Dear Committee Members:

Thank you for your agreement to participate in the April 10, 2000, Reproductive Health Drugs Advisory Committee Meeting. The purpose of this meeting is to discuss the use of Uprima (apomorphine HCl), given sublingually as a tablet, for the treatment of erectile dysfunction (ED). TAP Pharmaceuticals seeks approval for the 2, 3, and 4 mg strengths of apomorphine for this indication. The 2 and 4 mg doses have been studied in clinical trials. The 3 mg dose will be considered for approval based on the safety and efficacy profiles of the 2 and 4 mg doses (i.e. through "bracketing" of data). TAP Pharmaceuticals seeks a dosing regimen that begins with a 2 mg dose of apomophine, titrating upwards, if necessary, to a 3 or 4 mg dose.

All doses studied (2, 4, 5, and 6 mg) will be reviewed for assessment of safety, since data from each dose provides perspective on not only the safety profile of a given dose, but on the therapeutic index of this drug. Assessments of efficacy will primarily focus on data with the 2 and 4 mg doses for which approval is sought, although the individual clinical trials that used higher doses will include results from all dosing groups studied.

We hope that this background package is informative. To facilitate your review of this information, a very brief overview of each section, pointing out relevant issues and concerns, is provided. These sections reflect our preliminary position and should not be contrived as being final or as being FDA's "official" position on the safety and effectiveness of Uprima for the treatment of erectile dysfunction. Indeed, we are seeking your input to help us reach a final conclusion about whether the data support the safety and effectiveness of Uprima for this indication.

Section 1: Background

This brief overview of erectile dysfunction should provide you with some rudimentary knowledge of this condition, and provide some important historical perspective on three drugs that have been developed and approved for this indication (the injectable agent Caverject®, the intraurethral suppository Muse®, and the oral tablet Viagra®). The following are issues of particular relevance to the apomorphine application:

- The majority of clinical trials for apomorphine required that patients have a normal result on a nocturnal penile tumescence (NPT) test, and that they demonstrated an erection suitable for intercourse within 3 months of enrollment. Patients with a normal NPT test are presumed to have the capacity for spontaneous erotically-induced erections. It is important that the patient population studied be carefully reviewed to assure that the indication statement for apomorphine is fully supported.
- The drug Muse® provides important historical perspective. This is an approved drug for ED that causes hypotension and syncope (the same major safety concern noted with apomorphine). Notably, this drug has a relatively rapid onset of action and is metabolized very quickly.
- The drug Viagra® similarly provides important historical perspective, as it is the only approved oral agent for ED. Viagra® has an onset of action and duration of action fairly similar to apomorphine.

Section 2: Chemistry, Manufacturing and Controls

This section is provided as background information. At this time, there are no significant chemistry issues to be raised at the April meeting.

Section 3: Pharmacology and Toxicology

This section is provided as background information. At this time, there are no significant preclinical issues to be raised at the April meeting.

Section 4: Pharmacokinetics and Drug Interactions

This section describes basic pharmacokinetic information of relevance to apomorphine. The following issues are relevant to the apomorphine application:

- While pharmacokinetics of apomorphine are dose proportional, the intersubject variability in the bioavailability of apomorphine varies by 52-78% (for C_{max}) and by 40-52% (for AUC). Upon cross study comparisons, the C_{max} and AUC of apomorphine are not distinguishable between the 4 and 5 mg doses, or the 5 and 6 mg doses. In the individual subject, therefore, it may be difficult to reliably predict the serum levels and perhaps the safety and tolerability of a given dose of apomorphine.
- Apomorphine and alcohol interaction is a significant safety concern. A summary of four drug/alcohol interaction studies investigating this are included for review. A biopharmaceutical summary of the data and a clinical summary of the same data are both included in this package in this section.

Section 5: Statistical

Four clinical studies were reviewed for efficacy and a brief summary of results is included. The major conclusion is:

- Based on the primary, prespecified efficacy variable (percentage of home-use attempts resulting in erection firm enough for intercourse), all four studies demonstrate statistical evidence of efficacy for the 2 and 4 mg doses of apomorphine versus placebo.

Section 6: Clinical

A global summary of efficacy and safety is provided. Following this summary, individual study report summaries are provided for review as well.

Regarding efficacy, the following issues are raised for consideration:

- Trials generally enrolled healthy men "with no major organic component" of ED. Small trials in men with diabetes and status post prostatectomy were performed, and provide limited perspective on the efficacy of apomorphine in patients with organic ED.
- Apomorphine consistently showed a statistically significant improvement over placebo in controlled clinical trials. In addition, there is evidence of dose-responsiveness to support the efficacy of apomorphine. The clinical relevance of these statistically significant results, particularly for the 2 mg dose, should be considered carefully.
- Patients may have become unblinded to study drug assignment due to the common occurrence of nausea. This may have led to expectation bias and influenced efficacy results.
- Perhaps the most relevant efficacy data is found in Study M97-763. This study was placebo-controlled and included a dose titration arm that began with a 2 mg dose, titrating up to a 4 mg dose (the titration regimen that is recommended in the label). The success rate in this arm was statistically significant: 47.5% for apomorphine compared to 34.7% for placebo for the primary endpoint: percentage of home-use attempts that were adequate for intercourse. The clinical relevance of this degree of improvement should be considered.
- Many patients discontinued prematurely from 6-month open label trials due to lack of efficacy.

Regarding safety, the following issues are raised:

- The major area of concern is the occurrence of serious adverse events including syncope, hypotension, and bradycardia (i.e. vaso-vagal type symptoms) with the use of apomorphine.
- Nausea, dizziness, sweating, and somnolence are also raised as significant safety issues. Nausea, dizziness, sweating, and somnolence occurred in 32%, 18%, 14% and 14% of patients studied overall, and represent a tolerability profile that leads to concern. When data is limited to the 2 and 4 mg dose arms, the rates of these events affect 16%, 9%, 6% and 8% of patients. Nausea was the most common cause of study drug discontinuation (affecting 5% of patients overall).
- The nature of many of these safety issues lead to concern that men with organic ED (who were not studied in most of the apomorphine clinical trials and who may have significant underlying cardiovascular disease) may be at particular risk. The large majority (about 85%) of the overall population studied with apomorphine were under age 65 and did not have organic ED.
- Perhaps the most relevant safety data is also found in Study M97-763. This study was placebo-controlled and included a dose titration arm that began with a 2 mg dose, titrating up to a 4 mg dose (the titration regimen that is recommended in the label). The safety profile of apomorphine in this treatment arm versus placebo provides the clearest information on tolerability of the proposed regimen.
- Apomorphine appears to interact with alcohol, which may lead to additional safety concerns. Please refer to Section 4 (Pharmacokinetics and Pharmacodynamics) of this package for details of these studies.
- Apomorphine appears to interact with nitrates. This may lead to additional safety concerns. Details from this study can be found in this section, under the subsection entitled Study M98-930. Review of this information is important since the only other approved oral agent for ED, Viagra®, is contraindicated for use with nitrate therapy.
- It is notable that the large majority of patients who are given the option of dose titration end up on a 4 mg dose. Thus, it is felt that the review of safety should focus on the safety profile of the 4 mg dose (and doses just above this, which clarify the therapeutic window of safety for this drug).
- Many patients discontinued prematurely from 6-month open-label trials due to adverse events.

Section 7: Sponsor's Proposed Labeling:

A copy of the apomorphine labeling as proposed by TAP Pharmaceuticals is included for your reference.

In closing, please note that TAP Pharmaceuticals has prepared its own briefing document, which is being sent to you under separate cover. We thank you for your attention to this package, and look forward to an interactive and productive advisory panel meeting in April.

Sincerely,

_____

Marianne Mann, M.D., Deputy Director,
Division of Reproductive and Urologic Drug Products