerns regarding these issues

- Evidence of autooxidation has not been shown in vivo and the assumption of autooxidation occurring in all tissues has not been validated
- The autooxidation could not account for the most apomorphine eliminated
- The major elimination route of apomorphine after subcutaneous (SC) administration is not defined
- There are controversies regarding pharmacokinetic behaviors of apomorphine

  The controversies are summarized in the following table



| Aspects | Sublingual | Subcutaneous |
|---|---|---|
| Major route | Sulfate | Auto oxidation through in |

| | | vitro study |
|---|---|---|
| Sulfate | 59% of dose | 3 8 ± 1 0% |
| Hepatic impairment | The point estimates for mild, moderate and severe impairment classes were respectively 36%, 16%, and 62% higher for $C_{max}$, and 59%, 35%, and 68% higher for $AUC_{\infty}$ | $C_{max}$ 25% higher, AUC 9% higher in moderate impairment subject |
| Renal impairment | There was no significant change in mean $C_{max}$ The mean $AUC_{\infty}$ was significantly increased in subjects with moderate (52%) and severe (67%) renal impairment | $C_{max}$ 50% higher, AUC 27% higher in moderate impairment subject |

2 Protein binding

In original NDA submission, the statements in the proposed labeling regarding protein binding were not based on the results of study using clinically relevant concentrations

3 Drug interactions

Drug interaction studies with alcohol, vasodilators and antiemetic Tigan are recommended

**IV Summary of the Responses from the Sponsor**

The sponsor submitted the data about metabolism studies from ABC Laboratories that are publicly available (http //www abcPharmaservices com/dd/idd_Posters htm) These include both human and animal data

The results of animal studies conducted by ABC Laboratories indicated that approximately 73% (male) and 54% (female) of the dose was eliminated via urine in rats, while approximately 17% in males and 21% in females was eliminated via the feces In addition, 4 and 5 % of the dose was detected in the cage wash for males and females, respectively Utilizing an LC-MS/MS assay, the following metabolites in urine were identified apomorphine glucuronide, apomorphine sulfate, norapomorphine, norapomorphine glucuronide, norapomorphine sulfate, and isoapocodeine In plasma, apomorphine sulfate, apomorphine glucuronide, norapomorphine sulfate, and norapomorphine glucuronide were detected In feces, apomorphine glucuronide, apomorphine sulfate, norapomorphine, norapomorphine sulfate, and norapomorphine glucuronide were observed In bile the identified metabolites were apomorphine glucuronide, apomorphine sulfate, norapomorphine sulfate, isoapocodeine, and apocodeine glucuronide

In addition, the enterohepatic recirculation was possible It was evidenced by infusing bile collected from one set of rats subcutaneously injected with apomorphine into the duodenum of

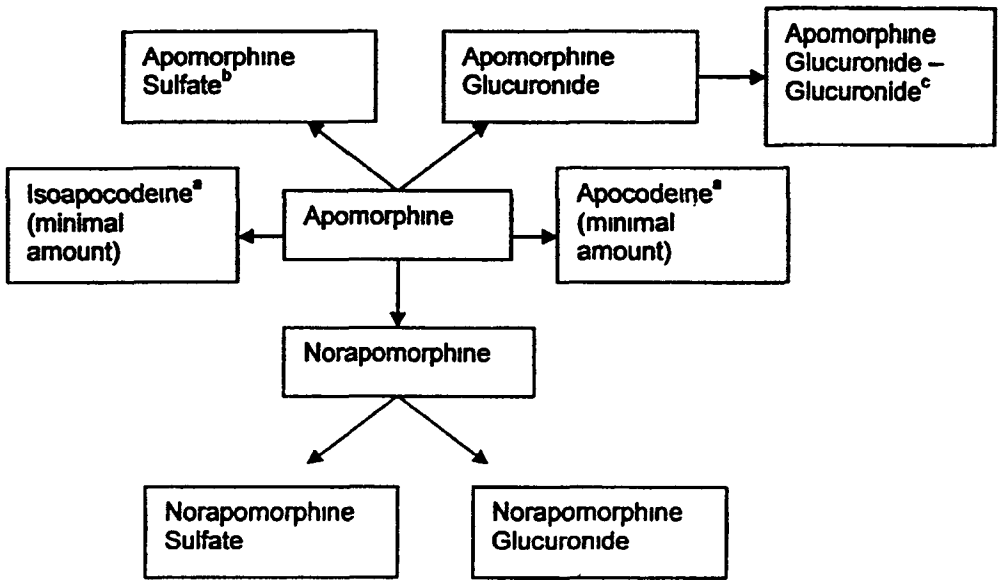
another set of rats and performing mass balance on bile, urine, and fecal samples collected The bile infused into the duodenum of the rats was absorbed with approximately 70% of that dose being detected in the urine and bile of those rats in 24-hours

The disposition of apomorphine in dogs, however, was contrary to that observed in the rat model Approximately 27% in males and 20% in females of the dose was eliminated via the urine Roughly 56% (in males) and 46% (in females) of the dose was excreted in the feces, while 7% and 11% of the dose was detected during cage washing for males and females, respectively In the plasma, urine, and bile the following metabolites were identified apomorphine sulfate, apomorphine glucuronide, and apomorphine glucuronide-glucuronide

A subcutaneously administered $^{14}$C-apomorphine cynomolgus monkey study was submitted in the original NDA In this study, the average results indicated that approximately 59% (range 48-74%) of the dose was eliminated via the urine, roughly 8% (range 7-10%) was eliminated via the feces, and approximately 25% (range 14-32%) was detected in the cage wash Utilizing an HPLC method, the following compounds were detected in the urine apomorphine, norapomorphine, apomorphine glucuronides, apomorphine sulfates, norapomorphine glucuronides, and norapomorphine sulfates In feces, approximately 50% was associated with apomorphine, another 10% was norapomorphine, and the remainder was associated with two peaks with a retention time of less than 10 minutes The plasma sample collected thirty minutes after the administration of apomorphine had approximately 35% apomorphine and 12% norapomorphine present based upon HPLC analysis Glucuronides were also present in the plasma based upon changes in the activity levels associated with compounds with HPLC retention times less than 10 minutes following incubation of the plasma sample with β-glucuronidase However, due to low levels, the quantitation of the glucuronides was not possible

ABC Laboratories reported the mass balance profile and metabolite identification for an approximately 2 mg (1 94 mg with approximately 80μCi of $^{14}$C) sublingually administered dose of a $^{14}$C-apomorphine solution in six healthy adult males The study demonstrated that approximately 93% of the dose was eliminated via the urine, while only 16% was excreted in the feces indicating that nearly the entire dose was absorbed into the systemic circulation Eleven compounds eliminated via the urine were identified using LC-MS/MS This metabolic identification assay accounted for almost 92% of the administered dose (accounting for 98 5% of the total radioactivity eliminated via the urine) The identified compounds eliminated via the urine were (in rank order from highest to lowest) apomorphine sulfate (~59% of the dose), norapomorphine glucuronide (~14%), apomorphine glucuronide (~12%), norapomorphine (~3%), apomorphine (~2%), norapomorphine sulfate (~1%), apocodeine (0 2%), and isoapocodeine <0 2%) The following figure shows the proposed metabolic pathways of apomorphine in rats, mice, dogs, monkeys, and humans

**Metabolic pathway of apomorphine in different species**




a this metabolite has not been detected in mice or monkeys
b this metabolite has not been detected in monkeys
c this metabolite has only been detected in dogs

Even though the human study uses a different route of administration (sublingual) than subcutaneous, the sponsor expects the metabolism of apomorphine to be very comparable The sponsor believes that both routes of administration bypass the first pass metabolism pathway and enter immediately into the systemic circulation Blood perfusing the buccal cavity will allow the absorbed apomorphine from a sublingual dosage form to directly enter the superior vena cava, thus bypassing the first pass effect of the liver (contrary to these statements, the bioavailability of sublingual formulation is 16-18% [redacted] 10-22% based on literature) For a subcutaneous dose, apomorphine will enter the systemic circulation through the vascular capillaries, thus bypassing the first pass effect Upon entrance into the systemic circulation, the metabolic pathway of apomorphine would not differ Although the sponsor did not state the bioavailability difference between these two formulations, they noted that the relative amounts of each metabolite being formed may potentially be different due to the sublingual dose being exposed to the enzymatic flora in the mouth They argued that the metabolites formed within the body should be qualitatively similar As a consequence, the sponsor believes that the metabolic identification performed on the sublingually administered dose of apomorphine would be expected to identify the metabolites that will be formed upon administration of apomorphine to a human via subcutaneous administration Thus, the view of metabolic pathway of apomorphine has been completely changed from the original NDA and based on these, the sponsor claims that there is sufficient data available to support the safe approval of this fast-track designated product On the other hand, they acknowledge the Agency's request for confirmation of the findings from ABC Laboratories and accordingly commits to conducting a $^{14}$C-apomorphine mass balance study in six healthy humans and a study in rats post approval The synthesis of $^{14}$C-apomorphine has been initiated and the expected submission date is January 2005

In response to the comments regarding protein binding, the sponsor will remove protein binding statements from the labeling until a study is completed as a post approval commitment

The sponsor agrees to perform, as a Phase IV commitment, a pharmacokinetic study addressing the different effects of a 250 mg TID (three times a day) versus 300 mg TID dosing regimens of trimethobenzamide on the pharmacokinetics of apomorphine The proposed protocol synopsis along with the study timeline is provided

The sponsor does not feel that studies of drug interactions between apomorphine and alcohol and between apomorphine and vasodilators are necessary They made several arguments

Apomorphine is 80-90% bound to plasma Apomorphine is also metabolized via glucuronidation and sulfation along with the cytochrome P450 (CYP) enzyme system (specifically CYP2B6, CYP2C8, and CYP3A4) In addition, the dopamine receptor sites (more specifically Dl, D2, D3, D4, and D5), are the sites of action for apomorphine The pharmacokinetic disposition, along with the pharmacologic characteristics, of alcohol is completely different from the properties of apomorphine Alcohol is eliminated via zero-order kinetics via alcohol dehydrogenase and CYP2E1 Alcohol does not possess protein binding characteristics and is administered via a different route than apomorphine (oral versus subcutaneous injection) Therefore, alcohol should not interfere with the pharmacologic or pharmacokinetic disposition of apomorphine

Nitrates also have a different metabolic route of elimination along with receptor sites as compared to apomorphine Nitrates are metabolized in the liver by nitrate reductases, while apomorphine is glucuronidated, sulfated, or metabolized by CYP2B6, CYP2C8, and CYP3A4 (Drug Facts and Comparisons, 1993 and NDA —— Study 90059) Nitrates are believed to be metabolized to free radical nitric oxide and work by stimulating intracellular cyclic guanosine monophosphate production to elicit their vasodilatory effects Apomorphine works on the Dl, D2, D3, D4, and D5 receptors throughout the body, and is approximately 88% bound to serum albumin and 33% bound to alpha1-acid glycoprotein Nitroglycerin is bound to plasma proteins, but isosorbide dinitrate and isosorbide mononitrate are not bound to plasma proteins Nitrates are administered on a chronic basis With apomorphine being gradually titrated, any effects of having nitrates on board will be adjusted for during titration of the patient to their therapeutic dose If nitrates are to be added to a patient already taking apomorphine, subsequent monitoring may be necessary as with any concomitantly administered cation that is plasma protein bound Therefore, the sponsor believes that with nitrates having a different metabolic pathway and working at different receptor sites, an interaction study is not necessary

**V Synopsis of Proposed Protocol for Mass Balance and Protein Binding Study**

[ ]

**Redacted** 3

**page(s) of trade secret and/or confidential commercial information (b4)**

## Appendix The sponsor's responses to CPB comments in the Approvable Letter

### CLINICAL PHARMACOLOGY & BIOPHARMACUETICS

**FDA Comment 1**

As discussed in the Pharmacology/Toxicology section above, it is not clear what the predominant circulating species is (are) in humans and what it was in the preclinical toxicity studies This information should be available prior to approval There is insufficient evidence to show the role of auto-oxidation in apomorphine elimination, although the apparent clearance of 230 L/h is higher than hepatic blood flow, which supports the existence of auto-oxidation of apomorphine The assumption that auto-oxidation occurs in tissues at the same rate as in plasma has not been validated Further, auto-oxidation could not account for most of the apomorphine eliminated. You should conduct a mass balance study to show the major elimination route and the percentage of elimination that each route accounts for

**Bertek Response**

As described in Bertek's response to FDA Pharmacology/Toxicology Comment #6 Bertek is proposing that this request be fulfilled as a post approval commitment. Bertek's minutes from an August 7, 2002 telephone conference between the Division and Bertek regarding this issue are provided in Attachment 26 Based upon the data from studies presented in the NDA along with data publicly available from ABC Laboratories about recent state of the art metabolism studies, there is sufficient data available to support the safe approval of this fast track designated product. The summary of the available data was presented in the response to Pharmacology/Toxicology Comment #6 Bertek acknowledges the Agency's request for confirmation of the ABC findings and accordingly commits to conducting a $^{14}$C-apomorphine mass balance study in six healthy humans A proposed protocol synopsis for this study is provided in Attachment 28 As was discussed during the August 7, 2003 telephone conference, Bertek anticipates that the sourcing of $^{14}$C-apomorphine, the conduct of the studies, analysis of results and final study availability could take up to 12-18 months, unduly delaying the approval of the referenced application. The synthesis of $^{14}$C-apomorphine has been initiated and will be completed the beginning of December with the qualification of the material being completed in the middle to end of December A summary from the laboratory describing this timeline is provided in Attachment 27 Bertek could then initiate the proposed study in January 2004 Timelines for this study is also provided in Attachment 28

**FDA Comment 2**

The basis for the labeling statement regarding plasma protein binding is not clear You did not conduct the protein binding study Based on the literature, plasma protein binding of apomorphine was estimated at greater than 99 9% over a range of 1257 ng/mL to 3112 ng/mL However, these concentrations are much higher than the therapeutic concentration (about 10 ng/mL) You should conduct a protein binding study using the clinically relevant concentration before putting the claim in the labeling

**Bertek Response:**

Bertek will remove protein binding data from the labeling until a protein binding study can be completed as a post approval commitment. Revised labeling deleting the protein binding information is provided in Attachment 2 Bertek further commits to the post-approval conduct of a study to determine the apomorphine plasma protein binding in humans This study will be conducted in conjunction with conjunction with the $^{14}C$-apomorphine study described in the above response The synopsis for the proposed study along with the timeline is provided in Attachment 28

**FDA Comment 3**

The antiemetic Tigan (trimethobenzamide) was administered during the clinical trial, but no formal pharmacokinetic drug interaction study has been conducted You should conduct such a study and, in that study, address the differential effect of Tigan 250mg and Tigan 300mg on the pharmacokinetics of apomorphine

**Bertek Response**

Bertek agrees to perform, as a Phase IV commitment, 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 Since Bertek does not feel it is ethical to administer apomorphine in healthy volunteers without an anti-emetic on-board, this study will only be addressing the differential effect of the two trimethobenzamide dosing regimens on apomorphine The proposed protocol synopsis along with the study timeline is provided in Attachment 39 The clinical effects of dosing a Parkinsonian patient with and without trimethobenzamide will be addressed in a separate study as described in Bertek's response to FDA Clinical Comment #5

**FDA Comment 4**

Drug interaction studies with alcohol and with vasodilators (including short-and long-acting nitrates) should be considered.

**Bertek Response:**

Bertek does not feel that these studies are necessary Apomorphine is 80 – 90% bound to plasma proteins (Study — # 8963 beginning on page 5-3-1, Volume 3 of the May 6, 2002 NDA) Apomorphine is also metabolized via glucuronidation and sulfation along with the cytochrome P450 (CYP) enzyme system (specifically CYP2B6, CYP2C8, and CYP3A4) (Study — Study —990059 beginning on page 5-1-203, Volume 1 of the May 6, 2002 NDA) In addition, the dopamine receptor sites (more specifically $D_1$, $D_2$, $D_3$, $D_4$, and $D_5$), are the sites of action for apomorphine The pharmacokinetic disposition, along with the pharmacologic characteristics, of alcohol is completely different from the aforementioned properties of apomorphine Alcohol is eliminated via zero-order kinetics via alcohol dehydrogenase and CYP2E1 Alcohol does not possess protein binding characteristics and is administered via a

different route than apomorphine (oral versus subcutaneous injection) (Rowland M and Tozer TN, 1995) Therefore, alcohol should not interfere with the pharmacologic or pharmacokinetic disposition of apomorphine

Nitrates also have a different metabolic route of elimination along with receptor sites as compared to apomorphine Nitrates are metabolized in the liver by nitrate reductases, while apomorphine is glucuronidated, sulfated, or metabolized by CYP2B6, CYP2C8, and CYP3A4 enzymes (Drug Facts and Comparisons, 1993 and NDA Study [redacted] 990059) Nitrates are believed to be metabolized to free radical nitric oxide and work by stimulating intracellular cyclic guanosine monophosphate production to elicit their vasodilatory effects Apomorphine works on the $D_1$, $D_2$, $D_3$, $D_4$, and $D_5$ receptors throughout the body, and is approximately 88% bound to serum albumin and 33% bound to $\alpha_1$-acid glycoprotein (ABC Poster Presentation *Plasma Protein Binding and Whole Blood Distribution of Apomorphine in Plasma and Blood from Human, Dog Rat, and Mouse* – see Attachment 21) Nitroglycerin is 60% bound to plasma proteins, but isosorbide dinitrate and isosorbide mononitrate are not bound to plasma proteins Nitrates are administered on a chronic basis With apomorphine being individually titrated, any effects of having nitrates on board will be adjusted for during titration of the patient to their therapeutic dose If nitrates are to be added to a patient already taking apomorphine, subsequent monitoring may be necessary as with any concomitantly administered medication that is plasma protein bound Therefore, with nitrates having a different metabolic pathway and working at different receptor sites, the need for an interaction study is not necessary

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/s/
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John Duan
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Ramana S Uppoor
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**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW**

| | | | |
|---|---|---|---|
| **NDA** | 21-264 | **SUBMISSION DATES** | July 11, 2003 |
| **DRUG NAME** | —— (Apomorphine hydrochloride) | | Aug. 1, 2003 |
| **DOSAGE STRENGTH** | Injection 10 mg/mL | | |
| **APPLICANT** | BERTEK Pharmaceuticals Inc<br>Morgantown, WV25504 | | |
| **REVIEWER** | John Duan, Ph D | | |
| **TEAM LEADERS** | Ramana Uppoor, Ph D | | |
| **TYPE OF SUBMISSION** | Meeting Request | | |
| Teleconference Date | August 7, 2003 | | |

## I Background

Apomorphine is a potent, short-acting, dopamine agonist Its mechanism of action involves the stimulation of dopamine receptors in the corpus striatum, which leads to anti-parkinsonian activity In this NDA, the applicant is seeking approval for subcutaneous injection formulation of Apomorphine indicated for the rescue treatment of "off episodes" associated with Parkinson's disease The Agency issued an approvable letter on July 2, 2003 in which the following issue was raised

The major elimination route of apomorphine after subcutaneous administration is not clear There is insufficient evidence to show the role of auto oxidation in apomorphine elimination although the apparent clearance of 230 L/h is higher than hepatic blood flow, which supports the existence of autooxidation of apomorphine The assumption, autooxidation occurs in tissues at the same rate as in plasma, has not been validated Further, the autooxidation could not account for the most apomorphine eliminated The applicant should conduct a mass balance study to show the major elimination route and the percentage each route accounts for We also asked that the auto oxidation products be characterized

The current submission provides new information from meeting posters (based on a mass balance study on sublingual formulation of apomorphine) regarding the elimination route of apomorphine and proposes to amend the original view in the NDA submission to reference the new information Primarily, the applicant wishes to conduct the required mass balance study post-approval (not pre-approval as requested in the approvable letter) with subcutaneous apomorphine to confirm the new metabolic information from these meeting posters The submission requests a meeting to discuss this issue

## COMMENTS

From Clinical Pharmacology and Biopharmaceutics perspective, we conveyed the following comments to the applicant

1 In the submission, the major elimination route of subcutaneous apomorphine is not clear

2 In literature, the major elimination route of apomorphine is not definite based on the

following observations

- Auto oxidation and sulfation were proposed in different publications for different formulations (i v and sublingual)
- The difference of bioavailability of subcutaneous (100%) and sublingual (10-22%) may make a difference in the distributions of these two formulations
- The big differences of per cent of sulfation (3 7% for i v and 59% for sublingual) can not be completely explained by the assay method differences

It was agreed by the Division that the mass balance study could be done post-approval However, in their response to the approvable letter, the applicant should describe in detail why they believe the new data are more accurate and that auto oxidation (which was originally the predominant pathway proposed) is now unimportant

## RECOMMENDATIONS

The comments were conveyed to the applicant during the teleconference No further action is necessary

/S/

John Duan, Ph D
Reviewer
Division of Pharmaceutical Evaluation I

8/11/03
Date

/S/

Ramana Uppoor, Ph D
Team Leader
Division of Pharmaceutical Evaluation I

08/11/03
Date

cc Orig 21,264
HFD-120 Division File
HFD-860 MMehta, CSahajwalla, RUppoor, JDuan
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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

| | | | |
|---|---|---|---|
| NDA | 21-264 | SUBMISSION DATES | January 7, 2003<br>March 18, 2003<br>April 28, 2003 |
| DRUG NAME | —— (Apomorphine hydrochloride) | | |
| DOSAGE STRENGTH | Injection 10 mg/mL | | |
| APPLICANT | BERTEK Pharmaceuticals Inc<br>Morgantown, WV25504 | | |
| REVIEWER. | John Duan, Ph D | | |
| TEAM LEADERS | Ramana Uppoor, Ph D, Joga Gobburu, Ph D | | |
| TYPE OF SUBMISSION | New Drug Application (1P) | | |

## I Executive Summary

Apomorphine is a potent, short-acting, dopamine agonist Its mechanism of action involves the stimulation of dopamine receptors in the corpus striatum, which leads to anti-parkinsonian activity In this NDA, the applicant is seeking approval for subcutaneous injection formulation of Apomorphine indicated for the rescue treatment of "off episodes" associated with Parkinson's disease

The literature showed that for subcutaneous (SC) administration, apomorphine is rapidly absorbed with a complete absorption The plasma to whole blood concentration ratio was equal to one Plasma protein binding of apomorphine was estimated at greater than 99 9% over a range of 1257 ng/mL to 3112 ng/mL Apomorphine is distributed into CSF with peak concentrations of less than 10% of the peak plasma concentration and occurring 10 to 20 minutes after those in the plasma Apomorphine is rapidly cleared from plasma Renal elimination of unchanged or conjugated R-apomorphine is not a major route of elimination in humans The catechol-O-methyl transferase (COMT) metabolite is undetectable In vitro study showed that apomorphine is subject to photo degradation and auto oxidation Following SC administration to the abdomen, apomorphine pharmacokinetics are most commonly described as biphasic The $t_{1/2\alpha}$ was 14 2 ± 6 8 minutes and $t_{1/2\beta}$ was 69 7 ± 26 minutes The influences of age, gender, weight, duration of Parkinson's disease, L-dopa dose and duration of therapy, and clinical state were not significant for apomorphine clearance in humans Possible pharmacokinetic as well as pharmacodynamic interactions between levodopa and apomorphine have been reported A strong correlation between the CSF concentration and effect was demonstrated The pharmacokinetics and pharmacodynamics have been described as "quantal" with a threshold concentration below which no therapeutic response is seen Increasing concentrations above the threshold may prolong the duration of therapeutic response, but do not elicit a greater magnitude of response

Although these literature studies provide a general understanding of the clinical pharmacology of apomorphine, there are several issues of concern It is not clear what the major route of elimination is and what proportion each route accounts for It is equivocal what the role of autooxidation is in the clearance of apomorphine The impacts of renal and hepatic impairment on the pharmacokinetics of apomorphine had not been previously studied

The applicant conducted 3 in vitro metabolism studies and 6 human pharmacokinetic studies The in vitro studies explored the metabolism routes, induction and inhibition potential of apomorphine The results showed that metabolism-based drug interaction is unlikely The pharmacokinetic parameters for apomorphine HCl obtained in these studies were similar to those reported in the literature The results indicated pharmacokinetic dose proportionality over the dosage range (2 mg to 8 mg) in idiopathic Parkinson's disease patients Apomorphine did not have a tendency to accumulate in patient's with idiopathic Parkinson's disease A PK/PD analysis in patients with Parkinson's Disease showed that the improvement in motor function following subcutaneous apomorphine administration occurred within 10 minutes (peak effect occurred around 40 minutes after dosing) and persisted for about 90 minutes The $EC_{50}$ in patients with Parkinson's disease is 10 7 ng/mL and 5 3 ng/mL for the UPDRS motor scores and the modified Webster step second test scores, respectively A simulation based on this model showed that doses more than 6 mg did not produce significant extra improvement of UPDRS motor scores compared to lower doses whereas dose-dependent decreases were shown for blood pressures (systolic and diastolic) and pulse Therefore, doses more than 6 mg are not recommended The dose increment is recommended to be 0 5 mg instead of 1 mg The interval for repeated dosing is recommended to be not less than 1 5 hours The apparent clearance of 225 L/h, which is higher than hepatic blood flow, supports the existence of autooxidation of apomorphine as an elimination route However, the in vivo evidences of autooxidation were not provided Further, autooxidation could not account for the most apomorphine eliminated The major route of elimination is not clear [redacted] A mass balance study is recommended to clarify this issue The patients with moderate hepatic impairment had 24% higher $C_{max}$ and 9% higher AUC compared to the normal subjects The patients with moderate renal impairment had 50% higher $C_{max}$ and 15% higher AUC compared to the normal subjects In patients with moderate renal impairment, the starting dose is recommended to be 1 mg (reduced from the proposed starting dose 2 mg) A cartridge (3-mL) was developed for use in a multiple use pen with benzyl alcohol as preservative, while the 2-mL ampoule was used in all the clinical trials conducted by the applicant In an amendment, two bioequivalence studies were submitted Based on the study results, and considering benzyl alcohol is not expected to interfere with the pharmacokinetics of apomorphine, the cartridge formulation is considered to be bioequivalent to the clinical formulation (ampoule formulation)

## A RECOMMENDATION

From Clinical Pharmacology and Biopharmaceutics perspective, the NDA is acceptable provided Comment 1 is addressed and labeling changes are appropriately made as per Section B below The following comments should be sent to the Medical Officer and the applicant

### *Comments to the Medical Officer*

1 The major elimination route of apomorphine after subcutaneous administration is not clear There is insufficient evidence to show the role of auto oxidation in apomorphine elimination although the apparent clearance of 225 L/h is higher than hepatic blood flow, which supports the existence of autooxidation of apomorphine The assumption, autooxidation occurs in tissues at the same rate as in plasma, has not been validated Further, the autooxidation could

not account for the most apomorphine eliminated The applicant should conduct a mass balance study to show the major elimination route and the percentage each route accounts for This issue, coupled with the comments from pharmacologist regarding the elimination route in animals, raised a concern for the possible accumulations of the unknown products in patients, which could be a potential problem, especially in long term therapy Therefore, a mass balance study (or other appropriate approach) in humans to clarify the elimination route of apomorphine after SC administration and identify the metabolic products is recommended to be a requirement prior to approval

2 Based on the PK/PD modeling and simulation, doses more than 6 mg do not provide further improvement measured by UPDRS motor scores although the duration of the improvement is longer On the other hand, the adverse events such as decreases of blood pressures and pulse are dose-dependent Therefore, dose selection should be based on the balance of benefit and risk Doses more than 6 mg are not recommended

3 By the same consideration, the dose increment is recommended to be 0 5 mg instead of 1 mg (as suggested by the applicant)

4 Since both effectiveness and adverse events are related to concentration, the starting dose of 2-mg for patients with moderate renal impairment would be equivalent to 3 mg (considering the 50% increase of $C_{max}$ in these patients) To avoid adverse events, the starting dose for patients with mild and moderate renal impairment is recommended to be 1 mg

5 In the proposed labeling, the applicant did not indicate the interval of repeated dosing For selection of the repeated dosing regimen, three factors are considered including the time to reach peak concentration, the delay between the plasma concentration and the effect, and the adverse event rate The repeated dose interval is recommended to be at least 90 minutes

6 Based on the results of the bioequivalence study, the cartridge formulation is considered bioequivalent to the clinical formulation (ampoule formulation) However, since the bioequivalence study was conducted at lower dose (2 mg), certain side effect of benzyl alcohol, such as irritation at injection site might not manifest Therefore, the safety of cartridge formulation should be monitored and reported The pharmacologist has contacted the applicant He will cover this issue

7 It is not clear what is the basis for the labeling statement regarding plasma protein binding The applicant did not conduct the protein binding study Based on the literature, plasma protein binding of apomorphine was estimated at greater than 99 9% over a range of 1257 ng/mL to 3112 ng/mL However, these concentrations are much higher than the therapeutic concentration (about 10 ng/mL) The applicant should conduct a protein binding study using the clinical relevant concentration before putting the statement in the labeling

8 Antiemetic trimethobenzamide was administrated during the clinical trial However, a formal drug interaction study using pharmacokinetic approach has not been conducted

9 Drug interaction with alcohol should be considered

there was a significant pharmacodynamic interaction between apomorphine SL (6 mg) and ethanol (0 6g/kg), with greater mean maximum drop from baseline in systolic and diastolic blood pressures noted when apomorphine SL was dosed with ethanol

*Comments to the Applicant*

1 The major elimination route of apomorphine after subcutaneous administration is not clear There is insufficient evidence to show the role of auto oxidation in apomorphine elimination although the apparent clearance of 225 L/h is higher than hepatic blood flow, which supports the existence of autooxidation of apomorphine The assumption, autooxidation occurs in tissues with the same rate as in plasma, has not been validated Further, the autooxidation could not account for the most apomorphine eliminated The applicant should conduct a mass balance study (or other appropriate approach) in humans to show the major elimination route and the percentage each route accounts for In addition, the metabolic products need to be identified

2 The literature showed that plasma protein binding of apomorphine to be greater than 99 9% over a range of 1257 ng/mL to 3112 ng/mL However, these concentrations are much higher than the therapeutic concentration (about 10 ng/mL) The applicant should conduct a protein binding study using the clinically relevant concentration before putting the statement in the labeling

3 Drug interaction with alcohol should be considered

**B LABELING RECOMMENDATIONS**

The recommended labeling changes are as follows

1 Clinical Pharmacology part

**Pharmacokinetics**

**Absorption** Apomorphine hydrochloride is a lipophilic compound that is rapidly absorbed (time to peak concentration ranges from 10 to — following subcutaneous administration into the abdominal wall After subcutaneous administration, apomorphine appears to have a bioavailability equal to that of an intravenous administration Apomorphine exhibited linear pharmacokinetics over a dose range of 2 to 8 mg following a single subcutaneous injection of apomorphine into the abdominal wall in patients with idiopathic Parkinson's disease —

**Distribution** The plasma-to-whole blood apomorphine concentration ratio is equal to one Mean (range) apparent volume of distribution was — Maximum concentrations in cerebrospinal fluid (CSF) are less than 10% of maximum plasma concentrations and occur 10 to 20 minutes later

**Metabolism and Elimination** The mean apparent clearance (range) was —L/hr (125 – 401 L/hr) The mean (range) terminal half-life was — minutes — minutes)

The route of metabolism in humans

**Special Populations** The clearance of apomorphine does not appear to be influenced by age, gender, weight, duration of Parkinson's disease, levodopa dose or duration of therapy

*Hepatic Impairment* In a study comparing subjects with hepatic impairment (moderately impaired as determined by the Child-Pugh classification method) to healthy matched volunteers, the $AUC_{0-\infty}$ and $C_{max}$ values increased approximately — and 25%, respectively, following a single subcutaneous administration of apomorphine into the abdominal wall Study in subjects with severe hepatic impairment has not been conducted (See PRECAUTIONS and DOSAGE AND ADMINISTRATION)

*Renal Impairment* In a study comparing renal impaired subjects (moderately impaired as determined by creatinine clearance) to healthy matched volunteers, the $AUC_{0-\infty}$ and $C_{max}$ values increased approximately 16% and 50%, respectively, following a single subcutaneous administration of apomorphine into the abdominal wall The mean time to peak concentrations and the mean terminal half-life of apomorphine were unaffected by the renal status of the individual

The starting dose for patients with mild or moderate renal impairment should be reduced Study in subjects with severe renal impairment has not been conducted (See PRECAUTIONS and DOSAGE AND ADMINISTRATION)

**Pharmacodynamics**

2 Precautions part Add the following
**Hepatic impairment** Caution should be exercised when administrating to patients with mild and moderate hepatic impairment due to the increased $C_{max}$ and AUC in these patients Study in subjects with severe hepatic impairment has not been conducted (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION)

**Renal impairment** The starting dose should be reduced to 1 mg when administrating to patients with mild or moderate renal impairment due to the increased $C_{max}$ and AUC in these patients Study in subjects with severe renal impairment has not been conducted (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION)

3 Precaution - Drug interaction part
**Drug Interactions** ***Carbidopa/levodopa*** Levodopa pharmacokinetics were unchanged when subcutaneous apomorphine and levodopa were coadministrated in patients However, motor response differences were significant The threshold levodopa concentration necessary for an improved motor response was reduced significantly, leading to an increased duration of effect without a change in the maximal response to levodopa therapy

***Other Drugs Eliminated Via Hepatic Metabolism*** Based upon an *in vitro* study, cytochrome P450 enzymes play a minor role in the metabolism of apomorphine *In vitro* studies have also demonstrated that drug interaction is unlikely due to apomorphine acting — inhibitor or an inducer of cytochrome P450 enzymes
***COMT Interactions*** A pharmacokinetic interaction of apomorphine with catechol-O-methyl transferase (COMT) inhibitors or drugs metabolized by this route is unlikely since —

4 Dosage and Administration part Add the following

When dosing patients with mild and moderate hepatic impairment, caution should be exercised due to the increased $C_{max}$ and AUC in these patients (see CLINICAL PHARMACOLOGY and PRECAUTIONS)

For patients with mild and moderate renal impairment, the testing dose and subsequently the starting dose should be reduced to 1 mg (see CLINICAL PHARMACOLOGY and PRECAUTIONS)

/S/

John Duan, Ph D — Date
Reviewer
Division of Pharmaceutical Evaluation I

/S/

Ramana Uppoor, Ph D — Date
Team Leader
Division of Pharmaceutical Evaluation I

/S/

Joga Gobburu, Ph D — Date
Team Leader
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CDR

## II Table of contents

## III Summary of Clinical Pharmacology and Biopharmaceutics Findings

R-apomorphine, a lipophilic compound, is a dopamine agonist that directly stimulates dopamine receptors in the corpus striatum, leading to anti-parkinsonian activity R-apomorphine is being evaluated for use via intermittent subcutaneous injection as abortive (rescue) therapy for acute refractory episodes of immobility or hypomobility ("off episodes") in patients with late stage Parkinson's disease The pharmacodynamic effects (motor effects) of apomorphine may follow a time profile similar to its pharmacokinetics

### 1 Summary of apomorphine clinical pharmacology in the literature

In the current NDA, the applicant submitted the background pharmacology information and a literature review of human pharmacokinetic studies from 19 literatures These include 10 studies for parenteral administration, 5 studies for sublingual administration, 2 studies for intranasal administration, 1 study for rectal administration, and 1 study for iontophoresis

#### *1 Absorption*

Oral administration is not an appropriate route of administration for apomorphine due to extensive first-pass metabolism forming glucuronidated and methylated products The bioavailability of apomorphine following oral administration is less than 5%

For subcutaneous (SC) administration, apomorphine is rapidly absorbed After SC administration at doses of 15-50 µg/kg to 15 Parkinsonian patients, the time to maximum concentration ($T_{max}$) of 7 8 minutes was observed Another study observed a $T_{max}$ of 16 minutes following SC doses of 237 ± 166 µg/kg/day to the abdomen of 15 Parkinsonian patients The difference in $T_{max}$ values was explained, in part, by the use of a more concentrated apomorphine solution (10 mg/mL versus 2 mg/mL), resulting in a smaller injection volume (and thus smaller absorption surface) in the latter investigation Other studies have observed $T_{max}$ values of 5 to 60 minutes following SC administration

In four subjects who received both IV and SC infusions of apomorphine, $C_{max}$ and AUC values were similar, indicating complete absorption from the SC route The absorption half-life of apomorphine has been estimated as 5 8 minutes following SC administration

The inter-subject variability in $C_{max}$ and AUC was high For a 30-µg/kg dose, $C_{max}$ differed almost ten-fold among patients and AUC differed five-fold Less variability was observed when a subject received the same dose on multiple occasions

The factors influencing the absorption of apomorphine include blood flow in SC tissues Peak drug concentrations were significantly reduced and delayed in pre-cooled skin, however, pre-warmed skin did not have appreciably more absorption than skin at ambient temperature Other factors that might contribute to variation in SC absorption include thickness of abdominal wall, quantity of adipose tissue, and local vascularization A trend to higher $C_{max}$ and shorter $T_{max}$ was observed in 5 subjects receiving 30 µg/kg SC bolus injections in the upper arm on one occasion

and the anterior abdominal wall on another Another study observed a trend to more complete absorption following SC injection in the abdominal wall rather than in the thigh

For sublingual (SL) administration, the mean $T_{max}$ was 30 to 60 minutes The bioavailability of SL apomorphine ranged from 10 to 22% of a parenteral apomorphine dose There was a similarity in $C_{max}$ and AUC of a 3-mg SC dose versus 30-mg SL dose The co-administration of vitamin C with 10-mg SL apomorphine did not increase the bioavailability over 10-mg SL apomorphine alone Absorption from the SL route appears slower than SC injection It is possible that this is formulation dependent

For intranasal administration, mean $T_{max}$ was 23 minutes The bioavailability of intranasal apomorphine was about 45% as compared to the subcutaneous route The absorption half-life was 8 6 minutes following intranasal administration

For rectal administration, mean $T_{max}$ was 16 to 128 minutes Mean apomorphine bioavailability following rectal administration varied between 14 6% and 40 2%

A transdermal dose of 18-mg apomorphine dissolved in 3 gram of water-soluble cream and applied to a 16 $in^2$ area over the anterior chest in one patient did not produce detectable plasma concentrations Similarly, passive transdermal application of apomorphine in ten patients did not lead to increased concentrations

The dose-linearity of apomorphine pharmacokinetics following two SC injections was evaluated in 6 patients over a range of 20 to 179 µg/kg A proportional relationship between dose and AUC was observed for some subjects, but a conclusion could not be made due to the overall variability of the normalized AUC (35% CV) Another study demonstrated evidence of linearity of apomorphine pharmacokinetics following single SC doses of 0 5 to 4 mg Body-weight related doses in ten patients were linearly correlated with both $C_{max}$ and AUC

*2 Distribution*

The apomorphine plasma to whole blood concentration ratio was equal to one Plasma protein binding of apomorphine was estimated at greater than 99 9% over a range of 1257 ng/mL to 3112 ng/mL, which is much higher than the therapeutic concentration (about 10 ng/mL)

The distribution of apomorphine into CSF has been described, with peak CSF concentrations of less than 10% of the peak plasma concentration occurring 10 to 20 minutes after those in the plasma A second peak CSF concentration occurring 60 to 90 minutes after dosing was observed in several subjects, the origin of which is unclear CSF concentrations appear to be more correlated with clinical motor responses than plasma concentrations Additionally, CSF apomorphine concentrations appear to be closely correlated with changes in CSF concentrations of dopamine and its metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA)

*3 Metabolism*

Apomorphine is subject to extensive first pass metabolism Potential metabolic routes for R-apomorphine include racemization to S-apomorphine, oxidation, metabolism by catechol-O-methyl transferase (COMT), glucuronidation and sulfation, and N-demethylation R-apomorphine is not inter-converted in the human body to S- apomorphine There is a small fraction of the dose eliminated in the urine as glucuronide conjugate in humans

In vitro studies show that R-apomorphine may be a substrate of COMT, resulting in the formation of apocodeine and isoapocodeine in a ratio of 81 1 In humans, these metabolites were not detected following intravenous infusions of R-apomorphine at 30 µg/kg over 15 minutes, thus pharmacokinetic interactions with COMT inhibitors are not expected

Additionally, an in vitro study showed that apomorphine is subject to photo degradation and auto oxidation Auto oxidation of apomorphine occurs in plasma (in vitro) with a half-life of 142 ± 35 minutes This rate of auto oxidation would account for only 1% of total clearance in the plasma volume However, if assuming the auto oxidation rate is the same in blood and body tissues, and substituting the blood volume by the volume of distribution in the calculations, auto oxidation could contribute as much as 30% to overall body clearance Performing the same calculation with the estimated auto oxidation half-life of 38 9 minutes the contribution of auto oxidation could account for 70% of the total clearance of apomorphine Since the observed total body clearance of apomorphine — mL/min/kg) is greater than hepatic blood flow, auto oxidation provides an explanation for some of the extra-hepatic elimination of apomorphine However, the degradation products formed upon autooxidation have not been identified

### *4 Elimination*

Apomorphine is rapidly cleared from plasma and the plasma half-life ($t_{1/2}$) is brief The short $t_{1/2}$ is explained in part by rapid degradation of apomorphine

Apomorphine could be excreted unchanged into the bile After IV administration, total renal excretion of apomorphine, apomorphine sulfate, and apomorphine glucuronide in humans were reported to be 0 3 ± 0 4%, 3 8 ± 1 0% and 6 0 ± 2 2% of an administered dose, respectively Thus, renal elimination of unchanged or conjugated R-apomorphine is not a major route of elimination for apomorphine in humans after IV administration

Following parenteral bolus administration, apomorphine pharmacokinetics are most commonly described as biphasic Following IV bolus injection the distribution half-life ($t_{1/2\alpha}$) was 7 2 ± 2 1 minutes and the terminal elimination half-life ($t_{1/2\beta}$) was 47 5 ± 9 9 minutes Following SC administration to the abdomen $t_{1/2\alpha}$ was 14 2 ± 6 8 minutes and $t_{1/2,\beta}$ was 69 7 ± 26 minutes Averaging results across SC and IV routes of administration in 11 of 15 patients, a two-compartment model disposition was observed with $t_{1/2\alpha}$ of 4 8 ± 1 1 minutes and an elimination half-life of 33 6 ± 3 9 minutes Other studies have reported mean terminal elimination half-lives of 41 to 49 minutes following IV administration

### *5 Special Populations*

The influences of age, gender, weight, duration of Parkinson's disease, L-dopa dose and duration of therapy, and clinical state were not significant factors for apomorphine clearance in humans Additionally, the large interpatient variability in $T_{max}$, $C_{max}$ and AUC observed was not related to age, gender or weight

The impacts of renal and hepatic impairment on the pharmacokinetics of apomorphine had not been previously studied

*6 Drug Interactions*

Levodopa peripheral pharmacokinetics were unchanged in a double-blind, randomized, two-way crossover study that evaluated the impact of subcutaneous apomorphine co-administration on the pharmacokinetics and pharmacodynamics of levodopa in patients However, motor response (MR) and PK/PD parameter differences were significant The threshold levodopa concentration necessary for a MR was reduced significantly leading to an increased duration of effect without a change in the maximal response to levodopa therapy

An open-label, randomized study in patients with Parkinson's disease compared the pharmacokinetic parameters of a half tablet of 25/100 Sinemet taken during the last third of an "on" period of apomorphine 3 mg injection with the pharmacokinetic parameters of the same dosage taken after the end of that "on" period In the former situation, the $C_{max}$ and bioavailability of both levodopa and carbidopa were significantly reduced Additionally, the duration of the "on" period was reduced to 107 minutes when Sinemet was given during the "on" period compared to 155 minutes when given after the "on" period The pharmacological mechanism for this interaction is unknown, however, the study results suggest that Sinemet should be taken after the end of an "on" period induced by apomorphine

The interaction of apomorphine with catechol-O-methyl transferase (COMT) inhibitors or drugs metabolized by this route is unlikely since an absence of COMT metabolism of apomorphine in humans has been reported for apomorphine

*7 PK/PD modeling*

Modeling approaches have been utilized to describe the relationship between apomorphine pharmacokinetics and pharmacodynamics (PK/PD) Ten Parkinson's patients were administered SC apomorphine of 0 5, 1, 2, and 4 mg doses and the clinical response and pharmacokinetic parameters were evaluated A successful fit to a sigmoidal Emax model was obtained to describe changes in the Columbia University Rating Scale (CURS) This modeling demonstrated evidence for a sigmoidal response relationship with the existence of a threshold level for response Dose increases above this threshold appeared to lead to prolongation of the motor response, but did not increase the magnitude of the motor response A short equilibrium half-life (6 minutes) between the plasma concentration and the effect concentration was observed

A strong correlation between the CSF concentration and effect was demonstrated in two Parkinson's patients Sigmoidal Emax models were successfully fit to the PK/PD data of the

subjects A short equilibrium period (10 and 20 minutes) between plasma and CSF peak concentrations was observed

A therapeutic window for apomorphine was described for ten Parkinson's disease patients by defining the minimum effective concentration (MEC), the minimal dyskinetic concentration (MDC) and the minimal toxic concentration (MTC) Of the five patients who demonstrated both a clinical benefit and an adverse event, the mean MEC was 3 9 ng/mL (1 4 to 5 3 ng/mL), and the mean MTC was 15 2 ng/mL (8 5 to 24 5 ng/mL) Substantial interindividual variability in this window between efficacy and toxicity was observed

Apomorphine pharmacokinetics and pharmacodynamics have been described as "quantal" with a threshold concentration below which no therapeutic response is seen Increasing concentrations above the threshold may prolong the duration of therapeutic response, but do not elicit a greater magnitude of response

In spite of these literature reports, it is not clear what the major route of elimination is and what portion each route accounts for The impacts of renal and hepatic impairment on the pharmacokinetics of apomorphine had not been previously studied The applicant conducted several studies to address some of these issues

## 2 The studies conducted by the applicant

### *1 In vitro studies*

Routes of apomorphine metabolism were investigated by incubating apomorphine with microsomes from human livers and studying the appearance of metabolites or the disappearance of apomorphine under various conditions Apomorphine was metabolized by human liver microsomes to a metabolite, M1, believed to be norapomorphine although its structure was not elucidated The formation of M1 appears to be catalyzed by multiple enzymes, including CYP2B6, CYP2C8 and CYP3A4/5 Other enzymes might play a role but could not be identified

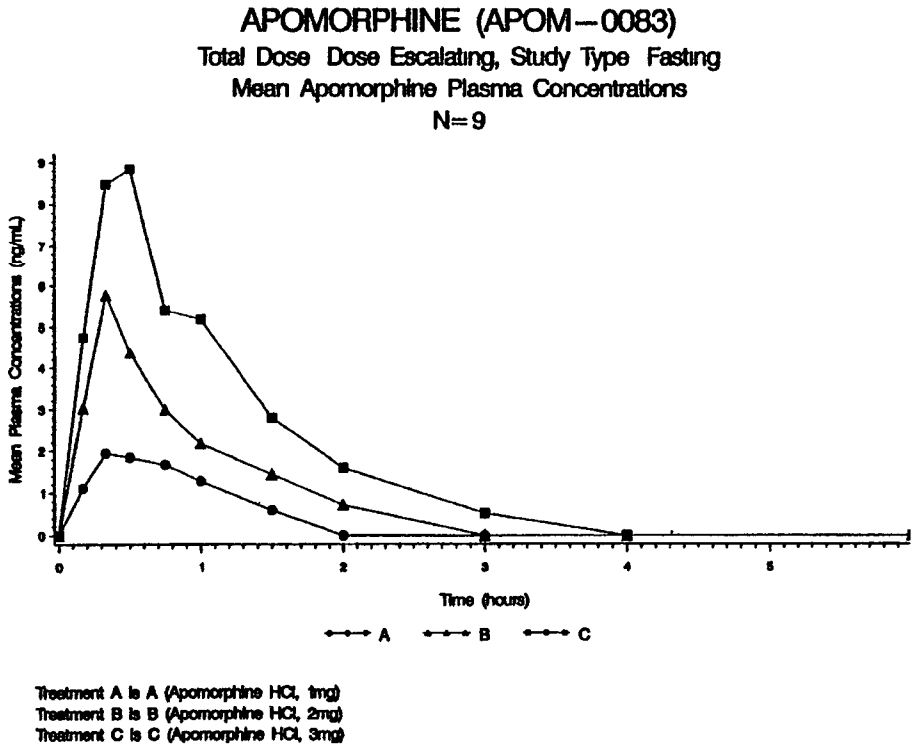
An evaluation of apomorphine as an inhibitor of human P450 enzymes in vitro was conducted in pooled human liver microsomes with the aim of ascertaining the potential of apomorphine to inhibit the metabolism of other drugs The results of this study showed that as a direct acting (metabolism-"independent") reversible inhibitor, 1) apomorphine appeared to be a competitive inhibitor of CYP2C9 with a Ki value of 370 µM, 2) apomorphine appeared to be a mixed inhibitor of CYP2C19, CYP2E1, CYP1A2 and CYP2D6 with Ki values of 440, 290, 55, and 50 µM, respectively, 3) apomorphine appeared to be a non-competitive inhibitor of CYP3A4/5 with a Ki value of 33 µM

Enzyme induction studies were conducted in cultured human hepatocytes to evaluate the capability of apomorphine to affect the metabolizing capacity of various cytochrome P450s and UDP-glucuronosyltransferase systems The data suggested that apomorphine HCl might be a weak inducer of CYP1A2, CYP2B6, CYP2E1, and CYP3A4/5 enzymes in human hepatocytes However, apomorphine HCl concentrations used in this induction study (8 8 to 88 µM) were significantly greater than the expected therapeutic plasma levels (approximately 0 04 µM)

These in vitro studies show that NADPH-dependent metabolism of apomorphine by human liver microsomes appears to be relatively minimal and the metabolism based drug interactions, either inhibition or induction by apomorphine, are unlikely at proposed doses of apomorphine

*2 In vivo studies*

The pharmacokinetic profiles for single doses of subcutaneous apomorphine HCl (1, 2, and 3 mg) injection in healthy adult male and female volunteers were determined The plasma concentration time curves are shown in the following figure




The single dose pharmacokinetic parameters for apomorphine hydrochloride in healthy volunteers calculated using noncompartmental techniques are summarized in Table below (Mean (% CV))

MEAN (%CV) APOMORPHINE HCL PHARMACOKINETIC PARAMETERS IN NINE HEALTHY MALE AND FEMALE SUBJECTS FOLLOWING A SINGLE, SUBCUTANEOUS INJECTION OF THE ASSIGNED TREATMENT UNDER FASTING CONDITIONS.

PROTOCOL NUMBER APOM-0083

| Treatment | Parameter | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | AUCL (ng x hr/mL) | AUCI (ng x hr/mL) | CPEAK (ng/mL) | TPEAK (hr) | KEL ($hr^{-1}$) | HALF (hr) | CL (L/hr) | VD (L) |
| A 1 mg n=3 | 1.856 (27.51) | 2.777 (20.01) | 2.060 (13 62) | 0.470 (51.59) | 1.026 (23 14) | 0 703 (25 80) | 369.5 (19 17) | 373 8 (29 99) |
| B 2 mg n=3 | 4 746 (19 40) | 6.046 (16.60) | 5 778 (6.59) | 0 330 (0 000) | 0.861 (15 89) | 0.820 (16 50) | 337.5 (17 85) | 393.4 (12 94) |
| C. 3 mg n=3 | 10.06 (22.60) | 10.90 (20 02) | 10.35 (27 17) | 0 443 (22.14) | 1.039 (15 42) | 0 680 (16 70) | 282.3 (19 06) | 276.3 (24 14) |

Source: Study Report APOM-0083 Section 14 1 Attachment 1 part 3 and part 5

The pharmacokinetic profiles and the parameters for subcutaneous apomorphine hydrochloride injection in patients with idiopathic Parkinson's disease were determined by noncompartment approach The pharmacokinetic parameters are presented in the following table

SINGLE-DOSE APOMORPHINE HCL PHARMACOKINETIC PARAMETERS IN FIVE (5) IDIOPATHIC PARKINSON'S DISEASE PATIENTS TAKING THREE (3) DIFFERENT DOSES OF APOMORPHINE SUBCUTANEOUSLY (data deleted)[1]

PROTOCOL NUMBER APOM-0073

| | Parameter | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | NAUCL[2] | NAUCI[2] | NCPEAK[3] | TPEAK (hr) | KEL ($hr^{-1}$) | HALF (hr) | CL[4] (L/hr) | VD[5] (L) |
| Mean Parameter Value | 4.643 | 4.960 | 4 867 | 0.227 | 0.988 | 0 720 | 225.0 | 230.4 |
| Coefficient of Variation (%) | 35 6 | 34.0 | 36.3 | 35 0 | 16 4 | 18.0 | 35 1 | 36.2 |
| Range | | | | | | | | |

[1] Patient 21 s Treatment Day 2 deleted due to incomplete concentration profile; Patient 11 s data deleted due to pre-dose apomorphine concentrations on Treatment Days 1 2, and 3.
[2] Dose normalized parameter is expressed as (ng·hr/mL)/ mg apomorphine
[3] Dose normalized parameter is expressed as (ng/mL)/ mg apomorphine
[4] Apparent clearance
[5] Apparent volume of distribution

Source: Study Report APOM-0073 Section 14.2 – Attachment 2, part 7

These pharmacokinetic parameters are similar to those reported in the literatures The table below compares the pharmacokinetic parameters between the patient study and the literature reports

| Parameters | Patient Study | Literature |
|---|---|---|
| AUCL (ng•hr/mL/mg) | 4 64 | 2 03-7 12 |
| CPEAK (ng/mL/mg) | 4 86 | 3 63-6 96 |
| V (L) | 230 | 203-276 6 |
| CL (L/h) | 225 | 228 |

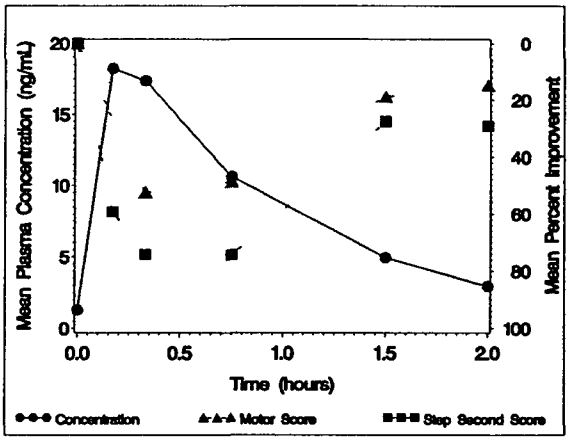
Although no definitive conclusion in regards to linearity can be made from the volunteer study due to the small number of subjects, the study conducted in patients demonstrated dose proportionality The following table shows the results from the dose normalized AUCL, AUCI, and CPEAK parameter regression analyses, indicating pharmacokinetic dose proportionality over the dosage interval studied (2 mg to 8 mg) in idiopathic Parkinson's disease patients

| Dependent | Coefficient | R-square |
|---|---|---|
| AUCL | 4 78 | 0 9161 |
| AUCI | 5 05 | 0 9181 |
| CPEAK | 5 17 | 0 8958 |

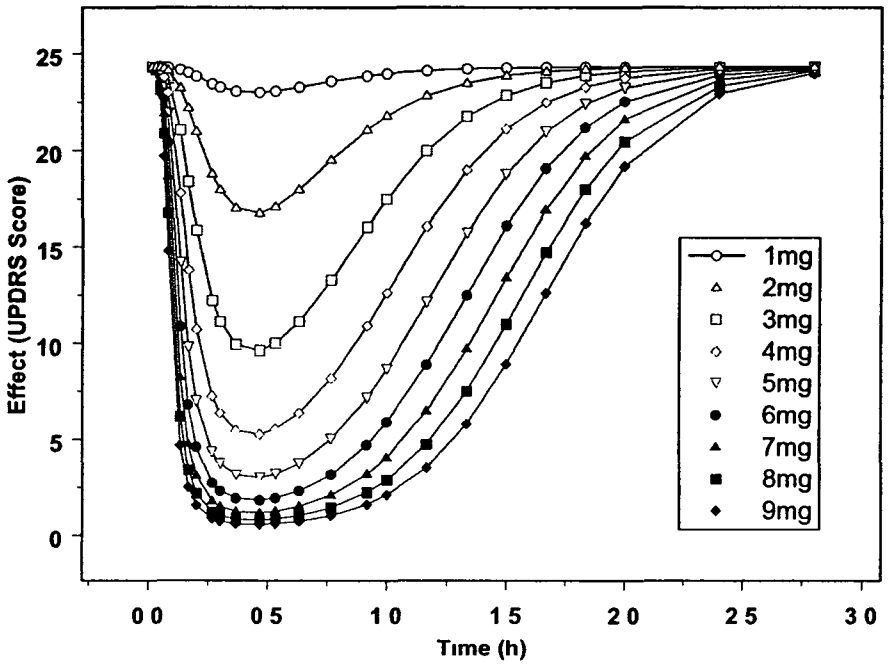
The study also indicated that apomorphine does not have a tendency to accumulate in patients with idiopathic Parkinson's disease

The apparent clearance of 225 L/h, which is higher than hepatic blood flow, supports the existence of autooxidation of apomorphine as an elimination route However, the assumptions of auto oxidation have not been validated The evidence of autooxidation has not been shown in vivo and the autooxidation products have not been identified Further, the autooxidation could not account for most of the apomorphine eliminated The major route of elimination is not obvious

The applicant conducted a PK/PD analysis in patients with Parkinson's Disease The improvement in motor function following subcutaneous apomorphine administration occurred within 10 minutes (peak effect occurred around 40 minutes after dosing) and persisted for about 90 minutes as shown in the following figure The EC50 in patients with Parkinson's disease is 10 7 ng/mL and 5 3 ng/mL for the UPDRS motor scores and the modified Webster step second test scores, respectively




Based on this model, the reviewer performed a simulation to show the motor improvement at different doses As shown in the following figure, doses more than 6 mg do not produce significant extra improvement of motor score although the duration of the effect may last longer On the other hand, decreases of blood pressures and pulse may be dose-dependent By balancing the benefit and risk, therefore, doses more than 6 mg are not recommended and the dose increment is recommended to be 0 5 mg instead of 1 mg at the beginning of the dose titration (please see Pharmacometrics review for details)




In the proposed labeling, the applicant did not indicate the interval of repeated dosing For selection of the repeated dosing regimen, three factors are considered including the time to reach peak concentration, the delay between the plasma concentration and the effect, and the adverse event rate The repeated dose interval is recommended to be at least 90 minutes (please see Pharmacometrics review for details)

The applicant performed studies in both hepatically impaired and renally impaired volunteers to determine whether the pharmacokinetics of apomorphine are altered in these populations Based on the results, the applicant hypothesized that neither hepatic impairment (mild or moderate) nor renal impairment (mild or moderate) would have a significant impact on apomorphine pharmacokinetics However, the 90% confidence intervals of the ratios (calculated by the reviewer) fall outside the limits the relevant Guidances suggest The patients with moderate hepatic impairment have 24% higher $C_{max}$ and 9% higher AUC compared to the normal subjects as shown in the following table

| Parameters | Ratio | 90% CI |
|---|---|---|
| $C_{max}$ | 124 8 | 85 6-181 9 |
| $AUC_{last}$ | 109 4 | 78 4-152 6 |
| $AUC_{inf}$ | 109 7 | 87 5-137 7 |

The patients with moderate renal impairment have 50% higher $C_{max}$ and 15 - 27% higher AUC compared to the normal subjects as shown in the following table

| Parameters | Ratio | 90% CI |
|---|---|---|

| | | |
|---|---|---|
| $C_{max}$ | 150 06 | 101 78-221 24 |
| $AUC_{last}$ | 127 80 | 98 26-166 21 |
| $AUC_{inf}$ | 115 88 | 88 53- 151 67 |

Based on a simulation, when dosing renally impaired patients, the onset and maximum effect are not different considerably from the normal renal function patients, whereas the duration of the effects is prolonged Since both effectiveness and adverse events are related to concentration, the starting dose of 2-mg for renally impaired patients would be equivalent to 3 mg (considering the 50% increase of $C_{max}$ in renally impaired patients) To avoid adverse events, the starting dose for renally impaired patients is recommended to be 1 mg (please see Pharmacometrics review for details)

A request was submitted to waive the requirements for in vivo bioavailability and bioequivalence for the 3-mL cartridge The cartridge was developed for use in a multiple use pen with benzyl alcohol as preservative, while the 2-mL ampoule was used in all the clinical trials In spite of the request, the applicant conducted studies to support the bioequivalence of the cartridge apomorphine formulation with 0 5% benzyl alcohol as compared to the ampoule apomorphine formulation without benzyl alcohol The reports for these studies are provided in an information amendment A phase I, open-label, two-way crossover study in healthy volunteers compared the pharmacokinetics of apomorphine HCl formulated with benzyl alcohol and delivered from a cartridge using a pen device versus apomorphine HCl formulated without benzyl alcohol delivered using a syringe manually filled from an ampoule During this study, the applicant discovered through in vitro testing that the small volume (0 02 mL) priming instructions used in this study did not repeatedly eliminate all of the air bubbles from the cartridge Therefore, the priming instructions were revised so that a larger priming dose setting is required (0 06 mL)

Due to the impact of the priming instructions on the accuracy of the dose delivered, the applicant conducted an additional study This was a phase I, open-label, three-way crossover study in healthy volunteers to compare the pharmacokinetics of apomorphine HCl formulated with benzyl alcohol versus apomorphine HCl formulated without benzyl alcohol It compared apomorphine HCl delivery from a cartridge using a pen device to that from a syringe manually-filled from an ampoule or cartridge The study results are summarized as follows

- The cartridge formulation delivered using a pen device was bioequivalent to the cartridge formulation delivered using a manually filled syringe

- The cartridge formulation containing benzyl alcohol (0 05% w/v) and delivered using a manually filled syringe was bioequivalent to the ampoule formulation without benzyl alcohol delivered using a syringe

- The cartridge formulation delivered using a pen device was bioequivalent to the ampoule formulation delivered using a manually filled syringe

Based on the study results, and considering benzyl alcohol is not expected to interfere with the pharmacokinetics of apomorphine, the cartridge formulation is considered to be bioequivalent to

the clinical formulation (ampoule formulation) However, since the bioequivalence study was conducted at lower dose (2 mg), certain side effect of benzyl alcohol, such as irritation at injection site might not manifest Therefore, the safety of cartridge formulation should be monitored and reported

In spite of these studies, one of the issues regarding the major elimination route of apomorphine has not been solved

The evidence of autooxidation has not been shown in vivo and the assumption of autooxidation occurring in all tissues has not been validated Further, the autooxidation could not account for the most apomorphine eliminated

In addition, there are controversies regarding pharmacokinetic behaviors of apomorphine between this NDA and —— sublingual tablets formulation of apomorphine The controversies are summarized in the following table

| Aspects | Sublingual | Subcutaneous |
|---|---|---|
| Major route | Sulfate | Auto oxidation (through in vitro study) |
| Sulfate | 59% of dose | 3 8 ± 1 0% |
| Hepatic impairment | The point estimates for mild, moderate and severe impairment classes were respectively 36%, 16%, and 62% higher for $C_{max}$, and 59%, 35%, and 68% higher for $AUC_{\infty}$ | $C_{max}$ 25% higher, AUC 9% higher in moderate impairment subjects |
| Renal impairment | There was no significant change in mean $C_{max}$ The mean $AUC_{\infty}$ was significantly increased in subjects with moderate (52%) and severe (67%) renal impairment | $C_{max}$ 50% higher, AUC 15-27% higher in moderate impairment subjects |

In order to resolve this issue, a mass balance study is needed to investigate the major routes of elimination after subcutaneous administration of apomorphine and the percentage each route accounts for Further, the products of the major route should be identified

## IV Question based review

### A General Attributes

***1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product? What is the proposed mechanism of drug action and therapeutic indications? What is the proposed dosage and route of administration?***

Apomorphine hydrochloride is a centrally active, dopamine receptor agonist with affinity for both $D_1$ and $D_2$ subfamilies of dopamine receptors Apomorphine hydrochloride is chemically designated as

— 6aβ-Aporphine-10,11-diol hydrochloride hemihydrate with a molecular formula of $C_{17}H_{17}NO_2 \bullet HCl \bullet 1/2H_2O$ Apomorphine Injection 10 mg/mL is a clear, colorless, sterile solution for subcutaneous injection and is available in 2 mL ampoules and 3 mL cartridges It is indicated for the rescue treatment of "off episodes" associated with Parkinson's disease It is for subcutaneous administration The proposed dosing regimen is to start with 2 mg dose and gradually titrated by 1 mg increments The average frequency of use was about 3 times per day

***2 What were the issues identified in the pre-NDA meeting? Did the applicant address these issues in the submission?***

The NDA was initially submitted on April 17, 2000 and a refuse-to-file letter was issued by the Agency on June 16, 2000 During a teleconference dated September 14, 2000, agreement was reached between the applicant and the Agency that the application could be re-submitted as a 'rolling submission' In the pre-NDA meeting dated January 10, 2002, the following agreements regarding the Clinical Pharmacology and Biopharmaceutics were reached

- The Human Pharmacokinetics and Bioavailability section of the NDA will consist of study reports, and a description of apomorphine pharmacokinetics compiled from literature reports
- In the Office of Clinical Pharmacology & Biopharmaceutics' review of August 3, 2000, it was pointed out that the effect of levodopa on pharmacokinetics and pharmacodynamics of apomorphine was not evaluated Mylan has conducted two studies (a 2- and 13-week study in rats) to evaluate the potential toxicity of a combination of subcutaneous injection of apomorphine and oral administration of levodopa/carbidopa As part of the 13-week study, toxicokinetics of apomorphine were assessed both with and without levodopa/carbidopa treatment Mylan is requested to submit these two studies also to OCPB for review
- Since levodopa will be concomitantly used with apomorphine, the pharmacokinetic and pharmacodynamic drug-drug interaction study between apomorphine and levodopa in humans should be conducted This study can be a Phase IV commitment

In the current submission, the applicant addressed these issues and submitted the requested information including the background pharmacology information and a literature review of

human pharmacokinetic studies from 19 literatures These include 10 studies for parenteral administration, 5 studies for sublingual administration, 2 studies for intranasal administration, 1 study for rectal administration, and 1 study for iontophoresis

The studies conducted by the applicant include 3 in vitro metabolism studies and 6 human pharmacokinetic studies Two preclinical studies, which evaluated the potential toxicity of a combination of subcutaneous injection of apomorphine and oral administration of levodopa/carbidopa, are also submitted

The drug interaction study between apomorphine and levodopa in humans has not been conducted However, sufficient literature information is provided and in clinical studies, most patients were on both levodopa and apomorphine Therefore, the study will not be requested as a Phase IV commitment

**B General Clinical Pharmacology**

***1 What is the basis for selecting the response endpoints, and how are they measured in clinical pharmacology and clinical studies?***

In patients with Parkinson's Disease, improvement in motor function following subcutaneous apomorphine administration was determined The Unified Parkinson's Disease Rating Scale (UPDRS) served as the primary clinical end point

***2 Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?***

Yes Please see Analytical Method

***3 What are the characteristics of the exposure-response relationships for efficacy and safety?***

*a) Based on PK parameters, what is the degree of linearity in the dose-concentration relationship?*

In a study reported in the literature, the dose-linearity of apomorphine pharmacokinetics following two SC injections was evaluated in 6 patients over a range of 20 to 179 µg/kg A proportional relationship between dose and AUC was observed for some subjects, but a conclusion could not be made due to the overall variability of the normalized AUC (35% CV) Another study demonstrated that following single SC doses of 0 5 to 4 mg, body-weight related doses in ten patients were linearly correlated with both $C_{max}$ and AUC

In the studies conducted by the applicant, although no definitive conclusion in regards to linearity could be made from a volunteer study due to small number of subjects, the study conducted in patients demonstrated dose proportionality The following table shows the results from AUCL, AUCI, and CPEAK parameter regression analyses, indicating pharmacokinetic dose proportionality over the dosage interval studied (2 mg to 8 mg) in idiopathic Parkinson's disease patients

| Dependent | Coefficient | R-square |
|---|---|---|
| AUCL | 4 78 | 0 9161 |
| AUCL | 5 05 | 0 9181 |
| CPEAK | 5 17 | 0 8958 |

The study also indicated that apomorphine does not have a tendency to accumulate in patients with idiopathic Parkinson's disease

*b) How is the onset and offset of the pharmacological response or clinical endpoint?*

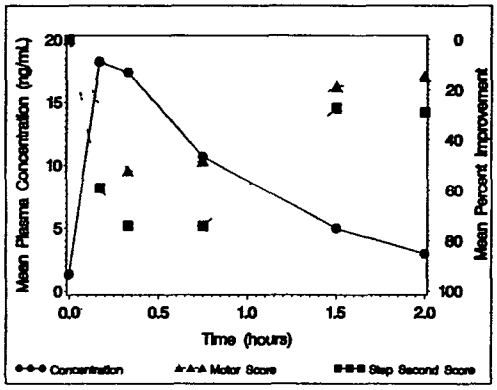
In the literature, modeling approaches have been utilized to describe the relationship between apomorphine pharmacokinetics and pharmacodynamics (PK/PD) Ten Parkinson's patients were administered SC apomorphine of 0 5, 1, 2, and 4 mg doses and the clinical response and pharmacokinetic parameters were evaluated A successful fit to a sigmoidal $E_{max}$ model was obtained to describe changes in the Columbia University Rating Scale (CURS) This modeling demonstrated evidence for a sigmoidal response relationship with the existence of a threshold level for response Dose increases above this threshold appeared to lead to prolongation of the motor response, but did not increase the magnitude of the motor response A short equilibrium half-life (6 minutes) between the plasma concentration and the effect concentration was observed

A literature study showed a strong correlation between the CSF concentration and effect in two Parkinson' s patients Sigmoidal $E_{max}$ models were successfully fit to the PK/PD data of the subjects A short equilibrium period (10 and 20 minutes) between plasma and CSF peak concentrations was observed

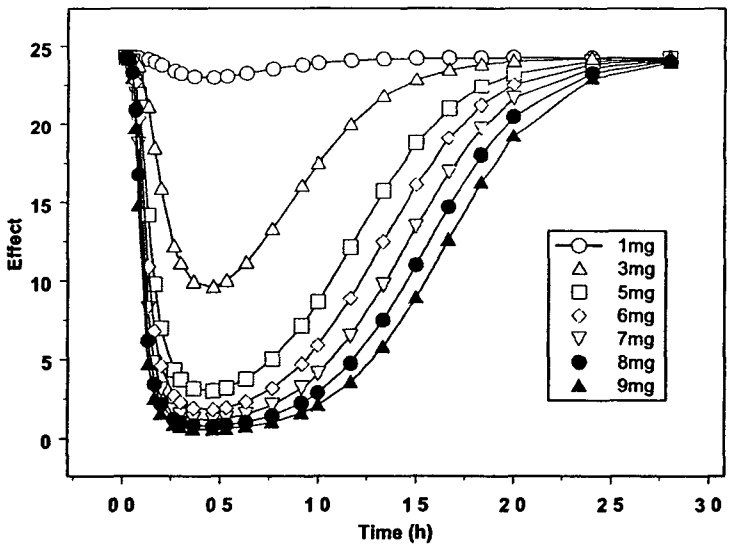
In another literature study, a therapeutic window for apomorphine was described for ten Parkinson's disease patients by defining the minimum effective concentration (MEC), the minimal dyskinetic concentration (MDC) and the minimal toxic concentration (MTC) Of the five patients who demonstrated both a clinical benefit and an adverse event, the mean MEC was 3 9 ng/mL (1 4 to 5 3 ng/mL), and the mean MTC was 15 2 ng/mL (8 5 to 24 5 ng/mL) Substantial interindividual variability in this window between efficacy and toxicity was observed

Apomorphine pharmacokinetics and pharmacodynamics have been described as "quantal" with a threshold concentration below which no therapeutic response is seen Increasing concentrations above the threshold may prolong the duration of therapeutic response, but do not elicit a greater magnitude of response

The applicant conducted a PK/PD analysis in patients with Parkinson's Disease The improvement in motor function following subcutaneous apomorphine administration occurred within 10 minutes (peak effect occurred around 40 minutes after dosing) and persisted for about 90 minutes as shown in the following figure The $EC_{50}$ in patients with Parkinson's disease is 10 7 ng/mL and 5 3 ng/mL for the UPDRS motor scores and the modified Webster step second test scores, respectively




Based on this model, the reviewer performed a simulation to show the motor improvement at different doses As shown in the following figure, doses more than 6 mg do not produce significant extra effectiveness On the other hand, the decreases of blood pressures and pulse may be dose-dependent Balancing the benefit and risk, therefore, doses more than 6 mg are not recommended and the dose increment is recommended to be 0 5 mg instead of 1 mg at the




beginning of the dose titration (please see Pharmacometrics review for details)

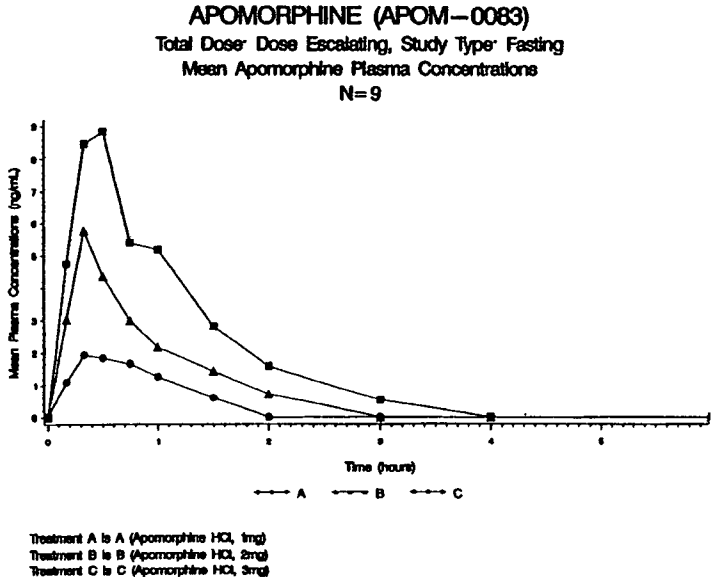
***4 How does the PK of the drug in healthy volunteers compare to that in patients?***

*a) What are the basic PK parameters?*

Following parenteral bolus administration, apomorphine pharmacokinetics are most commonly described as biphasic Following IV bolus injection the distribution half-life ($t_{1/2}\alpha$) was 7 2 ± 2 1 minutes and the terminal elimination half-life ($t_{1/2}\beta$) was 47 5 ± 9 9 minutes Following SC administration to the abdomen $t_{1/2}\alpha$ was 14 2 ± 6 8 minutes and $t_{1/2}\beta$ was 69 7 ± 26 minutes Averaging results across SC and IV routes of administration in 11 of 15 patients, a two-compartment model disposition was observed with $t_{1/2,\alpha}$ of 4 8 ± 1 1 minutes and an elimination

half-life of 33 6 ± 3 9 minutes Other studies have reported mean terminal elimination half-lives of 41 to 49 minutes following IV administration

The applicant obtained similar pharmacokinetic parameters to the literature reports The following figure shows the pharmacokinetic profiles for single doses of subcutaneous apomorphine hydrochloride (1, 2, and 3 mg) injection in healthy adult male and female volunteers




The single dose pharmacokinetic parameters for apomorphine HCl in healthy volunteers calculated using noncompartmental techniques are summarized in Table below (Mean (% CV))

**MEAN (%CV) APOMORPHINE HCL PHARMACOKINETIC PARAMETERS IN NINE HEALTHY MALE AND FEMALE SUBJECTS FOLLOWING A SINGLE, SUBCUTANEOUS INJECTION OF THE ASSIGNED TREATMENT UNDER FASTING CONDITIONS.**

**PROTOCOL NUMBER APOM-0083**

| Treatment | Parameter | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | AUCL (ng x hr/mL) | AUCI (ng x hr/mL) | CPEAK (ng/mL) | TPEAK (hr) | KEL ($hr^{-1}$) | HALF (hr) | CL (L/hr) | VD (L) |
| A 1 mg n=3 | 1.856 (27.51) | 2 777 (20 01) | 2 060 (13 62) | 0 470 (51.59) | 1.026 (23 14) | 0 703 (25 80) | 369.5 (19 17) | 373 8 (29 99) |
| B 2 mg n=3 | 4 746 (19 40) | 6 046 (16 60) | 5 778 (6.59) | 0 330 (0 000) | 0.861 (15 89) | 0 820 (16.50) | 337.5 (17 85) | 393.4 (12.94) |
| C. 3 mg n=3 | 10.06 (22.60) | 10.90 (20 02) | 10.35 (27 17) | 0 443 (22.14) | 1.039 (15 42) | 0 680 (16 70) | 282.3 (19 06) | 276.3 (24 14) |
| Source: Study Report APOM-0083 Section 14 1 Attachment 1 part 3 and part 5 | | | | | | | | |

The pharmacokinetic profiles and the parameters for subcutaneous apomorphine HCl injection in patients with idiopathic Parkinson's disease were determined by noncompartment approach as shown in the following table

SINGLE-DOSE APOMORPHINE HCL PHARMACOKINETIC PARAMETERS IN FIVE (5) IDIOPATHIC PARKINSON'S DISEASE PATIENTS TAKING THREE (3) DIFFERENT DOSES OF APOMORPHINE SUBCUTANEOUSLY (data deleted)[1]

PROTOCOL NUMBER APOM-0073

| | Parameter | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | NAUCL[2] | NAUCI[2] | NCPEAK[3] | TPEAK (hr) | KEL ($hr^{-1}$) | HALF (hr) | CL[4] (L/hr) | VD[5] (L) |
| Mean Parameter Value | 4.643 | 4.960 | 4.867 | 0.227 | 0.988 | 0.720 | 225.0 | 230.4 |
| Coefficient of Variation (%) | 35.6 | 34.0 | 36.3 | 35.0 | 16.4 | 18.0 | 35.1 | 36.2 |
| Range | | | | | | | | |

[1] Patient 21 s Treatment Day 2 deleted due to incomplete concentration profile; Patient 11 s data deleted due to pre-dose apomorphine concentrations on Treatment Days 1 2, and 3
[2] Dose normalized parameter is expressed as (ng·hr/mL)/ mg apomorphine
[3] Dose normalized parameter is expressed as (ng/mL)/ mg apomorphine
[4] Apparent clearance
[5] Apparent volume of distribution

Source: Study Report APOM-0073 Section 14.2 – Attachment 2, part 7

The table below compares the pharmacokinetic parameters between the study conducted in patient and the literature reports

| Parameters | PD patient study | Literature |
|---|---|---|
| AUCL (ng•hr/mL/mg) | 4 64 | 2 03-7 12 |
| CPEAK (ng/mL/mg) | 4 86 | 3 63-6 96 |
| V (L) | 230 | 203-276 6 |
| CL (L/h) | 225 | 228 |

*b Does mass balance study suggest renal or hepatic the major route of elimination?*

No mass balance study has been conducted Based on the literature, after IV infusion, total renal excretion of apomorphine, apomorphine sulfate, and apomorphine glucuronide in humans were 0 3 ± 0 4%, 3 8 ± 1 0% and 6 0 ± 2 2% of an administered dose, respectively Thus, the applicant concluded that renal elimination of unchanged or conjugated R-apomorphine is not a major route of elimination for apomorphine in humans Based on an in vitro study reported in the literature, the autooxidation could account for 30% of apomorphine clearance By the same logic, the applicant did the calculation using the degradation rate constant from another literature study and concluded that autooxidation could account for 30-70% of apomorphine clearance The evidence of autooxidation has not been shown in vivo and the assumption of autooxidation occurring in all tissues has not been validated Further, the autooxidation could not account for the most apomorphine eliminated The major elimination route of apomorphine after SC administration is not clear

In addition, there are controversies regarding pharmacokinetic behaviors of apomorphine between this NDA and L 1 sublingual tablets formulation of apomorphine The controversies are summarized in the following table

| Aspects | Sublingual | Subcutaneous |
|---|---|---|
| Major route | Sulfate | Auto oxidation (through in vitro study) |
| Sulfate | 59% of dose | 3 8 ± 1 0% |
| Hepatic impairment | The point estimates for mild, moderate and severe impairment classes were respectively 36%, 16%, and 62% higher for $C_{max}$, and 59%, 35%, and 68% higher for $AUC_{\infty}$ | $C_{max}$ 25% higher, AUC 9% higher in moderate impairment subject |
| Renal impairment | There was no significant change in mean $C_{max}$ The mean $AUC_{\infty}$ was significantly increased in subjects with moderate (52%) and severe (67%) renal impairment | $C_{max}$ 50% higher, AUC 15-27% higher in moderate impairment subject |

In order to resolve this issue, a mass balance study is needed to investigate the major routes of elimination after subcutaneous administration of apomorphine and the percentage each route accounts for and identify the products of the major route

5 ***What is the inter- and intra-subject variability of PK parameters in volunteers and patients?***

The inter-subject variability in $C_{max}$ and AUC was high For a 30 µg/kg dose, $C_{max}$ differed almost ten-fold among patients and AUC differed five-fold Less variability was observed when a subject received the same dose on multiple occasions

**C Intrinsic Factors**

***1 What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?***

Based on the literature, age, gender, weight, duration of Parkinson's disease, and clinical state were not found to be significant factors for apomorphine clearance in humans Additionally, the large interpatient variability in $T_{max}$, $C_{max}$ and AUC observed was not related to age, gender or weight

The applicant performed studies in both hepatically impaired (APOM-0053) and renally impaired (APOM-0058) volunteers to determine whether the pharmacokinetics of apomorphine are altered in these populations According to the results, the applicant hypothesized that neither (mild or moderate) hepatic impairment nor (mild or moderate) renal impairment would have a significant impact on apomorphine pharmacokinetics However, the 90% confidence intervals of the ratios (calculated by the reviewer) fall outside the limits the relevant Guidances suggest The

patients with hepatic impairment had 24% higher $C_{max}$ and 9% higher AUC compared to the normal subjects as shown in the following table

| Parameters | Ratio | 90% CI |
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| $C_{max}$ | 124 8 | 85 6-181 9 |
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The patients with renal impairment had 50% higher $C_{max}$ and 15-27% higher AUC compared to the normal subjects as shown in the following table

| Parameters | Ratio | 90% CI |
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| $C_{max}$ | 150 06 | 101 78-221 24 |
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Based on a simulation, when dosing renally impaired patients, the onset and maximum effect are not different considerably from the normal renal function patients, whereas the duration of the effects is prolonged Since both effectiveness and adverse events are related to concentration, the starting dose of 2-mg for renally impaired patients would be equivalent to 3 mg (considering the 50% increase of $C_{max}$ in renally impaired patients) To avoid adverse events, the starting dose for renally impaired patients is recommended to be 1 mg (please see Pharmacometrics review for details)

**D Extrinsic Factors**

***1 Is there an in vitro basis to suspect in vivo drug-drug interactions?***

Literatures indicated that apomorphine is subject to extensive first pass metabolism Potential metabolic routes for R-apomorphine include racemization to S-apomorphine, oxidation, metabolism by catechol-O-methyl transferase (COMT), glucuronidation and sulfation, and N-demethylation R-apomorphine is not inter-converted in the body to S-apomorphine Evidence supporting the lack of activity of the glucuronide conjugates, oxidation products and COMT derived metabolites has been reported There is a small fraction of the dose eliminated in the urine as glucuronide conjugate in humans

In vitro studies show that R-apomorphine may be a substrate of catechol-O-methyl transferase (COMT), resulting in the formation of apocodeine and isoapocodeine in a ratio of 81 1 In humans, these metabolites were not detected following intravenous infusions of R-apomorphine at 30 µg/kg over 15 minutes, thus pharmacokinetic interactions with COMT inhibitors are not expected

The applicant conducted three studies using human liver microsomes to investigate the metabolic pathway of apomorphine, enzyme inhibition and induction by apomorphine These in vitro studies showed that NADPH-dependent metabolism of apomorphine by human liver microsomes

appeared to be relatively minimal and the metabolism based drug interactions via either inhibition or induction by apomorphine, are unlikely

*2 Is apomorphine a substrate of CYP enzymes?*

Routes of metabolism of apomorphine was investigated by incubating the drug with microsomes from human livers and studying the appearance of metabolites or the disappearance of apomorphine under various conditions Apomorphine was metabolized by human liver microsomes to a metabolite, M1, believed to be norapomorphine although its structure was not elucidated The formation of M1 appears to be catalyzed by multiple enzymes, including CYP2B6, CYP2C8 and CYP3A4/5 Other enzymes might play a role but could not be unequivocally identified

*3 Is the drug an inhibitor and/or an inducer of CYP enzymes?*

Enzyme induction studies were conducted in cultured human hepatocytes to evaluate the capability of apomorphine to affect the metabolizing capacity of various cytochrome P450s and UDP-glucuronosyltransferase systems The data suggest that apomorphine HCl may be a weak inducer of CYP1A2, CYP2B6, CYP2E1, and CYP3A4/5 enzymes in human hepatocytes However, apomorphine HCl concentrations used in this induction study (8 8 to 88 μM) were significantly greater than those at expected therapeutic plasma levels (approximately 0 04 μM)

An evaluation of apomorphine as an inhibitor of human P450 enzymes in vitro was conducted in pooled human liver microsomes to assess the potential of apomorphine inhibiting the metabolism of other drugs The results of this study showed that as a direct acting (metabolism-"independent") reversible inhibitor, 1) apomorphine appeared to be a competitive inhibitor of CYP2C9 with a Ki value of 370 μM, 2) apomorphine appeared to be a mixed inhibitor of CYP2C19, CYP2E1, CYP1A2 and CYP2D6 with Ki values of 440, 290, 55, and 50 μM, respectively, 3) apomorphine appeared to be a non-competitive inhibitor of CYP3A4/5 with a Ki value of 33 μM These Ki values are much higher than the expected therapeutic plasma levels (approximately 0 04 μM) Therefore, the drug interaction caused by enzyme inhibition by apomorphine is unlikely

*4 Are there other metabolic/transporter pathways that may be important?*

Apomorphine is rapidly cleared from plasma and the plasma half-life ($t_{1/2}$) is brief The short $t_{1/2}$ is explained in part by rapid degradation of apomorphine Literature showed that apomorphine is subject to photo degradation and auto oxidation (please see B 4 b)

*5 What other co-medications are likely to be administered to the target patient population?*

An antiemetic, trimethobenzamide, (300 mg three times daily) three days prior to starting apomorphine, was used in the clinical trial No formal drug interaction studies have been conducted

*6 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?*

Literature showed that levodopa peripheral pharmacokinetics were unchanged in a double-blind, randomized, two-way crossover study that evaluated the impact of subcutaneous apomorphine co-administration on the pharmacokinetics and pharmacodynamics of levodopa in patients However, motor response (MR) and PK/PD parameter differences were significant The threshold levodopa concentration necessary for a MR was reduced significantly leading to an increased duration of effect without a change in the maximal response to levodopa therapy

An open-label, randomized study in patients with Parkinson's disease was reported in the literature to compare the pharmacokinetic parameters of a half tablet of 25/100 Sinemet taken during the last third of an "on" period of apomorphine 3 mg injection with the pharmacokinetic parameters of the same dosage taken after the end of that "on" period In the former situation, the $C_{max}$ and bioavailability of both levodopa and carbidopa were significantly reduced Additionally, the duration of the "on" period was reduced to 107 minutes when Sinemet was given during the "on" period compared to 155 minutes when given after the "on" period The pharmacological mechanism for this interaction is unknown, however, the study results suggest that Sinemet should be taken after the end of an "on" period induced by apomorphine

*7 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?*

The applicant did not conduct the protein binding study Based on the literature, plasma protein binding of apomorphine was estimated at greater than 99 9% over a range of 1257 ng/mL to 3112 ng/mL However, these concentrations are much higher than the therapeutic concentration (about 10 ng/mL) The applicant should conduct a protein binding study using the clinical relevant concentration before putting the claim in the labeling

**E General Biopharmaceutics**

*1 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?*

A request was submitted to waive the requirements for in vivo bioavailability and bioequivalence for the 3-mL cartridge It was developed for use in a multiple use pen with benzyl alcohol as preservative, while the 2-mL ampoule was used in all the clinical trials In spite of the request, the applicant conducted studies to support the bioequivalence of the cartridge apomorphine formulation with 0 5% benzyl alcohol as compared to the ampoule apomorphine formulation without benzyl alcohol The reports for these studies are provided in an information amendment The first study conducted was a phase I, open-label, two-way crossover study in healthy volunteers The study compared the pharmacokinetics of apomorphine HCl formulated with benzyl alcohol and delivered from a cartridge using a pen device versus apomorphine HCl formulated without benzyl alcohol delivered using a syringe manually filled from an ampoule During this study, the applicant discovered through in vitro testing that the small volume (0 02 mL) priming instructions used in this study did not repeatedly eliminate all of the air bubbles from the cartridge Therefore, the priming instructions were revised so that a larger priming dose setting is required (0 06 mL)

Due to the impact of the priming instructions on the accuracy of the dose delivered, the applicant conducted an additional study This was a phase I, open-label, three-way crossover study in healthy volunteers to compare the pharmacokinetics of apomorphine HCl formulated with benzyl alcohol versus apomorphine HCl formulated without benzyl alcohol It compared apomorphine HCl delivery from a cartridge using a pen device to that from a syringe manually-filled from an ampoule or cartridge The results are summarized as follows

- The cartridge formulation delivered using a pen device was bioequivalent to the cartridge formulation delivered using a manually-filled syringe
- The cartridge formulation containing benzyl alcohol (0 05% w/v) and delivered using a manually-filled syringe was bioequivalent to the ampoule formulation without benzyl alcohol delivered using a syringe
- The cartridge formulation delivered using a pen device was bioequivalent to the ampoule formulation delivered using a manually-filled syringe

Based on the study results, and considering benzyl alcohol is not expected to interfere with the pharmacokinetics of apomorphine, the cartridge formulation is considered to be bioequivalent to the clinical formulation (ampoule formulation) However, since the bioequivalence study was conducted at lower dose (2 mg), certain side effect of benzyl alcohol, such as irritation at injection site might not manifest Therefore, the safety of cartridge formulation should be monitored and reported

## F Analytical Section

***1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?***

Assay of apomorphine used

Its performance is summarized in the following tables

| Linearity (ng/mL) | LOQ (ng/mL) | Recovery % | | | Accuracy (%error) | | precision (%CV) | |
|---|---|---|---|---|---|---|---|---|
| | | Low | High | Internal standard | Intra-day | Inter-day | Intra-day | Inter-day |
| | | | | | | | | |

| Stability | | | | Stock solution stability | | | |
|---|---|---|---|---|---|---|---|
| Room temp | Freeze-thaw | -15°C | Post extraction | Apomorphine | | Internal standard | |
| | | | | 4°C | Room | 4°C | Room |
| | | | | | | | |

Based on current standard, the assay is acceptable

18 pages redacted from this section of the approval package consisted of draft labeling

**Appendix II Pharmacometrics Review**

**PHARMACOMETRICS REVIEW**

| | | |
|---|---|---|
| **NDA** | 21-264 | **SUBMISSION DATES** January 7, 2003<br>March 18, 2003<br>April 28, 2003 |
| **DRUG NAME** | [redacted] (Apomorphine hydrochloride) | |
| **DOSAGE STRENGTH** | Injection 10 mg/mL | |
| **APPLICANT** | BERTEK Pharmaceuticals Inc<br>Morgantown, WV25504 | |
| **REVIEWER** | John Duan, Ph D | |
| **TEAM LEADER** | Joga Gobburu, Ph D | |
| **TYPE OF SUBMISSION** | New Drug Application | |

Apomorphine is a potent, short-acting, dopamine agonist Its mechanism of action involves the stimulation of dopamine receptors in the corpus striatum, which leads to anti-parkinsonian activity The subcutaneous injection formulation of Apomorphine is developed for the rescue treatment of "off episodes" associated with Parkinson's disease ("On-off " is a phenomenon in which abrupt but transient fluctuations in the severity of parkinsonism occur unpredictably but frequently during the day The "off" period of marked bradykinesia has been shown to relate in some instances to falling plasma levels of levodopa During the "on" phase, dyskinesias are often conspicuous but mobility is increased) In the submission, a PK/PD analysis is provided This review evaluates this analysis

**Objectives**

The objectives of this review are to answer the following questions

1 What is a reasonable maximum dose?
2 What is a reasonable dose increment?
3 What is a reasonable repeated dosing regimen?
4 Should renal impairment patients be dosed differently?

**Data**

**Study APOM0073**

APOM0073 was an open-label study Unified Parkinson's Disease Rating Scale (UPDRS) motor scores and modified Webster's step second scores obtained over a two-hour period on three separate occasions from six patients with idiopathic Parkinson's disease were included in the population PK/PD analyses The patients had received active apomorphine treatment, and had established a clinically stable maintenance dose under APO401 for at least one month

This study consisted of a baseline visit followed by four treatment day visits Each treatment visit consisted of apomorphine HCl administration followed by a collection of pharmacodynamic measurements and blood samples for pharmacokinetic purposes After midnight on the evenings prior to the scheduled study dosing of apomorphine, no apomorphine was to be administered to the patient For Treatment Days 1 and 4, the patient's currently stable maintenance dose of

apomorphine (their "titrated dose") from the APO401 study was utilized For Treatment Days 2 and 3, the patients received their titrated dose plus or minus 2 mg according to the randomization scheme If the patient's titrated dose was less than 4 mg, then the lowest dose administered was 2 mg If the patient's titrated dose was greater than 8 mg, then the highest dose administered was 10 mg On Treatment Days 1, 2 and 3, only one dose of apomorphine was administered for study purposes following the first "Off' state in the morning On these days, no additional apomorphine injections were given from midnight until four hours after study apomorphine administration Concomitant medication was not allowed from 1 5 hours prior to study apomorphine dosing until 2 hours after apomorphine administration On Treatment Day 4, patients received three doses of study apomorphine at 1 5 hour intervals beginning with the first "Off' of the morning Concomitant medications for Treatment Day 4 were allowed without regard to study apomorphine dosing or pharmacokinetic sampling times

On Treatment Days 1, 2 and 3, 5 mL (1 x 5 mL) serial blood samples were collected at 0, 10, 20, and 45 minutes, and 1 5, 2, 3, and 4 hours after dosing On Treatment Day 4, 5 mL (1 x 5 mL) serial blood samples were collected at the following times relative to the first apomorphine dose 0, 20, 90, 110, 180, 200 and 270 minutes The 0, 90 and 180 minute blood collections were obtained within 5 minutes of apomorphine-administration on Treatment Day 4

The pharmacodynamic measurements taken during this study included a modified Webster Step-Seconds Test, the Unified Parkinson's Disease Rating Scale (UPDRS) assessment, dyskinesia assessment, and orthostatic "tilts" The Webster Step-Seconds Test was performed on each Treatment Day at each pharmacokinetic blood collection time period The UPDRS motor portion of the rating scale was computed using only questions 18 through 31, and was performed prior to apomorphine dosing and at 20 and 45 minutes, and 1 5, 2, 3, and 4 hours post-dose on Treatment Days 1, 2, and 3 On Treatment Day 4, the UPDRS motor score evaluation occurred prior to study apomorphine dosing and following each pharmacokinetic blood collection The assessment of dyskinesia was performed at each blood collection time point on Treatment Days 1, 2, 3, and 4 In addition, orthostatic "tilts" (encompassing systolic and diastolic blood pressure measurements and pulse rate) and ECG measurements were performed prior to each dose of apomorphine HCl during the pharmacokinetic blood collection interval and following the collection of each 20 minute blood sample on Treatment Day 4

***Study APO303***

This was a study entitled "Study of Orthostatic Changes upon Apomorphine Dose Initiation in Late Stage Parkinson's Disease patients A Dose Escalation Study with a Double-blind Placebo-Controlled Efficacy Determination at 4 mg " This was a sub-study using patients enrolled in AP0401 (the long-term open label safety protocol) to address the concerns regarding adverse events, particularly orthostatic hypotension, during dose introduction in apomorphine-naive patients This was a two-phase study that involved a controlled in-office dose titration phase followed by a 6-month outpatient open-label treatment phase Fifty-six patients were enrolled and analyzed for safety Dose escalation beginning at 2 mg and increasing by 2 mg increments to a maximum of 10 mg per dose by intermittent subcutaneous injection Maximum recommended daily dose limits were 10 injections per day, and 100 mg daily

**Method**

Mixed-effect PK/PD models were developed to characterize the relationship between apomorphine concentrations and motor scores as well as step second scores in patients These analyses were performed using NONMEM program (Version V, Level 1 1)

**PK model**

Bayesian estimates of pharmacokinetic parameters of individual subjects obtained from the NONMEM model were used to calculate the drug concentrations of each subject in PK/PD modeling The one-compartment model with first-order absorption and elimination was obtained through the subroutines ADVAN2 of the PREDPP portion of the NONMEM program The absorption rate constant (ka), apparent volume of distribution (V) and apparent clearance (CL) are modeled as follows

$ka = TVka \cdot \exp(\eta_{ka})$

$V = TVV \cdot \exp(\eta_{v})$

$CL = TVCL \cdot \exp(\eta_{CL})$

where TVka is the typical value of ka TVV is the typical value of V and TVCL is the typical value of CL Exponential error models were employed for the between-subject variability of ka, CL, and V ($\eta_{ka}$, $\eta_{v}$ and $\eta_{CL}$) Effect site drug concentrations (Ce) are used to correlate with delayed pharmacodynamic response A first order delay between plasma concentrations and effect site concentrations was characterized with an effect compartment model

**PD models**

The UPDRS-motor score PK/PD relationship is based on an inhibitory sigmoid Emax model

$$\text{Motor Score} = B_0 \times \left(1 - \frac{Emax \times Ce^n}{Ce^n + EC_{50}{}^n}\right)$$

where Bo is the baseline motor score, Emax is the maximum inhibitory effect, Ce is the drug concentration at the site of action, $EC_{50}$ is the drug concentration that causes 50% of the maximum effect, n is the Hill's sigmoid coefficient

Exponential error models were used for the between-subject variability (BSV) of $EC_{50}$ and Bo ($\eta_{EC}$ and $\eta_{Bo}$ as shown in the following equations)

$EC_{50} = TVEC \cdot \exp(\eta_{EC})$

$Bo = TVBo \cdot \exp(\eta_{Bo})$

where TVEC is the typical value of EC50 and TVBo is the typical value of Bo

The modified Webster's step second score PK/PD relationship is based on a stimulatory sigmoid Emax model Transformation of step second score is performed prior to PK/PD modeling

Transformed Score = 1000 / (step second score)