CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-805

CHEMISTRY REVIEW(S)

FEB 17 1998

DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-805 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 2/10/98

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE
ORIGINAL	2/7/97	2/10/97
Amendment (NC)	3/25/97	3/27/97
Amendment (BC)	11/21/97	11/24/97
Amendment (BC)	12/1/97	12/4/97
Amendment (BC)	12/22/97	12/23/97
Amendment (BC)	12/23/97	12/24/97
Amendment (BI)	12/31/97	1/2/98
Amendment (BC)	1/15/98	?
Amendment (BC)	2/3/98	2/4/98
Amendment (BC)	2/9/98	2/10/98
Amendment (BC)	2/10/98	2/10/98

NAME & ADDRESS OF APPLICANT:

Bayer Corporation Pharmaceutical Division
400 Morgan Lane
West Haven, CT 06516
(203) 812-3290

CONTACT:

Ann Marie Assuma, M.S.,
Associate Director, Regulatory Affairs

DRUG PRODUCT NAME

Proprietary: Cipro HC Otic
Established: ciprofloxacin hydrochloride and hydrocortisone otic suspension
Code #: BAY o 9867

PHARMACOLOGICAL CATEGORY/INDICATION:

Acute Diffuse Bacterial External Otitis.

DOSAGE FORM: Liquid Suspension

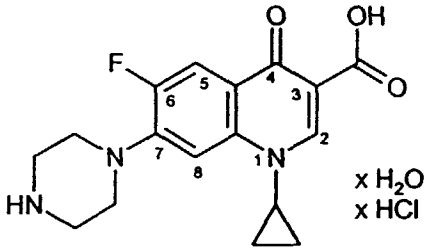
STRENGTHS: 0.2% Ciprofloxacin; 1% Hydrocortisone

ROUTE OF ADMINISTRATION: Otic

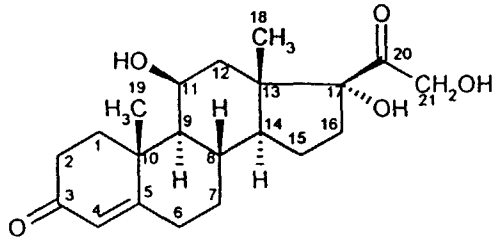
Rx/OTC: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Ciprofloxacin Hydrochloride, $C_{17}H_{19}N_3ClFO_3$, MW = 385.8
3-quinoline carboxylic acid, 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-, monohydrochloride, monohydrate
CAS - 86393-32-0



Hydrocortisone, $C_{21}H_{30}O_5$, MW = 362.5
pregn-4-ene-3,20-dione, 11,17,21-trihydroxy-,(11β)
CAS -50-23-7



SUPPORTING DOCUMENTS:

DMF DMF DMF DMF DMF DMF DMF DMF DMF
NDA 19-847; NDA 19-537;

RELATED DOCUMENTS: n/a

CONSULTS:

1. Trademark review (submitted 7/14/97); completed.
2. Site inspection, completed 12/1/97, acceptable.
3. Method validation. N/A
4. Environmental assessment (reviewed by Nancy Sager).

REMARKS/COMMENTS:

This NDA is submitted for Cipro HC Otic as a new non-sterile product for the treatment of acute diffuse bacterial external otitis. The drug product contains two active ingredients: antibacterial component, ciprofloxacin (as ciprofloxacin hydrochloride) and anti-inflammatory agent, hydrocortisone. There are two DMFs referenced for the drug substances: DMF) and DMF . These DMFs were reviewed and letters of deficiencies were sent to the respective sponsors. As for the trademark review (the original proprietary name: Cipro HC Otic Suspension), the applicant was advised (fax of 1/12/97) by the Labeling and Nomenclature Committee that the proper established name for this product is "ciprofloxacin hydrochloride and hydrocortisone otic suspension" instead of "ciprofloxacin hydrochloride/hydrocortisone otic suspension" and that "Otic Suspension" may be used as part of the proprietary name, although the Committee feels that this is redundant. In the 1/15/98 amendment the applicant agreed to use the established name recommended by the Committee and decided to continue using "Otic Suspension" as part of the proprietary name. However, later on in the subsequent labeling and package insert revision the applicant decided to use "Cipro HC Otic" as a proprietary name for this product.

CONCLUSIONS & RECOMMENDATIONS:

The NDA submission and amendments provide adequate information on the chemistry, manufacturing and controls for the production of Cipro HC Otic Suspension. The expiration date for the drug product approved in this NDA is 18 months and the final list of agreeable specifications for the Cipro HC Otic is included under SPECIFICATIONS AND METHODS FOR DRUG PRODUCT of this review. The applicant is committed to reevaluate the specification for once the real time stability data of 18 months for the product are available. Furthermore, the applicant is committed to investigate the possibility of This commitment was requested by the Division because of concerns that the large unused portion would be saved by the patient for future use despite potential problems. These problems include drug instability, the potential for inappropriate use, exacerbation of the drug-resistance

problem and environmental burden.

The related GMP and product specific inspections of the manufacturing facilities have been completed and found satisfactory. From the chemistry, manufacturing and controls point of view, the NDA is recommended for approval.

/S/

Dorota Matecka, Ph.D.
Review Chemist

/S/

Norman R. Schmuff, Ph.D.
Team Leader, HFD-590

cc: Org. NDA 20-805
HFD-590/Division File
HFD-830/ChenC/DivDir
HFD-590/SchmuffN/Team Leader
HFD-590/MateckaD/CHEM/
HFD-590/MANNE/MO
HFD-590/ELLISA/Pharm
HFD-590/DIONNEP/MICRO
HFD-590/RocheK/CSO
D-102/CKumkumian [#1 only]
HFC-130/JAllenHF

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-805

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Cipro HC Otic

(ciprofloxacin hydrochloride (0.2% w/v) and hydrocortisone (1.0% w/v))

Suspension

NDA 20-805

Food And Drug Administration
Center For Drug Evaluation And Research
Division of Anti-Infective Drug Products
(HFD-520)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-805

Cipro HC Otic

(ciprofloxacin hydrochloride (0.2% w/v) and hydrocortisone (1.0% w/v))

Suspension

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Cipro HC Otic Suspension, Bayer AG. has conducted a number of environmental studies and prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts of the use and disposal of the product. Detailed environmental information for ciprofloxacin was provided by the applicant in NDA 20-780. Hydrocortisone has been approved for use in both prescription and over-the-counter drugs for many years with no reported environmental effects.

Ciprofloxacin is a synthetic drug which is already available in the U.S. in various products such as Cipro Tablets (ciprofloxacin hydrochloride) and Cipro I.V. (ciprofloxacin, USP). Cipro HC Otic Suspension is used in the treatment of acute diffuse bacterial external otitis.

Ciprofloxacin may enter the environment from excretion by patient, from disposal of pharmaceutical waste or from emissions from manufacturing sites. The expected environmental aquatic concentration (EEC) from use is expected to be significantly less than expected introduction concentration (EIC) because the compound rapidly degrades when exposed to light. Ciprofloxacin may also enter the terrestrial environment because testing predicts that the compound will bind tightly to soils. As the drug is expected to persist in the environment for some time, the toxicity of ciprofloxacin to aquatic and terrestrial organisms was characterized. The results show that ciprofloxacin is

generally not toxic to aquatic and terrestrial organisms (each LC_{50} and EC_{50} divided by EIC is greater than 1000 and NOEC is greater than EIC).

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. In the United States returned drug product will be disposed of at a licensed incineration facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic procedures. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

12/17/97
DATE

/S/
PREPARED BY
Nancy B. Sager
Office of Pharmaceutical Science

12-18-97
DATE

CONCURRED
Eric B. Sheinin, Ph.D.
Director, Office of New Drug Chemistry
Center for Drug Evaluation and Research

Attachment: Environmental Assessment
Environmental Assessment (revision 1)

Cipro HC Otic Suspension

NDA SECTION 3

CHEMISTRY, MANUFACTURING, AND CONTROLS

Table of Contents **Page**

3.3 Environmental Assessment 558

ENVIRONMENTAL ASSESSMENT INFORMATION

CIPRO HC OTIC SUSPENSION

1. Date: December 2, 1996

2. Name of Applicant/Petitioner: Bayer Corporation
Pharmaceutical Division

3. Address: 400 Morgan Lane
West Haven, CT 06516

4. Description of the Proposed Action:

Bayer Corporation has filed an NDA (20-805) for Cipro HC Otic Suspension and hereby submits a "Tier 0" Environmental Assessment. The proposed action is manufacturing, bottling and packaging of Ciprofloxacin Hydrocortisone Otic Suspension (10 ml flint bottles) for the purpose of sale to the general public. Cipro HC Otic Suspension is a white to off-white opaque suspension containing a broad spectrum anti-bacterial agent Ciprofloxacin Hydrochloride 0.2% W/V combined with the anti-inflammatory corticosteroid Hydrocortisone 1.0% W/V. Cipro HC Otic Suspension is used for the treatment of acute diffuse bacterial external otitis. This product will be merchandised as a prescription only drug for use by consumers throughout the United States.

Manufacture of Drug Substances:

Ciprofloxacin Hydrochloride:

The pharmaceutical active ingredient Ciprofloxacin Hydrochloride is manufactured at the Bayer AG's production facility at Friedrich Ebert Street 217-319, Wuppertal-Elberfeld, Germany. The Ciprofloxacin Hydrochloride will be shipped to Bayer Corporation's facility in Myerstown, PA. The facilities are located in an urban environment. The surrounding area is hilly with a temperate climate.

Hydrocortisone:

The pharmaceutical active ingredient Hydrocortisone will be purchased from The manufacturing facility is located in Please reference DMF for any desired information on hydrocortisone.The Hydrocortisone will be shipped to Bayer Corporation's facility in Myerstown, PA.

Manufacture and Packaging of Drug Product:

Bayer Corporation's Consumer Care Division production facility in Myerstown, Pennsylvania will mix and blend the active ingredients Ciprofloxacin Hydrochloride and Hydrocortisone with the inactive components into Ciprofloxacin Hydrocortisone Otic Suspension (Cipro HC Otic Suspension). The Cipro HC Otic Suspension will be

bottled, packaged, and labeled in Myerstown and shipped to Bayer Corporation's Pharmaceutical Division's West Haven, CT location.

Bayer Corporation's Consumer Care Division production facility is located at 400 West Stoever Avenue in Myerstown, Pennsylvania on a 64.80 acre site.

The land uses around the site are residential to the north and east and agricultural to the west and south. Tulpehocken Creek runs adjacent to the north and west boundaries of the plant site. The climate of the region averages a temperature of 30°F during the winter and 68°F during the summer. The mean annual precipitation of the region is 35.4 inches.

Operations at the facility include manufacturing and warehousing of pharmaceutical products. Three major buildings totaling 380,000 square feet are positioned on the site to house the administration, production and warehousing operations. A wastewater neutralization facility controls pH of the site discharges from the effluent tank between 6.0 - 9.0.

All operations at the facility are conducted in compliance with all applicable federal, state and local regulations. The facility falls under the environmental regulatory control of the United States Environmental Protection Agency (USEPA) and the Pennsylvania Department of Environmental Protection. Wastewater discharges to the Publicly Owned Treatment Works are permitted by the Borough of Myerstown POTW Permit Numbers 3001 and 5001. The site operates with several emission points to the atmosphere which are maintained in compliance with permits issued by the Pennsylvania State Department of Environmental Protection.

Drug Product Distribution:

Cipro HC Otic Suspension will be stored in and distributed from Bayer Corporation's Pharmaceutical Division's West Haven, CT location. West Haven is in a urban setting with a generally flat to slightly hilly terrain and has a temperate climate. The product will be used throughout the US at hospitals, clinics and at patient's homes. It is not expected that the use of this product will be concentrated in any specific geographic region.

All returned goods are disposed of by incineration via a manifested isolated disposal program. Actual disposal will be managed through the office of the manager of environmental and safety affairs located in West Haven. The current main incineration facility for Bayer Corporation is Clean Harbors Inc. Clean Harbors is located at 385 Quincy Avenue in Braintree, MA. This is a permitted hazardous waste treatment, transfer and recovery facility with Environmental Protection Agency (EPA) identification number MAD053452637. As a permitted TSDF, the Braintree facility is regularly inspected by the Hazardous Waste personnel from both the State of Massachusetts as well as the Federal EPA. Braintree is located in an industrial urban setting on the water front in the greater Boston area.

The Clean Harbors incineration process utilized for the destruction of product waste from the West Haven site is a 2-stage incinerator. It's main chamber is of a fixed hearth horizontal design with a ram feeder, that is capable of processing approximately 300 lbs/hr of material at a temperature of approximately 1500° F. The second stage is a fixed hearth chamber where volatile gases are combusted at temperatures in excess of 2000° F. Following the secondary chamber is a wet scrubber designed and managed for volatile and acid gas removal.

5. Description of drug and identification of the chemical substances that are the subject of this proposed action:

Cipro HC Otic Suspension is a white to off-white opaque suspension containing a broad spectrum anti-bacterial agent Ciprofloxacin Hydrochloride 0.2% W/V combined with the anti-inflammatory corticosteroid Hydrocortisone 1.0% W/V.

5.1 Ciprofloxacin Hydrochloride (Faintly yellowish to light yellow crystalline substance, M.W. = 385.8)

Drug Name:	Ciprofloxacin Hydrochloride
CAS Number:	86393-32-0
Structural Formulae:	$C_{17}H_{18}FN_3O_3.HCl.H_2O$
Name:	Monohydrochloride monohydrate salt of 1-cyclopropyl -6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarbo xylic acid

5.2 DMF

Drug Name:	Hydrocortisone
CAS Number:	50-23-7
Structural Formulae:	C_{21}-H_{30}-O_5
Name:	11beta,17alpha,21trihydroxypregn-4-ene-3,20-dione

Material safety data sheets for Ciprofloxacin Hydrochloride and Hydrocortisone can be found in Appendix 1.

6. Introduction of substances into the environment:

6a. Manufacture of Drug Substance (Ciprofloxacin Hydrochloride) at the Bayer AG's Wuppertal-Elberfeld facilities:

Emissions are controlled routinely by the staff of Bayer AG's Department of Environmental Protection (WV-Umweltschutz) to assure compliance with the Federal Emissions Control Act (BImSchG) of the Federal Republic of Germany. According to this act, each manufacturing installation, regardless of the type of operation, is designated as a single "point source" which may not exceed the established emission limits. Waste water residues from the point source must be channeled to a specific WWTP. Water from the treatment plant must meet the requirements for "Treated Water" as established in the "Decree on the Disposal of Waste Water". According to the Technical Regulations on Waste Control, all solid organic residues resulting from the operation must be incinerated in a facility approved for disposal of industrial waste. Ash from the incinerator must be disposed of in a licensed landfill. A list of environmental laws and regulations which regulate Bayer AG are included in Appendix 2.

According to BImSchG the production of pharmaceutical active ingredients is further subject to the "Prevention of Harmful Effects on All Compartments of the Environment", e.g. Air Pollution, Water Pollution, Land Pollution, Noise, Vibration and Similar Phenomena.

Bayer AG holds all required licenses to manufacture Ciprofloxacin Hydrochloride in its Wuppertal-Elberfeld facilities. The licenses are granted by the Administrative District of Dusseldorf as outlined by the Federal Emissions Control Act. Records of emission controls carried out are maintained by Bayer AG's Department of Environmental Protection. A Certificate of Compliance for Bayer AG's Wuppertal-Elberfeld facilities is included in Appendix 3.

6b. Manufacture of Drug Substance (Hydrocortisone) at the facilities in France:

All the emissions (air and water) from the manufacturing operations for Hydrocortisone are in compliance with the permits issued for these manufacturing operations. A Certificate of Compliance for facility in France is included in Appendix 3.

6c. Manufacture and packaging of Drug Product (Cipro HC Otic Suspension) at Bayer Corporation's Myerstown, Pennsylvania Facility:

Cipro HC Otic Suspension (Ciprofloxacin Hydrocortisone Otic Suspension), the subject of the NDA, will be manufactured by mixing and blending the active ingredients Ciprofloxacin Hydrochloride and Hydrocortisone with pharmaceutical additives. The Cipro HC Otic Suspension will be filled into 10 ml flint bottles. The bottles will be packaged for shipment. All manufacturing, bottling and packaging operations are performed in compliance with Current Good Manufacturing Practices.

Wastes from the manufacturing, bottling and packaging of Cipro HC Otic Suspension will be mainly generated in the liquid aqueous phase during the washing of the manufacturing tank and equipment. Wastes will be managed in such a fashion as to have no significant impact on the production facilities compliance permit status relative to all federal, state and local environmental and safety laws and regulations.

No significant quantities of chemical substances should be emitted to the environment because of the controls exercised during manufacturing, bottling and packaging. Minuscule quantities of solids generated will be removed by extractive ventilation and will be collected by a prefilter followed by a HEPA filter. Liquid wastes from the first rinsing of the tank and equipment will be sent to an on site Process Waste Tank. When this tank is filled, the liquids are sent to Subsequent tank and equipment rinses will be sent to the effluent tanks where pH is adjusted before the liquid is discharged to the Publicly Owned Treatment Plant (Borough of Myerstown POTW Permit Numbers 3001 and 5001). Any solids accidentally spilled will be landfilled at Any liquids accidentally spilled will be sent to the on site

Liquid wastes in the on site will be sent to '

identification number is DED984073692 and operates an Oil Operations Permit under number 94-OP-1897. The wastewater permit for the operation is W-91-01, issued from the City of Wilmington, Department of Public Works. recycling technology is in compliance with all Environmental Protection Agency, and state environmental regulations.

Solid wastes in packaged containers will be landfilled at . which is operated at Waste containers that are brought to the facility are immediately placed in the landfill and covered. The facility operates a Solid Waste Disposal and Processing Facility Permit number 101427 from the Pennsylvania Department of Environmental Protection. The disposal area at Pine Grove uses two 100 mil high-density polyethylene membrane liners and a geocomposte clay liner. In addition, this dual liner system incorporates both leachate collection and witness collection piping systems, as well as geotextile fabric above and below the liners to guard against possible structural damage. This approach meets all and exceeds many requirements by the Commonwealth of Pennsylvania.

All the emissions (air and water) from the manufacturing operations for Cipro HC Otic Suspension are in compliance with the permits issued for these manufacturing operations. A Certificate of Compliance for Bayer Corporation's Myerstown, Pennsylvania facility is included in Appendix 3.

6d. Drug Product Distribution at Bayer Corporation in West Haven, CT:

Cipro HC Otic Suspension will be received in packaged form and will be distributed in the same packages from Bayer Corporation's Pharmaceutical Division's site in West Haven, CT.

There is no manufacturing and no packaging and, therefore, no impact upon the production facilities compliance permit status relative to all federal, state and local environmental and safety laws and regulations. Information regarding permits for air, liquid and solid emissions is provided. This information includes permit numbers, issuing agencies and the permit expiration dates, if applicable. A list of all applicable federal, state and local environmental and occupation laws/regulations is provided for Bayer Corporation's West Haven location. (see Appendix 4). A Certificate of Compliance for Bayer West Haven, CT is included in Appendix 3.

In conclusion, the storage and distribution of Cipro HC Otic Suspension from West Haven should have no effect on compliance with existing applicable emission requirements (including occupational) at the federal, state or local level. No modifications of any existing permits will be necessary to store and distribute this product.

6e. Expected introduction concentrations of Cipro HC Otic Suspension's pharmaceutical active ingredients Ciprofloxacin Hydrochloride and Hydrocortisone:

The Cipro HC Otic Suspension will be put on the US market in the fifth year after receiving marketing authorization in an amount of approximately bottles. Each bottle contains mg of Ciprofloxacin Hydrochloride and mg Hydrocortisone. This is equivalent to kg of Ciprofloxacin Hydrochloride and kg of Hydrocortisone.

The expected introduction concentration (EIC) entering into the aquatic environment from patient use is:

EIC-Aquatic (ppm) = A x B x C x D

where A = kg/year production
B = 1/liters per day entering POTW's*
C = year/365 days
D = 10^6 mg/kg (conversion factor)
* 1.115 x 10^{11} liters/day entering publicly owned treatment works

Ciprofloxacin Hydrochloride EIC-Aquatic (ppm) = 2.2 x 10^{-6} or 2.2 x 10^{-3} ppb

Hydrocortisone EIC-Aquatic (ppm) = 9.6 x 10^{-6} or 9.6 x 10^{-3} ppb

According to CDER's Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements issued November 1995, this E.A. qualifies for a Tier 0-classification. Therefore the format items 7,8,9,10,11 and 15 will not be submitted.

12. List of preparers:

This assessment was prepared by Gary G. Toczylowski, Manager of Environmental and Safety Affairs at Bayer Corporation, Pharmaceutical Division. He is familiar with the operations to be carried out and knowledgeable of the wastes to be generated.

Llew Williams, Manager of Environmental and Safety Affairs at Bayer Corporation's Myerstown, PA facility provided information on the drug product's manufacturing, bottling and packaging. He is familiar with the operations to be carried out and knowledgeable of the wastes to be generated.

Professional credentials for all the above are located in Appendix 5.

13. Certification:

The undersigned official certifies than the information presented is true, accurate and complete to the best of knowledge of the firm or agency responsible for the preparation of the environmental assessment.

Gary G. Toczylowski
Manager of Environmental and Safety Affairs
Bayer Corporation
Pharmaceutical Division
West Haven, CT

14. APPENDICES

APPENDIX 1 -	Material Safety Data Sheets
APPENDIX 2 -	Bayer AG Environmental Laws and Regulations
APPENDIX 3 -	Certificates of Compliance - Bayer Corporation's Facility in West Haven, CT; Bayer Corporation's Facility in Myerstown, PA; Bayer AG's Facilities in Wuppertal-Elberfeld, Germany, and Facility in France
APPENDIX 4 -	West Haven Regulatory Overview
APPENDIX 5 -	Curricula Vitae of the Preparers

Appendix 1

Material Safety Data Sheets

BAYER CORPORATION
PHARMACEUTICAL DIVISION
400 Morgan Lane
West Haven, CT 06516-4175

TRANSPORTATION EMERGENCY
CALL CHEMTREC: 800-424-9300
DISTRICT OF COLUMBIA: 202-483-7616

NON-TRANSPORTATION
BAYER EMERGENCY PHONE...: (203) 937-2000
BAYER INFORMATION PHONE.: (800) 662-2927

1. CHEMICAL PRODUCT IDENTIFICATION:

PRODUCT NAME.....: Cipro HC OTIC Suspension
PRODUCT CODE.....: Non-coded
CHEMICAL FAMILY.....: Aqueous suspension of ciprofloxacin hydrochloride and hydrocortisone

2. COMPOSITION/INFORMATION ON INGREDIENTS:

INGREDIENT NAME /CAS NUMBER	EXPOSURE LIMITS	CONCENTRATION (%)

***** HAZARDOUS INGREDIENTS *****

This pharmaceutical product is for human consumption under prescribed dosage. Under normal handling and use, these materials are not chemically hazardous under the criteria of the Federal OSHA Hazard Communication Standard 29 CFR 1910.1200. This Material Safety Data Sheet is not intended for industrial exposures.

3. HAZARDS IDENTIFICATION:

EMERGENCY OVERVIEW

Color: White to slightly yellow; Form: Liquid; Suspension; Odor: Odorless; Product poses little or no hazard if spilled and no unusual hazard if involved in a fire; See Potential Health Effects if the recommended dosage is exceeded.

POTENTIAL HEALTH EFFECTS:

ROUTE(S) OF ENTRY.....: Appropriate route of entry: ear drop application

HUMAN EFFECTS AND SYMPTOMS OF OVEREXPOSURE:
NOTE: This is a pharmaceutical material. Use only as directed. See product packaging and the Physicians' Desk Reference (PDR) for further information concerning adverse effects and drug interaction precautions.

ACUTE EFFECTS OF EXPOSURE.....: Acute overexposure to cipro may cause nausea, diarrhea, vomiting, headache, rash, phototoxicity, and abdominal pain/discomfort. Overdose of topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects.
CHRONIC EFFECTS OF EXPOSURE...: Chronic overexposure to cipro may cause tremor, restlessness, and light headedness. See Section 11 for further information on hydrocortisone.

CARCINOGENICITY.....: The components of this product are not listed by NTP, IARC or regulated as a carcinogen by OSHA.

MEDICAL CONDITIONS
AGGRAVATED BY EXPOSURE.....: Persons with preexisting hypersensitivity to any components in this product may be more susceptible to the effects of this product.

4. FIRST AID MEASURES:

FIRST AID FOR EYES.....: In case of contact, immediately flush eyes with plenty of water for at least 15 minutes. Call a physician.
FIRST AID FOR SKIN.....: Flush skin with plenty of soap and water. Contact a physician if irritation develops.
FIRST AID FOR INHALATION: Not applicable.
FIRST AID FOR INGESTION.: In case of overdose, induce vomiting or use gastric lavage. Contact poison control center or 203-937-2000.

5. FIRE FIGHTING MEASURES:

FLASH POINT.....: Not Applicable
AUTO-IGNITION TEMPERATURE.....: Not Applicable
EXTINGUISHING MEDIA.....: Water; Foam; Dry Chemical
SPECIAL FIRE FIGHTING PROCEDURES: Firefighters should be equipped with self-contained breathing apparatus to protect against potentially toxic and irritating fumes.

5. FIRE FIGHTING MEASURES (Continued)

UNUSUAL FIRE / EXPLOSION HAZARDS: None known.

6. ACCIDENTAL RELEASE MEASURES:

SPILL OR LEAK PROCEDURES.....: Use appropriate PERSONAL PROTECTIVE EQUIPMENT during clean up. Dike Spill. Prevent liquid from entering sewers, waterways, or low areas. Soak up with sawdust, sand or other absorbent material.

7. HANDLING AND STORAGE:

STORAGE TEMPERATURE(MIN/MAX): 86 F (30 C) Max.
SHELF LIFE.....: Do not use after expiration date.
SPECIAL SENSITIVITY.....: None known.
HANDLING/STORAGE PRECAUTIONS: Keep this and all drugs out of the reach of children. Avoid contact with eyes and skin. Wash thoroughly after handling. Store in a dry place away from excessive heat. Reseal containers immediately after use. Use normal precautions for storage of a drug.

8. PERSONAL PROTECTION:

EYE PROTECTION REQUIREMENTS.....: Safety glasses.
SKIN PROTECTION REQUIREMENTS.....: Chemical resistant gloves, long sleeved shirts and pants. Lab coat. Employees should wash their hands and face before eating, drinking or using tobacco products.
VENTILATION REQUIREMENTS.....: Under normal conditions of use, special ventilation is not required.
RESPIRATOR REQUIREMENTS.....: Under normal conditions of use, respiratory protection is not required.
WORK PRACTICES.....: Normal clinical practice. Use good personal hygiene - wash hands and exposed skin thoroughly with soap and water after each use.
ADDITIONAL PROTECTIVE MEASURES.....: Employers shall provide handwashing facilities which are readily accessible to employees. Educate and train employees in the safe use and handling of this product.

9. PHYSICAL AND CHEMICAL PROPERTIES:

PHYSICAL FORM.....: Liquid
APPEARANCE.....: Suspension
COLOR.....: White to slightly yellow
ODOR.....: Odorless
pH .....: 4.6 - 4.7
BOILING POINT.....: Not Applicable
MELTING/FREEZING POINT....: Not Applicable
SOLUBILITY IN WATER .....: Soluble
SPECIFIC GRAVITY .....: Not Applicable
BULK DENSITY.....: Not Established
VAPOR PRESSURE .....: Not Applicable

10. STABILITY AND REACTIVITY:

STABILITY.....: This is a stable material.
HAZARDOUS POLYMERIZATION...: Will not occur.
INCOMPATIBILITIES.....: Avoid strong oxidizing agents. See product packaging and the Physicians' Desk Reference (PDR) for drug interaction.
INSTABILITY CONDITIONS.....: None known.
DECOMPOSITION PRODUCTS.....: CO, CO2, oxides of nitrogen, and other potentially toxic fumes.

11. TOXICOLOGICAL INFORMATION:

See product insert for additional information concerning animal pharmacology.

TOXICITY DATA FOR: Ciprofloxacin
CARCINOGENICITY.....: After daily dosing to mice and rats for up to 2 years, there is no evidence that ciprofloxacin has any carcinogenic or tumorigenic effects in these species.
MUTAGENICITY.....: 2 of the 8 in vitro mutagenicity tests conducted with ciprofloxacin were positive, but 3 in vivo test systems gave negative results.
REPRODUCTION.....: Reproduction studies have been performed in rats and mice at doses up to 6 times the usual daily human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin.

TOXICITY DATA FOR: Hydrocortisone
MUTAGENICITY.....: Studies to determine mutagenicity with prednisolone and hydrocortisone have revealed negative results.
DEVELOPMENTAL TOXICITY: Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The

more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

1 Occupational Health Services Material Safety Data Sheet

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12. ECOLOGICAL INFORMATION:

NO ECOLOGICAL INFORMATION AVAILABLE

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13. DISPOSAL CONSIDERATIONS

WASTE DISPOSAL METHOD.....: Incineration is recommended. Waste disposal should be in accordance with existing federal, state and local environmental control laws.

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14. TRANSPORTATION INFORMATION:

TECHNICAL SHIPPING NAME.....: Aqueous suspension of ciprofloxacin hydrochloride and hydrocortisone
PRODUCT LABEL.....: Cipro HC OTIC Suspension

DOT (DOMESTIC SURFACE)

HAZARD CLASS OR DIVISION .....: Non-Regulated

IMO / IMDG CODE (OCEAN)

HAZARD CLASS DIVISION NUMBER...: Non-Regulated

ICAO / IATA (AIR)

HAZARD CLASS DIVISION NUMBER...: Non-Regulated

---

15. REGULATORY INFORMATION:

OSHA STATUS.....: This product is not hazardous under the criteria of the Federal OSHA Hazard Communication Standard 29 CFR 1910.1200.
TSCA STATUS.....: This product is exempt from TSCA Regulation under

15. REGULATORY INFORMATION (Continued)

Section 3 (2)(B)(vi) when used for pharmaceutical application.

CERCLA REPORTABLE QUANTITY..: None
SARA TITLE III:
SECTION 302 EXTREMELY
HAZARDOUS SUBSTANCES..: None
SECTION 311/312
HAZARD CATEGORIES.....: Exempt from SARA Section 311/312
SECTION 313
TOXIC CHEMICALS.....: None
RCRA STATUS.....: If discarded in its purchased form, this product would not be a hazardous waste either by listing or by characteristic. However, under RCRA, it is the responsibility of the product user to determine at the time of disposal, whether a material containing the product or derived from the product should be classified as a hazardous waste. (40 CFR 261.20-24)

INACTIVE INGREDIENTS: starch; microcrystalline cellulose; silicon dioxide; crospovidone; magnesium stearate; hydroxypropyl methylcellulose; titanium dioxide; polyethylene glycol; water.

16. OTHER INFORMATION:

HMIS RATINGS:	Health	Flammability	Reactivity
	1	0	0

0=Minimal 1=Slight 2=Moderate 3=Serious 4=Severe

Bayer's method of hazard communication is comprised of Product Labels and Material Safety Data Sheets. HMIS ratings are provided by Bayer as a customer service.

REASON FOR ISSUE.....: Establish MSDS
PREPARED BY.....: R. Ruppel-Kerr
APPROVED BY.....: G. Toczylowski
APPROVAL DATE.....: NONE
SUPERSEDES DATE.....: None
MSDS NUMBER.....: 29107

This information is furnished without warranty, expressed or implied, except that it is accurate to the best knowledge of Bayer Corporation. The data on this sheet relates only to the specific material designated herein. Bayer Corporation assumes no legal responsibility for use or reliance upon these data.

Appendix 2

Bayer AG Environmental Laws and Regulations

ENVIRONMENTAL ASSESSMENT

Bayer AG is regulated by the following environmental laws and regulations:

1. **"Bendesemissionsschutzgesetz"** (Federal Law for the Protection of the Environment against the Adverse Influences caused by Contamination of the Air by noise, vibration and similar events). Published in Federal Law Gazette, March 15, 1974, amended August 12, 1980.

2. **"Wasserhaushaltsgesetz"** (Federal Law for the Protection of Water) Published in Federal Law Gazette, October 16, 1976, amended March 28, 1980.

3. **"Abfallgesetz"** (Federal Law for Minimization and Disposal of Waste) Published August 27, 1986.

4. **"TA Luft"** (Clean Air Laws) Published in Joint Ministerial Gazette, February 27, 1986.

5. **"TA Lärm"** (Noise Protections Laws) Published in July 16, 1986.

6. **"Chemikaliegesetz"** (Federal Law for Protection Against Dangerous Chemicals), Published in Federal Law Gazette, September 16, 1980.

7. **"Gefahrstoffverordnung"** (Regulations for Dangerous Products)Published in Federal Law Gazette, August 28, 1986.

8. **"Druckbehälterverordnung"** (Regulations for Pressure Vessels for Compressed Gases) Published in Federal Law Gazette, February 27, 1980.

9. **"Störfallverordnung"** (Federal Law for Protection of the Environment) Published in Federal Law Gazette, June 27, 1980.

10. **"Verordnung über Anlagen Zur Lagerung, Abfüllung und Beförderung brennbarer Flüssigkeiten Zu Lande"** (Regulations for Facilities for Storage, Filling and Transport of Inflammable Liquids on Land) Published in Federal Law Gazette, February 27, 1980, amended May 3, 1982.

11. **"Gefahrgutverordnung Stra_e"** (Regulations for the Transport of Dangerous Products by Road) Published in Federal Law Gazette, July 22, 1985.

12. **"Gefahrgutverordnung Eisenbahn"** (Regulations for the Transport of Dangerous Products by Railway) Published in Federal Law Gazette, July 22, 1985.

13. **"Gefahrgutverordnung See"** (Regulations for the Transport of Dangerous Products by Sea) Published in Federal Law Gazette, July 27, 1985.

ENVIRONMENTAL ASSESSMENT

14. **"Gefahrgutverordnung Binnenschiffahrt"** (Regulations for the Transport of Dangerous Products on Waterways within Germany) Published in Federal Law Gazette,March 24, 1983.

15. **"IATA - DGR"** (Dangerous Goods Regulations, 28th edition.

16. **"Verordnung über Trinkwasser und über Wasser für Lebensmittelbetriebe"** (Regulations for Drinking Water and Food Handling Factories) Published Federal Law Gazette, may 22, 1986

17. **"Futtermittelgesetz"** (Federal Law on Feedstuffs) Published in Federal Law Gazette July 2, 1975.

18. **"Futtermittelverordnung"** (Regulations on Feedstuffs) Published in Federal Law Gazette, April 8, 1981.

19. **"Arbeitstättenverordnung"** (Regulations for the Working Place) Published Federal Law Gazette, May 20 , 1975

ENVIRONMENTAL ASSESSMENT

Appendix 3

Certificates of Compliance for
Bayer Corporation's Facility in West Haven, CT
and
Bayer Corporation's Facility in Myerstown, PA
and
Bayer AG's Facilities in Wuppertal-Elberfeld, Germany
and
Facility in France

ENVIRONMENTAL ASSESSMENT

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516

December 2, 1996

Environmental and Safety Compliance Statement

Bayer Corporation states it is in compliance with all environmental and safety emission requirements set forth in permits applicable to the storage and distribution of Cipro HC Otic Suspension at its facilities in West Haven, CT, as well as emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the storage and distribution of Cipro HC Otic Suspension at its facilities in West Haven, CT. There are currently no pending environmental or safety consent decrees and/or administrative orders against this facility concerning any emission standard.

Gary G. Toczylowski
Manager, Environmental and
Safety Affairs

ENVIRONMENTAL ASSESSMENT

Bayer

Consumer Care Division

Bayer Corporation
400 West Stoever Avenue
Myerstown, PA 17067

November 11, 1996

Environmental and Safety Compliance Statement

Bayer Corporation states it is in compliance with environmental and safety emission requirements set forth in permits applicable to the production of Ciprofloxacin drug product at its facilities in Myerstown, PA, as well as emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the production of Ciprofloxacin drug product at its facilities in Myerstown, PA. There are currently no pending environmental or safety consent decrees and/or administrative orders against this facility concerning any emission standard.

Llew Williams
Manager, Health, Environment
and Safety

Bayer AG

PH-TO Stab
Ökologie + Sicherheit

D-42096 Wuppertal
Telefon: (02 02) 36-1 (Vermittlung)
Tel.-Durchwahl: (02 02) 36-23 61
Fax-Durchwahl: (02 02) 36-26 35
Telex: 8591804 by d

Dr. Richter

Wuppertal, 19.11.96

Bayer Corporation
Pharmaceutical Division
Health Env. and Safety
Attn. Mr. G. Toczylowski

West Haven, CT 06516, USA

Certificates for Cipro HC Otic Suspension

Dear Gary,

Enclosed the original Certificates (already sent by fax today).

Kind regards

BAYER AG

i.V.

Bernd Richter

CERTIFICATE

To whom this may concern

It is hereby certified that the company

Bayer AG

with company headquarters in Leverkusen, Germany has permits to manufacture pharmaceutical active ingredients at a plant situated at

Friedrich Ebert Str. 217 - 319
Wuppertal- Elberfeld
Germany

under the relevant German laws for the protection of the environment.

Bayer AG is in compliance with all environmental and safety emission requirements set forth in permits applicable to the production of Ciprofloxacin at its facilities in Wuppertal, Germany as well as emission requirements set forth in applicable federal, state and local statutes and regulations applicable to the production of pharmaceutical active ingredients.

There are currently no pending environmental or safety consent decrees and/or administrative orders against this facility concerning any emission standard.

Dr. Koebernick
Bayer AG
PH-TO Elberfeld

CERTIFICATE

To whom this may concern

It is hereby certified that the company

Bayer AG

with company headquarters in Leverkusen, Germany has permits to manufacture pharmaceuticals at its plant situated at

Bayer-Werk
Leverkusen
Germany

under the relevant German laws for the protection of the environment.

Bayer AG is in compliance with all environmental and safety emission requirements set forth in permits applicable to the production of Ciprofloxacin drug products at its facilities in Leverkusen, Germany as well as emission requirements set forth in applicable federal, state and local statutes and regulations applicable to the production of pharmaceutical drug products.

There are currently no pending environmental or safety consent decrees and/or administrative orders against this facility concerning any emission standard.

H. Stillings
Bayer AG
PH-TO Leverkusen

December 3rd, 1996

CERTIFICATE

Object : **HYDROCORTISONE**
HYDROCORTISONE micronised

We certify that the Plant, where the above mentioned products are manufactured :

1. Is in compliance with French environmental laws.

2. Is in compliance with all emission requirements set forth in all permits

and should remain in compliance with these regulations in case of subsequent increase in production of the products at this facility.

C. CUSSATLEGRAS
Deputy Director
in charge of relations with administration

N. VOLTA
Plant Manager

November 18, 1996

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Central Document Room
12420 Parklawn Drive - Room 2-14
Rockville, MD 20852

Re: D.M.F. No. _____

Gentlemen:

As the U.S. agent of , we hereby authorize the incorporation by reference of any data in the above Master File covering the production of:

Hydrocortisone USP, BP

by Bayer Corporation, West Haven, Connecticut

in support of any NDA/ANDA or supplemental NDA/ANDA filed by that firm.

The above product is manufactured in plant located in France, in accordance with the methods described in the above Drug Master File and meets the specifications described therein.

The enclosed information is to be kept confidential within the meaning of Part 20 and Part 300, Sections 314.420 and 314.430 of the New Drug Regulations.

Very truly yours,

Regulatory Affairs Manager

cc: Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Attn: Andrew S. Verderame, Regulatory Affairs

November 18, 1996

Mr. Andrew S. Verderame
Regulatory Affairs
Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175

Re: _____ Drug Master File no. _____

Dear Mr. Verderame,

This is to advise that Drug Master File covering the production and controls of Hydrocortisone also includes an Environmental Impact Analysis (pages 302 through page 323) in which confirms that they meet all the requirements of the French Law. They also describe their actions to protect the environment regarding:

- effluents
- solvents
- rain water
- working personnel / occupational hygiene and safety
- Medical surveillance of personnel

Should you need any additional information, please let us know.

Sincerely yours,

Regulatory Affairs Manager

Appendix 4

West Haven Regulatory Overview

ENVIRONMENTAL ASSESSMENT

WEST HAVEN REGULATORY OVERVIEW

The proposed application to store and distribute Cipro HC Otic Suspension in the exiting Corporation facility located in West Haven, Connecticut could impact the following federal, state and local environmental and safety laws and regulations that the site is currently in compliance with. However, there are no negative impacts anticipated because the product will be received in the packaged form and will be shipped in the same packages. Internal handling procedures have been designed to mitigate these potential impacts.

1) State of Connecticut DEP, Regulations for the Abatement of Water Pollution. (Current permit # SP0000141, expires 7/31/95, permit renewal application submitted in first quarter of 1995).

2) State of Connecticut DEP, General Permit for the Discharge of Stormwater Associated with Industrial Activity. (No Permit # required only notification. Notification made on 11/20/92).

3) Federal EPA and State DEP, Hazardous and Solid Waste Regulations. (EPA # CTD046418059).

4) Federal EPA and State DEP, biomedical Waste Disposal and Tracking. (No Permit Required).

5) State DEP, Oil and Chemical Release Reporting Requirements. (No Permit Required).

6) OSHA, Response to Hazardous Waste and Handling of Hazardous Materials Release Emergencies, (HAZWOPER). (No Permit Required).

7) State of Connecticut DEP, Regulations for the Abatement of Air Pollution. (Three permits exist on site. All are associated with our fuel burning equipment on site, i.e., 2 boiler installations and 1 emergency generator). None of the dust collection or equipment utilized in the manufacture of products in West Haven has or requires DEP permits, due to the small size and lack of hazardous materials processed in them.

8) Federal Occupational Safety and Health Administration (OSHA) programs also apply to the West Haven facility. Although permits are not required, compliance with a wide variety of occupational safety programs is. In particular, OSHA regulatory required programs that impact the West Haven location the most include: the laboratory standard, blood borne pathogens, respiratory protection, lockout/tagout, personal protective equipment, hazard communication and process safety management.

ENVIRONMENTAL ASSESSMENT

CURRICULUM VITAE

Gary G. Toczylowski

I. TITLE

Manager, Safety and Environmental Affairs
Bayer Corporation, Pharmaceutical Division

II. MAJOR JOB RESPONSIBILITIES

Responsible for coordinating effective environmental and safety programs for all Pharmaceutical Division personnel reporting to West Haven. This includes direct responsibility for West Haven site personnel and divisional sales groups. Assistance is also provided to other Pharmaceutical Division personnel in the management of non-West Haven site programs.

Manage the implementation of all governmental and corporate safety and environmental directives affecting the West Haven site. Act as the site Chemical Hygiene Officer for all site laboratory operations including the Bayer Research Center. Ensure compliance with all applicable governmental environmental permits and programs, and act as the West Haven site representative to all local and State regulatory agencies.

III. EDUCATION

High School	1975 -	Bishop Klonowski, H.S. Scranton, PA
College - Bachelor of Science Env. Sciences	1979 -	Wilkes University Wilkes Barre, PA
- Masters of Science GeoEnv. Sciences	1984 -	Shippensburg University Shippensburg, PA

IV. EXPERIENCE

July 1989 to Present - Manager, Safety and Environmental Affairs, Bayer Corporation, West Haven. Responsible for managing the environmental and safety activities of the West Haven site, which includes acting as the site liaison with corporate and governmental entities, coordinating compliance efforts with all effected departments on all applicable regulations and provide needed environmental and safety training necessary to ensure compliance. Also, act as the

site Chemical Hygiene Officer for laboratory operations, and write all FDA Environmental Assessments.

April 1985 - July 1989 - Manager of Environmental and Chemical Safety, Cuno Incorporated, Meriden, CT. Responsible for ensuring compliance with all applicable environmental and chemical safety regulations for all Cuno facilities in the U.S.. Major areas of concern were wastewater management, hazardous waste management, underground storage tank management and controlling employee chemical exposures to process chemicals. Also, conducted environmental consulting activities for the Commercial Intertech Incorporated, the parent of Cuno.

1983 - 1990 - Project Environmental Consultant (part-time), Wexler Engineering, Farmington, CT. Responsible for sample collection and analysis, system simulations, operational evaluations and training and report preparations associated with a variety of environmental engineering projects.

March 1983 - April 1985 - Process Engineer and Chemist,

Water Pollution Control Facility, Town of Southington, CT. Responsible for the establishment and operation of all process control and laboratory sampling and analysis programs.

November 1981 - March 1983 - Chemist, Water Pollution Control Facility, Town of Plainville, CT. Responsible for the collection and analysis of samples form all phases of plant operations leading to recommendations of process control changes.

EDUCATIONAL EXPERIENCES

Instructor in Wastewater Treatment Systems Design, Berkshire Community College, Pittsfield, MA.

Instructor in Earth an Environmental Sciences, Central Connecticut State University, New Britain, CT.

V. PROFESSIONAL ASSOCIATIONS/LICENSES, REGISTRATION

- State of CT, Grade V, Wastewater Operators Certification
- Certified Hazardous Waste Operations Responder, currently fulfilling role as main site Emergency Coordinator
- Member of the Connecticut Forum of Regulated Environmental Professionals
- Member of the GMP Training and Education Association of Pharmaceutical Manufacturers
- Active Participant in the PMA s Environmental and Safety Committees
- Member of the National Safety Council

VI. SEMINAR ATTENDANCE

- GMP Regulations
- PMA Environmental and Safety Updates
- EPA and State DEP Environmental Updates
- Hazardous Waste Operations
- Key Issues in Wetland Regulation in CT
- New Haven Fire Training School Course Attendance

VII. OTHER DEVELOPMENT

- German Language Instruction Begun, 1992

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-805

PHARMACOLOGY REVIEW(S)

Review and Evaluation of Pharmacology and Toxicology Data
Division of Anti-Infective Drug Products, HFD-520

JAN 20 1998

NDA #: 20,805-000

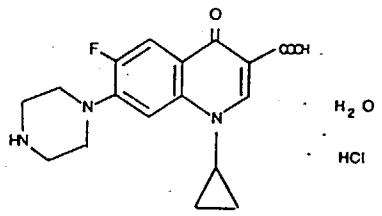
SPONSOR: Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
(203) 937-2000

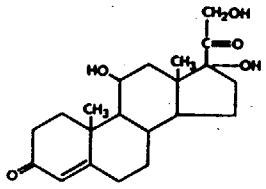
AUTHORIZED REPRESENTATIVE: Ann Marie Assumma, M.S.
Associate Director, Regulatory Affairs
(203) 812-3290

DRUG NAMES: Ciprofloxacin-Hydrocortisone Otic Suspension; Bay o 9867; 3-Quinolinecarboxylic acid; 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(piperazinyl), monohydrochloride, monohydrate

CATEGORY: Fluoroquinolone antibiotic with corticosteroid

STRUCTURAL FORMULA:





RELATED SUBMISSIONS: NDA 19-537 (ciprofloxacin tablets); NDA 19-847 (ciprofloxacin intravenous solution); NDA 19-992 (ciprofloxacin ophthalmic solution); IND
IND

NUMBER OF VOLUMES: 7 for Pharm/Tox (out of a total of 52)

DATE CDER RECEIVED: 2/10/97

DATE ASSIGNED: 2/12/97 (but volumes not delivered until 2/25/97)

DATE REVIEW STARTED: 2/25/97

DATE 1ST DRAFT COMPLETED: 1/14/98

DATE REVIEW ACCEPTED BY TEAM LEADER: January 20, 1998

REVIEW OBJECTIVES: To determine whether the nonclinical data submitted in this NDA adequately demonstrate the potential toxicity of ciprofloxacin-hydrocortisone otic suspension and to determine if this drug product meets safety standards allowing it to be approved for marketing for the indication of acute diffuse bacterial external otitis.

PROPOSED DOSAGE FORM AND ROUTE OF ADMINISTRATION:

Each 10 ml of the otic solution contains:

Ciprofloxacin HCL	mg (% w/v)	
Hydrocortisone	mg (% w/v)	
Polysorbate 20 (Tween 20)	mg	
Sodium Acetate, Trihydrate	mg	
Glacial Acetic Acid	mg	
Benzyl Alcohol	mg	
Modified Soy Lecithin	mg	(Phospholipon 90H)
Sodium Chloride	mg	
Polyvinyl Alcohol	mg	
Purified Water	ml	

pH 4.5-5.0 with 1N HCl or 1N NaOH

The recommended dosing regimen is 3 drops (about 90 µl, according to sponsor) of the suspension instilled into the affected ear(s) twice daily for 7 days. The proposed indication is acute diffuse bacterial external otitis in adults and children age 2 and older.

INDEX OF NONCLINICAL STUDIES SUBMITTED TO THIS NDA (and location of review):

Pharmacology Studies:

Data from general nonclinical pharmacology studies with ciprofloxacin have been submitted by the sponsor under NDAs 19,537 (ciprofloxacin HCl oral tablets) and 19,847 (ciprofloxacin intravenous solution). The general nonclinical pharmacology of Cipro HC otic suspension was not studied; however, measurable systemic levels of either active ingredient would not be expected even if 100% of the dose were absorbed- an extremely unlikely occurrence. A total daily dose of 360 µl Cipro HC Otic suspension contains only mg of ciprofloxacin and mg of hydrocortisone, assuming bilateral treatment.

Toxicology Studies:

Ciprofloxacin and the Inner Ear- A Morphological and Round Window Permeability Study (J Oto-Rhino-Laryngology 54: 5-9, 1992)
IND

Does Ciprofloxacin Affect the Inner Ear? A Preliminary Report (Scand J Infec Dis, Suppl 60: 28-34, 1989)
IND

Ototoxicity of Gyrase Antagonist Ciprofloxacin? (Adv Otorhinolaryngol 45: 175-180, 1990)
IND

Lack of Ciprofloxacin Ototoxicity after Repeated Ototopical Application (Antimicrobial Agents and Chemotherapy 35: 1014-1016, 1991)
IND

Lack of Ototoxicity of Topically Applied Ciprofloxacin: An Experimental Animal Study (Abstract from the Conference on Eustachian Tube and Middle Ear Diseases, p. 54, Geneva, Switzerland, 1989)
IND

Ciprofloxacin: Use as a Topical Otic Preparation (Arch Otolaryngol Head Neck Surg 118: 392-396, 1992)
IND

Ototoxicity of Ciprofloxacin by Chronic Intratympanic Application (Abstract No. 150 from the Seventeenth International Congress of Chemotherapy, Berlin, Germany, June 23-28, 1991)
IND

Ototoxicity of Ciprofloxacin (Eur Arch Otorhinolaryngol (Suppl 2): 58, 1991)
IND

Subacute (30 Day) Ototoxicity Study with Locally Applied 0.2% Ciprofloxacin in the Guinea Pig (Report No. MTD9416)
IND

Subacute (30 Day) Ototoxicity Study with Locally Applied 0.2% Ciprofloxacin + 1% Hydrocortisone in the Guinea Pig (Report No. MTD9422)
IND

Subacute (30 Day) Ototoxicity Study with Locally Applied Ciprofloxacin/Hydrocortisone Otic Suspension with Age-Related Degradation Product in the Guinea Pig (Report No. OTL896)
Reviewed below

A Dermal Irritancy Study of Cipro/Hydrocortisone Otic Suspension (0.2% Ciprofloxacin and 1.0% Hydrocortisone with Degradation Product), Administered Twice Daily, for 14 Days in Albino Rabbits (Project No. 55209)
Reviewed below

NDA 19,537 for Ciprofloxacin Hydrochloride Tablets (Miles, Inc.- former name of the sponsor of the current NDA)

NDA 19,537 for Ciprofloxacin Intravenous 1% Solution (Miles, Inc.- former name of the sponsor of the current NDA)

NDA 19,992 for Ciprofloxacin Hydrochloride Ophthalmic Solution (Alcon Laboratories- has authorized Bayer Corporation to cross-reference this NDA in support of the current submission)

Personal Communication from J. Miller to Robert Kowalski, March 13, 1995
IND

Pharmacokinetic (ADME) Studies:

Topical Ciprofloxacin for Chronic Suppurative Otitis Media: Systemic Absorption, Efficacy and Adverse Events (Pharmacotherapy 13 (6): 680, 1993)
Reviewed below

Ciprofloxacin (Bay o 9867): Concentration in Perilymph During a Pilot Toxicokinetics Study with Local Ototopically Applied 0.2% Ciprofloxacin in the Guinea Pig (Project 9429, Bayer Pharma Report No. 24255)
Reviewed below

Preliminary and Short Report: Percutaneous Absorption of Hydrocortisone-4-C^{14} in Two Human Subjects (J Invest Derm 25, pp. 281-283, 1955)
Reviewed below

Regional Variation in Percutaneous Penetration of ^{14}C Cortisol in Man (J Invest Derm 48 (2): 181-183, 1967)
Reviewed below

Quantifying Systemic Absorption of Topical Hydrocortisone in Erythroderma (Br J Derm 133: 403-408, 1995)
Reviewed below

Pituitary and Adrenal Responses to Ovine Corticotropin Releasing Factor and Vasopressin Injected into Young and Adult Guinea-Pigs (J Dev Physiol 14: 163-169, 1990)
Reviewed below

Diseased Skin Models in the Hairless Guinea Pig: In Vivo Percutaneous Absorption (Dermatologica 180: 8-12, 1990)
Reviewed below

REVIEWS OF NONCLINICAL STUDIES:

TOXICOLOGY:

As an amendment to this NDA (BP, dated 3/20/97 and received on 3/24/97), the sponsor provided raw data used to calculate the ABR threshold changes for each animal for studies 9416 (OTL 494), 9422 (OTL 694) and OTL 896. The raw data demonstrated the normal variability that exists between animals at baseline.

Subacute (30 Day) Ototoxicity Study with Locally Applied Ciprofloxacin/Hydrocortisone Otic Suspension with Age-Related Degradation Product in the Guinea Pig (Study No. OTL896)

Report dated 11/22/96, U.S. GLP

Vol. 10, pp. 1-93

Animals: NIH pigmented guinea pigs 5 males (35-42 days old, 250-283 g) and 5 females (42-49 days old, 248-287 g) were assigned to each group. Animals were unilaterally implanted with a cannula to the middle ear, proceeding from the bulla and terminating in the niche above the round window membrane. Surgery was not performed on all animals on the same day, but an attempt was made to implant at least one guinea pig per dose group on each surgery day.

Diet: Purina Mills Certified Guinea Pig Chow #5026 and tap water were available ad libitum.

Length of Study: The animals were treated with drug twice daily for 30 days. Drug treatment commenced on the day following cannula implantation. On study day 14, guinea pigs did not receive their morning dose of drug because the presence of fluid in the middle ear could interfere with the ABR readings measured that day. Auditory brainstem response (ABR) was measured in each animal prior to the implantation of the drug delivery catheter, on day 14, and on day 30 before termination. The frequencies used for ABR evaluation were 2, 8,

and 16 kHz. Cochleas were locally perfused with fixative (4% paraformaldehyde in phosphate buffer) after animals were beheaded; these organs were then immersed in fixative for at least 2 hours before further processing.

Drug Dose and Route of Administration: The two dosing groups were 0.2% Ciprofloxacin-1% Hydrocortisone Suspension with Age-Related Degradation Product, Batch M941201, and Control (normal saline). The following degradation products (amounts expressed as percentages of total ciprofloxacin or hydrocortisone, as applicable) were present in the suspension: ciprofloxacin ethylenediamine compound, 0.07%; 21-dehydrocorticosterone, 1.7%; ciproformamide, 0.4%. Each day at approximately 8 a.m. and 6 p.m., 10 μl of the appropriate solution was introduced into the middle ear via a surgically implanted catheter that terminated in the niche above the round window membrane. A positive control (e.g., neomycin) was not utilized in this study.

Results: No drug-related deaths or clinical symptoms of toxicity were observed. One control male animal appeared ill on the first day of dosing and was found dead on day 3. The investigators were unable to determine a cause of death. This animal was replaced. Another control male was sacrificed on day 13 due to a necrotic foot. Aspirates withdrawn from the cannulas prior to dosing the guinea pigs were occasionally noted as blood-tinged in some animals from each group. All surviving guinea pigs gained weight during the study. Necropsy did not include evaluation of internal organs other than the otic capsule.

ABR thresholds were within the accepted range of variability in the control guinea pigs. On day 30, the changes in ABR threshold fell within 12 dB of the baseline value at all frequencies tested (2, 8, and 16 kHz). In the group treated with ciprofloxacin/hydrocortisone suspension with the degradation products 6/10 guinea pigs had ABR threshold shifts $\geq$12 dB at one or more of the frequencies tested. Only 1 animal had a negative shift $\geq$12 dB at all 3 frequencies (-20, -46, and -12 at 2, 8, and 16 kHz, respectively) and 3 others had negative shifts $\geq$12 dB at 2 frequencies (-17 and -20 at 2 and 8 kHz; -18 and -20 at 2 and 8 kHz; -31 and -14 at 8 and 16 kHz). Two other guinea pigs had negative threshold shifts of -22 dB at 8 kHz only. All of these threshold shifts fell in a range indicative of slight to moderate hearing loss. Cytocochleograms did not reveal greater than "normal" hair cell loss in any guinea pig from either treatment group. This indicates that the slight to moderate hearing loss observed in some of the ciprofloxacin/hydrocortisone suspension-treated animals is not due to cochlear damage, but is likely a conductive loss. Examination of the middle ears with a dissecting microscope revealed very mild growth of fibrous tissue in the middle ears of 2/9 animals from the saline control group. In the drug-treated group middle ear reactions were observed with greater frequency (9/10 animals). These reactions consisted of fibrous or connective tissue growth (usually in the proximity of the windows and mild or moderate, but moderately heavy in one animal) or bone thickening. It should be noted, however, that one drug-treated animal with grossly "normal" middle ear had mild hearing loss (-22 dB) at 8 kHz and 4 other animals with middle ear reactions did not experience significant changes in ABR thresholds. Histopathology was not performed on tissue from the middle ears.

Ciprofloxacin-hydrocortisone otic suspension with degradation products instilled twice daily (at a volume of 10 μl) directly into the middle ear of guinea pigs did not appear to be toxic to the cochlea in this study. However, intratympanic administration of this drug product

caused fibrous tissue growth in the middle ear of most animals and was associated with slight to moderate hearing loss at one or more frequencies in 6/10 guinea pigs.

A Dermal Irritancy Study of Cipro/Hydrocortisone Otic Suspension (0.2% Ciprofloxacin and 1.0% Hydrocortisone with Degradation Product), Administered Twice Daily, for 14 Days in Albino Rabbits (Project No. 55209)

Report dated 11/14/96, U.S. GLP

Vol. 10, pp. 94-147

Animals: Five male New Zealand White rabbits , individually housed, 2-3 months old and 2.5-3.1 kg at the initiation of the study.

Diet: Tap water purified using reverse osmosis and sterilized with UV was provided *ad libitum* and 180 g of PMI Certified Rabbit Chow 5322 was given daily.

Drug Dose and Route of Administration: Each animal was treated with both 0.2% Ciprofloxacin-1% Hydrocortisone Suspension with Age-Related Degradation Product, Batch M941201-2, or normal saline (negative control). The following degradation products (amounts expressed as percentages of total ciprofloxacin or hydrocortisone, as applicable) were present in the suspension: ciprofloxacin ethylenediamine compound, 0.07%; 21-dehydrocorticosterone, 1.7%; ciproformamide, 0.4%. The test article was applied to the right side of the dorsum and the saline on the left.

Areas at least 7 X 11 cm were shaved on the backs of the animals on the day before the initiation of dosing. Rabbits were reshaved every 3 days during the treatment period and were fitted with Elizabethan collars. Compounds (at room temperature) were applied at a volume of 0.5 ml with a glass rod twice daily (at least 5 hours apart) for 14 days. The sites of application were scored for erythema and edema prior to each application (except for the first) using the Draize method after being washed with sterile water on clean gauze.

Length of Study: Rabbits were treated for 14 days and sacrificed on day 15.

Results: Neither drug-related clinical signs (excluding application site reactions) nor mortality were observed during the study. Neither erythema nor edema was observed at any site of saline application over the course of the study. "Very slight, barely perceptible erythema" was observed at the site of drug application in one rabbit 24 hours from treatment day 2 until the end of the study and in another from treatment day 5 until the end of the study. By day 12, 4/5 rabbits had "very slight, barely perceptible erythema" until the end of the study and well defined, pale red erythema was seen in the other animal. Edema was not observed at the sites of drug application for the first 6 days of treatment, but barely perceptible to slight edema was observed in 2/5 rabbits (one on days 7-15 and the other on days 14 and 15).

No treatment-related microscopic changes were observed in the skin at the sites of

application. The investigators put the drug product into the "non-irritant" category based upon the average erythema + edema scores for each week and for the entire treatment period (the averages were less than 1). To the reviewer, based upon the erythema scores (especially during week 2) the 0.2% Ciprofloxacin-1% Hydrocortisone Suspension with Age-Related Degradation Product appeared to be a very weak irritant to the intact skin of albino rabbits when applied twice daily for 2 weeks.

PHARMACOKINETICS:

A single clinical dose of Cipro® HC Otic Suspension (3 drops or approximately 90 μl) contains 180 μg of ciprofloxacin and 900 μg of hydrocortisone. An infected ear would receive 2 doses per day; thus, the maximum total daily doses of ciprofloxacin and hydrocortisone would be 0.72 mg and 3.6 mg, respectively. This product is supposed to be used by patients with intact tympanic membranes. If the entire amount of ciprofloxacin were absorbed following bilateral otic administration (unlikely even in a person with an open tympanic membrane), it is doubtful that a detectable plasma concentration of this drug would result in a human. It is also unlikely that the amount hydrocortisone in this product could lead to measurable changes in plasma cortisol above endogenous levels when used clinically as directed. All of the reports below can be found in volume 11 of the NDA.

Topical Ciprofloxacin for Chronic Suppurative Otitis Media: Systemic Absorption, Efficacy and Adverse Events (Pharmacotherapy 13 (6): 680, 1993)

Ciprofloxacin did not reach detectable levels in the plasma of pediatric patients (years of age) with tympanostomy tubes when 3 drops of 0.3% ciprofloxacin solution was administered t.i.d. for 7 days. Blood samples were drawn either prior to dosing on day 7 or one hour after dosing and an method with detection limit of 5 ng/ml was used to attempt to quantify ciprofloxacin.

Ciprofloxacin (Bay o 9867): Concentration in Perilymph During a Pilot Toxicokinetics Study with Local Ototopically Applied 0.2% Ciprofloxacin in the Guinea Pig (Project 9429, Bayer Pharma Report No. 24255)

A pilot toxicokinetic study was conducted with a 0.2% solution of ciprofloxacin using NIH pigmented guinea pigs. The in-life portion of the study was conducted at the

and the concentration of ciprofloxacin in the perilymph was quantitated using (quantitation limit ng/ml, detection limit ng/ml) at Bayer AG in Germany with BAY 12-8039 as an internal standard. Twice daily doses or single doses of 10 μl 0.2% ciprofloxacin solution or placebo were administered approximately 10 hours apart to the middle ear of the guinea pigs via a surgically implanted catheter that terminated in the niche above the round window membrane. Perilymph samples were harvested from 3 animals per time point 1 or 10 hours after the first dose or 10 hours after dosing on day 5 (the 11th dose).

One hour after a single intratympanic dose of ciprofloxacin solution, concentrations of ciprofloxacin in perilymph were 0.1, 3.05, and 4.81 μg/ml. Ten hours after a single dose,

perilymph concentrations were below the limit of detection in one guinea pig and 0.20 and 0.44 μg/ml in 2 others. Ten hours after the completion of multiple dosing, the concentrations of ciprofloxacin in the perilymph of 3 animals were below the limit of quantitation for the assay (between ng/ml). However, in the control animals, 0.41 μg/ml of ciprofloxacin was detected in the perilymph of one guinea pig. The authors of the report believed the sample to have been mislabeled, but the animal could have been incorrectly dosed. In the other 2 control animals, 6 and 22 ng/ml of ciprofloxacin was detected. These small amounts are below the limit of quantitation (but not detection) for the assay. Their presence calls into question the detection limits of the assay, the methods used by the analyzing lab to prevent cross-contamination of samples, and whether animals may have been dosed incorrectly during the in-life phase of the study.

The study appears to demonstrate the presence of ciprofloxacin in guinea pigs dosed intratympanically with a solution of 0.2% ciprofloxacin. Unfortunately, several errors related to the conduct of the study are apparent (mislabeled sample, dosing error, inaccurate preparation of quality control samples, or inaccurate detection of ciprofloxacin in perilymph or quality control samples). The pharmacologist finds this pilot study to have been too carelessly conducted to have much confidence in the results.

Preliminary and Short Report: Percutaneous Absorption of Hydrocortisone-4-C^{14} in Two Human Subjects (J Invest Derm 25, pp. 281-283, 1955)

Fifty-nine or 111 mg of radiolabeled 2.5% hydrocortisone ointment (containing petrolatum, cholesterol, multiwax and mineral oil in unspecified quantities) was applied to normal forearm skin of 2 hospitalized patients. Occlusive dressings remained in place for 6 days following application. Less than 1% of the radioactive dose applied to the skin was detected in the urine over this time period, suggesting limited absorption. When hydrocortisone was given to humans intravenously in a previous study, % of a radioactive dose was recovered in the urine within hours.

Regional Variation in Percutaneous Penetration of ^{14}C Cortisol in Man (J Invest Derm 48 (2): 181-183, 1967)

Radiolabeled hydrocortisone mg) dissolved in was applied to different parts of the body. Urine collection for 5 days demonstrated excretion of less than 1% of the dose applied to the arch of the foot or the ankle and about 1% of the dose applied to the dorsal or ventral forearm, the back, or the palm. Absorption at other sites included axilla, 3%, scalp, 4.4%, forehead, 7.7%, angle of jaw, 12%, and scrotum, 36%.

Quantifying Systemic Absorption of Topical Hydrocortisone in Erythroderma (Br J Derm 133: 403-408, 1995)

In 7 patients with erythroderma of clinically similar severity, 4-19% of a topical 500 mg dose of hydrocortisone was absorbed after 50 g of a 1% hydrocortisone cream (proprietary formula containing white petrolatum, macrogol 400, cetostearol, cetomacrogol 1000 and methyl parahydroxybenzoate with 60% water) was applied to affected areas of their skin.

Endogenous secretion of cortisol was suppressed using oral dexamethasone and plasma concentrations of cortisol were determined using a radioimmuno assay. Blood levels of cortisol following topical application of hydrocortisone cream were compared to those following an intravenous dose of 25 mg hydrocortisone.

Considering that peak plasma cortisol levels measured in this study after IV administration of 25 mg of hydrocortisone were 1000-1600 nmol/l and peak levels after a topical 500 mg dose were 300-1000 nmol/l, it is doubtful that the amount of hydrocortisone contained in Cipro® HC Otic Suspension could significantly alter normal endogenous blood levels of cortisol which range from nmol/l in the morning and about half of that at night.

Pituitary and Adrenal Responses to Ovine Corticotropin Releasing Factor and Vasopressin Injected into Young and Adult Guinea-Pigs (J Dev Physiol 14: 163-169, 1990)

The plasma cortisol level in control adult male guinea pigs was about 250 ng/ml.

Diseased Skin Models in the Hairless Guinea Pig: In Vivo Percutaneous Absorption (Dermatologica 180: 8-12, 1990)

In female hairless guinea pigs with intact skin, about % of a μg topical dose of radiolabeled hydrocortisone (dissolved in was recovered in urine and feces compared to about % of the same dose given intraperitoneally. Non-occlusive patches were used to cover the site of topical application. Stripping the skin with tape 15 times, inducing irritation with sodium lauryl sulfate % solution in contact with skin for hours), or delipidizing with chloroform/methanol (2/1 solution in contact with skin for 6 minutes) prior to application of hydrocortisone increased recovery by 3, 4, or 5.2 times, respectively, compared to intact skin.

LABELING:

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secret and/or

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commercial

information

SUMMARY AND EVALUATION:

Data from a pilot study conducted by the sponsor suggests that, in the guinea pig, ciprofloxacin can cross the round window membrane and penetrate into the perilymph when applied intratympanically. A report from the scientific literature indicated that ciprofloxacin can also cross the round window membrane of chinchillas and be detected in the perilymph.

Use of Cipro® HC Otic Suspension by humans is unlikely to result in significant systemic levels of ciprofloxacin or hydrocortisone because the recommended total daily dose (assuming bilateral treatment) of μl contains only mg of the former and mg of the latter. It is doubtful that a detectable plasma concentration of ciprofloxacin would be achieved or that the amount hydrocortisone in this product could lead to measurable changes in plasma cortisol above endogenous levels when this otic suspension is used as recommended.

Cipro® HC Suspension with age-related degradation products such as ciprofloxacin ethylenediamine compound, 21-dehydrocorticosterone, or ciproformamide appeared to be a very weak irritant to the intact skin of albino rabbits when applied twice daily for 2 weeks, based upon the induction of slight to well-defined, but pale erythema after multiple applications.

Intratympanic administration of 0.2% ciprofloxacin solution to guinea pigs twice daily for 30 days was not associated with loss of cochlear hair cells or hearing loss as measured using auditory brainstem response (ABR). In contrast, intratympanic administration of 10% neomycin over the same time period caused significant loss of both hearing and cochlear hair cells. Loss of cochlear hair cells was not observed in guinea pigs treated twice daily for 30 days with 0.2% ciprofloxacin/1% hydrocortisone suspension, with or without age-related degradation products (as above). However, a slight to moderate hearing loss, no greater than 15-20 dB in the majority of the affected guinea pigs, has been observed at one or more of the frequencies tested (2, 8, or 16 kHz) in about half of the animals dosed with ciprofloxacin/hydrocortisone suspension with degradation products and in 1-2 animals per group treated with the suspension vehicle, a hydrocortisone suspension, or ciprofloxacin/ hydrocortisone suspension. The negative changes in the ABR threshold appear to be conductive. Intratympanic administration of the suspensions was associated with fibrous tissue growth (usually mild to moderate) in the middle ear of the guinea pigs, but the presence of

such tissue did not correlate with any loss of hearing. The fibrous tissue proliferation may indicate slight irritation. Histopathologic examination of the middle ear tissues or tympanic membrane was not performed. Thus, it is not possible to determine whether microscopic lesions were present that may have correlated with the slight hearing loss observed at some frequencies in several of the guinea pigs. It should be emphasized that no cochlear hair cell loss was observed in any animal treated with ciprofloxacin/hydrocortisone otic suspension and the negative ABR threshold changes observed in some guinea pigs treated with this product were slight to moderate, did not occur most often at the high frequency (as has been observed with ototoxic drugs that damage the cochlea), and were not observed at all tested frequencies in the majority of the animals.

Based upon the guinea pig data, 0.2% ciprofloxacin/1% hydrocortisone should be reasonably safe for 7 days of therapy for acute otitis externa in adult and pediatric patients with intact tympanic membranes.

RECOMMENDATION: The pharmacologist has no objection to the approval of this NDA for 0.2% ciprofloxacin/1% hydrocortisone otic suspension. Suggested revisions to the sponsor's proposed label can be found above.

Amy L. Ellis, Ph.D.
Pharmacologist, HFD-520

Orig. NDA
cc:
HFD-520
HFD-520/Pharm Team Ldr/Osterberg
HFD-520/Pharm/Ellis
HFD-520/MO/E. Mann
HFD-520/MO Team Ldr/Roberts
HFD-590/Chem/Matecka
HFD-520/CSO/Roche
HFD-590/Micro/Dionne

Concurrence Only:
HFD-520/REOsterberg 1/20/98
HFD-520/LGavrilovich 1/21/98

Appendices:
IND 47,122-000
IND 47,121-002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-805

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA#:	20-805
APPLICANT:	Bayer Corporation Pharmaceutical Division
NAME OF DRUG:	CIPRO® HC OTIC SUSPENSION
INDICATION:	Acute Diffuse Bacterial External Otitis
DOCUMENTS REVIEWED:	Vol. 1.1, 1.15, Responses to request of information 8/7/97, 10/17/97, 10/24/97, 11/7/97, 11/14/97, 12/2/97
MEDICAL REVIEWER:	HFD-520: Eric Mann, M.D.

A: Introduction

Two studies for the treatment of acute, diffuse, bacterial external otitis using ciprofloxacin otic suspension with hydrocortisone (CIP-HC-SUSP) were conducted for this NDA submission. The two studies were similar in design with one conducted in the U.S. and the other in the Europe. Polymyxin B sulfate-neomycin sulfate-hydrocortisone otic suspension (PNH) was used in these studies as the active control. Ciprofloxacin otic solution without hydrocortisone (CIP-SOLN) was used as a control arm to show the added benefits of hydrocortisone component of CIP-HC-SUSP in reducing the time to end of pain.

Oral ciprofloxacin and intravenous ciprofloxacin had been approved for the treatment of various bacteriological infections, not including otic infections.

The protocol-specified window for the efficacy evaluation was 3 to 7 days post treatment. This criteria was not utilized in the original NDA submissions. In subsequent meetings the Division of Anti-Infective Drug Products (DAIDP) and the applicant agreed that the evaluation window should be expanded to 3 to 10 days post treatment. The applicant reclassified patients based on this agreement in the 11/14/97 and 12/2/97 submissions.

To verify the accuracy of the applicant's classification, a random sample of about 10% evaluable patients and 20% non-evaluable patients were drawn from the two studies. The medical officer (MO) examined and classified these patients as evaluable resolution, evaluable improvement, evaluable failure and non-evaluable. The MO's classification of these patients turned out to be exactly the same as those of the applicant, therefore the applicant's classification of the patients in these two studies was considered adequate and will be accepted for the primary efficacy analyses.

It appeared that the applicant's original plan was to pursue the approval of both CIP-HC-SUSP and CIP-SOLN for the proposed indication, and the employing of a step-wise testing procedure reflected this intention. However, the applicant's proposed label did not include CIP-SOLN even though the equivalence of CIP-SOLN and PNH was implied by the approval of CIP-HC-SUSP according to this testing procedure.

B: Study Design

Design and Conduct

Protocol D94-008: "Prospective, Controlled, Randomized, Non-blinded, Multi-center Clinical trial of Ciprofloxacin Otic Drops with or without Hydrocortisone versus Polymyxin B-Neomycin-Hydrocortisone Otic Drops in the Treatment of Acute, Diffuse, Bacterial External Otitis". This trial was conducted in the U.S..

Protocol SN 1439: "Prospective, Controlled, Randomized, Non-blinded, Multi-center Clinical trial of Ciprofloxacin Otic Drops with or without Hydrocortisone versus Polymyxin B-Neomycin-Hydrocortisone Otic Drops in the Treatment of Acute, Diffuse, Bacterial External Otitis". This trial was conducted in the Europe.

Both trials were to be non-blinded since solution and suspension are easily distinguishable. There were to be at least 20 centers and a total of 825 subjects participating in each trial. These patients were to be randomized into three treatment groups:

A. CIP-HC-SUSP 3 drops BID, 275 patients
B. CIP-SOLN 3 drops BID, 275 patients
C. PNH 3 drops for children and 4 drops for adults, TID, 275 patients

To be eligible, patients must be 2 years or older who present with acute, diffuse, bacterial otitis externa confirmed by clinical documentation within two days prior to therapy. The minimum clinical parameters for inclusion were:

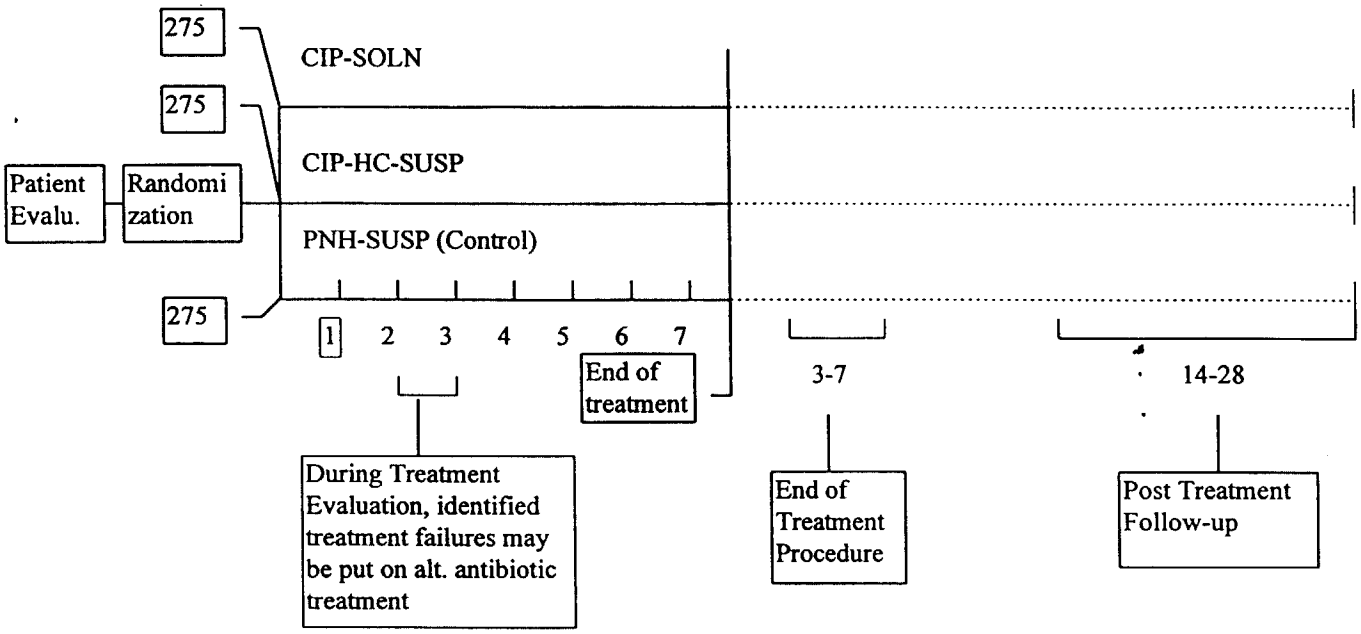
1. otalgia
2. edema of the external auditory canal
3. tenderness with movement of pinna

The signs and symptoms must have been present for less than three weeks. The patient was also required not to have any otitis externa within the 30 day period prior to entering the trials. Each patient were to be used in the trial only once.

After a patient was screened, appropriate study drug would be dispensed by the investigator after randomization.

Each trial was to be conducted over a 1 year period. Patients were to be treated for 7 days and then followed for an additional 14-28 days. The patients were to be evaluated on day 2-3 of treatment through telephone contact. If a patient had not responded clinically, a return office visit is required and if considered a treatment failure, he/she will be reevaluated including a culture

and then administered appropriate alternative antibiotics. The first post-treatment evaluation was to be carried out within 3-7 days after the last dose of trial drug. All treated patients were to be seen and evaluated at a follow-up visit, 14-28 days after the completion of trial drug therapy. The trials can be depicted as below:



At completion of therapy (3-7 days post-therapy), the clinical response was to be graded as follows:

Resolution: Absence of signs and symptoms related to the infection (relative to patient's pre-infection baseline). No additional anti-microbial is required.

Improvement: Improvement of most signs and symptoms related to the infection (relative to patient's trial entry baseline). No additional anti-microbial therapy is required.

Failure: No change, worsening or reappearance of the signs and symptoms of infection. Patient requires additional anti-microbial therapy.

No Evaluation: If data is missing or evaluation not possible due to patient non-availability.

At the 14-28 day follow-up, the clinical response will be graded as follows:

Continued Resolution: Clinically improved or resolved at end of therapy and resolved at 14-28 day follow-up.

Relapse:	Clinically improved or resolved at end of therapy, but reappearance of signs and symptoms of infection associated with otitis externa. Reinstitution of antibiotics required.
No Evaluation:	If data is missing or evaluation not possible due to patient non-availability.

At completion of therapy (3-7 days post-therapy), the bacteriologic response were to be graded as follows:

Eradication:	Causative organisms absent at the completion of therapy.
Presumed Eradication:	No material to culture and clinical resolution.
Persistence:	Causative organism present at the completion of therapy.
Indeterminate:	Bacteriological response to the study drug is not evaluable for any reason (i.e., post-treatment culture unobtainable, not performed when appropriate, negative pre-study culture).
Superinfection:	A new infection causing organism present at any time during therapy or up to seven days after completion of therapy.

All patients who were treatment failures during or at the end of trial drug therapy will be treated with an appropriate alternative anti-microbial and then clinically evaluated 14-28 days following the date of their treatment failure on trial drug.

Sample Size

The sample size evaluation was based on 90% power for proving the equivalence of each of the two treatment (suspension and solution) with PNH without adjustment for multiplicity. The equivalence limit was set to be 10%, meaning that the lower bound of the 95% confidence interval of the observed difference between rates of clinical resolution plus improvement at the end of therapy (evaluated 3-7 days post treatment) should be no more than 10% in order to declare equivalence. Since the trials were multi-center, the sample sizes were also inflated 15% over what would have been required for a single center study. The sample sizes were further adjusted to accommodate non-evaluable patients. Approximately 825 patients were to be enrolled in each trial.

Analysis Population

The applicant's analysis was to be based on the clinically evaluable patients. For a course of therapy to be judged valid for effectiveness evaluation, entry criteria must have been met; the

study drug must have been given for a minimum of 7 full days and 90% must have been administered unless an early treatment failure occurred; no other antimicrobial therapy must have been administered concomitantly with the trial drug during the trial period including the 3-7 and 14-28 day post-treatment follow-up period and a clinical response of the patient (primary efficacy variable) at the end of therapy (3-7 days post therapy) must have been determined.

Analysis Plan

The primary efficacy variables in this trial were to be based on the clinical response at the end of therapy (3-7 days post-therapy). The statistical comparison were to follow the following step-down procedure;

1. Establish efficacy of CIP-SOLN by establishing the equivalence in clinical response rates between this solution and PNH as measured by the rate of clinical resolution and improvement at post-treatment day 3-7.
2. If succeeded in step 1, then the efficacy of CIP-HC-SUSP will be established by the following:
   A. Establish the equivalence of this suspension and PNH using the same procedure as in step 1.
   B. To establish the superiority of the CIP-HC-SUSP to CIP-SOLN by comparing the times to relief of pain.

For Step 1 and Step 2A , the primary efficacy variables were to be the proportions of patients having a clinical response of resolution or improvement at the post-treatment day 3-7. Secondary efficacy variables include rate of clinical resolution at the 14-28 day follow-up and bacteriological responses (rate of eradication) at post-treatment day 3-7 and at the 14-28 day post-treatment follow-up.

For Step 2B, the primary variable of interest was to be the time-to-relief of pain (date and time of pain relief were recorded by the patient or guardian on a card). Secondary variables include reduction in pain scale and use of concomitant analgesics.

Patients who received less than 7 days of study drug would not be evaluated for efficacy, unless there was clinical evidence of therapeutic failure, and would be continued on other appropriate therapy.

The difference in clinical response rates for between two arms was to be estimated by the center-adjusted Mantel-Haenszel difference, which is the sum of the differences in each center weighted by its harmonic mean of the sizes of the two comparison arms (i.e., if the sample sizes of the two comparison arms are n_{h1} and n_{h2} for center h then the weight for the center h is $2n_{h1}n_{h2}/(n_{h1}+n_{h2})$ in calculating the overall difference in rates). The equivalencies in comparisons 1 and 2A were to be deemed to be true respectively if the lower bound of the corresponding center-adjusted 95% confidence interval for the difference between rates of success was greater than or equal to the

negative equivalence limit.

Time to pain relief were be analyzed by the proportional hazard model or a nonparametric method (such as the log rank test).

C: Applicant's Results

C.1. US Study: D94-008

Patient Disposition

Eight hundred forty two patients two years or older with acute otitis externa were enrolled at 30 clinical sites in the U.S.. All patients who have taken study medication were included in the safety analysis. A total of 703 (83%) patients were considered evaluable for efficacy. The following table provides the distribution of subjects randomized by treatment and reasons for non-evaluability. The major reasons for non-evaluability were entry criteria violation, non-compliance with the dosage regimen and end of trial evaluation out of 3-10 day window. There is no apparent difference between the treatment groups in the distribution of subjects with respect to reasons for non-evaluability.

Patient Disposition

	CIP-SOLN		CIP-HC-SUSP		PNH		Total	
Number of Patients Enrolled	285		282		275		842	
	Num.	%	Num.	%	Num.	%	Num.	%
Evaluable	239	84	236	84	228	83	703	83
Non-Evaluable	46	16	46	16	47	17	139	17
End of Trial Evaluation Out of Window	7	2.5	8	2.8	10	3.6	25	3.0
Entry Criteria Violation	16	5.6	19	6.7	14	5.1	49	5.8
Inadequate Duration of Treatment	1	0.4	0	0.0	1	0.4	2	0.2
Lost to Follow-up	3	1.1	7	2.5	2	0.7	12	1.4
Non-Compliance with the Subject Diary	0	0.0	2	0.7	1	0.4	3	0.4
Non-Compliance with the Dosage Regimen	15	5.3	8	2.8	14	5.1	37	4.4
Protocol Violation	4	1.4	2	0.7	5	1.8	11	1.3

Source: Table 3, Appendix 2 of 11/14/97 response

Baseline Characteristics

The application presents a comparison of baseline demographic and medical characteristics among the treatment arms for evaluable patients (Table 4 and 5 of 11/14/97 response). There were no apparent differences among treatment groups with respect to age, sex, race, health status, location of infection, debridement of the ear and the use of an ear wick prior to study entry.

Modification of the Analysis Plan

Four small centers (centers 1, 5, 12 and 20) were combined and treated as one center for the analysis of clinical and bacteriological responses controlling for possible center effect in the original NDA submission. In the 11/14/97 response, center 15 was also combined in addition to the 4 centers mentioned.

For the initial post-treatment visit, the window for the timing of the visit was expanded from 3-7 days post-treatment to 1-10 days post-treatment in the original submission. After discussions with DAIDP the window was changed to 3-10 days post-treatment.

One patient) was randomized to the PNH group, but received CIP-SOLN. This patient was included in the CIP-SOLN group in all the efficacy and safety analysis.

Clinical Response

The table below summarizes the treatment outcome at the end of therapy for evaluable patients. The assessment was done during 3-10 days post-treatment for patients who completed the full course of therapy. Early treatment failures were treated as failures for the 3-10 day analysis. For patients with bilateral infections, the response is the worse of the two.

Summary of Clinical Response at End of Therapy
Efficacy Evaluable

	CIP-SOLN (N=239)		CIP-HC-SUSP (N=236)		PNH (N=228)	
	N	%	N	%	N	%
Resolution	179	74.9	165	69.9	167	73.2
Improvement	40	16.7	45	19.1	31	13.6
Failure	17	7.1	23	9.7	29	12.7
Missing	3	1.3	3	1.3	1	0.4

Source: Table 17 of Appendix 2 of 11/14/97 response

After excluding the 7 patients with missing end of therapy evaluations, the treatment outcome can be summarized below:

Summary of Clinical Response at End of Therapy
Efficacy Evaluable with Non-missing Response

	CIP-SOLN (N=236)		CIP-HC-SUSP (N=233)		PNH (N=227)	
	N	%	N	%	N	%
Resolution	179	75.85	165	70.82	167	73.57
Improvement	40	16.95	45	19.31	31	13.66
Failure	17	7.20	23	9.87	29	12.78

Source: Table 17, 19 of Appendix 2 of 11/14/97 response

<u>Resolution + Improvement vs. Failure</u>

Clinical improvement or resolution was defined as the primary efficacy endpoint in the protocol. The overall rates of clinical resolution plus improvement at the end of therapy, the Mantel-Haenszel center-weighted differences in rates and their 95% confidence intervals are summarized below:

Confidence Intervals for Differences in Rates of Resolution + Improvement vs. Failure
Efficacy Evaluable with Non-missing Response

Rates of resolution + Improvement (%)			Differences (%)	
CIP-SOLN	CIP-HC-SUSP	PNH	CIP-SOLN - PNH	CIP-HC-SUSP - PNH
92.80	90.13	87.22	0.0520	0.0227
		95% C.I.	(-0.0009, 0.1049)	(-0.0339, 0.0793)

Source: Table 19 of Appendix 2 of 11/14/97 response

The estimated difference in the rates of resolution plus improvement versus failure between the CIP-SOLN group and the PNH group was 5.2%. A center-adjusted 95% confidence interval for this difference is (-0.09%, 10.49%). The lower bound of this confidence interval was greater than -10%, therefore the equivalence was established between the CIP-SOLN regimen and the PNH regimen in end of therapy clinical success rate with respect to resolution + improvement.

Similarly, the estimated lower bound of the 95% confidence interval for the difference in rates between the CIP-HC-SUSP group and PNH group was -3.4%, which was greater than -10%. therefore the equivalence was established between the CIP-HC-SUSP regimen and the PNH regimen in end of therapy clinical success rate.

Resolution versus improvement plus failure

In considering end of therapy resolution as success and improvement as failure, the rate of success can be summarized in the following table.

Confidence Intervals for Differences in Rates of Resolution vs. Improvement + Failure
Efficacy Evaluable with Non-missing Response

Rates of resolution (%)			Differences (%)	
CIP-SOLN	CIP-HC-SUSP	PNH	CIP-SOLN - PNH	CIP-HC-SUSP - PNH
75.85	70.82	73.57	0.0225	-0.0367
		95% C.I.	(-0.0532, 0.0982)	(-0.1142, 0.0409)

Source: Table 19 of Appendix 2 of 11/14/97 response

Note the success rates are all below 80%, therefore the equivalence delta is 20% (See DAIDP Guidance "CLINICAL DEVELOPMENT AND LABELING OF ANTI-INFECTIVE DRUG PRODUCTS"). Since the lower bound of the 95% confidence intervals for the difference in the success rates between CIP-SOLN and PNH and between CIP-HC-SUSP and PNH were -5.3% and -11.4%, respectively. Both were greater than -20%. A finding of equivalence is supported.

Resolution versus Failure with Improvement Reclassified as Resolution or Failure

Another secondary analysis was performed by classifying patients who were end of therapy improvement to either resolution or failure. Patients with mild clinical signs and symptoms who received no alternative antibiotic after the end of therapy evaluation and had a resolution of these signs or symptoms at the 14-28 day follow-up were consider as having had a clinical resolution

at the end of therapy. All other improvement patients were considered clinical failures.

According to this definition, 34 of the 40 improvement patients in CIP-SOLN, 35 of the 45 improvement patients in CIP-HC-SUSP, and 22 of the 31 improvement patients in PNH were reclassified as end of therapy resolutions and the other improvement patients as failures. The success rates based on this definition of resolution can be summarized below.

Rates of Resolution versus Failure with Improvement Reclassified
Efficacy Evaluable with Non-missing Response

Rates of resolution (%)			Differences (%)	
CIP-SOLN	CIP-HC-SUSP	PNH	CIP-SOLN - PNH	CIP-HC-SUSP - PNH
90.25	85.84	83.26	0.0654	0.0174
		95% C.I.	(0.0057, 0.1252)	(-0.0465, 0.0813)

Source: Table 19 of Appendix 2 of 11/14/97 response

The lower bounds of the 95% confidence intervals for the difference in success rates between CIP-SOLN and PNH and between CIP-HC-SUSP and PNH were greater than -15%, thus providing further support for the conclusion that CIP-SOLN and PNH and CIP-HC-SUSP and PNH were equivalent in end of therapy clinical response.

Subgroup Analysis: Age

Clinical response was analyzed by age group. The response rates for evaluable patients are displayed in the table below. Older patients tended to have a higher failure rate. This trend was observed for each of the three treatment groups.

Summary of Clinical Response at End of Therapy by Age
Efficacy Evaluable

Age Group	Clinical Response	CIP-SOLN (N=239)		CIP-HC-SUSP (N=236)		PNH (N=228)	
		N	%	N	%	N	%
years	Resolution	24	92.3	16	76.2	27	100
	Improvement	1	3.8	5	23.8	0	0
	Failure	1	3.8	0	0	0	0
years	Resolution	56	84.8	63	81.8	44	83.0
	Improvement	6	9.1	10	13.0	6	11.3
	Failure	4	6.1	3	3.9	3	5.7
	Missing	0	0	1	1.3	0	0
years	Resolution	24	88.9	17	81.0	27	79.4
	Improvement	2	7.4	2	9.5	4	11.8
	Failure	1	3.7	2	9.5	3	8.8
years	Resolution	75	62.5	69	59.0	69	60.5
	Improvement	31	25.8	28	23.9	21	18.4
	Failure	11	9.2	18	15.4	23	20.2
	Missing	3	2.5	2	1.7	1	0.9

Source: Table 21 of Appendix 2 of 11/14/97 response

Additional subgroup analysis will be carried out in the reviewer's analysis later.

Clinical response at Follow-up

Follow-up clinical evaluation for evaluable patients are summarized in the table below.

Summary of Clinical Response at Follow-up
Efficacy Evaluable

	CIP-SOLN (N=239)		CIP-HC-SUSP (N=236)		PNH (N=228)	
	N	%	N	%	N	%
Continued Resolution	200	83.7	196	83.1	178	78.1
Relapse	6	2.5	4	1.7	7	3.1
No Evaluation	0	0	0	0	1	0.4
Missing	33	13.8	36	15.3	42	18.4

Source: Table 17 of Appendix 2 of 11/14/97 response

For patients experiencing resolution or improvement at the end of therapy and having non-missing follow-up evaluations, the analysis results are summarized in the following table:

Rates of Continued Resolution versus Relapse

	CIP-SOLN		CIP-HC-SUSP		PNH	
	N	%	N	%	N	%
Continued Resolution	200	97.09	195	97.99	178	96.22
Relapse	6	2.91	4	2.01	7	3.78

Source: Table 19 of Appendix 2 of 11/14/97 response

	CIP-SOLN - PNH	CIP-HC-SUSP - PNH
Difference	0.0104	0.0148
95% CI	(-.0280, .0488)	(-.0183, .0479)

Statistical equivalence was again demonstrated for the CIP-SOLN and CIP-HC-SUSP when compared to PNH.

Bacteriologic Response

Of the 703 patients evaluable for efficacy analysis, 61% CIP-SOLN, 58% CIP-HC-SUSP and 59% PNH patients had one or more causative organisms isolated pre-therapy. The bacteriologic response for clinically evaluable patients is summarized in the table below:

Summary of Bacteriologic Response at End of Therapy
Efficacy Evaluable

	CIP-SOLN (N=239)		CIP-HC-SUSP (N=236)		PNH (N=228)	
	N	%	N	%	N	%
Eradication	117	49.0	107	45.3	99	43.4
Presumed Eradication	18	7.5	23	9.7	19	8.3
Persistence	3	1.3	3	1.3	13	5.7
Superinfection	8	3.3	4	1.7	4	1.8
Indeterminate	7	2.9	12	5.1	5	2.2
No Valid Pre-Rx Pathogen	83	34.7	86	36.4	84	36.8
Missing	3	1.3	1	0.4	4	1.8

Source: Table 18 of Appendix 2 of 11/14/97 response

Eradication + Presumed Eradication versus Persistence + Superinfection

Rates of Eradication + Presumed Eradication versus Persistence + Superinfection
Efficacy Evaluable with Non-missing Response

	CIP-SOLN		CIP-HC-SUSP		PNH	
	N	%	N	%	N	%
Era.+ prsumd Era.	135	92.47	128	94.81	118	87.41
Persistnc. + Superinfctn	11	7.53	7	5.19	17	12.59

Source: Table 19 of Appendix 2 of 11/14/97 response

	CIP-SOLN - PNH	CIP-HC-SUSP - PNH
Difference	0.0524	0.0698
95% CI	(-.0195, .1244)	(.0029, .1366)

This supports that CIP-SOLN and CIP-HC-SUSP are equivalent to PNH in their clinical responses.

Eradication + Presumed Eradication versus Persistence

Rates of Eradication + Presumed Eradication versus Persistence
Efficacy Evaluable with Non-missing Response

	CIP-SOLN		CIP-HC-SUSP		PNH	
	N	%	N	%	N	%
Era.+ prsumd Era.	135	97.83	128	97.69	118	90.08
Persistence	3	2.17	3	2.31	13	9.92

Source: Table 19 of Appendix 2 of 11/14/97 response

	CIP-SOLN - PNH	CIP-HC-SUSP - PNH
Difference	0.0729	0.0686
95% CI	(.0163, .1294)	(.0130, .1243)

This supports that CIP-SOLN and CIP-HC-SUSP are equivalent to PNH in their clinical responses.

Bacteriologic Response at Follow-up

The bacteriologic response of evaluable patients during follow-up are summarized below:

Summary of Bacteriologic Response at Follow-up
Efficacy Evaluable

	CIP-SOLN (N=239)		CIP-HC-SUSP (N=236)		PNH (N=228)	
	N	%	N	%	N	%
Eradication	43	18.0	49	20.8	43	18.9
Eradication with Recurrence	1	0.4	2	0.8	1	0.4
Eradication with Re-infection	2	0.8	1	0.4	1	0.4
Indeterminate	4	1.7	3	1.3	6	2.6
N.A.	11	4.6	7	3.0	17	7.5
No Valid Pre-Rx Pathogen	83	34.7	86	36.4	84	36.8
Missing	95	39.7	88	37.3	76	33.3

Source: Table 18 of Appendix 2 of 11/14/97 response

The response at follow-up for patients who had bacteria eradication at the end of therapy is presented in the following table:

Rates of Eradication versus Eradication with Recurrence + Eradication with Re-infection
For Subjects Valid for Efficacy Evaluation and With Non-missing Responses

	CIP-SOLN		CIP-HC-SUSP		PNH	
	N	%	N	%	N	%
Eradication	43	93.48	49	94.23	43	95.56
Recurrence + Reinfection	3	6.52	3	5.77	2	4.44

Source: Table 19 of Appendix 2 of 11/14/97 response

	CIP-SOLN - PNH	CIP-HC-SUSP - PNH
Difference	-0.0208	-0.0132
95% CI*	(-.1152, .0736)	(-.1016, .0751)

* Not adjusted for center effects

Time-to-relief of pain

Baseline

The pain score was measured on a scale of 0 - 15 with 15 representing the most severe pain. The baseline pain scores for evaluable patients are summarized in the two tables below. There were no apparent differences in the distribution of pain scores among the three treatment groups at baseline.

Distribution of Baseline Pain Score

	CIP-SOLN (N=239)			CIP-HC-SUSP (N=236)			PNH (N=228)		
Distribution	N	%	Cum %	N	%	Cum %	N	%	Cum %
Missing	5	2.1	2.1	0	0.0	0.0	3	1.3	1.3
≤ 1	9	3.8	5.9	9	3.8	3.8	3	1.3	2.6
> 1 - 5	54	22.6	28.5	59	25.0	28.8	49	21.5	24.1
> 5 - 8	68	28.5	56.9	59	25.0	53.8	65	28.5	52.6
> 8 -12	66	27.6	84.5	73	30.9	84.7	67	29.4	82.0
> 12	37	15.5	100	36	15.3	100.0	41	18.0	100.0

Summary of Baseline Pain Score

	CIP-SOLN (N=239)	CIP-HC-SUSP (N=236)	PNH (N=228)
Mean	7.798	7.757	8.223
Median	7.5	7.50	8.00
Std. Deviation	3.893	4.039	3.729
Range			

Time to end of pain

If the date and time of end of ear pain were recorded in the patient diary, then the time to end of ear pain was the interval between the time of the first dose and the time of the end of pain. If the date/time of end of pain were not recorded, then the time to end of pain was treated as administratively censored at the time of the last pain measurement entry in the patient's diary. For patients with bilateral infections, both valid for efficacy, the time to end of pain was defined as follows:

1. If end of pain was observed for both ears, the time to end of pain for the patient was the greater of the two time values and the observation was not censored.
2. If the time to end of pain was censored for at least one ear, the patient's time to end of pain was the greater of the time values and the observation was censored.

Among evaluable patients, 34 patients (14%) in the CIP-SOLN group, 30 patients (13%) in the CIP-HC-SUSP group, and 31 patients (14%) in the PNH group did not record a time to end of pain while under study observation. These patients were treated as censored at their last recorded value.

Survival functions for the time to end of ear pain for the three treatment groups were estimated by Kaplan-Meier product limit method. The median times to end of ear pain are summarized in the table below:

Median Number of Days to End of Ear Pain
Efficacy Evaluable

Treatment	# Observation	# Censored	Median	95% Confidence Interval	
				Lower Bound	Upper Bound
CIP-SOLN	239	34	4.67	4.031	4.885
CIP-HC-SUSP	236	30	3.79	3.389	4.104
PNH	228	31	4.07	3.747	4.715

The p-values of the log-rank test for pair-wise comparisons are displayed below.

	CIP-SOLN vs. CIP-HC-SUSP	CIP-HC-SUSP vs. PNH	CIP-SOLN vs. PNH
p-value	0.039	0.181	0.518

The protocol specified primary comparison for time to end of ear pain was CIP-HC-SUSP vs. CIP-SOLN. Since CIP-SOLN is a component of CIP-HC-SUSP, this analysis was required to show the contribution of the hydrocortisone component in CIP-HC-SUSP. The p-value of 0.039 indicates that hydrocortisone component in CIP-HC-SUSP is likely to be useful in reducing the number of days to end of ear pain.

Study Conclusion

The results of this study show both CIP-SOLN and CIP-HC-SUSP are as safe and effective as PNH for the treatment of acute diffuse bacterial external otitis. Further, it was shown that CIP-HC-SUSP was superior to CIP-SOLN in the time to end of pain, demonstrating the contribution of the hydrocortisone component in the CIP-HC-SUSP. Overall, this study demonstrates the effectiveness of the CIP-HC-SUSP in the treatment of acute diffuse bacterial external otitis.

C.2. European Study: SN 1439

Patient Disposition

Eight hundred forty two patients two years or older with acute otitis externa were enrolled at 30 clinical sites in 9 countries (Belgium, Denmark, France, Germany, Great Britain, Greece, Israel, Spain, Switzerland). All but 4 (2 in CIP-SOLN, 0 in CIP-HC-SUSP and 2 in PNH) patients were used in the safety analysis. A total of 583 (69%) patients were considered evaluable for efficacy. The following table provides the distribution of subjects randomized by treatment and reasons for non-evaluability. The major reasons for non-evaluability were end of trial evaluation out of 3-10 day window, non-compliance with the dosage regimen and missing diary. There is no apparent difference between the treatment groups in the distribution of subjects with respect to reasons for non-evaluability.

Patient Disposition

	CIP-SOLN		CIP-HC-SUSP		PNH		Total	
Number of Patients Enrolled	279		282		281		842	
	Num.	%	Num.	%	Num.	%	Num	%
Evaluable	185	66	207	73	191	68	583	69
Non-Evaluable	94	34	75	27	90	32	259	31
Outside Time Window	45	16.1	32	11.3	35	12.5	112	13.3
Entry Criteria Violation	6	2.2	4	1.4	9	3.2	19	3.0
Antimicrobial Therapy w/in Pre-Rx Window	0	0.0	1	0.4	0	0.0	1	0.1
Inadequate Duration of Treatment	4	1.4	4	1.4	3	1.1	11	1.3
Pt on Medication for < 7 Full Days	0	0.0	0	0.0	1	0.4	1	0.1
Lost to Follow-up	7	2.5	0	0.0	7	2.5	14	1.7
No Post-treatment Assessment	0	0.0	1	0.4	0	0.0	1	0.1
No End of Therapy Evaluation	5	1.8	4	1.4	2	0.7	11	1.3
No Visit Day 3-7	0	0.0	1	0.4	0	0.0	1	0.1
Diary Missing	9	3.2	11	3.9	9	3.2	29	3.4
Non-Compliance with Dosage Regimen	16	5.7	16	5.7	20	7.1	52	6.2
Concomitant Antimicrobial Therapy	0	0.0	0	0.0	3	1.1	3	0.4
>1 Dose Analgesic (Antiinflamm. Proper.)	1	0.4	0	0.0	0	0.0	1	0.1
Topical Steroid	1	0.4	0	0.0	0	0.0	1	0.1
Use of Penicillin Due to AE	0	0.0	1	0.4	0	0.0	1	0.1
NSAID	0	0.0	0	0.0	1	0.4	1	0.1

Source: Table 3, Appendix 2 of 12/2/97 response (diskette)

Baseline Characteristics

The application presents a comparison of baseline demographic and medical characteristics among the treatment arms for evaluable patients overall and within each region (Table 4, 4.1 - 4.5 of 12/2/97 response (diskette)). There were no apparent differences among treatment groups with respect to sex, race, health status, location of infection, debridement of the ear and the use of an ear wick prior to study entry. However, there appears to be a slight unbalance with respect to age among treatment groups (p-value 0.0830). The mean ages for CIP-SOLN, CIP-HC-SUSP and PNH treated patients were 41, 37 and 36 years old respectively (Table 5, 5.1 - 5.5 of 12/2/97 response (diskette)).

Modification of the Analysis Plan

For the initial post-treatment visit, the window for the timing of the visit was expanded from 3-7 days post-treatment as described in the protocol to unrestricted in the original submission. After discussions with DAIDP the window was changed to 3-10 days post-treatment.

Clinical Response

The table below summarizes the treatment outcome at the end of therapy for evaluable patients. The assessment was done during 3-10 days post-treatment for patients completed the full course

of therapy. Early treatment failures were carried forward. For patients with bilateral infections, response is the worse of the two.

Summary of Clinical Response at End of Therapy
Efficacy Evaluable

	CIP-SOLN (N=185)		CIP-HC-SUSP (N=207)		PNH (N=191)	
	N	%	N	%	N	%
Resolution	136	73.5	164	79.2	143	74.9
Improvement	23	12.4	28	13.5	28	14.7
Failure	26	14.1	15	7.2	20	10.5

Source: Table 17 of 12/2/97 response (diskette)

Resolution + Improvement vs. Failure

Clinical improvement or resolution was defined as the primary efficacy endpoint in the protocol. The overall rates of clinical resolution plus improvement at the end of therapy, the Mantel-Haenszel center-weighted differences in rates and their 95% confidence intervals are summarized below:

Confidence Intervals for Differences in Rates of Resolution + Improvement vs. Failure
Efficacy Evaluable with Non-missing Response

Rates of resolution + Improvement (%)			Differences (%)	
CIP-SOLN	CIP-HC-SUSP	PNH	CIP-SOLN - PNH	CIP-HC-SUSP - PNH
85.95	92.75	89.53	-0.0348	0.0316
		95% C.I.	(-0.1010, 0.0315)	(-0.0246, 0.0878)

Source: Table 19 of 12/2/97 response (diskette)

The estimated difference in the rates of resolution plus improvement versus failure between the CIP-SOLN group and the PNH group was -3.48%. A center-adjusted 95% confidence interval for this difference is (-10.10%, 3.15%). The lower bound of this confidence interval was less than -10%, therefore the equivalence was not established between the CIP-SOLN regimen and the PNH regimen in end of therapy clinical success rate.

The estimated lower bound of a 95% confidence interval for the difference in rates between the CIP-HC-SUSP group and PNH group was -2.46%, which was greater than -10%. therefore the equivalence was established between the CIP-HC-SUSP regimen and the PNH regimen in end of therapy clinical success rate.

Resolution versus improvement plus failure

In considering end of therapy resolution as success and improvement as failure, then the rate of success can be summarized in the following table.

Confidence Intervals for Differences in Rates of Resolution vs. Improvement + Failure
Efficacy Evaluable with Non-missing Response

Rates of resolution (%)			Differences (%)	
CIP-SOLN	CIP-HC-SUSP	PNH	CIP-SOLN - PNH	CIP-HC-SUSP - PNH
73.51	79.23	74.87	-0.0088	0.0485
		95% C.I.	(-0.0969, 0.0792)	(-0.0326, 0.1299)

Source: Table 19 of 12/2/97 response (diskette)

Note the success rates are all below 80%, therefore the equivalence delta is 20%. Since the lower bound of the 95% confidence intervals for the difference in the success rates between CIP-SOLN and PNH and between CIP-HC-SUSP and PNH were -9.69% and -3.26%, which were greater than -20%, the result of this analysis supported the conclusion that CIP-HC-SUSP and PNH were equivalent in end of therapy clinical response. It also suggested that CIP-SOLN and PNH were equivalent in clinical responses.

Resolution versus Failure with Improvement Reclassified as Resolution or Failure

Similar to the way it was done for Study D94-008, another secondary analysis was performed by reclassifying patients who were end of therapy improvement to either resolution or failure. Five of the 23 improvement patients in CIP-SOLN, 9 of the 28 improvement patients in CIP-HC-SUSP, and 3 of the 28 improvement patents in PNH were reclassified as end of therapy resolutions and the other improvement patients as failures. The success rates based on this definition of resolution can be summarized below.

Rates of Resolution versus Failure with Improvement Reclassified
Efficacy Evaluable with Non-missing Response

Rates of resolution (%)			Differences (%)	
CIP-SOLN	CIP-HC-SUSP	PNH	CIP-SOLN - PNH	CIP-HC-SUSP - PNH
76.22	83.57	76.44	0.0018	0.0764
		95% C.I.	(-0.0843, 0.0878)	(-0.0014, 0.1542)

Source: Table 19 of 12/2/97 response (diskette)

The lower bounds of the 95% confidence intervals for the difference in success rates between CIP-SOLN and PNH and between CIP-HC-SUSP and PNH were greater than -15%, thus providing further support that CIP-SOLN and PNH and CIP-HC-SUSP and PNH were equivalent in end of therapy clinical response.

Subgroup Analysis: Age

Clinical response was analyzed by age group. However, few patients were 16 years of age or younger. Therefore, no statistically meaningful conclusion was drawn based on the applicant's analysis, which was based on age categories 2-6, 7-12, 13-16 and >16 years old.

Subgroup analysis for gender and race will be carried out in the reviewer's analysis later.

Clinical response at Follow-up

Follow-up clinical evaluation for clinically evaluable patients at 3-10 days post treatment are summarized in the table below.

Summary of Clinical Response at Follow-up
Efficacy Evaluable

	CIP-SOLN (N=239)		CIP-HC-SUSP (N=236)		PNH (N=228)	
	N	%	N	%	N	%
Continued Resolution	140	75.7	171	82.6	149	78.0
Relapse	2	1.1	3	1.4	6	3.1
No Evaluation	1	0.5	1	0.5	1	0.5
Indeterminate	7	3.8	3	1.4	4	2.1
Missing	35	18.9	29	14.0	31	-16.2

Source: Table 17 of 12/2/97 response (diskette)

For patients experiencing resolution or improvement at the end of therapy and having non-missing follow-up evaluations, the analysis results are summarized in the following table:

Rates of Continued Resolution versus Relapse

	CIP-SOLN		CIP-HC-SUSP		PNH	
	N	%	N	%	N	%
Continued Resolution	140	98.59	171	98.28	149	96.13
Relapse	2	1.41	3	1.72	6	3.87

Source: Table 19 of 12/2/97 response (diskette)

	CIP-SOLN - PNH	CIP-HC-SUSP - PNH
Difference	0.0252	0.0224
95% CI	(-.0126, .0629)	(-.0156, .0604)

Statistical equivalence was demonstrated for the CIP-SOLN and CIP-HC-SUSP when compared to PNH.

Bacteriologic Response

The bacteriologic response for clinically evaluable patients is summarized in the table below:

Summary of Bacteriologic Response at End of Therapy
Valid for Efficacy Evaluation

	CIP-SOLN (N=185)		CIP-HC-SUSP (N=207)		PNH (N=191)	
	N	%	N	%	N	%
Eradication	77	41.6	93	44.9	69	36.1
Presumed Eradication	3	1.6	10	4.8	2	1.0
Persistence	6	3.2	11	5.3	18	9.4
Superinfection	4	2.2	6	2.9	5	2.6
Indeterminate	11	5.9	9	4.3	7	3.7
Missing	84	45.4	78	37.7	90	47.1

Source: Table 18 of 12/2/97 response (diskette)

Eradication + Presumed Eradication versus Persistence + Superinfection

Rates of Eradication + Presumed Eradication versus Persistence + Superinfection
Efficacy Evaluable with Non-missing Response

	CIP-SOLN		CIP-HC-SUSP		PNH	
	N	%	N	%	N	%
Era.+ prsumd Era.	80	88.89	103	85.83	71	75.53
Persistnc. + Superinfctn	10	11.11	17	14.47	23	24.47

Source: Table 19 of 12/2/97 response (diskette)

	CIP-SOLN - PNH	CIP-HC-SUSP - PNH
Difference	0.1350	0.1105
95% CI	(0.0233, .2466)	(.0031, .2179)

These results support that CIP-SOLN and CIP-HC-SUSP are equivalent to PNH in their clinical responses.

Eradication + Presumed Eradication versus Persistence

Rates of Eradication + Presumed Eradication versus Persistence
Efficacy Evaluable with Non-missing Response

	CIP-SOLN		CIP-HC-SUSP		PNH	
	N	%	N	%	N	%
Era.+ prsumd Era.	80	93.02	103	90.35	71	79.78
Persistence	6	7.98	11	9.65	18	20.22

Source: Table 19 of 12/2/97 response (diskette)

	CIP-SOLN - PNH	CIP-HC-SUSP - PNH
Difference	0.1381	0.1206
95% CI	(.0355, .2407)	(.0205, .2207)

Again it supports that CIP-SOLN and CIP-HC-SUSP are equivalent to PNH in their clinical responses.

Bacteriologic Response at Follow-up

The bacteriologic response of evaluable patients during follow-up are summarized below:

Summary of Bacteriologic Response at Follow-up
Efficacy Evaluable

	CIP-SOLN (N=239)		CIP-HC-SUSP (N=236)		PNH (N=228)	
	N	%	N	%	N	%
Eradication	16	8.6	25	12.1	19	9.9
Eradication with Recurrence	0	0.0	1	0.5	1	0.5
Indeterminate	1	0.5	3	1.4	1	0.5
N.A.	10	5.4	17	8.2	23	12.0
Missing	158	85.4	161	77.8	147	77.0

Source: Table 18 of 12/2/97 response (diskette)

Continued bacteriologic eradication was similar at the follow-up evaluations (100% CIP-SOLN, 96% CIP-HC-SUSP, 95% PNH). 95% confidence intervals were not available in the submission.

Time-to-relief of pain

Baseline

The baseline pain scores for evaluable patients are summarized in the two tables below. There were no apparent differences in the distribution of pain scores among the three treatment groups.

Distribution of Baseline Pain Score

	CIP-SOLN (N=185)			CIP-HC-SUSP (N=207)			PNH (N=191)		
Distribution	N	%	Cum %	N	%	Cum %	N	%	Cum %
Missing	35	18.9	18.9	38	18.4	18.4	29	15.2	15.2
≤ 1	4	2.2	21.1	4	1.9	20.3	5	2.6	17.8
> 1 - 5	25	13.5	34.6	24	11.6	31.9	29	15.2	33.0
> 5 - 8	28	15.1	49.7	32	15.5	47.4	37	19.4	52.4
> 8 -12	61	33.0	82.7	62	30.0	77.4	55	28.8	81.2
> 12	32	17.3	100	47	22.7	100.0	36	18.8	100.0

Source: Table 29 of 12/2/97 response (diskette)

Summary of Baseline Pain Score

	CIP-SOLN (N=185)	CIP-HC-SUSP (N=207)	PNH (N=191)
Mean	8.991	9.330	8.785
Median	10.000	9.75	9.00
Std. Deviation	3.751	3.860	3.843
Range			

Source: Table 29 of 12/2/97 response (diskette)

Time to end of pain

Among evaluable patients, 40 patients (22%) in the CIP-SOLN group, 34 patients (17%) in the CIP-HC-SUSP group, and 38 patients (20%) in the PNH group did not record a time to end of pain while under study observation. These patients were treated as censored observations at the time of their last recorded value.

Survival functions for the time to end of ear pain for the three treatment groups were estimated by Kaplan-Meier product limit method. The median time to end of ear pain were estimated based on these survival functions and they are summarized in the table below:

Median Number of Days to End of Ear Pain
Evaluable Patients

Treatment	# Observation	# Censored	Median	95% Confidence Interval	
				Lower Bound	Upper Bound
CIP-SOLN	184	40	4.59	4.063	4.951
CIP-HC-SUSP	205	34	4.00	3.563	4.688
PNH	189	38	4.06	3.833	4.538

Source: Table 33 of 12/2/97 response (diskette)

The p-values of the log-rank test for pair-wise comparisons are displayed below.

	CIP-SOLN vs. CIP-HC-SUSP	CIP-HC-SUSP vs. PNH	CIP-SOLN vs. PNH
p-value	0.344	0.829	0.420

Source: Table 33 of 12/2/97 response (diskette)

The p-value of 0.344 indicates that there was not sufficient evidence to conclude that hydrocortisone component in CIP-HC-SUSP is useful in reducing the number of days to end of ear pain.

Study Conclusion

The results of this study show both CIP-SOLN and CIP-HC-SUSP are as safe and effective as PNH for the treatment of acute diffuse bacterial external otitis. Further, treatment with CIP-HC-SUSP was associated with a slightly shorter median time to end of pain compared to CIP-SOLN

treatment. This numerical difference favoring CIP-HC-SUSP and demonstrating contribution of the hydrocortisone component, was not statistically significant in this study.

C.3. Comparison of US and European Study Results

Clinical Response

The clinical response of the individual trials and the combined trial is summarized in the table below to illustrate the comparability of study data between the US and Europe.

	CIP-SOLN			CIP-HC-SUSP			PNH		
Clinical Response	US n(%)	Euro n(%)	Combi. n(%)	US n(%)	Euro n(%)	Combi. n(%)	US n(%)	Euro n(%)	Combi. n(%)
Resolution	179(75)	136(74)	315(74)	165(70)	164(79)	329(74)	167(73)	143(75)	310(74)
Improvement	40(17)	23(12)	63(15)	45(19)	28(14)	73(16)	31(14)	28(15)	59(14)
Failure	17(7)	26(14)	43(10)	23(10)	15(7)	38(9)	29(13)	20(10)	49(12)
Missing	3(1)	0(0)	3(1)	3(1)	0(0)	3(1)	1(0)	0(0)	1(0)
Total	239	185	424	236	207	443	228	191	419

Source: Table 17 of 11/14/97 response and Table 17 of 12/2/97 response (diskette)

The overall clinical response of resolution plus improvement (primary efficacy variable) was quite similar across the three treatment groups and across the two pivotal trials. The US and European combined rate of resolution was 74%, and improvement ranged from 14 - 16%; the two ciprofloxacin otic arms were essentially identical. These US and European combined results very closely reflect the individual results for each treatment group in each of the two trials and indicate that ciprofloxacin otic is effective in the treatment of acute diffuse bacterial otitis externa having an overall rate of cure (resolution plus improvement) of 90%. These clinical results were reproducible across many study sites and across both the US and European trials.

Time to End of Ear Pain

In both the US and European trials, the contribution of hydrocortisone as determined by the time to end of pain was demonstrated, See the table below.

Treatment Group	Estimated Median Time (days)		95% Confidence Interval for Median			
	US	Europe	US		Europe	
CIP-SOLN	4.67	4.59	4.031	4.885	4.063	4.951
CIP-HC-SUSP	3.79	4.00	3.389	4.104	3.563	4.688
PNH	4.07	4.06	3.747	4.715	3.833	4.538

4.67 - 3.79 = 0.88 days = 21.1 hours
4.59 - 4.00 = 0.59 days = 14.2 hours

In the US trial the time to end of pain was significantly (i.e., reached traditional 0.05 level of significance) shorter for CIP-HC-SUSP than for CIP-SOLN (3.79 days vs. 4.67 days). In the European trial, although the difference in time to end of pain when comparing CIP-HC-SUSP

with CIP-SOLN was also shorter (4.00 days vs. 4.59 days) the difference was not statistically significant (p=0.344).

Bacteriologic Response

The data for the by patient bacteriologic response was somewhat more variable than that for the clinical response, see the table below. However, despite this variability the results show similarity across treatment arms and across both trials. The differences are of no apparent clinical significance and overall both ciprofloxacin dosage regimens can be considered highly effective in the treatment of acute diffuse bacterial otitis.

	CIP-SOLN			CIP-HC-SUSP			PNH		
Bacteriologic Response	US n(%)	Euro n(%)	Combi. n(%)	US n(%)	Euro n(%)	Combi. N(%)	US n(%)	Euro n(%)	Combi. n(%)
Erad/Pres Erad	135(98)	80(93)	215(96)	128(98)	103(90)	231(94)	118(90)	71(80)	189(86)
Persistence.	3(2)	6(7)	9(4)	3(2)	11(10)	14(6)	13(10)	18(20)	31(14)
Total	138	86	224	131	114	245	131	89	220

C.4. Summary of the Applicant's Analyses

The applicant presented several statistical analyses of the studies D94-008 (US) and SN 1439 (Europe) to demonstrate that CIP-SOLN and CIP-HC-SUSP are equivalent to PNH in healing acute external otitis and CIP-HC-SUSP is the preferred treatment because of more rapid resolution of ear pain. With most of the analysis based on evaluable patients these analyses showed that both CIP-SOLN and CIP-HC-SUSP were equivalent to PNH for treatment of acute external otitis with success rates (cure + improvement) at around 89%. These analyses also showed that CIP-HC-SUSP reduces time to end of ear pain compared to CIP-SOLN for the US Study but not the European Study.

D: Statistical Reviewer's Analyses and Comments

The applicant's analyses were based on clinically evaluable patients. The validity of these analyses relies upon the assumption that excluding non-evaluable patients will not introduce any biases. However, the percentages of patients who were clinically non-evaluable are high (17% in the US Study and 31% in the European study) and the applicant did not provide evidence to show that the treatment effects were the same for these patients. This will be explored in the subsection 2 below.

One patient was randomized to the PNH group but received CIP-SOLN. The applicant included this subject in the CIP-SOLN group. It is expected that classification of this patient into the CIP-SOLN group will not have an impact on the analyses.

The applicant's subgroup analyses on age and gender were incomplete and this issue will be addressed in subsection 5 below.

D.1. Clinical and bacteriologic evaluations based on clinically evaluable patients

In calculating the Mantel-Haenszel (M-H) 95% confidence intervals for the differences of proportions of clinical responses for the US study, the applicant grouped five small centers to one center to avoid deleting these centers from the M-H calculations, since the weight of a center is 0 if one of the comparison arms in that center had sample size 0. This manipulation had little impact in the resulting confidence intervals, as can be seen from the tables for the US study below.

In the protocol the applicant specified the formulas that were used to calculate the Mantel-Haenszel difference of proportions and its confidence interval. However, the reviewer's calculation for the European study based on the same formula yielded slightly different results, as is summarized in the tables for the European study.

A slightly different formula for the Mantel-Haenszel difference with continuity correction was also applied for the calculation. In all cases the resulting confidence bounds differ less than 0.01 from the confidence bounds using the applicant's formula. Only the results based on the applicant's formula will be used below.

US Study: CIP-SOLN vs. PNH

	Equiv.	Applicant: Grouped Center		Reviewer: Not Grouped	
	Δ	Diff	95% CI	Diff	95% CI
r+i vs. f	-0.1	0.0520	(-0.0009, 0.1049)	0.0572	(-0.0039, 0.1104)
r vs. i+f	-0.2	0.0225	(-0.0532, 0.0982)	0.0333	(-0.0429, 0.1095)
e+p vs. p+s	-0.1	0.0524	(-0.0195, 0.1244)	0.0527	(-0.0196, 0.1251)

US Study: CIP-HC-SUSP vs. PNH

	Equiv.	Applicant: Grouped Center		Reviewer: Not Grouped	
	Δ	Diff	95% CI	Diff	95% CI
r+i vs. f	-0.1	0.0227	(-0.0339, 0.0793)	0.0228	(-0.0340, 0.0795)
r vs. i+f	-0.2	-0.0367	(-0.1142, 0.0409)	-0.0374	(-0.1147, 0.0400)
e+p vs. p+s	-0.1	0.0698	(0.0029, 0.1366)	0.0736	(0.0072, 0.1401)

European Study: CIP-SOLN vs. PNH

	Equiv.	Applicant		Reviewer	
	Δ	Diff	95% CI	Diff	95% CI
r+i vs. f	-0.1	-0.0348	(-0.1010, 0.0315)	-0.0350	(-0.0950, 0.0251)
r vs. i+f	-0.2	-0.0088	(-0.0969, 0.0792)	-0.0117	(-0.0951, 0.0716)
e+p vs. p+s	-0.1	0.1350	(0.0233, 0.2466)	NA	NA

European Study: CIP-HC-SUSP vs. PNH

	Equiv.	Applicant		Reviewer	
	Δ	Diff	95% CI	Diff	95% CI
r+i vs. f	-0.1	0.0316	(-0.0246, 0.0878)	0.0356	(-0.0197, 0.0910)
r vs. i+f	-0.2	0.0485	(-0.0326, 0.1296)	0.0419	(-0.0367, 0.1204)
e+p vs. p+s	-0.1	0.1105	(0.0031, 0.2179)	NA	NA

r = resolution, I = improvement, f = failure

e+p = eradication + presumed eradication, p+s = persistence + superinfection

D.2. Clinical evaluation for ITT population

The ITT population includes all randomized patients who met entry criteria and took at least one dose of study medication. The disposition of these patients is summarized below :

Patient Disposition for ITT populations

US Study

	CIP-SOLN		CIP-HC-SUSP		PNH		Total	
Number of patients in ITT	269		263		261		793	
	Num.	%	Num.	%	Num.	%	Num.	%
Evaluable Resolution	179	66.5	165	62.7	167	64.0	511	64.4
Evaluable Improvement	40	14.9	45	17.1	31	11.9	116	14.6
Evaluable Failure	17	6.3	23	8.7	29	11.1	69	8.7
Non-Evaluable	33	12.3	30	11.4	34	13.0	97	12.2

European Study

	CIP-SOLN		CIP-HC-SUSP		PNH		Total	
Number of patients in ITT	273		277		272		793	
	Num.	%	Num.	%	Num.	%	Num.	%
Evaluable Resolution	136	49.8	164	59.2	143	52.6	443	55.9
Evaluable Improvement	23	8.4	28	10.1	28	10.3	79	8.8
Evaluable Failure	26	9.5	15	5.4	20	7.4	61	7.7
Non-Evaluable	88	32.2	70	25.3	81	29.8	239	30.1

Note that all patients with entry criteria violations are excluded in the tables above, consequently the percentages of patients who are non-evaluable are lower compared to the percentages presented by the applicant. A few patients were classified by the applicant as "Evaluable missing", a category which should be regarded as non-evaluable by the definitions in the protocol, and they were included in the "non-evaluable" category in the two tables above.

For the US study, the results for the primary analyses are stable against various assumptions made for the non-evaluable patients. When all non-evaluable patients are regarded as failures in the CIP-SOLN and CIP-HC-SUSP arms and successes in PNH arm, the lower bounds of the 95% confidence intervals for CIP-SOLN vs. PNH and CIP-HC-SUSP vs. PNH are -13.5% and -15.2% respectively. In both cases they are either greater than or almost equal to the equivalence delta of -15%, supporting the conclusion of equivalence of CIP-SOLN and CIP-HC-SUSP to PNH.

For the European study, the conclusion of equivalence is sensitive to the assumptions made on the non-evaluable patients due to the high percentage of patients who are non-evaluable at the end of therapy. For example, if we assume that among the non-evaluable patients, 50% in CIP-SOLN arm and 66% in the PNH arm were actually clinical successes, then the lower bound of the 95% confidence interval for CIP-SOLN vs. PNH would be less than the equivalence delta -15%. In this case CIP-SOLN would not be considered equivalent to PNH.

D.3. CIP-SOLN

In the US study, CIP-SOLN showed comparable treatment effects compared to PNH. The lower bound of the 95% confidence intervals were greater than the equivalence delta in both the primary analysis and the secondary analyses. The results can be summarized below:

US Study: CIP-SOLN vs. PNH

Comparisons	Est.	95% CI	Equiv. Δ
Clinical: Resolution + Improvement vs. Failure, EOT*	0.0520	(-0.0009,0.1049)	-0.10
Clinical: Resolution vs. Improvement + Failure, EOT	0.0225	(-0.0532,0.0982)	-0.20
Clinical: Resolution vs. Failure, Improvement reclassified, EOT	0.0654	(0.0057,0.1252)	-0.10
Clinical: Continued Resolution vs. Relapse, FU	0.0104	(-0.0280,0.0488)	-0.10
Bacteriologic: Eradication + Presumed Eradication vs. Persistence + Superinfection, EOT	0.0524	(-0.0195,0.1244)	-0.10
Bacteriologic: Eradication + Presumed Eradication vs. Persistence, EOT	0.0729	(0.0163, 0.1294)	-0.10

*: Primary comparison
EOT = End of Therapy
FU = Follow-Up

The results of the reviewer's analyses in the subsection 1 above were almost identical to that of the applicant. Furthermore, based on the study results in subsection 2, this conclusion is also robust against various assumptions made for the non-evaluable patients. Therefore the US study demonstrates that CIP-SOLN is comparable to PNH for the treatment of acute diffuse bacterial external otitis with respect to healing.

The results of the European study are less supportive of equivalence. In the European study, about 13.3% subjects had their EOT evaluations out of window and 3.4% of subjects with missing diary, compared to only 3% out of evaluation window and 0.4% with missing diary in the US study. This resulted in a smaller number of evaluable patients. This reduced power for the comparisons, and may have introduced biases into the estimates.

European Study: CIP-SOLN vs. PNH

Comparisons	Est.	95% CI	Equiv. Δ
Clinical: Resolution + Improvement vs. Failure, EOT*	-0.0348	(-0.1010,0.0315)	-0.10
Clinical: Resolution vs. Improvement + Failure, EOT	-0.0088	(-0.0969,0.0792)	-0.20
Clinical: Resolution vs. Failure, Improvement reclassified, EOT	0.0018	(-0.0843,0.0878)	-0.20
Clinical: Continued Resolution vs. Relapse, FU	0.0252	(-0.0126,0.0629)	-0.10
Bacteriologic: Eradication + Presumed Eradication vs. Persistence + Superinfection, EOT	0.0135	(0.0233,0.2466)	-0.15
Bacteriologic: Eradication + Presumed Eradication vs. Persistence, EOT	0.1381	(0.0355, 0.2407)	-0.10

*: Primary comparison
EOT = End of Therapy
FU = Follow-Up

The primary comparison failed to show the equivalence of CIP-SOLN and PNH in the applicant's analysis because the lower bound of the 95% confidence interval is less than -10%. However, the lower bound was -10.10% which was only slightly less than -10%.

As was seen by the analysis in the subsection 2, the conclusion of the equivalence here is sensitive to the assumptions made on the non-evaluable patients. A slight differentiation (16% or more) in the clinical success (resolution + improvement) rates between treatment arms could lead to the conclusion that there was not sufficient evidence to show the equivalence between CIP-SOLN and PNH.

D.4. CIP-HC-SUSP

According to the protocol, CIP-HC-SUSP will be considered for approval only if it meets the following criteria:

(a) CIP-SOLN is equivalent to PNH in clinical responses, and
(b) CIP-HC-SUSP is equivalent to PNH in clinical responses, and
(c) CIP-HC-SUSP reduces time to end-of-pain when compared to CIP-SOLN.

Requirement (a) has been considered in the subsection 3 above.

Next we consider requirement (b).

In the US study, all the primary and secondary comparisons for clinical and bacteriologic responses demonstrated that CIP-HC-SUSP is equivalent to PNH based on both the applicant's and the reviewer's analyses. These results are robust against various assumptions made on the

non-evaluable patients. CIP-SOLN has also been shown to be equivalent in clinical response to PNH in this study.

In the European study, all the primary and secondary comparisons for clinical and bacteriologic responses demonstrated that CIP-HC-SUSP was equivalent to PNH based on both the applicant's and the reviewer's analyses. However, the evidence for the equivalence of CIP-SOLN and PNH is sensitive to the assumptions made on the non-evaluable patients.

The requirement (c) is needed to demonstrate the added benefits of the hydrocortisone component in CIP-HC-SUSP. However, this contribution is only meaningful when it can be shown that the hydrocortisone component will not reduce the clinical benefits when added to CIP-SOLN. Therefore analysis should be done to examine the difference between CIP-HC-SUSP and CIP-SOLN with respect to clinical response. The clinical responses of CIP-HC-SUSP vs. CIP-SOLN for the evaluable patients are summarized below:

US Study: Difference in Rates of Resolution + Improvement vs. Failure
Efficacy Evaluable With Non-missing Response

Rates of resolution + Improvement (%)		Differences (%)
CIP-SOLN	CIP-HC-SUSP	CIP-HC-SUSP - PNH
92.80	90.13	-0.0316
	95%C.I.*	(-0.0764, 0.0242)

*Centers were not grouped

European Study: Difference in Rates of Resolution + Improvement vs. Failure
Efficacy Evaluable With Non-missing Response

Rates of resolution + Improvement (%)		Differences (%)
CIP-SOLN	CIP-HC-SUSP	CIP-HC-SUSP - PNH
85.95%	92.75%	0.0808
	95%C.I.*	(0.0237, 0.1380)

*Centers were not grouped

The lower bounds of the 95% confidence intervals were greater than -0.10 in both studies, therefore CIP-HC-SUSP and CIP-SOLN meet the established criteria for equivalence. This shows that hydrocortisone did not inhibit the therapeutic effects by more than 10% when added to CIP-SOLN.

Finally we turn to the requirement (c).

The applicant's analysis of time to pain relief was based on a log-rank test. Only patients clinically evaluable at the post treatment visit were used in this analyses. Both the US and the European studies showed numerical advantages of CIP-HC-SUSP over CIP-SOLN, but the difference was not statistically significant for the European study. The median difference was

estimated to be 21 hours in the US study and 14 hours in the European study, with p-values 0.039 for the US study and 0.344 for the European study. These results were confirmed by the reviewer's calculations using the same test.

US Study

Testing of superiority is usually based on an ITT population instead of an evaluable patients population. For the US study, the time to end-of-pain is summarized below:

Summary Statistics for Time to End of Ear Pain

Pain end	Efficacy evaluable	Reason for non-evaluable	Summary Statistics					
			CIP-HC-SUSP			CIP-SOLN		
			mean	sd	n	mean	sd	n
Yes	Yes		92.17	54.35	206	102.52	50.52	205
	No	Out of 3-10 day window	91.78	43.20	7	102.82	27.93	6
		Non-compli. with dosage	125.50	59.11	7	131.26	160.54	11
		Entry criteria violation	127.71	51.87	13	88.28	42.80	14
		Protocol violation	81.75	53.03	2	119.27	67.17	4
No	Yes		125.84	60.12	30	146.63	51.79	34
	No	Out of 3-10 day window	5.50	NA	1	24.00	NA	1
		Non-compli. with dosage	193.33	NA	1	158.57	39.90	4
		Entry criteria violation	142.25	47.01	6	201.46	65.11	2
		Other Reasons	*	*	7	*	*	4

The first column indicates if the time to end-of-pain was not censored. The second column shows if the patients were evaluable for efficacy. The summary statistics include mean, standard deviation and sample size for each subgroup. For censored patients, the summary statistics were calculated using the censoring times. In majority of the subgroups, the mean time to end-of-pain or time to censoring was shorter in the CIP-HC-SUSP arm than was in the CIP-SOLN arm.

The applicant used Cox regression analysis for time to end-of-pain in estimating the treatment differences. This analysis assumes that the censoring is non-informative, i.e., censored patients are similar to the non-censored patients. This may not be justifiable. A different approach will be described below.

First note that there were 35 patients who were entry criteria violators, and these patients will be excluded from the ITT population. For patients whose time to end-of-pain was censored, instead of assuming that they will follow the distribution of the non-censored patients, we assume that the average difference between the CIP-HC-SUSP arm and the CIP-SOLN arm for the time to end-of-pain in each center will be 0 had the complete follow-up available. At the same time, we assume that these patients had the same variability as the non-censored patients in each center. The last assumption is necessary in order to avoid inflating the statistical significance by reducing the patient level variance when these patients were assigned a fixed score 0. Technical details will be described in the statistical appendix. Based on this analysis, the estimated

difference in time to end-of-pain for CIP-HC-SUSP vs. CIP-SOLN is -9.68 hours, and the associated 95% confidence interval is (-19.0, -0.4) hours. The t-test yielded a p-value of 0.041. This suggest that hydrocortisone reduces time to end of ear pain when added to CIP-SOLN.

European Study
Since the applicant's analysis of the European trial did not support superiority, no further analyses were conducted in this review.

D.5. Subgroup Analysis

In the submission the applicant summarized the clinical response by the age groups (2-6, 7-12, 13-16 and ≥17 years). In the US study it was noted that older patients tended to have higher failure rates. In this section, we look at the impact of age on treatment effects more closely. In addition, the impact of gender and race will also be studied.

(1) Age

The clinical response rates of the 7-12 and 13-16 years old groups were quite similar across the three treatment arms. They will be grouped together in the following analysis.

The table below summarizes the success rates for each age by treatment subgroup among efficacy evaluable patients in the US study. Success here is defined as clinical resolution or improvement at the end of therapy evaluation.

US Study: Success rates by age and treatment groups

Age	CIP-SOLN	CIP-HC-SUSP	PNH
≤ 6 years	25/26=96.2%	21/21=100%	27/27=100%
7-16 years	88/93=94.6%	92/97=94.9%	81/87=93.1%
≥ 17 years	106/117=90.6%	97/115=84.4%	90/113=79.7%

The treatment differences between treatment groups for each age group were calculated using the center-adjusted Mantel-Haenszel method. The following table summarizes the estimated difference in success rates between treatment arms and their associated 95% confidence interval for each age subgroup.

US Study: Estimated treatment difference and 95% confidence interval

Age	CIP-SOLN vs. PNH			CIP-HC-SUSP vs. PNH			CIP-HC-SUSP vs. CIP-SOLN		
	diff.	LB	UB	diff.	LB	UB	diff.	LB	UB
≤ 6 years	-0.013	-0.290	0.264	0.000	-0.281	0.281	0.042	-0.227	0.312
7-16 years	0.026	-0.078	0.131	0.013	-0.090	0.116	-0.005	-0.102	0.092
≥ 17 years	0.105	0.002	0.209	0.024	-0.083	0.132	-0.063	-0.161	0.035

Relative to CIP-HC-SUSP and PNH, it appears that the treatment effects of CIP-SOLN is better among older patients than is among the younger ones. However, this trend is not statistically significant.

For the European study, since the vast majority of the patients were ≥ 17 years old (95%), it is impossible to estimate treatment differences with precision among patients ≤ 16 years old. Therefore subgroup analysis based on the classification above will not be discussed.

Overall, there is no strong evidence to suggest that the treatment differences between treatment groups are not homogeneous across different age groups.

(2) Gender

The tables below summarizes the success rates of males and females by treatment groups among efficacy evaluable patients.

US Study: Success rates by gender and treatment groups

Gender	CIP-SOLN	CIP-HC-SUSP	PNH
Male	107/117=91.5%	94/105=89.5%	106/118=89.8%
Female	112/119=94.1%	116/128=90.1%	92/109=84.4%

European Study: Success rates by gender and treatment groups

Gender	CIP-SOLN	CIP-HC-SUSP	PNH
Male	103/117=88.0%	115/122=94.3%	93/105=88.6%
Female	56/68=82.4%	77/85=90.6%	78/86=90.7%

The treatment differences between treatment subgroups were calculated using the center-adjusted Mantel-Haenszel method. The following tables summarizes estimated difference in success rates between treatment arms and their associated 95% confidence interval for each age subgroup.

US Study: Estimated treatment difference and 95% confidence interval

Gender	CIP-SOLN vs. PNH			CIP-HC-SUSP vs. PNH			CIP-HC-SUSP vs. CIP-SOLN		
	diff.	LB	UB	diff.	LB	UB	diff.	LB	UB
Male	0.019	-0.075	0.114	-0.019	-0.116	0.079	-0.039	-0.140	0.062
Female	0.093	-0.006	0.192	0.035	-0.065	0.135	-0.033	-0.121	0.055

European Study: Estimated treatment difference and 95% confidence interval

Gender	CIP-SOLN vs. PNH			CIP-HC-SUSP vs. PNH			CIP-HC-SUSP vs. CIP-SOLN		
	diff.	LB	UB	diff.	LB	UB	diff.	LB	UB
Male	-0.018	-0.116	0.079	0.074	-0.017	0.165	0.067	-0.022	0.156
Female	-0.048	-0.171	0.076	-0.003	-0.114	0.107	0.111	-0.010	0.232

There was considerable amount of overlap of the confidence intervals for males and females for each comparison in both studies. Overall, there is no evidence to suggest that the treatment differences between treatment groups are not homogeneous across gender groups.

(3) Race

The tables below summarizes the success rates for whites and non-whites by treatment groups among efficacy evaluable patients.

US Study: Success rates by race and treatment groups

Race	CIP-SOLN	CIP-HC-SUSP	PNH
White	201/218=92.2%	195/215=90.7%	185/211=87.7%
Non-white	18/18=100%	15/18=83.3%	13/16=81.3%

European Study: Success rates by race and treatment groups

Race	CIP-SOLN	CIP-HC-SUSP	PNH
White	156/181=86.2%	182/197=92.4%	165/185=89.2%
Non-white	3/4=75%	10/10=100%	6/6=100%

Due to the small number of non-white patients enrolled, there is not sufficient statistical power for testing of the race by treatment interactions.

In summary, there were no sufficient evidences to show that the treatment differences between any two treatments are not the same across different age, gender and race subgroups.

E. Overall Statistical Reviewer's Summary

Two pivotal open-label trials were conducted, one in the US and the other in the Europe. The high non-evaluable rates made the evaluation of these two studies difficult. This is especially true for the European study where the results depend upon how the non-evaluable patients were regarded in the analyses.

Nevertheless the results of the two pivotal clinical trials support the following based on the clinical responses and time to ear pain relief:

1. Both CIP-SOLN and CIP-HC-SUSP are equivalent to PNH with respect to resolution + improvement at day 3-10 post therapy. This was found in both the US and the European studies.

2. In the US study there is evidence that CIP-HC-SUSP is associated with a reduction in time to ear pain relief. However, in the European trial no statistically significant difference was established.

Statistical Appendix

1. Calculation of Center Adjusted Confidence Intervals

First we assume the time to pain relief had been observed for all patients. Then the calculation of the difference of the mean time to end-of-pain and it's confidence intervals could be based on center-adjusted Mantel-Haenszel (MH) difference. This difference was weighted by the harmonic mean of sample size per arm for each center. Mathematically, if n_{1h} and n_{2h} are the sample sizes of the two comparison arms 1 and 2 in center h, then the weight

$$w_h = \frac{n_{1h} n_{2h}}{n_{1h} + n_{2h}}$$

was used for center h in calculating the overall difference. Let $\bar{x}_{ih}$ and σ_{ih} be mean and standard deviation of the time to pain relief in center h for treatment arm i, and let $d_h = \bar{x}_{1h} - \bar{x}_{2h}$ be the difference between treatment arm 1 and arm 2 in center h, then the center-adjusted MH difference is

$$d = \frac{\sum w_h d_h}{\sum w_h},$$

and its variance can be estimated by

$$\frac{\sum w_h^2 (\frac{\sigma_{1h}^2}{n_{1h}} + \frac{\sigma_{2h}^2}{n_{2h}})}{(\sum w_h)^2}.$$

More weight was given to large and balanced centers than small or unbalanced centers. In the extreme case where one of the comparison arm had no patient, the weight became 0 and the center had no contribution in the evaluation.

2. Analysis for ITT population

In this section a method of dealing with incomplete follow-ups is proposed in order to analyze time to pain relief for the ITT population.

Let N_1 and N_2 be the number of patients in treatment arms 1 and 2. For center h and treatment arm k, $k = 1,2$, let n_{kh} and m_{kh} be the number of patients whose time to pain relief was completely observed and censored, respectively, let $N_{kh} = n_{kh} + m_{kh}$, and let $\bar{x}_{ih}$ and σ_{ih} be the mean and standard deviation based only on completers. Let $\bar{y}_{ih}$ be the mean time to pain relief for the incompleters had the complete follow-up were available. Then the mean difference in center h can be estimated by

$$D_h = (n_{1h}\bar{x}_{1h} + m_{1h}\bar{y}_{1h})/(n_{1h} + m_{1h}) - (n_{2h}\bar{x}_{2h} + m_{2h}\bar{y}_{2h})/(n_{2h} + m_{2h})$$
$$\approx \frac{n_{1h} + n_{2h}}{N_{1h} + N_{2h}}(\bar{x}_{1h} - \bar{x}_{2h}) + \frac{m_{1h} + m_{2h}}{N_{1h} + N_{2h}}(\bar{y}_{2h} - \bar{y}_{2h})$$

The approximation is valid if $\frac{n_{1h}}{N_{1h}} \approx \frac{n_{2h}}{N_{2h}}$ (i.e., the proportions of patients who were completers were approximately the same for the two treatment arms in each center).

Since we did not observe $\bar{y}_{ih}$, assumptions has to be made to calculate the treatment differences. Here we assume that the treatment difference was 0 for non-completers in each center, therefore $\bar{y}_{1h} - \bar{y}_{2h} \approx 0$ and treatment difference in each center can be estimated by

$$D_h \approx \frac{n_{1h} + n_{2h}}{N_{1h} + N_{2h}}(\bar{x}_{1h} - \bar{x}_{2h}).$$

The MH difference can be calculated by

$$D = \frac{\sum W_h D_h}{\sum W_h},$$

where the weights are based on the combined sample sizes of the completers and non-completers:

$$W_h = \frac{N_{1h}N_{2h}}{N_{1h} + N_{2h}}.$$

The estimated variance is

$$\frac{\sum W_h^2(\frac{\sigma_{1h}^2}{N_{1h}} + \frac{\sigma_{2h}^2}{N_{2h}})}{(\sum W_h)^2},$$

which is based on the combined sample size but uses the patient level variance estimation using only the completers.

/S/ 2/18/98

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This review contains 39 pages.