CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

STN/BLA 125075/0

Administrative Documents

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MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: October 27, 2003

FROM: Dale C. Slavin, Ph.D.
Regulatory Project Manager
Division of Review Management and Policy, HFM-588
Office of Drug Evaluation VI

TO: STN 125075/0

SUBJECT: SBA Equivalent for

- Product: efalizumab (Raptiva™)
- Manufacturer: Genentech, Incorporated
- License Number: 1048

Indications and Usage
For the treatment of adult patients (18 years or above) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Dosage Form, Route of Administration, and Recommended Dosage

- Efalizumab is supplied as a 150 mg single-use vial of lyophilized powder. It is supplied with a diluent syringe containing 1.3 mL of sterile water for injection (non-USP). The vial upon reconstitution is designed to deliver 125 mg of efalizumab in 1.25 mL as a subcutaneous injection.
- Each single-use vial of RAPTIVA contains 150 mg of efalizumab, 123.2 mg of sucrose, 6.8 mg of L-histidine hydrochloride monohydrate, 4.3 mg of L-histidine and 3 mg of polysorbate 20 and is designed to deliver 125 mg of efalizumab in 1.25 mL. No preservatives and no USP standard of Potency

Basis for Approval
The following reviews, filed in the CBER correspondence section of the license file for STN 125075/0, comprise the SBA equivalent for this application/supplement:

Discipline	Reviewer Name	Date
CMC		
Product	Steven Kozlowski, M.D.	10-24-03
Facility	Carol Rehkopf/Michelle Clark-Stuart	10-24-03
Device	Viola Hibbard	10-27-03
Clinical	Elektra Papadopoulos, M.D./Louis Marzella, M.D.	10-27-03

Consult Audiology	James Kane, Ph.D.	4-17-03
Preclinical Pharm/Tox	Andrea Weir, Ph.D.	10-23-03
Clinical Pharmacology	Anil Rajpal, Ph.D.	10-23-03
Statistical	Clare Gnecco, Ph.D.	9-3-03
Bioresearch Monitoring	Lloyd Johnson, Pharm.D.	10-22-03
Labeling Review		
Consult DCRCS	Jeanine Best, MSN, RN, PNP	9-30-03
Consult DMETS	Charlie Hoppes, RPh, MPH	10-9-03
Consult DDMAC	Catherine Miller	9-24-03

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

Date: October 24, 2003

To: Administrative File, STN 125075
Genentech, Inc., South San Francisco, CA

From: Carol Rehkopf, Biologist, CBER/OCBQ/DMPQ, MRB I CR

Through: Chiang Syin, Ph.D., CDER/OC/DMPQ/TFRB CS
Acting Branch Chief

Subject: Review memorandum for BLA: Genentech, Inc. – US License 1048
For approval of efalizumab for the treatment of moderate to severe plaque psoriasis

Action Due: October 28, 2003

Action Recommended: I recommend approval of this BLA

Summary:

Efalizumab is indicated for the treatment of moderate to severe plaque psoriasis in adult patients. It is a recombinant humanized monoclonal antibody to CD11a manufactured at Genentech, Inc., South San Francisco, California.

Review Narrative

Efalizumab is indicated for the treatment of moderate to severe plaque psoriasis in adult patients. Efalizumab is a recombinant humanized monoclonal antibody to CD11a. Other names used for this product include rhuMAb, anti-CD11a, and hu 1124 antibody. This is a humanized form of the murine monoclonal antibody MHM24. The human IgG1 framework contributes to 90% of the overall protein sequence.

Genentech, Inc., South San Francisco, CA is responsible for manufacturing, testing, releasing, and primary packaging of efalizumab drug substance and drug product. Secondary packaging and labeling will be performed by
The Sterile Water for Injection diluent in prefilled syringes will be manufactured

Drug Substance

Cell Banking

Cell banking The Master Cell Bank (MCB) is identified as This MCB was prepared using

I did not review the Characterization and Testing section of the BLA. I defer review of this section to the product office.

The following is the process flow according to the BLA.

Cell Culture

The following overview from the BLA depicts the cell culture process:

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Post Marketing Commitments

1. Genentech has committed to manufacture [redacted] validation lots using a revised validation protocol that includes [redacted] testing.

2. Genentech has committed to reevaluate [redacted] specification after obtaining [redacted] lots of commercial manufacturing history. This evaluation and supporting data will be submitted to the agency.

Copies To:
Dale Slavin
Steve Kozlowski
Michelle Clark-Stuart
Chiang Syin
Carol Rehkopf

Center for Devices and Radiological Health

(ODE/DOED/ENTB)

Audiology Review

To: Elektra Papadopoulos, M.D.

From: James K. Kane, Ph.D.

Date: 04/17/03

Through: Eric A Mann, M.D., Ph.D.
Branch Chief, ENTB

Re: STN 1250750 (BLA) CBER Consult

I have reviewed this submission and present the following summary and evaluation:

I. Background:

The sponsor, Genentec, Inc., is seeking FDA approval for the use of efalizumab in moderate to severe plaque psoriasis. Efalizumab is an immunosuppressive humanized monoclonal antibody, which blocks CD11a and thus may work by inhibiting lymphocyte activity and transmigration into tissue.

During a prior Phase II study (HUPS252) a subject experienced a serious adverse event of transient unilateral hearing loss. Consequently, audiological testing was performed in three subsequent clinical trials (HUPS254, HUPS256, ACD2058g). The CBER requested an Audiology review regarding the summary data submitted by the sponsor from these three studies, as well as the narrative reports of two serious adverse events (SAEs): S#642 from Study HUPS252 and S#19501 from Study ACD0258g. In addition, the reviewer was asked to respond to the following:

1. *With regard to bone conduction data, what (if any) is the value of correlation between air and bone conduction?*
2. *Does the consultant agree with definitions of hearing change?*
3. *Does the consultant agree with the overall assessment of the sponsor?*

Clinically significant changes from baseline sensitivity were categorized as "improved" vs. "no change" vs. "worsened" for the three subject groups: placebo, low-dose (1.0 mg/kg/wk) and high-dose (2.0 mg/kg/wk). Threshold measurements were obtained at three timelines:

- First Treatment (FT) Day 0 (Baseline)
  [prior to study drug administration]
- ±7 days of FT Day 84 (2nd Audiogram)
  [subjects who were "responders" at FT Day 84 entered the Observation (OB) period]
- ±7 days of Re-treatment (RT) Day 84 (3rd Audiogram)
  [subjects who relapsed during the OB subsequent to FT Day 84]

OR

- ±7 days of Extended Treatment (ET) Day 84 (3rd Audiogram) [subjects who were partial or non-responders at FT Day 84]

The criteria for meaningful threshold change by air conduction at frequencies from 500 Hz to 8000 Hz in one ear relative to a pretreatment assessment were the same in all studies:

≥ 20-dB increase or decrease in threshold at one or more frequencies in either ear

≥ 15-dB increase or decrease in threshold at two or more frequencies in either ear

≥ 10-dB increase or decrease in threshold at three or more frequencies in either ear

These threshold change criteria were taken from the 21 November 1997 Anti-Infective Drugs Advisory Committee 62nd Meeting (Center for Drug Evaluation and Research, FDA, Bethesda, MD).

II. Device Trade Name:

Efalizumab

III. Indications for Use:

Moderate to severe plaque psoriasis

IV. Reviewer Reponses:

Q#1: With regard to bone conduction data, what (if any) is the value of correlation between air and bone conduction?

The difference between air- and bone-conduction thresholds[1] in the same ear permits attributing the loss in hearing sensitivity to either the conductive pathway (outer- and / or middle-ear), the sensory transduction mechanism (cochlea) and / or associated neural pathways or both. Based on these threshold measurements, three types of hearing loss may be differentiated:

Conductive Hearing Loss: bone-conduction thresholds within the normal sensitivity range (0-25 dB HL), but air-conduction thresholds are poorer than bone-conduction by at least 15 dB.

[1] Air conduction testing assesses auditory sensitivity when the signal is transmitted through the outer-, middle-, and inner ear and then through the brain to the cortex. Testing may be performed using headphones, insert earphones, or via sound field. In contrast, bone conduction testing assesses auditory sensitivity when the signal is transmitted through the bones of the skull to the cochlea and then through the auditory pathways of the brain. A small oscillator is placed on the forehead or mastoid. The device stimulates the bones of the skull, which in turn stimulates both cochleae. This type of testing bypasses the outer- and middle-ear.

Sensorineural Hearing Loss: bone- and air-conduction thresholds within 10 dB of each other and all thresholds are greater than 25 dB HL.

Mixed Hearing Loss: both conductive and sensorineural components are present.

Threshold category changes ("Improved" vs. "No Change" vs. "Worsened"), based on the sponsor's three threshold-change criteria, reported for Study ACD2058g in Table 12.5.2-1 and Table 12.5.2-3 are based on air-conduction thresholds within the frequency range from .5 kHz – 8 kHz. In contrast, the summary data ("Treatment-Emergent Changes in Audiogram Testing") for Study ACD2058g reported in Table 3 only uses two categories ("Improved" vs. "Worsened") and does not specify air- or bone-conduction thresholds or the frequency range used for data categorization. The latter also applies to the results reported for Study HUPS254 (Table 1) and Study HUPS256 (Table 2). Even so, it is probable that all data represented the frequency range from .5 kHz – 8 kHz and were based on air-conduction thresholds. Therefore, it does not appear that bone-conduction data were necessary for study outcome results, at least for those reported in the above referenced tables.

It is this reviewer's opinion that unless there were some reason(s) to expect conductive involvement as a contributing factor to any potential changes in threshold sensitivity, then bone-conduction threshold assessment would have little utility in this clinical trial. Further, there was no mention of conductive or mixed hearing loss in the text or table footnotes in this submission, which would have required determining bone conduction thresholds. Also of note, the Anti-Infective Drugs Advisory Committee 62nd Meeting criteria for "*meaningful threshold change*" are based on air conduction thresholds only.

Q#2: Does the consultant agree with definitions of hearing change?

The rationale provided by the sponsor for using the Anti-Infective Drugs Advisory Committee 62nd Meeting criteria for meaningful threshold change was "*because they appeared to be more sensitive to changes in hearing than other widely used criteria.*" Comment on this decision is difficult because the reviewer does not know what *"other widely used criteria"* were considered or what was considered a limitation for any additional criteria reviewed by the sponsor.

In general, the current threshold change criteria appear acceptable, though there are a few limitations. First, if threshold determination were accomplished using 5 dB intensity increments, then the standard error of measurement for the psychophysical procedure would be 10 dB (±5 dB). Thus, the criterion of *"≥ 10-dB increase or decrease in threshold at three or more frequencies in either ear"* is problematic, regardless of the number of frequencies at which the change is noted, because it is impossible to know if the change resulted from measurement error or true physiological change. Notably, if this category of threshold change were eliminated, the conclusions drawn from the data reported in 12.5.2-1 would remain unchanged. In contrast, the 15 dB and 20 dB threshold changes are not confounded by measurement error.

Secondly, none of the current criteria say anything about threshold change at adjacent frequencies. For example, if thresholds changed by 15 dB at 500 Hz and 8000 Hz, how likely is it that such changes are related to the same underlying physiological event given that the test frequencies are several octaves apart? Intuitively, one would expect adjacent frequencies to be more affected by the same causal factor than those more distant from one another.

Thirdly, current criteria do not permit the categorization of sudden sensorineural hearing loss (SSNHL) from longer-term etiologies, e.g., drug ototoxicity. Stated differently, there is no temporal criterion between magnitude of hearing loss and the time course over

which it developed, e.g., a 30 dB change in threshold at three contiguous frequencies occurring over a period of less than three days. The inclusion of such a criterion would have facilitated classification of adverse events associated with the drug under investigation from other possible etiologies, e.g., viral, vascular.

Q#3: Does the consultant agree with the overall assessment of the sponsor?

Outcome results reported across the sponsor's three studies have been summarized below in Table 1, and are consistent with the conclusions of the sponsor.

Table 1. Treatment-Emergent Changes in Audiogram Testing: Data Collapsed Across Active Treatment Groups, Ears, Frequencies and Threshold Criteria

Data Source (Sponsor)	Study	Total Sample	Hearing Outcome: Improved (%)	Hearing Outcome: Worsened (%)
Table 1	HUPS254	N=30	20.0	16.7
Table 2	HUPS256	N=75	26.7	26.7
Table 3	ACD2058g	N=300	9.0	9.0

In general, negative outcomes were nullified by positive outcomes across all three studies. In the most recent study (ACD2058g), the percent of sample for both outcomes was smaller than in prior studies, probably related to reduced variability resulting from the increased sample size. Subgroup summaries from study ACD2058g by threshold change criterion, including the placebo group, for significant changes from baseline on FT Day 84 by air conduction (.5 kHz - 8 kHz) are presented in Table 2. The number of subjects contributing to each outcome category is indicated in parentheses.

Table 2. Significant changes from baseline on FT Day 84: Data Collapsed Across Treatment Groups (includes Placebo), Ears, and Frequencies for Study AFC2058g (n=456)

Criterion		Hearing Outcome: No Change (%)	Hearing Outcome: Improved (%)	Hearing Outcome: Worsened (%)
≥20 dB Change in one or more freqs.		89.4 (n=408)	4.8 (n=22)	5.7 (n=26)
≥15 dB Change in two or more freqs.		93.6 (n=427)	3.2 (n=15)	3.0 (n=14)
≥10 dB Change in three or more freqs.		91.6 (n=418)	4.8 (n=22)	3.5 (n=16)
By any of the three criteria		85.0 (n=388)	7.6 (n=35)	7.2 (n=33)

Again, regardless of threshold change criteria, there does not appear to be any consistent worsening of thresholds resulting from drug exposure.

The sponsor also reported extra-high-frequency (10 kHz – 16 kHz) threshold-change data from 201 subjects from Study ACD2058g based on a ≥20 dB change at any

frequency within this range. Not all clinical sites had the expertise or capability to conduct this additional assessment, thus the smaller sample size for this group vs. the .5 kHz – 8 kHz sample. It should be noted that test measurement variability associated with extra-high-frequency assessment is known to be larger than that within the .5 kHz – 8 kHz range so the single ≥20 dB change criterion was appropriate. Even so, no significant between group differences were observed. That is, only 2 subjects in the placebo group (n=62), 4 subjects in the low-dose drug group (n=65) and 5 subjects in the high-dose drug group (n=65) demonstrated change from baseline thresholds. Therefore, one may conclude that the study drug did not have a negative effect on auditory sensitivity for this frequency range either.

Lastly, the sponsor examined the drug and placebo subgroups (Re-treatment-Active Drug [RT-A], Extended Treatment-Active Drug ET-A], Re-treatment-Control [RT-C), Extended Treatment-Control [ET-C]) and, again, found about equal proportions of subjects improving and worsening, consistent with the rest of the study outcome analyses.

Adverse Event Reports:

Two adverse events were reported by the sponsor, one from Study HUPS252 (S#642) and one from Study ACD0258g (S#19501). The associated audiometric data for each subject were requested from the sponsor during a conference call on 4/7/03.

Study HUPS252 (S#642): Review of the additional information supported the conclusion by the otolaryngologist, in contrast to the principal investigator, that the adverse event for S#642 was likely not related to the study drug, and more likely resulted from viral cochleitis. Namely, the sensorineural loss experienced in the left ear occurred within 24 hours of the sixth dose (10/26/98) and was severe / profound throughout the audiometric range (.25 kHz – 8 kHz). Some recovery was noted over time; the last audiogram (2/4/99) showed an essentially flat sensorineural loss with fair (76%) word recognition ability.

Study ACD0258g (S#19501): Review of the limited additional information did not provide support for the principal investigator's opinion that the hearing loss was not related to the study drug. That is, baseline audiometric data (3/21/00) showed hearing sensitivity within normal limits bilaterally. Initial drug administration was on March 22, 2000, and within 13 hours the subject reported mild to moderate vertigo, chills, arthralgia, myalgia, thirst and severe laryngismus. The subject did not seek medical assessment but self-treated with Gatorade and aspirin. The laryngismus was reported to have resolved within "hours" with the other symptoms resolving within two days.

No mention was made of hearing loss until March 31, at which time it was reported that *"an audiogram reveled a moderate hearing loss"* which lasted 11 days. The textual description does not state if the loss was unilateral or bilateral and specific audiometric data were not provided. However, the additional audiometric data provided by the sponsor (labeled Visit+ in Table 14.3.6/21) showed air conduction thresholds for the right ear poorer from baseline by 25 dB at .5 kHz, 1 kHz, and 8 kHz, and poorer by 20 dB at 6 kHz. Even with these threshold changes, though, hearing sensitivity for the right ear remained in the borderline-normal and/or in the mild loss range (25 dB - 30 dB HL) No thresholds were in the moderate loss range (40 dB - 60 dB HL). The final audiometric data in Table 14.3.6/21 showed that on April 10, 2000, hearing sensitivity had returned to baseline.

The above noted threshold changes for the right ear do not meet generally accepted otologic criteria for sudden onset sensorineural hearing loss (i.e., a 30 dB change in threshold at three contiguous frequencies occurring over a period of less than three

days), which most commonly result from vascular or viral cochlear insult. Also, the occurrence of the five other symptoms (which included vestibular symptoms) during the same time-period suggests that all symptoms were related to the same causal factor. Stated differently, it is more likely than not the transient, slight / mild change in hearing sensitivity noted for the right ear was related to the study drug.

V. Reviewer's Conclusions:

The data do not suggest any ototoxicity related to efalizumab.

James K. Kane, Ph.D.
James K. Kane, Ph.D.
Scientific Reviewer / Audiology

April 17, 2003
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration
Office of Device Evaluation
9200 Corporate Avenue
Rockville, MD 20850

Date: October 7, 2003

From: Viola Hibbard, Nurse Consultant
DAGID/GHDB, HFZ-480

Subject: STN 125075/0
Concluding Consult Review

To: Dr. Steven Kozlowski, Laboratory of Molecular and Developmental Immunology, Division of Monoclonal Antibodies

N29B RM3NN22, HFM 561

Phone: 301-827-0719 Fax: 301-827-0852

Dale Slavin, CSO, OTRR/DARP, HFM-588

Through: Patricia Cricenti, Branch Chief, CDRH/ODE/DAGID/GHDB, (HFZ-480) /S/ for PxC 10/27/03

I. Introduction and Consult Progression

This consult review is the second one for this specific device intended as a container closure system for diluents to be used for the drug Efalizumab as described in the following paragraph. This follow-up consult is based on new information that was not originally available. The consult dated June 16, 2003 was provided limited to the information in the Drug Master File [redacted] With further conversation with the sponsor and a hard copy of the entire Drug Master File, it was discovered that the device was described in the device master file [redacted] A letter of authorization was found in the drug master file from dated December 12, 2001 (copy enclosed). To avoid further confusion, it should be noted that Master File [redacted] describes the same device as [redacted] I placed a call to Aileen Gilbert, Regulatory Affairs Specialist at [redacted] who provided a letter that confirmed no change to the and a list of applications authorized to cross reference.

The application is for a new BLA from Genentech for Efalizumab intended for the treatment of adult patients with chronic plaque psoriasis. The diluent for the monoclonal antibody is provided in a pre-filled syringe. The diluent syringe manufactured by [redacted] delivers 1.3mL of SWFI and will be included in the final Drug Product package. [redacted] obtains the device components from [redacted] that is provided sterile. [redacted] fills the sterile syringe using [redacted] The product is used for the reconstitution and administration with a 25 gauge needle.

This review is limited to the sterile empty device. [redacted] of components with SWFI and solution stability is not included. Diluents for drug reconstitution are not the domain of CDRH.

II. Device Description

This pre-filled device is produced by — s. The review is based on information provided in Drug Master File No. — and Device Master File —

The device component review:

A. The container closure system is composed of [redacted]

Consult Reviewer Comments: The glass material used in the manufacturing meets the U.S.P. requirements. This material was used in preamendment devices and continues to be used in drug/device combinations up to the current date. It is considered safe for this intended use.

B. [redacted]

C. [redacted]

The stoppers are provided sterile.

D. [redacted]

III. —

[redacted]

The syringe components are provided sterile. Sterility information provided in the — meets all of the criteria required for —— for this intended use.

IV. Conclusions

Based on the review of the master files and the additional information the sponsor has provided, I find this device safe and effective for this intended use.

/S/

Viola Hibbard, RN., BSN
VSH@CDRH.fda.gov
301-594-1287 X173
Attachments-3

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MEMORANDUM

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

DATE: September 30, 2003

TO: Karen Weiss, M.D., Acting Director
Office of Therapeutics, Research and Review (OTRR)
Division of Application Review and Policy (DARP)

VIA: Dale Slavin, Consumer Safety Officer
Office of Therapeutics, Research and Review (OTRR)
Division of Application Review and Policy (DARP)

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Toni Piazza-Hepp, Pharm. D., Acting Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review of Patient Labeling for Raptiva (efalizumab), BLA 125075/0

The patient labeling which follows represents the revised risk communication materials of the Patient Labeling for Raptiva (efalizumab), BLA 125075/0. It has been reviewed by our office and DDMAC. We have simplified the wording, made it consistent with the PI, removed promotional language and other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications, not to provide detailed information about the condition), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds. These revisions are based on draft labeling submitted by the sponsor on December 27, 2002 and proposed Agency revisions. Patient information should always be consistent with the prescribing information. All future changes to the PI should also be reflected in the PPI

Please let us know if you have any questions. Comments to the review Division are bolded, italicized, and underlined. We can provide marked-up and clean copies of the revised document in Word if requested by the review division.

Please call us if you have any questions.

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CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: 8/1/03	DESIRED COMPLETION DATE: 10/1/03 PDUFA DATE: 10/27/03	ODS CONSULT #: 03-0222

TO:

Glen D. Jones, Ph.D.
Director, Division of Application Review and Policy
Office of Therapeutics Research and Review
HFM-588

THROUGH:

Dale Slavin
Project Manager
Office of Therapeutics Research and Review
HFM-588

PRODUCT NAME: **Raptiva** (Efalizumab) for Injection 125 mg **BLA#: 125075/0**	**BLA SPONSOR:** Genentech, Inc.

SAFETY EVALUATOR: Charlie Hoppes, RPh, MPH

SUMMARY:
In response to a consult from the Division of Application Review and Policy (HFM-588) in the Office of Therapeutics Research and Review, the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Raptiva" to determine the potential for confusion with approved proprietary and established names as well as pending names.

RECOMMENDATIONS:

1. DMETS has no objection to the use of the proprietary name Raptiva. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the supplemental BLA. A re-review of the name prior to BLA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.

2. DMETS recommends implementation of the labeling revisions as outlined in Section III.

3. DDMAC finds the proposed name, Raptiva, acceptable from a promotional perspective.

/S/ 10/7/03

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

/S/ 10/9/03

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: September 29, 2003

BLA# 125075/0

NAME OF DRUG: Raptiva (Efalizumab) for Injection 125 mg

BLA HOLDER: Genentech Inc.

I. INTRODUCTION:

This consult is written in response to a request from the Division of Application Review and Policy (HFM-588) in CBER's Office of Therapeutics Research and Review, to review the proposed proprietary name Raptiva. The container labels (vial and syringe), blister tray labeling, carton labeling, professional package insert labeling, and an Information Leaflet for Patients and Caregivers were reviewed for possible interventions in minimizing medication errors.

In a Memorandum dated September 30, 2003, the Division of Surveillance, Research, and Communication Support (DSRCS, HFD-410), reviewed and made recommendations to improve the comprehension level of the Medication Guide. DMETS has also reviewed this labeling from a medication error perspective.

PRODUCT INFORMATION

Raptiva (efalizumab) for injection is indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis. The usual dosage is 0.7 mg/kg subcutaneously as a single conditioning dose then 1 mg/kg weekly not to exceed a total of 200 mg. After reconstitution, the resultant solution must be used within 8 hours and unused solution is to be discarded. Each Raptiva carton contains four trays. Each tray contains one 125 mg vial of Raptiva, one 1.3 mL pre-filled syringe containing Sterile Water for Injection, two alcohol prep pads, and two 25 guage, 5/8" needles. Raptiva must be stored under refrigeration.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or

[1] MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

look-alike to "Raptiva" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies for the name, consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Raptiva. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proposed name, Raptiva, acceptable from a promotional perspective.

2. The Expert Panel identified three proprietary names that were thought to have the potential for confusion with Raptiva. These products are listed in Table 1 (below), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage form(s)	Usual Dose*	Others**
Raptiva	Efalizumab for Injection, 125 mg	Subcutaneously inject First dose: 0.7 mg/kg Then: 1 mg/kg weekly not to exceed 200 mg total	
Optivar	Azelastine Hydrochloride Ophthalmic Solution, 0.05%	Instill one drop into each affected eye twice a day.	SA/LA
Retin-A	Tretinoin Cream USP, 0.025%, 0.05%, and 0.1% Tretinoin Gel USP, 0.01%, 0.025%, 0.04%, and 0.1% Tretinoin Topical Solution USP, 0.05%	Apply once a day in the evening.	LA
Sustiva	Efavirenz Capsules, 50 mg, 100 mg, and 200 mg Efavirenz Tablets, 600 mg	600 mg orally once daily.	LA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

[3] The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 00-03, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov/maintrademarks.htm .

[5] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

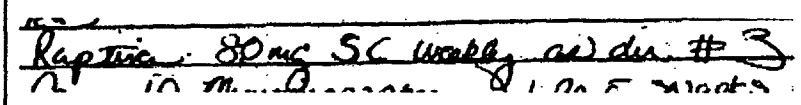
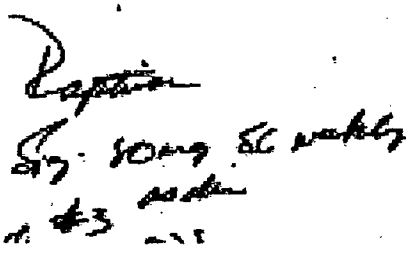
B. PHONETIC ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

DMETS' Phonetic Orthographic Computer Analysis (POCA) database was unavailable to search at the time of this review.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA to determine the degree of confusion of "Raptiva" with U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 127 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for "Raptiva" (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

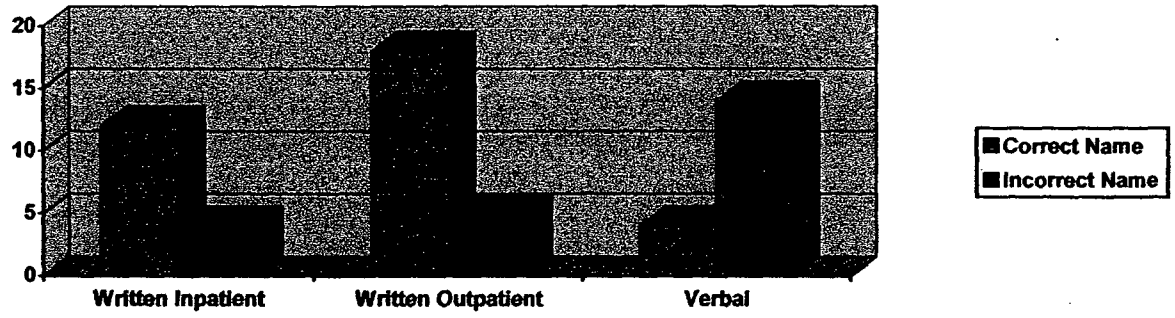
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Inpatient RX: 	Raptiva 80 mg SC weekly as directed. # 3
Outpatient RX: 	

2. Results:

The results for "Raptiva" are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted "Raptiva" (%)	Incorrectly Interpreted (%)
Written Inpatient	43	16 (37%)	12 (75%)	4 (25%)
Written Outpatient	41	23 (56%)	18 (78%)	5 (22%)
Verbal	43	18 (42%)	4 (22%)	14 (78%)
Total	127	57 (45%)	34 (60%)	23 (40%)



Among participants in the written prescription studies, 9 of 39 respondents (23%) interpreted the name incorrectly. The interpretations were misspelled variations of "Raptiva". Incorrect interpretations of written prescriptions included: *Raptina* (2 occurrences), *Raptivan, Raptur, Raptira* (2 occurrences), *Raptivar* (2 occurrences), and *Daptiven.* None of the interpretations are similar to a currently marketed drug product.

Among participants in the verbal prescription studies, 14 of 18 (78%) interpreted the name incorrectly. The interpretations were phonetic variations of "Raptiva". Incorrect interpretations of verbal prescriptions included: *Reptiva* (8 occurrences), *Rapteva* (2 occurrences), *Repteeva, Rativa, Optiva,* and *Repteava.* None of the interpretations are similar to a currently marketed drug product.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proposed proprietary name "Raptiva", the primary concerns raised related to look-alike and sound-alike confusion with names already in the U.S. marketplace. The products considered to have potential for name confusion with Raptiva were Optivar, Retin-A, and Sustiva.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that "Raptiva" can be confused with other products in the U.S. marketplace. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to small sample size. Most of the incorrect interpretations for the verbal and written prescription studies were phonetic/misspelled interpretations of "Raptiva".

1. *Optivar* and *Raptiva* may sound similar when spoken and look similar when written. Optivar is the proprietary name for azelastine hydrochloride ophthalmic solution, 0.05%. Optivar is indicated for the treatment of itching of the eye associated with allergic conjunctivitis. The recommended dose is one drop instilled into each affected eye twice a day. Optivar is available as 6 mL ophthalmic solution in a 10 mL translucent container which must be stored between 2° and 25°C (36° and 77°F). The names Optivar and Raptiva each have three syllables. The first syllable in each name share short vowel sounds and end in the letter "p". The second syllable of each name (tiv) is identical in script and sound. The last syllable of each name "var" vs. "va" sound especially alike if the "r" is de-emphasized. The names may look especially alike when written in lower case cursive (see sample below).

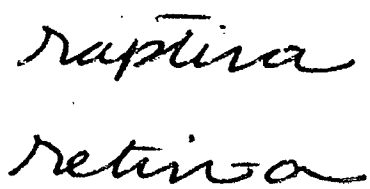
The names share the letters "ptiva". Also, if the letters "ra" in "raptiva" are written in lower case, they may appear similar to an "o", especially if the up stroke of the "r" comes in close proximity to a skinny "a". The two products are similar in that they would both be stored under refrigeration. Despite sound-alike/look-alike properties and similar storage conditions, the products also have differences which serve to distinguish them from one another. Raptiva is a product for which patient information is both available and required. Wide differences between Optivar and Raptiva in route of administration, indications (eye drop for eye ailments vs. subcutaneous injection for psoriasis), coupled with patient/caregiver information would most likely raise clarifying questions in the case of any confusion. Although it is possible for the names to be confused, the risk of dispensing the wrong medication should be low based on these product differences and others for Optivar and Raptiva, including dosage forms (ophthalmic solution vs. powder for injection), dosing directions and administration units (instill/drop vs. inject/mL),

dosing regimens (twice daily vs. once weekly), strengths (0.05% vs. 125 mg), and routes of administration (ophthalmic vs. subcutaneous injection), respectively.

2. *Retin-A* and *Raptiva* may look similar when written. Retin-A is the proprietary name for tretinoin, which is available in cream, gel, and topical solution dosage forms. Retin-A is indicated for topical application in the treatment of acne vulgaris. The usual recommended dosage is one application daily at bedtime. Retin-A is available in the dosage forms and strengths appearing in the table below.

Dosage Form	Available Strengths	Product Name
Cream	0.025%	RETIN-A
Cream	0.05%	RETIN-A
Cream	0.1%	RETIN-A
Gel	0.01%	RETIN-A
Gel	0.025%	RETIN-A
Gel	0.04%	RETIN-A MICRO
Gel	0.1%	RETIN-A MICRO
Solution	0.05%	RETIN-A

The names Retin-A and Raptiva may look especially alike when the "-A" is written in lower case (see writing sample below). The "p" in Raptiva is somewhat distinctive, however, and may serve to differentiate this name pair orthographically (written).



Despite some look-alike properties, the products also have differences which serve to differentiate them. Raptiva is a product for which patient information is both available and required. Wide differences between Retin-A and Raptiva in route of administration, (topical preparations vs. subcutaneous injection), coupled with patient/caregiver information would most likely raise clarifying questions in the case of any confusion. Although it is possible for the names to be confused, the risk of dispensing the wrong medication should be low based on lack of convincing look-alike properties and product differences for Retin-A and Raptiva, including dosage forms (cream, gel, and topical solution vs. powder for injection), indications of use (for acne vs. for plaque psoriasis), dosing directions (apply vs. inject), dosing regimens (once daily at bedtime vs. once weekly), strengths (expressed in percentages 0.01%, 0.025%, 0.04%, 0.05%, and 0.1% vs. 125 mg), different storage conditions (room temperature vs. refrigerated), and route of administration (topical vs. subcutaneous injection), respectively.

3. *Sustiva* and *Raptiva* may look similar when written. Sustiva is efavirenz, an HIV-1 specific, non-nucleoside, reverse transcriptase inhibitor (NNRTI). Sustiva in combination

with other antiretroviral agents is indicated for the treatment of HIV-1 infection. The recommended dosage of Sustiva is 600 mg orally, once daily, in combination with a protease inhibitor and/or nucleoside analogue reverse transcriptase inhibitors (NRTIs). Sustiva is available 50 mg, 100 mg, and 200 mg, capsules and 600 mg tablets for oral administration. Orthographic similarity between Sustiva and Raptiva may be attributed to the shared letters "tiva", which are identically placed in each seven letter, three syllable name.

Sus[redacted]
Rap[redacted]

The names may look especially similar when scripted in lower case letters (see writing sample below). The "p" in Raptiva is somewhat distinctive, however, and may serve to differentiate this name pair orthographically (written).

Despite sound-alike/look-alike properties and similar storage conditions, the products also have differences which serve to distinguish them from one another. Raptiva is a product for which patient information is both available and required. Wide differences between Sustiva and Raptiva in dosage forms and route of administration (tablet for oral administration vs. powder for subcutaneous injection), coupled with patient/caregiver information would most likely raise clarifying questions in the case of any confusion. Although it is possible for the names to be confused, the risk of dispensing the wrong medication should be low based on these product differences for Sustiva and Raptiva, including dosage form (solid oral dosage form vs. powder for injection), indications of use (for the treatment of HIV-1 infection vs. for plaque psoriasis), dosing directions and administration units (take/capsule or tablet vs. inject/mL), dosing regimens (once daily vs. once weekly), strengths (50 mg, 100 mg, 200 mg, and 600 mg vs. 125 mg), storage conditions (room temperature vs. refrigeration), and route of administration (oral administration vs. subcutaneous injection), respectively.

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES:

DMETS reviewed, container labels (vial and syringe), blister tray labeling, carton labeling, professional package insert labeling, and an Information Leaflet for Patients and Caregivers for possible interventions in minimizing medication errors. DMETS has identified several areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

1. Revise to read, "Sterile Water for Injection", rather than, ——— ——— where this name appears in your labels and labeling. Information regarding reconstitution should appear separate from the product name.

2. We note that product labeling indicates that when 1.3 mL diluent is added to the 125 mg vial, the resultant concentration is 100 mg/mL. Please note that 125mg/1.3 mL is equal to 96 mg/mL rather than 100 mg/mL. If the resultant concentration is actually 96 mg/mL, this may translate to an under dosing of patients. Please comment. We also request that the final volume after reconstitution be included throughout labels and labeling.

B. CONTAINER LABEL (. ——— Prefilled Syringe)

1. See first General Comment above.

2. Bold the statement, "For drug diluent use.", and relocate the statement to appear on the principal display panel.

3. Relocate the NDC code to appear at the top of the label.

C. CONTAINER LABEL (125 mg Vial)

1. Include the route of administration to immediately follow the expression of strength on the principal display panel.

2. Revise the proper (established) name following the proprietary name of your drug product to include the dosage form as follows, "Raptiva (Efalizumab) for Injection".

3. Revise the third sentence in the reconstitution instructions to read, "...use with enclosed Sterile...", (add "enclosed").

4. Add the following sentence to the reconstitution instructions: "Once reconstituted the resultant solution contains 100 mg/mL efalizumab." We also refer you to comment A.2. above regarding the concentration of efalizumab and final vial volume.

D. BLISTER TRAY LID LABELING

1. Please refer to GENERAL COMMENTS and comments under CONTAINER LABEL as appropriate.

2. Identify the micro-organism used in the manufacture of this product as required by 21 CFR 610.61(q).

E. CARTON LABELING

1. Please refer to GENERAL COMMENTS and comments under CONTAINER LABEL as appropriate.

2. Include reference to the diluent in the "Carton contains" statement.

3. Identify the micro-organism used in the manufacture of this product as required by 21 CFR 610.61(q).

4. Reprint "Contents" and "Vial Contents" sections appearing on Panel 4. to also appear on the principal display panel.

5. Include instructions for reconstitution including the information requested under comment C.5. above. We also refer you to comment A.2. above regarding the concentration of efalizumab and final vial volume.

F. PACKAGE INSERT LABELING

1. GENERAL COMMENTS

   a. Reprint the full text of the medication guide at the end of the labeling.

   b. When preparing final print labeling, revise to include the proper name in conjunction with the trade name at least once in each column of running text.

2. PRECAUTIONS SECTION

   Reorder subsections to be in accordance with 21 CFR 201.57 to prevent health practitioners from overlooking important information. For example, the "Information for Patients" subsection should immediately follow the "General" subsection.

3. DOSAGE AND ADMINISTRATION SECTION

   a. Provide instructions regarding the proper disposal of used product.

   b. Clearly explain that the patient should be informed of the proper volume of the reconstituted solution (100 mg/mL efalizumab), that should be administered.

   c. Add the following information in the "Preparation and Administration" subsection: "Once reconstituted the resultant solution contains 100 mg/mL efalizumab."

   d. Please comment on whether it is necessary for the person preparing this product to wear personal protective equipment.

   e. Add an instruction regarding proper use of alcohol pads in the Preparation and Administration process.

   f. Revise the first sentence in "Usual Dose" to read, "...doses of 1 mg/kg...", (delete terminal "0" to prevent misinterpretation of "1" as "10").

   g. Revise the sixth sentence in the "Preparation and Administration" subsection to read, "To prepare the RAPTIVA solution, remove needle cap and slowly...".

   h. Make a statement in the "Administration" subsection regarding recapping the needle and its proper disposal.

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pages of trade

secret and/or

confidential

commercial

information

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: October 17, 2003

From: Carol Rehkopf, CBER, DMPQ, HFM-675
Michelle Clark-Stuart, CDER, DMPQ
Steven Kozlowski, M.D., CDER, OBP, DMA
Michelle Frazier-Jessen, Ph.D., CDER, OBP, DMA

Subject: Recommendation for approval of Genentech, Inc., South San Francisco, CA manufacturing facility for efalizumab.

To: Establishment Inspection File (EIF)
BLA File: STN 125075

We have reviewed and evaluated Genentech's. responses to the form FDA-483, List of Observations, dated June 27, 2003. The written statements of corrective actions, which have been taken to correct the deficiencies noted during the pre-approval inspection, appear to be adequate and complete. All corrective actions should be verified during the next routine GMP inspection of the firm.

Therefore, we recommend that the facility be considered for approval for the production of efalizumab on the basis of the pre-approval inspection provided that all other considerations are in compliance with applicable regulations and standards.

/s/

Carol Rehkopf, CBER, DMPQ

/s/

Michelle Clark-Stuart, CDER, DMPQ

/s/

Steven Kozlowski, M.D., CDER, OBP/DMA

/s/

Michelle Frazier-Jessen, Ph.D., CDER, OBP/DMA

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

Date: October 24, 2003

To: File [Novartis – STN 125075]

Through: Chiang Syin,Ph.D., CDER/OC~~BQ~~/DMPQ/TFRB CS
Acting Branch Chief

From: Carol Rehkopf, Biologist, CBER/OCBQ/DMPQ/MRB I CR

Subject: Review Memorandum – BLA for efalizumab for the treatment of moderate to severe plaque psoriasis in adult patients at Genentech, Inc., South San Francisco, CA

Summary This supplement was submitted to provide a monoclonal antibody, efalizumab, for the treatment of moderate to severe plaque psoriasis in adult patients.

Review Comments I reviewed the Environmental Assessment Information included in this submission.

The firm states that there are no extraordinary circumstances that exist which may significantly affect the quality of the human environment.

This submission qualifies for a Categorical Exclusion per CFR § 25.31(c).