EXCLUSIVITY SUMMARY for NDA # 20-708 SUPPL # 005

Trade Name Lupron Depot **Generic Name** leuprolide acetate
Applicant Name TAP Holdings Inc **HFD** 580

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?
   YES /___/ NO /X/

   b) Is it an effectiveness supplement?

   YES /X/ NO /___/

   If yes, what type? (SE1, SE2, etc.) SE7

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /X/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   To demonstrate equivalence between two lupron depot formulations.

d) Did the applicant request exclusivity?

YES /___/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /✓/ NO /___/

If yes, NDA # 20-263 Drug Name Lupron Depot PeD

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # _____

Investigation #_, Study # _____

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # ____ YES /___/ NO /___/ Explain: _____

Investigation #2

IND # ____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

/S/

_____ 2/4/99

Signature Date
Title:_____

/S/

_____ 2/11/99

Signature of Division Director Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

FD & C (Act 306 (k) (1)

TAP Holdings Inc. Certifies that we did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) [section 306 (a) or (b)] in connection with this application.

The clinical study M96-506 involving patients was conducted in compliance with the institutional review board regulations in part 56 and the informed consent regulations in part 50.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 21, 1999

FROM: Lisa A. Kammerman, Ph.D., Team Leader (HFD-715) LAK 2/11/99

TO: NDA 20-708, SE8-005

SUBJECT: Comparison of Lupron Depot 3 Month 11.25 mg vs Lupron Depot-1 Month 3.75 mg

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Background

TAP Holdings has submitted a supplement for Lupron Depot 3 Month 11.25 mg. The submission consists of a single study (M96-506) comparing Lupron Depot-3 month 11.25 mg with Lupron Depot-1 Month 3.75 mg for the indication of endometriosis. The lack of statistical significance between the treatment groups for numerous endpoints is the basis for the applicant's conclusion that the two formulations are similar. This memorandum focuses on the statistical issues surrounding this conclusion for the patient and clinical evaluations of pain. Clinical assessments of pain used a four point scale (none=1, mild=2, moderate=3, severe=4) while the patient assessments used an analog scale ranging from "0" for "no pain" to "10" for "intolerable pain".

Statistical Methodology

Summary

For the pain variables, the applicant compared mean change from baseline using a two-way analysis of covariance (ANCOVA) with the baseline value as the covariate and effects for treatment, investigator, and treatment-by-investigator interaction. Contrast statements were used to compare treatment groups.

The means and standard errors presented in the study report are estimated from the ANCOVA model; they are not the observed values. LSMEANS, which equally weights the mean for each center, estimated the means shown as part of the results of the analyses. The standard errors are the mean-squared errors (MSE) from the fitted models.

Comments

The description of the statistical methodology used to conclude "similarity" between the two treatment groups is deficient. The main issues follow.

- The lack of statistical significance between the treatment groups for numerous endpoints is the basis for the applicant's conclusion that the two formulations are similar. This approach is inappropriate. 95% confidence intervals, adjusted both for multiple comparisons and for multiple endpoints, should have been constructed for the differences between treatments and then assessed to see if clinically important differences were excluded by the intervals.

  The clinically important differences should have been defined in the study protocol. Sample size estimates should have been based on these differences. The estimates should have also reflected multiple comparisons and multiple endpoints. The protocol, however, did not include sample size calculations, nor does the submission present a rationale for the sample size studied.

- The submission does not contain the results of the tests for the treatment-by-investigator interaction included in the ANCOVA model, nor does it summarize the results by investigator. Therefore, I cannot assess whether the treatment differences were consistent across investigators or whether treatment-by-investigator interactions existed. The applicant's comparison of treatments using contrast statements assumes no qualitative interactions between treatment and investigator.

- Of the eight investigators, one (Martens) enrolled only two patients, one per treatment group. The ANCOVA model as described in the submission cannot accommodate these sparse data. The summary tables suggest, however, that the data from all patients were analyzed. The submission does not address how the data from this center were included in the analyses.

- An assumption of ANCOVA is that the relationship between the outcome variable (change from baseline) and the covariate (baseline value) is linear, and that the slope of the linear relationship is identical across treatment groups. The submission does not address these issues.

- The ANCOVA of the clinical assessments of pain implicitly assumes the four-point scale is linear. For example, a reduction in pain from severe to moderate is treated the same as a reduction from mild to none. The submission does not address the linearity of the four point scale.

- For each endpoint, mean changes from baseline to each treatment visit were analyzed. In the absence of identifying a primary timepoint, these results should have been adjusted for multiple comparisons.

- The impact both of study dropouts and of the use of last observation carried forward on the interpretation of the analyses was not discussed in the study report. At 24 weeks, 6 (of 20)

patients randomized to Lupron 3.75 mg and 2 (of 21) patients randomized to Lupron 11.25 mg did not contribute to the analyses. The "final" analysis, however, included all patients randomized.

Statistical Reviewer's Analyses

For each of the clinician and patient assessments of pain, and for estradiol levels, I constructed 95% confidence intervals around the difference between the two treatment groups. These were done for the "final" analyses only using the ANCOVA model estimates of means and standard errors. The results are on the next page.

A positive number in the "Difference" column favors a greater decrease from baseline for the 11.25-mg treatment group. Similarly for the Lower and Upper limits of the 95% confidence intervals. For example, the interpretation of the confidence interval for the clinical assessment of dysmenorrhea is: with 95% confidence, the 11.25 mg treatment group could change from baseline as many as .17 units fewer than the 3.75 mg treatment group to as many as .770 units greater than the 3.74 mg treatment group.

These intervals, however, can only be interpreted if the statistical issues raised above can be assumed to have no impact on the study results. If so, then clinical judgement must be used to interpret the 95% confidence intervals to determine whether the 11.25 mg treatment group is similar to the 3.75 mg treatment group.

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APPEARS THIS WAY
ON ORIGINAL

Statistical Reviewer's Construction of 95% Confidence Intervals based on Tables 13, 14, and 16 in Study Report

Variable	Within Group Change from Baseline (SE)		'3.75 mg - 11.25 mg		95% Confidence Interval	
	3.75 mg	11.25 mg	Difference	SE	Lower Limit	Upper Limit
Table 13 -- Clinical Evaluation						
Dysmenorrhea	-1.9 (.17)	-2.2 (.17)	0.3	0.24	-0.170	0.770
Pelvic Pain	-1.6 (.18)	-1.5 (.18)	-0.1	0.26	-0.610	0.410
Pelvic Tenderness	-1.5 (.18)	-1.8 (.17)	0.4	0.25	-0.090	0.890
Pelvic Induration	-1.2 (.16)	-1.3 (.16)	0.1	0.23	-0.351	0.551
Table 14 -- Patient Evaluation						
Dysmenorrhea	-5.9 (.51)	-7.9 (.52)	1.5	0.73	0.069	2.931
Pelvic Pain	-4.6 (.71)	-3.8 (.78)	-0.8	1.06	-2.878	1.278
Table 16 -- Estradiol Levels						
Estradiol	-4.5 (.41)	-4.5 (.41)	0.1	0.58	-1.037	1.237

Source: Tables 13, 14, and 16 of Study Report for M96-506

Note: The estimates of the mean and standard errors reported in this table are estimated from the ANCOVA models fit by the applicant. The study report did not address the assumptions of the ANCOVA models, treatment-by-investigator interactions, the linearity of the pain scales, and the impact of study dropouts (see text of memorandum). Therefore, the confidence intervals must be interpreted with the assumption that these issues do not impact the results.

Summary

Based on the information provided in the study report I cannot sufficiently evaluate the applicant's conclusion that the 3.75 mg and 11.25 mg treatment groups are "similar". The applicant used an inappropriate approach to reach their conclusion. "Lack of statistical significance" between the treatment groups is insufficient for concluding "similarity".

The appropriate approach to evaluating "similarity" is to construct confidence intervals around the treatment differences for the endpoints of interest. Then the intervals can be inspected to determine whether they exclude clinically meaningful differences between the groups. Preferably, these differences are defined *a priori*.

Although I was able to construct 95% confidence intervals from the information provided in the study report, these intervals must be interpreted in view of my comments on the appropriateness of the ANCOVA, the linearity of the clinician and patient scales, and the impact of dropouts. If these issues can be ignored or have no influence then the 95% confidence intervals are interpretable.

cc:
Archival NDA 20-708 (SE8-005)
HFD-580
HFD-580/Mann/Allen/Safran/Kish
HFD-715/Nevius/Kammerman

C Kish

Internal Meeting Minutes

Date: January 19, 1999 **Time:** 10:00 AM - 11:00 AM **Location:** Parklawn C/R 17B-43

NDA 20-708/S-005 **Drug Name:** Lupron (leuprolide acetate) Depot

Type of Meeting: Status/Labeling

Meeting Chair: Marianne Mann, M.D.

Meeting Recorder: Christina Kish

FDA Attendees:
Marianne Mann, M.D. - Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP;HFD-580)
Shelley Slaughter, M.D., Ph.D. - Medical Officer Team Leader, DRUDP (HFD-580)
Susan Allen, M.D. - Medical Officer, DRUDP (HFD-580)
Julian Safran, M.D. - Medical Officer, DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics; Division of Pharmaceutical Evaluation II (DPE II) @ DRUDP (HFD-580)
Johnny Lau, R.Ph., Ph.D. - Pharmacokinetics Reviewer, DPE II @ DRUDP (HFD-580)
Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Christina Kish - Project Manager, DRUDP (HFD-580)

Meeting Objectives:
To discuss the status of reviews and the proposed changes in the sponsor's labeling as a result of supplement review.

Discussion Points:

- Background
  - the sponsor submitted this efficacy supplement in response to Phase 4 commitments for NDAs 19-943 and 20-708 as requested by the Biopharmaceutic reviewer and Clinical Division to update their labeling with multiple dose pharmacokinetic/pharmacodynamic (PK/PD) information
  - the sponsor has submitted comparative PK/PD data on their 4 weeks and 12 weeks injectable depots
  - the sponsor has also submitted updated labeling incorporating the information from the PK/PD study
- Clinical Pharmacology
  - the review is complete and the supplement should be approved
  - PK/PD between the two formulations is comparable
  - the sponsor's proposed paragraph incorporating the data has been revised and should be communicated to the sponsor

- Clinical
  - the Medical Officers have reviewed the Lupron label and have several changes (see attached)
  - a teleconference should be arranged as soon as possible to discuss the changes to the label
  - if there is insufficient time for the sponsor to provide the information to be requested in the labeling update or for that information to be reviewed; the labeling changes proposed by the Medical Officers will be requested in a Supplement Request letter in which a time frame for submission of the labeling supplement is specified
  - the clinical review of this application is complete and is with the supervisor for sign-off

Decisions Reached:

- the Efficacy Supplement may be approved
- the sponsor will be contacted and a teleconference arranged to discuss further modifications to the currently approved label
- depending on the time frame for response to the labeling changes; the efficacy supplement may be approved without the clinical modifications
- if the sponsor is unable to provide the revised labeling in sufficient time to meet the goal date of the current Efficacy Supplement, a Supplement Request in which the clinical modifications to the label are requested may be issued to the sponsor

Unresolved Issues: none

Action Items:

Item	person responsible	time frame
1. Set up telecon with sponsor	C.Kish	ASAP

/S/
Minutes Preparer 1/28/99

/S/ 1/29/99
Concurrence, Chair

cc:
Orig. IND
HFD-580
MEETING ATTENDEES
HFD-580/CKish/1.19.99/n 20708.im
Concurrence:MMann 1.21.99/JSafran 1.22.99/AParekh 1.25.99/JLau 1.22.99/SAllen 1.26.99/SSlaughter 1.27.99
No response:LKammerman

MEETING MINUTES